Industria y Comercio
SUPERINTENDENCIA
República de Colombia
Ministerio de Comercio, Industria y Turismo

PROPIEDAD INDUSTRIAL

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

SOLICITUD DE PCT

PATENTE DE INVENCION
PCT ENTRADA EN FASE NACIONAL

21. EXPEDIENTE No. 07-33168

54. TITULO: **INHIBIDORES PIRIDILO DE SEÑALIZACION DE HEDGEHOG**

52. CLASIFICACION INTERNACIONAL: **C07D 213/40** ; A61K 31/4418

71. SOLICITANTE: **GENENTECH, INC. y CURIS INCORPORATI N**

DOMICILIO: **1DNA Way, South San Francisco, CA 94080-4990, ESTADOS UNIDOS DE AMERICA y 61 Moulton Street, Cambridge, MA 02138, ESTADOS UNIDOS DE AMERICA**

74. APODERADO: **Dra. MARGARITA CASTELLANOS A.**

22. BOGOTA, D.C., 02 ABR. 2007

F.R. 02-04-2007
Poder, Cesión

Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad I
División de Nuevas Crea

Rad: 07-033168- -00000-0000 Dep. 2020 NUECREACIONES
Fec: 2007-04-02 14:16:57
Tra. 11 PATENTEIYII
Eve: 378 FASENACIONALI
Act 411 PRESENTACION
Folios: 574

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRÁMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION (X) MODELO DE UTILIDAD ( )	(X)	( )
- Indicación de que se solicita la concesión de una patente	(X)	( )
- Datos de identificación del solicitante o de la persona que presenta la solicitud	(X)	( )
- Descripción de la invención	(X)	( )
- Dibujos de ser estos pertinentes	( )	( )
- Comprobante de pago de las tasas establecidas	(X)	( )

COMPLETA (X) INCOMPLETA ( )

DISEÑO INDUSTRIAL ( )

- Indicación de que se solicita el registro de 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	( )	( )

C MPLETA ( ) INCOMPLETA ( )

EZQUEMA DE TRAZADO ( )

- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta la solicitud	( )	( )
- Representación gráfica del Esquema de Trazado	( )	( )
- Comprobante de pago de las tasas establecidas	( )	( )

COMPLETA ( ) INCOMPLETA ( )

Firma responsable: Claudia Maria Cortes

Fecha: _____

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad 07-033168- -00000-0000
Fec 2007-04-02 14 16 57 Dep 2020 NUECREACIONES
Tra 11 PATENTEIYII
Eve 378 FASENACIONALI
Act 411 PRESENTACION Folios 574

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

SOLICITUD DE:

(1)

[X] Patente de invención — [ ] Patente de Modelo de Utilidad.

[X] Capítulo I — [ ] Capítulo II

(2) SOLICITANTE (71)

Nombre: **GENENTECH, INC. y CURIS INCORPORATION**
Dirección: **1 DNA Way, South San Francisco, CA 94080-4990, ESTADOS UNIDOS DE AMERICA, y 61 Moulton Street, Cambridge, MA 02138, ESTADOS UNIDOS DE AMERICA**
Nacionalidad o Domicilio: **South San Francisco, CA, ESTADOS UNIDOS DE AMERICA y Cambridge, MA, ESTADOS UNIDOS DE AMERICA**
Lugar de Constitución **ESTADOS UNIDOS DE AMERICA**
Teléfono Fax
E-mail

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

(3) REPRESENTANTE O APODERADO (74)

Nombre **MARGARITA CASTELLANOS A.**
Dirección **CALLE 94A No 7A-09**
Teléfono **610 7420** Fax **610 0706**
E-mail info@castellanosyco.com

IDENTIFICACIÓN
C C [X] NIT [ ]
C E [ ] Otro [ ]
Cual
Número **39'779 654** TPA **70,819**

(4) INVENTOR (ES) (72)

Nombre **VER ANEXO # 1**
Dirección:
Nacionalidad o Domicilio

(5) PCT (86)

Solicitud Internacional No **PCT/US2005/031284** Fecha **02/09/2005**
Publicación Internacional No. **WO 2006/028958 A2** Fecha **16/03/2006**

(6) Título (54) **INHIBIDORES PIRIDILO DE SEÑALIZACION DE HEDGEHOG**

(7) Clasificación Internacional (51) **C07D 213/40**

(8) Prioridad

SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	02/09/2004	60/607,367

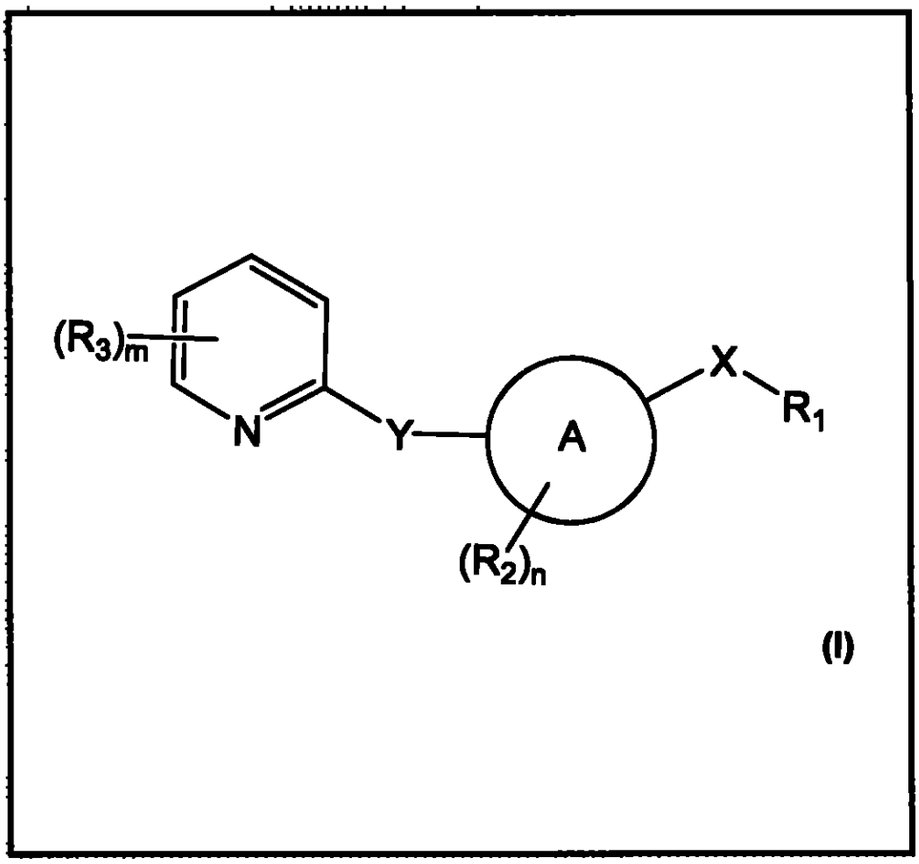
(9) Comprobante de pago No. **07-25,186** **Fecha** **Marzo 28 de 2007**

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página

(10) Anexos

- [X] Comprobante de pago de la tasa de presentación de la solicitud
- [X] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [X] Poderes si fuere el caso, junto con la sustitución del mismo a mi favor
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [X] Copia de la solicitud internacional (Resumen, descripción reivindicaciones, dibujos)
- [X] Traducción de la solicitud internacional al castellano (Resumen descripción reivindicaciones dibujos)
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA)
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso copia del contrato de acceso
- [ ] De ser el caso documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso certificado de depósito del material biológico
- [X] Arte final 12x12
- [ ] De ser el caso información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante relacionadas parcial o totalmente con la invención de esta solicitud
- [ ] De ser el caso modificaciones efectuadas a la solicitud internacional
- [X] Otros Tarjeta Propietario, y Extracto para la Publicación

(11) FIGURA CARACTERISTICA



(I)

(12) Solicito la concesión de la patente,

NOMBRE: MARGARITA CASTELLANOS ABONDANO

FIRMA:

C.C. No. 39'779 654 Usaquén - TPA 70 819 C.S.J.

02 ABR. 2007

CASTELLANOS & CO LTDA
ABOGADOS
Calle 94 A No. 7 A-09
Bogotá, D.C. – COLOMBIA

ANEXO # 1

INVENTOR(ES) (72)

	NOMBRE	DIRECCION	NACIONALIDAD O DOMICILIO
1	JANET GUNZNER	2908 Pine Avenue, Berkeley, CA 94705, ESTADOS UNIDOS DE AMERICA	ESTADOUNIDENSE
2	DANIEL SUTHERLIN	820 Maple Avenue, South San Francisco, CA 94080, ESTADOS UNIDOS DE AMERICA	ESTADOUNIDENSE
3	MARK STANLEY	284 Lauren Avenue, Pacifica, CA 94044, ESTADOS UNIDOS DE AMERICA	ESTADOUNIDENSE
4	LIANG BAO	25 Poncetta Drive # 225, Daly City, CA 94015, ESTADOS UNIDOS DE AMERICA	CHINA
5	GEORGETTE CASTANEDO	1320 Woodside Rd., Redwood City, CA 94061, ESTADOS UNIDOS DE AMERICA	ESTADOUNIDENSE
6	REBECCA LALONDE	330 Myrtle St., Redwood City, CA 94062, ESTADOS UNIDOS DE AMERICA	ESTADOUNIDENSE
7	SHUMEI WANG	831 Comet Drive, Foster City, CA 94404, ESTADOS UNIDOS DE AMERICA	CANADIENSE
8	MARK REYNOLDS	175 Linda Vista, Millbrae, CA 94030, ESTADOS UNIDOS DE AMERICA	ESTADOUNIDENSE
9	SCOTT SAVAGE	615 Ansel Rd. # 305, Burlingame, CA 94010, ESTADOS UNIDOS DE AMERICA	ESTADOUNIDENSE
10	KIMBERLY MALESKY	360 Green Street, Apt. # 7, San Francisco, CA 94133, ESTADOS UNIDOS DE AMERICA	ESTADOUNIDENSE
11	MICHAEL DINA	1003 San Antonio Circle, # 205, Daly City, CA 94014, ESTADOS UNIDOS DE AMERICA	ESTADOUNIDENSE

4
5

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176089-2

RECIBO OFICIAL DE CAJA : 07 - 25,186
FECHA : MARZO 28 DE 2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad. 07-033168- -00000-0000
Fec. 2007-04-02 14:16:57 Dep. 2020 NUEVACREACIONES
Tra. 11 PATENTES
Cde 378 FASENACIONAL
Act 411 PRESENTACION Folios 574

C O N S I G N A C I O N

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAG	Vr. PAGO
ALVARO CASTELLANOS	CONSIGNACION	BANCO POPULAR	050-00110-6	51032097	27/03/2007	5,597,000.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
		TOTAL : $	482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

5
6

CASTELLANOS & CO
ABOGADOS
Calle 94 A No. 7 A-09
Bogotá, D.C. – COLOMBIA

Señor

Jefe de la División de Nuevas Creaciones

Superintendencia de Industria y Comercio

Ministerio de Comercio, Desarrollo, Industria y Turismo

E. S. D.

Ref.: **PODER** conferido por la sociedad **GENENTECH, INC.**

Yo, **XIMENA CASTELLANOS ABONDANO**, mayor de edad, identificada y domiciliada como aparece al pié de mi firma, atentamente manifiesto a Uds. que sustituyo en la Dra. **MARGARITA CASTELLANOS ABONDANO**, el poder que me confirió la sociedad **GENENTECH, INC.**, con domicilio en **1 DNA Way, South San Francisco, California 94080, ESTADOS UNIDOS DE AMERICA**, debidamente legalizado por Apostilla, bajo el No. **166860** el día **4 de Septiembre de 2003**, con las mismas facultades que me fueron conferidas, para tramitar la solicitud de Patente PCT Entrada en Fase Nacional, en Colombia, para: **"INHIBIDORES PIRIDILO DE SEÑALIZACION DE HEDGEHOG".-**

Del Señor Jefe,

Ximena Castellanos Abondano
C.C. No. **39.773.330** de Usaquén
T.P.A. No. **58.236** del C.S.J.
Carrera 9 No. 93-09 – Bogotá, D.C.
Teléfonos: 6107420 – 6107480

Acepto

Margarita Castellanos Abondano
C.C. No. **39.779.654** de Usaquén
T.P.A. No. **70.819** del C.S.J.
Carrera 9 No. 93-09 – Bogotá, D.C.
Teléfonos: 6107420 – 6107480

Bogotá, D.C.
XCA/MCA/ P1465

AUTENTICACIÓN DE FIRMA
MEDIANTE COMPARECENCIA PERSONAL
(Art. 84 C.R.C. mod. Decr. 2282 de 1989, art. 1 mod. 36)
Ante el Notario Cuarenta y Uno (41) del círculo de esta ciudad compareció personalmente:
identificado con C.C.
expedida en: y tarjeta profesional de abogado(a) No. del Consejo Superior de la Judicatura, con documento dirigido a
y declaró que la firma puesta en éste escrito es suya.

Firma del declarante

En Bogotá D.C. a 28 MAR. 2007

AUTORIZÓ ESTA DILIGENCIA EL SUSCRITO NOTARIO

REPUBLICA DE COLOMBIA
Círculo de Santafé de Bogotá, D.C.
NOTARIA 41
Carrera 12 Nº 93-26
AGUSTIN MORALES RIVEIRA
ORIGINAL

AUTENTICACIÓN DE FIRMA
MEDIANTE COMPARECENCIA PERSONAL
(Art. 84 C.R.C. mod. Decr. 2282 de 1989, art. 1 mod. 36)
Ante el Notario Cuarenta y Uno (41) del círculo de esta ciudad compareció personalmente:
identificada con C.C.
expedida en: y tarjeta profesional de abogado(a) No. del Consejo Superior de la Judicatura, con documento dirigido a
y declaró que la firma puesta en este escrito es suya.

Firma del declarante

En Bogotá D.C. a 28 MAR. 2007

AUTORIZÓ ESTA DILIGENCIA EL SUSCRITO NOTARIO

REPUBLICA DE COLOMBIA
Círculo de Santafé de Bogotá, D.C.
NOTARIA 41
Carrera 12 Nº 93-26
AGUSTIN MORALES RIVEIRA
ORIGINAL

6
7

PODER

El (los) suscrito (s) Genentech, Inc.

domiciliado (s) en 1 DNA Way
South San Francisco, California
94080, EE. UU. de A.

nombra(n) por el presente a **XIMENA CASTELLANOS A. y/o MARGARITA CASTELLANOS A.** abogadas con oficinas en la Carrera 9 No. 93-09, Bogotá - Colombia para

y para obtener la protección de mi (nuestra) propiedad industrial y con este fin autorizamos a dichos apoderados para que nos representen ante cualesquiera autoridades o personas de los órdenes administrativo, contencioso-administrativo y judicial en todo lo relacionado con los siguientes actos y gestiones:

a) Obtención de patentes de invención , modelos y dibujos industriales; registro de marcas de fábrica, de servicio, colectivas o defensivas y de denominaciones de origen; depósito de nombres y enseñas comerciales; su renovación prórroga, inscripción de traspaso y cambio de nombre o domicilio, cancelación voluntaria y el registro de licencias de uso de esos derechos; b) Para la obtención de Registros Sanitarios; c) Acciones de oposición, observación, cancelación, nulidad, medidas cautelares y en general los juicios civiles, penales, administrativos o contencioso-administrativos que promovamos o se nos promuevan, pudiendo en todos los actos y gestiones arriba determinados sustituir éste mandato, transigir, desistir, recibir, cancelar, renunciar, aceptar notificaciones y nombrar apoderados judiciales y extrajudiciales.

Dado y firmado hoy Agosto 28, 2003

en South San Francisco, California, EE. UU. A.

Por Genentech, Inc.
Mark T. Kresnak - Abogado Sección Patentes
Signatario autorizado por la sociedad

(Notary should execute on other side)
(Consular legalization necessary)

POWER F ATTORNEY

I (we) the undersigned Genentech, Inc.

of 1 DNA Way
South San Francisco, California 94080
U S A.

hereby grant(s) Power of Attorney to **XIMENA CASTELLANOS A.** and **MARGARITA CASTELLANOS A.** attorneys residing at Carrera 9 No 93-09 Bogotá - COLOMBIA to

and to obtain the protection of my (our) industrial property, for which purpose we authorize the said attorneys to represent us before any authorities or persons, specially those, administrative contentious and judicial, in all matters concerning the following :

a) Obtention of patents, models and designs; registration of trademarks, service, collective and defensive marks, and of designations of origin; the deposit of commercial names and ensigns; its renewal , extension, recording of assignments, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rigths; b) For de obtennon of Sanitary Registrations; c) Actions of opposition, cancellation, nullity, infringement, granting of licenses; and in general the civil, criminal and administrative suits related to those rigths; actions and suits instituted by, or against us; and that in all the above matters they may substitute this Power of Attorney, compromise, desist, cancel, receive, renounce acts, notifications and appoint attorneys in fact, in or out of Court .

Given and signed this

In South San Francisco, California, USA

By August 28, 2003
Mark T. Kresnak
Section Patent Counsel
Authorized Corporate Signatory

(Notary should execute on other side)
(Consular legalization necessary)

ALVARO CASTELLANOS M. & CIA.
ABOGADOS COLOMBIA
Carrera 9 No. 93-09 - P.O. Box 6349 - Bogotá, Colombia.
Tels. (571) 610 7420 /60 / 80 - Fax. (571) 610 0706 - e-mail acastell@impsat.net.co

Esta copia coincide con el original que tuve a la vista.
Bogotá, D.C.
28 MAR 2007
AGUSTIN MORALES RIVERA
NOTARIO CUARENTA Y UNO

7
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CERTIFICACION DE UN REPRESENTANTE

Hoy, 28 de Agosto de 19 2003
compareció (eron) personalmente

a quien (es) conozco como la (s) persona (s) que firma (n) este documento en representación de la Sociedad / Compañía denominada

Yo, Mark T. Kresnak,

Certifico:
a) Que Genentech, Inc.
es una Sociedad / Compañía legalmente constituida y existente de acuerdo con las leyes de Delaware, EE. UU. de A.

b) Que el domicilio de dicha Sociedad / Compañía es 1 DNA Way South San Francisco, California 94080, Estados Unidos de América

c) Que el objeto u objetos para los cuales se otorga el presente poder están comprendidos dentro del objeto social de la mencionada Sociedad / Compañía.

d) Que el Sr. Yo mismo
estoy autorizado para otorgar el presente poder. Lo anterior está probado por medio de los siguientes documentos, que certifico he visto*:
Artículos de constitución de fecha Junio de 1999, y Estatutos de fecha Junio de 1999, ambos pudiendo ser modificados

(Ciudad) South San Francisco,
(Estado) California
Hoy: 28 de Agosto de 19 2003
(Notario Público)

*Los documentos deben identificarse con fecha y origin.

*Adjunto autenticación Notarial

Certification of Officer

On this 28 day of August 19 2003
personally appeared

whom I know to be the person (s) who signed this document as representative(s) of the Corporation / Company named

I, Mark T. Kresnak,

I Certify:
a) That Genentech, Inc.
is a Corporation / Company legally constituted and in existence in accordance with the laws of Delaware, USA.

b) That the domicile of said Corporation / Company is 1 DNA Way South San Francisco, California 94080, USA.

c) That the purpose or purposes for which the present Power of Attorney is granted are comprised within the object set forth in the charter of the mentioned Corporation / Company.

d) That I am
authorized to grant the present Power of Attorney. The aforementioned was duly proven through the following documents and I duly certify having seen them*:
Articles of Incorporation dated June, 1999, Bylaws dated June, 1999, both as maybe amended from time to time.

(City) South San Francisco
(State) California
this 28 day of August 2003
(Notary Public)

* Documents must be identified with date and origin.

* Attach Notary Acknowledgement

Esta copia coincide con el original que tuve a la vista.
Bogotá, 28 MAR 2007
AGUSTIN MORALES RIVEIRA
NOTARIO CUARENTA Y UNO

8

9

CALIFORNIA ALL-PURPOSE ACKNOWLEDGMENT

State of California
County of San Mateo } ss.

On 8/28/03 (Date) before me, Teri Renshaw, Notary Public (Name and Title of Officer (e.g., "Jane Doe, Notary Public"))

personally appeared Mark T. Kvesnak (Name(s) of Signer(s))

☒ personally known to me
☐ proved to me on the basis of satisfactory evidence

to be the person(s) whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies), and that by his/her/their signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

TERI RENSHAW
Commission # 1272761
Notary Public - California
San Mateo County
My Comm. Expires Aug 3, 2004

WITNESS my hand and official seal.

Signature of Notary Public

OPTIONAL

Though the information below is not required by law, it may prove valuable to persons relying on the document and could prevent fraudulent removal and reattachment of this form to another document.

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☐ Partner — ☐ Limited ☐ General
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☐ Other: _____

Signer Is Representing: _____

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28 MAR 2007
AGUSTIN GONZALES RIVEIRA
NOTARIO CUARENTA Y UNO

9
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State of California

SECRETARY OF STATE

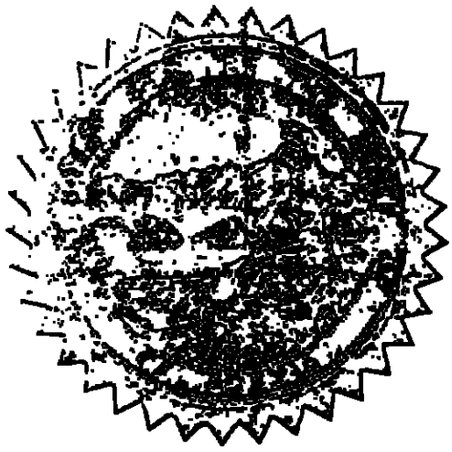
APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. *Country: United States of America*
   This public document
2. *has been signed by TERI RENSHAW*
3. *acting in the capacity of Notary Public, State of California*
4. *bears the seal/stamp of TERI RENSHAW, Notary Public, State of California*

CERTIFIED

5. *At Sacramento, California*
6. *the 4th day of September 2003*
7. *by Deputy Secretary of State, State of California*
8. *No. 166860*
9. *Seal/Stamp:*

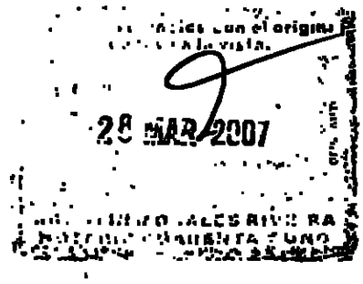


10. *Signature*

KEVIN SHELLEY
Secretary of State

BY

NP-24 A (REV. 1-03)



10
11

----------TRADUCCION OFICIAL No. 030005----------

de un documento escrito en INGLES, el cual para su identificación lleva el sello de la Traductora e Intérprete Oficial, Res. 2755/68 y 01144/97 de Minjusticia, al igual que la presente.----------

(Anexos a un documento de poder de Genentech, Inc.)

RECONOCIMIENTO PARA FINES GENERALES

ESTADO DE CALIFORNIA

CONDADO DE SAN MATEO

Hoy día 28 DE Agosto DE 2003, ante mí Teri Renshaw, Notario Público compareció personalmente Mark T. Kresnak (x) a quien conozco personalmente o quien probó ante mí con base en prueba satisfactoria ser la persona(s) cuyo nombre está suscrito en el instrumento adjunto y reconoció ante mí que había otorgado el mismo en su calidad autorizada y que con su firma en el instrumento, la persona o entidad en nombre de la cual actuó dicha persona, otorgó el instrumento.

DA FE mi firma y sello oficial.

(fdo) ilegible

Firma del Notario

(Sello): TERI RENSHAW

Comisión No. 1272761

Notario Público – California

Condado de San Mateo

Mi comisión vence Agosto 3, 2004

1

DORA [illegible] DE BERNAL
TRADUCTORA E INTERPRETE OFICIAL
RES. 02755
28 MAR 2007
AGUSTIN MORALES RIVEIRA
NOTARIO CUARENTA Y UNO

INFORMACION OPCIONAL

Aunque la siguiente información no se exige por ley, puede ser valiosa para personas que confían en el documento y puede evitar la remoción e inserción fraudulenta de este formato a otro documento.

Título o tipo de documento: ----------

Fecha documento:------Número de páginas- Firmantes (distintos a los arriba nombrados: ninguno,

(Resto del formato en blanco)

ESTADO DE CALIFORNIA

SECRETARIO DE ESTADO

APOSTILLA

(Convención de La Haya del 5 de Octubre 1961)

1. País: Estados Unidos de América

   Este documento público

2. Ha sido firmado por TERI RENSHAW
3. Actuando en su carácter de Notario Público, Estado de California
4. Lleva el sello de TERI RENSHAW, Notario Público, Estado de California

CERTIFICADO

5. EN Sacramento, California .
6. El día 4 de Septiembre de 2003
7. por el Secretario de Estado Delegado, Estado de California
8. No. 166860

2

DORA DUQUE DE BERNAL
TRADUCTORA E INTERPRETE OFICIAL
DES. 02755 797

28 MAR 2007

AGUSTIN MORALES RIVEIRA
NOTARIO CUARENTA Y UNO

MINISTERIO DE
[illegible]

230388

P. Doble de 3

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[illegible]
LAS FIRMAS ESTAMPADAS

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2007 SET 11 P 2:44

[illegible]
BOGOTA D.C.



12
13

9. Sello: (sello)

10. Firma

(fdo) Kevin Shelley

KEVIN SHELLEY

Secretario de Estado

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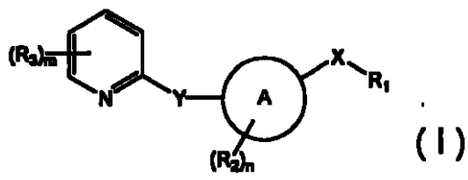
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(54) Title: PYRIDYL INHIBITORS OF HEDGEHOG SIGNALLING



(I)

(57) Abstract: The invention provides novel inhibitors of hedgehog signaling that are useful as a therapeutic agents for treating malignancies where the compounds have the general formula I: wherein A, X, Y, R_1, R_2, R_3, R_4, and n are as described herein.

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PYRIDYL INHIBITORS OF HEDGEHOG SIGNALLING

This application claims priority to provisional patent application 60/607,367 filed on 02 September 2004.

FIELD OF THE INVENTION

The present invention relates to organic compounds useful for therapy and/or prophylaxis in a mammal, in particular to pyridyl compounds that inhibit the hedgehog signaling pathway and are useful in the treatment of hyperproliferative diseases and angiogenesis mediated diseases.

BACKGROUND OF THE INVENTION

Hedgehog (Hh) protein was first identified in Drosophila melanogaster as a segment-polarity gene involved in embryo patterning (Nusslein-Volhard et al., Roux. Arch. Dev. Biol. 193: 267-282 (1984)). Three orthologs of Drosophila hedgehog (Sonic, Desert and Indian) were later identified to occur in all vertebrates including fish, birds and mammals. Desert hedgehog (DHh) is expressed principally in the testes, both in mouse embryonic development and in the adult rodent and human; Indian hedgehog (IHh) is involved in bone development during embryogenesis and in bone formation in the adult; and, Sonic hedgehog (SHh) is expressed at high levels in the notochord and floor plate of developing vertebrate embryos. In vitro explant assays as well as ectopic expression of SHh in transgenic animals have shown that SHh plays a key role in neuronal tube patterning (Echelard et al., supra.; Ericson et al., Cell 81: 747-56 (1995); Marti et al., Nature 375: 322-5 (1995); Krauss et al., Cell 75, 1432-44 (1993); Riddle et al., Cell 75: 1401-16 (1993); Roelink et al, Cell 81:445-55 (1995); Hynes et al., Neuron 19: 15-26 (1997)). Hh also plays a role in the development of limbs (Krauss et al., Cell 75: 1431-44 (1993); Laufer et al., Cell 79, 993-1003 (1994)), somites (Fan and Tessier-Lavigne, Cell 79, 1175-86 (1994); Johnson et al., Cell 79: 1165-73 (1994)), lungs (Bellusci et al., Develop. 124: 53-63 (1997) and skin (Oro et al., Science 276:

817-21 (1997)). Likewise, IHh and DHh are involved in bone, gut and germinal cell development (Apelqvist et al., Curr. Biol. 7: 801-4 (1997); Bellusci et al., Dev. Suppl. 124: 53-63 (1997); Bitgood et al., Curr. Biol. 6: 298-304 (1996); Roberts et al., Development 121: 3163-74 (1995)).

Human SHh is synthesized as a 45 kDa precursor protein that upon autocatalytic cleavage yields a 20 kDa N-terminal fragment that is responsible for normal hedgehog signaling activity; and a 25 kDa C-terminal fragment that is responsible for autoprocessing activity in which the N-terminal fragment is conjugated to a cholesterol moiety (Lee, J.J., et al. (1994) Science 266, 1528- 1536; Bumcrot, D.A., et al. (1995), Mol. Cell Biol. 15, 2294-2303; Porter, J.A., et al. (1995) Nature 374, 363- 366). The N-terminal fragment consists of amino acid residues 24-197 of the full-length precursor sequence which remains membrane-associated through the cholesterol at its C-terminus (Porter, J.A., et al. (1996) Science 274, 255- 258; Porter, J.A., et al. (1995) Cell 86, 21-34). Cholesterol conjugation is responsible for the tissue localization of the hedgehog signal.

At the cell surface, the Hh signal is thought to be relayed by the 12 transmembrane domain protein Patched (Ptc) (Hooper and Scott, Cell 59: 751-65 (1989); Nakano et al., Nature 341: 508-13 (1989)) and the G-protein-coupled-like receptor Smoothened (Smo) (Alcedo et al., Cell 86: 221-232 (1996); van den Heuvel and Ingham, Nature 382: 547-551 (1996)). Both genetic and biochemical evidence support a receptor model where Ptc and Smo are part of a multicomponent receptor complex (Chen and Struhl, Cell 87: 553-63 (1996); Marigo et al., Nature 384: 176-9 (1996); Stone et al., Nature 384: 129-34 (1996)). Upon binding of Hh to Ptc, the normal inhibitory effect of Ptc on Smo is relieved, allowing Smo to transduce the Hh signal across the plasma membrane. However, the exact mechanism by which Ptc controls Smo activity still has yet to be clarified.

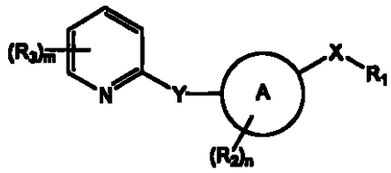
The signaling cascade initiated by Smo results in activation of Gli transcription factors that translocate into the nucleus where they control transcription of target genes. Gli has been shown to influence transcription of Hh pathway inhibitors such as Ptc and Hip1 in a negative feedback loop indicating that tight control the Hh pathway activity is required for proper cellular differentiation and organ formation. Uncontrolled activation of Hh signaling pathway are associated with malignancies in particular those of the brain, skin and muscle as well as angiogenesis. An explanation for this is that Hh pathway has been shown to regulate cell proliferation in adults by activation of genes involved in cell cycle progression such as cyclin D

which is involved in G1-S transition. Also, SHh blocks cell-cycle arrest mediated by p21, an inhibitor of cyclin dependent kinases. Hh signaling is further implicated in cancer by inducing components in the EGFR pathway (EGF, Her2) involved in proliferation as well as components in the PDGF (PDGFα) and VEGF pathways involved in angiogenesis. Loss of function mutations in the Ptc gene have been identified in patients with the basal cell nevus syndrome (BCNS), a hereditary disease characterized by multiple basal cell carcinomas (BCCs). Dysfunctional Ptc gene mutations have also been associated with a large percentage of sporadic basal cell carcinoma tumors (Chidambaram et al., Cancer Research 56: 4599-601 (1996); Gailani et al., Nature Genet. 14: 78-81 (1996); Hahn et al., Cell 85: 841-51 (1996); Johnson et al., Science 272: 1668-71 (1996); Unden et al., Cancer Res. 56: 4562-5; Wicking et al., Am. J. Hum. Genet. 60: 21-6 (1997)). Loss of Ptc function is thought to cause an uncontrolled Smo signaling in basal cell carcinoma. Similarly, activating Smo mutations have been identified in sporadic BCC tumors (Xie et al., Nature 391: 90-2 (1998)), emphasizing the role of Smo as the signaling subunit in the receptor complex for SHh.

Various inhibitors of hedgehog signaling have been investigated such as Cyclopamine, a natural alkaloid that has been shown to arrest cell cycle at G0-G1 and to induce apoptosis in SCLC. Cyclopamine is believed to inhibit Smo by binding to its heptahelical bundle. Forskolin has been shown to inhibit the Hh pathway downstream from Smo by activating protein kinase A (PKA) which maintains Gli transcription factors inactive. Despite advances with these and other compounds, there remains a need for potent inhibitors of the hedgehog signaling pathway.

SUMMARY OF THE INVENTION

In one aspect of the present invention there is provided novel hedgehog inhibitors having the general formula (I)



I

wherein

A is a carbocycle or heterocycle;

X is alkylene, $NR_4C(O)$, $NR_4C(S)$, $N(C(O)R_1)C(O)$, NR_4SO, NR_4SO_2, $NR_4C(O)NH$, $NR_4C(S)NH$, $C(O)NR_4$, $C(S)NR_4$, NR_4PO or $NR_4PO(OH)$;

Y is absent, CHR_4, O, S, SO, SO_2 or NR_4;

R_1 is selected from the group consisting of alkyl, a carbocycle or a heterocycle each of which is optionally substituted with hydroxyl, halogen, amino, carbonyl, nitro, cyano, acyl, alkyl, haloalkyl, alkylsulfonyl, alkylsulfinyl, alkoxy, alkylcarbamoyl, alkanoylamine, alkylsulfamoyl, alkylsulfonamide, a carbocycle or a heterocycle; wherein said amino, alkyl, acyl, alkylsulfonyl, alkylsulfinyl, alkoxy, alkylcarbamoyl, alkanoylamine, alkylsulfamoyl, alkylsulfonamide, carbocycle and heterocycle substituent is optionally substituted with amino, halogen, hydroxyl, carbonyl, or a carbocycle or heterocycle that is optionally substituted with hydroxyl, amino, halogen, haloalkyl, alkyl, alkoxy or acyl;

R_2 is halogen, hydroxyl, alkyl, acyl or alkoxy each optionally substituted with hydroxyl, halogen, amino, nitro, alkyl, acyl, alkylsulfonyl or alkoxy;

R_3 is halogen, hydroxyl, carboxyl, alkyl, acyl, alkoxy, alkoxycarbonyl, carbamoyl, alkylsulfide, alkylsulfinyl, alkylsulfonyl, a carbocycle or a heterocycle wherein each alkyl, acyl, alkoxy, alkoxycarbonyl, carbamoyl, alkylsulfide, alkylsulfinyl, alkylsulfonyl, carbocycle and heterocycle is optionally substituted with hydroxyl, halogen, amino, nitro, alkyl, acyl, alkylsulfonyl or alkoxy;

R_4 is H or alkyl;

m is 0-3;

n is 0-3;

and salts and solvates thereof.

In another aspect of the invention, there are provided compositions comprising compounds of formula I and a carrier, diluent or excipient.

In another aspect of the invention, there is provided a method for treating cancer comprising administering an effective amount of a compound of formula I to a mammal in need thereof.

In another aspect of the invention, there is provided a method for inhibiting hedgehog signaling in a cell comprising contacting said cell with a compound of formula I.

In another aspect of the invention, there is provided a method for treating a disease or condition associated with the hedgehog signaling in a mammal, comprising administering to said mammal an effective amount of a compound of formula I.

In another aspect of the invention, there are provided processes for preparing compounds of the invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

"Acyl" means a carbonyl containing substituent represented by the formula -C(O)-R in which R is H, alkyl, a carbocycle, a heterocycle, carbocycle-substituted alkyl or heterocycle-substituted alkyl wherein the alkyl, alkoxy, carbocycle and heterocycle are as defined herein. Acyl groups include alkanoyl (e.g. acetyl), aroyl (e.g. benzoyl), and heteroaroyl.

"Alkyl" means a branched or unbranched, saturated or unsaturated (i.e. alkenyl, alkynyl) aliphatic hydrocarbon group, having up to 12 carbon atoms unless otherwise specified. When used as part of another term, for example "alkylamino", the alkyl portion is preferably a saturated hydrocarbon chain, however also includes unsaturated hydrocarbon carbon chains such as "alkenylamino" and "alkynylamino. "Alkylphosphinate" means a –P(O)R-alkyl group wherein R is H, alkyl, carbocycle-alkyl or heterocycle-alkyl. Examples of preferred alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 2,2-dimethylbutyl, n-heptyl, 3-heptyl, 2-methylhexyl, and the like. The terms "lower alkyl" "C_1-C_4 alkyl" and "alkyl of 1 to 4 carbon atoms" are synonymous and used interchangeably to mean methyl, ethyl, 1-propyl, isopropyl, cyclopropyl, 1-butyl, sec-butyl or t-butyl. Unless specified, substituted, alkyl groups may contain one (preferably), two, three or four substituents which may be the same or different. Examples of the above substituted alkyl groups include, but are not limited to; cyanomethyl, nitromethyl, hydroxymethyl, trityloxymethyl, propionyloxymethyl, aminomethyl, carboxymethyl, carboxyethyl, carboxypropyl, alkyloxycarbonylmethyl, allyloxycarbonylaminomethyl, carbamoyloxymethyl, methoxymethyl, ethoxymethyl, t-butoxymethyl, acetoxymethyl, chloromethyl, bromomethyl, iodomethyl, trifluoromethyl, 6-hydroxyhexyl, 2,4-dichloro(n-butyl), 2-amino(iso-propyl), 2-carbamoyloxyethyl and the like. The alkyl group may also be substituted with a carbocycle group. Examples include cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, and cyclohexylmethyl groups, as well as the corresponding –ethyl, -propyl, -butyl, -pentyl, -hexyl groups, etc. Preferred substituted alkyls are substituted methyls e.g. a methyl group substituted by the same substituents as the "substituted C_n-C_m alkyl" group. Examples of the substituted methyl group include groups such as hydroxymethyl, protected hydroxymethyl (e.g. tetrahydropyranyloxymethyl), acetoxymethyl, carbamoyloxymethyl, trifluoromethyl, chloromethyl, carboxymethyl, bromomethyl

and iodomethyl.

"Amidine" or "amidino" means the group -C(NH)-NRR wherein each R is independently H, OH, alkyl, alkoxy, a carbocycle, a heterocycle, a carbocycle-substituted alkyl or a heterocycle-substituted alkyl; or both R groups together form a heterocycle. A preferred amidine is the group -C(NH)-NH_2.

"Amino" denotes primary (i.e. –NH_2) , secondary (i.e. –NRH) and tertiary (i.e. –NRR) amines wherein R is independently alkyl, a carbocycle (e.g. aryl) , a heterocycle (e.g. heteroaryl), carbocycle-substituted alkyl (e.g. benzyl) or a heterocycle-substituted alkyl or alternatively two R groups together with the nitrogen atom from which they depend form a heterocycle. Particular secondary and tertiary amines are alkylamine, dialkylamine, arylamine, diarylamine, aralkylamine and diaralkylamine. Particular secondary and tertiary amines are methylamine, ethylamine, propylamine, isopropylamine, phenylamine, benzylamine dimethylamine, diethylamine, dipropylamine and diisopropylamine.

"Amino-protecting group" as used herein refers to a derivative of the groups commonly employed to block or protect an amino group while reactions are carried out on other functional groups on the compound. Examples of such protecting groups include carbamates, amides, alkyl and aryl groups, imines, as well as many N-heteroatom derivatives which can be removed to regenerate the desired amine group. Preferred amino protecting groups are Boc, Fmoc and Cbz. Further examples of these groups are found in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", 2nd ed., John Wiley & Sons, Inc., New York, NY, 1991, chapter 7; E. Haslam, "Protective Groups in Organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapter 5, and T.W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, NY, 1981. The term "protected amino" refers to an amino group substituted with one of the above amino-protecting groups.

"Aryl" when used alone or as part of another term means a carbocyclic aromatic group whether or not fused having the number of carbon atoms designated or if no number is designated, up to 14 carbon atoms. Aryl groups include phenyl, naphthyl, biphenyl, phenanthrenyl, naphthacenyl, and the like (see e.g. *Lang's Handbook of Chemistry* (Dean, J. A., ed) 13th ed. Table 7-2 [1985]). In a particular embodiment aryl may be phenyl. Substituted phenyl or substituted aryl denotes a phenyl group or aryl group substituted with one, two, three, four or five, such as 1-2, 1-3 or 1-4 substituents chosen, unless otherwise specified, from halogen (F, Cl, Br, I), hydroxy, protected hydroxy, cyano, nitro, alkyl (for example C_1-C_6 alkyl), alkoxy (for example C_1-C_6 alkoxy),

benzyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, aminomethyl, protected aminomethyl, trifluoromethyl, alkylsulfonylamino, arylsulfonylamino, heterocyclylsulfonylamino, heterocyclyl, aryl, or other groups specified. One or more methyne (CH) and/or methylene (CH_2) groups in these substituents may in turn be substituted with a similar group as those denoted above. Examples of the term "substituted phenyl" includes but is not limited to a mono- or di(halo)phenyl group such as 2-chlorophenyl, 2-bromophenyl, 4-chlorophenyl, 2,6-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 3-chlorophenyl, 3-bromophenyl, 4-bromophenyl, 3,4-dibromophenyl, 3-chloro-4-fluorophenyl, 2-fluorophenyl and the like; a mono- or di(hydroxy)phenyl group such as 4-hydroxyphenyl, 3-hydroxyphenyl, 2,4-dihydroxyphenyl, the protected-hydroxy derivatives thereof and the like; a nitrophenyl group such as 3- or 4-nitrophenyl; a cyanophenyl group, for example, 4-cyanophenyl; a mono- or di(lower alkyl)phenyl group such as 4-methylphenyl, 2,4-dimethylphenyl, 2-methylphenyl, 4-(iso-propyl)phenyl, 4-ethylphenyl, 3-(n-propyl)phenyl and the like; a mono or di(alkoxy)phenyl group, for example, 3,4-dimethoxyphenyl, 3-methoxy-4-benzyloxyphenyl, 3-methoxy-4-(1-chloromethyl)benzyloxy-phenyl, 3-ethoxyphenyl, 4-(isopropoxy)phenyl, 4-(t-butoxy)phenyl, 3-ethoxy-4-methoxyphenyl and the like; 3- or 4-trifluoromethylphenyl; a mono- or dicarboxyphenyl or (protected carboxy)phenyl group such 4-carboxyphenyl, ; a mono- or di(hydroxymethyl)phenyl or (protected hydroxymethyl)phenyl such as 3-(protected hydroxymethyl)phenyl or 3,4-di(hydroxymethyl)phenyl; a mono- or di(aminomethyl)phenyl or (protected aminomethyl)phenyl such as 2-(aminomethyl)phenyl or 2,4-(protected aminomethyl)phenyl; or a mono- or di(N-(methylsulfonylamino))phenyl such as 3-(N-methylsulfonylamino))phenyl. Also, the term "substituted phenyl" represents disubstituted phenyl groups where the substituents are different, for example, 3-methyl-4-hydroxyphenyl, 3-chloro-4-hydroxyphenyl, 2-methoxy-4-bromophenyl, 4-ethyl-2-hydroxyphenyl, 3-hydroxy-4-nitrophenyl, 2-hydroxy-4-chlorophenyl, and the like, as well as trisubstituted phenyl groups where the substituents are different, for example 3-methoxy-4-benzyloxy-6-methyl sulfonylamino, 3-methoxy-4-benzyloxy-6-phenyl sulfonylamino, and tetrasubstituted phenyl groups where the substituents are different such as 3-methoxy-4-benzyloxy-5-methyl-6-phenyl sulfonylamino. Substituted phenyl groups include 2-chlorophenyl, 2-aminophenyl, 2-bromophenyl, 3-methoxyphenyl, 3-ethoxy-phenyl, 4-benzyloxyphenyl, 4-methoxyphenyl, 3-ethoxy-4-benzyloxyphenyl, 3,4-diethoxyphenyl, 3-methoxy-4-benzyloxyphenyl, 3-methoxy-4-(1-chloromethyl)benzyloxy-phenyl, 3-methoxy-4-(1-chloromethyl)benzyloxy .-6- methyl sulfonyl aminophenyl groups. Fused aryl rings may also be substituted with any (for example 1, 2 or 3) of the substituents specified herein in the same manner as substituted alkyl groups.

"Carbamoyl" means an aminocarbonyl containing substituent represented by the formula -$C(O)N(R)_2$ in which R is H, hydroxyl, alkoxy, alkyl, a carbocycle, a heterocycle, carbocycle-substituted alkyl or alkoxy, or heterocycle-substituted alkyl or alkoxy wherein the alkyl, alkoxy, carbocycle and heterocycle are as herein defined. Carbamoyl groups include alkylaminoecarbonyl (e.g. ethylaminocarbonyl, Et-NH-CO-), arylaminocarbonyl (e.g. phenylaminocarbonyl), aralkylaminocarbonyl (e.g. benzoylaminocarbonyl) a heterocycleaminocarbonyl (e.g. piperizinylaminocarbonyl), and in particular a heteroarylaminocarbonyl (e.g. pyridylaminocarbonyl).

"Carbocyclyl", "carbocyclic", "carbocycle" and "carbocyclo" alone and when used as a moiety in a complex group such as a carbocycloalkyl group, refers to a mono-, bi-, or tricyclic aliphatic ring having 3 to 14 carbon atoms and preferably 3 to 7 carbon atoms which may be saturated or unsaturated, aromatic or non-aromatic. Preferred saturated carbocyclic groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups and more preferred are cyclopropyl and cyclohexyl and most preferred is cyclohexyl. Preferred unsaturated carbocycles are aromatic e.g. aryl groups as previously defined, the most preferred being phenyl. The terms "substituted carbocyclyl", "substituted carbocycle" and "substituted carbocyclo" unless otherwise specified mean these groups substituted by the same substituents as the "substituted alkyl" group.

"Carboxy-protecting group" as used herein refers to one of the ester derivatives of the carboxylic acid group commonly employed to block or protect the carboxylic acid group while reactions are carried out on other functional groups on the compound. Examples of such carboxylic acid protecting groups include 4-nitrobenzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, pentamethylbenzyl, 3,4-methylenedioxybenzyl, benzhydryl, 4,4'-dimethoxybenzhydryl, 2,2',4,4'-tetramethoxybenzhydryl, alkyl such as t-butyl or t-amyl, trityl, 4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4',4"-trimethoxytrityl, 2-phenylprop-2-yl, trimethylsilyl, t-butyldimethylsilyl, phenacyl, 2,2,2-trichloroethyl, beta-(trimethylsilyl)ethyl, beta-(di(n-butyl)methylsilyl)ethyl, p-toluenesulfonylethyl, 4-nitrobenzylsulfonylethyl, allyl, cinnamyl, 1-(trimethylsilylmethyl)prop-1-en-3-yl, and like moieties. The species of carboxy-protecting group employed is not critical so long as the derivatized carboxylic acid is stable to the condition of subsequent reaction(s) on other positions of the molecule and can be removed at the appropriate point without disrupting the remainder of the molecule. In particular, it is important not to subject a carboxy-protected molecule to strong nucleophilic bases, such as lithium hydroxide or NaOH, or reductive conditions employing highly activated metal hydrides such as $LiAlH_4$. (Such harsh removal conditions are also to be avoided when removing amino-protecting groups and hydroxy-protecting

groups, discussed below.) Preferred carboxylic acid protecting groups are the alkyl (e.g. methyl, ethyl, t-butyl), allyl, benzyl and p-nitrobenzyl groups. Similar carboxy-protecting groups used in the cephalosporin, penicillin and peptide arts can also be used to protect a carboxy group substituents. Further examples of these groups are found in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", 2nd ed., John Wiley & Sons, Inc., New York, N.Y., 1991, chapter 5; E. Haslam, "Protective Groups in Organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, N.Y., 1973, Chapter 5, and T.W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, NY, 1981, Chapter 5. The term "protected carboxy" refers to a carboxy group substituted with one of the above carboxy-protecting groups.

"Guanidine" means the group -NH-C(NH)-NHR wherein R is H, alkyl, a carbocycle, a heterocycle, a carbocycle-substituted alkyl, or a heterocycle-substituted alkyl. A particular guanidine group is -NH-C(NH)-NH_2.

"Heterocyclic group", "heterocyclic", "heterocycle", "heterocyclyl", or "heterocyclo" alone and when used as a moiety in a complex group such as a heterocycloalkyl group, are used interchangeably and refer to any mono-, bi-, or tricyclic, saturated or unsaturated, aromatic (heteroaryl) or non-aromatic ring having the number of atoms designated, generally from 5 to about 14 ring atoms, where the ring atoms are carbon and at least one heteroatom (nitrogen, sulfur or oxygen) and preferably 1 to 4 heteroatoms. "Heterocyclosulfonyl" means a –SO_2-heterocycle group; "heterocyclosulfinyl" means a –SO-heterocycle group. Typically, a 5-membered ring has 0 to 2 double bonds and 6- or 7-membered ring has 0 to 3 double bonds and the nitrogen or sulfur heteroatoms may optionally be oxidized (e.g. SO, SO_2), and any nitrogen heteroatom may optionally be quaternized. Preferred non-aromatic heterocycles include morpholinyl (morpholino), pyrrolidinyl, oxiranyl, oxetanyl, tetrahydrofuranyl, 2,3-dihydrofuranyl, 2H-pyranyl, tetrahydropyranyl, thiiranyl, thietanyl, tetrahydrothietanyl, aziridinyl, azetidinyl, 1-methyl-2-pyrrolyl, piperazinyl and piperidinyl. A "heterocycloalkyl" group is a heterocycle group as defined above covalently bonded to an alkyl group as defined above. Preferred 5-membered heterocycles containing a sulfur or oxygen atom and one to three nitrogen atoms include thiazolyl, in particular thiazol-2-yl and thiazol-2-yl N-oxide, thiadiazolyl, in particular 1,3,4-thiadiazol-5-yl and 1,2,4-thiadiazol-5-yl, oxazolyl, preferably oxazol-2-yl, and oxadiazolyl, such as 1,3,4-oxadiazol-5-yl, and 1,2,4-oxadiazol-5-yl. Preferred 5-membered ring heterocycles containing 2 to 4 nitrogen atoms include imidazolyl, preferably imidazol-2-yl; triazolyl, preferably 1,3,4-triazol-5-yl; 1,2,3-triazol-5-yl, 1,2,4-triazol-5-yl, and tetrazolyl, preferably 1H-tetrazol-5-yl. Preferred benzo-fused 5-membered heterocycles are benzoxazol-2-yl, benzthiazol-2-yl and benzimidazol-2-yl. Preferred 6-membered heterocycles contain one to three nitrogen atoms and optionally a

sulfur or oxygen atom, for example pyridyl, such as pyrid-2-yl, pyrid-3-yl, and pyrid-4-yl; pyrimidyl, preferably pyrimid-2-yl and pyrimid-4-yl; triazinyl, preferably 1,3,4-triazin-2-yl and 1,3,5-triazin-4-yl; pyridazinyl, in particular pyridazin-3-yl, and pyrazinyl. The pyridine N-oxides and pyridazine N-oxides and the pyridyl, pyrimid-2-yl, pyrimid-4-yl, pyridazinyl and the 1,3,4-triazin-2-yl groups, are a preferred group. Substituents for optionally substituted heterocycles, and further examples of the 5- and 6-membered ring systems discussed above can be found in W. Druckheimer *et al.*, U.S. Patent No. 4,278,793.

"Heteroaryl" alone and when used as a moiety in a complex group such as a heteroaralkyl group, refers to any mono-, bi-, or tricyclic aromatic ring system having the number of atoms designated where at least one ring is a 5-, 6- or 7-membered ring containing from one to four heteroatoms selected from the group nitrogen, oxygen, and sulfur, and preferably at least one heteroatom is nitrogen (*Lang's Handbook of Chemistry, supra*). Included in the definition are any bicyclic groups where any of the above heteroaryl rings are fused to a benzene ring. Heteroaryls in which nitrogen or oxygen is the heteroatom are preferred. The following ring systems are examples of the heteroaryl (whether substituted or unsubstituted) groups denoted by the term "heteroaryl": thienyl, furyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, thiatriazolyl, oxatriazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, thiazinyl, oxazinyl, triazinyl, thiadiazinyl, oxadiazinyl, dithiazinyl, dioxazinyl, oxathiazinyl, tetrazinyl, thiatriazinyl, oxatriazinyl, dithiadiazinyl, imidazolinyl, dihydropyrimidyl, tetrahydropyrimidyl, tetrazolo[1,5-b]pyridazinyl and purinyl, as well as benzo-fused derivatives, for example benzoxazolyl, benzofuryl, benzothiazolyl, benzothiadiazolyl, benzotriazolyl, benzoimidazolyl and indolyl. A particularly preferred group of "heteroaryl" include; 1,3-thiazol-2-yl, 4-(carboxymethyl)-5-methyl-1,3-thiazol-2-yl, 4-(carboxymethyl)-5-methyl-1,3-thiazol-2-yl sodium salt, 1,2,4-thiadiazol-5-yl, 3-methyl-1,2,4-thiadiazol-5-yl, 1,3,4-triazol-5-yl, 2-methyl-1,3,4-triazol-5-yl, 2-hydroxy-1,3,4-triazol-5-yl, 2-carboxy-4-methyl-1,3,4-triazol-5-yl sodium salt, 2-carboxy-4-methyl-1,3,4-triazol-5-yl, 1,3-oxazol-2-yl, 1,3,4-oxadiazol-5-yl, 2-methyl-1,3,4-oxadiazol-5-yl, 2-(hydroxymethyl)-1,3,4-oxadiazol-5-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-thiadiazol-5-yl, 2-thiol-1,3,4-thiadiazol-5-yl, 2-(methylthio)-1,3,4-thiadiazol-5-yl, 2-amino-1,3,4-thiadiazol-5-yl, 1H-tetrazol-5-yl, 1-methyl-1H-tetrazol-5-yl, 1-(1-(dimethylamino)eth-2-yl)-1H-tetrazol-5-yl, 1-(carboxymethyl)-1H-tetrazol-5-yl, 1-(carboxymethyl)-1H-tetrazol-5-yl sodium salt, 1-(methylsulfonic acid)-1H-tetrazol-5-yl, 1-(methylsulfonic acid)-1H-tetrazol-5-yl sodium salt, 2-methyl-1H-tetrazol-5-yl, 1,2,3-triazol-5-yl, 1-methyl-1,2,3-triazol-5-yl, 2-methyl-1,2,3-triazol-5-yl, 4-methyl-1,2,3-triazol-5-yl, pyrid-2-yl N-oxide, 6-methoxy-2-(n-oxide)-pyridaz-3-yl, 6-hydroxypyridaz-3-yl, 1-methylpyrid-2-yl, 1-methylpyrid-4-yl, 2-hydroxypyrimid-4-yl, 1,4,5,6-tetrahydro-5,6-dioxo-4-methyl-as-triazin-3-yl, 1,4,5,6-tetrahydro-4-(formylmethyl)-5,6-dioxo-as-

triazin-3-yl, 2,5-dihydro-5-oxo-6-hydroxy-astriazin-3-yl, 2,5-dihydro-5-oxo-6-hydroxy-as-triazin-3-yl sodium salt, 2,5-dihydro-5-oxo-6-hydroxy-2-methyl-astriazin-3-yl sodium salt, 2,5-dihydro-5-oxo-6-hydroxy-2-methyl-as-triazin-3-yl, 2,5-dihydro-5-oxo-6-methoxy-2-methyl-as-triazin-3-yl, 2,5-dihydro-5-oxo-as-triazin-3-yl, 2,5-dihydro-5-oxo-2-methyl-as-triazin-3-yl, 2,5-dihydro-5-oxo-2,6-dimethyl-as-triazin-3-yl, tetrazolo[1,5-b]pyridazin-6-yl and 8-aminotetrazolo[1,5-b]-pyridazin-6-yl. An alternative group of "heteroaryl" includes; 4-(carboxymethyl)-5-methyl-1,3-thiazol-2-yl, 4-(carboxymethyl)-5-methyl-1,3-thiazol-2-yl sodium salt, 1,3,4-triazol-5-yl, 2-methyl-1,3,4-triazol-5-yl, 1H-tetrazol-5-yl, 1-methyl-1H-tetrazol-5-yl, 1-(1-(dimethylamino)eth-2-yl)-1H-tetrazol-5-yl, 1-(carboxymethyl)-1H-tetrazol-5-yl, 1-(carboxymethyl)-1H-tetrazol-5-yl sodium salt, 1-(methylsulfonic acid)-1H-tetrazol-5-yl, 1-(methylsulfonic acid)-1H-tetrazol-5-yl sodium salt, 1,2,3-triazol-5-yl, 1,4,5,6-tetrahydro-5,6-dioxo-4-methyl-as-triazin-3-yl, 1,4,5,6-tetrahydro-4-(2-formylmethyl)-5,6-dioxo-as-triazin-3-yl, 2,5-dihydro-5-oxo-6-hydroxy-2-methyl-as-triazin-3-yl sodium salt, 2,5-dihydro-5-oxo-6-hydroxy-2-methyl-as-triazin-3-yl, tetrazolo[1,5-b]pyridazin-6-yl, and 8-aminotetrazolo[1,5-b]pyridazin-6-yl.

"Hydroxy-protecting group" as used herein refers to a derivative of the hydroxy group commonly employed to block or protect the hydroxy group while reactions are carried out on other functional groups on the compound. Examples of such protecting groups include tetrahydropyranyloxy, benzoyl, acetoxy, carbamoyloxy, benzyl, and silylethers (e.g. TBS, TBDPS) groups. Further examples of these groups are found in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", 2nd ed., John Wiley & Sons, Inc., New York, NY, 1991, chapters 2-3; E. Haslam, "Protective Groups in Organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapter 5, and T.W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, NY, 1981. The term "protected hydroxy" refers to a hydroxy group substituted with one of the above hydroxy-protecting groups.

"Pharmaceutically acceptable salts" include both acid and base addition salts. "Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, carbonic acid, phosphoric acid and the like, and organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, gluconic acid, lactic acid, pyruvic acid, oxalic acid, malic acid, maleic acid, maloneic acid, succinic acid, fumaric acid, tartaric acid, citric acid, aspartic acid, ascorbic acid, glutamic acid, anthranilic acid, benzoic acid,

cinnamic acid, mandelic acid, embonic acid, phenylacetic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicyclic acid and the like.

"Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic nontoxic bases includes salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, TEA, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperizine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic non-toxic bases are isopropylamine, diethylamine, ethanolamine, trimethamine, dicyclohexylamine, choline, and caffeine.

"Phosphinate" means –P(O)R-OR wehrein each R is independently H, alkyl, carbocycle, heterocycle, carbocycloalkyl or heterocycloalkyl. Particular phosphinate groups are alkylphosphinate (i.e. –P(O)R-O-alkyl), for example –P(O)Me-OEt.

"Sulfamoyl" means $-SO_2-N(R)_2$ wherein each R is independently H, alkyl, carbocycle, heterocycle, carbocycloalkyl or heterocycloalkyl. Particular sulfamoyl groups are alkylsulfamoyl, for example methylsulfamoyl ($-SO_2-NHMe$); arylsulfamoyl, for example phenylsulfamoyl; aralkylsulfamoyl, for example benzylsulfamoyl.

"Sulfinyl" means a –SO-R group wherein R is alkyl, carbocycle, heterocycle, carbocycloalkyl or heterocycloalkyl. Particular sulfinyl groups are alkylsulfinyl (i.e. –SO-alkyl), for example methylsulfinyl; arylsulfinyl (i.e. –SO-aryl) for example phenylsulfinyl; aralkylsulfinyl, for example benzylsulfinyl.

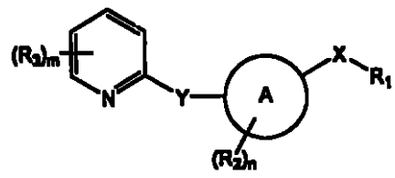
"Sulfonamide" means $-NR-SO_2-R$ wherein each R is independently H, alkyl, carbocycle, heterocycle, carbocycloalkyl or heterocycloalkyl), a carbocycle or a heterocycle. Particular sulfonamide groups are alkylsulfonamide (e.g. $-NH-SO_2-$alkyl), for example methylsulfonamide; arylsulfonamdie (i.e. $-NH-SO_2-$aryl) for example phenylsulfonamide; aralkylsulfonamide, for example benzylsulfonamide.

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"Sulfonyl" means a $-SO_2$-R group wherein R is alkyl, carbocycle, heterocycle, carbocycloalkyl or heterocycloalkyl. Particular sulfonyl groups are alkylsulfonyl (i.e. $-SO_2$-alkyl), for example methylsulfonyl; arylsulfonyl, for example phenylsulfonyl; aralkylsulfonyl, for example benzylsulfonyl.

The phrase "and salts and solvates thereof" as used herein means that compounds of the inventions may exist in one or a mixture of salts and solvate forms. For example a compound of the invention may be substantially pure in one particular salt or solvate form or else may be mixtures of two or more salt or solvate forms.

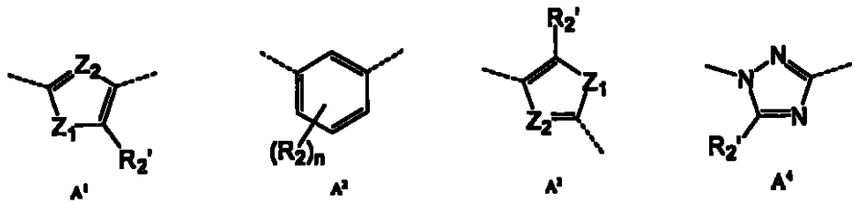
The present invention provides novel compounds having the general formula I:



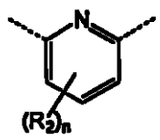
I

wherein A, X, Y, R_1, R_2, and R_3 are as defined herein.

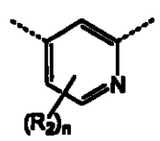
A is a carbocycle or heterocycle ring substituted with 0 to 3 (e.g. n is 0-3) R_2 groups selected from the group consisting of halogen, hydroxyl, alkyl, acyl or alkoxy each optionally substituted with hydroxyl, halogen, amino, nitro, alkyl, acyl, alkylsulfonyl or alkoxy;. In a particular embodiment, A is optionally substituted aryl or heteroaryl. In particular embodiment A is optionally substituted benzene, thiophene, thiazole, imidazole, pyrrole, N-alkyl pyrrole, pyridine, pyrazole or N-alkyl pyrazole. In a particular embodiment A is a ring selected from the group consisting of A^1, A^2, A^3, A^4 A^5, A^6 and A^7:



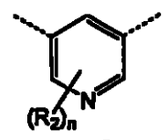
A^1 A^2 A^3 A^4



A^3



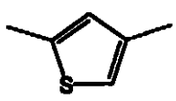
A^6



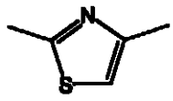
A^7

wherein Z_1 is O, S or NR_5 wherein R_5 is H or alkyl; Z_2 is CH, $CR_{2'}$ or N; R_2 is halogen, hydroxyl, alkyl, acyl or alkoxy each optionally substituted with hydroxyl, halogen, amino, nitro, alkyl, acyl, alkylsulfonyl or alkoxy; $R_{2'}$ is H, halogen, hydroxyl, alkyl, acyl or alkoxy each optionally substituted with hydroxyl, halogen, amino, nitro, alkyl, acyl, alkylsulfonyl or alkoxy; and n is 0-3. In a particular embodiment A is the ring of formula A^1. In a particular embodiment, A is the ring of formula A^1 wherein Z_1 is S and Z_2 is CH or N. In another embodiment, A is the ring of formula A^1 wherein Z_1 is S and Z_2 is CH, i.e. thiophene. In another embodiment, A is the ring of formula A^1 wherein Z_1 is S and Z_2 is N, i.e. thiazole. In another embodiment, A is the ring of formula A^1 wherein $R_{2'}$ is H. In embodiment, A is the ring of formula A^1 wherein $R_{2'}$ is methyl. In another embodiment, A is the ring A^1 wherein $R_{2'}$ is methyl. In a particular embodiment A is ring A^2. In another embodiment, A is the ring of formula A^1 wherein R_2 may be absent, i.e. n is 0. In another embodiment, n is 1 and R_2 is Cl. In another particular embodiment A is the ring of formula A^3. In an embodiment, A is a ring of formula A^3 wherein Z_1 is S and Z_2 is N, i.e. a thiazole. In another embodiment, A is a ring of formula A^3 wherein Z_1 is S, Z_2 is N and R_2' is Cl. In another embodiment, A is a ring of formula A^3 wherein Z_1 is S, Z_2 is CH (i.e. thiophene) and R_2' is Cl.

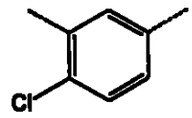
In a particular embodiment A is the ring A^{1a}, A^{1b}, A^{2a}, A^{3a}, A^{3b}, A^{4a}, A^{5a}, A^{6a}, A^{7a},:



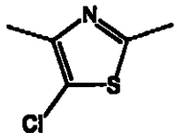
A^{1a}



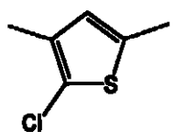
A^{1b}



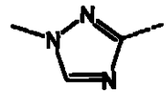
A^{2a}



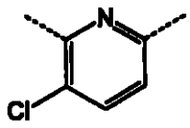
A^{3a}



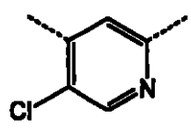
A^{3b}



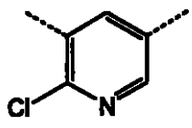
A^{4a}



A^{5a}



A^{6a}



A^{7a}

In a particular embodiment A is the ring of formula A^{1a}. In another embodiment A is the ring of formula A^{1b}. In another embodiment A is the ring of formula A^{2a}. In another embodiment A is the ring of formula A^{3a}. In another embodiment A is the ring of formula A^{3b}. In another embodiment A is the ring of formula A^{4a}.

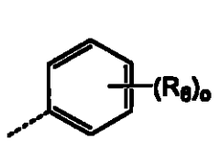
X is alkylene, $NR_4C(O)$, $NR_4C(S)$, $N(C(O)R_1)C(O)$, NR_4SO, NR_4SO_2, $NR_4C(O)NH$, $NR_4C(S)NH$, $C(O)NR_4$, $C(S)NR_4$, NR_4PO or $NR_4PO(OH)$ wherein R_4 is H or alkyl. In a particular embodiment X is $NR_4C(O)$ which forms an amide linkage between ring A and R_1. In another embodiment, X is $N_4C(S)$, which forms a thioamide linkage between ring A and R_1. In another embodiment, X is $NR_4C(O)NH$ which forms a urea linkage between ring A and R_1. In another embodiment X is $NR_4C(S)NH$ which with NR_2 forms a thiourea linkage between ring A and R_1. In another embodiment X is $N(C(O)R_1)C(O)$ i.e. a nitrogen with two $-C(O)R_1$ groups pending therefrom.

Y is absent, CHR_4, O, S, SO, SO_2 or NR_4 wherein R_4 is as defined herein. In a particular embodiment Y is CHR_4. In a particular embodiment Y is NR_4. In a particular embodiment Y is O. In a particular embodiment Y is S. In a particular embodiment Y is SO. In a particular embodiment Y is SO_2. In another embodiment Y is absent i.e. ring A is directly attached to the pyridyl ring at the 2-position.

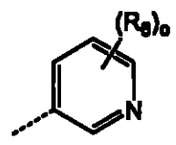
R_1 is selected from the group consisting of alkyl, a carbocycle or a heterocycle each of which is optionally substituted with hydroxyl, halogen, amino, carboxyl, amidino, guanidino, carbonyl (i.e. =O), nitro, cyano, acyl, alkyl, haloalkyl, sulfonyl, sulfinyl, alkoxy, akylthio, carbamoyl, acylamino, sulfamoyl, sulfonamide, a carbocycle or a heterocycle; wherein said amino, amidino, alkyl, acyl, sulfonyl, sulfinyl, alkoxy, alkylthio, carbamoyl, acylamino, sulfamoyl, sulfonamide, carbocycle and heterocycle substituent is optionally substituted with, halogen, haloakyl, hydroxyl, carboxyl, carbonyl, or an amino, alkyl, alkoxy, acyl, sulfonyl, sulfinyl, phosphinate, carbocycle or heterocycle that is optionally substituted with hydroxyl, carboxyl, carbonyl, amino, halogen, haloalkyl, alkyl, alkoxy, alkylthio, sulfonyl, sulfinyl; acyl, a carbocycle or a heterocycle.

In another embodiment R_1 is selected from the group consisting of alkyl, a carbocycle or a heterocycle each of which is optionally substituted with hydroxyl, halogen, amino, carbonyl, nitro, cyano, acyl, alkyl, haloalkyl, alkylsulfonyl, alkylsulfinyl, alkoxy, alkylcarbamoyl (i.e. -CONR-alkyl wherein R is H or alkyl), alkanoylamine (i.e. -NRCO-alkyl wherein R is H or alkyl), alkylsulfamoyl (i.e. $-SO_2NR$-alkyl wherein R is H or alkyl), alkylsulfonamide (i.e. $-NR-SO_2$-alkyl wherein R is H or alkyl), a carbocycle or a heterocycle; wherein said amino, alkyl, acyl, alkylsulfonyl, alkylsulfinyl, alkoxy, alkylcarbamoyl, alkanoylamine, alkylsulfamoyl, alkylsulfonamide, carbocycle and heterocycle substituent is optionally substituted with amino, halogen, hydroxyl, carbonyl, or a carbocycle or heterocycle that is optionally substituted with hydroxyl, amino, halogen, haloalkyl, alkyl, alkoxy or acyl.

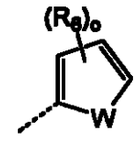
In a particular embodiment R_1 is an optionally substituted aryl or heteroaryl. In a particular embodiment R_1 is an optionally substituted phenyl group. In another particular embodiment R_1 is an optionally substituted pyridine group. In a particular embodiment R_1 is of formula IIa, IIb, IIc, IId, IIe, IIf, IIg, IIh, IIi, IIj, IIk, IIl, IIm, IIn or IIo:



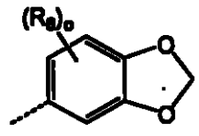
IIa



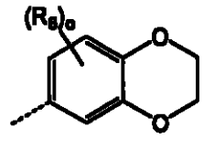
IIb



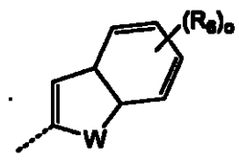
IIc



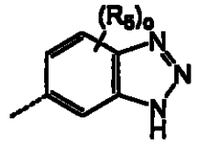
IId



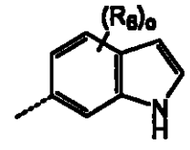
IIe



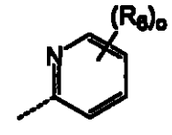
IIf



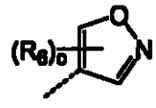
IIg



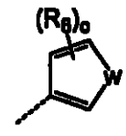
IIh



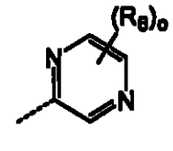
IIi



IIj

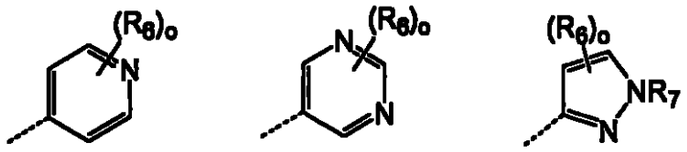


IIk



III

30
31



IIm IIn IIo

wherein W is O, S or NR_7 wherein R_7 is H, alkyl, acyl, a carbocycle or a heterocycle wherein said alkyl, acyl, carbocycle and heterocycle are each optionally substituted with 1-3 amino, halogen, hydroxyl and haloalkyl; o is 0-3. In a particular embodiment W is S.

R_6 in each instance is independently hydroxyl, halogen, amino, carboxyl, amidino, guanidino, carbonyl, nitro, cyano, acyl, alkyl, haloalkyl, sulfonyl, sulfinyl, alkoxy, alkylthio, carbamoyl, acylamino, sulfamoyl, sulfonamide, a carbocycle or a heterocycle; wherein said amino, amidino, alkyl, acyl, sulfonyl, sulfinyl, alkoxy, alkylthio, carbamoyl, acylamino, sulfamoyl, sulfonamide, carbocycle and heterocycle substituent is optionally substituted with, halogen, haloakyl, hydroxyl, carboxyl, carbonyl, or an amino, alkyl, alkoxy, acyl, sulfonyl, sulfinyl, phosphinate, carbocycle or heterocycle that is optionally substituted with hydroxyl, carboxyl, carbonyl, amino, halogen, haloalkyl, alkyl, alkoxy, alkylthio, sulfonyl, sulfinyl, acyl, a carbocycle or a heterocycle.

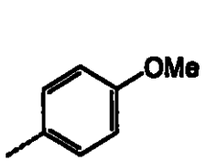
In a particular embodiment R_6 in each instance is independently hydroxyl, halogen, amino, carbonyl, nitro, cyano, acyl, alkyl, sulfonyl, alkylsulfonyl, alkylsulfinyl, alkoxy, alkylcarbamoyl, alkanoylamine, alkylsulfamoyl, alkylsulfonamide, a carbocycle or a heterocycle; wherein said amino, alkyl, carbonyl, acyl, sulfonyl, alkylsulfonyl, alkylsulfinyl, alkoxy, alkylcarbamoyl, alkanoylamine, alkylsulfamoyl, alkylsulfonamide, carbocycle and heterocycle substituent is optionally substituted with amino, halogen, hydroxyl, carbonyl, or a carbocycle or heterocycle that is optionally substituted with hydroxyl, amino, halogen, haloalkyl, alkyl, alkoxy or acyl.

In a particular embodiment R_6 is independently in each instance optionally substituted alkyl (e.g. methyl, trifluoromethyl, dimethylaminomethyl, piperidinylmethyl, morpholinomethyl, thiomorpholinomethyl); halogen (e.g. chloro); alkoxy (e.g. methoxy); carbonyl (e.g. morpholinocarbonyl, acetyl); a heterocycle (e.g. morpholino, N-methyl-piperazin-4-yl, N-acetyl-piperazin-4-yl, 1H-1,2,4-triazole); alkylamino (e.g. i-butylamino, benzylamino, hydroxyethylamino, methoxyethylamino, dimethylaminoethylamino, morpholinoethylamino, morpholinopropylamino, pyrrolidin-2-one-substituted propylamino, imidazole-ethylamino, imidazole-propylamino); arylamino (e.g. phenylamino); alkylcarbamoyl (e.g. dimethylcarbamoyl,

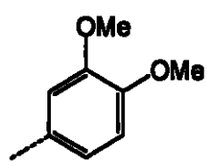
i-butylaminocarbonyl); alkylsulfamoyl (e.g. propylaminosulfonyl, i-butylaminosulfonyl, dimethylaminosulfonyl, dimethylaminoethyl hydroxyethylaminosulfonyl, methoxyethylaminosulfonyl, methoxypropylaminosulfonyl, methylsulfonylethylaminosulfonyl, imidazole-substituted propylaminosulfonyl, hydroxypropylaminosulfonyl, 2-hydroxypropylaminosulfonyl); or sulfonyl (e.g. methylsulfonyl, ethylsulfonyl, aminosulfonyl, dimethylaminopropylsulfonyl, N-methyl-piperazin-4-yl-sulfonyl, morpholino-4-yl-sulfonyl, trifluoromethylsulfonyl).

In a particular embodiment R_7 is H. In another particular embodiment R_7 is optionally substituted acyl. In another particular embodiment R_7 is optionally substituted alkyl (e.g. methyl). In another particular embodiment R_7 is optionally substituted acyl (e.g. acetyl, benzoyl). In another particular embodiment R_7 is an optionally substituted aryl group (e.g. phenyl, benzyl).

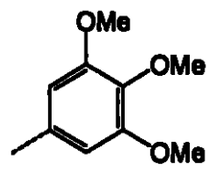
In a particular embodiment R_1 is the group of formula IIa. In such embodiment R_6 may be alkoxy and o is 1, 2 or 3. Particular IIa groups are IIa^1 - IIa^{28}:



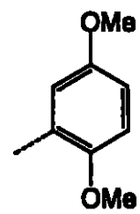
IIa^1



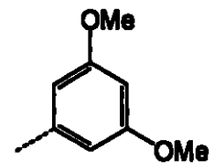
IIa^2



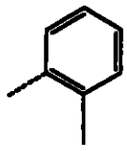
IIa^3



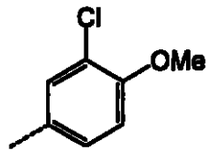
IIa^4



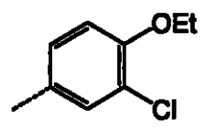
IIa^5



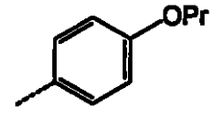
IIa^6



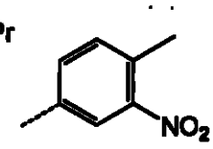
IIa^7



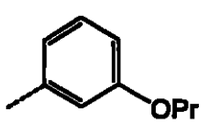
IIa^8



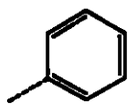
IIa^9



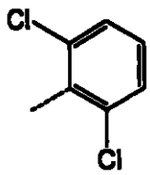
IIa^{10}



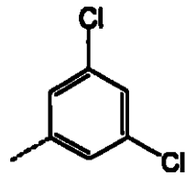
IIa[11]



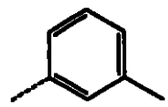
IIa[12]



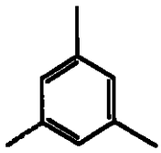
IIa[13]



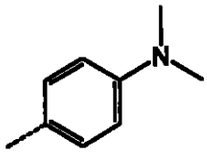
IIa[14]



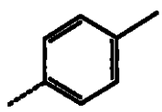
IIa[15]



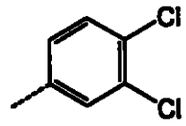
IIa[16]



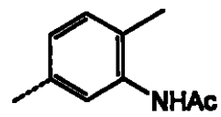
IIa[17]



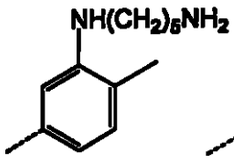
IIa[18]



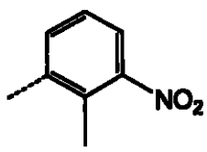
IIa[19]



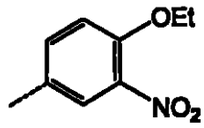
IIa[20]



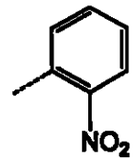
IIa[21]



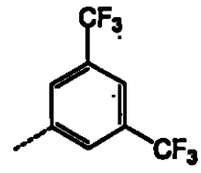
IIa[22]



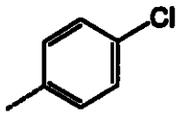
IIa[23]



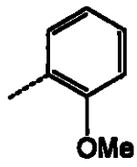
IIa[24]



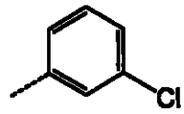
IIa[25]



IIa[26]

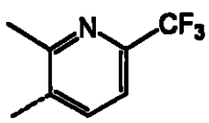


IIa[27]

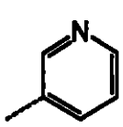


IIa[28]

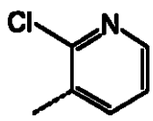
In another particular embodiment R_1 is the group of formula IIb. In such embodiment R_6 may be alkyl or haloalkyl (e.g. CF_3). Particular IIb groups are IIb[1] - IIb[3]:



IIb[1]



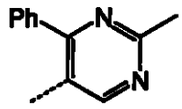
IIb[2]



IIb[3]

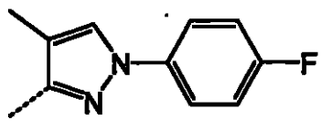
In a particular embodiment R_1 is the group of formula IIc. In such embodiment W may be S and o is 0. In another particular embodiment R_1 is the group of formula IId. In such embodiment o may be 0. In another particular embodiment R_1 is the group of formula IIe. In such embodiment o may be 0. In another particular embodiment R_1 is the group of formula IIf. In such embodiment o may be 0.

In another particular embodiment R_1 is the group of formula IIn. In such embodiment o may be 0 or 2 and R_6 may be alkyl or aryl. In a particular embodiment, group IIn has the formula IIn[1]:



IIn[1]

In another particular embodiment R_1 is the group of formula IIo. In such embodiment o may be 0 or 2 and R_6 may be alkyl or aryl. In a particular embodiment, group IIo has the formula IIo[1]:



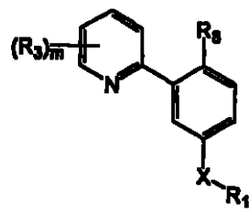
IIo[1]

R_2 is halogen, hydroxyl, alkyl, acyl or alkoxy each optionally substituted with hydroxyl, halogen, amino, nitro, alkyl, acyl, alkylsulfonyl or alkoxy. n is 0-3, for example 0 or 1. In a particular embodiment R_2 is hydroxyl. In a particular embodiment R_2 is alkyl or alkyl substituted with halogen, methyl or trifluoromethyl. In a particular embodiment R_2 is acyl, for example alkanoyl e.g. acetyl. In a particular embodiment R_2 is halogen, for example Cl or F. In another particular embodiment R_2 is alkoxy, for example methoxy or ethoxy.

R_3 is halogen, hydroxyl, carboxyl, alkyl, acyl, alkoxy, alkoxycarbonyl, carbamoyl, alkylsulfide, sulfinyl, sulfonyl, a carbocycle or a heterocycle wherein each alkyl, acyl, alkoxy, alkoxycarbonyl, carbamoyl, alkylsulfide, sulfinyl, sulfonyl, carbocycle and heterocycle is optionally substituted

with hydroxyl, halogen, amino, nitro, alkyl, acyl, sulfonyl or alkoxy. In a particular embodiment R_3 is halogen, hydroxyl, carboxyl, alkyl, acyl, alkoxy, alkoxycarbonyl, carbamoyl, alkylsulfide, alkylsulfinyl, alkylsulfonyl, a carbocycle or a heterocycle wherein each alkyl, acyl, alkoxy, alkoxycarbonyl, carbamoyl, alkylsulfide, alkylsulfinyl, alkylsulfonyl, carbocycle and heterocycle is optionally substituted with hydroxyl, halogen, amino, nitro, alkyl, acyl, alkylsulfonyl or alkoxy; while m is 0 to 3. In a particular embodiment, R_3 is halogen (e.g. F), carboxyl, or optionally substituted alkyl (e.g. methyl, hydroxymethyl, dimethylaminomethyl), alkoxycarbonyl (e.g. methoxycarbonyl) or carbamoyl (e.g. dimethylaminocarbonyl). In a particular embodiment m is 0, i.e. R_3 is absent. In another particular embodiment m is 1-3.

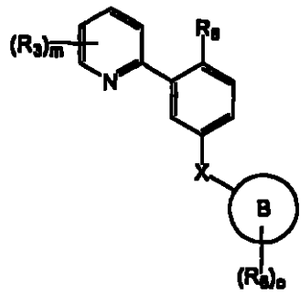
In a particular embodiment, compounds of the invention are represented by the general formula Ib:



Ib

wherein X, R_1, R_3 and m are as defined herein and R_8 is halogen. In an embodiment, compounds of the invention have the general formula Ib and X is NR_4CO. In further embodiment, compounds are of formula Ib and R_3 is H or methyl.

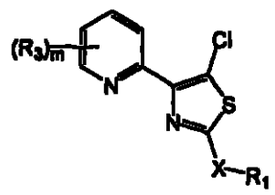
In another particular embodiment, compounds of the invention are represented by the general formula Ib':



Ib'

wherein X, R_3, R_6, m and o are as defined herein; R_8 is a halogen; and ring B is a carbocycle or heterocycle. In a particular embodiment R_8 is Cl. In a particular embodiment ring B is phenyl or pyridyl. In a particular embodiment X is $NR_4C(O)$ and R_4 is as defined herein.

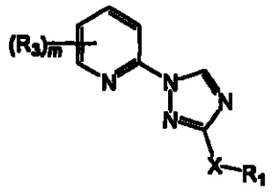
In another particular embodiment, compounds of the invention have the general formula Ic:



Ic

wherein X, R_1, R_3 and m are as defined herein. In an embodiment, compounds of the invention have the general formula.Ib and X is NR_4CO. In a further embodiment, compounds are of formula Ic and R_3 is H or methyl and m is 0 or 1.

In another particular embodiment, compounds of the invention have the general formula Id:

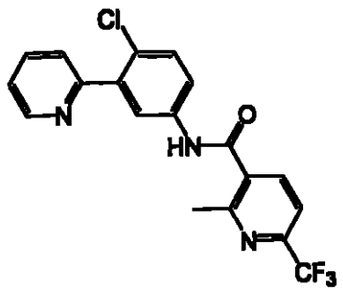


Id

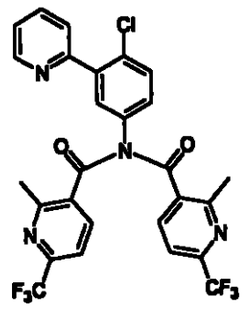
wherein X, R_1, R_3 and m are as defined herein. In an embodiment, compounds of the invention have the general formula Ib and X is NR_4CO. In a further embodiment, compounds are of formula Id and R_3 is H, Cl or trifluoromethyl and m is 0 or 1.

Particular compounds of the invention include, but are not limited to the following:

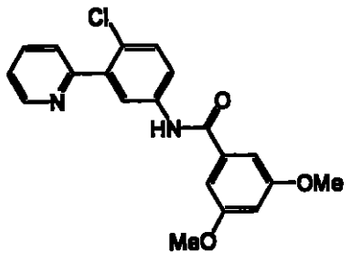
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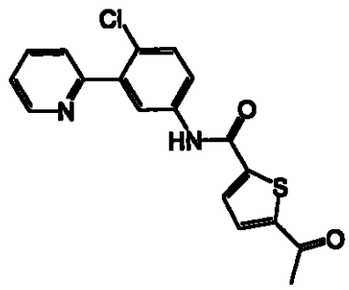
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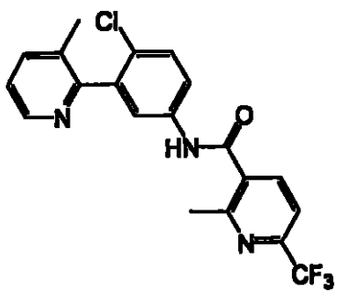
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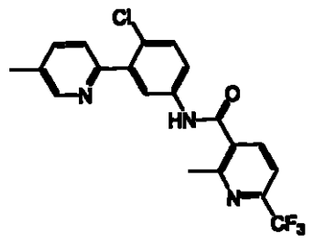
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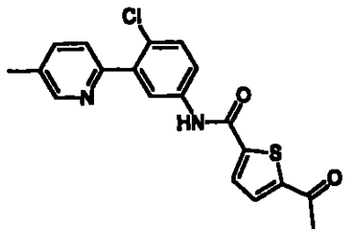
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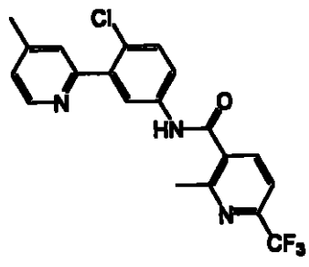
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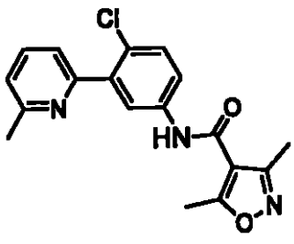
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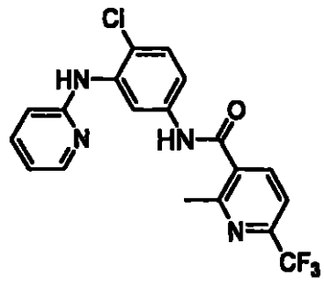
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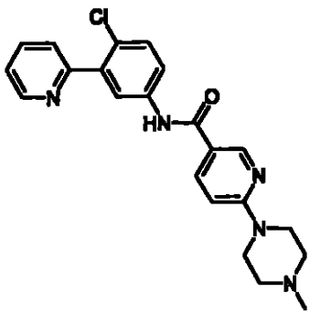
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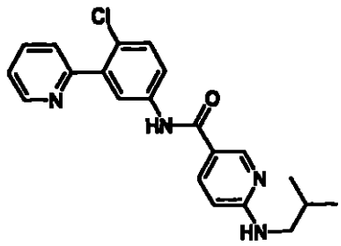
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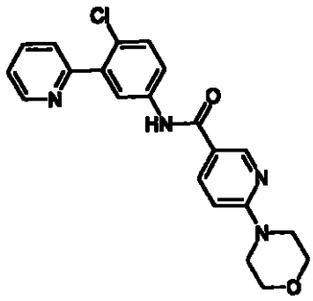
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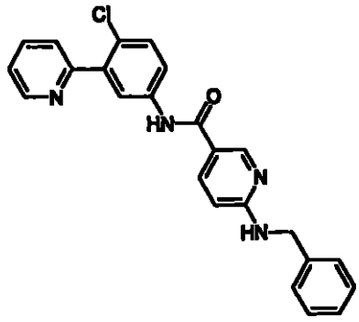
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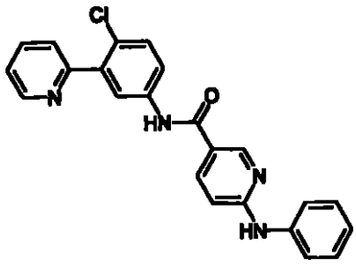
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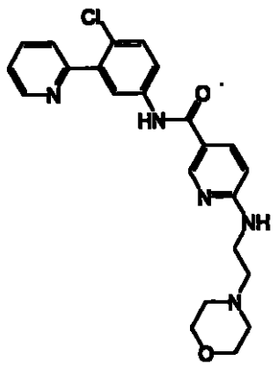
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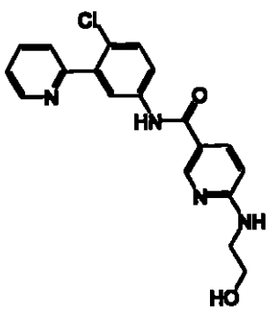
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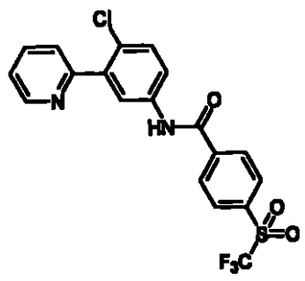
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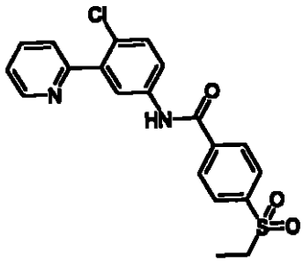
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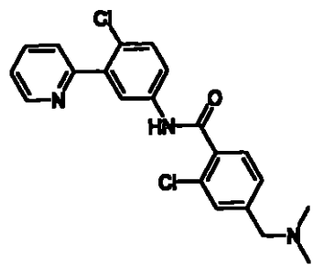
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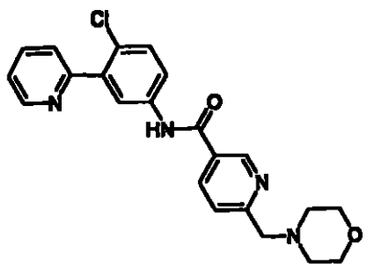
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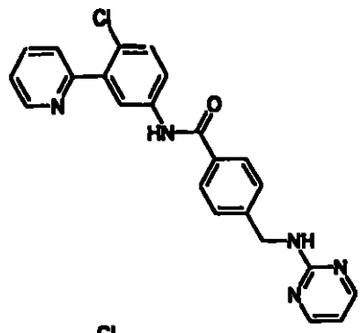
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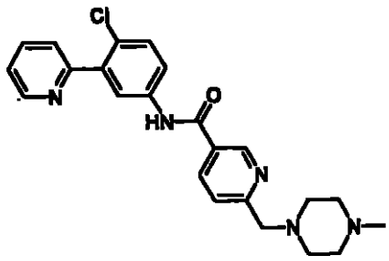
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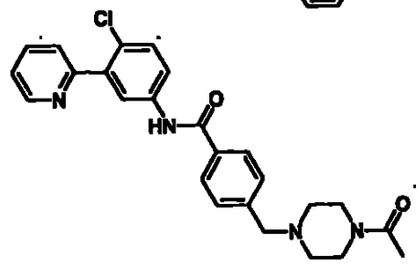
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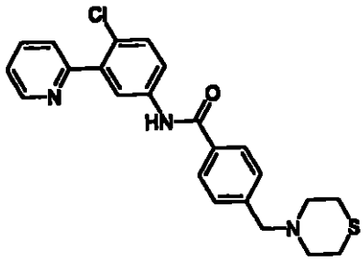
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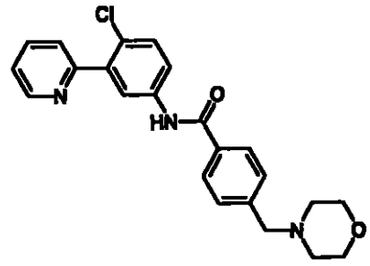
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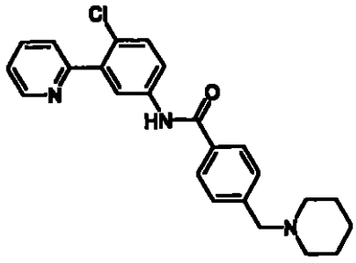
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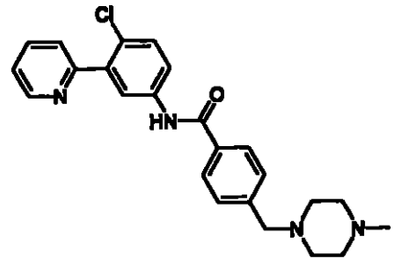
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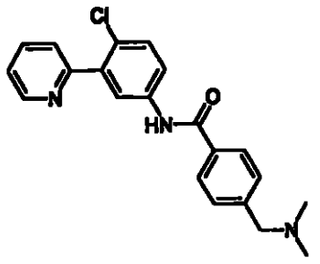
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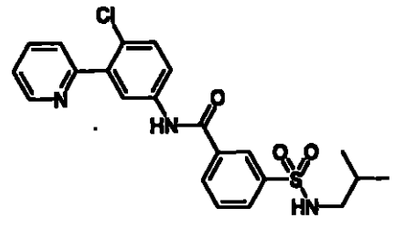
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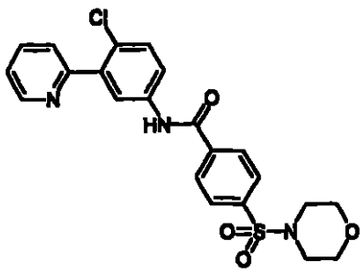
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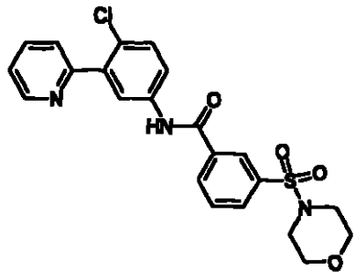
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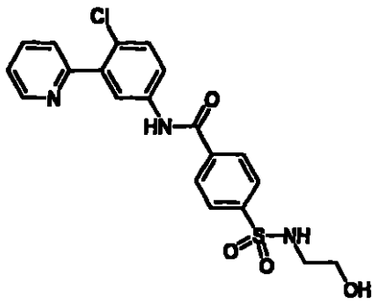
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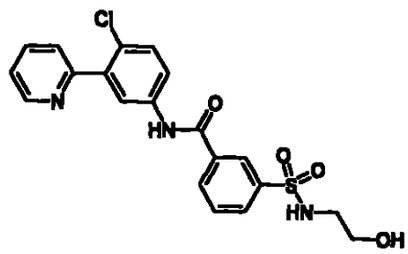
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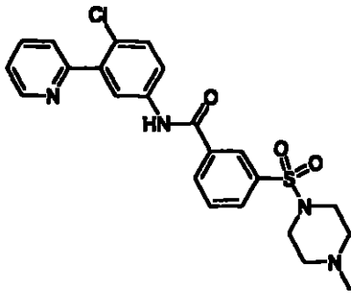
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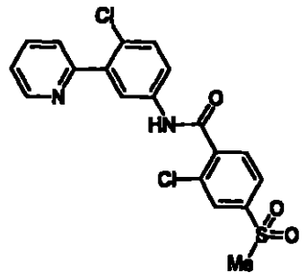
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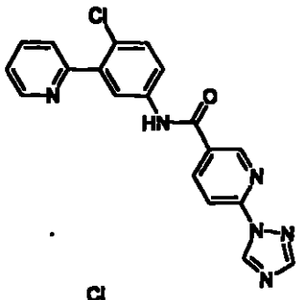
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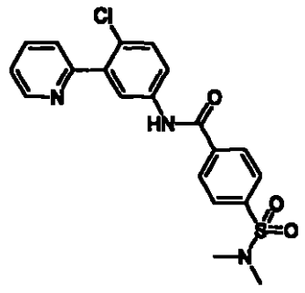
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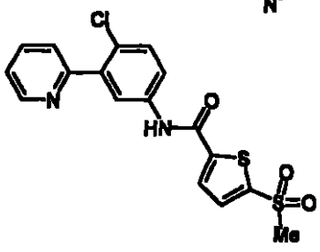
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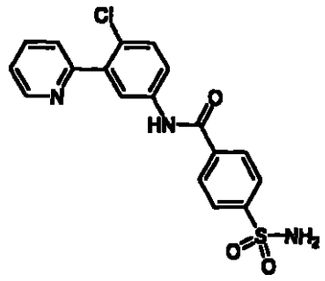
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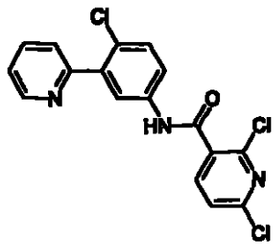


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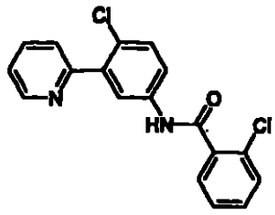


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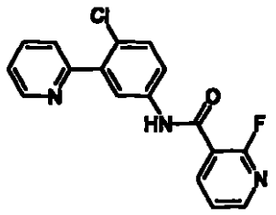
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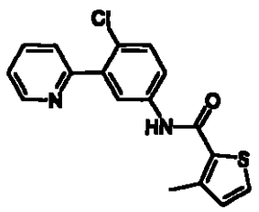
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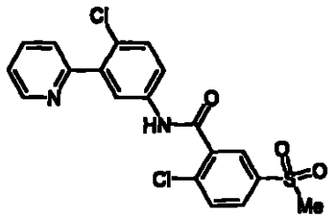
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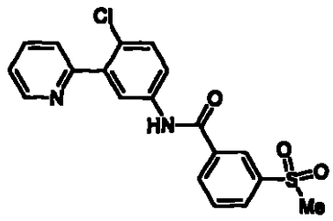
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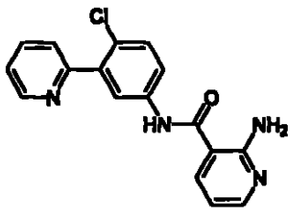
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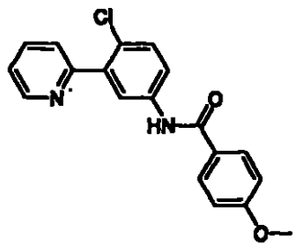
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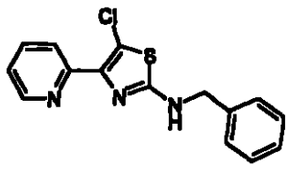
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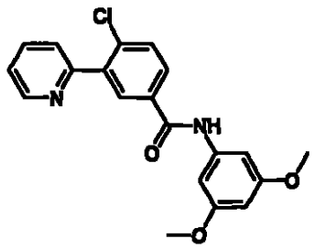
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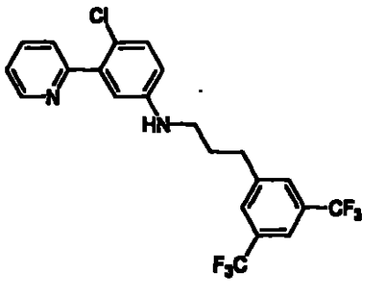
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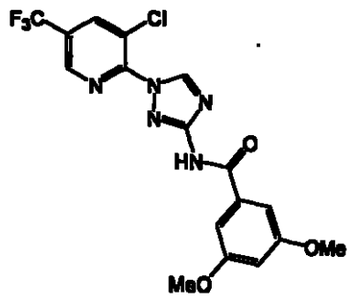
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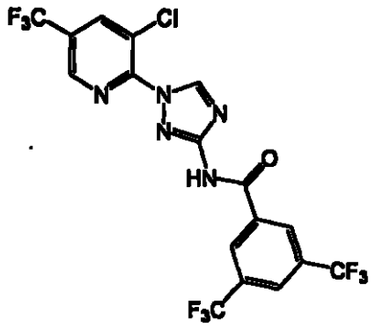
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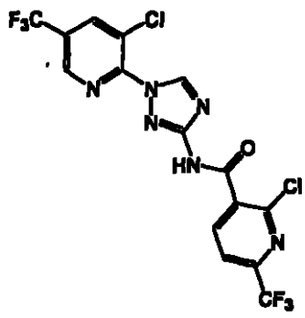
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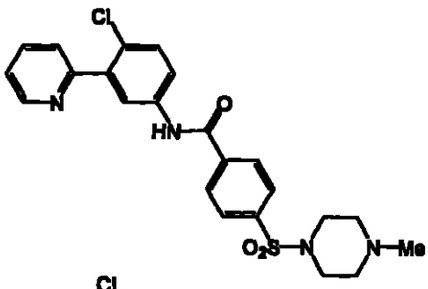
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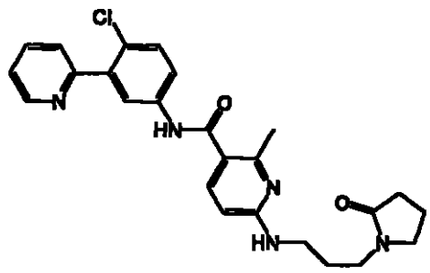
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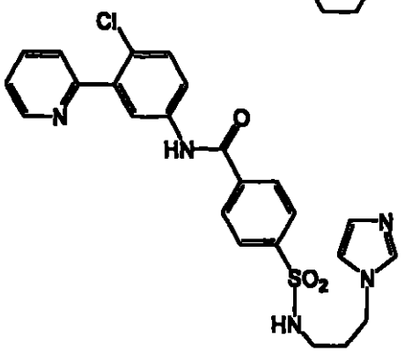
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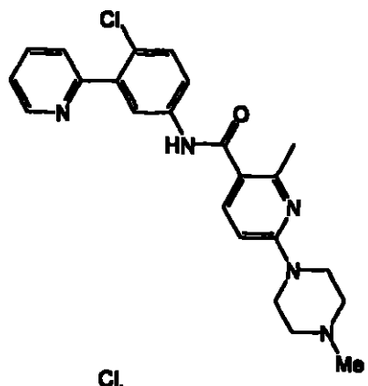
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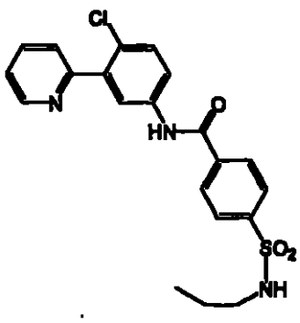
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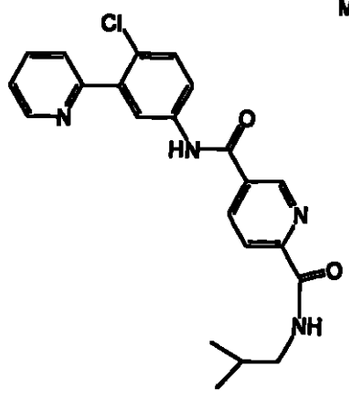
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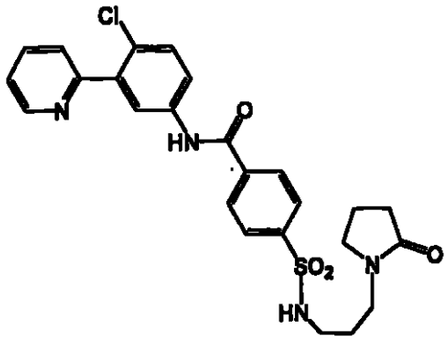


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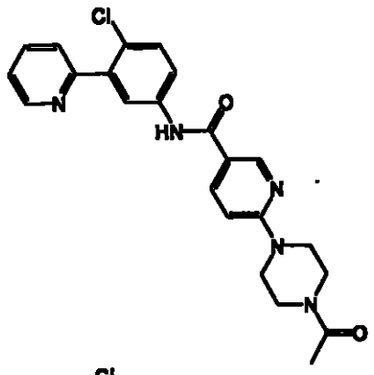


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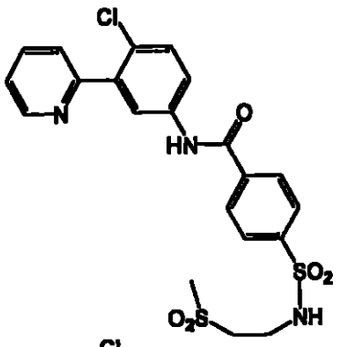
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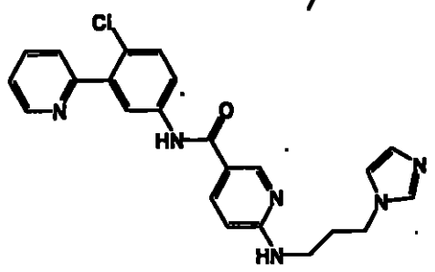
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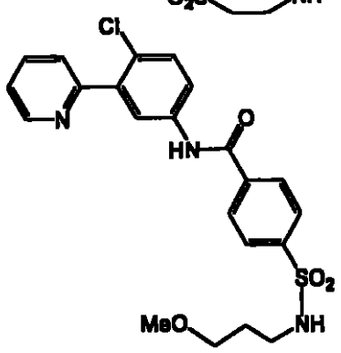
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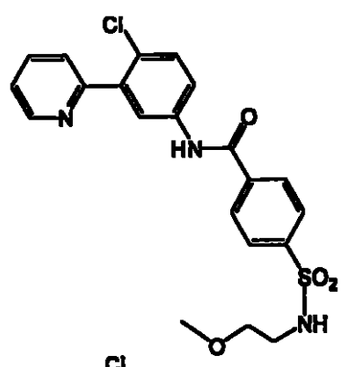
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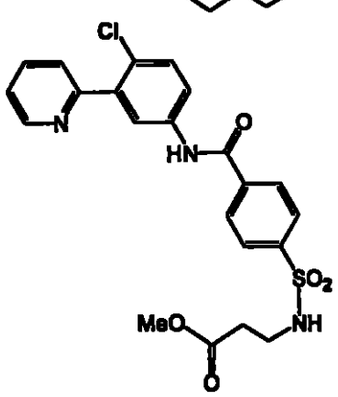
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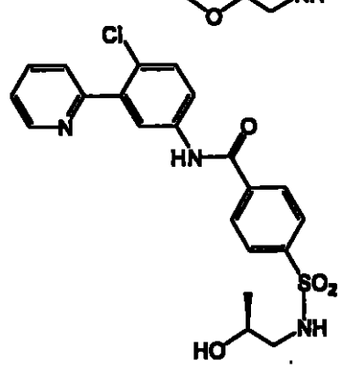
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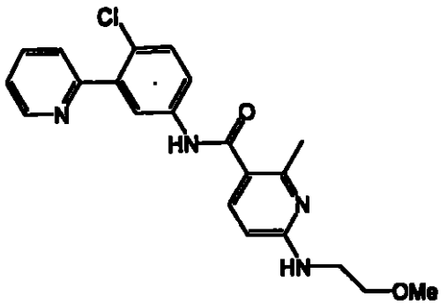


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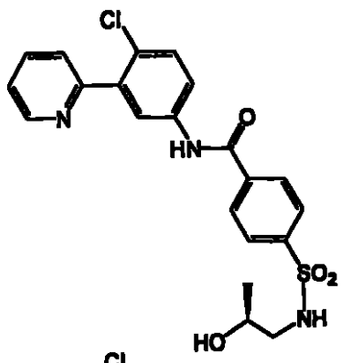


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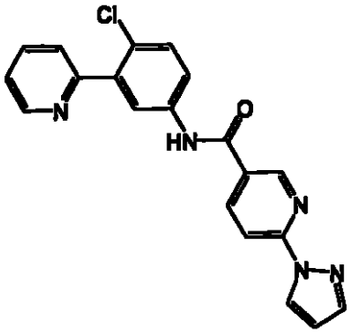
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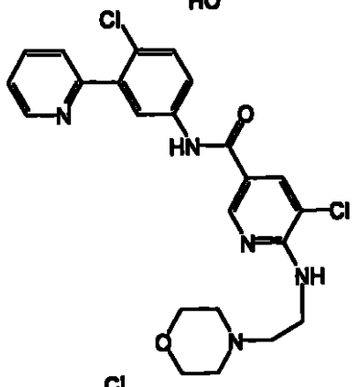
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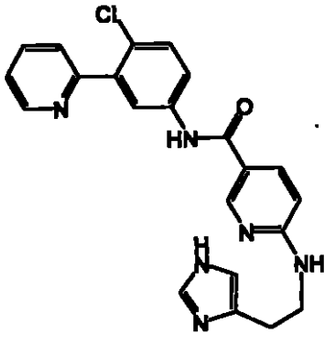
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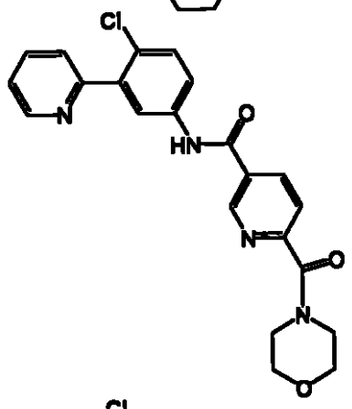
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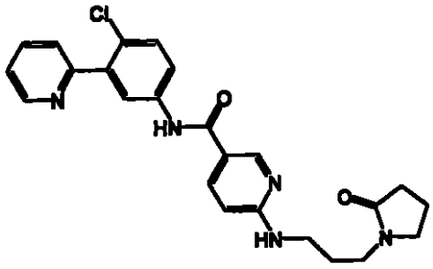
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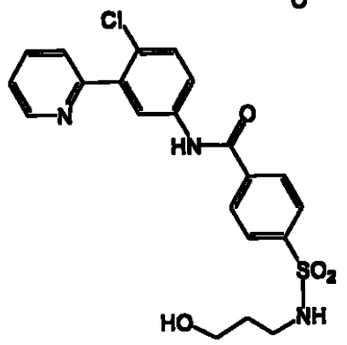
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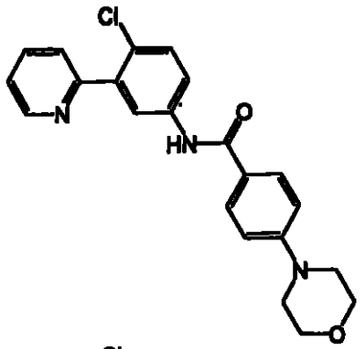


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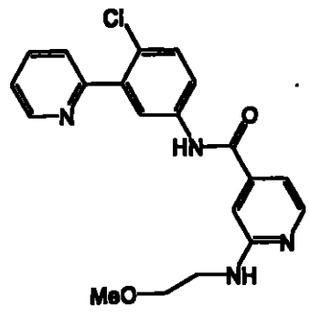


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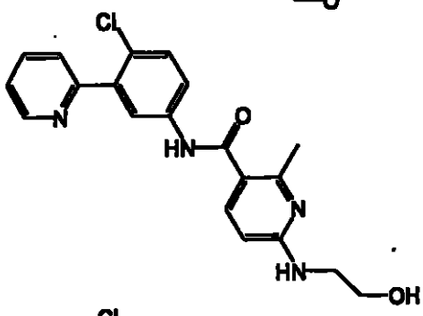
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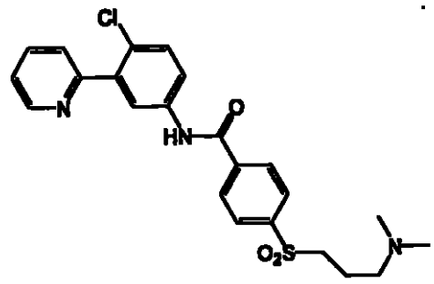
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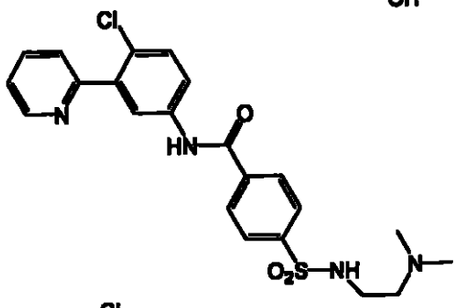
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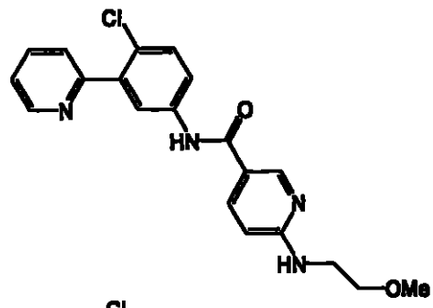
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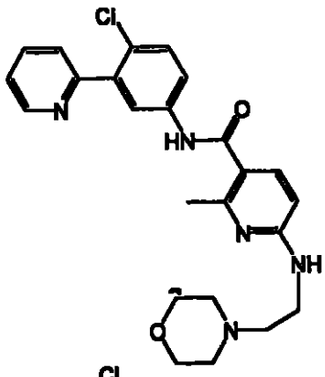
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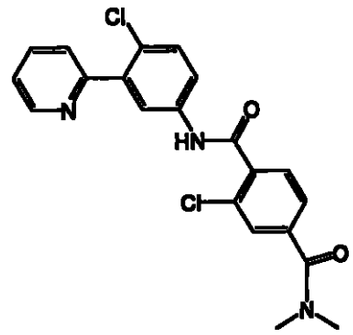
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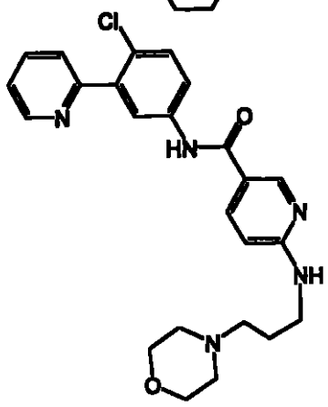
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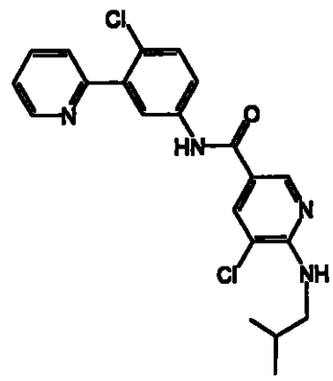
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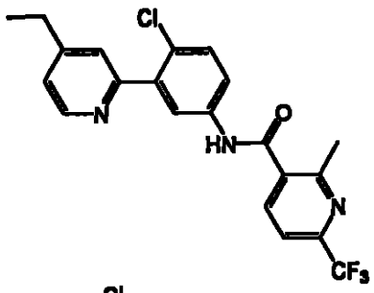
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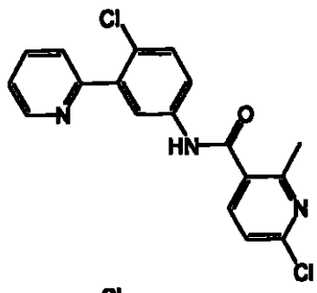
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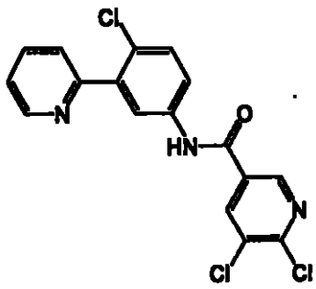
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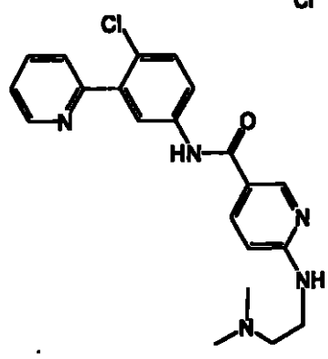
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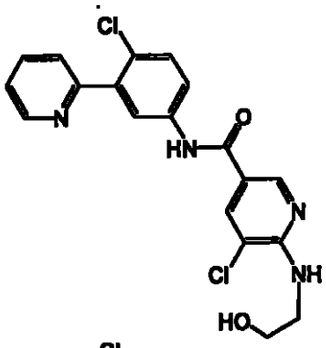
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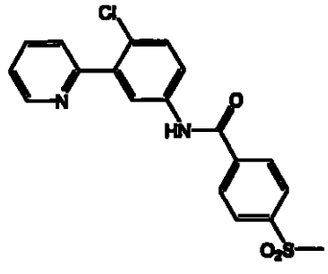
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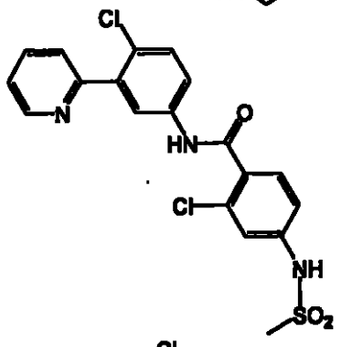
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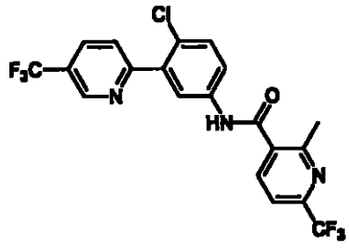
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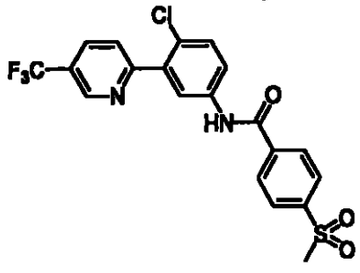
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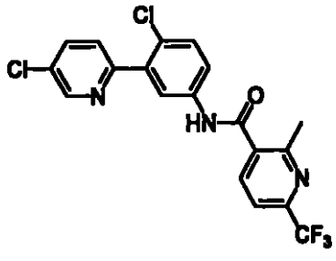
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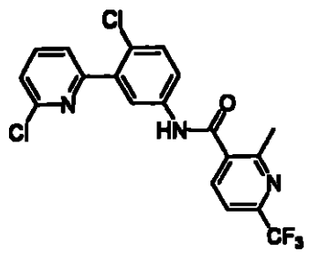
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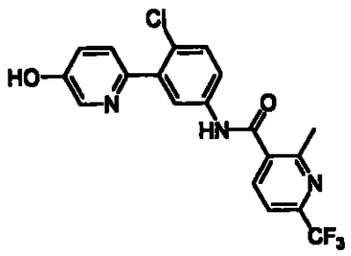


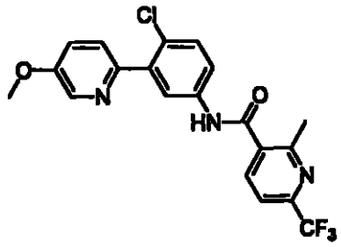
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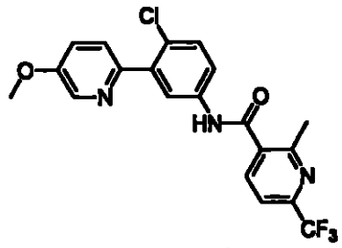


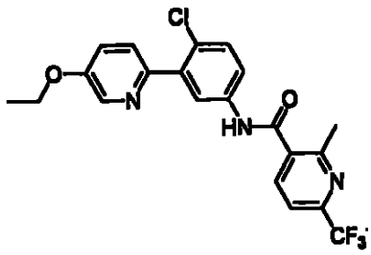
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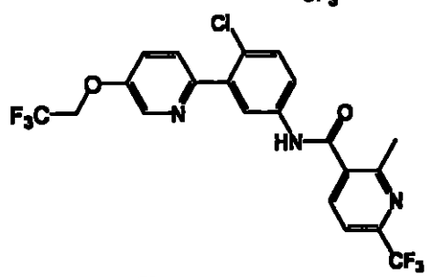
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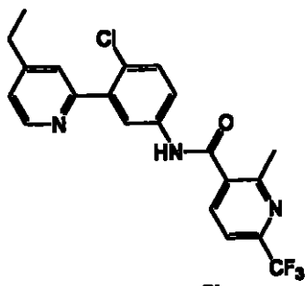
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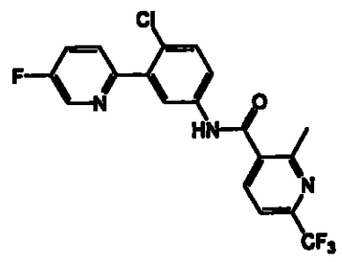
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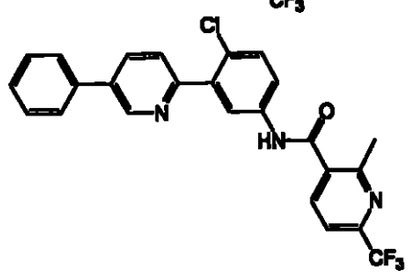
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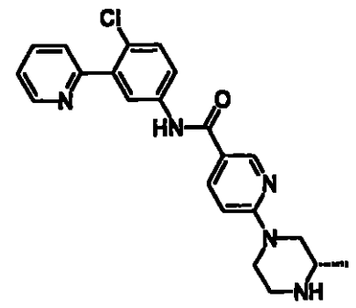
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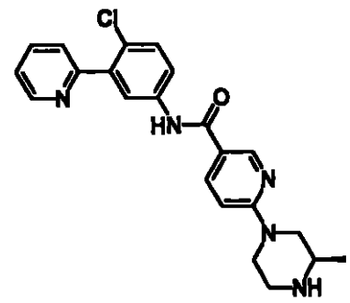
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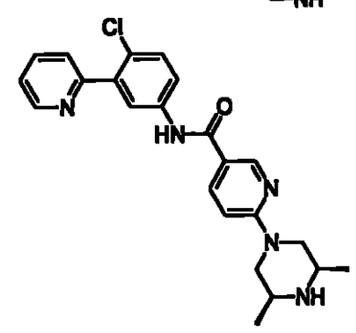
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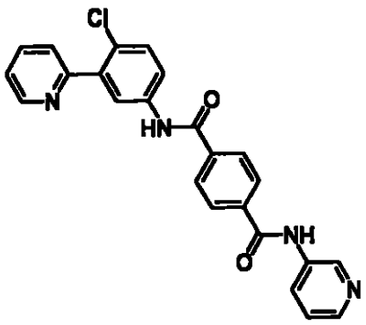
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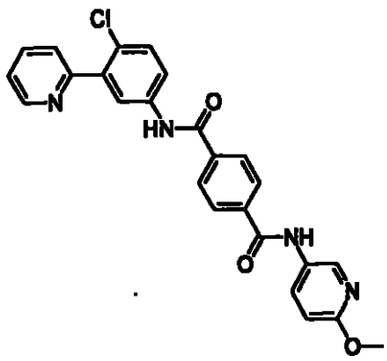
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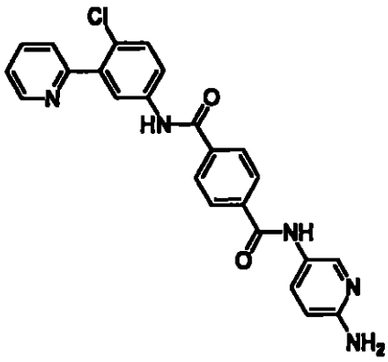
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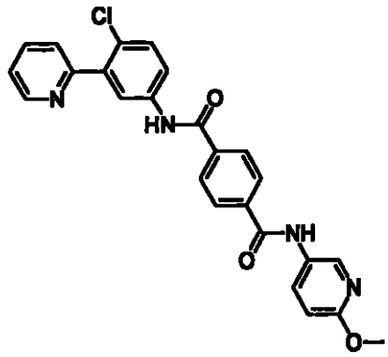
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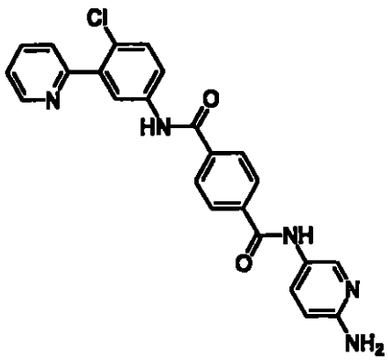
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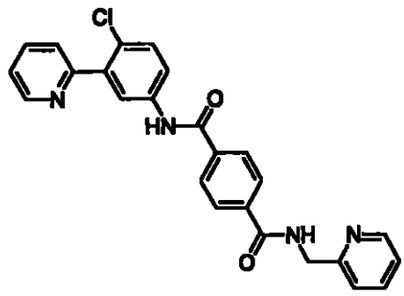
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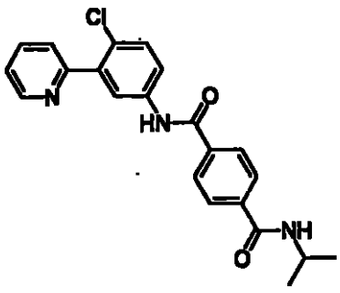
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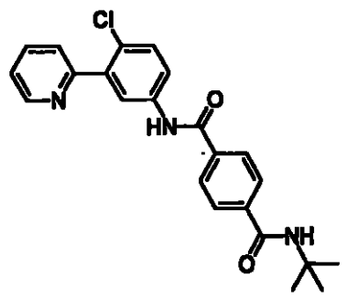
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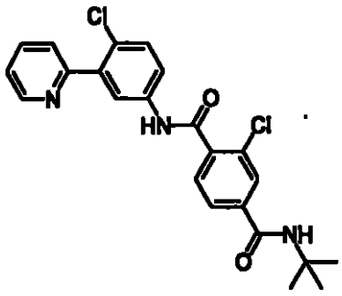
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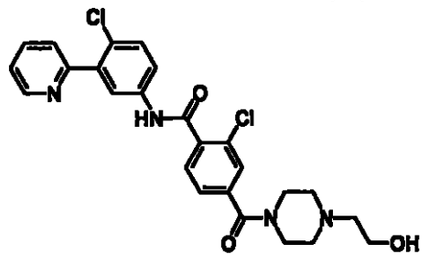
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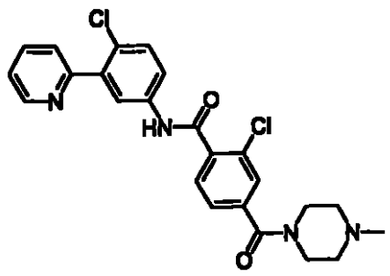


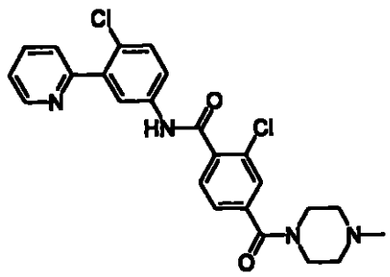
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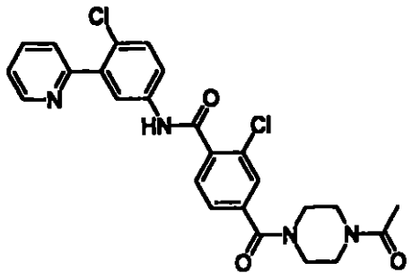


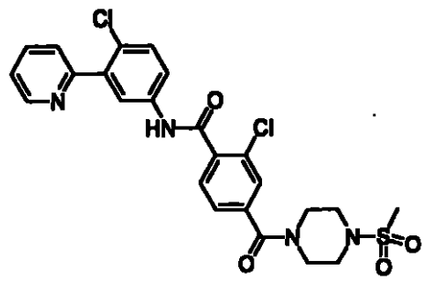
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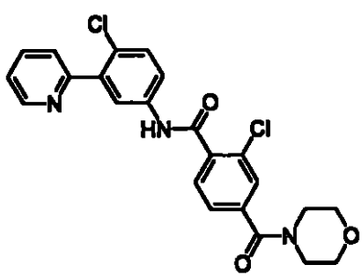


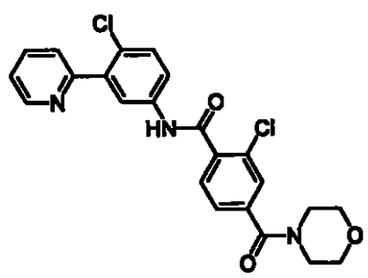
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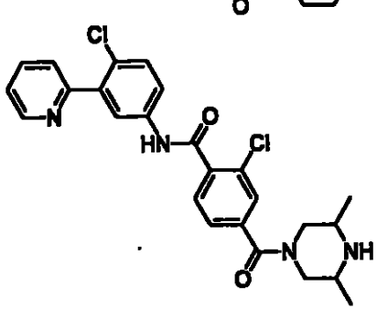
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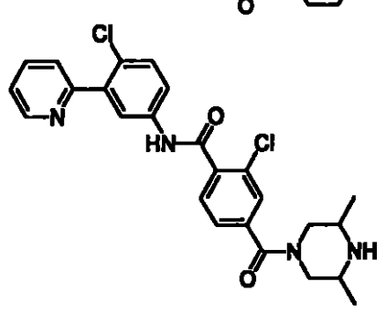
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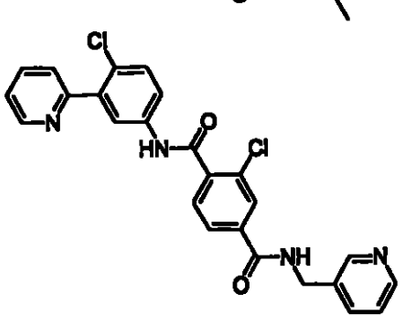
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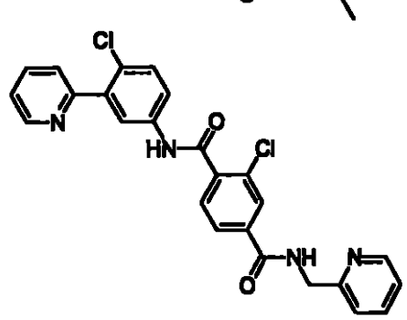
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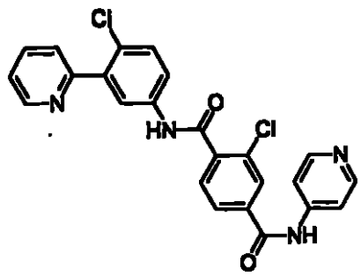
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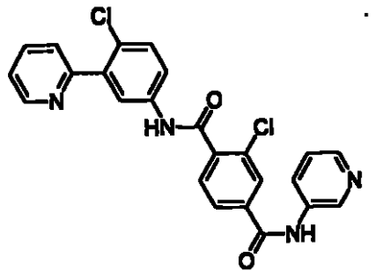
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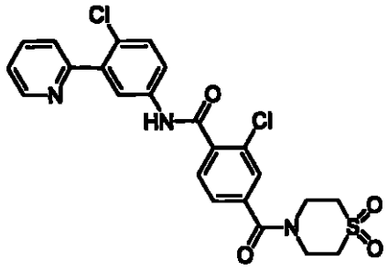
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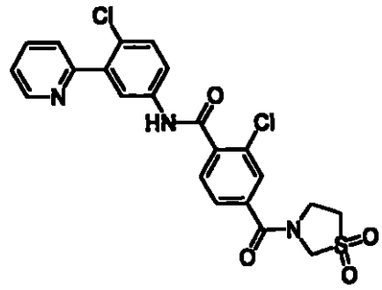
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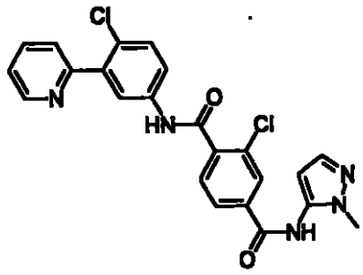
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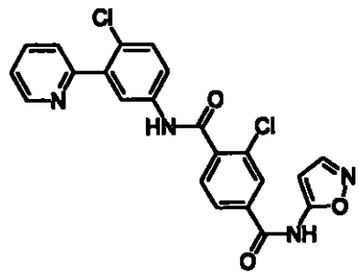
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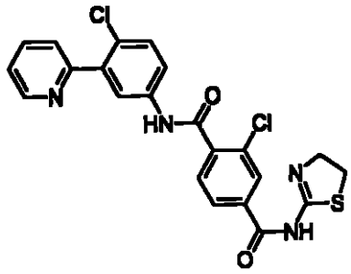
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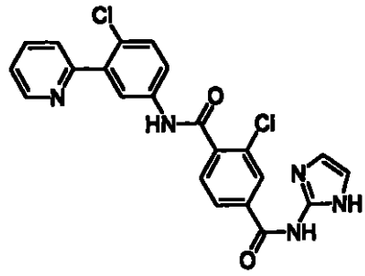
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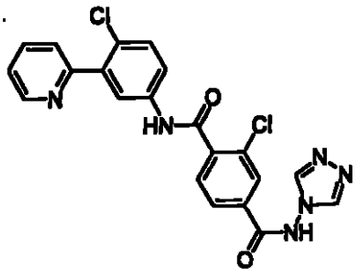
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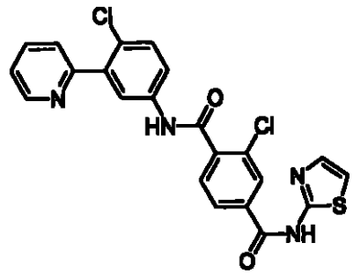
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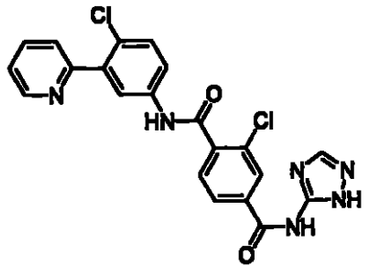
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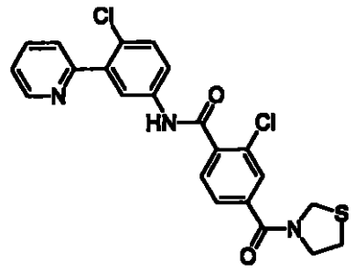
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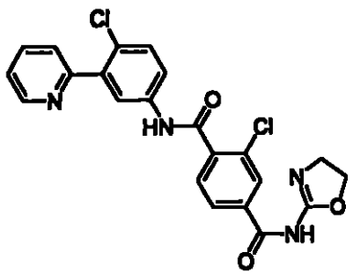
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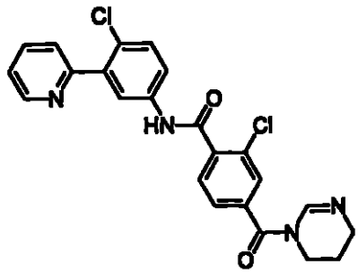
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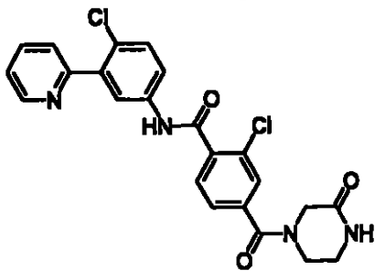
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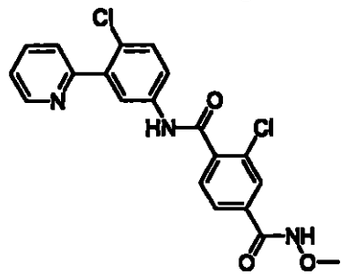
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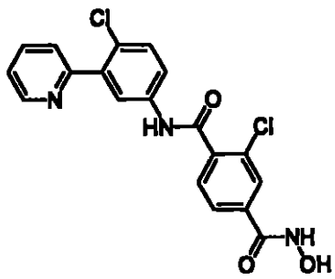
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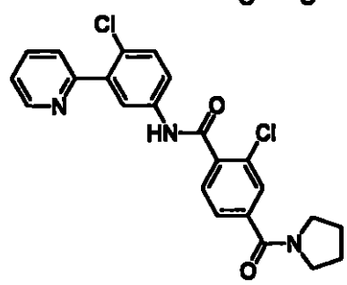
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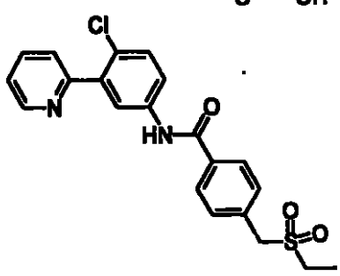
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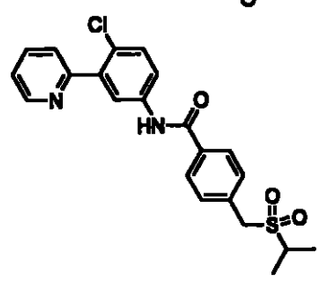
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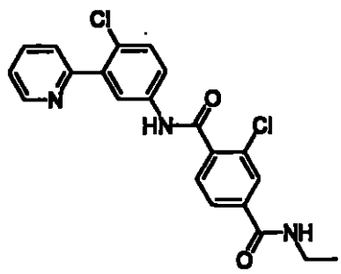
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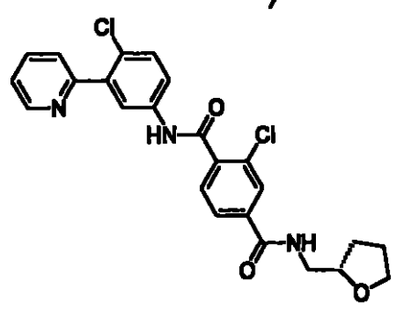
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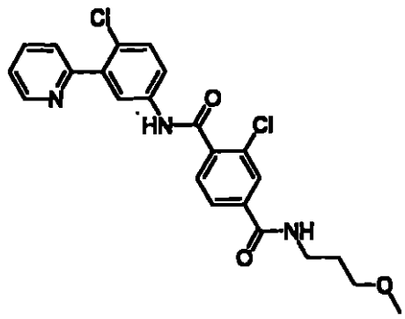
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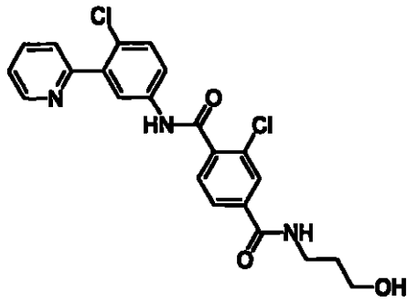
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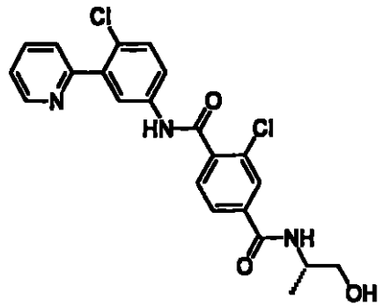
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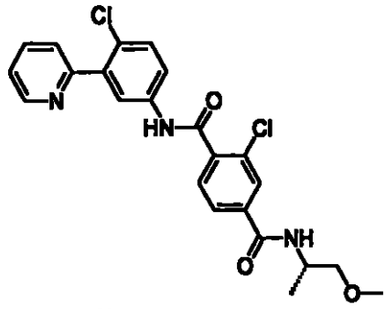
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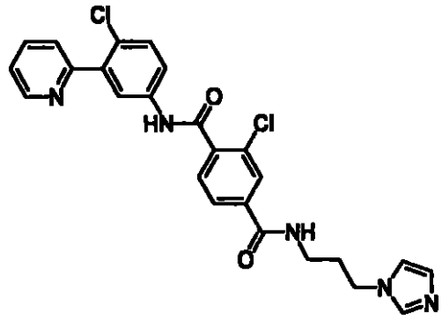
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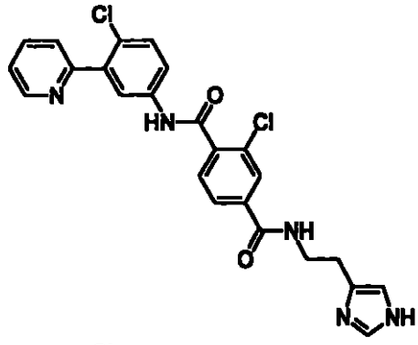
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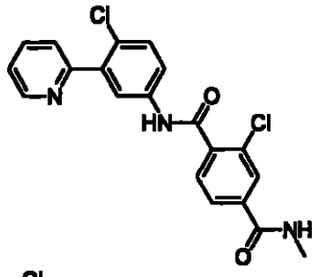
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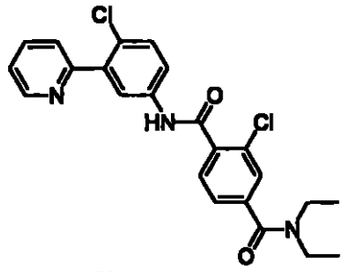
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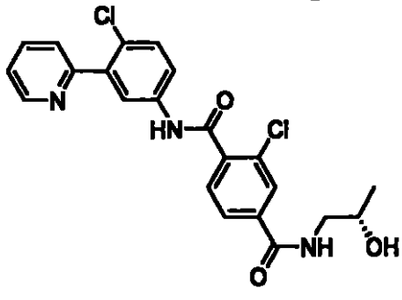
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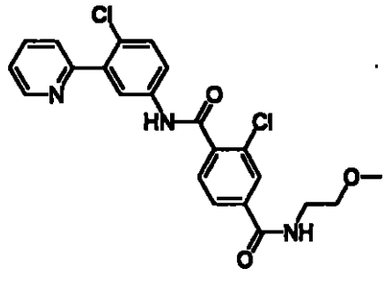
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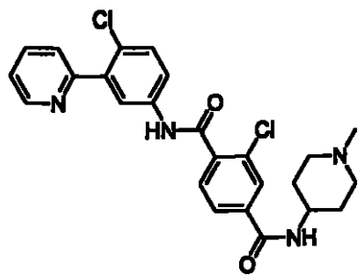
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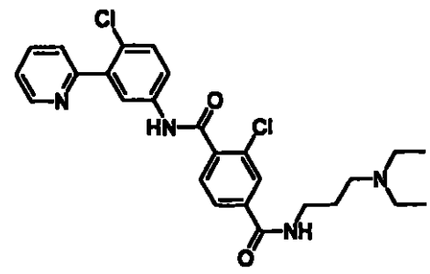
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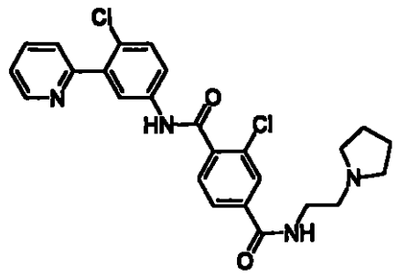
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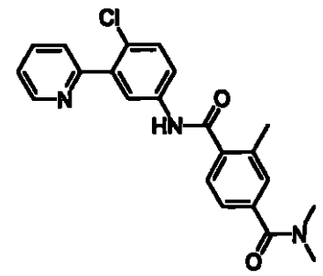
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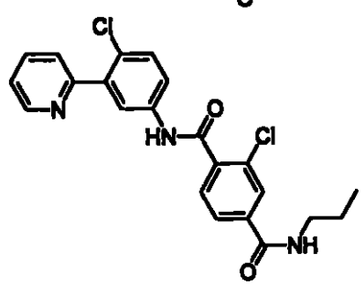
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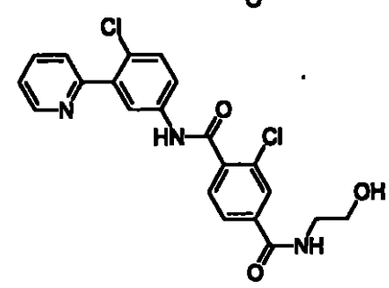
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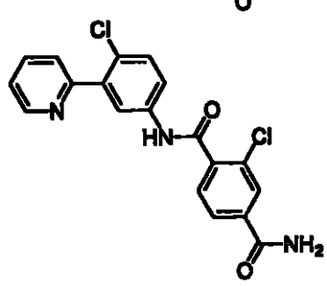
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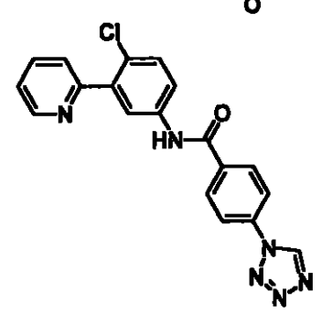
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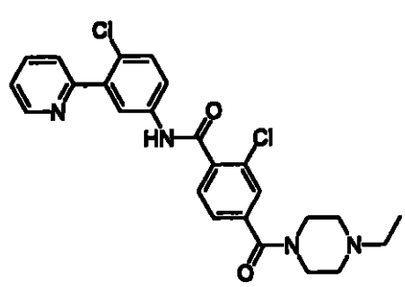
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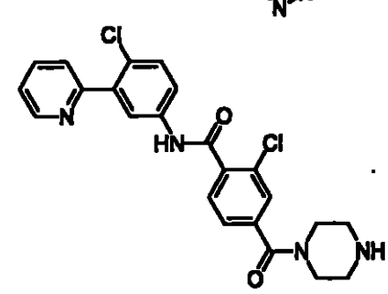
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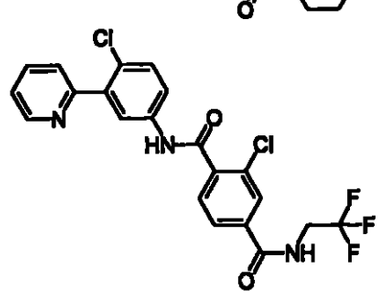
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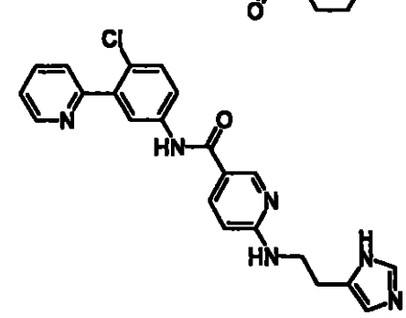
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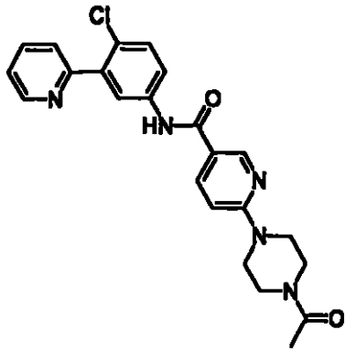
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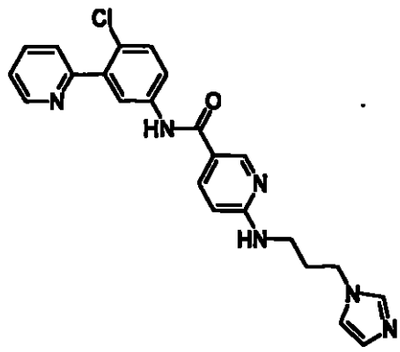
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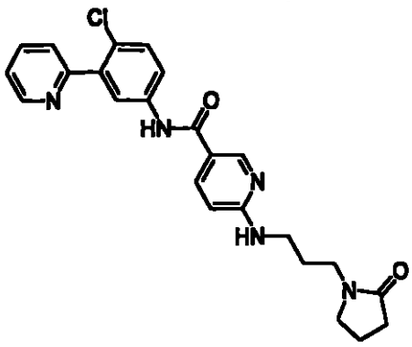
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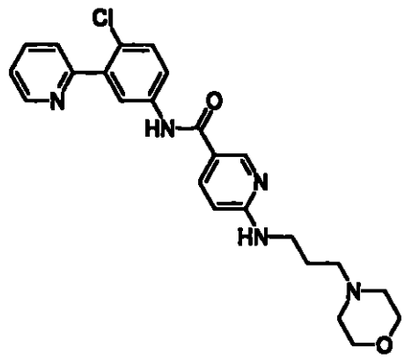
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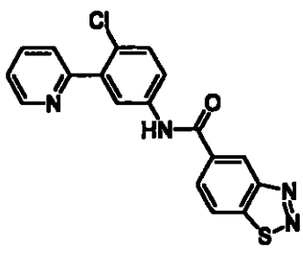
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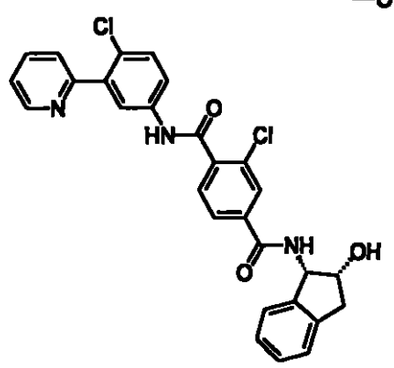
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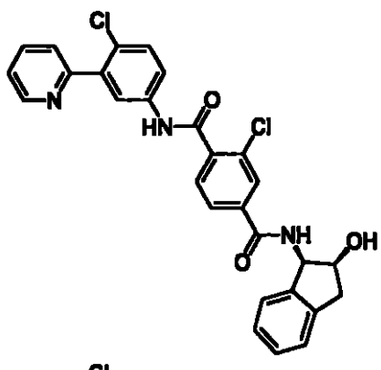
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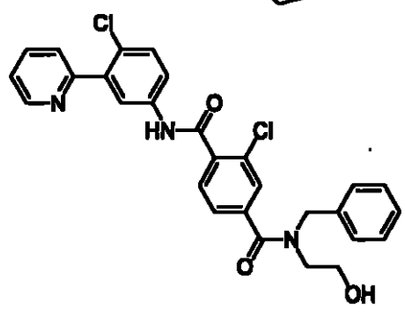
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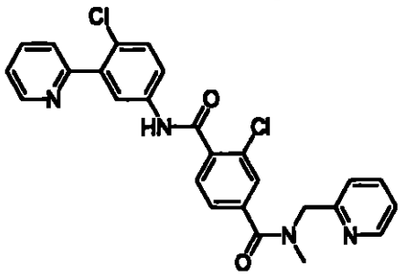
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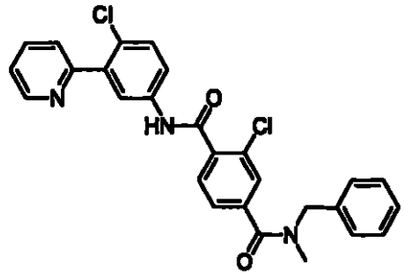
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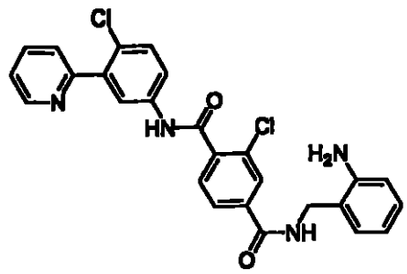
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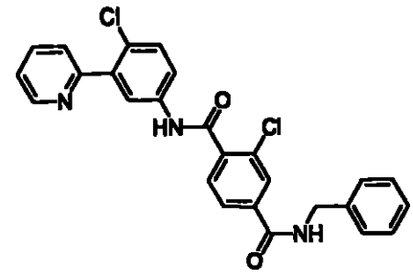
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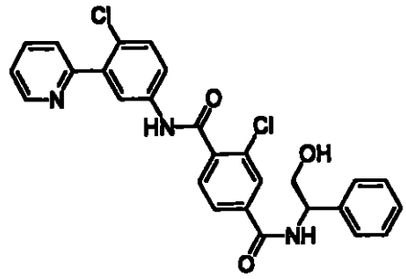
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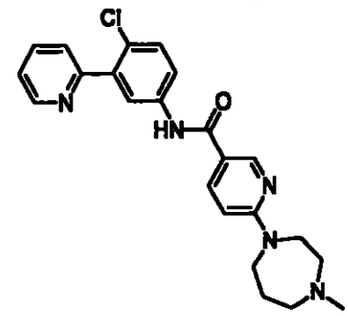
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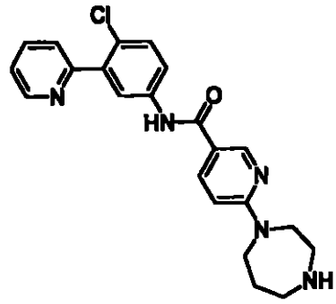
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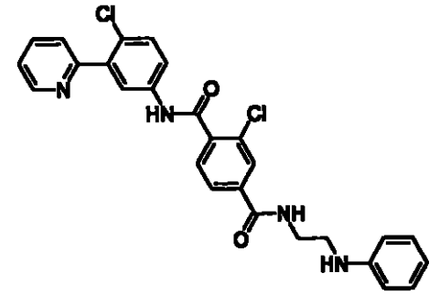
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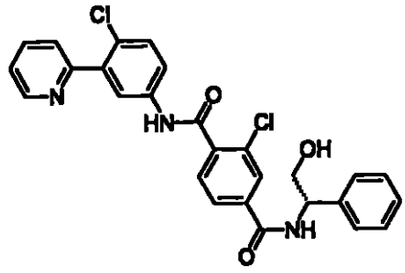
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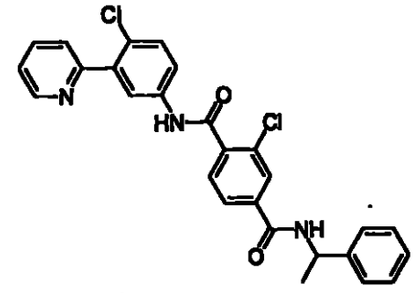
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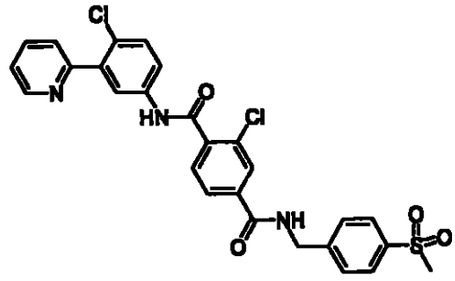
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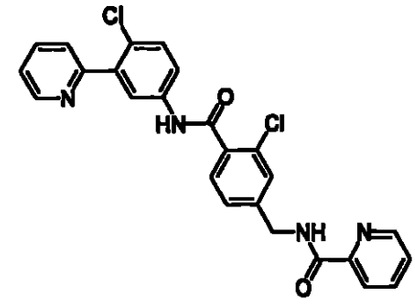
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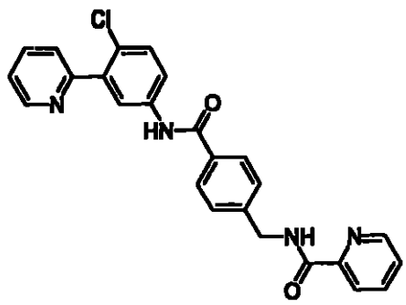
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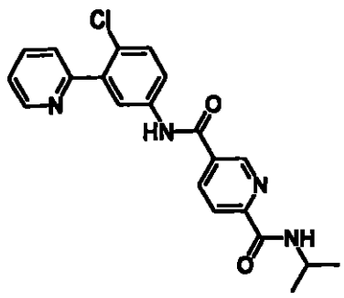
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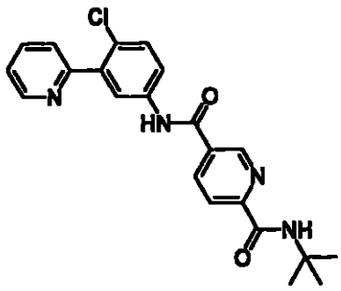
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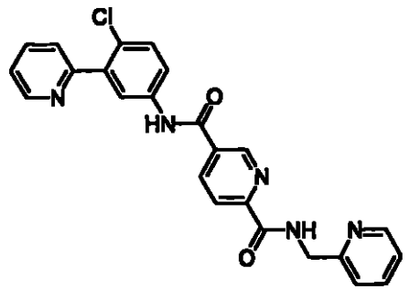
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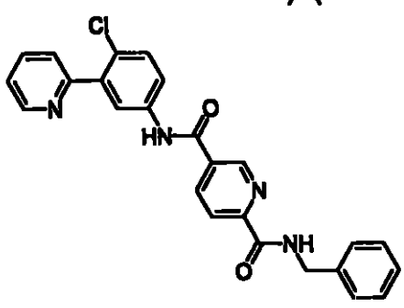
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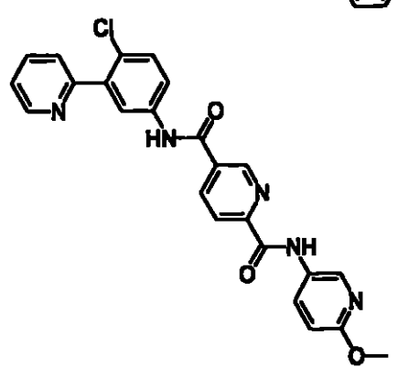
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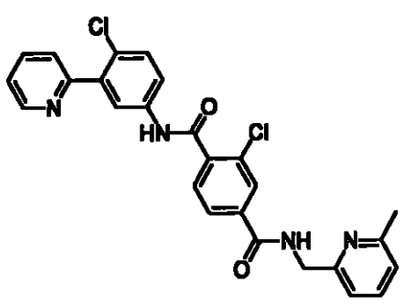
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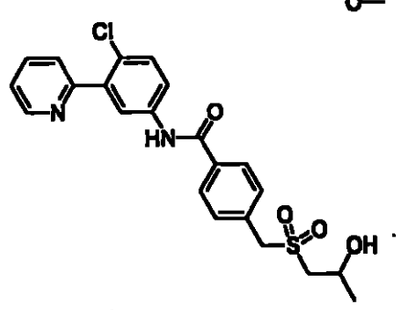
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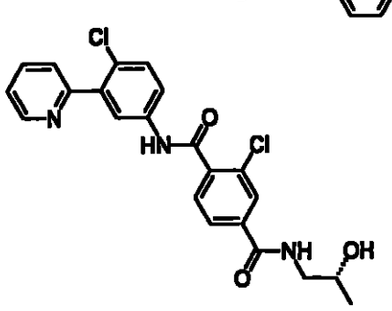
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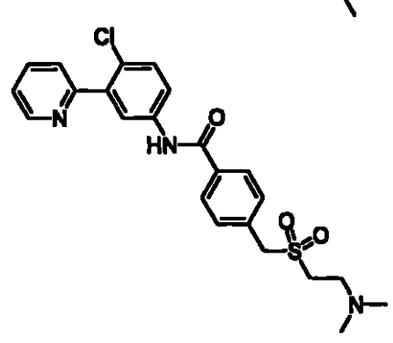
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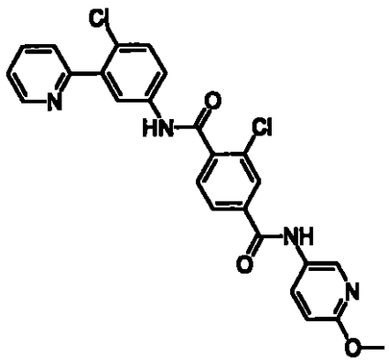
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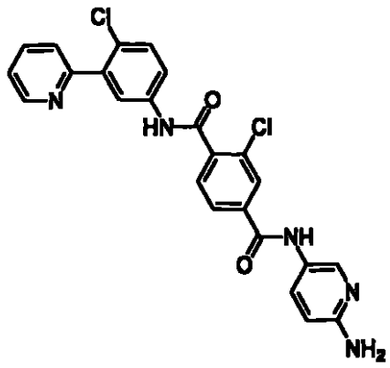
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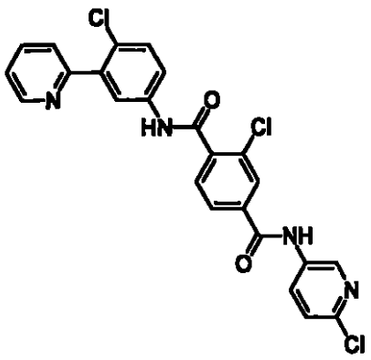
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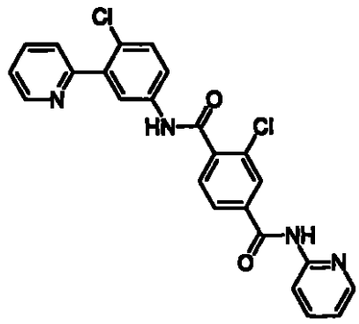
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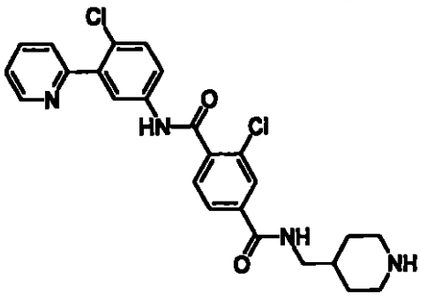
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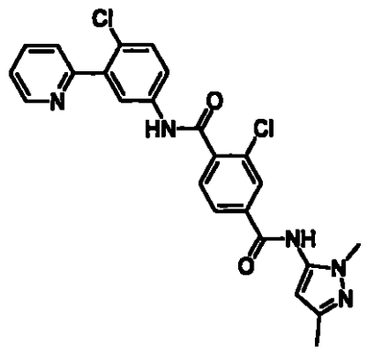
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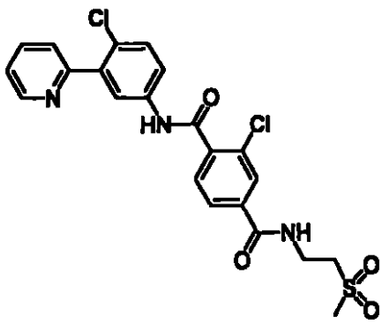
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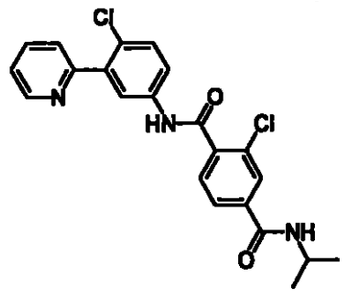
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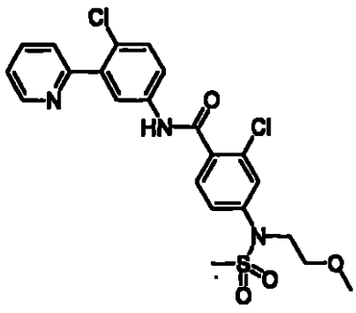
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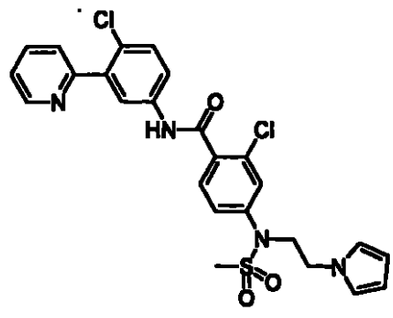
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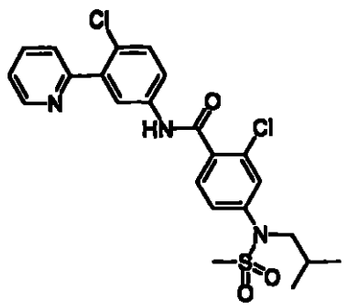


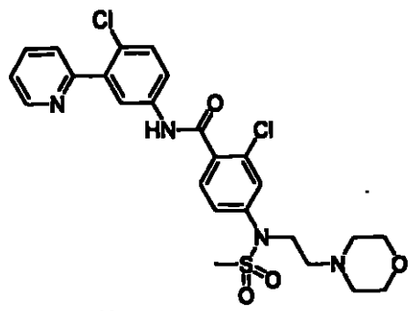
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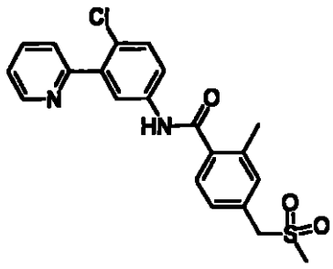


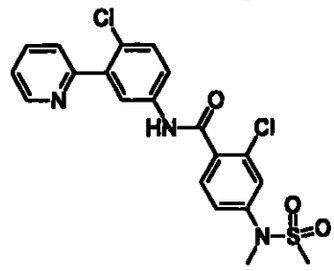
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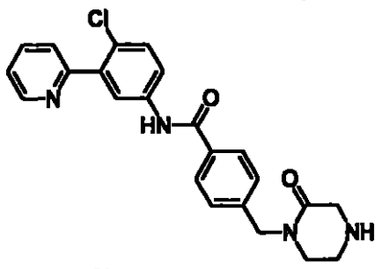
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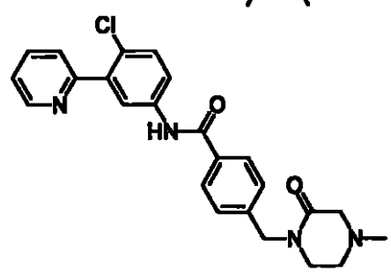
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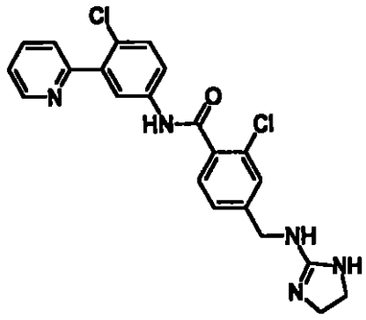
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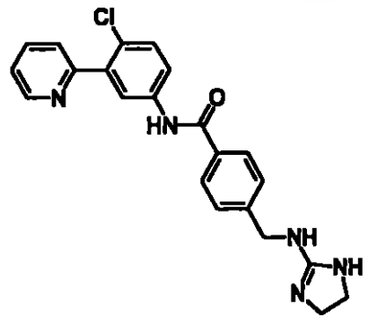
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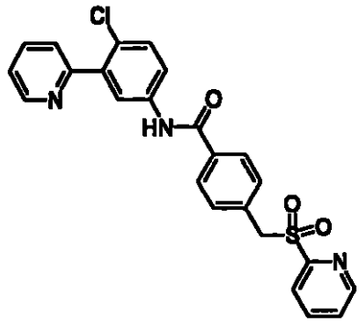
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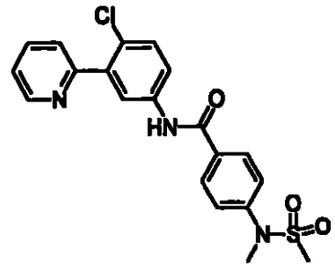
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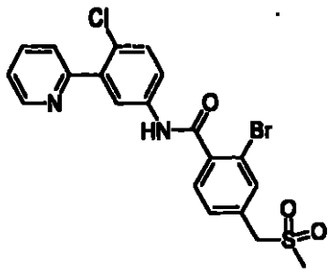
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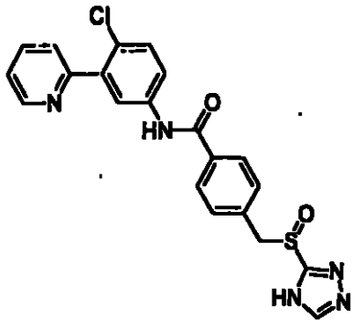
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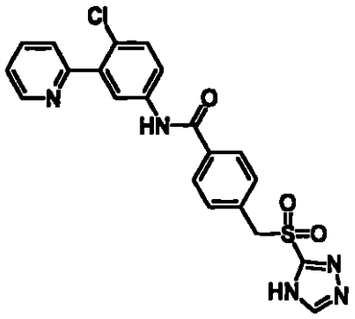
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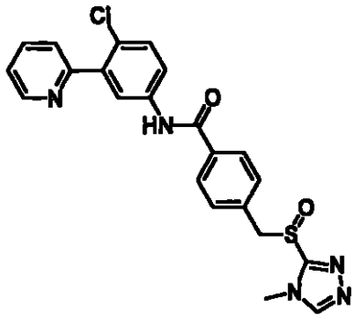
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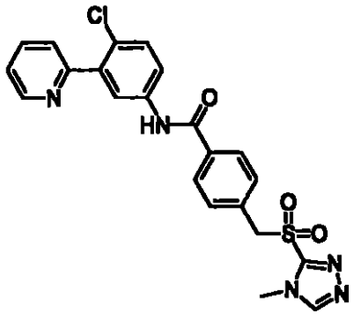
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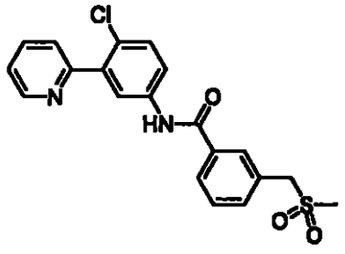
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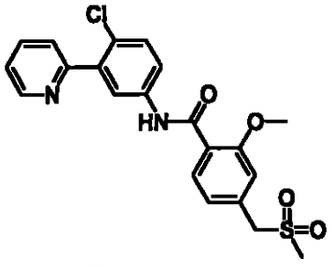
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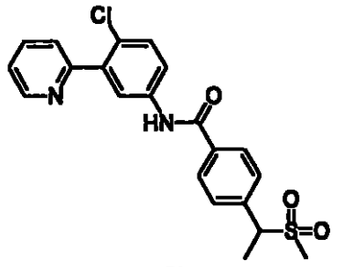
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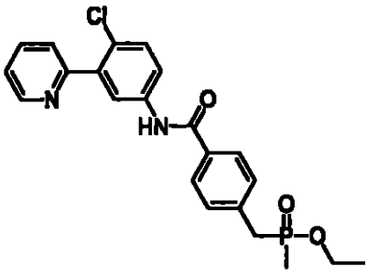
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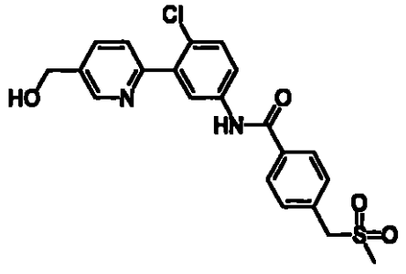
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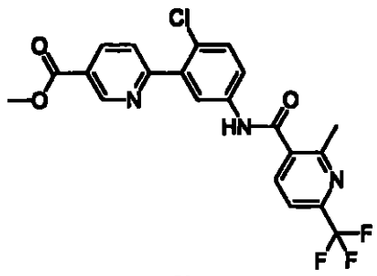
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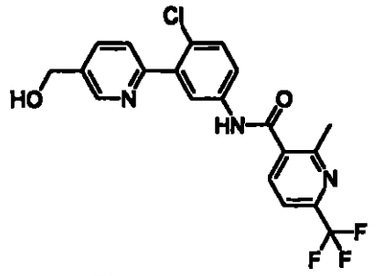


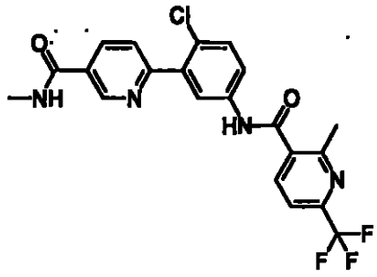
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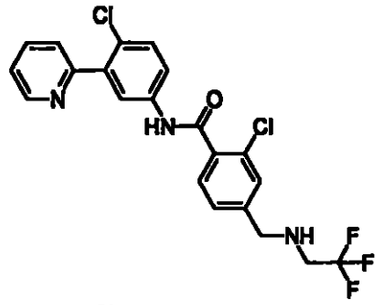


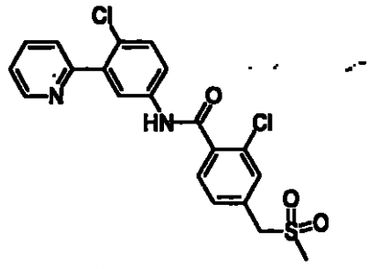
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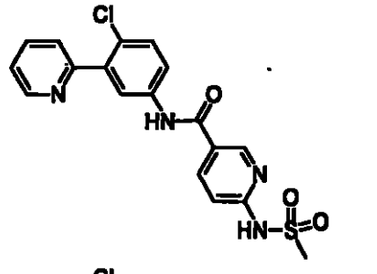
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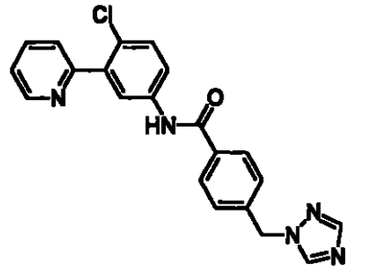
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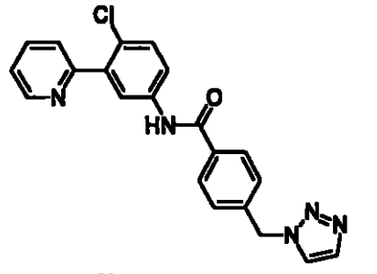
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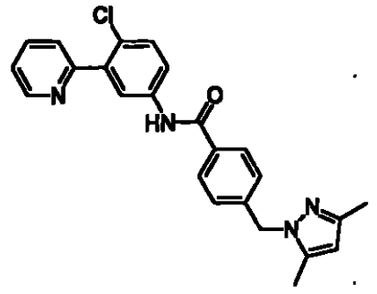
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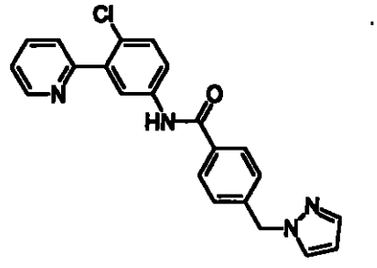
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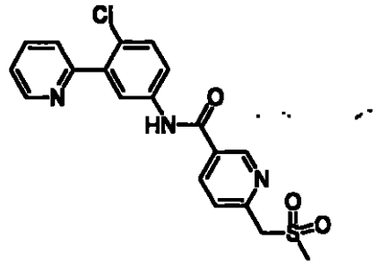
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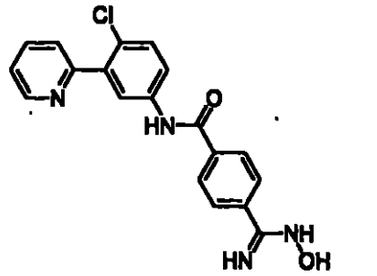
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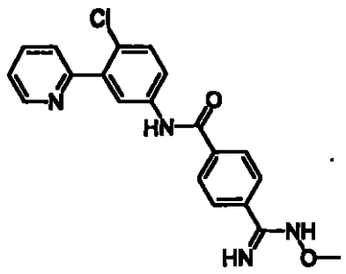
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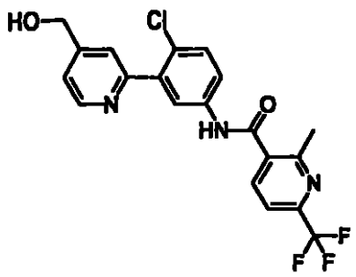
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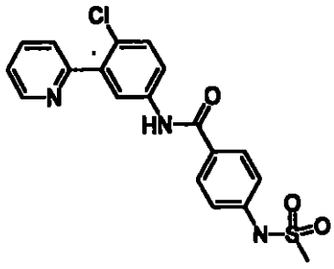
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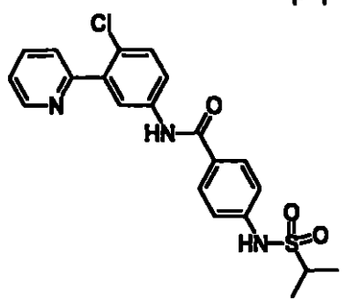
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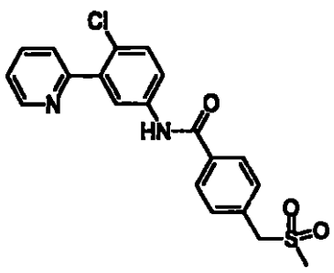
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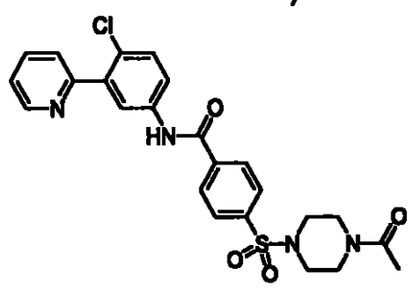
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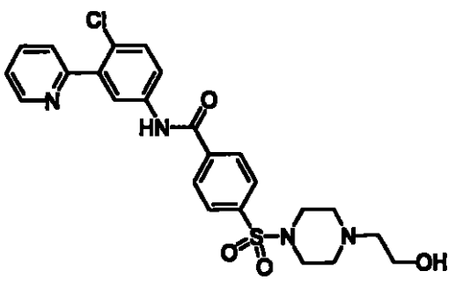
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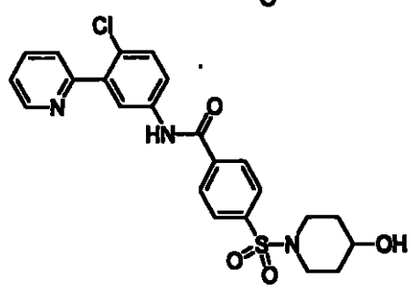
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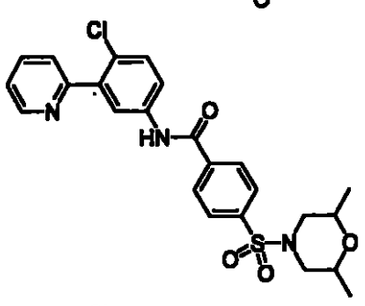
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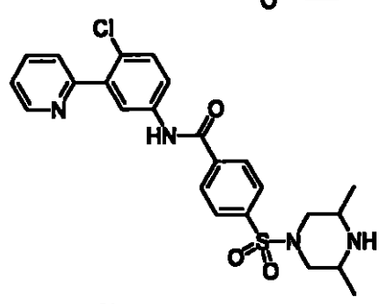
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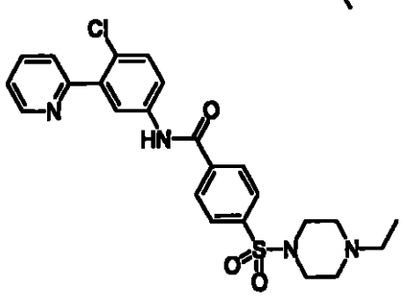
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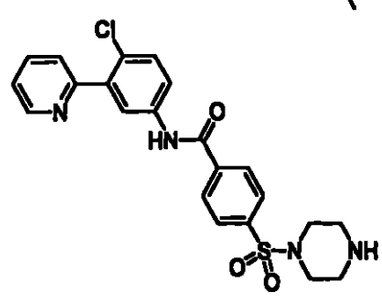
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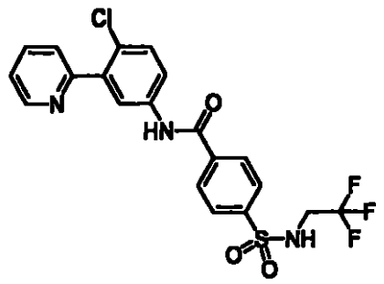


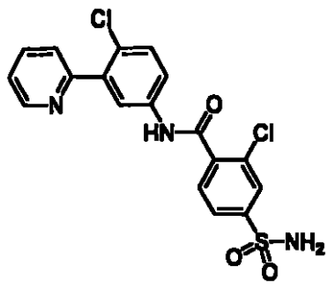
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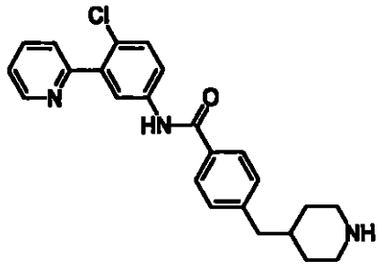


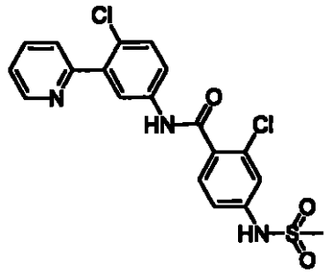
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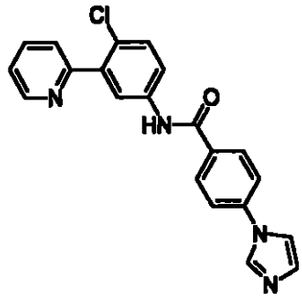


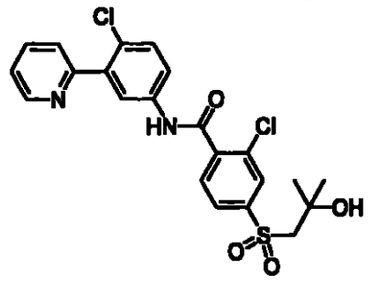
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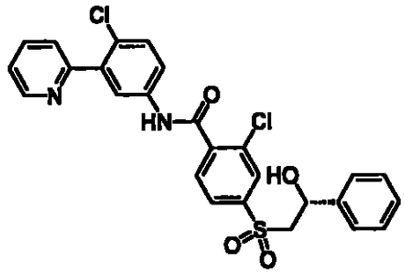
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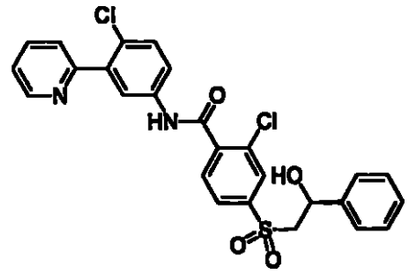
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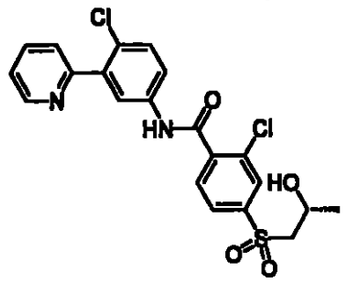
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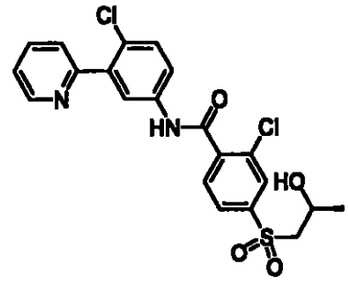
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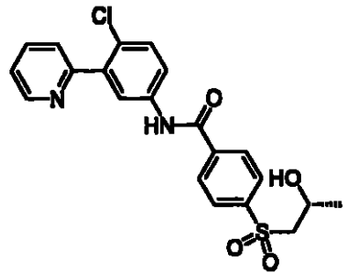
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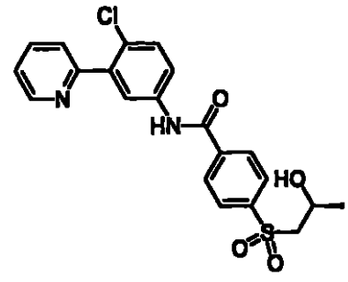
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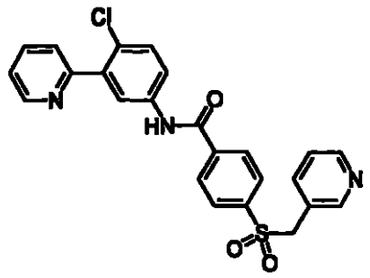
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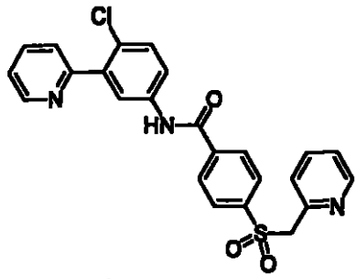
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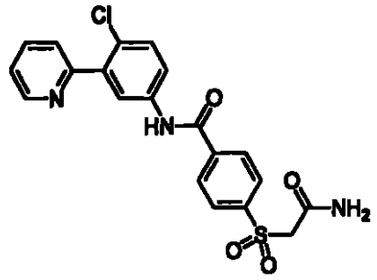
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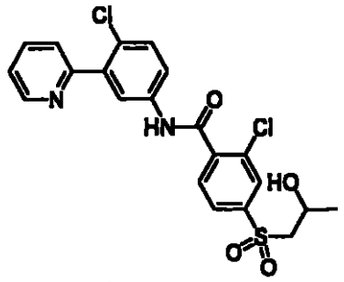
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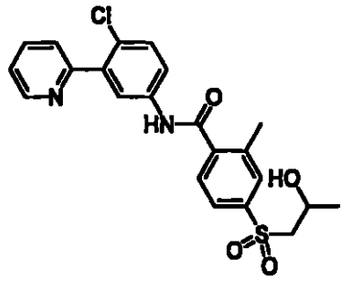
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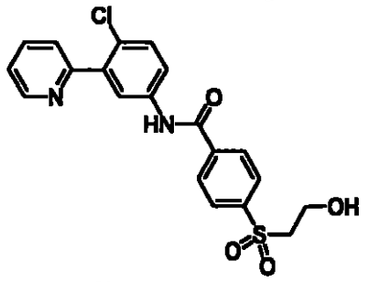
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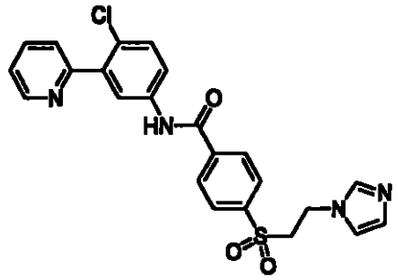
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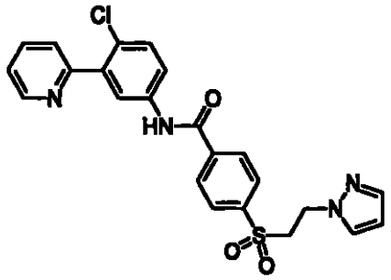
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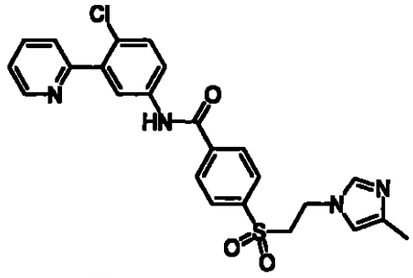
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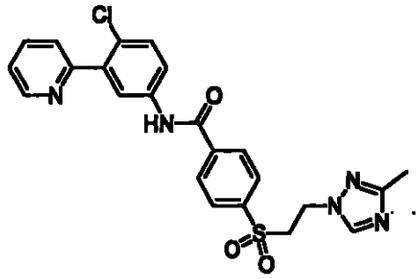
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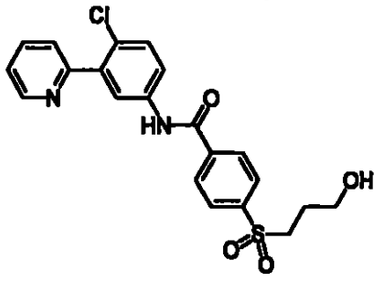
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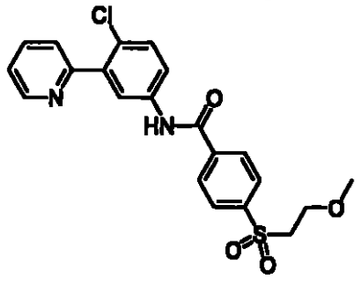
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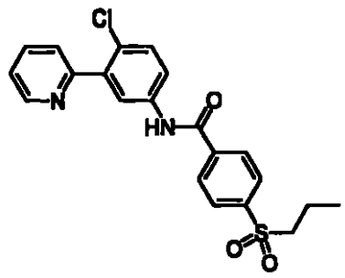
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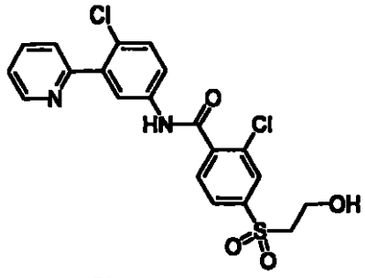
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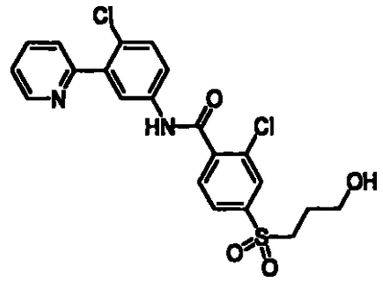
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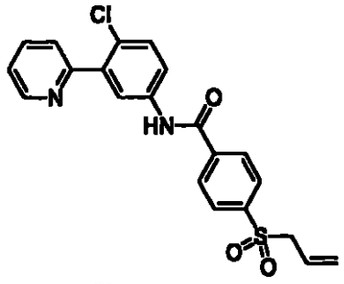
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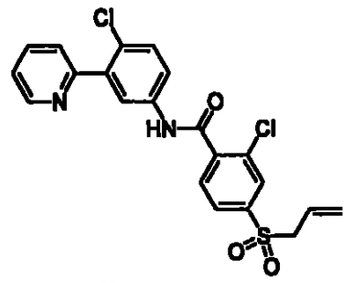
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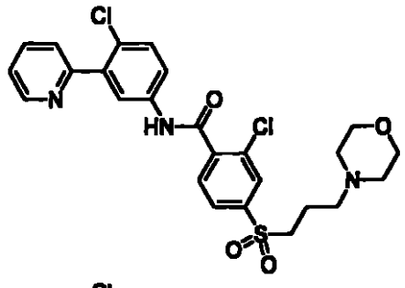
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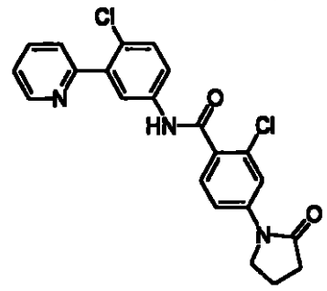
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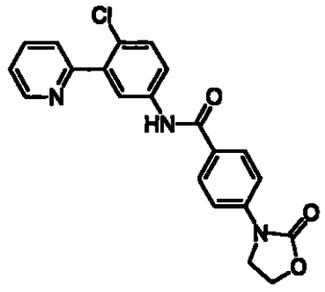
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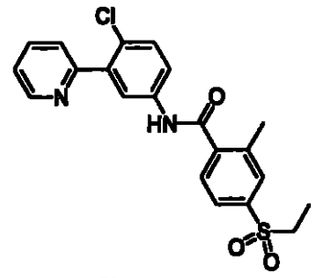
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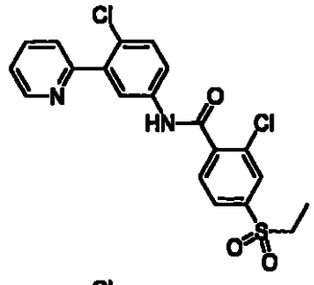
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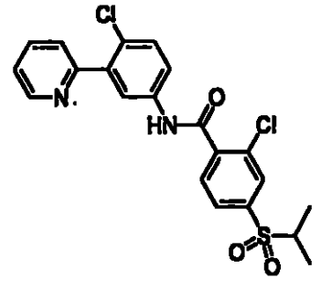
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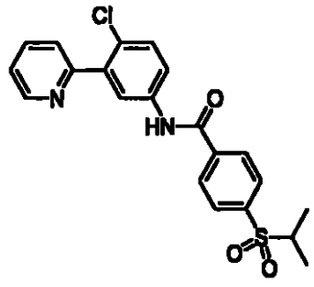
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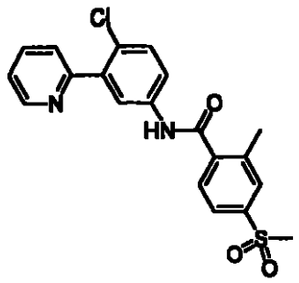
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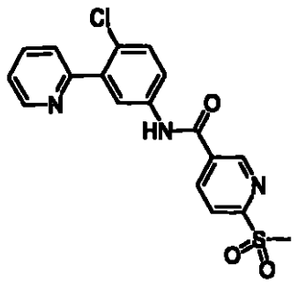
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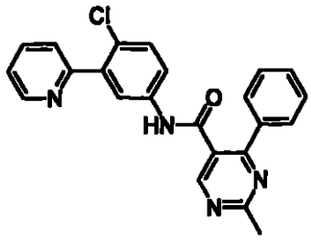
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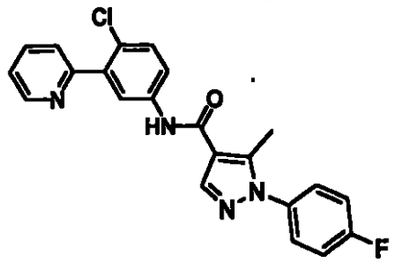
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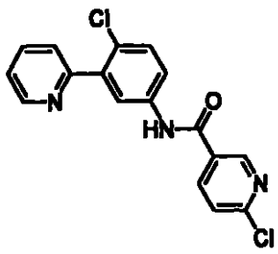
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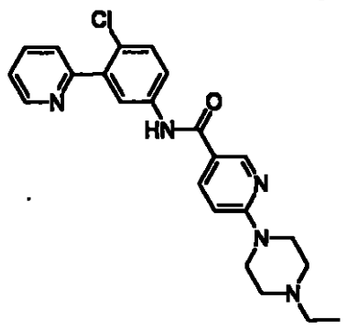
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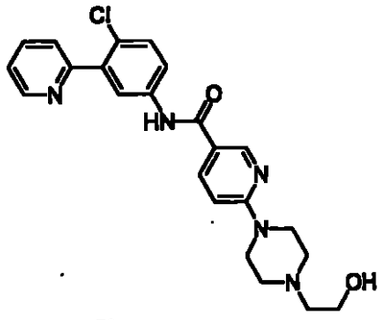
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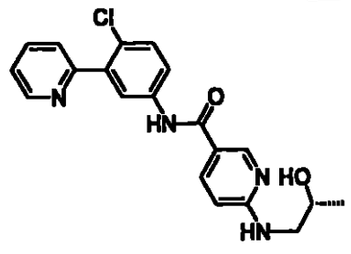
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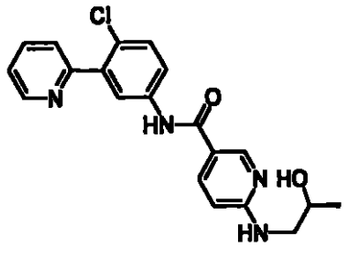
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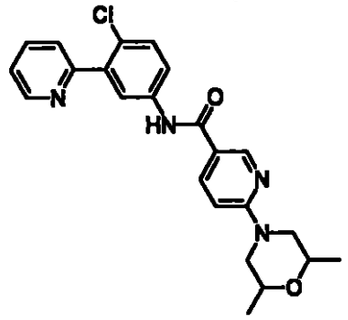
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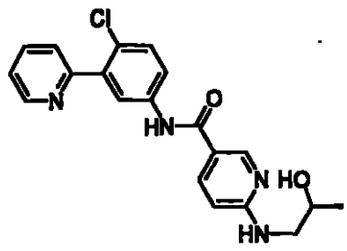
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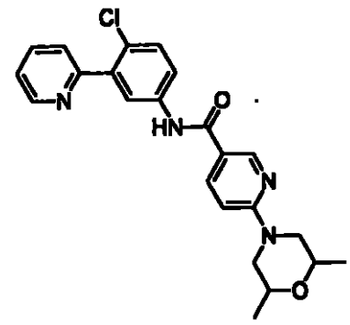
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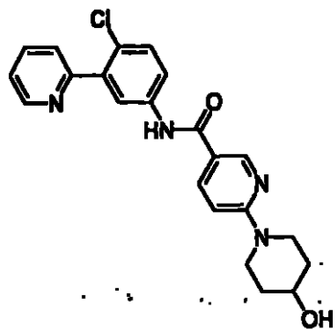
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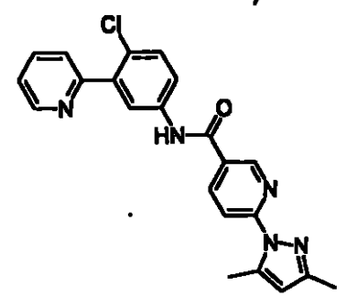
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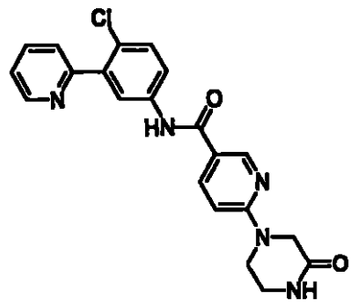
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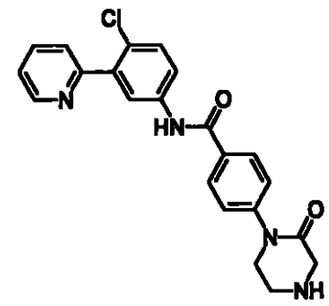
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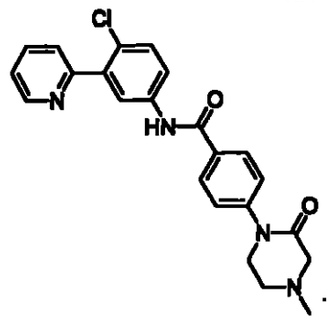
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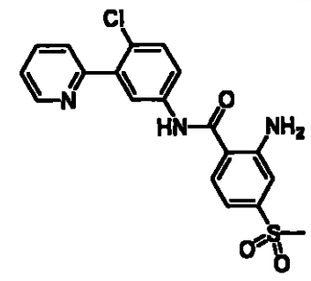
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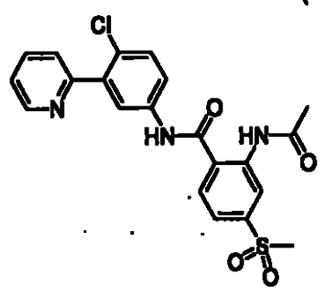
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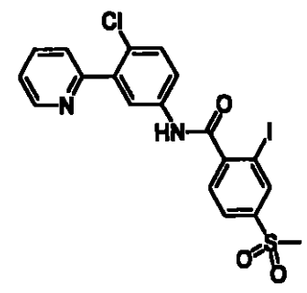
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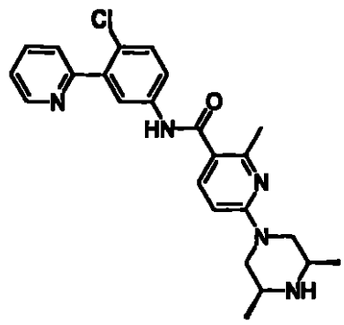


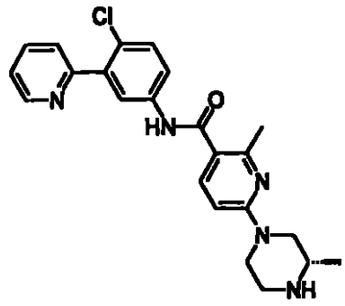
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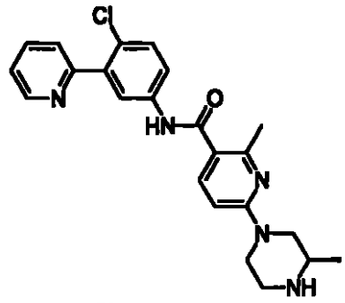


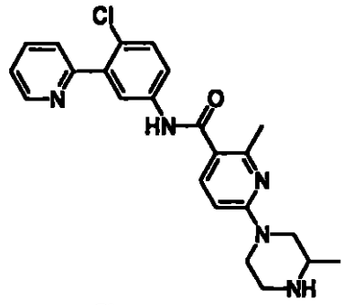
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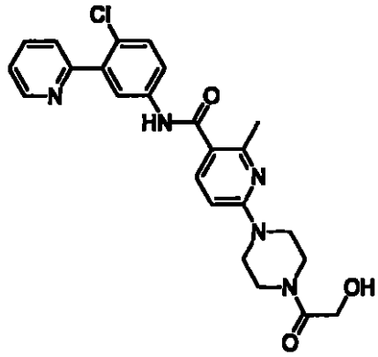
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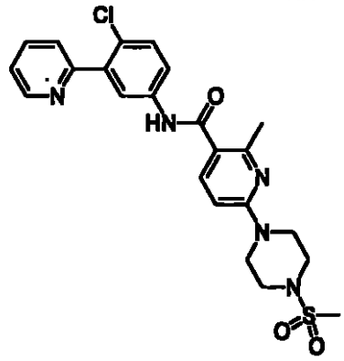
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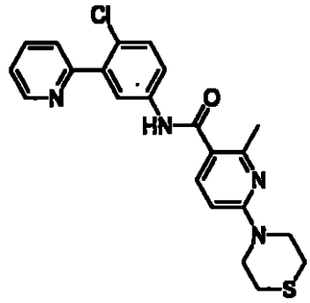
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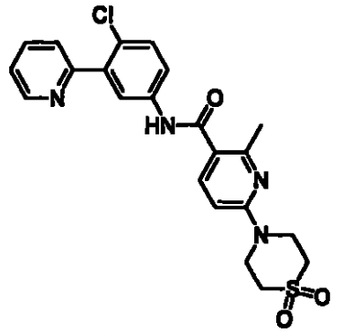
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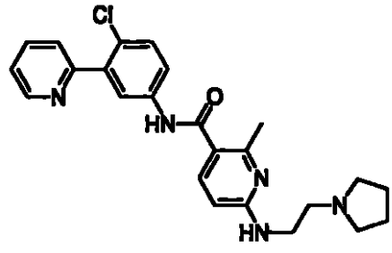
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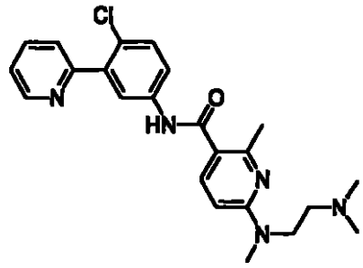
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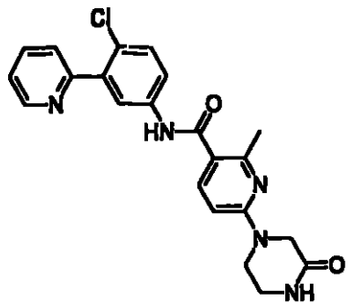
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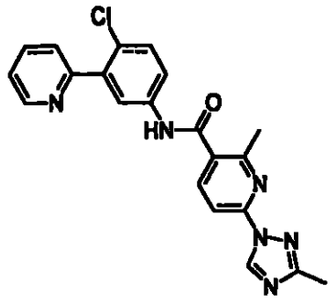
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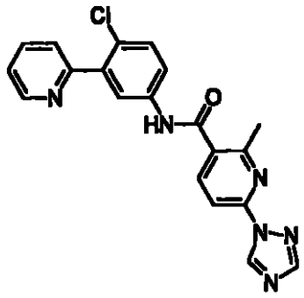
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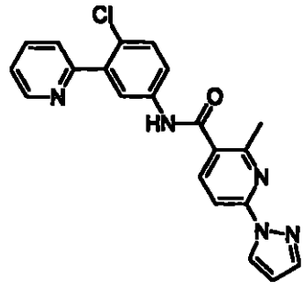
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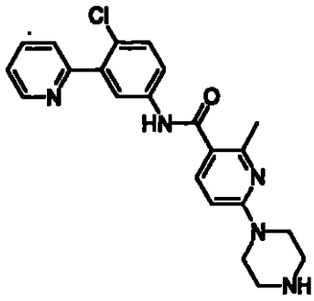
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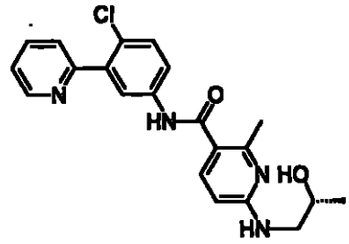
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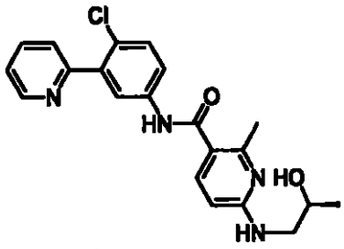
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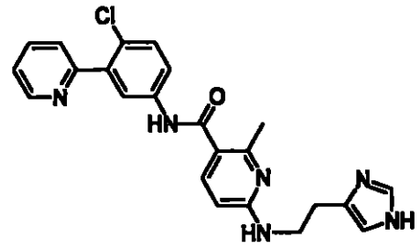
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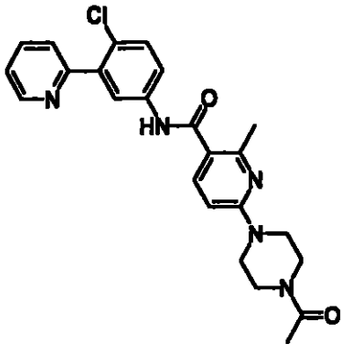
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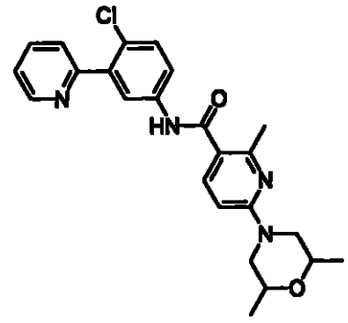
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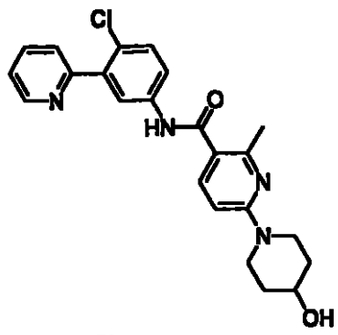


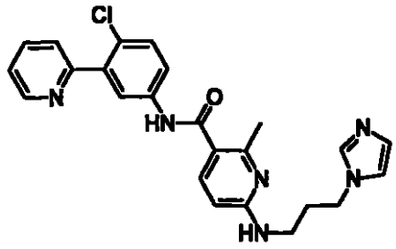
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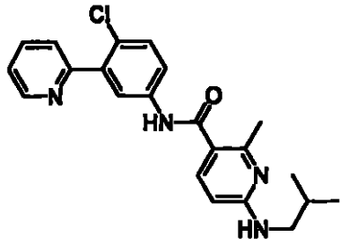


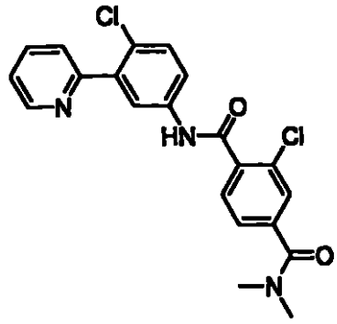
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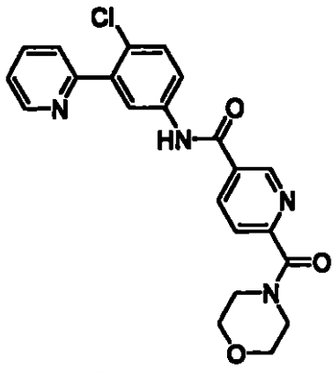


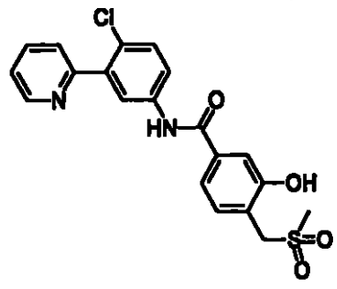
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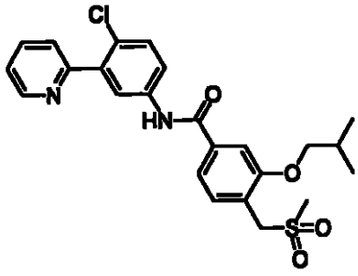
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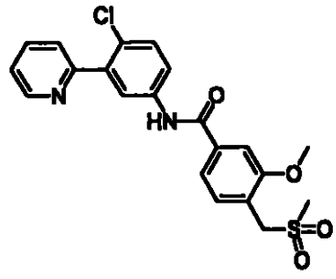
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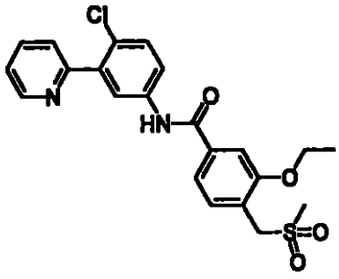
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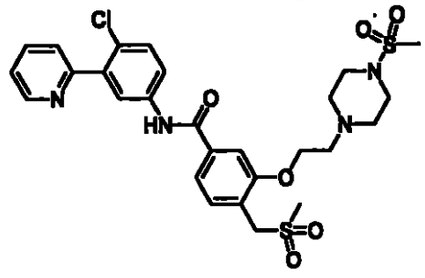
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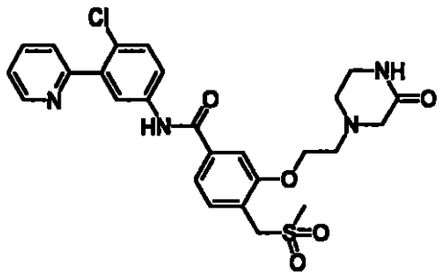
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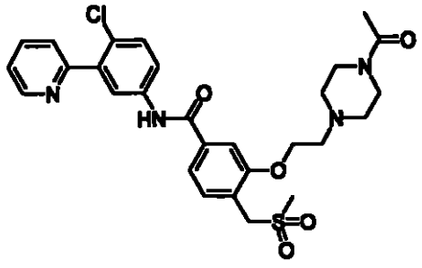
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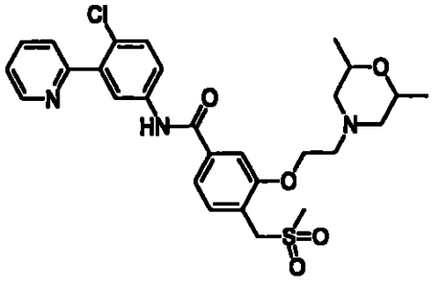
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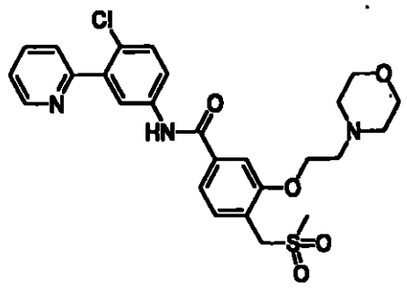
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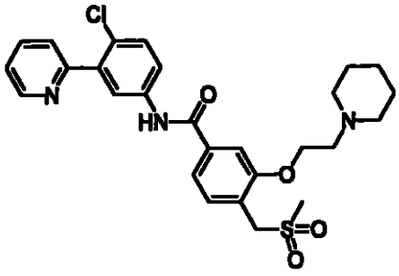
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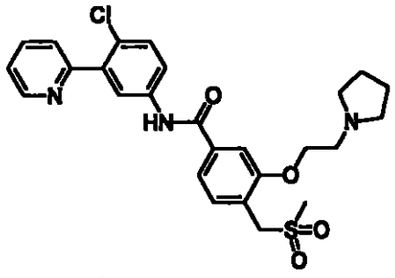
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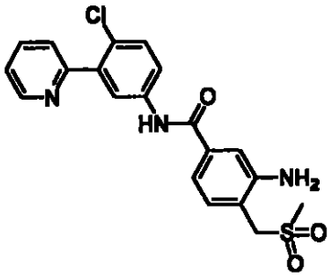
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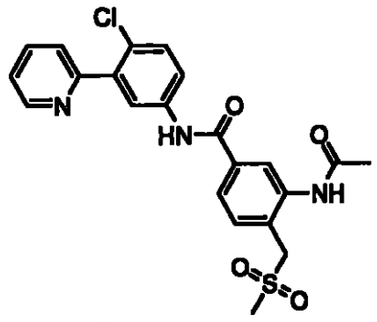
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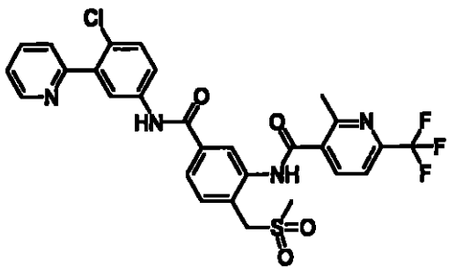
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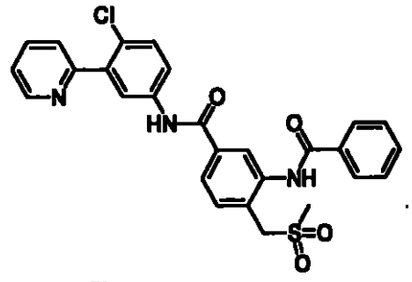
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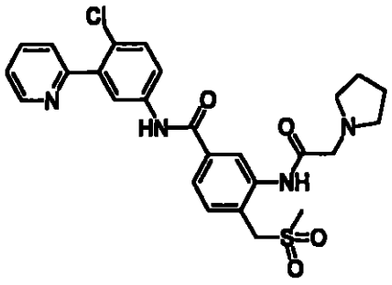
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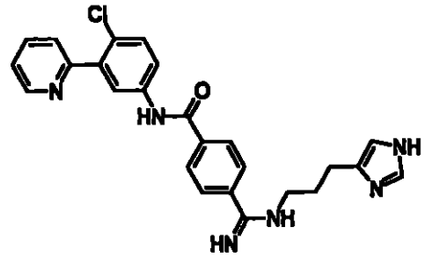
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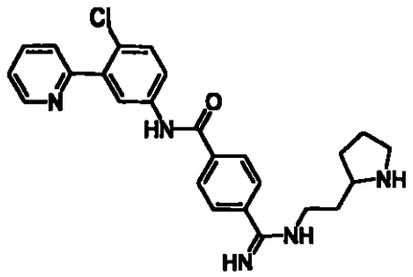
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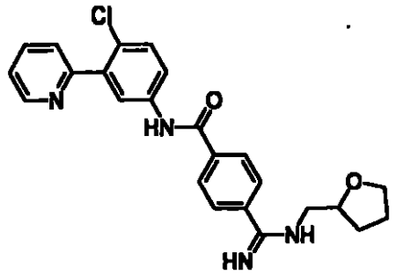
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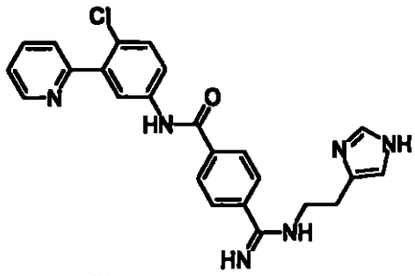
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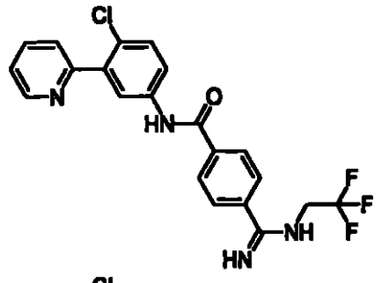
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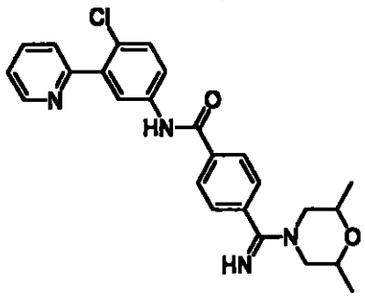
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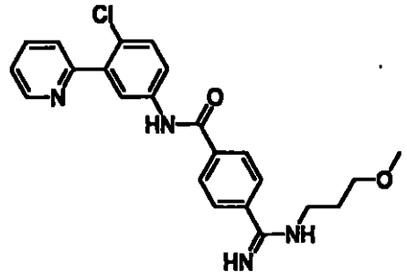
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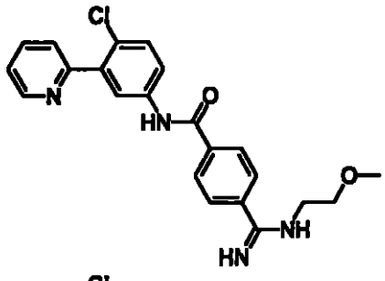
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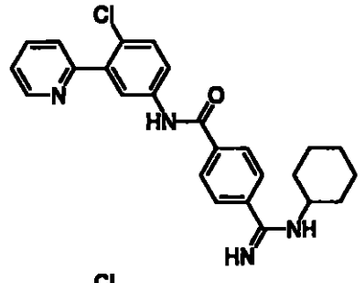
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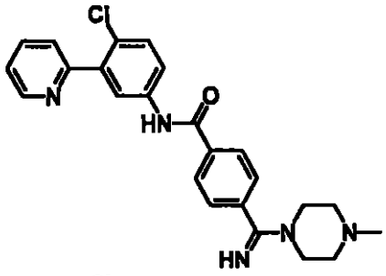
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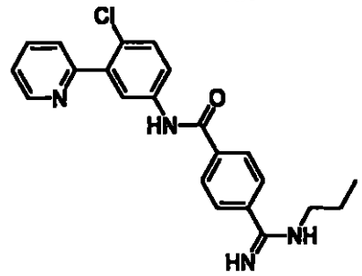
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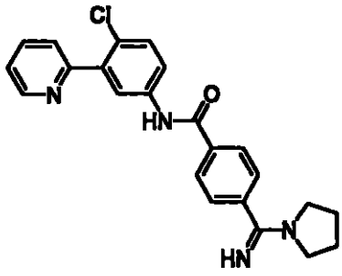
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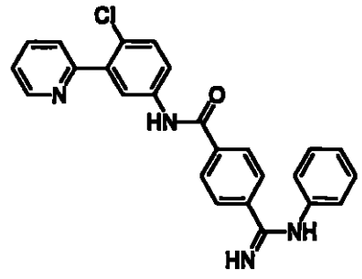
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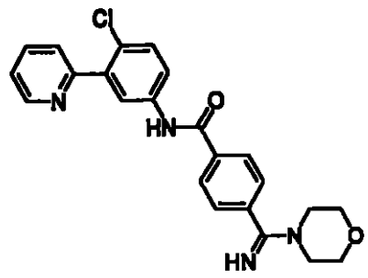
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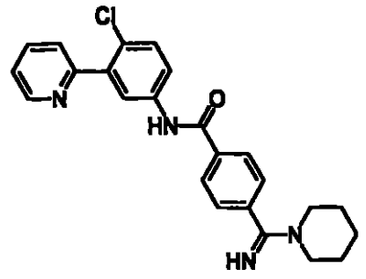
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Compounds of the invention may contain one or more asymmetric carbon atoms. Accordingly, the compounds may exist as diastereomers, enantiomers or mixtures thereof. The syntheses of the compounds may employ racemates, diastereomers or enantiomers as starting materials or as intermediates. Diastereomeric compounds may be separated by chromatographic or crystallization methods. Similarly, enantiomeric mixtures may be separated using the same techniques or others known in the art. Each of the asymmetric carbon atoms may be in the R or S configuration and both of these configurations are within the scope of the invention.

The invention also encompasses prodrugs of the compounds described above. Suitable prodrugs include known amino-protecting and carboxy-protecting groups which are released, for example hydrolyzed, to yield the parent compound under physiologic conditions. A particular class of prodrugs are compounds in which a nitrogen atom in an amino, amidino, aminoalkyleneamino, iminoalkyleneamino or guanidino group is substituted with a hydroxy (OH) group, an alkylcarbonyl (-CO-R) group, an alkoxycarbonyl (-CO-OR), an acyloxyalkyl-alkoxycarbonyl (-CO-O-R-O-CO-R) group where R is a monovalent or divalent group and as defined above or a group having the formula -C(O)-O-CP1P2-haloalkyl, where P1 and P2 are the same or different and are H, lower alkyl, lower alkoxy, cyano, halo lower alkyl or aryl. Prodrug compounds may be prepared by reacting the compounds of the invention described above with an activated acyl compound to bond a nitrogen atom in the compound of the invention to the carbonyl of the activated acyl compound. Suitable activated carbonyl compounds contain a good leaving group bonded to the carbonyl carbon and include acyl halides, acyl amines, acyl pyridinium salts, acyl alkoxides, in particular acyl phenoxides such as p-nitrophenoxy acyl, dinitrophenoxy acyl, fluorophenoxy acyl, and difluorophenoxy acyl. The reactions are generally exothermic and are carried out in inert solvents at reduced temperatures such as –78 to about 50 °C. The reactions are usually also carried out in the presence of an inorganic base such as potassium carbonate or sodium bicarbonate, or an organic base such as an amine, including pyridine, TEA, etc. One manner of preparing prodrugs is described in USSN 08/843,369 filed April 15, 1997

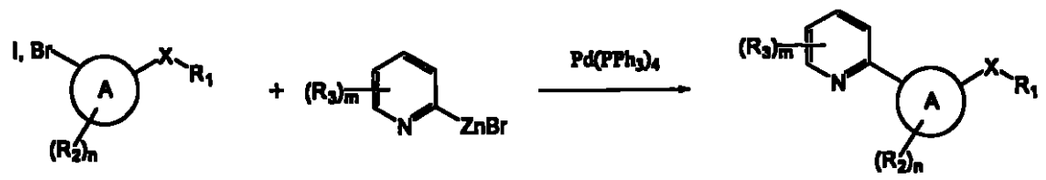
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(corresponding to PCT publication WO9846576) the contents of which are incorporated herein by reference in their entirety.

SYNTHESIS

Compounds of the invention are prepared using standard organic synthetic techniques from commercially available starting materials and reagents. It will be appreciated that synthetic procedures employed in the preparation of compounds of the invention will depend on the particular substituents present in a compound and that various protection and deprotection procedures may be required as is standard in organic synthesis. Compounds of the invention in which Y is absent may prepared by a Negishi coupling procedure according to the following general scheme 1:

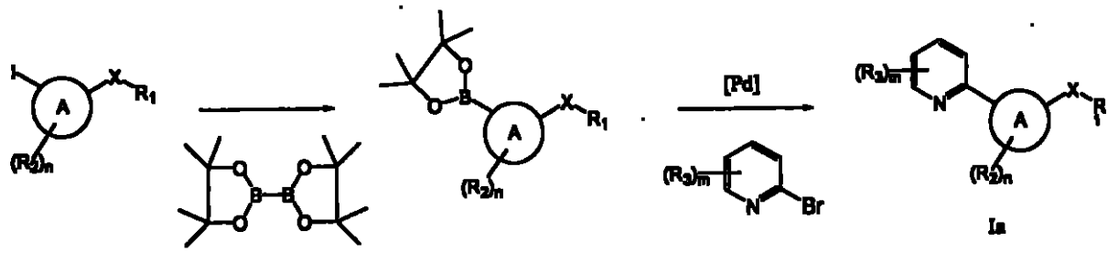
scheme 1



Ia

in which the pyridyl zinc bromide (or alternatively pyridylzinc chloride) is reacted with an iodo or bromo substituted ring A to give the final compound Ia. Alternatively, compounds Ia of the invention may be prepared using a Suzuki coupling reaction of a borylated ring A to provide direct linkage between the appropriate pyridyl and ring A according to scheme 2.

scheme 2

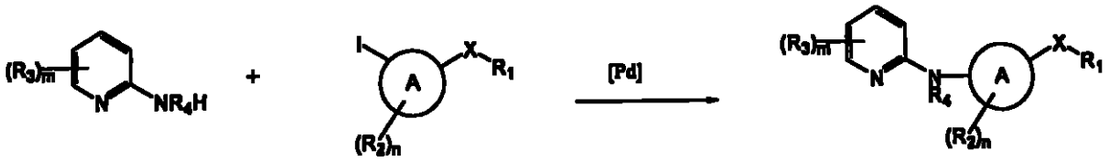


Ia

A halogen-substituted ring A is reacted with a boron ester such as pinacol diborane in the presence of palladium catalyst such as $PdCl_2(dppf)$ and the resulting boronate ester is heated with a 2-halogen-substituted pyridine and a palladium catalyst to give a final compound Ia of the invention.

Compounds of the invention in which Y is NR_4 may prepared by palladium catalyzed amination of halogen-substituted ring A with the desired 2-aminopyridine according to scheme 3.

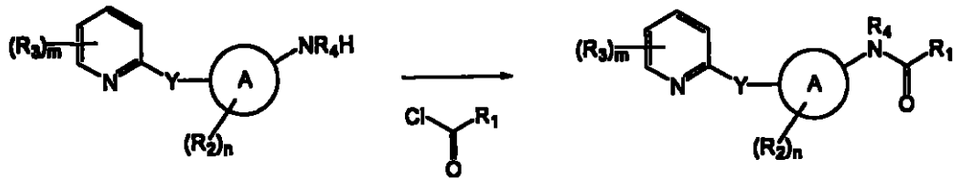
scheme 3



Ib

Compounds of the invention in which X is NR_4CO may be prepared by the general scheme 4 in which amine-substituted ring A is reacted with the desired acid chloride Cl-C(O)-R_1.

scheme 4

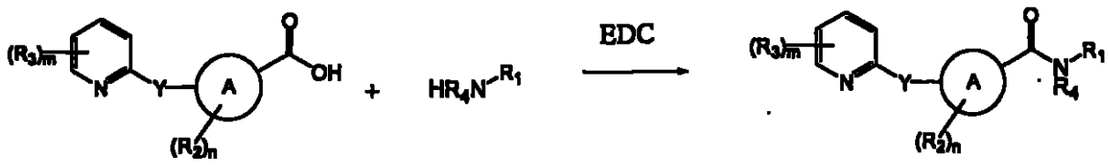


Alternatively, such compounds may be prepared from by EDC catalyzed coupling of a carboxy-substituted ring A with an amine-substituted R_1 group, i.e. R_1-NR_4H. The same scheme may be used to prepare thioamide compounds of the invention, i.e. X is $NR_4C(S)$, by employing an appropriate thio acid chloride Cl-C(S)-R_1 in the acylation step.

Compounds of the invention in which X is $C(O)NR_4$ may be similarly prepared by reacting an amine-substituted ring A with a carboxy-substituted R_1 group and EDC catalyst according to scheme 5.

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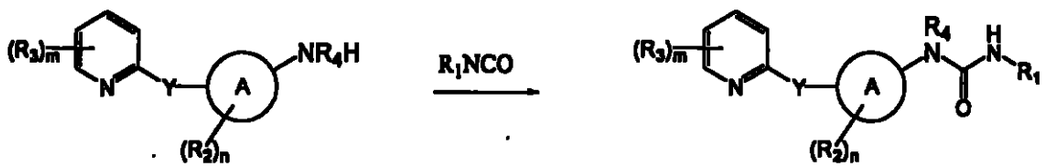
scheme 5



A similar scheme may be used to prepare thioamide compounds of the invention, i.e. X is $C(S)NR_4$, by employing an appropriate thioic acid-substituted ring A (e.g. -C(S)OH) or by converting the amide with Lawesson's reagent..

Compounds of the invention in which X is $NR_4C(O)NH$ may be prepared according to the general scheme 6 by reacting amine-substituted ring A with the appropriate isocyanate R_1-NCO.

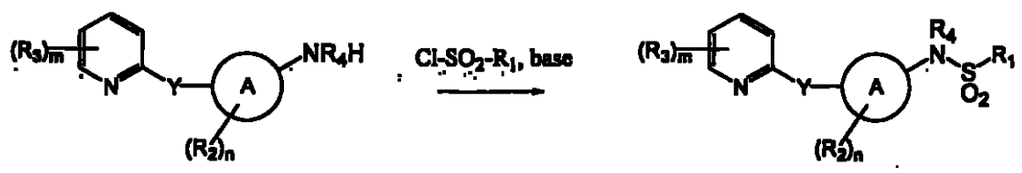
Scheme 6



The same scheme may be used to prepare thiourea compounds of the invention, i.e. X is $NR_4C(S)NH$, by employing an appropriate isothiocyanate R_1-NCS in place of the isocyanate R_1-NCO.

Compounds of the invention in which X is NR_4SO_2 may be prepared according to the general scheme 7 by reacting an amine-substituted ring A with the appropriate sulfonyl chloride R_1-$S(O_2)Cl$ in the presence of a non-nucleophilic base such as TEA or diisopropylethylamine to form the desired sulfonamide .

Scheme 7

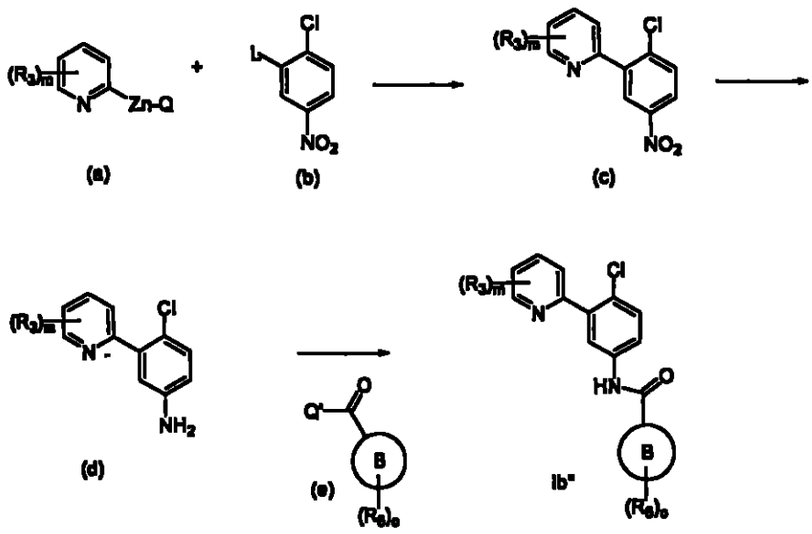


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Compounds of the invention in which X is NR_4SO are similarly prepared using the appropriate sulfinyl chloride R_1-SO-Cl instead of the sulfonyl chloride R_1-S(O_2)Cl.

Compounds of the invention having the structure of formula Ib' in which X is NHCO (i.e. formula Ib'') may be prepared according to the general scheme 8 in which R_3, R_6, m and o are as defined herein and Q is Cl, Br or I; Q' is halogen, OH, OR wherein R is an activating group; L is Br, I or OTf (e.g. O-SO2-CF_3):

Scheme 8



The zinc halide pyridine reagent (a) is reacted with 2-chloro-5-nitro-benzene reagent (b) in a Negishi coupling reaction in the presence of a suitable catalyst such as palladium tetrakis(triphenylphosphine) complex ($Pd(PPh_3)_4$). In a particular embodiment, the palladium tetrakis(triphenylphosphine) catalyst is stablized with triphenylphosphine (PPh_3). In a particular embodiment Q is Br. In a particular embodiment L is I. In a particular embodiment, the coupling reaction is performed from about 50°C to about 60°C.

The nitrobenzene reagent (b) may be obtained from activating the corresponding amine (i.e. 2-chloro-5-nitroaniline) in an aqueous sulfuric acid solution with sodium nitrite and displacing with an L group (e.g. with KI, KBr). In a particular embodiment, L is I. In a particular embodiment the reaction is performed at less than about 15°C.

The resulting intermediate (c) is reduced, for example with Fe, Zn or $SnCl_2$ in presence of acid to give the amine intermediate (d). In a particular embodiment, intermediate (c) is reduced with Fe,

for example, in the presence of AcOH in EtOH. In a particular embodiment, intermediate (c) is reduced with Zn, for example in the presence of AcOH in EtOH. In a partiuclar embodiment, intermediate (c) is reduced with $SnCl_2$, for example in the presence of HCl in EtOH. In a particular embodiment the reduction reaction is performed at about 60°C.

Finally, intermediate (d) is reacted with an activated acid (e) to yield final compound Ib''. In a particular embodiment, the activated acid (e) is an acid halide (e.g. Q' is chloride) or activated ester (e.g. Q' is O-EDC). In a particular embodiment the final reaction is performed at about 0°C.

The compounds of the invention inhibit the hedgehog signaling and are useful for the treatment of cancers associated with aberrant hedgehog signaling, for example when Patched fails to, or inadequately, represses Smoothened (Ptc loss-of-function phenotype) and/or when Smoothened is active regardless of Patched repression (Smo gain-of-function phenotype). Examples of such cancer types include basal cell carcinoma, neuroectodermal tumors such as medullablastoma, meningioma, hemangioma, glioblastoma, pancreatic adenocarcinoma, squamous lung carcinoma, small-cell lung carcinoma, non-small cell lung carcinoma, chondrosarcoma, breast carcinoma, rhabdomyosarcoma, oesophageal cancer, stomach cancer, biliary tract cancer, renal carcinoma, thyroid carcinoma. Compounds of the invention may be administered prior to, concomitantly with, or following administration of other anticancer treatments such as radiation therapy or chemotherapy. Suitable cytostatic chemotherapy compounds include, but are not limited to (i) antimetabolites, such as cytarabine, fludarabine, 5-fluoro-2'-deoxyuiridine, gemcitabine, hydroxyurea or methotrexate; (ii) DNA-fragmenting agents, such as bleomycin, (iii) DNA-crosslinking agents, such as chlorambucil, cisplatin, cyclophosphamide or nitrogen mustard; (iv) intercalating agents such as adriamycin (doxorubicin) or mitoxantrone; (v) protein synthesis inhibitors, such as L-asparaginase, cycloheximide, puromycin or diphteria toxin; (Vi) topoisomerase I poisons, such as camptothecin or topotecan; (vii) topoisomerase II poisons, such as etoposide (VP-16) or teniposide; (viii) microtubule-directed agents, such as colcemid, colchicine, paclitaxel, vinblastine or vincristine; (ix) kinase inhibitors such as flavopiridol, staurosporin, STI571 (CPG 57148B) or UCN-01 (7-hydroxystaurosporine); (x) miscellaneous investigational agents such as thioplatin, PS-341, phenylbutyrate, ET-18- OCH_3, or farnesyl transferase inhibitors (L-739749, L-744832); polyphenols such as quercetin, resveratrol, piceatannol, epigallocatechine gallate, theaflavins, flavanols, procyanidins, betulinic acid and derivatives thereof; (xi) hormones such as glucocorticoids or fenretinide; (xii) hormone antagonists, such as tamoxifen, finasteride or LHRH antagonists. In a particular embodiment,

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compounds of the present invention are coadministered with a cytostatic compound selected from the group consisting of cisplatin, doxorubicin, taxol, taxotere and mitomycin C.

Another class of active compounds which can be used in the present invention are those which are able to sensitize for or induce apoptosis by binding to death receptors ("death receptor agonists"). Such agonists of death receptors include death receptor ligands such as tumor necrosis factor a (TNF-α), tumor necrosis factor ß (TNF-ß, lymphotoxin-α) , LT-ß (lymphotoxin-ß), TRAIL (Apo2L, DR4 ligand), CD95 (Fas, APO-1) ligand, TRAMP (DR3, Apo-3) ligand, DR6 ligand as well as fragments and derivatives of any of said ligands. In a particular embodiment, the death receptor ligand is TNF-α. In another particular embodiment the death receptor ligand is Apo2L/TRAIL. Furthermore, death receptors agonists comprise agonistic antibodies to death receptors such as anti-CD95 antibody, anti-TRAIL-R1 (DR4) antibody, anti-TRAIL-R2 (DR5) antibody, anti-TRAIL-R3 antibody, anti-TRAIL-R4 antibody, anti-DR6 antibody, anti-TNF-Rl antibody and anti-TRAMP (DR3) antibody as well as fragments and derivatives of any of said antibodies.

For the purpose of sensitizing cells for apoptosis, the compounds of the present invention can be also used in combination with radiation therapy. The phrase "radiation therapy" refers to the use of electromagnetic or particulate radiation in the treatment of neoplasia. Radiation therapy is based on the principle that high-dose radiation delivered to a target area will result in the death of reproducing cells in both tumor and normal tissues. The radiation dosage regimen is generally defined in terms of radiation absorbed dose (rad), time and fractionation, and must be carefully defined by the oncologist. The amount of radiation a patient receives will depend on various consideration including the location of the tumor in relation to other organs of the body, and the extent to which the tumor has spread. Examples of radiotherapeutic agents are provided in, but not limited to, radiation therapy and is known in the art (Hellman, Principles of Radiation Therapy, Cancer, in Principles I and Practice of Oncology, 24875 (Devita et al., 4th ed., vol 1, 1993). Recent advances in radiation therapy include three-dimensional conformal external beam radiation, intensity modulated radiation therapy (IMRT), stereotactic radiosurgery and brachytherapy (interstitial radiation therapy), the latter placing the source of radiation directly into the tumor as implanted "seeds". These newer treatment modalities deliver greater doses of radiation to the tumor, which accounts for their increased effectiveness when compared to standard external beam radiation therapy.

Ionizing radiation with beta-emitting radionuclides is considered the most useful for radiotherapeutic applications because of the moderate linear energy transfer (LET) of the ionizing

particle (electron) and its intermediate range (typically several millimeters in tissue). Gamma rays deliver dosage at lower levels over much greater distances. Alpha particles represent the other extreme, they deliver very high LET dosage, but have an extremely limited range and must, therefore, be in intimate contact with the cells of the tissue to be treated. In addition, alpha emitters are generally heavy metals, which limits the possible chemistry and presents undue hazards from leakage of radionuclide from the area to be treated. Depending on the tumor to be treated all kinds of emitters are conceivable within the scope of the present invention. Furthermore, the present invention encompasses types of non-ionizing radiation like e.g. ultraviolet (UV) radiation, high energy visible light, microwave radiation (hyperthermia therapy), infrared (IR) radiation and lasers. In a particular embodiment of the present invention UV radiation is applied.

Compounds of the invention inhibit angiogenesis and are therefore useful in the treatment of diseases or conditions mediated by angiogenesis such as tumors, in particular solid tumors such as colon, lung, pancreatic, ovarian, breast and glioma. Furthermore, compounds of the invention are useful for treating macular degeneration e.g. wet age-related macular degeneration. Compounds of the invention are also useful for treating inflammatory/immune diseases such as Crohn's, inflammatory bowel disease, Sjogren's syndrome, asthma, organ transplant rejection, systemic lupus erythmatoses, rheumatoid arthritis, psoriatic arthritis, psoriasis and multiple sclerosis. Compounds of the invention are also useful as a depilatory.

The invention also includes pharmaceutical compositions or medicaments containing the compounds of the invention and a therapeutically inert carrier, diluent or excipient, as well as methods of using the compounds of the invention to prepare such compositions and medicaments. Typically, the compounds of the invention used in the methods of the invention are formulated by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed into a galenical administration form. The pH of the formulation depends mainly on the particular use and the concentration of compound, but may range from about 3 to about 8. A particular formulation is an acetate buffer at pH 5. The compounds for use herein may be in a sterile formulation. The compound may be stored as a solid composition, although lyophilized formulations or aqueous solutions are acceptable.

The composition of the invention will be formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the

particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The "effective amount" of the compound to be administered will be governed by such considerations, and is the minimum amount necessary to decrease hedgehog pathway signaling or else is the minimum amount necessary to cause reduction in size, volume or mass of a tumor that is responsive to hedgehog signaling, or a reduction in the increase in size, volume or mass of such a tumor relative to the increase in the absence of administering the compound of the invention. Alternatively "effective amount" of the compound means the amount necessary to reduce the number of malignant cells or the rate in increase of the number of malignant cells. Alternatively, "effective amount" is the amount of the compound of the invention required to increase survival of patients afflicted with an anti-hedgehog pathway sensitive tumor. Such amount may be below the amount that is toxic to normal cells, or the mammal as a whole. With respect to non-malignant indications, "effective amount" means the amount of compound of the invention required to decrease severity of the particular indication or symptoms thereof.

Generally, the initial pharmaceutically effective amount of the compound of the invention administered parenterally per dose will be in the range of about 0.01 to about 100 mg/kg, for example about 0.1 to about 20 mg/kg of patient body weight per day, for example about 0.3 to about 15 mg/kg/day. Oral unit dosage forms, such as tablets and capsules, may contain from about 25 to about 1000 mg of the compound of the invention.

The compound of the invention may be administered by any suitable means, including oral, topical, transdermal, parenteral, subcutaneous, rectal, intraperitoneal, intrapulmonary, and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. An example of a suitable oral dosage form is a tablet containing about 25mg, 50mg, 100mg, 250mg, or 500mg of the compound of the invention compounded with about 90-30 mg anhydrous lactose, about 5-40 mg sodium croscarmellose, about 5-30mg polyvinylpyrrolidone (PVP) K30, and about 1-10 mg magnesium stearate. The powdered ingredients are first mixed together and then mixed with a solution of the PVP. The resulting composition can be dried, granulated, mixed with the magnesium stearate and compressed to tablet form using conventional equipment. An aerosol formulation can be prepared by dissolving the compound, for example 5-400 mg, of the invention in a suitable buffer solution, e.g. a phosphate buffer, adding a tonicifier, e.g. a salt such sodium chloride, if desired. The solution is typically filtered, e.g. using a 0.2 micron filter, to remove impurities and contaminants. Topical formulations include ointments, creams, lotions,

powders, solutions, pessaries, sprays, aerosols and capsules. Ointments and creams may be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents and/or solvents. Such bases may include water and/or an oil such a liquid paraffin or a vegetable oil such as arachis oil or castor oil or a solvent such as a polyethylene glycol. Thickening agents which may be used include soft paraffin, aluminum stearate, cetostearyl alcohol, polyethylene glycols, microcrystalline wax and beeswax. Lotions may be formulated with an aqueous or oily base and may contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents or thickening agents. Powders for external application may be formed with the aid of any suitable powder base e.g. talc, lactose or starch. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilizing agents or suspending agents.

EXAMPLES

The invention will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the invention. Abbreviations used herein are as follows:

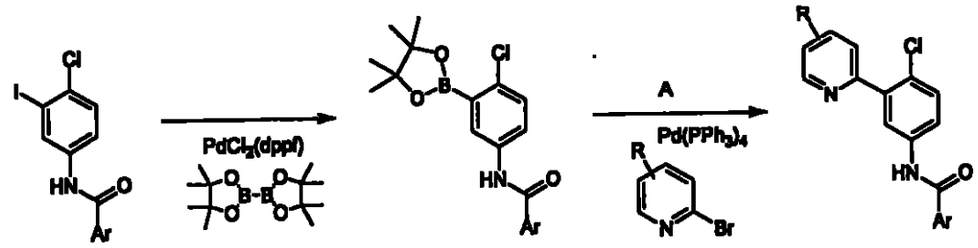
BuOH: butanol;
DIPEA: diisopropylethylamine;
DMA: NN-dimethylacetamide;
DMAP: 4-dimethylaminopyridine;
DME: 1,2-dimethoxyethane;
DMF: dimethylformamide;
EDC: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide;
HATU: O-(7-Azobenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate;
HPLC: high pressure liquid chromatography
MPLC: medium pressure liquid chromatography
NBS: N-Bromosuccinimide;
TEA: Triethylamine;
TASF: tris(dimethylamino)sulfonium difluorotrimethylsilicate;
THF: tetrahydrofuran;
EtOH: Ethanol;
MeOH: Methanol;
□L: microlitre

All reagents were obtained commercially unless otherwise noted. Reactions were performed using oven-dried glassware under an atmosphere of nitrogen. Air and moisture sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated under reduced pressure (ca. 15 mm Hg) by rotary evaporation. Unless otherwise noted all solvents used were obtained commercially. Chromatographic purification of products was accomplished by use of an Isco CombiFlash Companion and media. Reaction times are given for illustration only. The course of reactions was followed by thin-layer chromatography (TLC) and liquid chromatography-mass spectrometry (LC-MS). Thin-layer chromatography (TLC) was performed on EM Science silica gel 60 F_{254} plates (250 μm). Visualization of the developed chromatogram was accomplished by fluorescence quenching. LC-MS were acquired with a Shimadzu 10AD LC on a Phenomenex column (50 x 4.6 mm, 5 μm) operating at 3 mL/min. A Shimadzu SPD-10A detector monitoring at 214 and 254 nm was used. Single quadrupole mass spectrometry was performed on an Applied Biosystems mass spectrometer. Nuclear magnetic resonance (NMR) spectra were acquired on a Varian Inova spectrometer operating at 400 MHz for ^1H and are referenced internally to tetramethylsilane (TMS) in parts per million (ppm). Data for ^1H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sext, sextet; hept, heptet; m, multiplet; bm, broad multiplet), and integration. The structure and purity of all final products were assessed by at least one of the following techniques: LC-MS, NMR, TLC.

Example 1 General Procedure

Compounds of examples 2-51 were prepared according to the following general procedures.

A: Suzuki Coupling Procedure

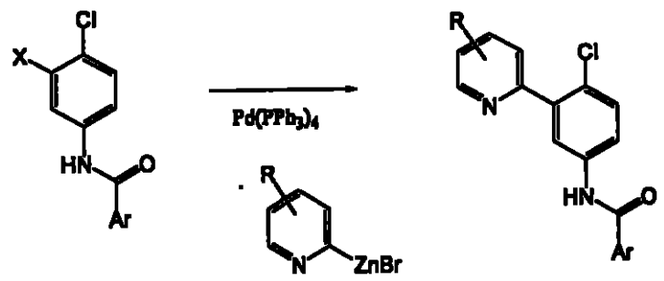


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2 M aq. Potassium carbonate (5.0 eq) and 4:1 toluene:ethanol mixture (2.5 mL) were added to a microwave vial charged with the appropriate boronate ester (2.6 eq), aryl halide (0.35 mmol, 1.0 eq), and $Pd(PPh_3)_4$ (0.04 eq). The vial was sealed and heated with stirring in the microwave to 160 °C for ten minutes. The solution was poured onto 2 M aq. Sodium hydroxide (20 mL), extracted with ethyl acetate (2 x 20 mL), dried ($MgSO_4$), and concentrated. Purification of the crude product by chromatography on silica gel (conditions given below) afforded the desired product.

B: Negishi Coupling Procedure



X = I or Br

R = H, 3-Me, 4-Me, 5-Me, 6-Me

Aryl zinc bromide (0.5 M in THF, 2.5 eq) was added to an oven-dried microwave vial charged with the appropriate aryl halide (1.0 eq) and $Pd(PPh_3)_4$ (0.04 eq). The vial was sealed and heated with stirring in the microwave to 140 °C for 10 minutes. The crude reaction mixture was concentrated and purified by chromatography on silica gel (conditions given below) to afford the desired product.

C: Iron Reduction of Aryl Nitro Group



R = I or pyridin-2-yl

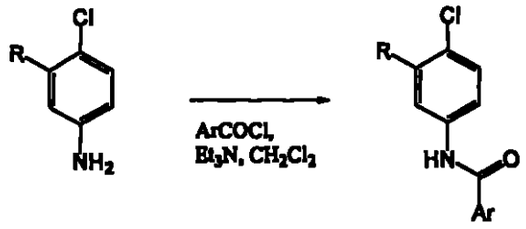
The appropriate nitro aryl (1 mmol, 1 eq) in AcOH/EtOH (1:1, 0.42 M) was added slowly to a solution of Iron powder (6.0 eq) in AcOH/EtOH (1:2, 2 M) at 60 °C. The solution was stirred at

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70 °C for 30-60 minutes. The reaction mixture was cooled to 23 °C, filtered through celite, washed with ethyl acetate, and concentrated. The oily residue was dissolved in ethyl acetate (30 mL), washed with saturated aq. $NaHCO_3$ (2 x 15 mL) and water (2 x 10 mL), dried ($MgSO_4$), and concentrated. The oily residue was used with out further purification.

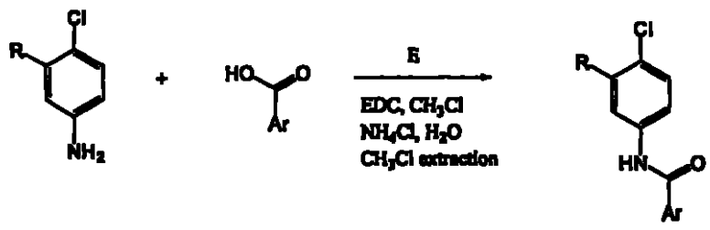
D: Amide Bond Formation



R = I or pyridin-2-yl

Acid chloride (1.05-1.1 eq) was added to a solution of aniline (1.0 eq) and TEA (1.1-1.5 eq) in methylene chloride at the indicated temperature. The solution was stirred for 0.5-3 hours, poured onto saturated aq. $NaHCO_3$, extracted twice with methylene chloride, dried ($MgSO_4$), and concentrated. Purification of the crude product by chromatography on silica gel (conditions given below) afforded the desired product.

E: EDC Amide Bond Formation



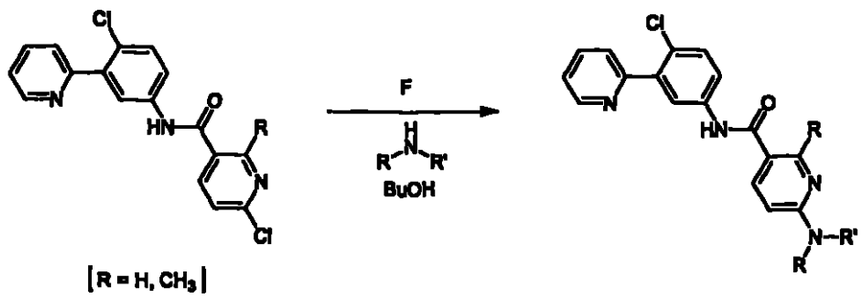
R = I or pyridin-2-yl

Carboxylic acid (1.1 eq) was added to a solution of aniline (1.0 eq) and EDC (1.4 eq) in methylene chloride (0.7 M in aniline). The solution was stirred at 23 °C for 2 hours, poured onto a 1:1 mixture of saturated aq. NH_4Cl and water, extracted twice with methylene chloride, dried ($MgSO_4$), and concentrated. Purification of the crude product by chromatography on silica gel (conditions given below) afforded the desired product.

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F: addition of amines to 2-chloropyridine

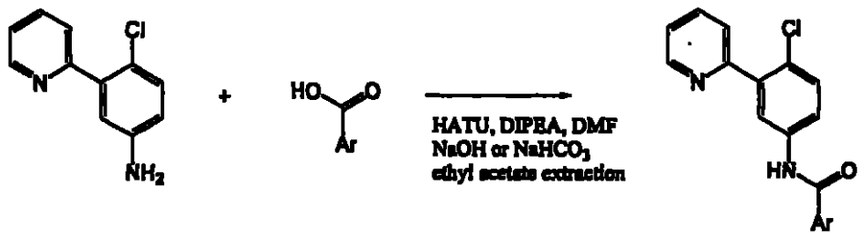


[R = H, CH_3]

NHRR' = ethanolamine, analine, benzylamine, 2-methylpropylamine, N-methylpiperazine, morpholine, 2-morpholinoethylamine

Primary or secondary amine (5 eq) in either BuOH or a mixture of BuOH/ethylene gylcol was heated to 170 to 220 °C for 20 min in a sealed tube. The BuOH was removed under reduced pressure. In cases where ethylene glycol was used, the reaction was diluted with water, and the product was extracted into ethyl acetate, dried ($MgSO_4$), and concentrated. The crude residue was purified by reverse phase HPLC to afford the desired product.

G: Amide bond coupling with HATU

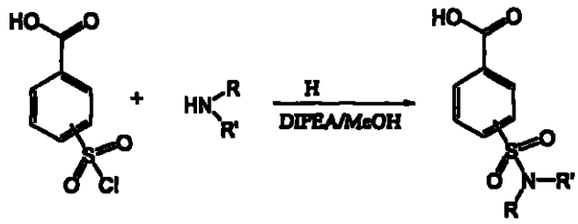


Aniline (1.0 eq) was added to a mixture of carboxylic acid (1.1 eq), HATU (1.1 eq) and DIPEA (2 eq) in DMF (0.1 - 0.2 M). After stirring overnight, the reaction mixture was diluted with 0.1 N sodium hydroxide or saturated $NaHCO_3$, extracted into ethyl acetate and the combined organic layers were washed with brine. The organic layer was dried ($MgSO_4$), concentrated and the crude mixture was purified by reverse phase HPLC.

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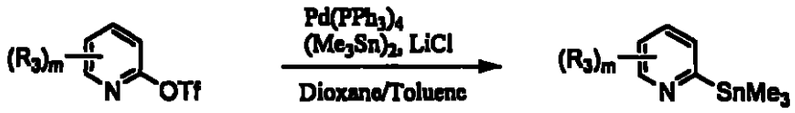
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H: Preparation of sulfonamide benzoic acids



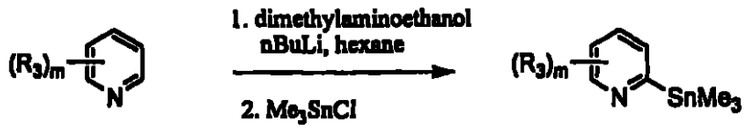
Chlorosulfonylbenzoic acid (1.0 eq) was added to a solution of amine (1.1 eq) in 10-20% DIPEA/methanol (1 M) at 4 °C. After 1 h, the reaction mixture was concentrated, and the crude residue was purified by reverse phase HPLC.

I: Stannylation of 2-pyridyl triflates



A solution of tetrakis-triphenylphosphinepalladium (0.04 eq.) in toluene (1 mL) was added to degassed solution of aryltriflate (1 eq), bis-trialkyltin (1.05 eq), and lithium chloride (3 eq) in dioxane. Heated to reflux for 2 hours, cooled to 23 °C, diluted with ethyl acetate, washed with 10% $NH_4OH_{(aq)}$ and brine, dried ($MgSO_4$) and concentrated. The crude material was used without further purification.

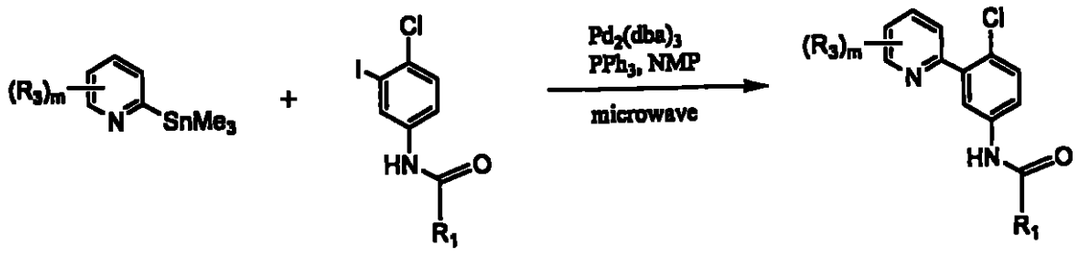
J: Stannylation of substituted pyridines



n-Butyl lithium (6 eq, 2.5 M in hexanes) was added dropwise to a solution of dimethylaminoethanol (3 eq) in hexane at 0 °C. The solution was stirred at 0 °C for thirty minutes before dropwise addition of the substituted pyridine (1 eq). The solution was stirred at 0 °C for an additional hour, then cooled to –78 °C. A solution of trialkyltin in hexane was added dropwise. The solution was stirred at –78 °C for thirty minutes, warmed to 0 °C, quenched with water, extracted twice with ether, dried ($MgSO_4$), and concentrated.

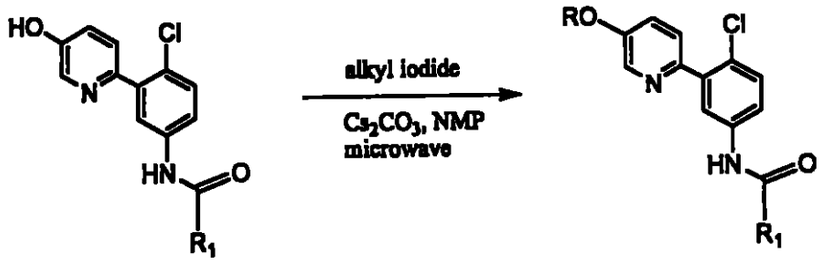
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K: Stille Coupling



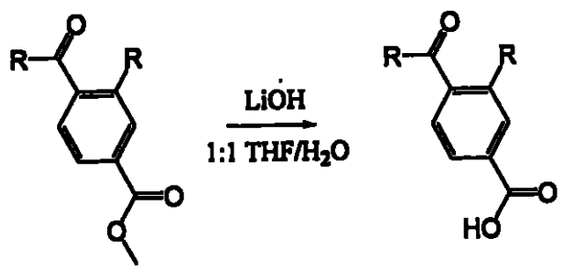
Palladium catalyst (0.02 eq) was added to a degassed solution of aryliodide (1 eq), arylstannane (2 eq), and triphenylphosphine (0.16 eq) in NMP. Heated in the microwave to 130 °C for 15 minutes. The reaction mixture was diluted with ethylacetate, washed with 10% $NH_4OH_{(aq)}$ and brine, dried ($MgSO_4$), concentrated and purified by silica gel chromatography.

L: Synthesis of alkylethers



A solution of hydroxypyridine (1 eq), alkyliodide (excess), and cesium carbonate in NMP was heated in the microwave to 100 °C for ten minutes. The reaction mixture was diluted with ethylacetate, washed with 10% $NH_4OH_{(aq)}$ and brine, dried ($MgSO_4$), concentrated and purified by silica gel chromatography.

M: Methyl Ester Saponification

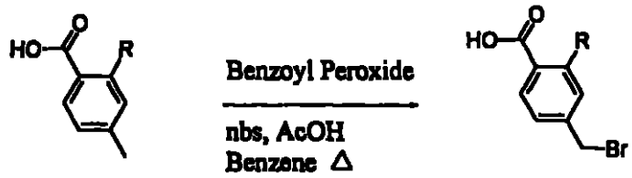


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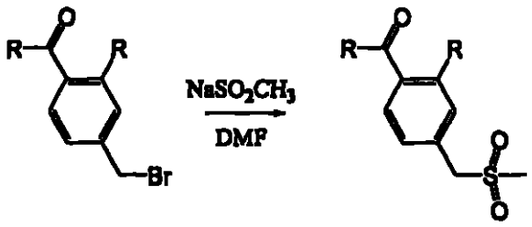
The methyl ester (1eq) was hydrolyzed with LiOH (2eq) in 50/50 THF/water mix. Upon completion of the reaction the THF was evaporated under reduced pressure and the solution is acidified with HCl to pH 2. The resultant solid was filtered and dried to give the pure acid.

N: Bromination in the presence of a free acid functionality



The paramethylbenzoic acid (1eq) was combined with Benzoyl Peroxide (0.1eq) and N-Bromosuccinimde (0.9eq) in a solution of 5%AcOH in Benzene and heated in the microwave at 120°C for 5-15minutes. The product was separated from the starting material and di-bromo product via ISCO flash chromatography with an ethyl acetate (with 1% AcOH) and hexanes solvent system.

O: Sodium Methanesulfinate displacement of Bromine

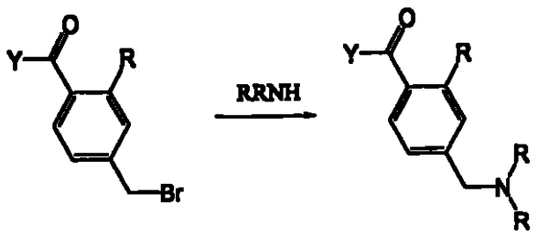


To the bromine starting material (1eq) was added sodium methanesulfinate (2eq) in DMF and heated to 120°C in the microwave for 5 minutes. Alternatively, the reaction was heated to 60°C in an oil bath for several hours until completed. Reaction mixture was concentrated under reduced pressure and extracted in ethyl acetate and water. The organic layer was dried over Magnesium Sulfate, filtered and concentrated in vacuo to yield generic methylsulfone.

P: Amine displacement of Bromine

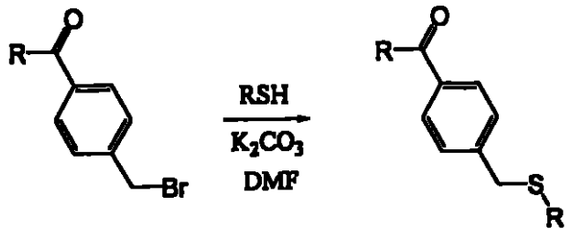
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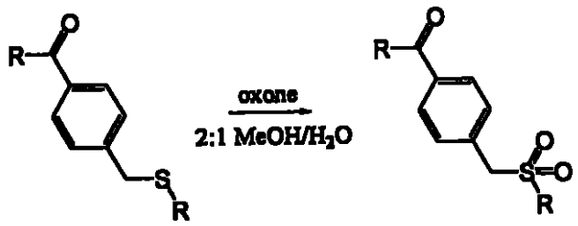
To the bromo starting material (1eq) was added appropriate amine (3eq) in either DMSO or BuOH and stirred at room temperature until complete. For less nucleophilic amines or anilines, the reactions were forced to completion using microwave conditions ranging from 150°-170°C for 15 minutes. Crude reactions were concentrated to dryness and either extracted with ethyl acetate and saturated bicarbonate if the reaction resulted in an intermediate or purified via HPLC if the reaction resulted in a final product.

Q: Thiol displacement of halogen



The paramethylbromo benzoate (1eq) was treated with Potassium (or Cesium) Carbonate (1.5eq) and appropriate thiol derivative (1,1eq) in DMF (or CH_3CN) and stirred overnight at room temperature. The DMF was evaporated in vacuo and the reaction was extracted with ethyl acetate and water. The organic layer was dried over Magnesium Sulfate , filtered and concentrated to yield the thiol or derivatized thiol compound.

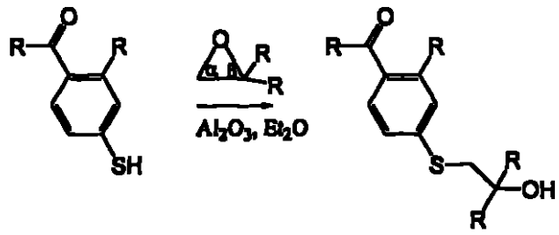
R: Oxone Oxidation



Derivatized thiol (1eq) was dissolved in MeOH while Oxone (2eq) was seperately dissolved in half the amount of water. Once all the oxone was dissolved, the solution was added to the thiol in MeOH solution at once and stirred until complete. The MeOH was evaporated in vacuo and the

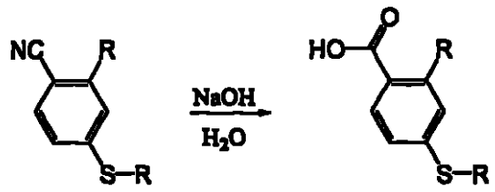
remaining water was extracted twice with Ethyl Acetate. The organic layer was dried over Magnesium Sulfate and concentrated to yield the sulfone.

S: Thiolysis of epoxides at alumina surfaces



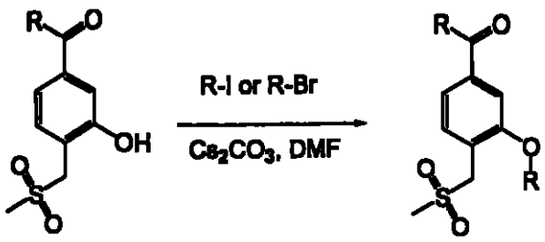
A mixture of epoxides (1.0 eq), thiophenol (1.5 eq) and neutral aluminum oxide (~70 eq) in diethyl ether was stirred for 3 h at room temperature while being monitored by TLC. The reaction mixture was filtered through Celite, washed with ethyl acetate and concentrated. Purified by silica gel chromatography (0-40% ethyl acetate/hexane) to yield β-hydroxysulfide product.

T: Conversion of nitrile group to carboxylic acid



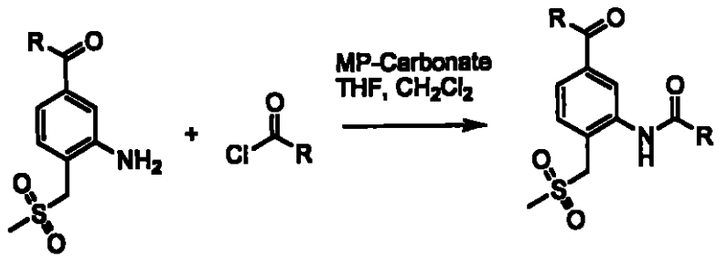
A solution of benzonitrile (1.0 eq) and sodium hydroxide (2.0 eq) in H_2O was heated to 120 °C for 2h. The reaction mixture was cooled to room temperature and acidified with HCl to pH 2. The resulting solid was filtered to afford the pure acid product.

U. Alkylation of phenols



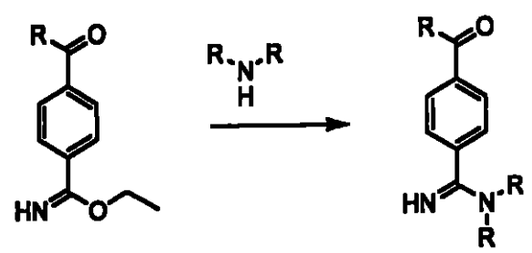
The phenol was dissolved in DMF (1.0 ml). Cesium carbonate (1.0 eq.) and an alkyl bromide or alkyl iodide (1.0 to 2.0 eq.) were added, and the reaction was stirred at room temperature for 18 hrs or 50°C for 1 to 24 hours. The reaction was quenched in water, and extracted with ethyl acetate twice. The organic extracts were washed with water once, brine once, dried with $MgSO_4$, and evaporated to a crude oil which was purified on reverse phase HPLC.

V. Amide bond formation with an acid chloride and an aniline



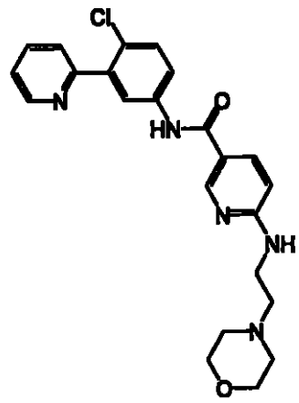
The aniline was dissolved in THF (1.5 ml) and dichloromethane (1.5 ml). MP-Carbonate (1.5 eq.) and an acid chloride (1.1 eq.) were added, and the solution was stirred at room temperature for 18 hours. The reaction was diluted with methanol and dichloromethane, and filtered to remove the MP-Carbonate. The mother liquors were evaporated to a solid and purified by reverse phase HPLC.

W. Amidine formation from an imidate



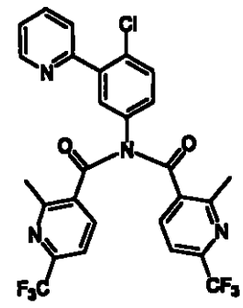
A solution of freshly formed imidate in methanol was treated with a primary or secondary amine (1.5 eq.) at room temperature for 18 hours. The methanol was removed on a rotary evaporator and the residue purified by reverse phase HPLC.

Example 2 6-(2-morpholinoethylamino)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)pyridine-3-carboxamide



Procedure F was performed using *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-chloro-3-carboxamide (50 mg) and 2-morpholinoethylamine in butanol (0.5 mL). The crude reaction was purified by reverse phase HPLC to yield 6-(2-morpholinoethylamino)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)pyridine-3-carboxamide as a white solid. MS (Q1) 438.3 $(M)^+$.

Example 3 *N,N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-bis[6-(trifluoromethyl)-2-methylpyridine-3]-carboxamide



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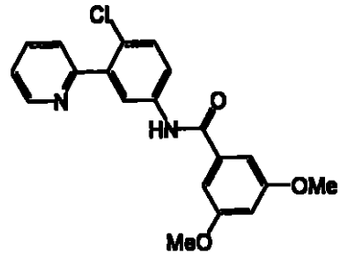
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Procedure B was performed with 2-pyridylzinc bromide (4 mL, 2.0 mmol, 0.5 M in THF) and 3-bromo-4-chloro-nitrobenzene (236 mg, 1.0 mmol). Purified by chromatography on silica gel (10% ethyl acetate/hexanes) to yield 2-(2-chloro-5-nitrophenyl)pyridine as a light yellow solid.

Procedure C was performed with 2-(2-chloro-5-nitrophenyl)pyridine (122 mg, 0.52 mmol) to yield 4-chloro-3-(pyridin-2-yl)aniline as a light yellow solid, which was used without further purification.

Procedure D was performed using 4-chloro-3-(pyridin-2-yl)aniline (40 mg, 0.2 mmol). The crude residue was purified by silica gel chromatography (15-60% ethyl acetate/hexanes) to yield *N,N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-bis[6-(trifluoromethyl)-2-methylpyridine-3]-carboxamide as an oily residue: TLC R_f = 0.42 (35% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.72 (m, 1H), 7.84 (d, 2H0, 7.77 (dd, 1H), 7.68 (m, 1H), 7.57 (d, 1H), 7.51 (m, 3H), 7.33 (m, 1H), 7.12 (dd, 1H), 2.78 (s, 6H); MS (Q1) 579 $(M)^+$.

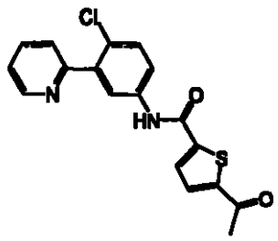
Example 4 *N*-(4-Chloro-3-(pyridin-3-yl)phenyl)-3,5-dimethoxybenzamide



4-Chloro-3-(pyridin-2-yl)aniline (40 mg, 0.2 mmol) was used in procedure D with 3,5-dimethoxybenzoyl chloride (43 mg, 0.216 mmol) at 23 °C for 2 hours. The crude residue was purified by crystallization (CH_2Cl_2/hexanes) to yield *N*-(4-chloro-3-(pyridin-3-yl)phenyl)-3,5-dimethoxybenzamide as an off-white solid: TLC R_f = 0.30 (15% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.72 (m, 1H), 7.91 (m, 1H), 7.88 (dd, 1H), 7.78 (m, 2H), 7.74 (dd, 1H), 748 (d, 1H), 7.35 (m, 1H), 6.96 (d, 2H), 6.62 (t, 1H), 3.82 (s, 6H); MS (Q1) 369 $(M)^+$.

Example 5 5-Acetyl-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)thiophene-2-carboxamide

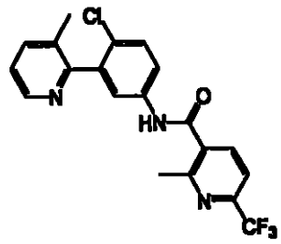
93
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4-Chloro-3-iodoaniline (2.5 g, 9.88 mmol) was used in Procedure E with 5-acetylthiophene-2-carboxylic acid (1.85 g, 10.8 mmol) at 23 °C for 2 hours. The crude material was purified by silica gel chromatography (20-100% ethyl acetate/hexanes) to yield 5-Acetyl-*N*-(4-chloro-3-iodophenyl)thiophene-2-carboxamide as a yellow solid.

5-Acetyl-*N*-(4-chloro-3-iodophenyl)thiophene-2-carboxamide (202 mg, 0.5 mmol) was used in Procedure B with 2-pyridylzincbromide (2.5 mL, 1.25 mmol, 0.5 M in THF). Purified by silica gel chromatography (10-100% ethyl acetate/hexanes) to yield 5-acetyl-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)thiophene-2-carboxamide as a yellow solid: TLC R_f = 0.19 (50% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.96 (bs, 1H), 8.67 (d, 1H), 7.79 (dt, 1H), 7.68 (m, 3H), 7.61 (d, 1H), 7.58 (d, 1H), 7.37 (d, 1H), 7.32 (m, 1H), 2.58 (s, 3H); MS (Q1) 357.0 $(M)^+$.

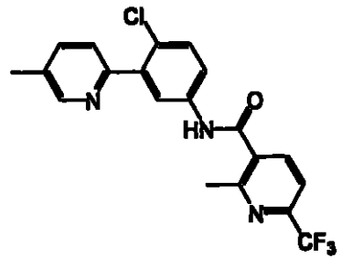
Example 6 *N*-(4-Chloro-3-(3-methylpyridin-2-yl)phenyl)-6-(trifluoromethyl)-2-methylpyridine-3-carboxamide



N-(4-Chloro-3-iodophenyl)-6-(trifluoromethyl)-2-methylpyridine-3-carboxamide (142 mg, 0.32 mmol) was used in Procedure B with 6-methyl-2-pyridylzinc bromide (1.75 mL, of a 0.5 M in THF). Purified by silica gel chromatography (5-100% Ethyl acetate/Hexanes) to yield *N*-(4-chloro-3-(3-methylpyridin-2-yl)phenyl)-6-(trifluoromethyl)-2-methylpyridine-3-carboxamide as a white solid: TLC R_f = 0.23 (30% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.81 (bs, 1H), 7.95 (dd, 1H), 7.67 (m, 3H), 7.53 (t, 2H), 7.38 (d, 1H), 7.07 (d, 1H), 2.71 (s, 3H), 2.43 (s, 3H); MS (Q1) 406.1 $(M)^+$.

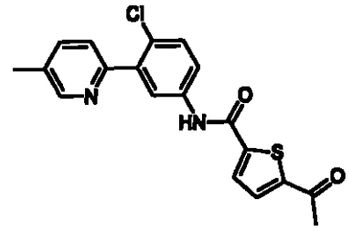
74
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Example 7 *N*-(4-Chloro-3-(5-methylpyridin-2-yl)phenyl)-6-(trifluoromethyl)-2-methylpyridine-3-carboxamide



N-(4-Chloro-3-iodophenyl)-6-(trifluoromethyl)-2-methylpyridine-3-carboxamide (150 mg, 0.34 mmol) was used in Procedure B with 4-methyl-2-pyridylzinc bromide (1.7 mL of a 0.5 M in THF). Purified by silica gel chromatography (5-75% Ethyl acetate/Hexanes) to yield *N*-(4-chloro-3-(5-methylpyridin-2-yl)phenyl)-6-(trifluoromethyl)-2-methylpyridine-3-carboxamide as a white solid: TLC R_f = 0.23 (35% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.62 (bs, 1H), 8.12 (dd, 1H), 7.89 (d, 1H), 7.58 (d, 1H), 7.47 (m, 3H), 7.18 (d, 1H), 6.89 (d, 1H), 2.62 (s, 3H), 2.38 (s, 3H); MS (Q1) 406.3 $(M)^+$.

Example 8 5-Acetyl-*N*-(4-chloro-3-(5-methylpyridin-2-yl)phenyl)thiophene-2-carboxamide

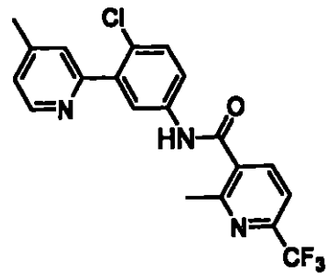


5-Acetyl-*N*-(4-chloro-3-iodophenyl)thiophene-2-carboxamide (203 mg, 0.5 mmol), was used in Procedure B with 4-methyl-2-pyridylzinc bromide (2.5 mL, 1.25 mmol, 0.5 M in THF). Purified by silica gel chromatography (30-100% ethyl acetate/hexanes) to yield 5-acetyl-*N*-(4-chloro-3-(5-methylpyridin-2-yl)phenyl)thiophene-2-carboxamide as a yellow solid: TLC R_f = 0.25 (50% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.52 (bs, 1H), 8.51 (d, 1H), 7.60 (m, 4H), 7.39 (s, 1H), 7.29 (d, 1H), 7.14 (d, 1H), 2.55 (s, 3H), 2.42 (s, 3H); MS (Q1) 371 $(M)^+$.

95

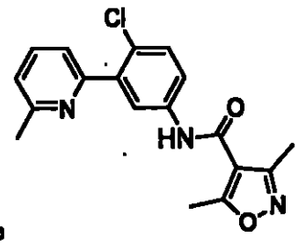
96

Example 9 *N*-(4-Chloro-3-(4-methylpyridin-2-yl)phenyl)-6-(trifluoromethyl)-2-methylpyridine-3-carboxamide



Procedure B was performed with *N*-(4-Chloro-3-iodophenyl)-6-(trifluoromethyl)-2-methylpyridine-3-carboxamide (440 mg, 1.0 mmol) and 4-methyl-2-pyridylzinc bromide (5 mL of a 0.5 M solution in THF). The crude residue was purified silica gel chromatography (5-100% Ethyl acetate/Hexanes) to yield *N*-(4-chloro-3-(4-methylpyridin-2-yl)phenyl)-6-(trifluoromethyl)-2-methylpyridine-3-carboxamide as a white solid: TLC R_f = 0.43 (35% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.39 (bs, 1H), 8.11 (dd, 1H), 7.87 (s, 1H), 7.61 (d, 1H), 7.59 (d, 1H), 7.49 (m, 3H), 2.66 (s, 3H), 2.21 (s, 3H); MS (Q1) 406.1 $(M)^+$.

Example 10 *N*-(4-chloro-3-(6-methylpyridin-2-yl)phenyl)-3,5-dimethylisoxazole-4-carboxamide

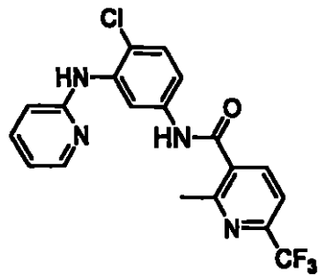


4-Chloro-3-iodoaniline (1.01 g, 4 mmol) was used in procedure E with 3,5-dimethyl-4-isoxazolecarboxylic acid (0.565 g, 4 mmol), EDC (1.32 g, 6.8 mmol), TEA (0.5 mL), DMAP (50 mg, 0.4 mmol) at 23 °C for overnight. The crude reaction was purified by silica gel chromatography (0-15% ethyl acetate/CH_2Cl_2) to yield 3,5-dimethyl-*N*-(4-chloro-3-iodophenyl)isoxazole-4-carboxamide as a white solid.

Procedure B was performed with 3,5-dimethyl-*N*-(4-chloro-3-iodophenyl)isoxazole-4-carboxamide (190 mg, 0.5 mmol) and 3-methyl-2-pyridylzinc bromide (2.5 mL of a 0.5 M solution in THF). The crude reaction was purified by silica gel chromatography (5-100% Ethyl acetate/Hexanes) to yield *N*-(4-chloro-3-(6-methylpyridin-2-yl)phenyl)-3,5-dimethylisoxazole-4-carboxamide as a white solid: TLC R_f = 0.43 (50% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.52 (bs, 1H), 7.68 (m, 2H), 7.48 (m, 3H), 2.70 (s, 3H), 2.49 (s, 3H), 2.21 (s, 3H); MS (Q1) 342.3 $(M)^+$.

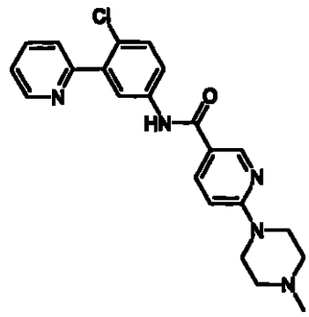
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Example 11 *N*-(4-chloro-3-(pyridin-2-ylamino)phenyl)-6-(trifluoromethyl)-2-methylpyridine-3-carboxamide



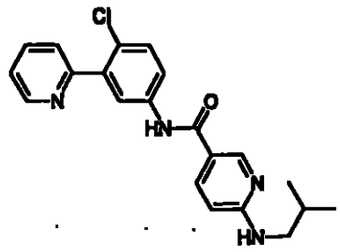
N-(4-Chloro-3-iodophenyl)-6-(trifluoromethyl)-2-methylpyridine-3-carboxamide (220 mg, 0.5 mmol), 2-aminopyridine (40 mg, 0.42 mmol), potassium *t*-butoxide (66 mg, 0.59 mmol), $Pd_2(dba)_3$ (20 mg, 0.21 mmol), dppf (24 mg, 0.042 mmol) in toluene (2.1 mL) were heated to 100 °C for 1.5 days. The solution was cooled to 23 °C, diluted with ether, filtered through celite, washed with ethyl acetate, and concentrated. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-ylamino)phenyl)-6-(trifluoromethyl)-2-methylpyridine-3-carboxamide as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.53 (s, 1H), 9.68 (s, 1H), 8.05 (m, 2H), 7.85 (m, 2H), 7.55 (d, 1H), 7.26 (d, 1H), 7.13 (dd, 1H), 6.91 (t, 1H), 6.88 (d, 1H), 2.75 (s, 3H); MS (Q1) 407.0 $(M)^+$.

Example 12 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(4-methylpiperazin-1-yl)pyridine-3-carboxamide



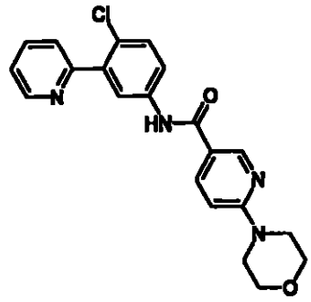
Procedure F was performed using *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-chloro-3-carboxamide (50 mg) and *N*-methylpiperazine in butanol (0.5 mL). The crude reaction was purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(4-methylpiperazin-1-yl)pyridine-3-carboxamide as a white solid. MS (Q1) 408.4 $(M)^+$.

Example 13 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(isobutylamino)pyridine-3-carboxamide



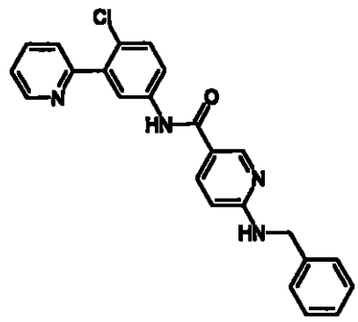
Procedure F was performed using *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-chloro-3-carboxamide (50 mg) and 2-methylpropylamine in butanol (0.5 mL). The crude reaction was purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(isobutylamino)pyridine-3-carboxamide as a white solid. MS (Q1) 381.1 $(M)^+$.

Example 14 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-morpholinopyridine-3-carboxamide



Procedure F was performed using *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-chloro-3-carboxamide (50 mg) and morpholine in butanol (0.5 mL). The crude reaction was purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-morpholinopyridine-3-carboxamide as a white solid. MS (Q1) 401.3 $(M)^+$.

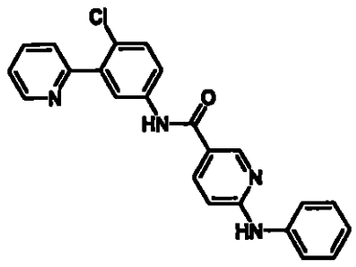
Example 15 6-(benzylamino)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)pyridine-3-carboxamide



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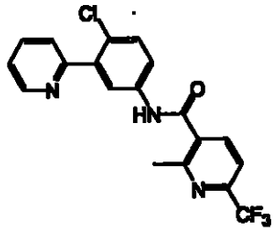
Procedure F was performed using *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-chloro-3-carboxamide (50 mg) and benzylamine in butanol (0.5 mL). The crude reaction was purified by reverse phase HPLC to yield 6-(benzylamino)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)pyridine-3-carboxamide as a white solid. MS (Q1) 415.1 $(M)^+$.

Example 16 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(phenylamino)pyridine-3-carboxamide



Procedure F was performed using *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-chloro-3-carboxamide (50 mg) and analine in butanol (0.5 mL). The crude reaction was purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(phenylamino)pyridine-3-carboxamide as a white solid. MS (Q1) 401.0 $(M)^+$.

Example 17 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-6-(trifluoromethyl)-2-methylpyridine-3-carboxamide



Procedure C was performed with 1-chloro-2-iodo-4-nitrobenzene (283 mg, 1 mmol) to produce 4-chloro-3-iodoaniline which was used without further purification.

Procedure D was performed with 4-chloro-3-iodoaniline (225 mg, 0.889 mmol) and 6-(trifluoromethyl)-2-methylpyridine-3-carbonyl chloride (237 mg, 0/93 mmol, 1.05 eq) at 0 °C for 30 minutes. The crude residue was purified by silica gel chromatography (2-50% ethyl acetate/hexanes) to yield *N*-(4-chloro-3-iodophenyl)-6-(trifluoromethyl)-2-methylpyridine-3-carboxamide as a white solid.

Procedure B was performed using *N*-(4-Chloro-3-iodophenyl)-6-(trifluoromethyl)-2-methylpyridine-3-carboxamide (88 mg, 0.2 mmol) with 2-pyridylzinc bromide (1 mL, 0.5 mmol, 0.5 M in THF). Purified by silica gel chromatography (10-80% ethyl acetate/hexanes) to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(trifluoromethyl)-2-methylpyridine-3-carboxamide as a yellow solid: TLC R_f= 0.28 (35% ethyl acetate/hexanes); TLC R_f= 0.28 (35% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) 8.88 (bs, 1H), 8.41 (d, 1H), 7.96 (dd, 1H), 7.74 (m, 4H), 7.52 (d, 1H), 7.22 (m, 1H), 2.75 (s, 3H); MS (Q1) 392 $(M)^+$.

An alternative synthetic procedure is as follows. 75g (435 mmol) of 2-chloro-5-nitroaniline was added to a solution of water (600 mL) and conc. sulfuric acid (60 mL) in a 3L 3-neck flask equipped for mechanical stirring. The solution was cooled to 0 °C and a solution of sodium nitrite (34.2 g, 496 mmol) in water (130 mL) was added slowly. The mixture was stirred for ½ hr. and then a solution of potassium iodide (130 g, 783 mmol) in water (520 mL) was added dropwise over ½ hr keeping the temperature below 15°C. The solution was stirred for 2 hr, then extracted with EtOAc (3 x 500 mL). The combined organic extracts were washed with sat. $Na_2S_2O_3$ (2x 500 mL), dried (Na_2SO_4), and concentrated. The crude iodide was dissolved in hot iPrOH (500 mL) and hexanes (200 mL) were added. The reaction was allowed to cool with stirring and the product was collected by suction filtration after stirring at 0°C for 2hr yielding 90g (318 mmol, 73%) 2-chloro-5-nitro-iodobenzene as a light tan crystalline solid.

The 2-chloro-5-nitro-iodobenzene (5g, 17.6 mmol) was dissolved in 5 mL DMA in an oven dried flask and a 0.5M solution of 2-pyridylzincbromide (53 mL, 26.5 mmol, 0.5 M in THF) was added. The solution was degassed with N_2 for ½ hr., the PPh_3 (0.185g, 0.7 mmol) and $Pd(PPh_3)_4$ (0.825g, 0.7 mmol) were added, rinsed in with several mLs THF and the solution was degassed for a further 10 min before heating to 60°C under N_2. The reaction was complete by TLC in ~8h, cooled to RT, and poured into a 1:1 mixture of EtOAc/2.5N NaOH (500 mL). This solution was stirred for 10 min, passed through a course fritted filter containing celite to remove the solid, and then extracted. The organics were washed with brine and concentrated to a brown solid. The combined aqueous layers were backextracted with Et_2O (1 x 200 mL). This was used to suspend the crude product, which was extracted with 1N HCl (1 x 200 mL, 3 x 100 mL). The combined aqueous extracts were cooled to 0°C, diluted with EtOAc (250 mL), and made basic with 10N NaOH (100 mL). This solution was separated, the aqueous layer extracted with EtOAc, and the combined organics were dried over Na_2SO_4 and charcoal with stirring. This solution was filtered through celite and concentrated to yield pure 4-chloro-3-(pyridin-2-yl)nitrobenzene (2.47g, 10.5 mmol, 60% yield) which was used in the next reaction without further purification.

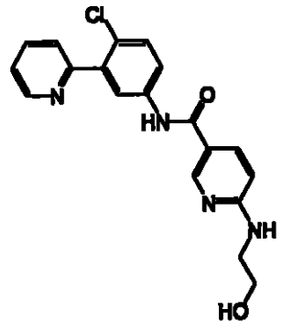
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4-chloro-3-(pyridin-2-yl)nitrobenzene (1.47g, 6.26 mmol) was suspended in EtOH (35 mL), and the $SnCl_2$ (3.87g; 20.4 mmol) and conc. HCl (5 mL) were added and rinsed in with a further 5 mLs EtOH. The solution was placed in a 40°C oil bath and heated to 60°C. The solution was stirred at 60°C for 1 ½ hr., cooled to RT and diluted with 1 N HCl (100 mL). This solution was poured into an Et_2O/1 N HCl solution (100 mL:150 mL) and extracted. The aqueous layer was diluted with EtOAc (250 mL), cooled to 0°C, and made basic with 10 N NaOH (50 mL). This solution was extracted (EtOAc, 2x), and the combined organics were washed with brine and dried over Na_2SO_4 and charcoal. Suction filtration through celite gave a clear colorless solution which was concentrated to yield 4-chloro-3-(pyridine-2-yl)aniline (1.21g, 5.93 mmol, 94% yield) as a cream colored crystalline solid which was used in the next reaction without further purification.

6-(trifluoromethyl)-2-methylpyridine-3-carbonyl chloride (1.68g, 7.51 mmol) in 3 mL THF was added dropwise to a solution of 4-chloro-3-(pyridine-2-yl)aniline (1.21g, 5.93 mmol) in THF (15 mL) at 0°C. The solution was stirred for 10 min., poured into EtOAc and washed with saturated aq. $NaHCO_3$ (2x), and brine. The organics were dried (Na_2SO_4) and concentrated. The crude product was suspended in iPrOAc/Et_2O (10 mL, 1:1), stirred at 0°C for ½ hr, and collected by suction filtration to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(trifluoromethyl)-2-methylpyridine-3-carboxamide (2.04g, 5.21 mmol, 88% yield) as a white solid: TLC R_f = 0.28 (35% EtOAc/Hex); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.88 (bs, 1H), 8.41 (d, 1H), 7.96 (dd, 1H), 7.74 (m, 4H), 7.52 (d, 1H), 7.22 (m, 1H), 2.75 (s, 3H); MS (Q1) 392 $(M)^+$.

Example 18 6-(2-hydroxyethylamino)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)pyridine-3-carboxamide

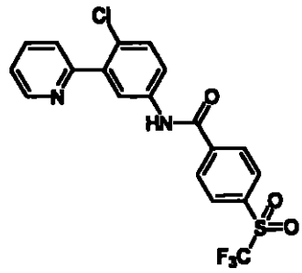


Procedure F was performed using *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-chloro-3-carboxamide (50 mg) and ethanolamine in butanol (0.5 mL). The crude reaction was purified by reverse phase HPLC to yield 6-(2-hydroxyethylamino)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)pyridine-3-carboxamide as a white solid. MS (Q1) 369.0 $(M)^+$.

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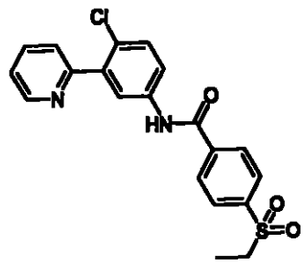
Example 19 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(trifluoromethylsulfonyl)benzamide



4-(trifluoromethylthio)benzoic acid (200 mg, 0.9 mmol) was dissolved in water (2 mL) and acetic acid (4 mL) and treated with potassium permanganate (711 mg, 4.5 mmol) at room temperature. The reaction was allowed to stir for 16 h, diluted with ethyl acetate and washed with water. The organic layer was dried ($MgSO_4$) and concentrated to yield 4-(trifluoromethylsulfone)benzoic acid.

General procedure G was performed using 4-(trifluoromethylsulfone)benzoic acid and 4-chloro-3-(pyridin-2-yl)aniline. The crude reaction mixture was purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(trifluoromethylsulfonyl)benzamide. MS (Q1) 440.95 $(M)^+$.

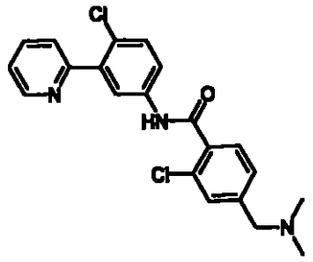
Example 20 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(ethylsulfonyl)benzamide



General procedure G was performed using 4-(ethylthio)benzoic acid and 4-chloro-3-(pyridin-2-yl)aniline to produce *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(ethylthio)benzamide.

A solution of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(ethylthio)benzamide (40 mg, 0.11 mmol) in MeOH (3 mL), cooled to 0° C was treated with oxone (133 mg, 0.22 mmol), and the ice bath was removed. After 1h of stirring, the reaction mixture was concentrated, and the residue was dissolved in ethyl acetate. The organic solution was washed with water, dried ($MgSO_4$) and concentrated. The crude reaction mixture was purified by reverse phase HPLC to yeild *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(ethylsulfonyl)benzamide. MS (Q1) 401.0 $(M)^+$.

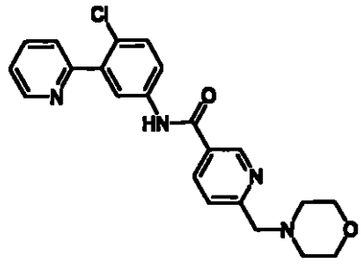
Example 21 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((dimethylamino)methyl) benzamide



General procedure G was used to couple 4-(BOC-aminomethyl)-2-chloro-benzoic acid and 4-chloro-3-(pyridin-2-yl)aniline to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)-phenyl)-4-(BOC-aminomethyl)-benzamide with . The crude reaction mixture was treated to TFA and trace water for 1 h prior to concentrating to dryness to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)-phenyl)-4-(aminomethyl)-benzamide.

2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(aminomethyl)benzamide (80 mg, 0.20 mmol) was dissolved in DMF (5 mL) and treated with AcOH (10 uL), paraformaldehyde (43 mg, 0.47 mmol), and sodium triacetoxyborohydride (125 mg, 0.59 mmol). After stirring for 16 h, the solvent was evaporated and the residue was dissolved in ethyl acetate. The organic layer was washed with 1 N Sodium hydroxide, dried ($MgSO_4$) and concentrated. The crude product was purified by reverse phase HPLC to produce 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((dimethylamino)methyl) benzamide. MS (Q1) 400.0 $(M)^+$.

Example 22 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(morpholinomethyl)pyridine-3-carboxamide

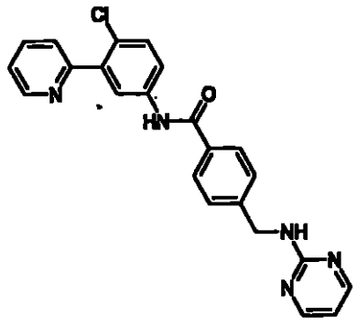


6-methylnicotinic acid (100 mg 0.14 mmol) was dissolved in 10% AcOH/benzene (1 mL) and treated with NBS (117 mg, 0.18 mmol) and benzoylperoxide (18 mg, 0.07 mmol). The reaction mixture was heated in a sealed microwave reactor at 120° C for 1 min. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), concentrated and purified by silica gel chromatography to yield 6-(bromomethyl)pyridine-3-carboxylic acid.

6-(bromomethyl)pyridine-3-carboxylic acid was coupled to 4-chloro-3-(pyridin-2-yl)aniline as described in general procedure E to yield 6-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)pyridine-3-carboxamide.

6-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)pyridine-3-carboxamide was dissolved in DMSO (1 mL) treated with morpholine (33 uL) for 1 h. The reaction was concentrated, and the crude residue was purified by reverse phase HPLC to produce *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(morpholinomethyl)pyridine-3-carboxamide. MS (Q1) 409.3 $(M)^+$.

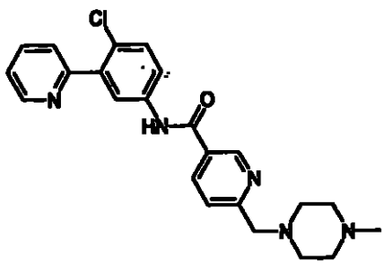
Example 23 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((pyrimidin-2-ylamino)methyl)benzamide



4-(bromomethyl)benzoic acid was coupled to 4-chloro-3-(pyridin-2-yl)aniline as described in general procedure E to yield 4-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide.

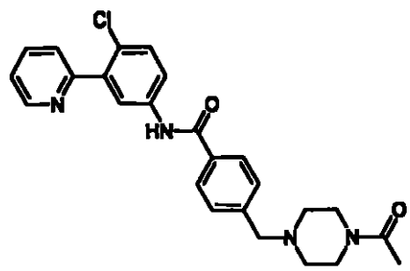
4-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide (85 mg) was dissolved in DMSO (0.5 mL) and treated with 2-aminopyridine (59 mg) at 150° C in a sealed microwave reactor for 5 min. The reaction mixture was concentrated, and the crude residue was purified by reverse phase HPLC to produce pure *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((pyrimidin-2-ylamino)methyl)benzamide. MS (Q1) 416.3 $(M)^+$.

Example 24 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-((4-methylpiperazin-1-yl)methyl)pyridine-3-carboxamide



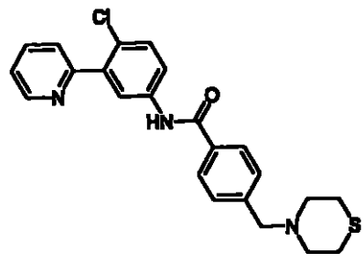
6-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)pyridine-3-carboxamide was dissolved in 1 mL of DMSO and stirred for 1 h with *N*-methylpiperazine. The reaction was concentrated, and the crude residue was purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-((4-methylpiperazin-1-yl)methyl)pyridine-3-carboxamide as a pure product. MS (Q1) 422.3 $(M)^+$.

Example 25 4-((4-acetylpiperazin-1-yl)methyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl) benzamide



6-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)pyridine-3-carboxamide (85 mg) was dissolved in DMSO (1 mL) and stirred for 1 h with N-acetylpiperazine. The reaction mixture was concentrated, and the crude residue was purified by revered phase HPLC to yield 4-((4-acetylpiperazin-1-yl)methyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl) benzamide. MS (Q1) 449.1 $(M)^+$.

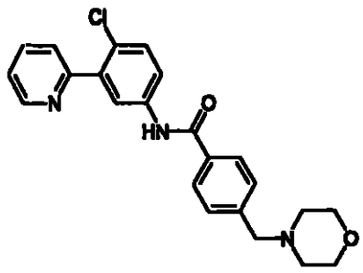
Example 26 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(thiomorpholinomethyl)benzamide



4-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide (85 mg) was dissolved in DMSO (1 mL) and stirred for 1 h with thiomorpholine. The reaction mixture was concentrated, and the crude residue was purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(thiomorpholinomethyl)benzamide. MS (Q1) 424.0 $(M)^+$.

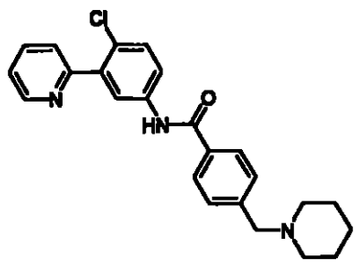
Example 27 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(morpholinomethyl)benzamide

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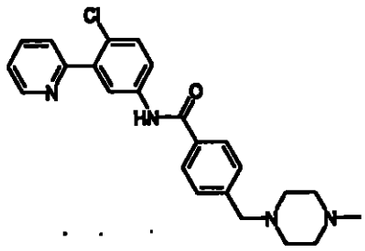
4-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide (85 mg) was dissolved in DMSO (1 mL) and stirred for 1 h with morpholine. The reaction mixture was concentrated, and the crude residue was purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(morpholinomethyl)benzamide. MS (Q1) 408.4 $(M)^+$.

Example 28 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((piperidin-1-yl)methyl)benzamide



4-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide (85 mg) was dissolved in DMSO (1 mL) and stirred for 1 h with piperdine. The reaction mixture was concentrated, and the crude residue was purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((piperidin-1-yl)methyl)benzamide. MS (Q1) 406.4 $(M)^+$.

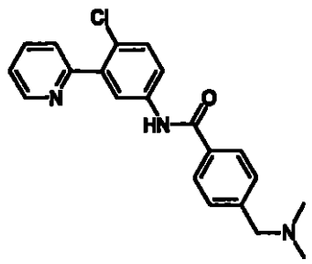
Example 29 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((4-methylpiperazin-1-yl)methyl) benzamide



4-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide (85 mg) was dissolved in DMSO (1 mL) and stirred for 1 h with methylpiperazine. The reaction mixture was concentrated, and the crude residue was purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((4-methylpiperazin-1-yl)methyl) benzamide. MS (Q1) 421.3 $(M)^+$.

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107

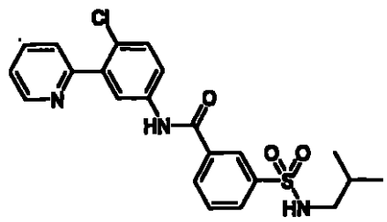
Example 30 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((dimethylamino)methyl)benzamide



Procedure G was used to couple BOC-4-(aminomethyl)benzoic acid (48 mg) with 4-chloro-3-(pyridin-2-yl)aniline (35 mg). The crude reaction mixture was treated with TFA (1 mL) containing trace amounts of water for 1 h. The reaction mixture was concentrated to yield 4-(aminomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide.

4-(aminomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide (80 mg) was dissolved in DMF (5 mL) and treated with AcOH (10 □L), paraformaldehyde (48 mg), and sodium triacetoxyborohydride (125 mg) for 16 h. The reaction mixture was concentrated, and the crude residue was dissolved in ethyl acetate and washed with 1 N sodium hydroxide, dried ($MgSO_4$) and concentrated. The crude product was purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((dimethylamino)methyl)benzamide. MS (Q1) 365.0 $(M)^+$.

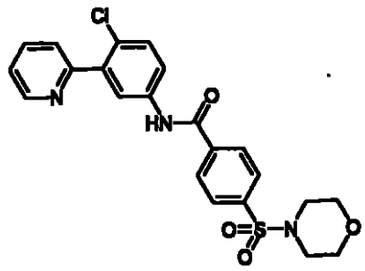
Example 31 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-[(2-methylpropyl)aminosulfonyl]-benzamide



Procedure H was performed to couple 3-(chlorosulfonyl)benzoic acid with *sec*-butyl amine to produce 3-(sec-butylsulfamoyl)benzoic acid which was purified by reverse phase HPLC.

Procedure G was used to couple 3-(sec-butylsulfamoyl)benzoic acid with 4-chloro-3-(pyridin-2-yl)aniline (28 mg) to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-[(2-methylpropyl)aminosulfonyl]-benzamide. MS (Q1) 444.0 $(M)^+$.

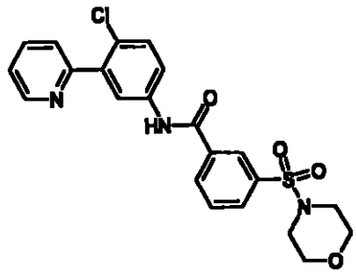
Example 32 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(4-morpholinylsulfonyl)-benzamide



Procedure H was performed to couple 4-(chlorosulfonyl)benzoic acid with morpholine to produce 4-(morpholinosulfamoyl)benzoic acid which was purified by reverse phase HPLC.

Procedure G was used to couple 4-(morpholinosulfamoyl)benzoic acid with 4-chloro-3-(pyridin-2-yl)aniline (34 mg) to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(4-morpholinylsulfonyl)-benzamide. MS (Q1) 458.1 $(M)^+$.

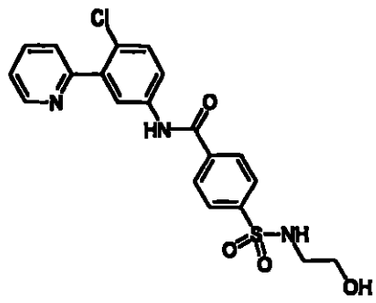
Example 33 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-(4-morpholinylsulfonyl)-benzamide



Procedure H was performed to couple 3-(chlorosulfonyl)benzoic acid with morpholine to produce 3-(morpholinosulfamoyl)benzoic acid which was purified by reverse phase HPLC.

Procedure G was used to couple 3-(morpholinosulfamoyl)benzoic acid with 4-chloro-3-(pyridin-2-yl)aniline (25 mg) to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-(4-morpholinylsulfonyl)-benzamide. MS (Q1) 458.1 $(M)^+$.

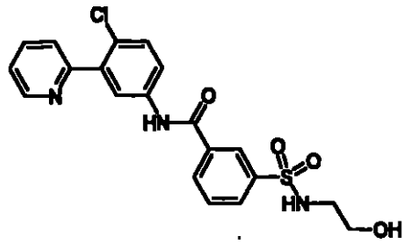
Example 34 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-[(2-hydroxyethyl)amino]sulfonyl]-benzamide



Procedure H was performed to couple 4-(chlorosulfonyl)benzoic acid with ethanolamine to produce 4-(2-hydroxyethylsulfamoyl)benzoic acid which was purified by reverse phase HPLC.

Procedure G was used to couple 4-(2-hydroxyethylsulfamoyl)benzoic acid with 4-chloro-3-(pyridin-2-yl)aniline (42 mg) to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-[(2-hydroxyethyl)amino]sulfonyl]-benzamide. MS (Q1) 431.9 $(M)^+$.

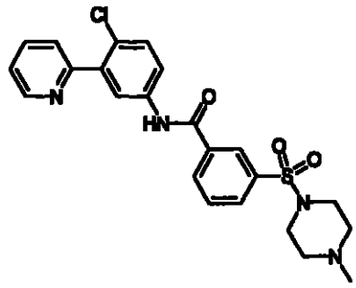
Example 35 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-[(2-hydroxyethyl)amino]sulfonyl]-benzamide



Procedure H was performed to couple 3-(chlorosulfonyl)benzoic acid with ethanolamine to produce 3-(2-hydroxyethylsulfamoyl)benzoic acid which was purified by reverse phase HPLC.

Procedure G was used to couple 3-(2-hydroxyethylsulfamoyl)benzoic acid with 4-chloro-3-(pyridin-2-yl)aniline (42 mg) to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-[(2-hydroxyethyl)amino]sulfonyl]-benzamide. MS (Q1) 432.0 $(M)^+$.

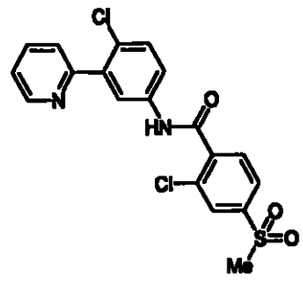
Example 36 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-(4-morpholinylsulfonyl)-benzamide



Procedure H was performed to couple 3-(chlorosulfonyl)benzoic acid with piperazine to produce 3-(N-methylpiperazinosulfamoyl)benzoic acid which was purified by reverse phase HPLC.

Procedure G was used to couple 3-(N-methylpiperazinosulfamoyl)benzoic acid with 4-chloro-3-(pyridin-2-yl)aniline (50 mg) to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-(4-morpholinylsulfonyl)-benzamide. MS (Q1) 471.0 $(M)^+$.

Example 37 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide

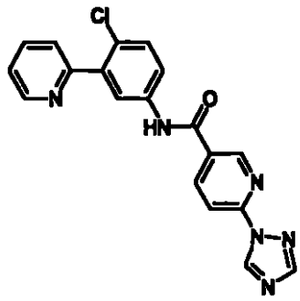


Procedure G was used to couple 4-chloro-3-(pyridin-2-yl)aniline (50 mg) and 2-chloro-4-methylsulfonylbenzoic acid to produce 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide. MS (Q1) 421.0 $(M)^+$. The product was then dissolved in 1 N HCl solution followed by freebasing with 0.5 N NaOH solution (pH to 11). The resulting precipitate was filtered and vacuum-dry.

Procedure D may also be used to couple 4-chloro-3-(pyridin-2-yl)aniline and 2-chloro-4-(methylsulfonyl)benzoyl chloride to produce 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide which is collected by suction filtration and the HCl salt is washed with Et_2O (or alternatively with MTBE). This material is freebased using EtOAc/aq $NaHCO_3$ and the organics are dried and concentrated to the solid freebase. This material is then crystallized from acetone:EtOAc (80:20, approx 10mL/g) which is then finally recrystallized from hot slurry of iPrOAc. 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide HCl salt may

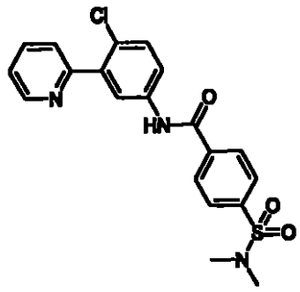
also be dissolved in distilled water followed by freebasing with 0.5 N NaOH solution (pH to 11) and filtering and vacuum drying the precipitate.

Example 38 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(1*H*-1,2,4-triazol-1-yl)pyridine-3-carboxamide



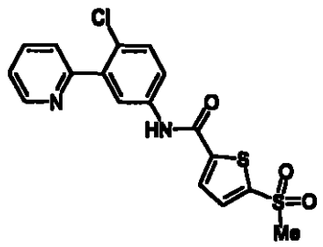
Procedure G was used to couple 4-chloro-3-(pyridin-2-yl)aniline (40 mg) and 6-(1*H*-1,2,4-triazol-1-yl)pyridine-3-carboxylic acid to produce *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(1*H*-1,2,4-triazol-1-yl)pyridine-3-carboxamide. MS (Q1) 377.0 $(M)^+$.

Example 39 N-(4-chloro-3-(pyridin-2-yl)phenyl)-4-[(dimethylamino)sulfonyl]-benzamide



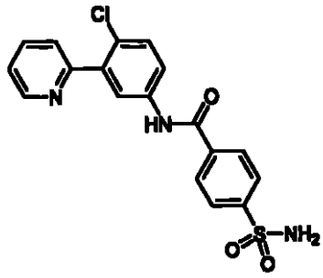
Procedure G was used to couple 4-chloro-3-(pyridin-2-yl)aniline (50 mg) and 4-[(dimethylamino)sulfonyl]benzoic acid to produce N-(4-chloro-3-(pyridin-2-yl)phenyl)-4-[(dimethylamino)sulfonyl]-benzamide. MS (Q1) 416.0 $(M)^+$.

Example 40 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-5-(methylsulfonyl)thiophene-2-carboxamide



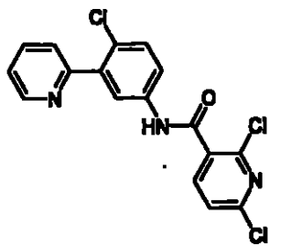
Procedure G was used to couple 4-chloro-3-(pyridin-2-yl)aniline (40 mg) and 5-(methylsulfonyl)thiophene-2-carboxylic acid to produce *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-5-(methylsulfonyl)thiophene-2-carboxamide. MS (Q1) 393.0 $(M)^+$.

Example 41 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(aminosulfonyl)-benzamide



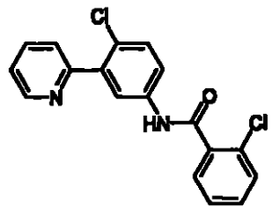
Procedure G was used to couple 4-chloro-3-(pyridin-2-yl)aniline (30 mg) and 4-carboxybenzenesulfonamide to produce *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(aminosulfonyl)-benzamide. MS (Q1) 388.0 $(M)^+$.

Example 42 2,6-dichloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)pyridine-3-carboxamide



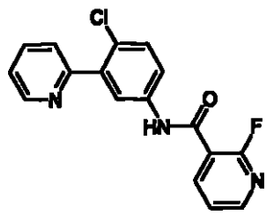
Procedure G was used to couple 4-chloro-3-(pyridin-2-yl)aniline (50 mg) and 2,6-dichloronicotinic acid to produce 2,6-dichloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)pyridine-3-carboxamide. MS (Q1) 378.1 $(M)^+$.

Example 43 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide



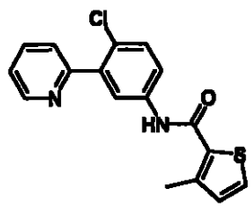
Procedure G was used to couple 4-chloro-3-(pyridin-2-yl)aniline (50 mg) and 2-chlorobenzoic acid to produce 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide. MS (Q1) 343.1 $(M)^+$.

Example 44 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-fluoropyridine-3-carboxamide



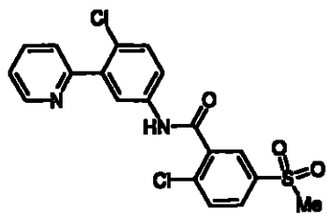
Procedure G was used to couple 4-chloro-3-(pyridin-2-yl)aniline (50 mg) and 2-fluoronicotinic acid to produce *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-fluoropyridine-3-carboxamide. MS (Q1) 328.1 $(M)^+$.

Example 45 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-methylthiophene-2-carboxamide



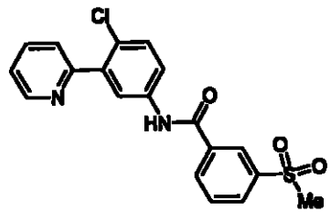
Procedure G was used to couple 4-chloro-3-(pyridin-2-yl)aniline (50 mg) and 3-methyl-2-thiophenecarboxylic acid to produce *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-methylthiophene-2-carboxamide. MS (Q1) 329.0 $(M)^+$.

Example 46 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-5-(methylsulfonyl)benzamide



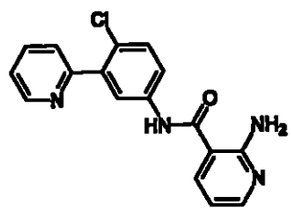
Procedure G was used to couple 4-chloro-3-(pyridin-2-yl)aniline and 2-chloro-5-(methanesulfonyl)benzoic acid to produce 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-5-(methylsulfonyl)benzamide. MS (Q1) 420.95 $(M)^+$.

Example 47 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-(methylsulfonyl)benzamide



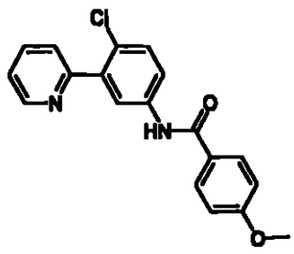
Procedure G was used to couple 4-chloro-3-(pyridin-2-yl)aniline and 3-(methanesulfonyl)benzoic acid to produce *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-(methylsulfonyl)benzamide. MS (Q1) 387.2 $(M)^+$.

Example 48 2-amino-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)pyridine-3-carboxamide



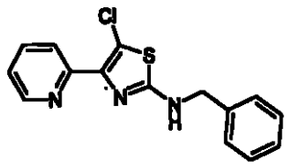
Procedure G was used to couple 4-chloro-3-(pyridin-2-yl)aniline (50 mg) and 2-aminonicotinic acid to produce 2-amino-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)pyridine-3-carboxamide. MS (Q1) 325.2 $(M)^+$.

Example 49 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-methoxybenzamide



Procedure G was used to couple 4-chloro-3-(pyridin-2-yl)aniline and 4-methoxylbenzoic acid to produce *N*-(4-chloro-3-(pyridin-2-yl)phonyl)-4-methoxybenzamide. MS (Q1) 341.2 $(M)^+$.

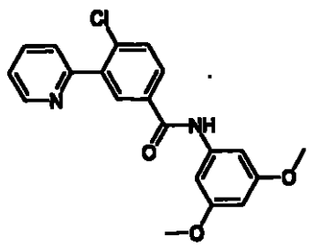
Example 50 *N*-benzyl-5-chloro-4-(pyridin-2-yl)thiazol-2-amine



A solution of 2-(Bromoacetyl)pyridine hydrobromide (100 mg, 0.36 mmol) in ethanol (2 mL) was treated with 1-benzyl-2-thiourea (90 mg, 0.54 mmol). The resulting yellow solution was concentrated, and the crude residue was purified on reverse phase HPLC to produce *N*-benzyl-4-(pyridin-2-yl)thiazol-2-amine.

A solution of *N*-benzyl-4-(pyridin-2-yl)thiazol-2-amine (60 mg, 0.23 mmol) in DMF (2 mL) was cooled to 0 °C and treated with *N*-chlorosuccinimide (33 mg, 0.25 mmol), and the reaction mixture was allowed to warm to room temperature. The solvent was evaporated, and the product was purified on reverse phase HPLC to produce *N*-benzyl-5-chloro-4-(pyridin-2-yl)thiazol-2-amine. MS (Q1) 302.2 $(M)^+$.

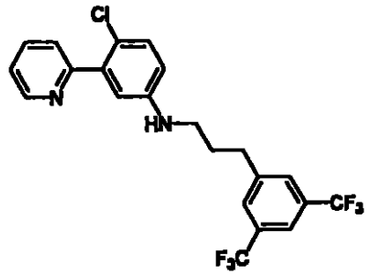
Example 51 4-chloro-*N*-(3,5-dimethoxyphenyl)-3-(pyridin-2-yl)benzamide



A solution of 3-bromo-4-chlorobenzoic acid (250 mg, 1.1 mmol) in DMF (2 mL) was treated with PyBop (550 mg, 1.1 mmol) and DIPEA (370 uL, 2.1 mmol). After stirring the reaction mixture for 5 min. 3,5-dimethoxy analine (105 mg, 0.69 mmol) was added and the reaction was stirred for 16 h. The reaction mixture was diluted with ethyl acetate and washed with 0.1 N HCl, 0.1 N sodium hydroxide and Brine, successively. The organic layer was dried ($MgSO_4$) and concentrated, and crude 3-bromo-4-chloro-*N*-(3,5-dimethoxyphenyl)benzamide was used without further purification.

3-bromo-4-chloro-*N*-(3,5-dimethoxyphenyl)benzamide was dissolved in 0.5 M 2-pyridylzincbromide (2.5 mL) and treated with $Pd(PPh_3)_4$ (20 mg, 0.02 mmol). The reaction mixture was heated to 155° C in a sealed tube for 20 min. in a microwave reactor. The resultant solution was diluted with Ethyl acetate and washed with 0.1 N sodium hydroxide and then brine. The organic layer was dried ($MgSO_4$) and concentrated, and the crude residue was partially purified by silica gel chromatography. Pure 4-chloro-*N*-(3,5-dimethoxyphenyl)-3-(pyridin-2-yl)benzamide was obtained by a second purification on reverse phase HPLC. MS (Q1) 369.1 $(M)^+$.

Example 52 *N*-(3-(3,5-bis(trifluoromethyl)phenyl)propyl)-4-chloro-3-(pyridin-2-yl)benzenamine

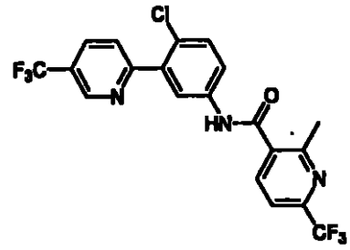


A solution of 3,5-bis(trifluoromethyl)hydrocinnamic acid (1.0 g, 3.5 mmol) and TEA (0.46 g, 4.5 mmol) in THF (16 mL) was cooled to –40°C (ethanol-water/dry ice bath). To this mixture was dropwise added isobutyl chloroformate (0.56 g, 4.1 mmol) and stirring was continued for another 1.5 hours while the temperature of the cooling bath was maintained between –40 °C and –20 °C. Solid $NaBH_4$ (0.53 g, 14 mmol) was added, followed by H_2O (1.3 mL). The cloudy mixture was stirred overnight while warming to room temperature. After concentrating in vacuo, the residue was partitioned between ethyl acetate and water. The aqueous layer was acidified to pH 1 with 37% HCl and extracted with ethyl acetate. The combined organic layers were washed sequentially with saturated $NaHCO_3$, and brine, then dried ($MgSO_4$) and concentrated. The resulting oil was purified by flash silica gel chromatography (6:4 ethyl ether-hexane) to yield 3-[3',5'-bis(trifluoromethyl)phenyl]-1-propanol.

3-[3',5'-bis(trifluoromethyl)phenyl]-1-propanol (0.88 g, 3.2 mmol) and CBr_4 (1.3 g, 4.0 mmol) were dissolved in CH_2Cl_2 (5 mL) and cooled to 0°C. Triphenylphosphine (1.3 g, 4.8 mmol) was added in three portions over 0.5 h. The mixture was stirred at 0 °C for 10 min., then diluted with pentane (30 mL) and sat. $NaHCO_3$ (30 mL). The aqueous layer was separated and washed with ethyl ether, and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel flash chromatography (99:1 ethyl ether-hexane) to yield 0.8 g, (74%) of the 3-[3',5'-bis(trifluoromethyl)phenyl]-1-bromopropane.

4-chloro-3-(2'-pyridyl)aniline (10 mg, 0.05 mmol), 3-[3',5'-bis(trifluoromethyl)phenyl]-1-bromopropane (34 mg, 0.1 mmol) and K_2CO_3 (14 mg, 0.1 mmol) in DMF (1 mL) was stirred at 100°C overnight. The reaction mixture was acidified with 1N HCl (aq.) and extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The crude was purified by preparative HPLC to yield *N*-(3-(3,5-bis(trifluoromethyl)phenyl)propyl)-4-chloro-3-(pyridin-2-yl)benzenamine.

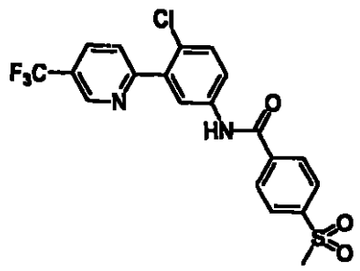
Example 53 *N*-(4-chloro-3-(5-(trifluoromethyl)pyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide



N-(4-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide (~ 0.5 mmol) was used in Procedure A with 5-trifluoromethyl-2-bromopyridine (113 mg, 0.5 mmol). Purified by silica gel chromatography (5-50% ethyl acetate/hexanes) to yield *N*-(4-chloro-3-(5-(trifluoromethyl)pyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide as a white foam: TLC R_f = 0.30 (15% ethyl acetate/hexanes); MS (Q1) 460 $(M)^+$.

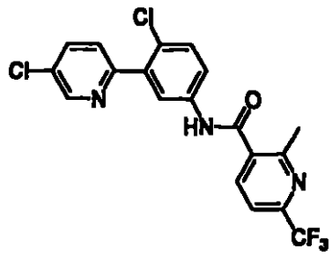
Example 54 *N*-(4-chloro-3-(5-(trifluoromethyl)pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide

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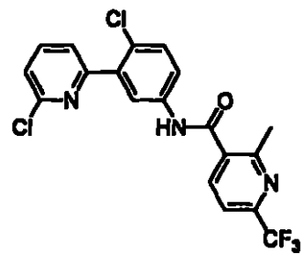
N-(4-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-(methylsulfonyl)benzamide (~ 1.0 mmol) was used in Procedure A with 5-trifluoromethyl-2-bromopyridine (226 mg, 1 mmol). Purified by silica gel chromatography (0-10% acetone/dichloromethane) to yield *N*-(4-chloro-3-(5-(trifluoromethyl)pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide as a white solid: MS (Q1) 455 $(M)^+$.

Example 55 *N*-(4-chloro-3-(5-chloropyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide



5-chloropyridin-2-yl trifluoromethanesulfonate (4.12 mmol) was used in Procedure I with trimethyltin chloride to yield 5-chloro-2-(trimethylstannyl)pyridine. The crude material (~4 mmol) was used in Procedure K with *N*-(4-chloro-3-iodophenyl)-2-methyl-6-(trifluoromethyl)nicotinamide (2 mmol). Purified by silica gel chromatography (0-50% ethyl acetate/hexane) to yield *N*-(4-chloro-3-(5-chloropyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide as a white solid: TLC R_f = 0.48 (25% ethyl acetate/hexanes); MS (Q1) 427 $(M)^+$.

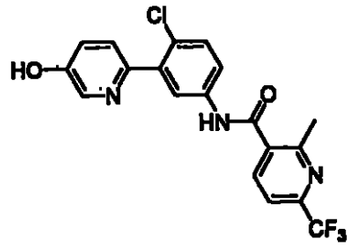
Example 56 *N*-(4-chloro-3-(6-chloropyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide



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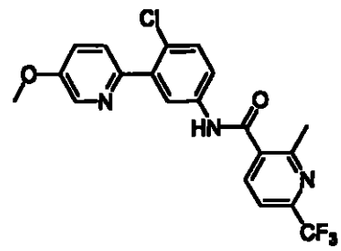
6-chloropyridin-2-yl trifluoromethanesulfonate (4.12 mmol) was used in Procedure I with trimethyltin chloride to yield 2-chloro-6-(trimethylstannyl)pyridine. The crude material (~4 mmol) was used in Procedure K with *N*-(4-chloro-3-iodophenyl)-2-methyl-6-(trifluoromethyl)nicotinamide (2 mmol). Purified by silica gel chromatography (5-45% ethyl acetate/hexane) to yield *N*-(4-chloro-3-(6-chloropyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide as a white solid: TLC R_f= 0.45 (25% ethyl acetate/hexanes); MS (Q1) 426 $(M)^+$.

Example 57 *N*-(4-chloro-3-(5-hydroxypyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide



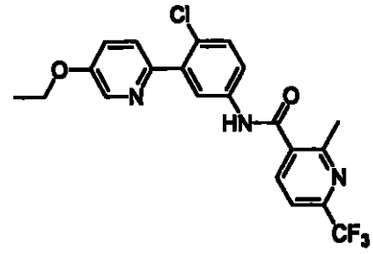
3-(triisopropylsilyloxy)pyridine (2.66 mmol) was used in Procedure J with hexamethyldistannane to yield 5-(triisopropylsilyloxy)-2-(trimethylstannyl)pyridine. The crude material (~0.55 mmol) was used in Procedure K with *N*-(4-chloro-3-iodophenyl)-2-methyl-6-(trifluoromethyl)nicotinamide (0.17 mmol). Purified by silica gel chromatography (0-40% ethyl acetate/hexane) to yield *N*-(4-chloro-3-(5-(triisopropylsilyloxy)pyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide as a yellow oil. *N*-(4-chloro-3-(5-(triisopropylsilyloxy)pyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide (1 mmol) was treated with TBAF (2 mL, 1 M in THF) in THF (1 mL) at 23 °C for thirty minutes, concentrated, redissolved in ethyl acetate, washed with brine, dried ($MgSO_4$), and concentrated. The crude solid was purified by silica gel chromatography (0-10 % isopropanol/dichloromethane) to yield *N*-(4-chloro-3-(5-hydroxypyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide as a white solid: TLC R_f= 0.59 (10% ethyl acetate/hexanes); MS (Q1) 408 $(M)^+$.

Example 58 *N*-(4-chloro-3-(5-methoxypyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide



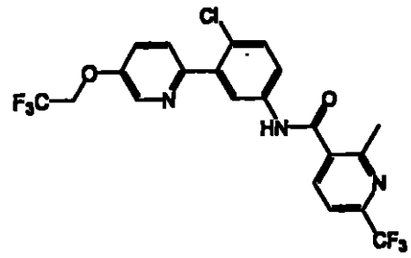
N-(4-chloro-3-(5-hydroxypyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide (0.12 mmol) was used in Procedure L with excess iodomethane. Purified by silica gel chromatography (0-100% ethyl acetate/hexane) to yield *N*-(4-chloro-3-(5-methoxypyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide as a white solid: TLC R_f = 0.57 (50% ethyl acetate/hexanes); MS (Q1) 423$(M)^+$.

Example 59 *N*-(4-chloro-3-(5-ethoxypyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide



N-(4-chloro-3-(5-hydroxypyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide (0.05 mmol) was used in Procedure L with excess iodoethane. Purified by silica gel chromatography (0-100% ethyl acetate/hexane) to yield *N*-(4-chloro-3-(5-ethoxypyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide as a white solid: TLC R_f = 0.64 (50% ethyl acetate/hexanes); MS (Q1) 436 $(M)^+$.

Example 60 *N*-(4-chloro-3-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide

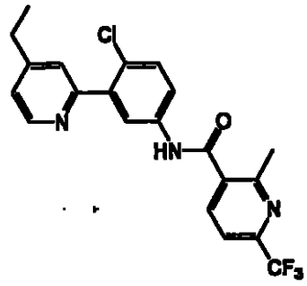


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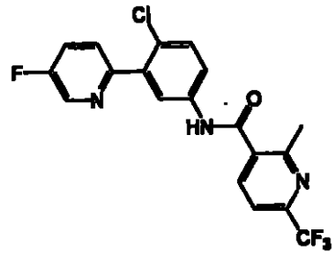
N-(4-chloro-3-(5-hydroxypyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide (0.12 mmol) was used in Procedure L with excess trifluoroethyl iodide. Purified by silica gel chromatography (0-40% ethyl acetate/hexane) to yield *N*-(4-chloro-3-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide as a white solid: TLC R_f= 0.64 (40% ethyl acetate/hexanes); MS (Q1) 490 $(M)^+$.

Example 61 *N*-(4-chloro-3-(4-ethylpyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide



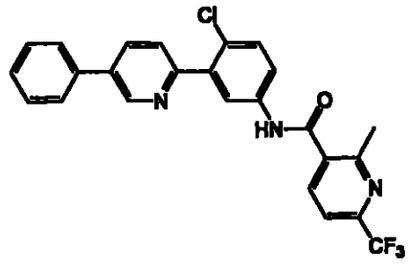
N-(4-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide (~ 1 mmol) was used in Procedure A with 4-ethyl-2-bromopyridine (1 mmol). Purified by silica gel chromatography (0-60% ethyl acetate/hexanes) to yield *N*-(4-chloro-3-(4-ethylpyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide as a tan solid: MS (Q1) 419 $(M)^+$.

Example 62 *N*-(4-chloro-3-(5-fluoropyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide



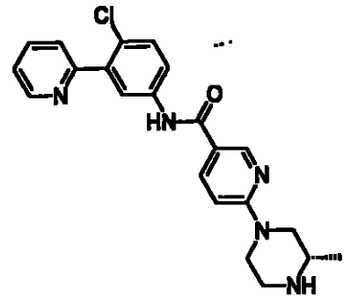
N-(4-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide (~ 1 mmol) was used in Procedure A with 5-fluoro-2-bromopyridine (1 mmol). Purified by silica gel chromatography (5-45% ethyl acetate/hexanes) to yield *N*-(4-chloro-3-(5-fluoropyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide as a tan solid: MS (Q1) 409 $(M)^+$.

Example 63 *N*-(4-chloro-3-(5-phenylpyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)-nicotinamide



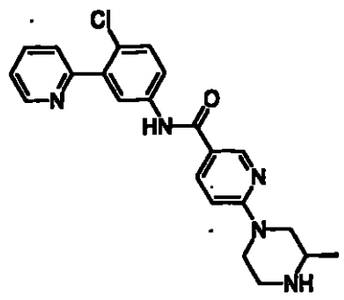
5-phenylpyridin-2-yl trifluoromethanesulfonate (1.5 mmol) was used in Procedure J with trimethyltin chloride to yield 5-phenyl-2-(trimethylstannyl)pyridine. The crude material (~1.25 mmol) was used in Procedure K with *N*-(4-chloro-3-iodophenyl)-2-methyl-6-(trifluoromethyl)nicotinamide (1 mmol). Purified by silica gel chromatography (1% acetone/methylene chloride) to yield *N*-(4-chloro-3-(5-phenylpyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamideas a tan solid: TLC R_f = 0.15 (1% acetone/methylene chloride); MS (Q1) 467 $(M)^+$.

Example 64 (*S*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(3-methylpiperazin-1-yl)nicotinamide



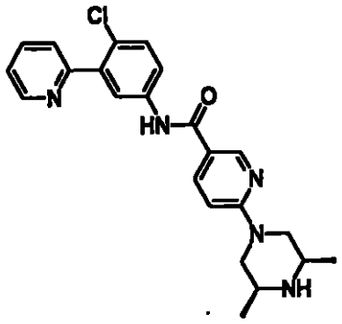
Procedure F was performed using N-(4-chloro-3-(pyridin-2-yl)phenyl)-6-chloro-3-carboxamide (50 mg) and 75 mg of (S)-2-methylpiperazine in 0.75 mL of butanol at 160°C for 60 min. Purification by reverse phase HPLC yielded (*S*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(3-methylpiperazin-1-yl)nicotinamide. MS (Q1) 408 $(M)^+$.

Example 65 (*R*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(3-methylpiperazin-1-yl)nicotinamide



Procedure F was performed using N-(4-chloro-3-(pyridin-2-yl)phenyl)-6-chloro-3-carboxamide (50 mg) and 75 mg of (R)-2-methylpiperazine in 0.75 mL of butanol at 160°C for 60 min. Purification by reverse phase HPLC yielded (*R*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(3-methylpiperazin-1-yl)nicotinamide. MS (Q1) 408 $(M)^+$.

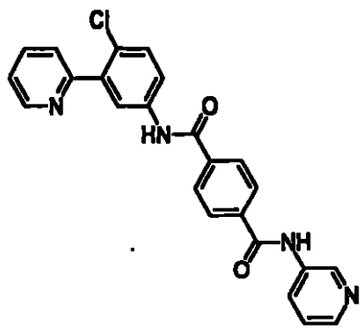
Example 66 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-((3*S*,5*R*)-3,5-dimethylpiperazin-1-yl)nicotinamide



Procedure F was performed using N-(4-chloro-3-(pyridin-2-yl)phenyl)-6-chloro-3-carboxamide (75 mg) and 114 mg of 2,6-dimethylpiperazine in 1 mL of butanol at 160°C for 60 min. Purification by reverse phase HPLC yielded *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-((3*S*,5*R*)-3,5-dimethylpiperazin-1-yl)nicotinamide. MS (Q1) 422.1 $(M)^+$.

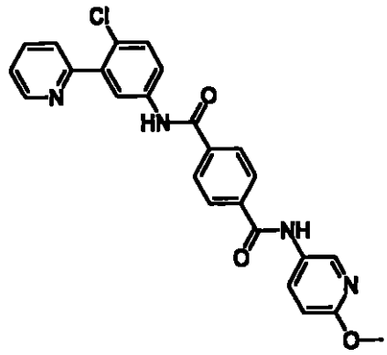
Example 67 N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(pyridin-3-yl)terephthalamide

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320 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 400 mg of 4-(methoxycarbonyl)benzoic acid via Procedure G to give methyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoate. 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoate was then hydrolyzed via Prodedure M to give 550 mg of 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid. 50 mg of 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 3-aminopyridine via Procedure G. The organic layer was evaporated to dryness and purified on reverse phase HPLC to yield N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(pyridin-3-yl)terephthalamide. MS (Q1) 429 $(M)^+$.

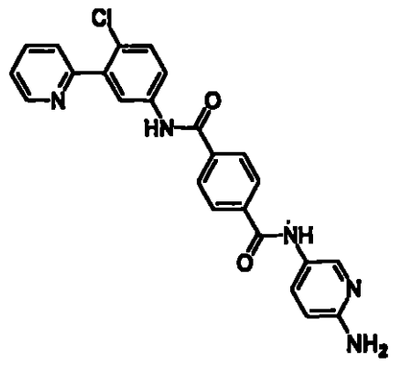
Example 68 N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(6-methoxypyridin-3-yl)terephthalamide



50 mg of 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 2-methoxy-5-aminopyridine via Procedure G. The product was purified on reverse phase HPLC to yield N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(6-methoxypyridin-3-yl)terephthalamide. MS (Q1) 459 $(M)^+$.

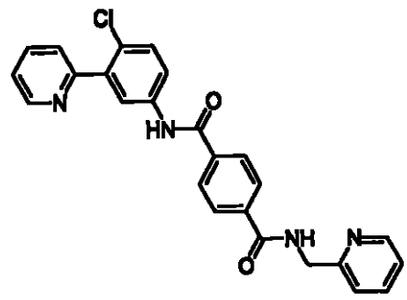
Example 69 N^1-(6-aminopyridin-3-yl)-N^4-(4-chloro-3-(pyridin-2-yl)phenyl)terephthalamide

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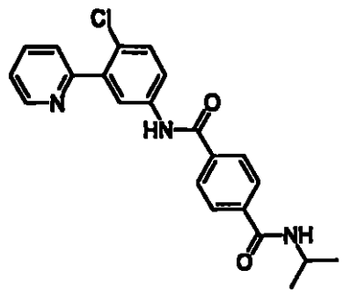
50 mg of 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 2,5-diaminopyridine via Procedure G. The prodcut was purified on reverse phase HPLC to yield N^1-(6-aminopyridin-3-yl)-N^4-(4-chloro-3-(pyridin-2-yl)phenyl)terephthalamide. MS (Q1) 444 $(M)^+$.

Example 70 N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(pyridin-2-ylmethyl)terephthalamide



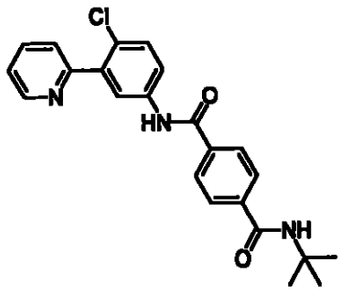
50 mg of 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 2-(aminomethyl)pyridine via Procedure G. The product was purified on reverse phase HPLC to yield N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(pyridin-2-ylmethyl)terephthalamide. MS (Q1) 443 $(M)^+$.

Example 71 N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-isopropylterephthalamide



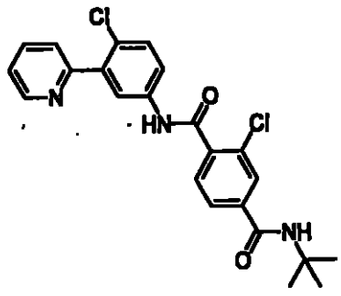
50 mg of 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to isopropylamine via Procedure G. The product was purified on reverse phase HPLC to yield *N*^{1}-(4-chloro-3-(pyridin-2-yl)phenyl)-*N*^{4}-isopropylterephthalamide. MS (Q1) 394 $(M)^+$.

Example 72 *N*^{1}-*tert*-butyl-*N*^{4}-(4-chloro-3-(pyridin-2-yl)phenyl)terephthalamide



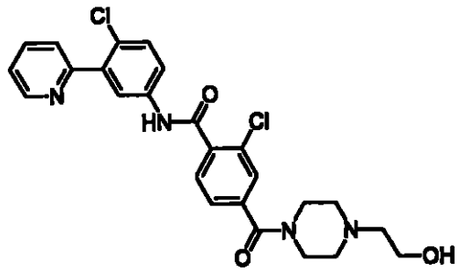
50 mg of 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to *tert*-butylamine via Procedure G. The product was purified on reverse phase HPLC to yield *N*^{1}-*tert*-butyl-*N*^{4}-(4-chloro-3-(pyridin-2-yl)phenyl)terephthalamide. MS (Q1) 408 $(M)^+$.

Example 73 *N*^{4}-*tert*-butyl-2-chloro-*N*^{1}-(4-chloro-3-(pyridin-2-yl)phenyl)terephthalamide



67 mL of 2-chloro-1,4-dimethylbenzene and 356 g of Potassium Permanganate were refluxed in 1.5 L of H_2O for several hours and monitored for disappearance of starting material by TLC. The Potassium Permanganate was filtered and the reaction mixture was acidified and filtered to yield 2-chloroterephthalic acid. 46.8 g of 2-chloroterephthalic acid was treated with a saturated HCl gas solution in MeOH overnight at room temperature. The reaction mixture was concentrated, subjected to basic workup and dried to yield the dimethyl 2-chloroterephthalate. 20 g of dimethyl 2-chloroterephthalate was cooled to 0°C in DCM and 87 mL of a 1M in DCM solution of BBr_3 was added dropwise over several hours. The reaction mixture was subsequently warmed to room temperature and stirred until complete. Following basic workup, 2-chloro-4-(methoxycarbonyl)benzoic acid was purified by ISCO Combi-Flash. 959 mg of 2-chloro-4-(methoxycarbonyl)benzoic acid was coupled to 750 mg of 4-chloro-3-(pyridin-2-yl)aniline via procedure G. 1 g of methyl 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoate was hydrolyzed via Procedure M to give 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid. 50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to *tert*-butylamine via Procedure G. The product was purified on reverse phase HPLC to yield N^4-*tert*-butyl-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)terephthalamide. MS (Q1) 443.2 $(M)^+$.

Example 74 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(4-(2-hydroxyethyl)piperazine-1-carbonyl)benzamide

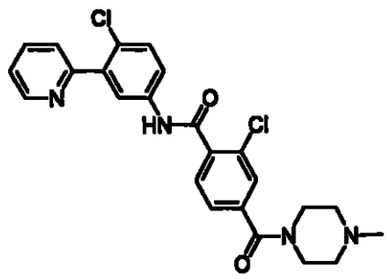


50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to N-(2-hydroxyethyl)piperazine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(4-(2-hydroxyethyl)piperazine-1-carbonyl)benzamide. MS (Q1) 499 $(M)^+$.

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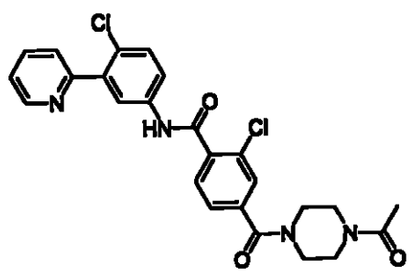
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Example 75 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(4-methylpiperazine-1-carbonyl)benzamide



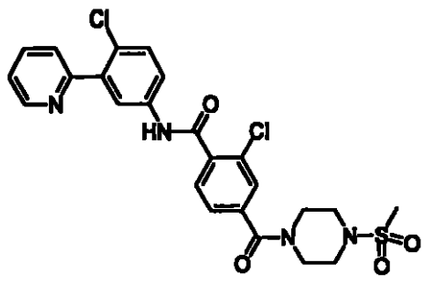
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 1-methylpiperazine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(4-methylpiperazine-1-carbonyl)benzamide. MS (Q1) 469 $(M)^+$.

Example 76 4-(4-acetylpiperazine-1-carbonyl)-2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide



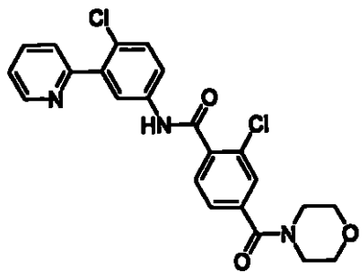
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 1-acetylpiperazine via Procedure G. The product was purified on reverse phase HPLC to yield 4-(4-acetylpiperazine-1-carbonyl)-2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide. MS (Q1) 497 $(M)^+$.

Example 77 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(4-(methylsulfonyl)piperazine-1-carbonyl)benzamide



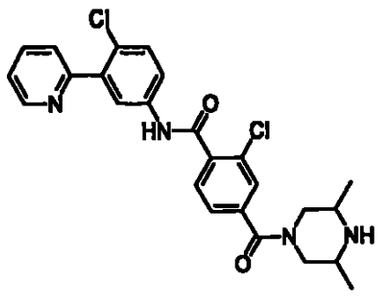
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 1-sulfonylpiperazine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(4-(methylsulfonyl)piperazine-1-carbonyl)benzamide. MS (Q1) 533 $(M)^+$.

Example 78 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(morpholine-4-carbonyl)benzamide



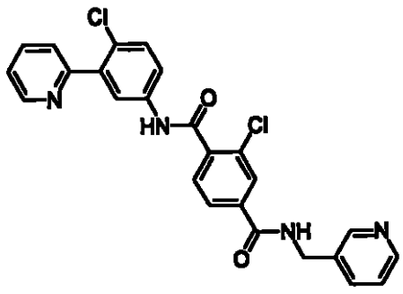
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to morpholine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(morpholine-4-carbonyl)benzamide. MS (Q1) 456 $(M)^+$.

Example 79 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(3,5-dimethylpiperazine-1-carbonyl)benzamide



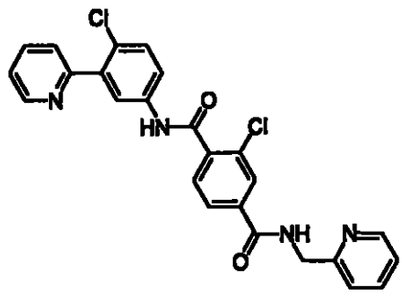
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 2,6-dimethylpiperazine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(3,5-dimethylpiperazine-1-carbonyl)benzamide. MS (Q1) 483 $(M)^+$.

Example 80 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(pyridin-3-ylmethyl)terephthalamide



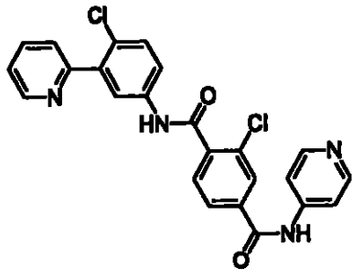
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 3-(aminomethyl)pyridine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(pyridin-3-ylmethyl)terephthalamide. MS (Q1) 477 $(M)^+$.

Example 81 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(pyridin-2-ylmethyl)terephthalamide



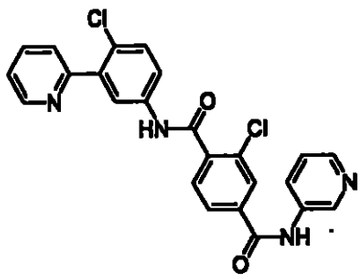
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 2-(aminomethyl)pyridine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(pyridin-2-ylmethyl)terephthalamide. MS (Q1) 477 $(M)^+$.

Example 82 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(pyridin-4-yl)terephthalamide



50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 4-aminopyridine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(pyridin-4-yl)terephthalamide. MS (Q1) 463 $(M)^+$.

Example 83 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(pyridin-3-yl)terephthalamide

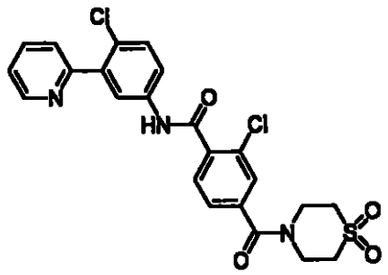


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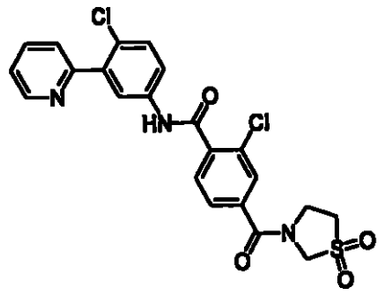
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 3-aminopyridine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(pyridin-3-yl)terephthalamide. MS (Q1) 463 $(M)^+$.

Example 84 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(thiomorpholine-4-carbonyl)benzamide (S-oxidized thiomorpholine)



100 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to thiomorpholine via Procedure G. Crude 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(thiomorpholine-4-carbonyl)benzamide was reacted via Procedure R to oxidize the thiomorpholine sulfur and purified via reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(thiomorpholine-4-carbonyl)benzamide (in which the thiomorpholline sulfur is oxidized to SO_2). MS (Q1) 504 $(M)^+$.

Example 85 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(thiazolidine-3-carbonyl)benzamide (S-oxidized thiazolidine)

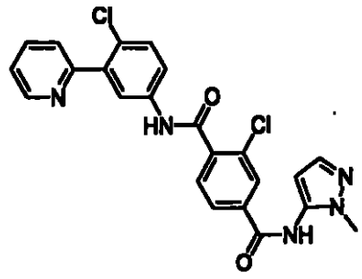


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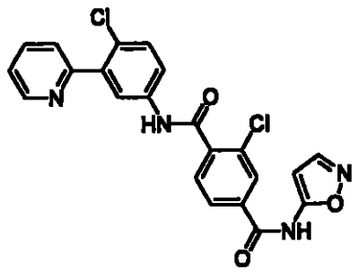
100 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to thiazolidine via Procedure G. Crude 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(thiazolidine-3-carbonyl)benzamide was reacted via Procedure R and purified via reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(thiazolidine-3-carbonyl)benzamide (in which the thiazolidine sulfur is oxidized to SO_2). MS (Q1) 490 $(M)^+$.

Example 86 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(1-methyl-1*H*-pyrazol-5-yl)terephthalamide



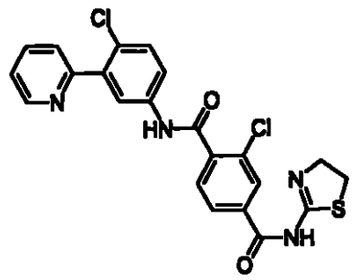
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 5-amino-1-methylpyrazole via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(1-methyl-1*H*-pyrazol-5-yl)terephthalamide. MS (Q1) 466 $(M)^+$.

Example 87 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(isoxazol-5-yl)terephthalamide



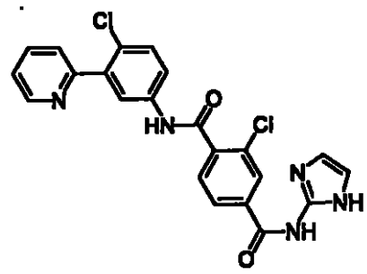
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 5-aminoisoxazole via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(isoxazol-5-yl)terephthalamide. MS (Q1) 463 $(M)^+$.

Example 88 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(4,5-dihydrothiazol-2-yl)terephthalamide



50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 2-amino-4,5-dihydrothiazole via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(4,5-dihydrothiazol-2-yl)terephthalamide. MS (Q1) 471 $(M)^+$.

Example 89 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(1*H*-imidazol-2-yl)terephthalamide

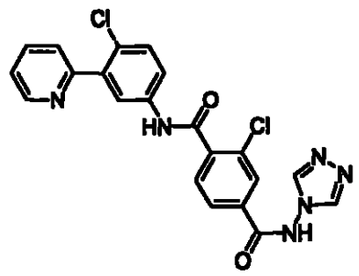


50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 2-aminoimidazole via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(1*H*-imidazol-2-yl)terephthalamide. MS (Q1) 452 $(M)^+$.

Example 90 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(4*H*-1,2,4-triazol-4-yl)terephthalamide

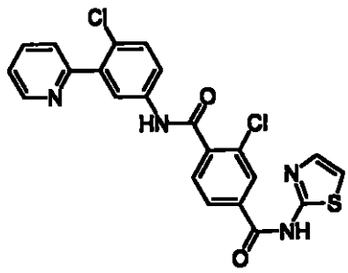
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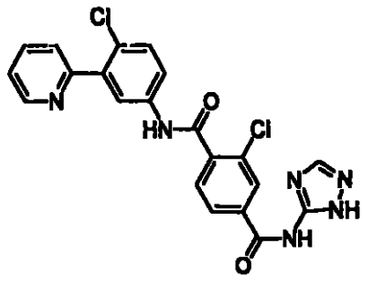
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 4-amino-1,2,4-triazole via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(4*H*-1,2,4-triazol-4-yl)terephthalamide. MS (Q1) 453 $(M)^+$.

Example 91 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(thiazol-2-yl)terephthalamide



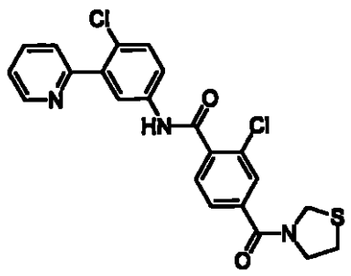
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 2-aminothiazole via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(thiazol-2-yl)terephthalamide. MS (Q1) 469 $(M)^+$.

Example 92 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(1*H*-1,2,4-triazol-5-yl)terephthalamide



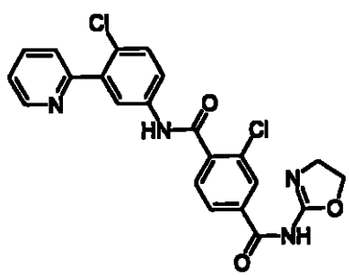
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 3-amino-1,2,4-triazole via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-*N*^{1}-(4-chloro-3-(pyridin-2-yl)phenyl)-*N*^{4}-(1*H*-1,2,4-triazol-5-yl)terephthalamide. MS (QI) 453 $(M)^+$.

Example 93 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(thiazolidine-3-carbonyl)benzamide



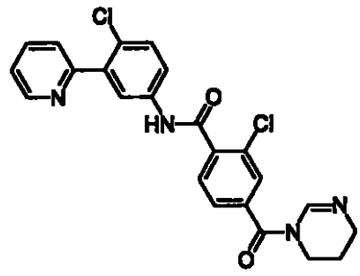
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to thiazoline via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(thiazolidine-3-carbonyl)benzamide. MS (QI) 459 $(M)^+$.

Example 94 2-chloro-*N*^{1}-(4-chloro-3-(pyridin-2-yl)phenyl)-*N*^{4}-(4,5-dihydrooxazol-2-yl)terephthalamide



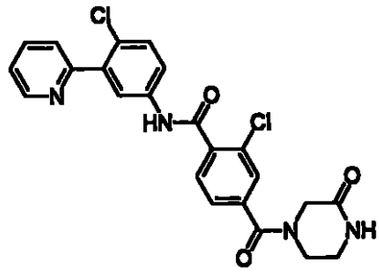
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 2-amino-4,5-dihydrooxazole via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-*N*^{1}-(4-chloro-3-(pyridin-2-yl)phenyl)-*N*^{4}-(4,5-dihydrooxazol-2-yl)terephthalamide. MS (Q1) 456 $(M)^+$.

Example 95 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(1,4,5,6-tetrahydropyrimidine-1-carbonyl)benzamide



50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 1,4,5,6-tetrahydropyrimidine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(1,4,5,6-tetrahydropyrimidine-1-carbonyl)benzamide. MS (Q1) 454 $(M)^+$.

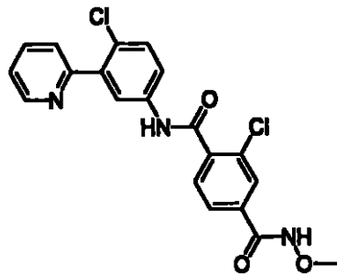
Example 96 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(3-oxopiperazine-1-carbonyl)benzamide



50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 3-oxopiperazine via Procedure G. The product was purified on reverse phase HPLC to yield 2-

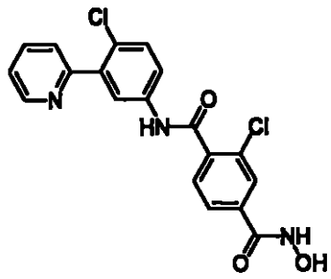
chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(3-oxopiperazine-1-carbonyl)benzamide. MS (Q1) 470 $(M)^+$.

Example 97 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-methoxyterephthalamide



75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to *N*-methylhydroxylamine hydrochloride via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-methoxyterephthalamide. MS (Q1) 417 $(M)^+$.

Example 98 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-hydroxyterephthalamide

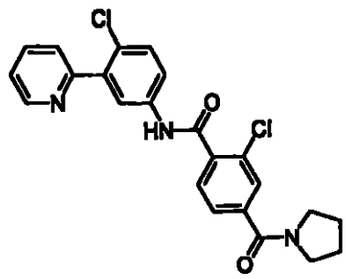


75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to hydroxylamine hydrochloride via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-hydroxyterephthalamide. MS (Q1) 403 $(M)^+$.

Example 99 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(pyrrolidine-1-carbonyl)benzamide

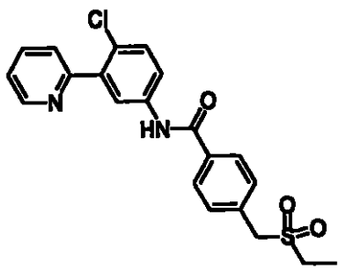
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75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to pyrolidine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(pyrrolidine-1-carbonyl)benzamide. MS (Q1) 441 $(M)^+$.

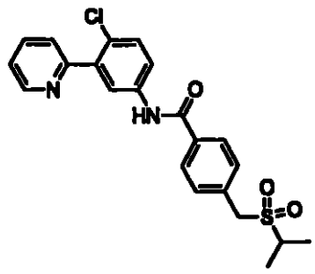
Example 100 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(ethylsulfonylmethyl)benzamide



Ethanesulfonyl chloride was reduced to sodium ethanesulfinate according to the procedure in J. Med. Chem. 1989, vol. 32, no. 11, p2436. Briefly, 2.5 ml of ethanesulfonyl chloride was added dropwise to a solution of 3.67 g of sodium carbonate and 5.51 g of sodium sulfate in 13 mL of water. After completion of the reaction the water was evaporated and the solids were suspended in ethanol and heated to 80° C for 1 h prior to filtering the solids. The filtrate was then evaporated to give 2.5 grams of the sodium ethanesulfinate. 293 mg of the sodium ethansulfinate was combined with 230 mg of methyl (4-bromoethyl)benzoate in 2 mL of DMF and heated to 120 C for 5 min in a microwave reactor. The reaction was then extracted with Ethyl Acetate and Brine to give 250 mg of methyl 4-(ethylsulfonylmethyl)benzoate after evaporation of the organic layer. 200 mg of methyl 4-(ethylsulfonylmethyl)benzoate was hydrolyzed via Procedure M to give 119 mg of 4-(ethylsulfonylmethyl)benzoic acid.

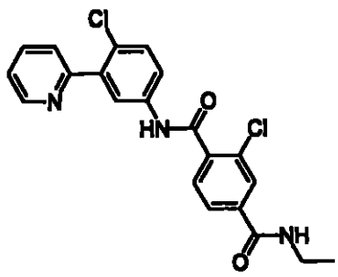
50 mg of 4-(ethylsulfonylmethyl)benzoic acid was coupled with 67mg of 4-chloro-3-(pyridin-2-yl)aniline via Procedure G. This product was recrystallized from methanol to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(ethylsulfonylmethyl)benzamide. MS (Q1) 415 $(M)^+$.

Example 101 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(isopropylsulfonylmethyl)benzamide



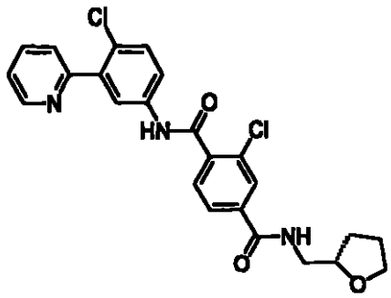
N-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(isopropylsulfonylmethyl)benzamide was prepared using the same procedure as *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(ethylsulfonylmethyl)benzamide except propane-2-sulfonyl chloride was substituted for ethanesulfonyl chloride. The product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(isopropylsulfonylmethyl)benzamide. MS (Q1) 429 $(M)^+$.

Example 102 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-ethylterephthalamide



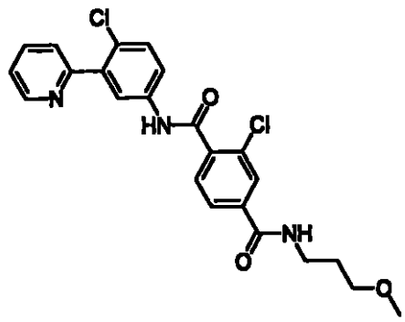
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to ethylamine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-ethylterephthalamide. MS (Q1) 415 $(M)^+$.

Example 103 (*S*)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-((tetrahydrofuran-2-yl)methyl)terephthalamide



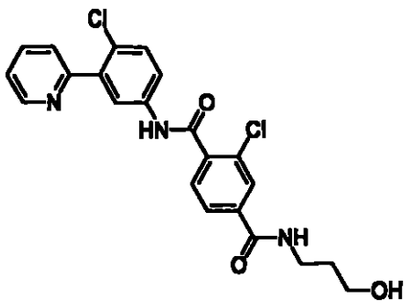
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to (S)-(+)-tetrahydrofurylamine via Procedure G. The product was purified on reverse phase HPLC to yield (*S*)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-((tetrahydrofuran-2-yl)methyl)terephthalamide. MS (Q1) 471 $(M)^+$.

Example 104 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(3-methoxypropyl)terephthalamide



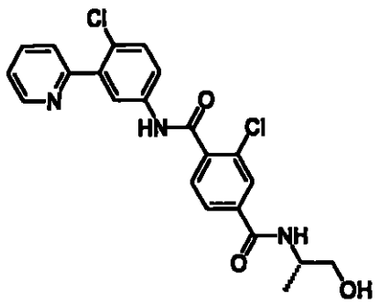
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 3-methoxypropylamine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(3-methoxypropyl)terephthalamide. MS (Q1) 459 $(M)^+$.

Example 105 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(3-hydroxypropyl)terephthalamide



75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 3-hydroxypropylamine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(3-hydroxypropyl)terephthalamide. MS (Q1) 445 $(M)^+$.

Example 106 (*S*)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(1-hydroxypropan-2-yl)terephthalamide

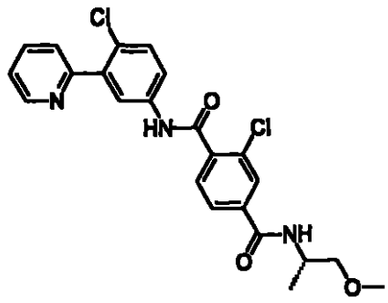


75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to (S)-2-amino-1-propanol via Procedure G. The product was purified on reverse phase HPLC to yield (*S*)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(1-hydroxypropan-2-yl)terephthalamide. MS (Q1) 445 $(M)^+$.

Example 107 (*S*)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(1-methoxypropan-2-yl)terephthalamide

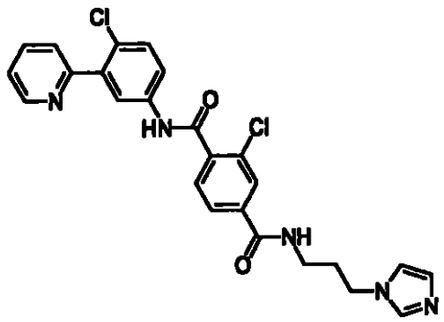
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75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to (S)-1-methoxy-2-propylamine via Procedure G. The product was purified on reverse phase HPLC to yield (*S*)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(1-methoxypropan-2-yl)terephthalamide. MS (Q1) 459 $(M)^+$.

Example 108 N^4-(3-(1*H*-imidazol-1-yl)propyl)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)terephthalamide

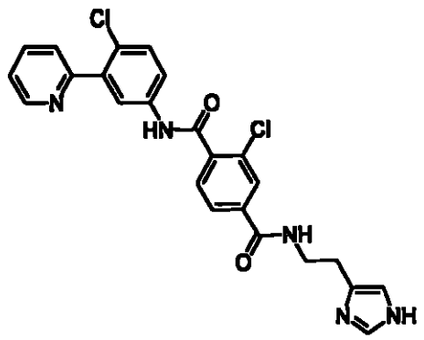


75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 1-(3-aminopropyl)imidazole via Procedure G. The product was purified on reverse phase HPLC to yield N^4-(3-(1*H*-imidazol-1-yl)propyl)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)terephthalamide. MS (Q1) 495 $(M)^+$.

Example 109 N^4-(2-(1*H*-imidazol-4-yl)ethyl)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)terephthalamide

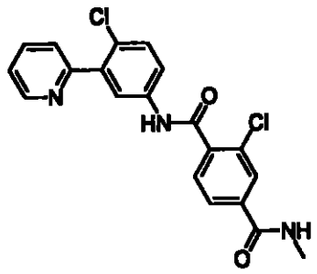
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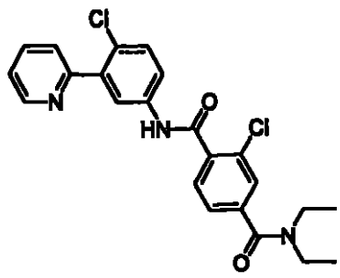
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to hystamine via Procedure G. The product was purified on reverse phase HPLC to yield N^4-(2-(1*H*-imidazol-4-yl)ethyl)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)terephthalamide. MS (Q1) 481 $(M)^+$.

Example 110 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-methylterephthalamide



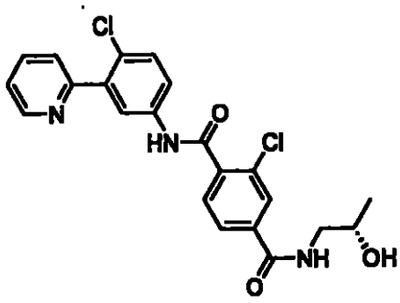
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to methylamine hydrochloride via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-methylterephthalamide. MS (Q1) 401 $(M)^+$.

Example 111 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4,N^4-diethylterephthalamide



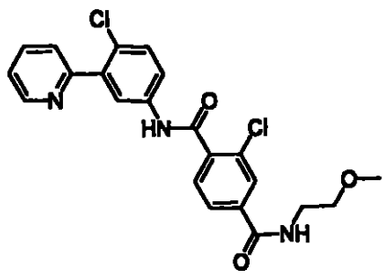
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to diethylamine hydrochloride via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4,N^4-diethylterephthalamide. MS (Q1) 443 $(M)^+$

Example 112 (*S*)-2-chloro-*N*1-(4-chloro-3-(pyridin-2-yl)phenyl)-*N*4-(2-hydroxypropyl)-terephthalamide



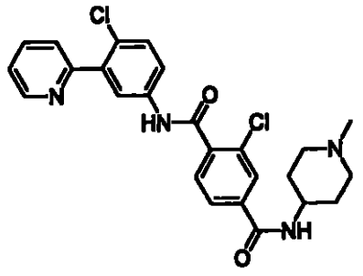
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to (S)-1-amino-2-propanol via Procedure G. The product was purified on reverse phase HPLC to yield (*S*)-2-chloro-*N*1-(4-chloro-3-(pyridin-2-yl)phenyl)-*N*4-(2-hydroxypropyl)terephthalamide. MS (Q1) 444 $(M)^+$.

Example 113 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-methoxyethyl)terephthalamide



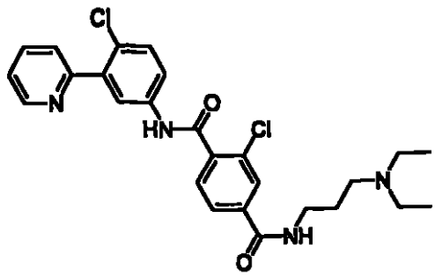
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 2-methoxyethanamine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-methoxyethyl)terephthalamide. MS (Q1) 444 $(M)^+$.

Example 114 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(1-methylpiperidin-4-yl)terephthalamide



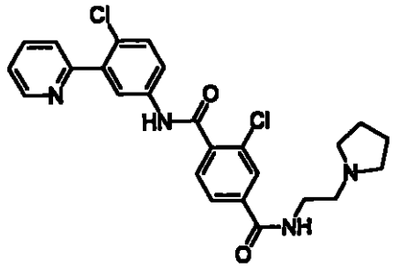
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 4-amino-1-methylpiperidine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(1-methylpiperidin-4-yl)terephthalamide. MS (Q1) 483 $(M)^+$.

Example 115 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(3-(diethylamino)propyl)terephthalamide



75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to N,N-diethylpropylenediamine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(3-(diethylamino)propyl)terephthalamide. MS (Q1) 499 $(M)^+$.

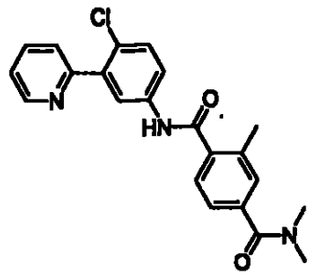
Example 116 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-(pyrrolidin-1-yl)ethyl)terephthalamide



75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to N-(2-aminoethyl)pyrrolidine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-(pyrrolidin-1-yl)ethyl)terephthalamide. MS (Q1) 483 $(M)^+$.

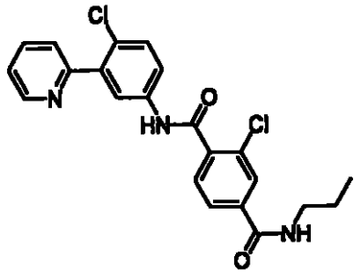
Example 117 N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4,N^4,2-trimethylterephthalamide

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In a sealed tube, 1.94 g of dimethyl 2-bromoterephthalate was dissolved in 4 mL of HMPA and degassed with nitrogen prior to adding 1.1 mL of tetramethyl tin and 0.077 g of palladium tetrakistriphenylphosphene. After sealing the tube, the reaction was heated to 65° C for 16 h. The reaction was then partitioned into ethylether and water and extracted. The organic layers were washed with 5% ammonium hydroxide, 1N HCl, again with 5% ammonium hydroxide, and finally with water. Filtration of the solvent through sodium sulfate and evaporation gave 1.44 g of crude dimethyl 2-methylterephthalate. 210 mg of dimethyl 2-methylterephthalate was hydrolyzed via Procedure M to give 4-(methoxycarbonyl)-3-methylbenzoic acid. Silica gel chromatography was performed (0% to 70% EtOAc gradient in Hexanes) to yield 115 mg of 4-(methoxycarbonyl)-3-methylbenzoic acid. 4-(methoxycarbonyl)-3-methylbenzoic acid was then coupled to dimethylamine hydrochloride via Procedure G. The crude methyl 4-(dimethylcarbamoyl)-2-methylbenzoate was then hydrolyzed via Procedure M to give 110 mg of 4-(dimethylcarbamoyl)-2-methylbenzoic acid. 4-chloro-3-(pyridin-2-yl)aniline was coupled to 110 mg of 4-(dimethylcarbamoyl)-2-methylbenzoic acid via Procedure G to yield N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4,N^4,2-trimethylterephthalamide. MS (Q1) 394 $(M)^+$.

Example 118 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-propylterephthalamide

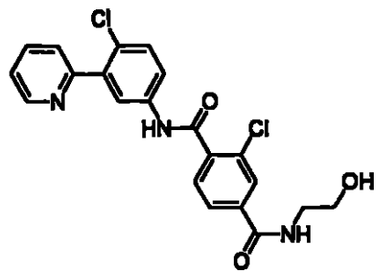


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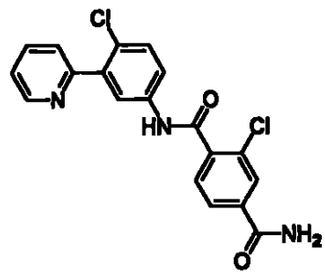
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to propylamine via Procedure G The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-propylterephthalamide MS (Q1) 430 $(M)^+$

Example 119 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-hydroxyethyl)terephthalamide



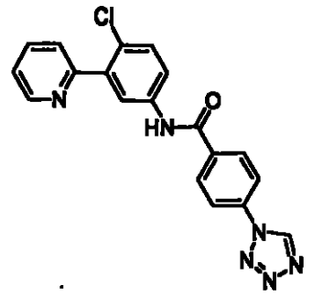
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to propanolamine via Procedure G The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-hydroxyethyl)terephthalamide MS (Q1) 428 $(M)^+$

Example 120 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)terephthalamide



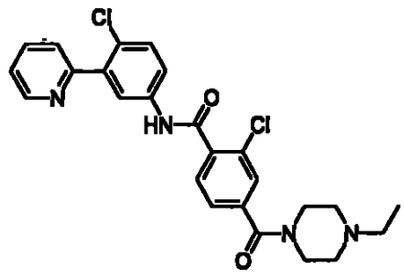
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to ammonium chloride via Procedure G The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)terephthalamide. MS (Q1) 386 $(M)^+$

Example 121 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(1*H*-tetrazol-1-yl)benzamide



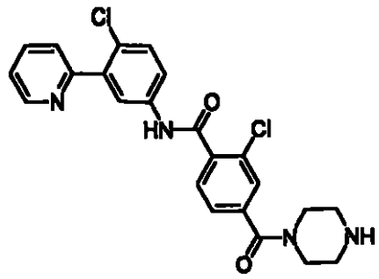
Procedure G was used to couple 4-chloro-3-(pyridin-2-yl)aniline (50 mg) and 4-(1*H*-tetrazol-1-yl)benzoic acid to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(1*H*-tetrazol-1-yl)benzamide. MS (Q1) 421.0 $(M)^+$.

Example 122 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(4-ethylpiperazine-1-carbonyl)benzamide



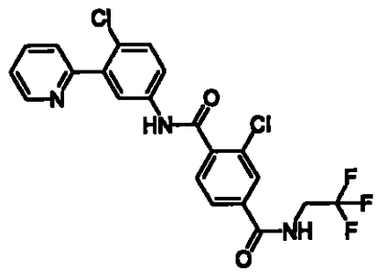
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 1-ethylpiperazine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(4-ethylpiperazine-1-carbonyl)benzamide. MS (Q1) 483 $(M)^+$.

Example 123 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(piperazine-1-carbonyl)benzamide



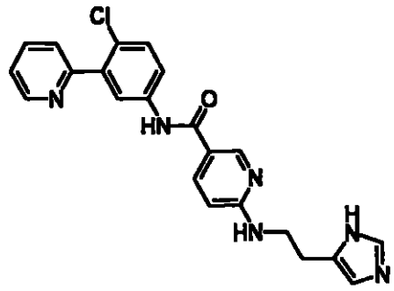
50 mg 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to Boc-piperazine via Procedure G. The organic layer was evaporated to dryness and treated with TFA. After 1 h the TFA was removed and the crude was purified on reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(piperazine-1-carbonyl)benzamide. MS (Q1) 455 $(M)^+$.

Example 124 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2,2,2-trifluoroethyl)terephthalamide



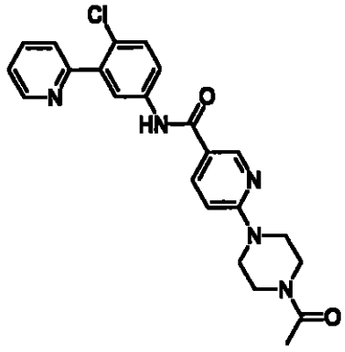
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 2,2,2-trifluoroethylamine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2,2,2-trifluoroethyl)terephthalamide. MS (Q1) 469 $(M)^+$.

Example 125 6-(2-(1*H*-imidazol-5-yl)ethylamino)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide



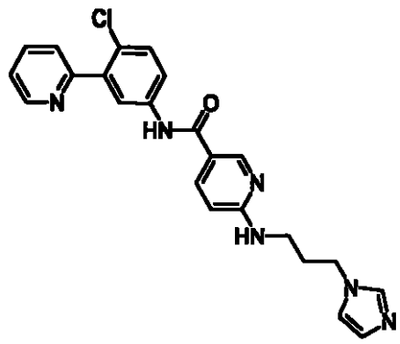
Procedure F was performed using *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-chloro-3-carboxamide (50 mg) and 100 mg of hystamine in butanol (0.5 mL). The crude reaction was purified by reverse phase HPLC to yield 6-(2-(1*H*-imidazol-5-yl)ethylamino)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide. MS (Q1) 419 $(M)^+$.

Example 126 6-(4-acetylpiperazin-1-yl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide



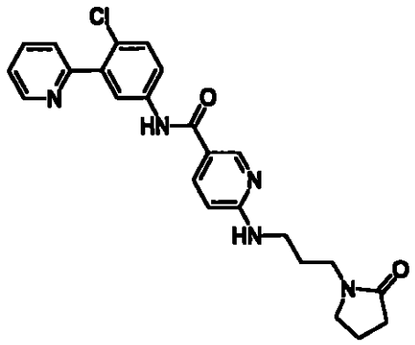
Procedure F was performed using *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-chloro-3-carboxamide (50 mg) and 0.12 mL of acetylpiperazine in butanol (0.5 mL). The crude reaction was purified by reverse phase HPLC to yield 6-(4-acetylpiperazin-1-yl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide. MS (Q1) 436 $(M)^+$.

Example 127 6-(3-(1*H*-imidazol-1-yl)propylamino)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide



Procedure F was performed using *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-chloro-3-carboxamide (50 mg) and 125 mg of 1-(3-aminopropyl)imidazole in butanol (0.5 mL). The crude reaction was purified by reverse phase HPLC to yield 6-(3-(1*H*-imidazol-1-yl)propylamino)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide. MS (Q1) 433 $(M)^+$.

Example 128 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(3-(2-oxopyrrolidin-1-yl)propylamino)nicotinamide

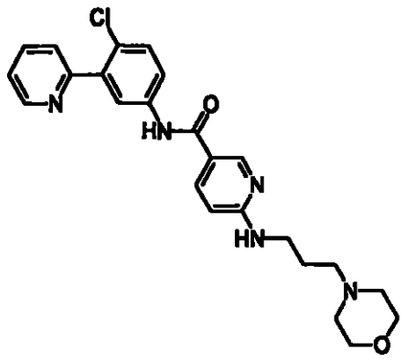


Procedure F was performed using *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-chloro-3-carboxamide (50 mg) and 0.42 mL of 1-(3-aminopropyl)-2-pyrrolidinone in butanol (0.5 mL). The crude reaction was purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(3-(2-oxopyrrolidin-1-yl)propylamino)nicotinamide. MS (Q1) 450 $(M)^+$.

Example 129 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(3-morpholinopropylamino)nicotinamide

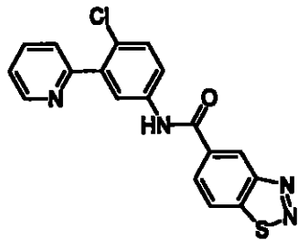
153

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Procedure F was performed using *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-chloro-3-carboxamide (50 mg) and 0.14 mL of N-(3-aminopropyl)morpholine in butanol (0.5 mL). The crude reaction was purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(3-morpholinopropylamino)nicotinamide. MS (Q1) 452 $(M)^+$.

Example 130 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzo[d][1,2,3]thiadiazole-5-carboxamide

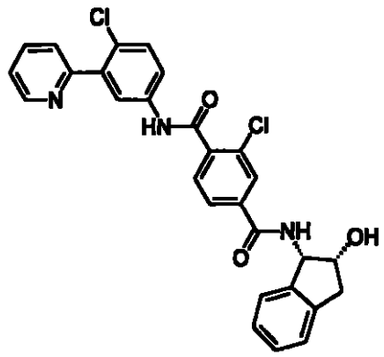


50 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to benzo-1,2,3-thiadiazole-5-carboxylic acid via Procedure G. The crude product was purified via reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzo[d][1,2,3]thiadiazole-5-carboxamide. MS (Q1) 367 $(M)^+$.

Example 131 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)terephthalamide

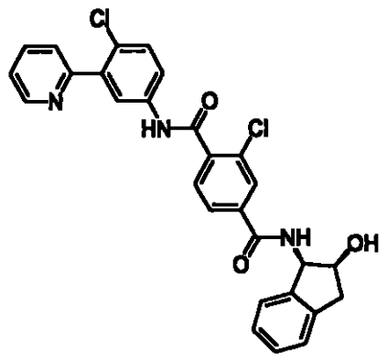
154

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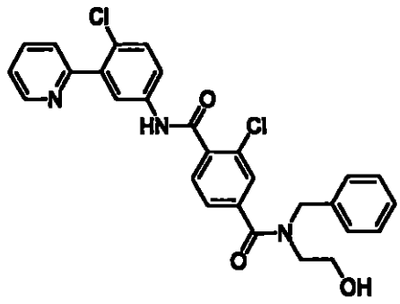
60 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to (1*S*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-ol via Procedure G. The crude product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)terephthalamide. MS (Q1) 518.2 $(M)^+$.

Example 132 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-((1*R*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)terephthalamide



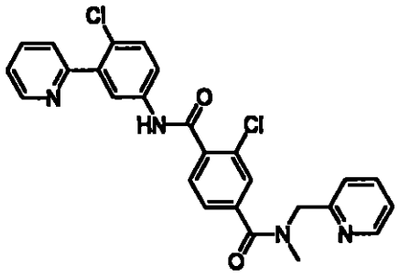
60 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol via Procedure G. The crude product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-((1*R*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)terephthalamide. MS (Q1) 518.2 $(M)^+$.

Example 133 N^4-benzyl-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-hydroxyethyl)-terephthalamide



40 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 2-(benzylamino)ethanol via Procedure G. The crude product was purified on reverse phase HPLC to yield N^4-benzyl-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-hydroxyethyl)terephthalamide. MS (Q1) 520 $(M)^+$.

Example 134 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-methyl-N^4-(pyridin-2-ylmethyl)terephthalamide

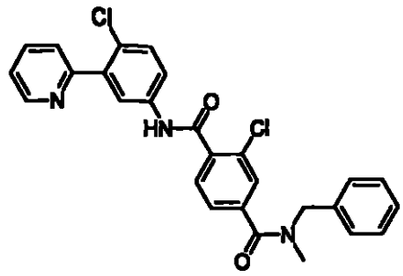


40 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to *N*-methyl-1-(pyridin-2-yl)methanamine via Procedure G. The crude product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-methyl-N^4-(pyridin-2-ylmethyl)terephthalamide. MS (Q1) 491 $(M)^+$.

Example 135 N^4-benzyl-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-methylterephthalamide

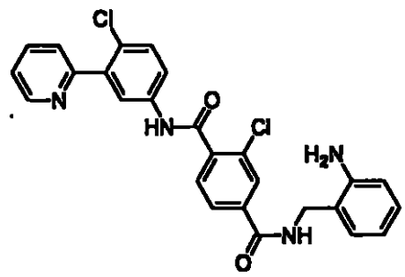
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40 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to *N*-methyl-1-phenylmethanamine via Procedure G. The crude product was purified on reverse phase HPLC to yield N^4-benzyl-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-methylterephthalamide. MS (Q1) 490.1 $(M)^+$.

Example 136 N^4-(2-aminobenzyl)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)terephthalamide

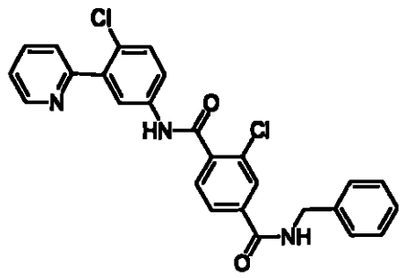


60 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to N^1-phenylethane-1,2-diamine via Procedure G. The crude product was purified on reverse phase HPLC to yield N^4-(2-aminobenzyl)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)terephthalamide. MS (Q1) 491 $(M)^+$.

Example 137 N^4-benzyl-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)terephthalamide

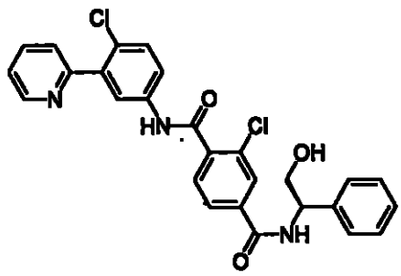
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60 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to benzylamine via Procedure G. The crude product was purified on reverse phase HPLC to yield N^4-benzyl-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)terephthalamide. MS (Q1) 476 $(M)^+$.

Example 138 (*R*)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-hydroxy-1-phenylethyl)terephthalamide

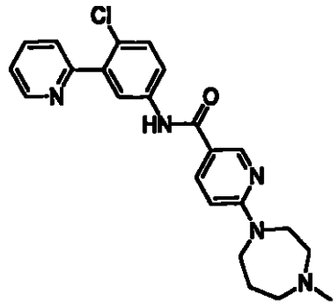


60 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to (*R*)-2-amino-2-phenylethanol via Procedure G. The crude product was purified on reverse phase HPLC to yield (*R*)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-hydroxy-1-phenylethyl)terephthalamide. MS (Q1) 506 $(M)^+$.

Example 139 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(4-methyl-1,4-diazepan-1-yl)nicotinamide

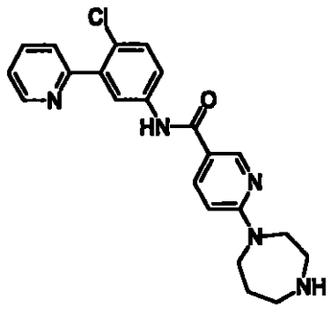
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50 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide was reacted with 1-methyl-1,4-diazepane via Procedure F. The reaction was evaporated to dryness and purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(4-methyl-1,4-diazepan-1-yl)nicotinamide. MS (Q1) 422 $(M)^+$.

Example 140 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(1,4-diazepan-1-yl)nicotinamide

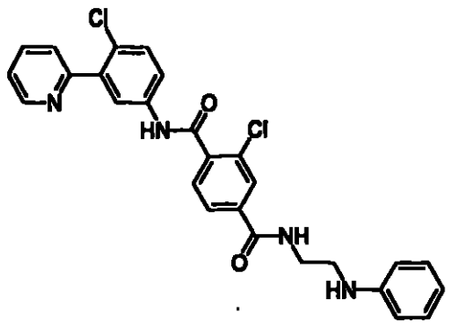


50 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide was reacted with 1,4-diazepane via Procedure F. The reaction was evaporated to dryness and purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(1,4-diazepan-1-yl)nicotinamide. MS (Q1) 408 $(M)^+$.

Example 141 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-(phenylamino)ethyl)terephthalamide

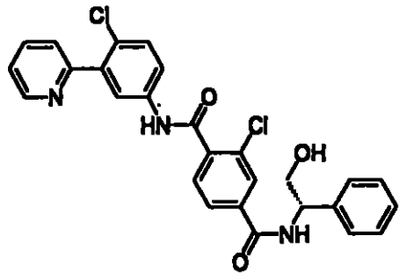
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62 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to N^1-phenylethane-1,2-diamine via Procedure G. The crude product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-(phenylamino)ethyl)terephthalamide. MS (Q1) 505.1 $(M)^+$.

Example 142 (*S*)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-hydroxy-1-phenylethyl)terephthalamide

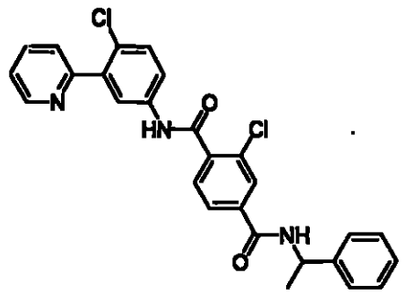


62 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to (*S*)-2-amino-2-phenylethanol via Procedure G. The crude product was purified on reverse phase HPLC to yield (*S*)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-hydroxy-1-phenylethyl)terephthalamide. MS (Q1) 506 $(M)^+$.

Example 143 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(1-phenylethyl)terephthalamide

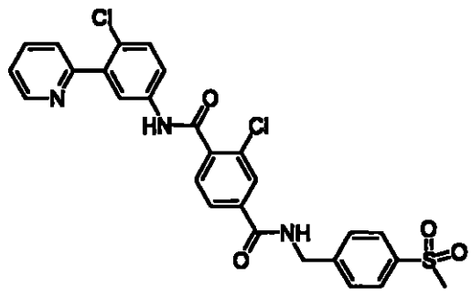
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62 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 1-phenylethanamine via Procedure G. The crude product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(1-phenylethyl)terephthalamide. MS (Q1) 490.1 $(M)^+$.

Exampl 144 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(4-(methylsulfonyl)benzyl)-terephthalamide .

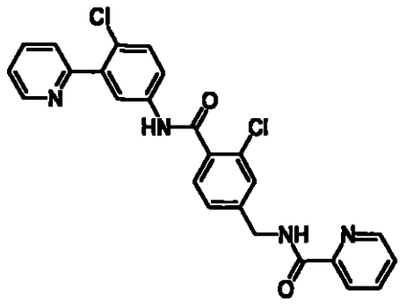


62 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to (4-(methylsulfonyl)phenyl)methanamine via Procedure G. The crude product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(4-(methylsulfonyl)benzyl)terephthalamide. MS (Q1) 554 $(M)^+$.

Example 145 *N*-(3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzyl)picolinamide

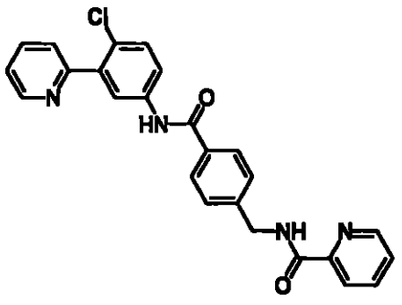
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75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-((*tert*-butoxycarbonylamino)methyl)-2-chlorobenzoic acid via Procedure G to yield *tert*-butyl 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzylcarbamate. *Tert*-butyl 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzylcarbamate was subsequently treated with 4N HCl in Dioxane to remove the Boc protecting group and form the HCl salt of 4-(aminomethyl)-2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide. 54 mg of the crude HCl salt of 4-(aminomethyl)-2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide was coupled to picolinic acid via Procedure G. The crude product was purified by reverse phase HPLC to yield *N*-(3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzyl)picolinamide. MS (Q1) 477.3 $(M)^+$.

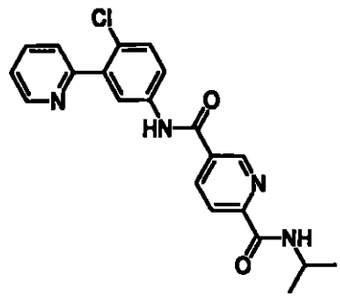
Example 146 *N*-(4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzyl)picolinamide



75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-((*tert*-butoxycarbonylamino)methyl)benzoic acid via Procedure G to yield *tert*-butyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzylcarbamate. *Tert*-butyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzylcarbamate was subsequently treated with 4N HCl in Dioxane to remove the Boc protecting group and form the HCl salt of 4-(aminomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide. 50 mg of the crude HCl salt of 4-(aminomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide was coupled to picolinic acid via Procedure G. The crude product was

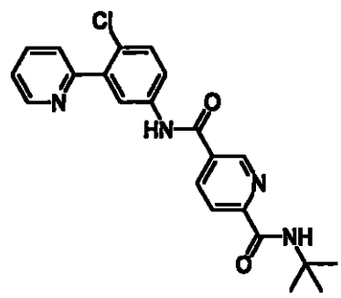
purified by reverse phase HPLC to yield *N*-(4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzyl)picolinamide. MS (Q1) 443.3 $(M)^+$.

Example 147 N^5-(4-chloro-3-(pyridin-2-yl)phenyl)-N^2-isopropylpyridine-2,5-dicarboxamide



250 mg of 5-(methoxycarbonyl)picolinic acid was coupled to isopropylamine via Procedure G. Crude methyl 6-(isopropylcarbamoyl)nicotinate was hydrolyzed via Procedure M to yield 227 mg of 6-(isopropylcarbamoyl)nicotinic acid. 60 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 6-(isopropylcarbamoyl)nicotinic acid via Procedure G. The crude product was purified by reverse phase HPLC to yield N^5-(4-chloro-3-(pyridin-2-yl)phenyl)-N^2-isopropylpyridine-2,5-dicarboxamide. MS (Q1) 395.1 $(M)^+$.

Example 148 N^2-*tert*-butyl-N^5-(4-chloro-3-(pyridin-2-yl)phenyl)pyridine-2,5-dicarboxamide



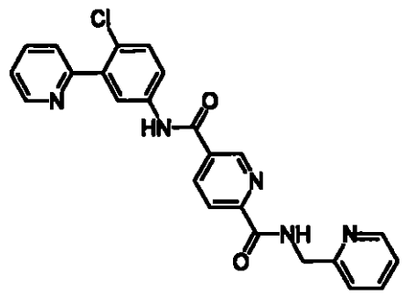
250 mg of 5-(methoxycarbonyl)picolinic acid was coupled to *tert*-butylamine via Procedure G. Crude methyl 6-(*tert*-butylcarbamoyl)nicotinate was hydrolyzed via Procedure M to yield 250 mg of 6-(*tert*-butylcarbamoyl)nicotinic acid. 60 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 6-(*tert*-butylcarbamoyl)nicotinic acid via Procedure G. The crude product was purified by reverse

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phase HPLC to yield N^2-*tert*-butyl-N^5-(4-chloro-3-(pyridin-2-yl)phenyl)pyridine-2,5-dicarboxamide. MS (Q1) 409 $(M)^+$.

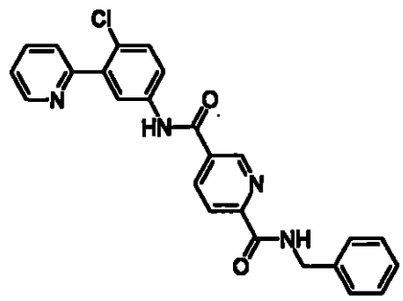
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Example 149 N^5-(4-chloro-3-(pyridin-2-yl)phenyl)-N^2-(pyridin-2-ylmethyl)pyridine-2,5-dicarboxamide



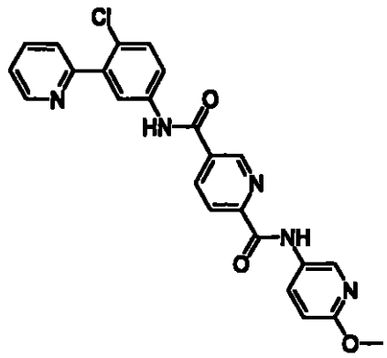
250 mg of 5-(methoxycarbonyl)picolinic acid was coupled to pyridin-2-ylmethanamine via Procedure G. Crude methyl 6-(pyridin-2-ylmethylcarbamoyl)nicotinate was hydrolyzed via Procedure M to yield 250 mg of 6-(pyridin-2-ylmethylcarbamoyl)nicotinic acid. 60 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 6-(pyridin-2-ylmethylcarbamoyl)nicotinic acid via Procedure G. The crude product was purified by reverse phase HPLC to yield N^5-(4-chloro-3-(pyridin-2-yl)phenyl)-N^2-(pyridin-2-ylmethyl)pyridine-2,5-dicarboxamide. MS (Q1) 444.1 $(M)^+$.

Example 150 N^2-benzyl-N^5-(4-chloro-3-(pyridin-2-yl)phenyl)pyridine-2,5-dicarboxamide



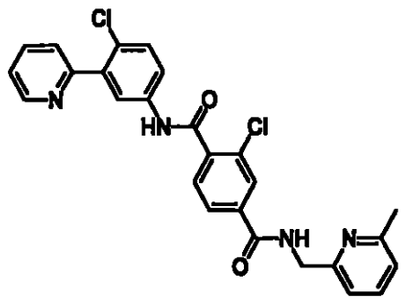
250 mg of 5-(methoxycarbonyl)picolinic acid was coupled to benzylamine via Procedure G. Crude methyl 6-(benzylcarbamoyl)nicotinate was hydrolyzed via Procedure M to yield 300 mg of 6-(benzylcarbamoyl)nicotinic acid. 60 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 6-(benzylcarbamoyl)nicotinic acid via Procedure G. The crude product was purified by reverse phase HPLC to yield N^2-benzyl-N^5-(4-chloro-3-(pyridin-2-yl)phenyl)pyridine-2,5-dicarboxamide. MS (Q1) 443.1 $(M)^+$.

Example 151 N^5-(4-chloro-3-(pyridin-2-yl)phenyl)-N^2-(6-methoxypyridin-3-yl)pyridine-2,5-dicarboxamide



250 mg of 5-(methoxycarbonyl)picolinic acid was coupled to 6-methoxypyridin-3-amine via Procedure G. Crude methyl 6-(6-methoxypyridin-3-ylcarbamoyl)nicotinate was hydrolyzed via Procedure M to yield 196 mg of 6-(6-methoxypyridin-3-ylcarbamoyl)nicotinic acid. 60 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 6-(6-methoxypyridin-3-ylcarbamoyl)nicotinic acid via Procedure G. The crude product was recrystallized to yield pure N^5-(4-chloro-3-(pyridin-2-yl)phenyl)-N^2-(6-methoxypyridin-3-yl)pyridine-2,5-dicarboxamide. MS (Q1) 460 $(M)^+$.

Example 152 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-((6-methylpyridin-2-yl)methyl)-terephthalamide

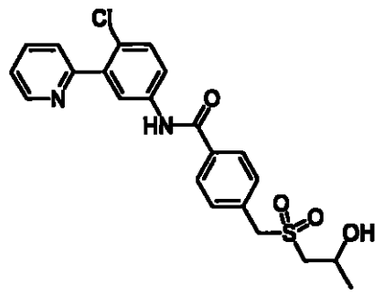


2.5 mL of Diisopropylazodicarboxylate in 1.5mL of THF was added dropwise to a solution of 250 mg of (6-methylpyridin-2-yl)methanol, 2.8g of Triphenylphosphine and 1.6 g of isoindoline-1,3-dione in anhydrous THF at room temperature. The reaction was stirred for 2 hours and monitored

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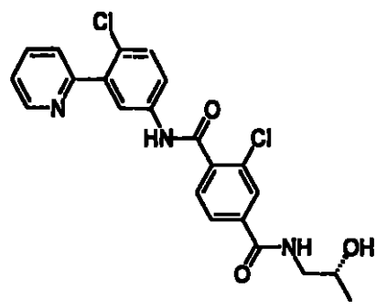
by TLC. Upon completion, the solvent was concentrated, the crude material was extracted in water and Chloroform 3 times and dried over Magnesium Sulfate. The crude was purified via ISCO Combi-Flash to yield 2-((6-methylpyridin-2-yl)methyl)isoindoline-1,3-dione. 350 mg of 2-((6-methylpyridin-2-yl)methyl)isoindoline-1,3-dione was treated with 440 µL of Hydrazine Monohydrate in EtOH and refluxed for several hours to yield (6-methylpyridin-2-yl)methanamine. The crude (6-methylpyridin-2-yl)methanamine was evaporated and directly coupled to 50mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid via Procedure G. The crude product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-((6-methylpyridin-2-yl)methyl)terephthalamide. MS (Q1) 491.1 $(M)^+$.

Example 153 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((2-hydroxypropylsulfonyl)methyl)benzamide



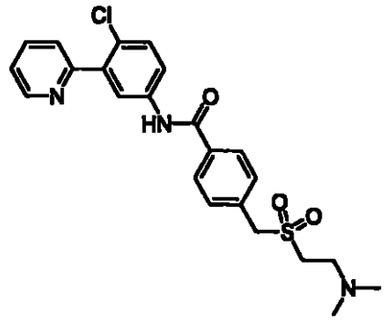
1 g of methyl 4-(bromomethyl)benzoate was reacted with 1-mercaptopropan-2-ol via Procedure Q. 1 g of methyl 4-((2-hydroxypropylthio)methyl)benzoate was oxidized with 2g of MCPBA in DCM at –78°C to form crude methyl 4-((2-hydroxypropylsulfonyl)methyl)benzoate. The reaction was evaporated and purified by ISCO Combi-Flash to yield 567 mg of pure methyl 4-((2-hydroxypropylsulfonyl)methyl)benzoate which was subsequently hydrolyzed via Procedure M to give 328 mg of 4-((2-hydroxypropylsulfonyl)methyl)benzoic acid. 50 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-((2-hydroxypropylsulfonyl)methyl)benzoic acid via Procedure G. The crude product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((2-hydroxypropylsulfonyl)methyl)benzamide. MS (Q1) 445.3 $(M)^+$.

Example 154 (*R*)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-hydroxypropyl)terephthalamide



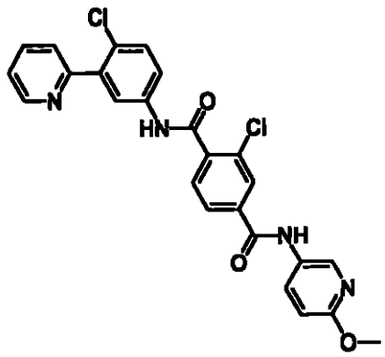
100 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to (*R*)-2-amino-2-phenylethanol via Procedure G. The crude product was purified on reverse phase HPLC to yield (*R*)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-hydroxypropyl)terephthalamide. MS (Q1) 444.3 $(M)^+$.

Example 155 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((2-(dimethylamino)ethylsulfonyl)methyl)-benzamide



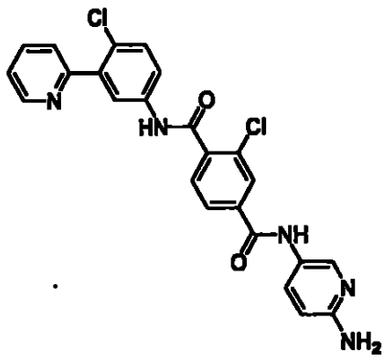
500 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-(bromomethyl)benzoic acid via Procedure E. 170 mg of 4-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide was reacted with 2-(dimethylamino)ethanethiol hydrochloride via Procedure Q. 140mg of crude *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((2-(dimethylamino)ethylthio)methyl)benzamide was reacted with oxone via Procedure R. The crude product was purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((2-(dimethylamino)ethylsulfonyl)methyl)benzamide. MS (Q1) 458.3 $(M)^+$.

Example 156 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(6-methoxypyridin-3-yl)terephthalamide



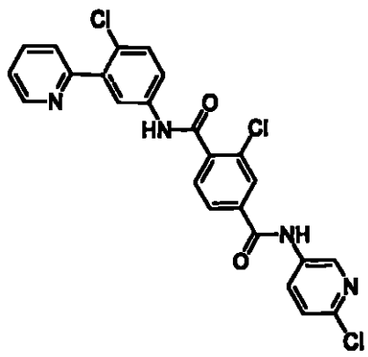
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 6-methoxypyridin-3-amine via Procedure G. The crude product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(6-methoxypyridin-3-yl)terephthalamide. MS (Q1) 493 $(M)^+$.

Example 157 N^4-(6-aminopyridin-3-yl)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-terephthalamide



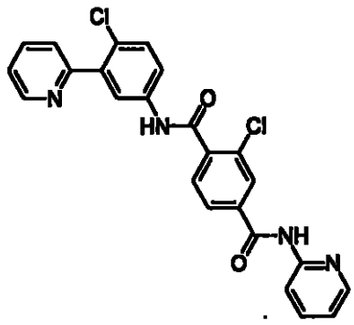
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to pyridine-2,5-diamine via Procedure G. The crude product was purified on reverse phase HPLC to yield N^4-(6-aminopyridin-3-yl)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)terephthalamide. MS (Q1) 478 $(M)^+$.

Example 158 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(6-chloropyridin-3-yl)terephthalamide



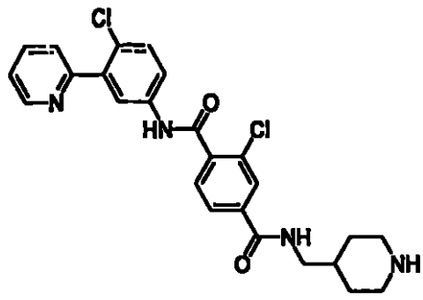
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 6-chloropyridin-3-amine via Procedure G. The crude product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(6-chloropyridin-3-yl)terephthalamide. MS (Q1) 497 $(M)^+$.

Example 159 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(pyridin-2-yl)terephthalamide



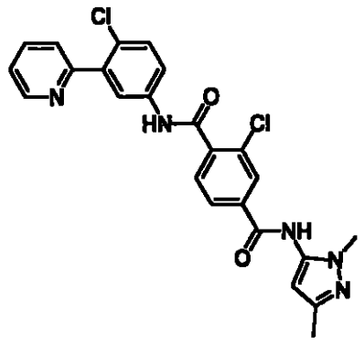
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to pyridin-2-amine via Procedure G. The crude product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(pyridin-2-yl)terephthalamide. MS (Q1) 463 $(M)^+$.

Example 160 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(piperidin-4-ylmethyl)terephthalamide



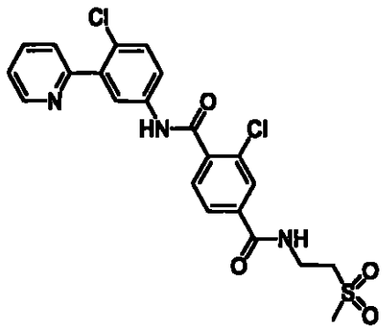
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to piperidin-4-ylmethanamine via Procedure G. The crude product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(piperidin-4-ylmethyl)terephthalamide. MS (Q1) 483 $(M)^+$.

Example 161 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(1,3-dimethyl-1*H*-pyrazol-5-yl)terephthalamide



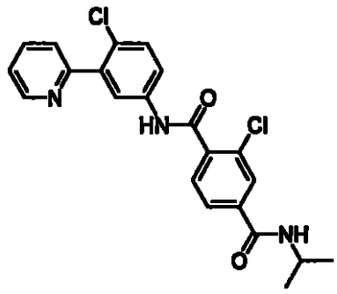
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 1,3-dimethyl-1*H*-pyrazol-5-amine via Procedure G. The crude product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(1,3-dimethyl-1*H*-pyrazol-5-yl)terephthalamide. MS (Q1) 480 $(M)^+$.

Example162 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-(methylsulfonyl)ethyl)-terephthalamide



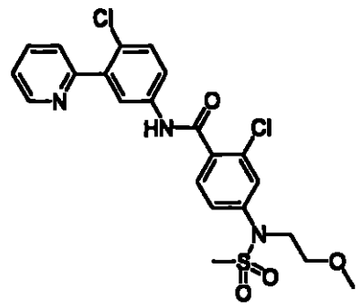
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 2-(methylsulfonyl)ethanamine via Procedure G. The crude product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-(methylsulfonyl)ethyl)terephthalamide. MS (Q1) 492 $(M)^+$.

Example 163 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-isopropylterephthalamide



50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to isopropylamine via Procedure G. The crude product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-isopropylterephthalamide. MS (Q1) 428 $(M)^+$.

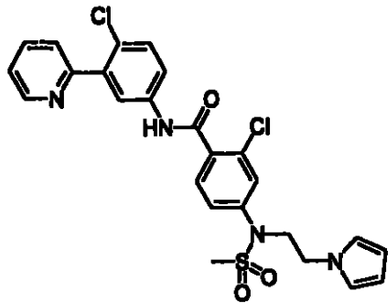
Example 164 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-(2-methoxyethyl)methylsulfonamido)benzamide



To 5 g of methyl 2-chloro-4-nitrobenzoate in 100 mL of EtOH was added 20 g of Tin (II) Chloride in portions. The reaction was heated to 55°C and monitored by TLC until complete. Solvent was concentrated and extraction was performed in Ethyl Acetate and water with TEA to reduce emulsions. The organic layer was dried over Magnesium Sulfate, filtered and concentrated to give 3.9 g of methyl 4-amino-2-chlorobenzoate. 1 g of methyl 4-amino-2-chlorobenzoate was cooled to 0°C in DCM with 485 µL of Pyridine before Methanesulfonyl Chloride was added dropwise. The reaction was allowed to warm to room temperature and stir overnight. Solvent was concentrated and the crude material was dissolved in Ethyl Acetate and extracted with saturated bicarbonate solution and then brine. The crude material was dried over Magnesium Sulfate, filtered and concentrated to give 1.54 g of methyl 2-chloro-4-(methylsulfonamido)benzoate. 107 µL of 1-bromo-2-methoxyethane and 556 mg of Cesium Carbonate were added to 150 mg of methyl 2-chloro-4-(methylsulfonamido)benzoate in DMF and stirred at room temperature for 16 hours. The reaction mixture was extracted in Ethyl Acetate twice with saturated bicarbonate and once with brine, dried over Magnesium Sulfate, filtered and concentrated to give methyl 2-chloro-4-(*N*-(2-methoxyethyl)methylsulfonamido)benzoate. 182 mg of methyl 2-chloro-4-(*N*-(2-methoxyethyl)methylsulfonamido)benzoate was hydrolyzed via Procedure M to yield 169 mg of crude 2-chloro-4-(*N*-(2-methoxyethyl)methylsulfonamido)benzoic acid. 65 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 2-chloro-4-(*N*-(2-methoxyethyl)methylsulfonamido)benzoic acid via Procedure G. The crude product was purified by reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-(2-methoxyethyl)methylsulfonamido)benzamide. MS (Q1) 494 $(M)^+$.

Example 165 4-(*N*-(2-(1*H*-pyrrol-1-yl)ethyl)methylsulfonamido)-2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide

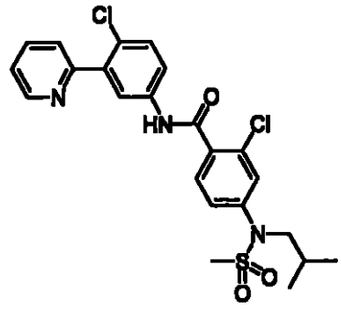
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200 μL of 1-(2-bromoethyl)-1*H*-pyrrole and 556 mg of Cesium Carbonate were added to 150 mg of methyl 2-chloro-4-(methylsulfonamido)benzoate in DMF and stirred at room temperature for 16 hours. The reaction mixture was extracted in Ethyl Acetate twice with saturated bicarbonate and once with brine, dried over Magnesium Sulfate, filtered and concentrated to give methyl 4-(*N*-(2-(1*H*-pyrrol-1-yl)ethyl)methylsulfonamido)-2-chlorobenzoate. 230 mg of methyl 4-(*N*-(2-(1*H*-pyrrol-1-yl)ethyl)methylsulfonamido)-2-chlorobenzoate was hydrolyzed via Procedure M to yield 221 mg of crude 4-(*N*-(2-(1*H*-pyrrol-1-yl)ethyl)methylsulfonamido)-2-chlorobenzoic acid.

64 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-(*N*-(2-(1*H*-pyrrol-1-yl)ethyl)methylsulfonamido)-2-chlorobenzoic acid via Procedure G. The crude product was purified by reverse phase HPLC to yield 4-(*N*-(2-(1*H*-pyrrol-1-yl)ethyl)methylsulfonamido)-2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide. MS (Q1) 529 $(M)^+$.

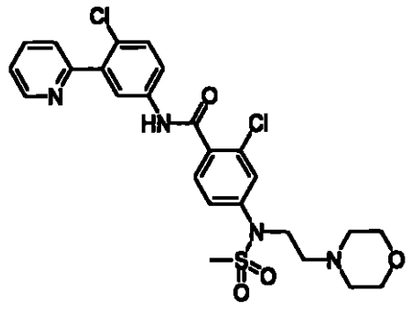
Example 166 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-isobutylmethylsulfonamido)-benzamide



175 μL of 1-iodo-2-methylpropane and 740 mg of Cesium Carbonate were added to 200 mg of methyl 2-chloro-4-(methylsulfonamido)benzoate in 2 mL of DMF and stirred in the microwave at 140°C for 30 minutes. The reaction mixture was extracted in Ethyl Acetate twice with water, dried over Magnesium Sulfate, filtered, concentrated and purified on ISCO Combi-Flash to give methyl

2-chloro-4-(*N*-isobutylmethylsulfonamido)benzoate. 120 mg of methyl 2-chloro-4-(*N*-isobutylmethylsulfonamido)benzoate was hydrolyzed via Procedure M to yield 110 mg of crude 2-chloro-4-(*N*-isobutylmethylsulfonamido)benzoic acid. 75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 2-chloro-4-(*N*-isobutylmethylsulfonamido)benzoic acid via Procedure G. The crude product was purified by reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-isobutylmethylsulfonamido)benzamide. MS (Q1) 492 $(M)^+$. 174

Example 167 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-(2-morpholinoethyl)methylsulfonamido)benzamide

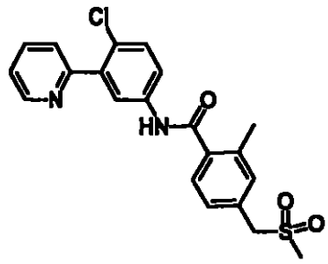


1.2 g of 4-(2-chloroethyl)morpholine and 2.5 g of Cesium Carbonate were added to 334 mg of methyl 2-chloro-4-(methylsulfonamido)benzoate in 7 mL of DMF and stirred in the microwave at 150°C for 30 minutes. The reaction mixture was extracted in Ethyl Acetate twice with water, dried over Magnesium Sulfate, filtered, concentrated to give crude methyl 2-chloro-4-(*N*-(2-morpholinoethyl)methylsulfonamido)benzoate. 476 mg of methyl 2-chloro-4-(*N*-(2-morpholinoethyl)methylsulfonamido)benzoate was hydrolyzed via Procedure M and purified by reverse phase HPLC to yield 460 mg of crude 2-chloro-4-(*N*-(2-morpholinoethyl)methylsulfonamido)benzoic acid. 100 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 2-chloro-4-(*N*-(2-morpholinoethyl)methylsulfonamido)benzoic acid via Procedure G. The crude product was purified by reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-(2-morpholinoethyl)methylsulfonamido)benzamide. MS (Q1) 549 $(M)^+$.

Example 168 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-4-(methylsulfonylmethyl)benzamide

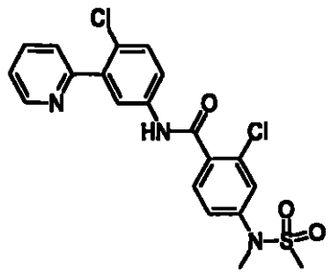
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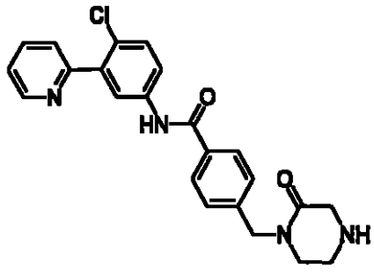
410 mg of dimethyl 2-methylterephthalate was hydrolyzed via Procedure M and purified by ISCO Combi-Flash to afford 4-(methoxycarbonyl)-3-methylbenzoic acid. 255 mg of 4-(methoxycarbonyl)-3-methylbenzoic acid was cooled to O°C in 2 mL of THF before a solution of 2.6 mL of 1M BH_3-THF complex in THF was added dropwise. The ice bath was subsequently removed and the reaction was stirred at room temperature until reaction stalled out at ~50% complete by TLC. The reaction was re-cooled to 0°C and another 2.6 mL of BH_3-THF was added dropwise before the ice bath was removed. Upon completion, the reaction was re-cooled to 0°C and quenched with 3N HCl dropwise. The aqueous layer was extracted 2 times with Ethyl Acetate and the organic layer was then extracted once with bicarbonate solution and brine, dried over Magnesium Sulfate, filtered and concentrated to give methyl 4-(hydroxymethyl)-2-methylbenzoate. 220 mg of methyl 4-(hydroxymethyl)-2-methylbenzoate was cooled to 0°C in 5 mL of DCM before adding 260 mg of Triphenylphosphine and 395 mg of NBS. The reaction was concentrated and directly purified via ISCO Combi-Flash to give pure methyl 4-(bromomethyl)-2-methylbenzoate. 255 mg of methyl 4-(bromomethyl)-2-methylbenzoate was reacted via Procedure O to give methyl 2-methyl-4-(methylsulfonylmethyl)benzoate. 250 mg of methyl 2-methyl-4-(methylsulfonylmethyl)benzoate was then hydrolyzed upon heating to 45°C for 1 hour via Procedure M to give 2-methyl-4-(methylsulfonylmethyl)benzoic acid. 202 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 2-methyl-4-(methylsulfonylmethyl)benzoic acid via Procedure G. The crude product was purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-4-(methylsulfonylmethyl)benzamide. MS (Q1) 415 $(M)^+$.

Example 169 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-methylmethyl-sulfonamido)benzamide



78 μL of iodomethane and 447 mg of Cesium Carbonate were added to 300 mg of methyl 2-chloro-4-(methylsulfonamido)benzoate in 3 mL of DMF and stirred at room temperature for 16 hours. The reaction mixture was extracted in Ethyl Acetate twice with saturated bicarbonate and once with brine, dried over Magnesium Sulfate, filtered and concentrated to give crude methyl 2-chloro-4-(*N*-methylmethylsulfonamido)benzoate. 295 mg of methyl 2-chloro-4-(*N*-methylmethylsulfonamido)benzoate was hydrolyzed via Procedure M to yield 249 mg of 2-chloro-4-(*N*-methylmethylsulfonamido)benzoic acid. 100 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 2-chloro-4-(*N*-methylmethylsulfonamido)benzoic acid via Procedure G. The crude product was purified by reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-methylmethylsulfonamido)benzamide. MS (Q1) 450 $(M)^+$.

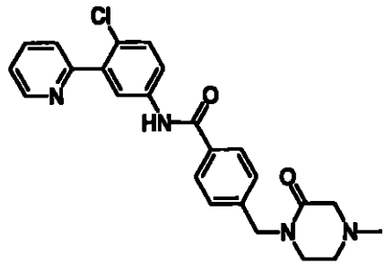
Example 170 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((2-oxopiperazin-1-yl)methyl)benzamide



500 mg of methyl 4-(bromomethyl)benzoate was reacted with 480 mg of *tert*-butyl 3-oxopiperazine-1-carboxylate and 1 g of Cesium Carbonate in 9 mL of DMF at 45°C. Upon completion, the reaction was extracted in Ethyl Acetate 2 times saturated bicarbonate, dried over Magnesium Sulfate, filtered and concentrated to give *tert*-butyl 4-(4-(methoxycarbonyl)benzyl)-3-oxopiperazine-1-carboxylate. 613 mg of *tert*-butyl 4-(4-(methoxycarbonyl)benzyl)-3-oxopiperazine-1-carboxylate was hydrolyzed via Procedure M to give 4-((4-(*tert*-butoxycarbonyl)-2-oxopiperazin-1-yl)methyl)benzoic acid. 200 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled

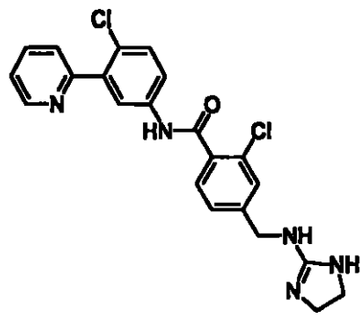
to 4-((4-(*tert*-butoxycarbonyl)-2-oxopiperazin-1-yl)methyl)benzoic acid via Procedure G. The crude product was extracted twice with saturated bicarbonate in Ethyl Acetate, dried over Magnesium Sulfate, filtered and concentrated to give crude *tert*-butyl 4-(4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzyl)-3-oxopiperazine-1-carboxylate. 4N HCl was subsequently added to crude *tert*-butyl 4-(4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzyl)-3-oxopiperazine-1-carboxylate and concentrated to give the HCl salt of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((2-oxopiperazin-1-yl)methyl)benzamide. The reaction was purified by reverse phase HPLC to give pure *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((2-oxopiperazin-1-yl)methyl)benzamide. MS (Q1) 421.3 $(M)^+$.

Example 171 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((4-methyl-2-oxopiperazin-1-yl)methyl)benzamide



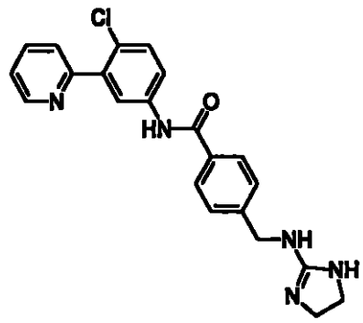
To 200 mg of the HCl salt of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((2-oxopiperazin-1-yl)methyl)benzamide was added 55 mg of Paraformaldehyde and 185 mg of Sodium Triacetoxyborohydride in 1 mL of 2% AcOH in DMF. After completion, the reaction is extracted once with bicarbonate and brine in Ethyl Acetate, dried over Magnesium Sulfate, concentrated and purified by reverse phase HPLC to give pure *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((4-methyl-2-oxopiperazin-1-yl)methyl)benzamide. MS (Q1) 435.3 $(M)^+$.

Example 172 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((4,5-dihydro-1*H*-imidazol-2-ylamino)methyl)benzamide



100 mg of the crude HCl salt of 4-(aminomethyl)-2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide was reacted with 72 mg of 1-(4,5-dihydro-1*H*-imidazol-2-yl)-3,5-dimethyl-1*H*-pyrazole and 100 µL of DIPEA in 500 µL of DMF in the microwave at 150°C for 5 minutes. The crude product was concentrated to dryness and purified by reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((4,5-dihydro-1*H*-imidazol-2-ylamino)methyl)benzamide. MS (Q1) 440 $(M)^+$.

Example 173 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((4,5-dihydro-1*H*-imidazol-2-ylamino)methyl)benzamide

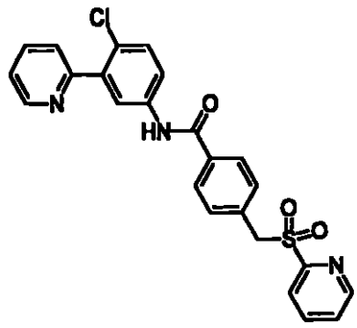


100 mg of the crude HCl salt of 4-(aminomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide was reacted with 80 mg of 1-(4,5-dihydro-1*H*-imidazol-2-yl)-3,5-dimethyl-1*H*-pyrazole and 110 µL of DIPEA in 1 mL of DMF in the microwave at 150°C for 5 minutes. The crude product was concentrated to dryness and purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((4,5-dihydro-1*H*-imidazol-2-ylamino)methyl)benzamide. MS (Q1) 406 $(M)^+$.

Example 174 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((pyridin-2-ylsulfonyl)methyl)benzamide

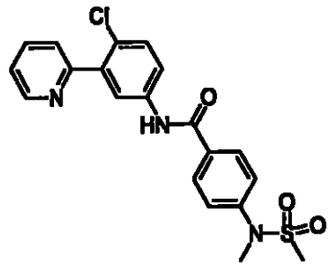
178

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500 mg of methyl 4-(bromomethyl)benzoate was reacted with pyridine-2-thiol via Procedure Q. 260 mg of methyl 4-((pyridin-2-ylthio)methyl)benzoate was reacted via Procedure R to give methyl 4-((pyridin-2-ylsulfonyl)methyl)benzoate. 275 mg of methyl 4-((pyridin-2-ylsulfonyl)methyl)benzoate was hydrolyzed via Procedure M to give 4-((pyridin-2-ylsulfonyl)methyl)benzoic acid. 75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-((pyridin-2-ylsulfonyl)methyl)benzoic acid via Procedure G. The crude product was purified by reverse phase HPLC to yield pure *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((pyridin-2-ylsulfonyl)methyl)benzamide. MS (Q1) 464.1 $(M)^+$.

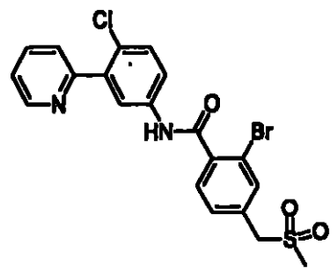
Example 175 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-methylmethylsulfonamido)benzamide



500 mg of methyl 4-(methylamino)benzoate was cooled to 0°C in DCM with 270 µL of Pyridine before 260 µL Methanesulfonyl Chloride was added dropwise. Reaction was allowed to warm to room temperature and stir overnight. Solvent was concentrated and the crude material was dissolved in Ethyl Acetate and extracted with 0.1N NaOH solution twice. Crude material was dried over Magnesium Sulfate, filtered and concentrated to give methyl 4-(*N*-methylmethylsulfonamido)benzoate. 698 mg of methyl 4-(*N*-methylmethylsulfonamido)benzoate was hydrolyzed via Procedure M to give 4-(*N*-methylmethylsulfonamido)benzoic acid. 100 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-(*N*-methylmethylsulfonamido)benzoic acid via

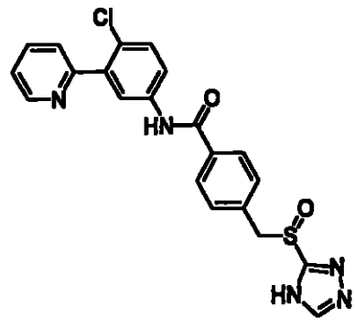
Procedure G. The crude product was purified by reverse phase HPLC to yield pure *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-methylmethylsulfonamido)benzamide. MS (Q1) 416.3 $(M)^+$.

Example 176 2-bromo-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide



1.2 g of 2-bromo-4-methylbenzoic acid was brominated via Procedure N. 100 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 160 mg of 2-bromo-4-(bromomethyl)benzoic acid via Procedure E. 213 mg of 2-bromo-4-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide was reacted via Procedure O to give 2-bromo-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide which was purified by reverse phase HPLC to afford pure 2-bromo-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide. MS (Q1) 481.2 $(M)^+$.

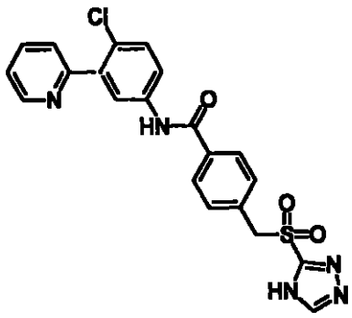
Example 177 4-((4*H*-1,2,4-triazol-3-ylsulfinyl)methyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide



500 mg of methyl 4-(bromomethyl)benzoate was reacted with 4*H*-1,2,4-triazole-3-thiol via Procedure Q. 542 mg of methyl 4-((4*H*-1,2,4-triazol-3-ylthio)methyl)benzoate was subsequently reacted via Procedure R to give an approximate 1:9 mixture of methyl 4-((4*H*-1,2,4-triazol-3-

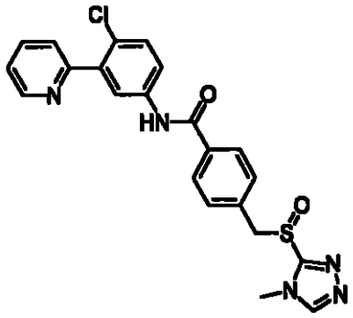
ylsulfinyl)methyl)benzoate and methyl 4-((4*H*-1,2,4-trinzol-3-ylsulfonyl)methyl)benzoate. The mixture of 467 mg was hydrolyzed via Procedure M to give 4-((4*H*-1,2,4-triazol-3-ylsulfinyl)methyl)benzoic acid and 4-((4*H*-1,2,4-triazol-3-ylsulfonyl)methyl)benzoic acid. 107 mg of the mixture of 4-((4*H*-1,2,4-triazol-3-ylsulfinyl)methyl)benzoic acid and 4-((4*H*-1,2,4-triazol-3-ylsulfonyl)methyl)benzoic acid was coupled to 75 mg of 4-chloro-3-(pyridin-2-yl)aniline via Procedure G. The mixture was seperated on reverse phase HPLC to give 4-((4*H*-1,2,4-triazol-3-ylsulfinyl)methyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide. MS (Q1) 438.1 $(M)^+$.

Example 178 4-((4*H*-1,2,4-triazol-3-ylsulfonyl)methyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-benzamide



107 mg of a mixture of 4-((4*H*-1,2,4-triazol-3-ylsulfinyl)methyl)benzoic acid and 4-((4*H*-1,2,4-triazol-3-ylsulfonyl)methyl)benzoic acid was coupled to 75 mg of 4-chloro-3-(pyridin-2-yl)aniline via Procedure G. The mixture was seperated on reverse phase HPLC to give 4-((4*H*-1,2,4-triazol-3-ylsulfonyl)methyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide. MS (Q1) 454.3 $(M)^+$.

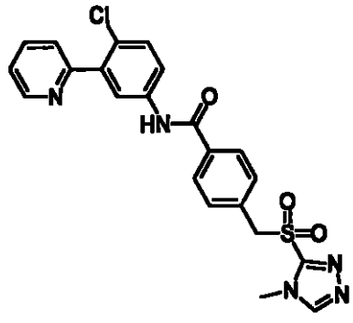
Example 179 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((4-methyl-4*H*-1,2,4-triazol-3-ylsulfinyl)-methyl)benzamide



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500 mg of methyl 4-(bromomethyl)benzoate was reacted with 4-methyl-4*H*-1,2,4-triazole-3-thiol via Procedure Q. 804 mg of methyl 4-((4-methyl-4*H*-1,2,4-triazol-3-ylthio)methyl)benzoate was subsequently reacted via Procedure R to give an approximate 1:9 mixture of methyl 4-((4-methyl-4*H*-1,2,4-triazol-3-ylsulfinyl)methyl)benzoate and methyl 4-((4-methyl-4*H*-1,2,4-triazol-3-ylsulfonyl)methyl)benzoate. The mixture of 740 mg was hydrolyzed via Procedure M to give 4-((4-methyl-4*H*-1,2,4-triazol-3-ylsulfinyl)methyl)benzoic acid and 4-((4-methyl-4*H*-1,2,4-triazol-3-ylsulfonyl)methyl)benzoic acid. 114 mg of the mixture of 4-((4-methyl-4*H*-1,2,4-triazol-3-ylsulfinyl)methyl)benzoic acid and 4-((4-methyl-4*H*-1,2,4-triazol-3-ylsulfonyl)methyl)benzoic acid was coupled to 75 mg of 4-chloro-3-(pyridin-2-yl)aniline via Procedure G. The mixture was seperated on reverse phase HPLC to give *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((4-methyl-4*H*-1,2,4-triazol-3-ylsulfinyl)methyl)benzamide. MS (Q1) 452.3 $(M)^+$.

Example 180 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((4-methyl-4*H*-1,2,4-triazol-3-ylsulfonyl)-methyl)benzamide

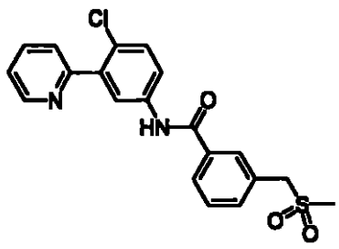


114 mg of the mixture of 4-((4-methyl-4*H*-1,2,4-triazol-3-ylsulfinyl)methyl)benzoic acid and 4-((4-methyl-4*H*-1,2,4-triazol-3-ylsulfonyl)methyl)benzoic acid was coupled to 75 mg of 4-chloro-3-(pyridin-2-yl)aniline via Procedure G. The mixture was separated on reverse phase HPLC to give *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((4-methyl-4*H*-1,2,4-triazol-3-ylsulfonyl)methyl)benzamide. MS (Q1) 468.1 $(M)^+$.

Example 181 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-(methylsulfonylmethyl)benzamide

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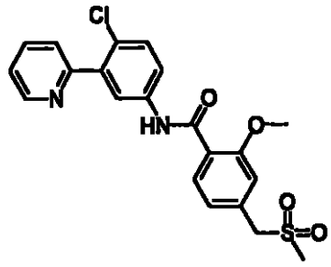
183



300 mg of methyl 3-(bromomethyl)benzoate was reacted via Procedure O to give methyl 3-(methylsulfonylmethyl)benzoate. 230 mg of methyl 3-(methylsulfonylmethyl)benzoate was reacted via Procedure M to give 3-(methylsulfonylmethyl)benzoic acid.

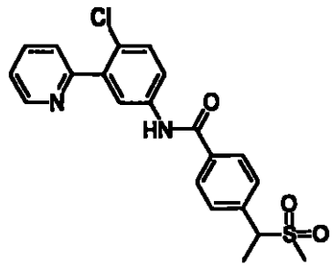
75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 3-(methylsulfonylmethyl)benzoic acid via Procedure G. The crude product was purified by reverse phase HPLC to yield pure *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-(methylsulfonylmethyl)benzamide. MS (Q1) 401 $(M)^+$.

Example 182 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methoxy-4-(methylsulfonylmethyl)benzamide



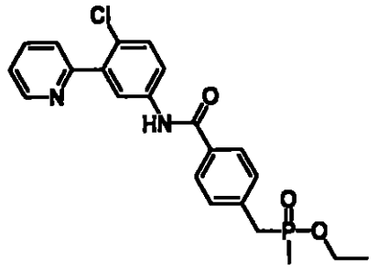
900 mg of 2-methoxy-4-methylbenzoic acid was brominated via Procedure N to afford 4-(bromomethyl)-2-methoxybenzoic acid. 100 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 132 mg of 4-(bromomethyl)-2-methoxybenzoic acid via Procedure E. 211 mg of 4-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methoxybenzamide was reacted via Procedure O and purified by reverse phase HPLC to yield pure *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methoxy-4-(methylsulfonylmethyl)benzamide. MS (Q1) 431 $(M)^+$.

Example 183 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(1-(methylsulfonyl)ethyl)benzamide



75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 93 mg of 4-(1-bromoethyl)benzoic acid via Procedure E. 153 mg of 4-(1-bromoethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide was reacted via Procedure O and purified by reverse phase HPLC to give pure *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(1-(methylsulfonyl)ethyl)benzamide. MS (Q1) 415.3 $(M)^+$.

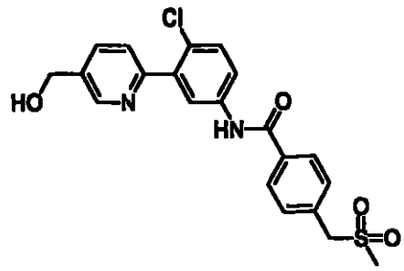
Example 184 ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzyl(methyl)phosphinate



90 mg of 4-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide was reacted with 45 µL of diethyl methylphosphonite in the microwave at 120°C for 5 minutes. The reaction was evaporated to dryness and purified by reverse phase HPLC to give pure ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzyl(methyl)phosphinate. MS (Q1) 429 $(M)^+$.

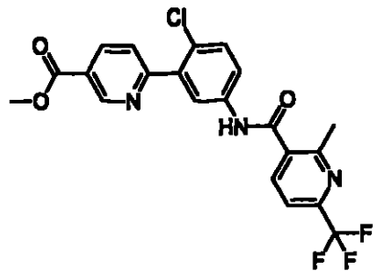
Example 185 *N*-(4-chloro-3-(5-(hydroxymethyl)pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide

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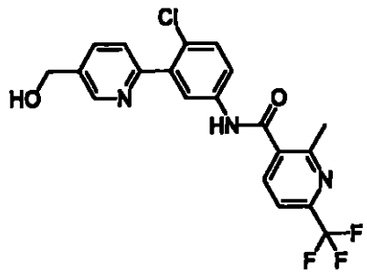
75 mL of (5-methylpyridin-2-yl)zinc(II) bromide was reacted with 4 g of 1-chloro-2-iodo-4-nitrobenzene via Procedure B. To 935 mg of 2-(2-chloro-5-nitrophenyl)-5-methylpyridine in 5 mL of Sulfuric Acid was slowly added 2.25 g of Chromium (III) Oxide and the reaction was stirred for several hours at room temperature until complete. Icewater was added to dilute the reaction and the aqueous layer was extracted 3 times with Ethyl Acetate. The organic layers were combined, dried over Magnesium Sulfate, filtered and concentrated to give 6-(2-chloro-5-nitrophenyl)nicotinic acid. 704 mg of 6-(2-chloro-5-nitrophenyl)nicotinic acid was esterified with 3.1 mL of 4N HCl in Dioxane in 20 mL of MeOH. The reaction was concentrated and subjected to basic workup, dried over Magnesium Sulfate, filtered and concentrated to give methyl 6-(2-chloro-5-nitrophenyl)nicotinate. 681 mg of methyl 6-(2-chloro-5-nitrophenyl)nicotinate was treated with 2.1 g of Tin (II) Chloride and 1 mL of HCl in 25 mL of EtOH. Upon completion, EtOH was concentrated and the reaction was extracted with Ethyl Acetate and water with TEA to decrease emulsions. The organic layer was dried over Magnesium Sulfate, filtered and concentrated to give crude methyl 6-(5-amino-2-chlorophenyl)nicotinate. 296 mg of methyl 6-(5-amino-2-chlorophenyl)nicotinate was coupled to 266 mg of 4-(methylsulfonylmethyl)benzoic acid via Procedure G. To 518 mg of methyl 6-(2-chloro-5-(4-(methylsulfonylmethyl)benzamido)phenyl)nicotinate at 0°C in 20 mL of EtOH was slowly added 640 mg of Sodium Borohydride. The reaction was subsquently refluxed for 1 hour until complete, quenched with water and extracted with Ethyl Acetate. The organic layer was dried over Magnesium Sulfate, filtered, concentrated and purified by reverse phase HPLC to give pure *N*-(4-chloro-3-(5-(hydroxymethyl)pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide. MS (Q1) 431.1 $(M)^+$.

Example 186 6-(2-chloro-5-(2-methyl-6-(trifluoromethyl)nicotinamido)phenyl)nicotinate



200 mg of methyl 6-(5-amino-2-chlorophenyl)nicotinate was treated with 255 µL of 2-methyl-6-(trifluoromethyl)nicotinoyl chloride via Procedure D and purified by reverse phase HPLC to give pure 6-(2-chloro-5-(2-methyl-6-(trifluoromethyl)nicotinamido)phenyl)nicotinate. MS (Q1) 450 $(M)^+$.

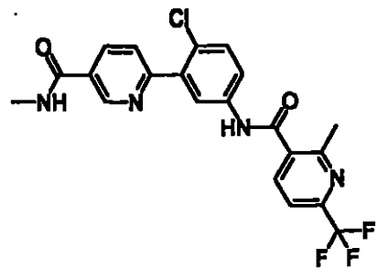
Example 187 *N*-(4-chloro-3-(5-(hydroxymethyl)pyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide



To 110 mg of methyl 6-(2-chloro-5-(2-methyl-6-(trifluoromethyl)nicotinamido)phenyl)nicotinate at 0°C in 5 mL of EtOH was slowly added 148 mg of Sodium Borohydride. The reaction was subsquently refluxed for 1 hour until complete, quenched with water and extracted with Ethyl Acetate. The organic layer was dried over Magnesium Sulfate, filtered, concentrated and purified by reverse phase HPLC to give pure *N*-(4-chloro-3-(5-(hydroxymethyl)pyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide. MS (Q1) 422.1 $(M)^+$.

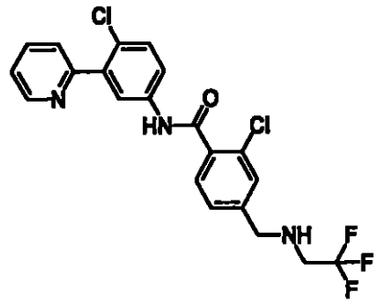
Example 188 *N*-(4-chloro-3-(5-(methylcarbamoyl)pyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide

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187



120 mg of 6-(2-chloro-5-(2-methyl-6-(trifluoromethyl)nicotinamido)phenyl)nicotinate was hydrolyzed via Procedure M. 112 mg of 6-(2-chloro-5-(2-methyl-6-(trifluoromethyl)nicotinamido)phenyl)nicotinic acid was coupled to Methylamine Hydrochloride via Procedure G and purified by reverse phase HPLC to give pure *N*-(4-chloro-3-(5-(methylcarbamoyl)pyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide. MS (Q1) 449 $(M)^+$.

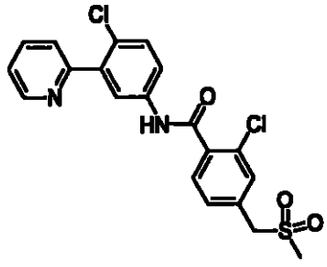
Example 189 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((2,2,2-trifluoroethylamino)methyl)benzamide.



To 24.9 g of 2-chloro-4-(methoxycarbonyl)benzoic acid and 2 mL of Sulfuric Acid in 350 mL of DCM was added isobutylene gas at –78°C until the solvent was saturated and capped off securely. Let go several days at room temperature and re-cool to –78°C before removing cap. Concentrate solvent, extract with Ethyl Acetate and bicarbonate, dry with Magnesium Sulfate, filter and concentrate to give 31.4 g of 1-*tert*-butyl 4-methyl 2-chloroterephthalate. 3.35 g of 1-*tert*-butyl 4-methyl 2-chloroterephthalate was hydrolyzed via Procedure M. 2.5 g of 4-(*tert*-butoxycarbonyl)-3-chlorobenzoic acid was was cooled to 0°C in 25 mL of THF before a solution of 19.5 mL of 1M BH_3-THF complex in THF was added dropwise. The ice bath was subsequently removed and the reaction was stirred at room temperature until reaction stalled out at ~50% complete by TLC. The reaction is re-cooled to 0°C and another 19.5 mL of BH_3-THF is added dropwise before the ice

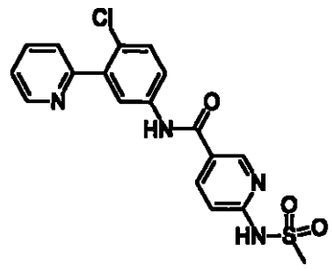
bath is removed. Upon completion, the reaction is re-cooled to 0°C and quenched with 3N HCl dropwise. The aqueous layer was extracted two times with Ethyl Acetate and the organic layer was then extracted once with bicarbonate solution and brine, dried over Magnesium Sulfate, filtered and concentrated to give *tert*-butyl 2-chloro-4-(hydroxymethyl)benzoate. 564 mg of *tert*-butyl 2-chloro-4-(hydroxymethyl)benzoate was cooled to 0°C in 5 mL of DCM before adding 665 mg of Triphenylphosphine and 417 mg of NBS. Reaction was concentrated and directly purified via ISCO Combi-Flash to give pure *tert*-butyl 2-chloro-4-(hydroxymethyl)benzoate. 147 mg of *tert*-butyl 4-(bromomethyl)-2-chlorobenzoate was reacted with 2,2,2-trifluoroethanamine in DMSO via Procedure P. 141 mg of *tert*-butyl 2-chloro-4-((2,2,2-trifluoroethylamino)methyl)benzoate was treated with 4N HCl in Dioxane at 45°C and concentrated to give 2-chloro-4-((2,2,2-trifluoroethylamino)methyl)benzoic acid. 50 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 75 mg of 2-chloro-4-((2,2,2-trifluoroethylamino)methyl)benzoic acid via Procedure G . The crude product was purified by reverse phase HPLC to give pure 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((2,2,2-trifluoroethylamino)methyl)benzamide. MS (Q1) 454.6 $(M)^+$.

Example 190 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide



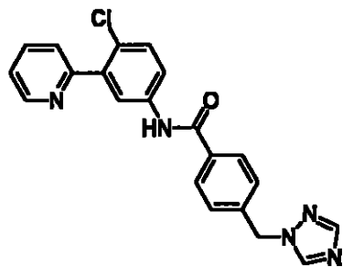
3.01 g of *tert*-butyl 4-(bromomethyl)-2-chlorobenzoate was reacted via Procedure O to give *tert*-butyl 2-chloro-4-(methylsulfonylmethyl)benzoate. 1.2 g of *tert*-butyl 2-chloro-4-(methylsulfonylmethyl)benzoate was treated with 10 mL of 4N HCl in Dioxane at 45°C and concentrated upon completion to give crude 2-chloro-4-(methylsulfonylmethyl)benzoic acid. 775 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 1 g of 2-chloro-4-(methylsulfonylmethyl)benzoic acid via Procedure G. The crude product was purified by reverse phase HPLC to give pure 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide. MS (Q1) 435 $(M)^+$.

Example 191 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(methylsulfonamido)nicotinamide



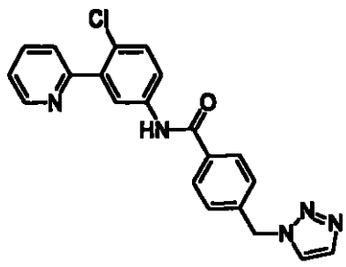
100 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide was reacted with methanesulfonamide and 108 μL of 2-*tert*-Butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine via Procedure F. The crude reaction was concentrated to dryness and purified by reverse phase HPLC to give pure *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(methylsulfonamido)nicotinamide. MS (Q1) 403 $(M)^+$.

Example 192 4-((1*H*-1,2,4-triazol-1-yl)methyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide



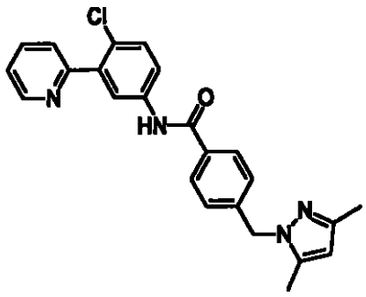
88 mg of 4-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide was coupled to 45 mg of 1*H*-1,2,4-triazole via Procedure P. The reaction was evaporated to dryness and purified by reverse phase HPLC to yield 4-((1*H*-1,2,4-triazol-1-yl)methyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide. MS (Q1) 390 $(M)^+$.

Example 193 4-((1*H*-1,2,3-triazol-1-yl)methyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide



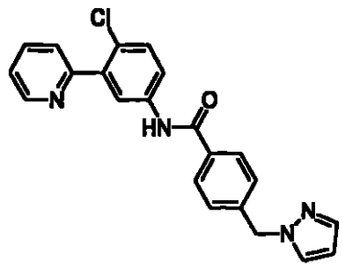
88 mg of 4-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide was coupled to 40 μL of 1*H*-1,2,3-triazole via Procedure P. The reaction was evaporated to dryness and purified by reverse phase HPLC to yield 4-((1*H*-1,2,3-triazol-1-yl)methyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide. MS (Q1) 390.1 $(M)^+$.

Example 194 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((3,5-dimethyl-1*H*-pyrazol-1-yl)methyl)benzamide



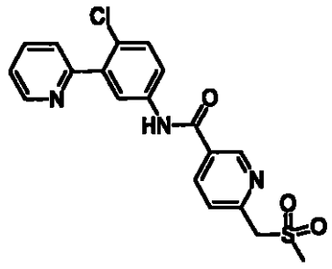
70 mg of 4-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide was coupled to 50 mg of 3,5-dimethyl-1*H*-pyrazole via Procedure P. The reaction was evaporated to dryness and purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((3,5-dimethyl-1*H*-pyrazol-1-yl)methyl)benzamide. MS (Q1) 417.3 $(M)^+$.

Example 195 4-((1*H*-pyrazol-1-yl)methyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide



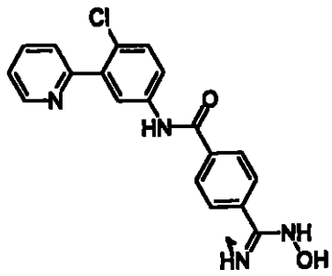
70 mg of 4-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide was coupled to 36 mg of 1*H*-pyrazole via Procedure P. The reaction was evaporated to dryness and purified by reverse phase HPLC to yield 4-((1*H*-pyrazol-1-yl)methyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide. MS (Q1) 389.3 $(M)^+$.

Example 196 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(methylsulfonylmethyl)nicotinamide



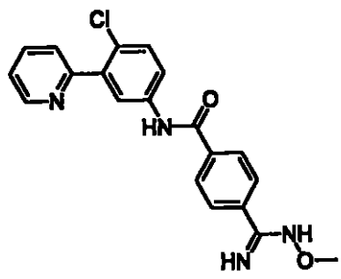
1.2 g of 6-methylnicotinic acid was brominated via Procedure N to give 6-(bromomethyl)nicotinic acid. 75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 87 mg of 6-(bromomethyl)nicotinic acid via Procedure E. 145 mg of 6-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide was reacted via Procedure O and purified by reverse phase HPLC to yield pure *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(methylsulfonylmethyl)nicotinamide. MS (Q1) 402 $(M)^+$.

Example 197 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-hydroxycarbamimidoyl)benzamide



240 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 207 mg of 4-cyanobenzoic acid via Procedure G. To 445 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-cyanobenzamide and 2.5 mL of DIPEA in 10 mL of EtOH was added 793 mg Hydroxylamine Hydrochloride and heated to 60°C until reaction was complete. The solvent was subsequently evaporated, extracted twice with water in Ethyl Acetate, dried with Magnesium Sulfate, filtered and concentrated. The crude product was purified by reverse phase HPLC to give pure *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-hydroxycarbamimidoyl)benzamide. MS (Q1) 367.4 $(M)^+$.

Example 198 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-methoxycarbamimidoyl)benzamide

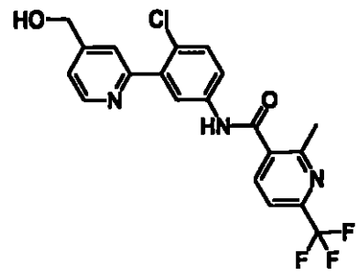


100 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-hydroxycarbamimidoyl)benzamide was cooled to 0°C in 1.5 mL of Dioxane. 5 mL of 2N NaOH was slowly added followed by dropwise addition of 33 µL of dimethylsulfate. The ice bath was removed and reaction was stirred at room temperature for 1 hour. The reaction was subsequently evaporated and extracted with water twice in Ethyl Acetate, dried with Magnesium Sulfate, filtered and concentrated to yield pure *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-methoxycarbamimidoyl)benzamide. MS (Q1) 381 $(M)^+$.

Example 199 *N*-(4-chloro-3-(4-(hydroxymethyl)pyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide

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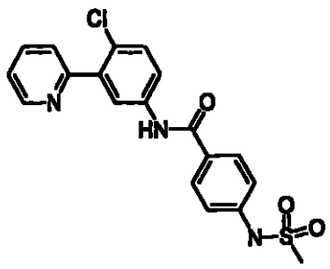
193



75 mL of (4-methylpyridin-2-yl)zinc(II) bromide was reacted with 4 g of 1-chloro-2-iodo-4-nitrobenzene via Procedure B. To 300 mg of 2-(2-chloro-5-nitrophenyl)-4-methylpyridine in 1.5 mL of Sulfuric Acid was slowly added 362 mg of Chromium (III) Oxide and the reaction was stirred for several hours at room temperature until complete. Icewater was added to dilute the reaction and the aqueous layer was extracted 3 times with Ethyl Acetate. The organic layers were combined, dried over Magnesium Sulfate, filtered and concentrated to give 2-(2-chloro-5-nitrophenyl)isonicotinic acid. 300 mg of 2-(2-chloro-5-nitrophenyl)isonicotinic acid was esterified with 750 µL of 4N HCl in Dioxane in 10 mL of MeOH at 55°C for 16 hours. The reaction was concentrated and subjected to basic workup, dried over Magnesium Sulfate, filtered and concentrated to give methyl 2-(2-chloro-5-nitrophenyl)isonicotinate. 259 mg of methyl 2-(2-chloro-5-nitrophenyl)isonicotinate was treated with 200 mg of Tin (II) Chloride and 500 µL of HCl in 10 mL of EtOH. Upon completion, EtOH was concentrated and the reaction was extracted with Ethyl Acetate and water with TEA to decrease emulsions. The organic layer was dried over Magnesium Sulfate, filtered and concentrated to give crude methyl 2-(5-amino-2-chlorophenyl)isonicotinate. 240 mg of methyl methyl 2-(5-amino-2-chlorophenyl)isonicotinate was treated with 204 µL of 2-methyl-6-(trifluoromethyl)nicotinoyl chloride via Procedure D. To 100 mg of methyl 2-(2-chloro-5-(2-methyl-6-(trifluoromethyl)nicotinamido)phenyl)isonicotinate at 0°C in 5 mL of EtOH was slowly added 135 mg of Sodium Borohydride. The reaction was subsquently refluxed for 1 hour until complete, quenched with water and extracted with Ethyl Acetate. The organic layer was dried over Magnesium Sulfate, filtered, concentrated and purified by reverse phase HPLC to give pure *N*-(4-chloro-3-(4-(hydroxymethyl)pyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide. MS (Q1) 422.1 $(M)^+$.

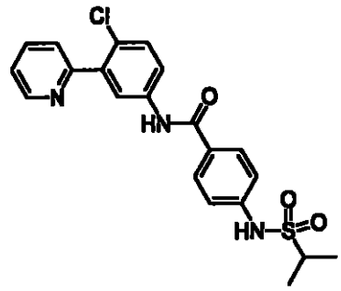
Example 200 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylamide)benzamide

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300 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 270 mg of 4-nitrobenzoic acid via Procedure G. To 520 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-nitrobenzamide in 2.5 mL of HCl in 10 mL of EtOH was added 1.3 g of Tin (II) Chloride and stirred at 55°C. Upon completion, the reaction was concentratd and extracted with Ethyl Acetate in water with TEA to reduce emulsions. The organic layer was dried over Magnesium Sulfate, filtered and concentrated to give 4-amino-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide. 100 mg of 4-amino-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide was reacted with 30 µL of Methanesulfonyl Chloride and 90 µL DIPEA in 500 µL DCM. The reaction mixture was evaporated, subjected to basic workup conditions and purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylamide)benzamide. MS (Q1) 402 $(M)^+$.

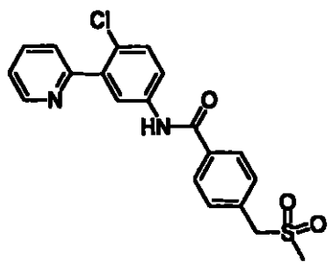
Example 201 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(1-methylethylsulfonamido)benzamide



151 mg of 4-amino-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide was reacted with 105 µL of propane-2-sulfonyl chloride and 205 µL DIPEA in 500 µL DCM. The reaction mixture was evaporated, subjected to basic workup conditions and purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(1-methylethylsulfonamido)benzamide. MS (Q1) 430 $(M)^+$.

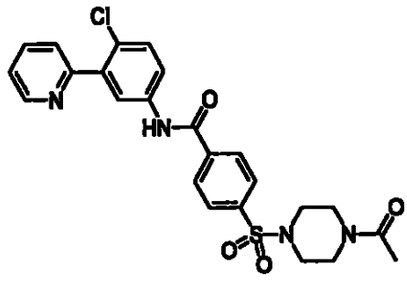
Example 202 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide

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1 g of methyl 4-(bromomethyl)benzoate was reacted via Procedure O. 2.77 g of methyl 4-(methylsulfonylmethyl)benzoate was hydrolyzed via Procedure M. 1g of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 1.15 g of 4-(methylsulfonylmethyl)benzoic acid via Procedure G. The crude product was subjected to basic workup and recrystallized with 1:1 Ratio of Isopropylacetate and Ether to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide. MS (Q1) 401 $(M)^+$.

Example 203 4-(4-acetylpiperazin-1-ylsulfonyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide

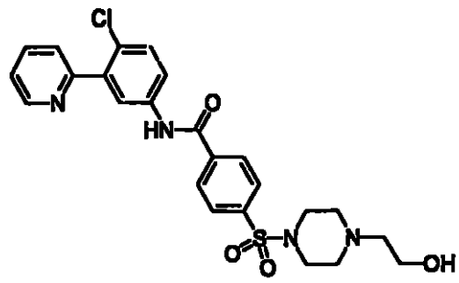


1 g of 4-(chlorosulfonyl)benzoic acid was reacted with 646 µL of 1-(piperazin-1-yl)ethanone via Procedure H. 75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 125 mg of 4-(4-acetylpiperazin-1-ylsulfonyl)benzoic acid via Procedure G and purified by reverse phase HPLC to yield 4-(4-acetylpiperazin-1-ylsulfonyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide. MS (Q1) 499.4 $(M)^+$.

Example 204 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(4-(2-hydroxyethyl)piperazin-1-ylsulfonyl)benzamide

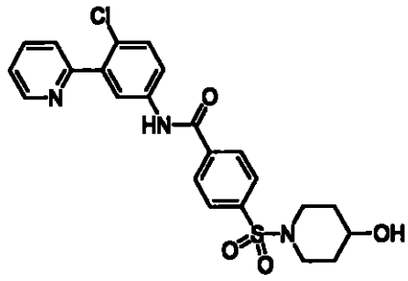
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1 g of 4-(chlorosulfonyl)benzoic acid was reacted with 615 µL of 2-(piperazin-1-yl)ethanol via Procedure H. 75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 125 mg of 4-(4-(3-hydroxypropyl)piperazin-1-ylsulfonyl)benzoic acid by Procedure G and purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(4-(2-hydroxyethyl)piperazin-1-ylsulfonyl)benzamide. MS (Q1) 501.3 $(M)^+$.

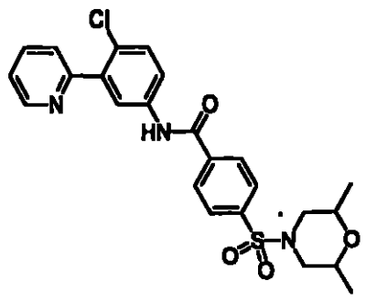
Example 205 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(4-hydroxypiperidin-1-ylsulfonyl)benzamide



1 g of 4-(chlorosulfonyl)benzoic acid was reacted with 506 µL of piperidin-4-ol via Procedure H. 75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 114 mg of 4-(4-hydroxypiperidin-1-ylsulfonyl)benzoic acid via Procedure G and purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(4-hydroxypiperidin-1-ylsulfonyl)benzamide. MS (Q1) 472.3 $(M)^+$.

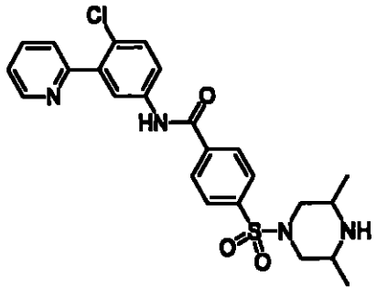
Example 206 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2,6-dimethylmorpholinosulfonyl)benzamide

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1 g of 4-(chlorosulfonyl)benzoic acid was reacted with 616 μL of 2,6-dimethylmorpholine via Procedure H. 75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 120 mg of 4-(2,6-dimethylmorpholinosulfonyl)benzoic acid via Procedure G and purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2,6-dimethylmorpholinosulfonyl)benzamide. MS (Q1) 486.3 $(M)^+$.

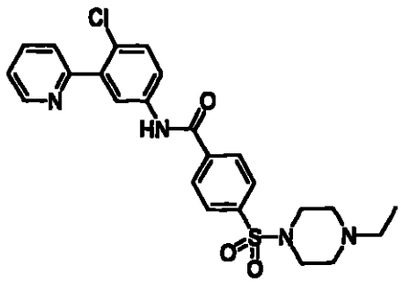
Example 207 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(3,5-dimethylpiperazin-1-ylsulfonyl)benzamide



1 g of 4-(chlorosulfonyl)benzoic acid was reacted with 570 mg of 2,6-dimethylpiperazine via Procedure H. 75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 119 mg of 4-(3,5-dimethylpiperazin-1-ylsulfonyl)benzoic acid via Procedure G and purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(3,5-dimethylpiperazin-1-ylsulfonyl)benzamide. MS (Q1) 485.4 $(M)^+$.

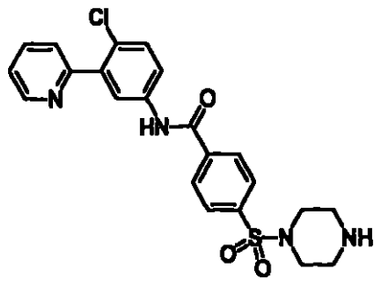
Example 208 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(4-ethylpiperazin-1-ylsulfonyl)benzamide

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1 g of 4-(chlorosulfonyl)benzoic acid was reacted with 570 mg of 1-ethylpiperazine via Procedure H. 75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-(4-ethylpiperazin-1-ylsulfonyl)benzoic acid via Procedure G and purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(4-ethylpiperazin-1-ylsulfonyl). MS (Q1) 485 $(M)^+$.

Example 209 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(piperazin-1-ylsulfonyl)benzamide

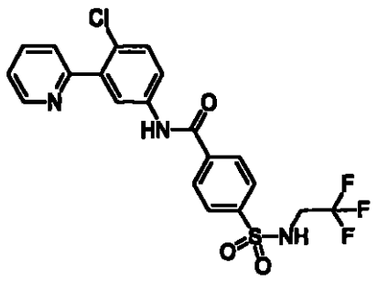


1 g of 4-(chlorosulfonyl)benzoic acid was reacted with 931 mg of *tert*-butyl piperazine-1-carboxylate via Procedure H. 75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 150 mg of 4-(4-(*tert*-butoxycarbonyl)piperazin-1-ylsulfonyl)benzoic acid via Procedure G. The crude product was subjected to basic workup conditions, treated with TFA to remove the Boc group and purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(piperazin-1-ylsulfonyl)benzamide. MS (Q1) 457.1 $(M)^+$.

Example 210 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-(2,2,2-trifluoroethyl)sulfamoyl)benzamide

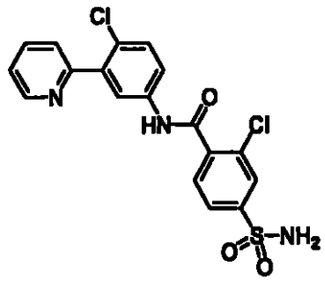
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1 g of 4-(chlorosulfonyl)benzoic acid was reacted with 500 μL of 2,2,2-trifluoroethanamine via Procedure H. 60 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 92 mg of 4-(*N*-(2,2,2-trifluoroethyl)sulfamoyl)benzoic acid by Procedure G and purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-(2,2,2-trifluoroethyl)sulfamoyl)benzamide. MS (Q1) 470 $(M)^+$.

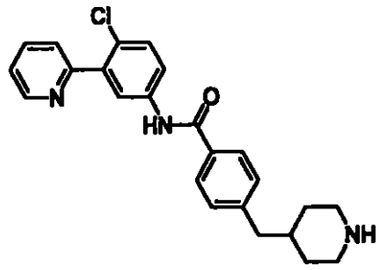
Example 211 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-sulfamoylbenzamide



A solution of 818 mg of Sodium Nitrite in 13 mL of water was added dropwise to a solution of 2g of methyl 4-amino-2-chlorobenzoate in 5 mL of HCl and 15 mL of AcOH at 0°C. The reaction was removed from the ice bath and stirred at room temperature for 15 minutes. Simultaneously a solution of 460 mg of Copper II Chloride Dihydrate in 1 mL of water was added to a saturated solution of sulfur dioxide gas in 10 mL of AcOH at 0°C. The cooled solution containing Copper II Chloride and sulfur dioxide gas was slowly added to the re-cooled initial solution containing Sodium Nitrite. The reaction was warmed to room temperature and stirred until gas no longer evolved. The reaction was filtered through celite and poured into a beaker of stirred icewater until a yellow-orange solid crashed out. The icewater solution was filtered thru a Buchner funnel to collect the methyl 2-chloro-4-(chlorosulfonyl)benzoate precipitate and was dried for 24 hours under vacuum. 1g of methyl 2-chloro-4-(chlorosulfonyl)benzoate was added to a solution of 2 mL of 2M solution of Ammonia in MeOH and 970 μL DIPEA in 5 mL MeOH. Upon completion the

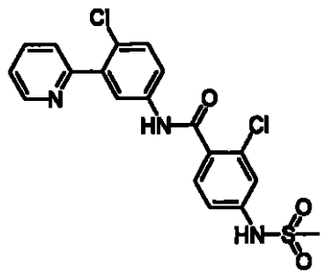
reaction was concentrated, extracted twice with saturated bicarbonate, dried with Magnesium Sulfate, filtered and concentrated to give methyl 2-chloro-4-sulfamoylbenzoate. 777 mg of methyl 2-chloro-4-sulfamoylbenzoate was hydrolyzed via Procedure M to yield crude 2-chloro-4-sulfamoylbenzoic acid. 75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 91 mg of crude 2-chloro-4-sulfamoylbenzoic acid via Procedure G. The crude product was purified by reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-sulfamoylbenzamide. MS (Q1) 422 $(M)^+$.

Example 212 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(piperidin-4-ylmethyl)benzamide



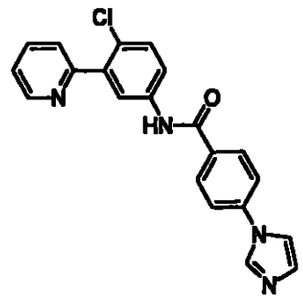
75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 125 mg of 4-((1-(*tert*-butoxycarbonyl)piperidin-4-yl)methyl)benzoic acid via Procedure G. The crude product was treated with 4N HCl in Dioxane, evaporated and purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(piperidin-4-ylmethyl)benzamide. MS (Q1) 406.1 $(M)^+$.

Example 213 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonamido)benzamide



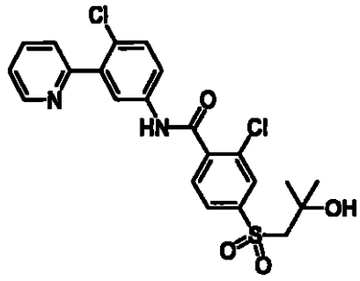
4.2 g of methyl 2-chloro-4-(methylsulfonamido)benzoate was hydrolyzed via Procedure M. 1 g of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 1.35 g of 2-chloro-4-(methylsulfonamido)benzoic acid via Procedure G. The crude product was purified by reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonamido)benzamide. MS (Q1) 436.1 $(M)^+$.

Example 214 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(1*H*-imidazol-1-yl)benzamide



75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 78 mg of 4-(1*H*-imidazol-1-yl)benzoic acid via Procedure G . The crude product was purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(1*H*-imidazol-1-yl)benzamide. MS (Q1) 375.3 $(M)^+$.

Example 215 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxy-2-methylpropylsulfonyl)-benzamide

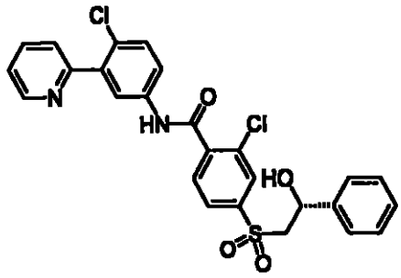


8 g of methyl 4-amino-2-chlorobenzoate was dissolved in 16 mL of MeOH, 8 mL of H_2O and 8 mL of concentrated hydrochloric acid and was then cooled to 0 °C. A solution of 3.9 g of sodium nitrite in 15 mL of H_2O was added dropwise over 30 min. The reaction was stirred at 0 °C for an additional 1h. The cold diazonating mixture was added to a solution of 13.8 g of potassium ethyl xanthate in 10 mL of H_2O at 50~60 °C. The reaction was heated to 65 °C for 2h and monitored by TLC until complete. The mixture was cooled to 25 °C and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. Purified by silica gel chromatography (0-10% ethyl acetate/hexane) to afford methyl 2-chloro-4-(ethoxycarbonothioylthio)benzoate. A solution of 2.6 g of sodium hydroxide in 20 mL of H_2O was added to 5.9 g of methyl 2-chloro-4-(ethoxycarbonothioylthio)benzoate in 40 mL of EtOH The reaction mixture was heated to 70 °C for 1h. Upon completion, the mixture was cooled to 25 °C,

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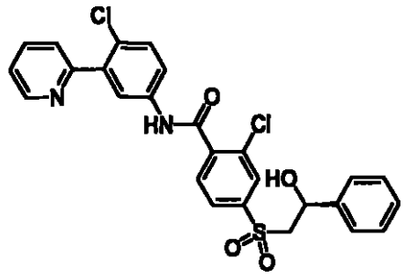
and then acidified to pH 3 by the addition of 10 N HCl. The solid was filtered and washed with H_2O to give 2-chloro-4-mercaptobenzonic acid. 3.8 g of 2-chloro-4-mercaptobenzonic acid in 40 mL of 5% sulfuric acid-methanol was refluxed under nitrogen atmosphere for 3h. After concentration of the reaction mixture, 10 mL of H_2O was added and the resulting mixture was made alkaline with sodium hydrogen carbonate, and extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to yield methyl 2-chloro-4-mercaptobenzoate. 80 mg of isobutylene oxide was reacted with methyl 2-chloro-4-mercaptobenzoate via Procedure S to afford methyl 2-chloro-4-(2-hydroxy-2-methylpropylthio)benzoate. 190 mg of methyl 2-chloro-4-(2-hydroxy-2-methylpropylthio)benzoate was hydrolyzed via Procedure M to give 2-chloro-4-(2-hydroxy-2-methylpropylthio)benzoic acid. 160 mg of 2-chloro-4-(2-hydroxy-2-methylpropylthio)benzoic acid was reacted via procedure R to give 2-chloro-4-(2-hydroxy-2-methylpropylsulfonyl)benzoic acid. 60 mg of 4-chloro-3-(pyridine-2-yl)aniline was coupled to 2-chloro-4- (2-hydroxy-2-methylpropylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxy-2-methylpropylsulfonyl)benzamide. MS (Q1) 479.1 $(M)^+$.

Example 216 (*R*)-2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxy-2-phenylethylsulfonyl)benzamide



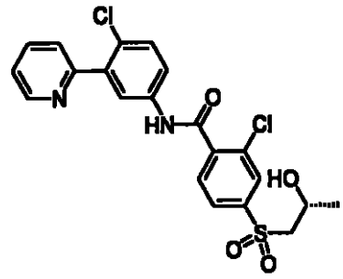
150 mg of (*R*)-styrene oxide was reacted with methyl 2-chloro-4-mercaptobenzoate via Procedure S to afford (*R*)-methyl 2-chloro-4-(2-hydroxy-2-phenylethylthio)benzoate. 190 mg of (*R*)-methyl-2-chloro-4-(2-hydroxy-2-phenylethylthio)benzoate was hydrolyzed via Procedure M to give (*R*)-2-chloro-4-(2-hydroxy-2-phenylethylthio)benzoic acid. 170 mg of (*R*)-2-chloro-4-(2-hydroxy-2-phenylethylthio)benzoic acid was reacted via Procedure R to give (*R*)-2-chloro-4-(2-hydroxy-2-phenylethylsulfonyl)benzoic acid. 60 mg of 4-chloro-3-(pyridine-2-yl)aniline was coupled to (*R*)-2-chloro-4-(2-hydroxy-2-phenylethylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield (*R*)-2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxy-2-phenylethylsulfonyl)benzamide. MS (Q1) 527.2 $(M)^+$.

Example 217 (*S*)-2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxy-2-phenylethylsulfonyl)benzamide



119 mg of (*S*)-styrene oxide was reacted with methyl 2-chloro-4-mercaptobenzoate via Procedure S to afford (*S*)-methyl 2-chloro-4-(2-hydroxy-2-phenylethylthio)benzoate. 230 mg of (*S*)-methyl-2-chloro-4-(2-hydroxy-2-phenylethylthio)benzoate was hydrolyzed via Procedure M to give (*S*)-2-chloro-4-(2-hydroxy-2-phenylethylthio)benzoic acid. 180 mg of (*S*)-2-chloro-4-(2-hydroxy-2-phenylethylthio)benzoic acid was reacted via Procedure R to give (*S*)-2-chloro-4-(2-hydroxy-2-phenylethylsulfonyl)benzoic acid. 60 mg of 4-chloro-3-(pyridine-2-yl)aniline was coupled to (*S*)-2-chloro-4-(2-hydroxy-2-phenylethylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield (*S*)-2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxy-2-phenylethylsulfonyl)benzamide. MS (Q1) 527.0 $(M)^+$.

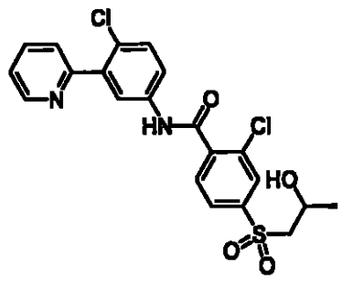
Example 218 (*R*)-2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxypropylsulfonyl)-benzamide



140 mg of (*R*)-propylene oxide was reacted with methyl 2-chloro-4-mercaptobenzoate via Procedure S to afford (*R*)-methyl 2-chloro-4-(2-hydroxypropylthio)benzoate. 435 mg of (*R*)-methyl-2-chloro-4-(2-hydroxypropylthio)benzoate was hydrolyzed via Procedure M to give (*R*)-2-

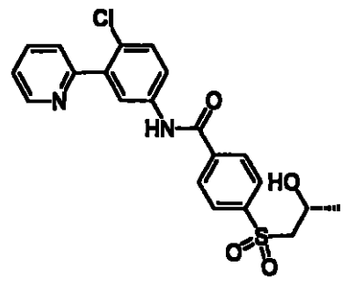
chloro-4-(2-hydroxypropylthio)benzoic acid. 403 mg of (*R*)-2-chloro-4-(2-hydroxypropylthio)benzoic acid was reacted via Procedure R to give (*R*)-2-chloro-4-(2-hydroxypropylsulfonyl)benzoic acid. 298 mg of 4-chloro-3-(pyridine-2-yl)aniline was coupled to (*R*)-2-chloro-4-(2-hydroxypropylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield (*R*)-2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxypropylsulfonyl)benzamide. MS (Q1) 465.1 $(M)^+$.

Example 219 (*S*)-2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxypropylsulfonyl)-benzamide



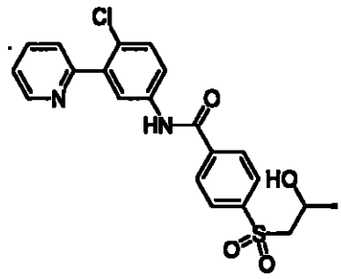
86 mg of (*S*)-propylene oxide was reacted with methyl 2-chloro-4-mercaptobenzoate via Procedure S to afford (*S*)-methyl 2-chloro-4-(2-hydroxypropylthio)benzoate. 275 mg of (*S*)-methyl-2-chloro-4-(2-hydroxypropylthio)benzoate was hydrolyzed via Procedure M to give (*S*)-2-chloro-4-(2-hydroxypropylthio)benzoic acid. 220 mg of (*S*)-2-chloro-4-(2-hydroxypropylthio)benzoic acid was reacted via Procedure R to give (*S*)-2-chloro-4-(2-hydroxypropylsulfonyl)benzoic acid. 70 mg of 4-chloro-3-(pyridine-2-yl)aniline was coupled to (*S*)-2-chloro-4-(2-hydroxypropylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield (*S*)-2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxypropylsulfonyl)benzamide. MS (Q1) 465.0 $(M)^+$

Example 220 (*R*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxypropylsulfonyl)benzamide



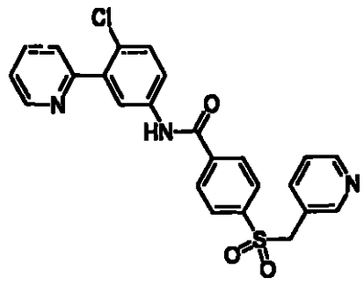
100 mg of (*R*)-propylene oxide was reacted with methyl 4-mercaptobenzoate via Procedure S to afford (*R*)-methyl 4-(2-hydroxypropylthio)benzoate. 169 mg of (*R*)-methyl 4-(2-hydroxypropylthio)benzoate was reacted via Procedure R to give (*R*)-methyl 4-(2-hydroxypropylsulfonyl)benzoate. 179 mg of (*R*)-methyl 4-(2-hydroxypropylsulfonyl)benzoate was hydrolyzed via Procedure M to give (*R*)-4-(2-hydroxypropylsulfonyl)benzoic acid. 45 mg of 4-chloro-3-(pyridine-2-yl)aniline was coupled to (*R*)-4-(2-hydroxypropylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield (*R*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxypropylsulfonyl)benzamide. MS (Q1) 431.2 $(M)^+$.

Example 221 (*S*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxypropylsulfonyl)benzamide



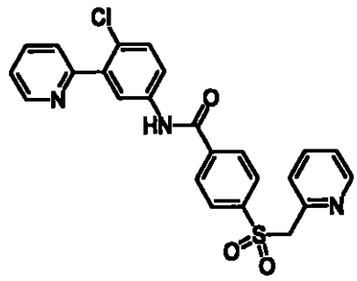
150 mg of (*S*)-propylene oxide was reacted with methyl 4-mercaptobenzoate via Procedure S to afford (*S*)-methyl 4-(2-hydroxypropylthio)benzoate. 650 mg of (*S*)-methyl 4-(2-hydroxypropylthio)benzoate was reacted via Procedure R to give (*S*)-methyl 4-(2-hydroxypropylsulfonyl)benzoate. 350 mg of (*S*)-methyl 4-(2-hydroxypropylsulfonyl)benzoate was hydrolyzed via Procedure M to give (*S*)-4-(2-hydroxypropylsulfonyl)benzoic acid. 45 mg of 4-chloro-3-(pyridine-2-yl)aniline was coupled to (*S*)-4-(2-hydroxypropylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield (*S*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxypropylsulfonyl)benzamide. MS (Q1) 431.3 $(M)^+$.

Example 222 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(pyridin-3-ylmethylsulfonyl)benzamide



1g of 3-(bromomethyl)pyridine hydrobromide was reacted with methyl 4-mercaptobenzoate via Procedure Q to afford methyl 4-(pyridin-3-ylmethylthio)benzoate. 980 mg of methyl 4-(pyridin-3-ylmethylthio)benzoate was reacted via Procedure R to give methyl 4-(pyridin-3-ylmethylsulfonyl)benzoate. 760 mg of methyl 4-(pyridin-3-ylmethylsulfonyl)benzoate was hydrolyzed via Procedure M to give 4-(pyridin-3-ylmethylsulfonyl)benzoic acid. 60 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-(pyridin-3-ylmethylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(pyridin-3-ylmethylsulfonyl)benzamide. MS (Q1) 464.1 $(M)^+$.

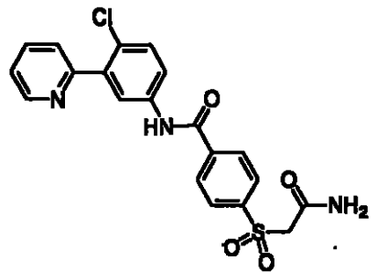
Example 223 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(pyridin-2-ylmethylsulfonyl)benzamide



1g of 2-(bromomethyl)pyridine hydrobromide was reacted with methyl 4-mercaptobenzoate via Procedure Q to afford methyl 4-(pyridin-2-ylmethylthio)benzoate. 500 mg of methyl 4-(pyridin-2-ylmethylthio)benzoate was reacted via Procedure R to give methyl 4-(pyridin-2-ylmethylsulfonyl)benzoate. 470 mg of methyl 4-(pyridin-2-ylmethylsulfonyl)benzoate was hydrolyzed via Procedure M to give 4-(pyridin-2-ylmethylsulfonyl)benzoic acid. 70 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-(pyridin-2-ylmethylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(pyridin-2-ylmethylsulfonyl)benzamide. MS (Q1) 464.1 $(M)^+$.

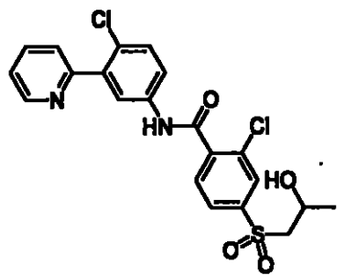
Example 224 4-(2-amino-2-oxoethylsulfonyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide

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2.5 g of 2-bromoacetamide was reacted with methyl 4-mercaptobenzoate via Procedure Q to afford methyl 4-(2-amino-2-oxoethylthio)benzoate. 2.6 g of methyl 4-(2-amino-2-oxoethylthio)benzoate was reacted via Procedure R to give methyl 4-(2-amino-2-oxoethylsulfonyl)benzoate. 1 g of methyl 4-(2-amino-2-oxoethylsulfonyl)benzoate was hydrolyzed via Procedure M to give 4-(2-amino-2-oxoethylsulfonyl)benzoic acid. 150 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-(2-amino-2-oxoethylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield 4-(2-amino-2-oxoethylsulfonyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide. MS (Q1) 430.2 $(M)^+$.

Example 225 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxypropylsulfonyl)benzamide

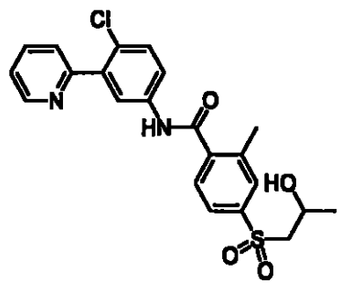


2 g of 2-chloro-4-fluorobenzonitrile was reacted with 1-mercapto-2-propanol via Procedure Q to afford 2-chloro-4-(2-hydroxypropylthio)benzonitrile. 2.5 g of 2-chloro-4-(2-hydroxypropylthio)benzonitrile was reacted via Procedure T to give 2-chloro-4-(2-hydroxypropylthio)benzoic acid. 2.1 g of 2-chloro-4-(2-hydroxypropylthio)benzoic acid was reacted via Procedure R to give 2-chloro-4-(2-hydroxypropylsulfonyl)benzoic acid. 70 mg of 4-

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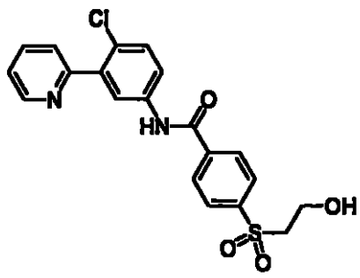
chloro-3-(pyridin-2-yl)aniline was coupled to 2-chloro-4-(2-hydroxypropylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxypropylsulfonyl)benzamide. MS (Q1) 465.2 $(M)^+$.

Example 226 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxypropylsulfonyl)-2-methylbenzamide



2 g of 4-bromo-2-methylbenzonitrile was reacted with 1-mercapto-2-propanol via Procedure Q to afford 4-(2-hydroxypropylthio)-2-methylbenzonitrile. 950 mg of 4-(2-hydroxypropylthio)-2-methylbenzonitrile was reacted via Procedure T to give 4-(2-hydroxypropylthio)-2-methylbenzoic acid. 1.0 g of 4-(2-hydroxypropylthio)-2-methylbenzoic acid was reacted via Procedure R to give 4-(2-hydroxypropylsulfonyl)-2-methylbenzoic acid. 100 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-(2-hydroxypropylsulfonyl)-2-methylbenzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxypropylsulfonyl)-2-methylbenzamide. MS (Q1) 445.3 $(M)^+$.

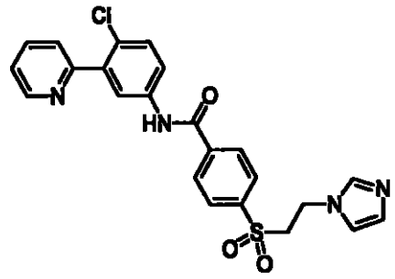
Example 227 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxyethylsulfonyl)benzamide



5 g of 4-fluorobenzonitrile was used in Procedure Q with 2-mercaptoethanol to afford 4-(2-hydroxyethylthio)benzonitrile. 900 mg of 4-(2-hydroxyethylthio)benzonitrile was reacted via

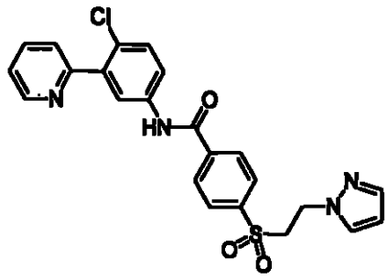
Procedure T to give 4-(2-hydroxyethylthio)benzoic acid. 1.0 g of 4-(2-hydroxyethylthio)benzoic acid was reacted via Procedure R to give 4-(2-hydroxyethylsulfonyl)benzoic acid. 80 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-(2-hydroxyethylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxyethylsulfonyl)benzamide. MS (Q1) 417.0 $(M)^+$.

Example 228 4-(2-(1*H*-imidazol-1-yl)ethylsulfonyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide



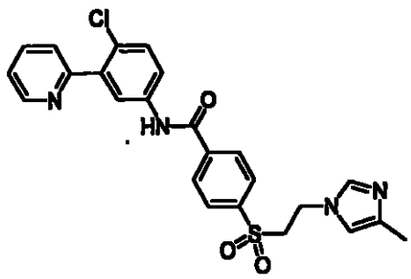
4 g of 4-(2-hydroxyethylthio)benzonitrile was reacted via Procedure R to yield 4-(2-hydroxyethylsulfonyl)benzonitrile. 3.0 g of triphenylphosphine was added to a solution of 2 g of 4-(2-hydroxyethylsulfonyl)benzonitrile and 4.7 g of carbon tetrabromide in dichloromethane at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1h. The mixture was diluted with dichloromethane, washed with H_2O, dried ($MgSO_4$) and evaporated. Purified by silica gel chromatography (0-70% ethyl acetate/hexane) to afford 4-(2-bromoethylsulfonyl)benzonitrile. 250 mg of 4-(2-bromoethylsulfonyl)benzonitrile was used in Procedure P with imidazole to give 4-(2-(1*H*-imidazol-1-yl)ethylsulfonyl)benzonitrile. 300 mg of 4-(2-(1*H*-imidazol-1-yl)ethylsulfonyl)benzonitrile was reacted via Procedure T to give 4-(2-(1*H*-imidazol-1-yl)ethylsulfonyl)benzoic acid. 60 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-(2-(1*H*-imidazol-1-yl)ethylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield 4-(2-(1*H*-imidazol-1-yl)ethylsulfonyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide. MS (Q1) 467.1 $(M)^+$.

Example 229 4-(2-(1*H*-pyrazol-1-yl)ethylsulfonyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide



250 mg of 4-(2-bromoethylsulfonyl)benzonitrile was used in Procedure P with pyrazole to yield 4-(2-(1*H*-pyrazole-1-yl)ethylsulfonyl)benzonitrile. 300 mg of 4-(2-(1*H*-pyrazole-1-yl)ethylsulfonyl)benzonitrile was reacted via Procedure T to give 4-(2-(1*H*-pyrazole-1-yl)ethylsulfonyl)benzoic acid. 75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-(2-(1*H*-pyrazole-1-yl)ethylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield 4-(2-(1*H*-pyrazol-1-yl)ethylsulfonyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide. MS (Q1) 467.0 $(M)^+$.

Example 230 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-(4-methyl-1*H*-imidazol-1-yl)ethylsulfonyl)benzamide

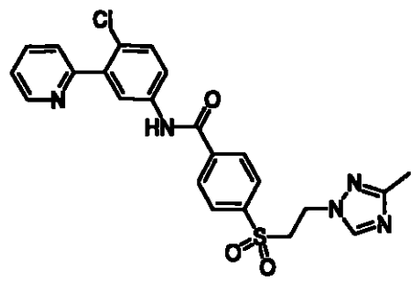


270 mg of 4-(2-bromoethylsulfonyl)benzonitrile was used in Procedure P with 4-methylimidazole to yield 4-(2-(4-methyl-1*H*-imidazole-1-yl)ethylsulfonyl)benzonitrile. 320 mg of 4-(2-(4-methyl-1*H*-imidazole-1-yl)ethylsulfonyl)benzonitrile was reacted via Procedure T to give 4-(2-(4-methyl-1*H*-imidazole-1-yl)ethylsulfonyl)benzoic acid.

70 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-(2-(4-methyl-1*H*-imidazole-1-yl)ethylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-(4-methyl-1*H*-imidazol-1-yl)ethylsulfonyl)benzamide. MS (Q1) 481.0 $(M)^+$.

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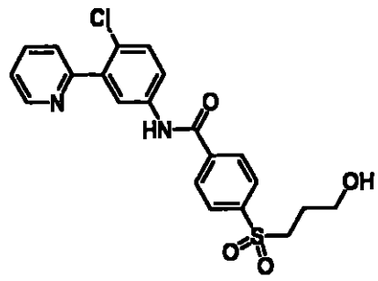
Example 231 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-(3-methyl-1*H*-1,2,4-triazol-1-yl)ethylsulfonyl)benzamide.



To a stirred suspension of 10 g of thiosemicarbazide in 100 mL of pyridine was slowly added 7.8 ml of acetyl chloride at 0 °C. The temperature was maintained throughout the addition (0 °C - 4 °C). The reaction mixture was allowed to warm to room temperature and stirred for 16 h. Evaporation gave 1-acetyl thiosemicarbazide. The crude 1-acetyl thiosemicarbazide was dissolved in 70 mL of MeOH and 12 g of sodium methoxide, and was refluxed for 10 h. The solvent was removed and the residue was dissolved in H_2O, then acidified to pH 2 by the addition of 1N HCl. The resulting solid was filtered and washed with H_2O to give 3-methyl-1,2,4-triazole-5-thiol. 1 g of 3-methyl-1,2,4-triazole-5-thiol was added to a solution of 61 mg of sodium nitrite in 3 ml of nitric acid and 6 mL of H_2O at 0 °C. The reaction mixture was stirred for 1h at 0 °C, and basified with saturated sodium carbonate and concentrated. The residue was dissolved with MeOH and filtered. The filtrate was evaporated to give 3-methyl-1,2,4-triazole. 230 mg of 4-(2-bromoethylsulfonyl)benzonitrile was used in Procedure P with 3-methyl-1,2,4-triazole to yield 4-(2-(3-methyl-1*H*-1,2,4-triazole-1-yl)ethylsulfonyl)benzonitrile. 310 mg of 4-(2-(3-methyl-1*H*-1,2,4-triazole-1-yl)ethylsulfonyl)benzonitrile was reacted via Procedure T to give 4-(2-(3-methyl-1*H*-1,2,4-triazole-1-yl)ethylsulfonyl)benzoic acid.

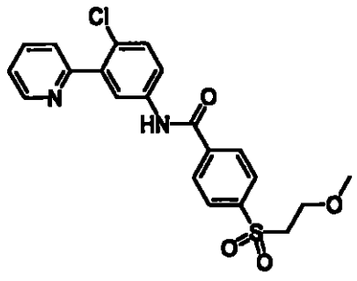
60 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-(2-(3-methyl-1*H*-1,2,4-triazole-1-yl)ethylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-(3-methyl-1*H*-1,2,4-triazol-1-yl)ethylsulfonyl)benzamide. MS (Q1) 482.1 $(M)^+$.

Example 232 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(3-hydroxypropylsulfonyl)benzamide



5 g of 4-fluorobenzonitrile was used in Procedure Q with 3-mercapto-1-propanol to afford 4-(3-hydroxypropylthio)benzonitrile. 1.8 g of 4-(3-hydroxypropylthio)benzonitrile was reacted via Procedure T to give 4-(3-hydroxypropylthio)benzoic acid. 1.2 g of 4-(3-hydroxypropylthio)benzoic acid was reacted via Procedure R to give 4-(3-hydroxypropylsulfonyl)benzoic acid. 50 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-(3-hydroxypropylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(3-hydroxypropylsulfonyl)benzamide. MS (QI) 431.3 $(M)^+$.

Example 233 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-methoxyethylsulfonyl)benzamide



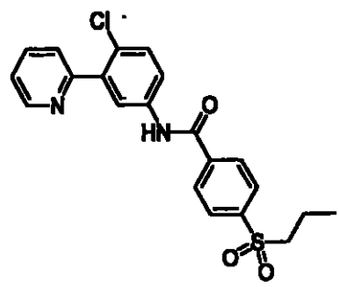
A mixture of 500 mg of methyl 4-mercaptobenzoate, 1.6 g of potassium carbonate, 1.2 g of 2-bromoethylmethylether and 329 mg of tetrabutylammonium iodide in 10 mL of acetone was refluxed for 16 h. The reaction mixture was diluted with ethyl acetate, washed with H_2O and concentrated. Purified by silica gel chromatography (0-50% ethyl acetate/ hexane) to yield 4-(2-methoxyethylthio)benzoate. 240 mg of 4-(2-methoxyethylthio)benzoate was reacted via Procedure R to give 4-(2-methoxyethylsulfonyl)benzoate. 120 mg of 4-(2-methoxyethylsulfonyl)benzoate was hydrolyzed via Procedure M to yield 4-(2-methoxyethylsulfonyl)benzoic acid. 50 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-(2-methoxyethylsulfonyl)benzoic acid via

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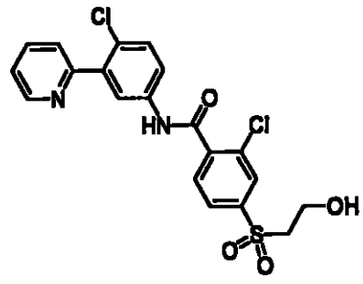
Procedure G. The product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-methoxyethylsulfonyl)benzamide. MS (Q1) 431.0 $(M)^+$.

Example 234 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(propylsulfonyl)benzamide



1 g of 4-fluorobenzonitrile was used in Procedure Q with 1-propanethiol to afford 4-(propylthio)benzonitrile. 860 mg of 4-(propylthio)benzonitrile was reacted via Procedure T to give 4-(propylthio)benzoic acid. 700 mg of 4-(propylthio)benzoic acid was reacted via Procedure R to give 4-(propylsulfonyl)benzoic acid. 60 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-(propylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(propylsulfonyl)benzamide. MS (Q1) 415.0 $(M)^+$.

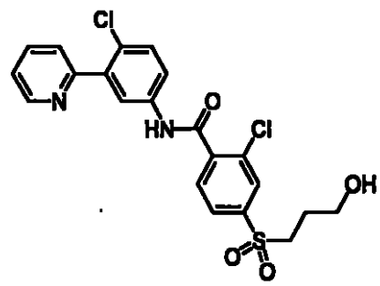
Example 235 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxyethylsulfonyl)benzamide



4 g of 2-chloro-4-fluorobenzonitrile was used in Procedure Q with 2-mercaptoethanol to afford 2-chloro-4-(2-hydroxyethylthio)benzonitrile. 1 g of 2-chloro-4-(2-hydroxyethylthio)benzonitrile was reacted via Procedure T to give 2-chloro-4-(2-hydroxyethylthio)benzoic acid. 1 g of 2-chloro-4-(2-hydroxyethylthio)benzoic acid was reacted via Procedure R to yield 2-chloro-4-(2-

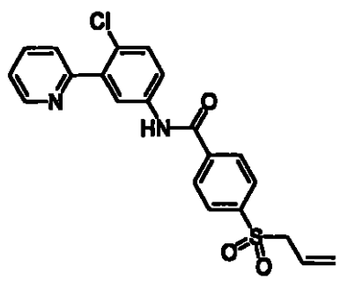
hydroxyethylsulfonyl)benzoic acid. 50 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 2-chloro-4-(2-hydroxyethylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxyethylsulfonyl)benzamide. MS (Q1) 451.0(M)$^+$.

Example 236 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(3-hydroxypropylsulfonyl)benzamide



4 g of 2-chloro-4-fluorobenzonitrile was used in Procedure Q with 3-mercapto-1-propanol to afford 2-chloro-4-(3-hydroxypropylthio)benzonitrile. 1 g of 2-chloro-4-(3-hydroxypropylthio)benzonitrile was reacted via Procedure T to give 2-chloro-4-(3-hydroxypropylthio)benzoic acid. 1.2 g of 2-chloro-4-(3-hydroxypropylthio)benzoic acid was reacted via Procedure R to yield 2-chloro-4-(2-hydroxypropylsulfonyl)benzoic acid. 75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 2-chloro-4-(2-hydroxypropylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(3-hydroxypropylsulfonyl)benzamide. MS (Q1) 465.0 (M)$^+$.

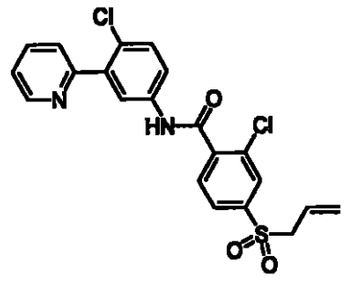
Example 237 4-(allylsulfonyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide



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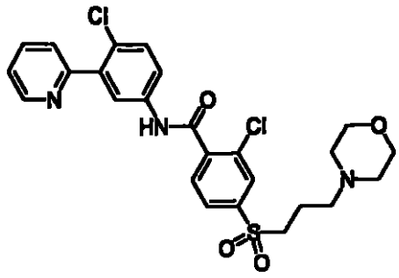
7.3 g of 4-(3-hydroxypropylthio)benzonitrile was reacted via Procedure R to yield 4-(3-hydroxypropylsulfonyl)benzonitrile. 1.9 g of NBS was added to a solution of 2 g of 4-(3-hydroxypropylsulfonyl)benzonitrile and 2.8 g of triphenylphosphine in 10 mL of dichloromethane at 0 °C. The reaction mixture was stirred at 0 ~5 °C for 1h. The mixture was diluted with dichloromethane, washed with H_2O, dried ($MgSO_4$) and evaporated. Purified by silica gel chromatography (10-70% ethyl acetate/hexane) to afford 4-(3-bromopropylsulfonyl)benzonitrile. 300 mg of 4-(3-bromopropylsulfonyl)benzonitrile was reacted via Procedure T to give 4-(allylsulfonyl)benzoic acid. 40 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-(allylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield 4-(allylsulfonyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide. MS (Q1) 413.2 $(M)^+$.

Example 238 4-(allylsulfonyl)-2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide



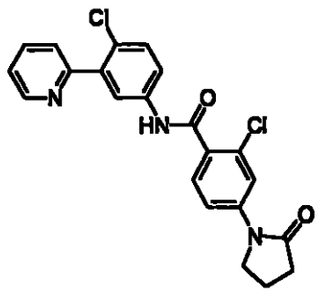
115 mg of NBS was added to a solution of 200 mg of 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(3-hydroxypropylsulfonyl)benzamide and 169 mg of triphenylphosphine in 3 mL of dichloromethane at 0 °C. The reaction mixture was stirred at 0 ~5 °C for 1h. The mixture was diluted with dichloromethane, washed with H_2O, dried ($MgSO_4$) and evaporated. Purified by prep TLC plate (60% ethyl acetate/hexane) to afford 4-(3-bromopropylsulfonyl)-2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide. 60 mg of 4-(3-bromopropylsulfonyl)-2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide and 111 mg of cesium carbonate in 0.5 mL of DMF were heated to 100 °C in a sealed microwave reactor for 20 min. The reaction mixture was evaporated, and the product was purified on reverse phase HPLC to yield 4-(allylsulfonyl)-2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide. MS (Q1) 448.0 $(M)^+$.

Example 239 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(3-morpholinopropylsulfonyl)-benzamide



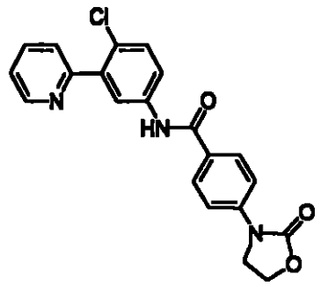
120 mg of 4-(3-bromopropylsulfonyl)-2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide was used in Procedure P with morpholine to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(3-morpholinopropylsulfonyl)benzamide. MS (Q1) 534.0 $(M)^+$.

Example 240 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-oxopyrrolidin-1-yl)benzamide



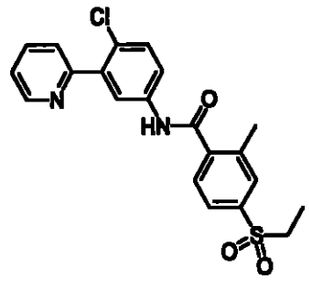
A mixture of 500 mg of 2-chloro-4-florobenzonitrile, 821 mg of 2-pyrrolidinone and 3 g of cesium carbonate in 5 mL of DMF was heated to 100 °C in a sealed microwave reactor for 15 min. The reaction mixture was diluted with ethyl acetate, washed with H_2O, dried ($MgSO_4$) and evaporated. Purified by silica gel chromatography (20-80% ethyl acetate/hexane) to afford 2-chloro-4-(2-oxopyrrolidin-1-yl)benzonitrile. 890 mg of 2-chloro-4-(2-oxopyrrolidin-1-yl)benzonitrile was reacted via Procedure T to give 2-chloro-4-(2-oxopyrrolidin-1-yl)benzoic acid. 80 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 2-chloro-4-(2-oxopyrrolidin-1-yl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-oxopyrrolidin-1-yl)benzamide. MS (Q1) 426.2 $(M)^+$.

Example 241 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-oxooxazolidin-3-yl)benzamide



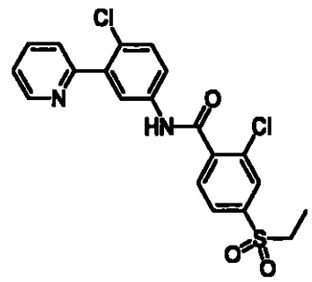
A mixture of 1 g of methyl 4-iodobenzoate, 399 mg of 2-oxozolidone, 1.1 g of potassium carbonate, 34 mg of N, N'-dimethylethylenediamine and 73 mg of copper iodide in 10 mL of toluene was heated to 150 °C in a sealed microwave reactor for 2h. The reaction mixture was diluted with ethyl acetate, washed with H_2O, dried ($MgSO_4$) and evaporated. Purified by silica gel chromatography (20-70% ethyl acetate/hexane) to afford methyl 4-(2-oxooxazolidin-3-yl)benzoate. 530 mg of methyl 4-(2-oxooxazolidin-3-yl)benzoate was hydrolyzed via Procedure M to give 4-(2-oxooxazolidin-3-yl)benzoic acid. 70 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-(2-oxooxazolidin-3-yl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-oxooxazolidin-3-yl)benzamide. MS (Q1) 394.2 $(M)^+$.

Example 242 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(ethylsulfonyl)-2-methylbenzamide



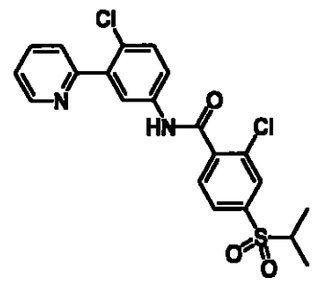
4 g of 4-bromo-2-methylbenzonitrile was used in Procedure Q with ethanethiol to afford 4-(ethylthio)-2-methylbenzonitrile. 2 g of 4-(ethylthio)-2-methylbenzonitrile was reacted via Procedure R to give 4-(ethylsulfonyl)-2-methylbenzonitrile. 2.5 g of 4-(ethylsulfonyl)-2-methylbenzonitrile was reacted via Procedure T to give 4-(ethylsulfonyl)-2-methylbenzoic acid. 75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-(ethylsulfonyl)-2-methylbenzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(ethylsulfonyl)-2-methylbenzamide. MS (Q1) 415.0 $(M)^+$.

Example 243 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(ethylsulfonyl)benzamide



4 g of 2-chloro-4-fluorobenzonitrile was used in Procedure Q with ethanethiol to afford 2-chloro-4-(ethylthio)benzonitrile. 2 g of 2-chloro-4-(ethylthio)benzonitrile was reacted via Procedure T to give 2-chloro-4-(ethylthio)benzoic acid. 1.5 g of 2-chloro-4-(ethylthio)benzoic acid was reacted via Procedure R to yield 2-chloro-4-(ethylsulfonyl)benzoic acid. 75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 2-chloro-4-(ethylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(ethylsulfonyl)benzamide. MS (Q1) 435.1 $(M)^+$.

Example 244 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(isopropylsulfonyl)benzamide



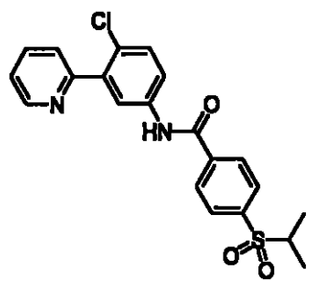
2 g of 2-chloro-4-fluorobenzonitrile was used in Procedure Q with 2-propanethiol to afford 2-chloro-4-(isopropylthio)benzonitrile. 1.6 g of 2-chloro-4-(isopropythio)benzonitrile was reacted via Procedure T to give 2-chloro-4-(isopropylthio)benzoic acid. 1 g of 2-chloro-4-(isopropylthio)benzoic acid was reacted via Procedure R to give 2-chloro-4-(isopropylsulfonyl)benzoic acid. 75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 2-chloro-4-(isopropylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse

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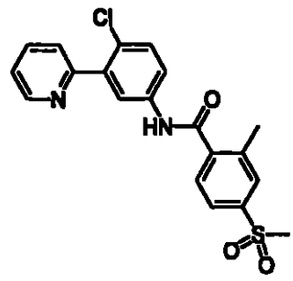
phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(isopropylsulfonyl)benzamide. MS (Q1) 449.1 $(M)^+$.

Example 245 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(isopropylsulfonyl)benzamide



2 g of 4-fluorobenzonitrile was used in Procedure Q with 2-propanethiol to afford 4-(isopropylthio)benzonitrile. 900 mg of 4-(isopropythio)benzonitrile was reacted via Procedure T to give 4-(isopropylthio)benzoic acid. 730 mg of 4-(isopropylthio)benzoic acid was reacted via Procedure R to give 4-(isopropylsulfonyl)benzoic acid. 75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-(isopropylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(isopropylsulfonyl)benzamide. MS (Q1) 415.0 (M)

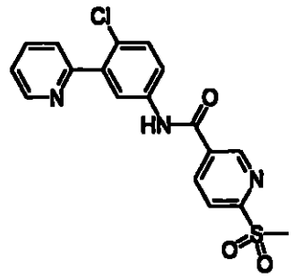
Example 246 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-4-(methylsulfonyl)benzamide



A solution of 500 mg of 4-bromo-2-methylbenzonitrile and 268 mg of sodium thiomethoxide in 3 mL of DMF was stirred for 1h. The reaction mixture was diluted with ethyl acetate, washed with H_2O, dried ($MgSO_4$) and evaporated to afford 2-methyl-4-(methylthio)benzonitrile. 400 mg of 2-methyl-4-(methylthio)benzonitrile was reacted via Procedure T to give 2-methyl-4-

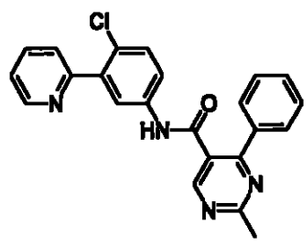
(methylthio)benzoic acid. 430 mg of 2-methyl-4-(methylthio)benzoic acid was reacted via Procedure R to yield 2-methyl-4-(methylsulfonyl)benzoic acid. 60 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 2-methyl-4-(methylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-4-(methylsulfonyl)benzamide. MS (Q1) 401.0 $(M)^+$.

Example 247 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(methylsulfonyl)nicotinamide



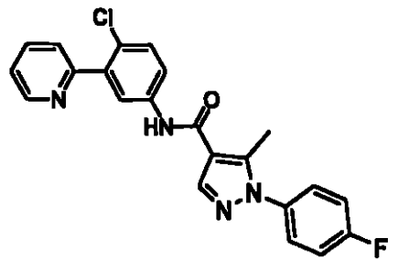
1 g of methyl 6-chloronicotinate was reacted via Procedure O to yield methyl 6-(methylsulfonyl)nicotinate. 1 g of methyl 6-(methylsulfonyl)nicotinate was hydrolyzed via Procedure M to give 6-(methylsulfonyl)nicotinic acid. 100 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 6-(methylsulfonyl)nicotinic acid via Procedure G. The product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(methylsulfonyl)nicotinamide. MS (Q1) 388.1 $(M)^+$.

Example 248 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-4-phenylpyrimidine-5-carboxamide



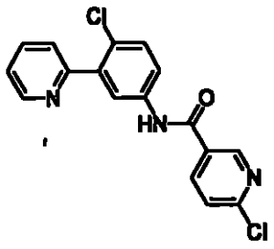
50 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-methyl-2-phenyl-5-pyrimidine carboxylic acid via Procedure G. The product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-4-phenylpyrimidine-5-carboxamide. MS (Q1) 401.1 $(M)^+$.

Example 249 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-1-(4-fluorophenyl)-5-methyl-1*H*-pyrazole-4-carboxamide



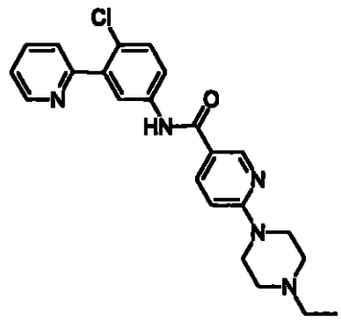
50 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 1-(4-fluorophenyl)-5-methyl-1*H*-pyrazole-4-carboxylic acid via Procedure G. The product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-1-(4-fluorophenyl)-5-methyl-1*H*-pyrazole-4-carboxamide. MS (Q1) 407.0 $(M)^+$.

Example 250 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide



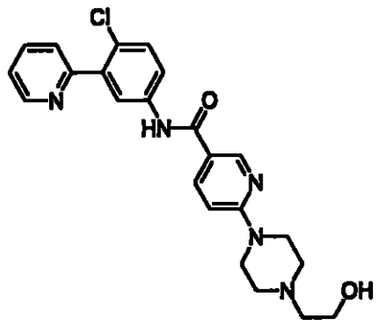
A mixture of 450 mg of 4-chloro-3-(pyridin-2-yl)aniline, 427 mg of 6-chloronicotinyl chloride and 1.9 g of PS-DIEA in 10 mL of dichloromethane was shook on the shaker for 3h. The reaction mixture was filtered and washed with dichloromethane. The filtrate was concentrated to yield 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide. MS (Q1) 344.2 $(M)^+$.

Example 251 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(4-ethylpiperazin-1-yl)nicotinamide



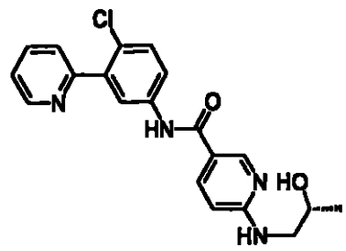
Procedure F was performed using 50 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide and 93 μL of 1-ethylpiperazine in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(4-ethylpiperazin-1-yl)nicotinamide. MS (Q1) 422.0 $(M)^+$.

Example 252 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(4-(2-hydroxyethyl)piperazin-1-yl)nicotinamide



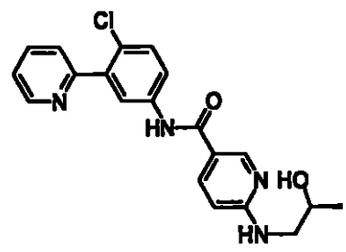
Procedure F was performed using 50 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide and 90 μL of 1-(2-hydroxyethyl)piperazine in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(4-(2-hydroxyethyl)piperazin-1-yl)nicotinamide. MS (Q1) 438.0 $(M)^+$.

Example 253 (*R*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(2-hydroxypropylamino)nicotinamide.



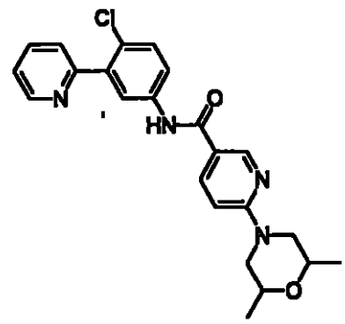
Procedure F was performed using 50 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide and 57 μL of R-1-Amino-2–propanol in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield (*R*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(2-hydroxypropylamino)nicotinamide. MS (Q1) 383.4 $(M)^+$.

Example 254 (*S*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(2-hydroxypropylamino)nicotinamide



Procedure F was performed using 50 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide and 57 μL of S-1-Amino-2–propanol in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield (*S*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(2-hydroxypropylamino)nicotinamide. MS (Q1) 383.4 $(M)^+$.

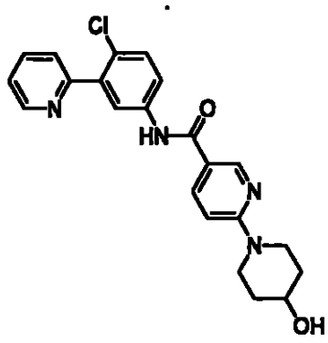
Example 255 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(2,6-dimethylmorpholino)nicotinamide



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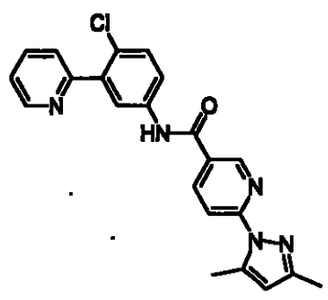
Procedure F was performed using 50 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide and 90 μL of 2,6-dimethylmorpholine in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(2,6-dimethylmorpholino)nicotinamide. MS (Q1) 423.4 $(M)^+$.

Example 256 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(4-hydroxypiperidin-1-yl)nicotinamide



Procedure F was performed using 50 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide and 74 mg of 4-hydroxypiperidine in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(4-hydroxypiperidin-1-yl)nicotinamide. MS (Q1) 409.3 $(M)^+$.

Example 257 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(3,5-dimethyl-1*H*-pyrazol-1-yl)nicotinamide

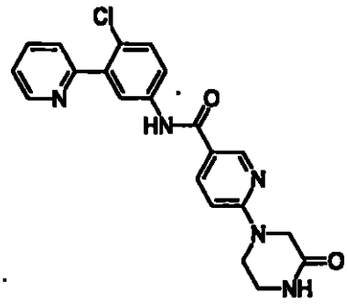


21 mg of sodium hydride was added to a solution of 84 mg of 3,5-dimethylpyrazole in 2 mL of DMF. The reaction mixture was stirred for 10 min, and then added 100 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide. The reaction was heated to 140 °C for 16h. The

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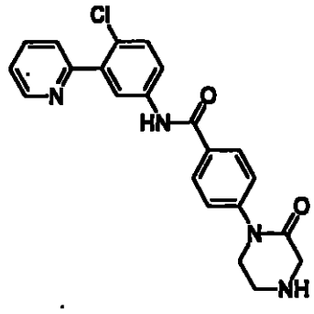
mixture was quenched with MeOH and evaporated. The product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(3,5-dimethyl-1*H*-pyrazol-1-yl)nicotinamide. MS (Q1) 404.3 $(M)^+$.

Example 258 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(3-oxopiperidin-1-yl)nicotinamide



Procedure F was performed using 50 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide and 29 mg of piperazin-2-one in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(3-oxopiperidin-1-yl)nicotinamide. MS (Q1) 408.3 $(M)^+$.

Example 259 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-oxopiperazin-1-yl)benzamide

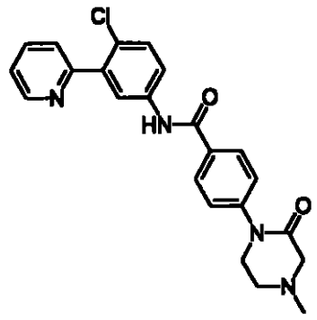


A mixture of 1 g of methyl 4-iodobenzoate, 920 mg of 4-Boc-piperazinone, 1.1 g of potassium carbonate, 32 mg of N, N'-dimethylethylenediamine and 70 mg of copper iodide in 10 mL of toluene was heated to 150 °C in a sealed microwave reactor for 3h. The reaction mixture was diluted with ethyl acetate, washed with H_2O, dried ($MgSO_4$) and evaporated. Purified by silica gel chromatography (20-80% ethyl acetate/hexane) to afford tert-butyl 4-(4-

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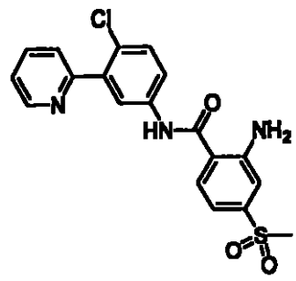
(methoxycarbonyl)phenyl)-3-oxopiperazine-1-carboxylate. 500 mg of tert-butyl 4-(4-(methoxycarbonyl)phenyl)-3-oxopiperazine-1-carboxylate was hydrolyzed via Procedure M to give 4-(4-(tert-buthoxycarbonyl)-2-oxopiperazin-1-yl)benzoic acid. 100 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-(4-(tert-buthoxycarbonyl)-2-oxopiperazin-1-yl)benzoic acid via Procedure G. The reaction mixture was diluted with ethyl acetate, washed with 0.1 N sodium hydroxide and brine, dried ($MgSO_4$) and evaporated to afford tert-butyl 4-(4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)phenyl)-3-oxopiperazine-1-carboxylate. 300 mg of crude tert-butyl 4-(4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)phenyl)-3-oxopiperazine-1-carboxylate was treated with TFA (2 mL) containing trace amounts of H_2O for 1h. The reaction mixture was evaporated and the crude product was purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-oxopiperazin-1-yl)benzamide. MS (Q1) 407.3 $(M)^+$.

Example 260 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(4-methyl-2-oxopiperazin-1-yl)benzamide



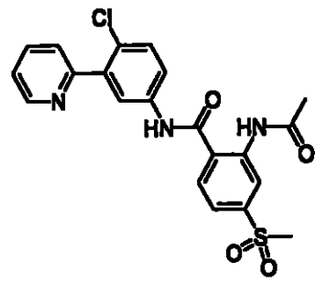
120 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-oxopiperazin-1-yl)benzamide was dissolved in 2 mL of DMF and then treated with 53 mg of paraformaldehyde, 187 mg of sodium triacetoxyborohydride and 0.2 mL of AcOH. After stirring 16 h, the reaction mixture was evaporated and the crude product was purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(4-methyl-2-oxopiperazin-1-yl)benzamide. MS (Q1) 421.3 $(M)^+$.

Example 261 2-amino-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide



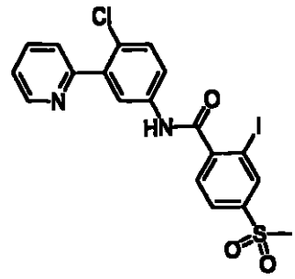
2.2 g of methyl 4-(methylsulfonyl)-2-nitrobenzoate was reacted via Procedure C to afford methyl 2-amino-4-(methylsulfonyl)benzoate. 500 mg of methyl 2-amino-4-(methylsulfonyl)benzoate was hydrolyzed via Procedure M to give 2-amino-4-(methylsulfonyl)benzoic acid. 100 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 2-amino-4-(methylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield 2-amino-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide. MS (Q1) 402.0 $(M)^+$.

Example 262 2-acetamido-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide



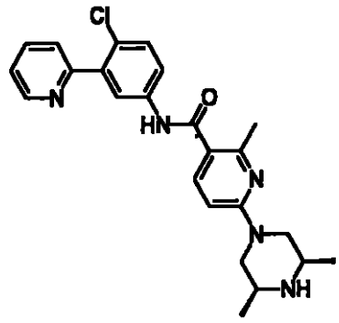
20 μL of acetyl chloride was added to a solution of 90 mg of 2-amino-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide in 2 mL of pyridine at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2h. The reaction was quenched with MeOH and evaporated. The product was purified on reverse phase HPLC to yield 2-acetamido-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide. MS (Q1) 444.0 $(M)^+$.

Example 263 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-iodo-4-(methylsulfonyl)benzamide



600 mg of methyl 2-amino-4-(methylsulfonyl)benzoate was added to a solution of 4 mL of H_2O and 1 mL of concentrated sulfuric acid. The solution was cooled to 0 °C and a solution of 206 mg of sodium nitrite in 1 mL of H_2O was added slowly. The reaction mixture was stirred for 2 h and then a solution of 782 mg of potassium iodide in 2 mL of H_2O was added dropwise at 0 °C. The reaction was allowed to warm to room temperature and stirred for 5 h. The mixture was extracted with ethyl acetate. The combined organic extracts were washed with saturated $Na_2S_2O_3$, dried ($MgSO_4$) and evaporated. Purified by silica gel chromatography (5-50% ethyl acetate/hexane) to afford methyl 2-iodo-4-(methylsulfonyl)benzoate. 160 mg of methyl 2-iodo-4-(methylsulfonyl)benzoate was hydrolyzed via Procedure M to give 2-iodo-4-(methylsulfonyl)benzoic acid. 60 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 2-iodo-4-(methylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-iodo-4-(methylsulfonyl)benzamide. MS (Q1) 513.0 $(M)^+$.

Example 264 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-((3*S*,5*R*)-3,5-dimethylpiperazin-1-yl)-2-methylnicotinamide

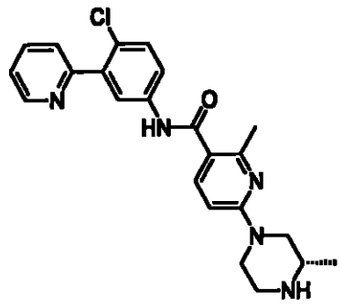


Stoichiometric amounts (0.04 mol) of methyl propiolate and ethyl 3-aminocrotonate were heated to 140 °C for 1h. 1 g of the crude (2E,4Z)-methyl-4-(1-aminoethylidene)-5-oxooct-2-enoate in 4 mL of DMF was heated to 230 °C in a sealed microwave reactor for 40 min. The reaction mixture was

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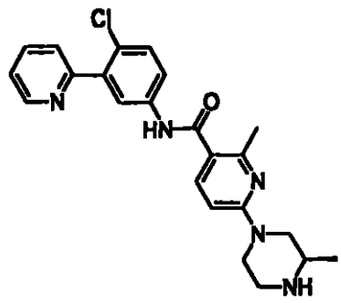
diluted with ethyl acetate, washed with H_2O, dried ($MgSO_4$) and evaporated to afford crude ethyl 6-hydroxy-2-methylnicotinate. A mixture of 800 mg of crude ethyl 6-hydroxy-2-methylnicotinate in 4 mL of phosphorus oxychloride was heated to 150 °C in a sealed microwave reactor for 15 min. The reaction mixture was poured into ice/water, extracted with diethyl ether. The combined organic layers were dried ($MgSO_4$) and evaporated. Purified by silica gel chromatograph (0-20% ethyl acetate/hexane) to yield ethyl 6-chloro-2-methylnicotinate. 400 mg of ethyl 6-chloro-2-methylnicotinate was hydrolyzed via Procedure M to give 6-chloro-2-methylnicotinic acid. 300 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 6-chloro-2-methylnicotinic acid via Procedure G. The reaction mixture was diluted with ethyl acetate, washed with 0.1 N sodium hydroxide and brine, dried ($MgSO_4$) and evaporated to afford 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide. Procedure F was performed using 100 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 128 mg of 2,6-dimethylpiperazine in 1 mL of BuOH. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-((3*S*,5*R*)-3,5-dimethylpiperazin-1-yl)-2-methylnicotinamide. MS (Q1) 436.3 $(M)^+$.

Example 265 (*S*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(3-methylpiperazin-1-yl)nicotinamide



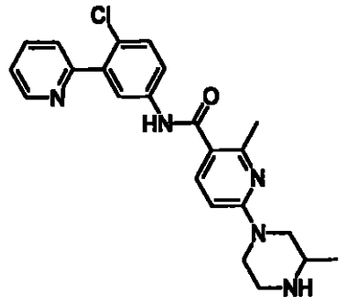
Procedure F was performed using 100 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 112 mg of S-(-)-2-methylpiperizine in 1 mL of BuOH. Purified by reverse phase HPLC to yield (*S*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(3-methylpiperazin-1-yl)nicotinamide. MS (Q1) 422.3 $(M)^+$.

Example 266 (*R*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(3-methylpiperazin-1-yl)nicotinamide.



Procedure F was performed using 100 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 112 mg of R-(+)-2-methylpiperizine in 1 mL of BuOH. Purified by reverse phase HPLC to yield (*R*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(3-methylpiperazin-1-yl)nicotinamide. MS (Q1) 422.3 $(M)^+$.

Example 267 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(3-methylpiperazin-1-yl)nicotinamide

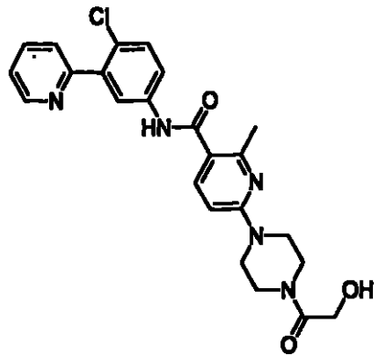


Procedure F was performed using 100 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 112 mg of 2-methylpiperizine in 1 mL of BuOH. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(3-methylpiperazin-1-yl)nicotinamide. MS (Q1) 422.3 $(M)^+$.

Example 268 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(4-(2-hydroxyacetyl)piperazin-1-yl)-2-methylnicotinamide

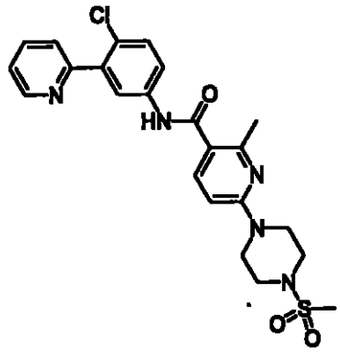
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100 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(piperazin-1-yl)nicotinamide was coupled to glycolic acid via Procedure G. The product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(4-(2-hydroxyacetyl)piperazin-1-yl)-2-methylnicotinamide. MS (Q1) 466.3 $(M)^+$.

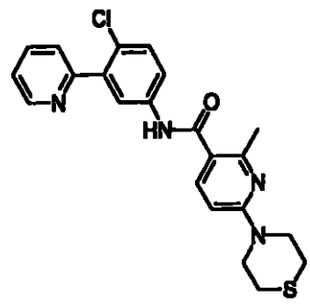
Example 269 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(4-(methylsulfonyl)piperazin-1-yl)nicotinamide



1.3 mL of methanesulfonyl chloride was slowly added to a solution of 2 g of 1-Boc–piperazine and 1.3 mL of pyridine in 6 mL of dichloromethane at 0 ° C. The reaction mixture was allowed to warm to room temperature and stirred for 2h while being monitored by TLC. Upon completion, the mixture was diluted with dichloromethane, washed with H_2O, dried ($MgSO_4$) and evaporated. Purified by silica gel chromatograph (20-100% ethyl acetate/hexane) to afford tert-butyl-4-(methylsulfonyl)piperazine-1-carboxylate. 930 mg of tert-butyl-4-(methylsulfonyl)piperazine-1-carboxylate was treated with 4N HCl in dioxane for 2h. The reaction mixture was evaporated to give the HCl salt of 1-(methylsulfonyl)piperazine. Procedure F was performed using 50 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide, 69 mg of 1-(methylsulfonyl)piperazine and DIEPA(1 eq) in 0.5 mL of BuOH. Purified by reverse phase

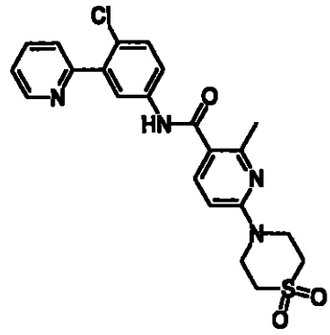
HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(4-(methylsulfonyl)piperazin-1-yl)nicotinamide. MS (Q1) 486.3 $(M)^+$.

Example 270 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-thiomorpholinonicotinamide



Procedure F was performed using 90 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 78 µL of thiomorpholine in 1 mL of BuOH. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-thiomorpholinonicotinamide. MS (Q1) 425.3 $(M)^+$.

Example 271 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-sulfonylmorpholinonicotinamide

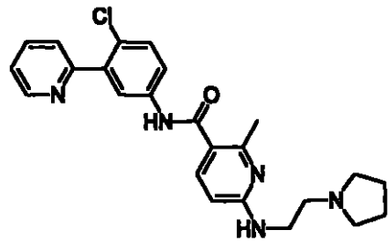


100 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-thiomorpholinonicotinamide was reacted via produce R. The product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-sulfonylmorpholinonicotinamide. MS (Q1) 457.3 $(M)^+$.

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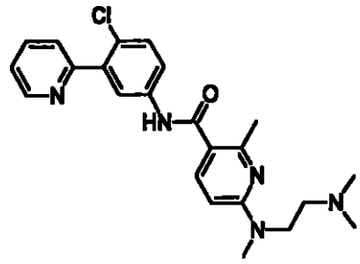
233

Example 272 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(2-(pyrrolidin-1-yl)ethylamino)-nicotinamide



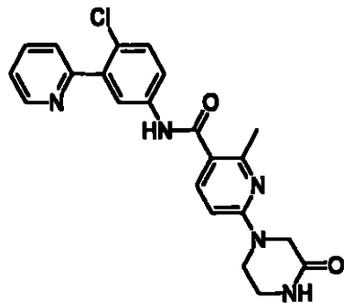
Procedure F was performed using 100 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 70 μL of 1-(2-aminoethyl)pyrrolidine in 1 mL of BuOH. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(2-(pyrrolidin-1-yl)ethylamino)nicotinamide. MS (Q1) 436.0 $(M)^+$.

Example 273 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-((2-(dimethylamino)ethyl)(methyl)amino)-2-methylnicotinamide



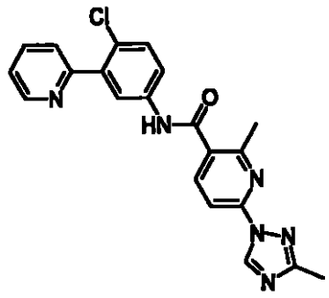
Procedure F was performed using 60 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 66 μL of N,N,N'-trimethylethylenediamine in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-((2-(dimethylamino)ethyl)(methyl)amino)-2-methylnicotinamide. MS (Q1) 424.0 $(M)^+$.

Example 274 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(3-oxopiperazin-1-yl)nicotinamide



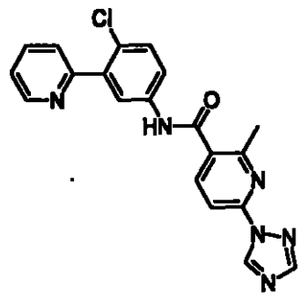
Procedure F was performed using 100 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 84 mg of piperazine-2-one in 1 mL of BuOH. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(3-oxopiperazin-1-yl)nicotinamide. MS (Q1) 422.3 $(M)^+$.

Example 275 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(3-methyl-1*H*-1,2,4-triazol-1-yl)nicotinamide



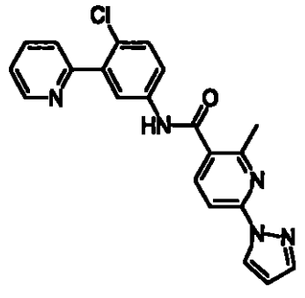
A mixture of 57 mg of 3-methyl-1,2,4-triazol and 16 mg of sodium hydride in 2 mL of DMF was stirred for 10 min. 80 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide was added. The reaction was heated to 140 °C for 16h. The reaction mixture was quenched with MeOH and evaporated. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(3-methyl-1*H*-1,2,4-triazol-1-yl)nicotinamide. MS (Q1) 405.3 $(M)^+$.

Example 276 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(1*H*-1,2,4-triazol-1-yl)nicotinamide



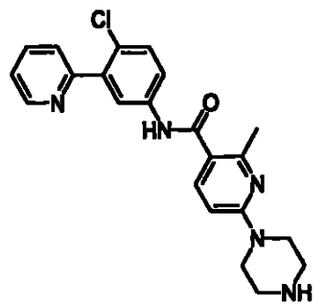
A mixture of 41 mg of 1,2,4-triazol and 14 mg of sodium hydride in 2 mL of DMF was stirred for 10 min. 70 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide was added. The reaction was heated to 140 °C for 6h. The reaction mixture was quenched with MeOH and evaporated. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(1*H*-1,2,4-triazol-1-yl)nicotinamide. MS (Q1) 391.4 $(M)^+$.

Example 277 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(1*H*-pyrazol-1-yl)nicotinamide



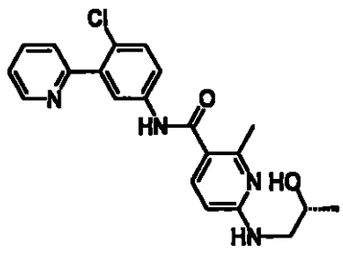
A mixture of 52 mg of pyrazole and 18 mg of sodium hydride in 2 mL of DMF were stirred for 10 min. 90 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide was added. The reaction was heated to 140 °C for 5h. The reaction mixture was quenched with MeOH and evaporated. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(1*H*-pyrazol-1-yl)nicotinamide. MS (Q1) 390.0 $(M)^+$.

Example 278 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(piperazin-1-yl)nicotinamide



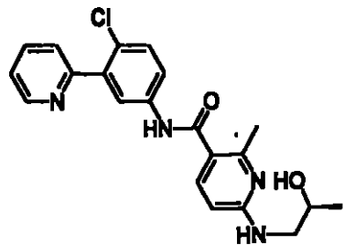
Procedure F was performed using 80 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 209 mg of 1-Boc-piperizine in 1 mL of BuOH. The reaction mixture was evaporated to afford tert-butyl 4-(5-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)-6-methylpyridin-2-yl)piperazine-1-carboxylate. 150 mg of tert-butyl 4-(5-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)-6-methylpyridin-2-yl)piperazine-1-carboxylate was treated with TFA (1 mL) containing trace amounts of H_2O for 2 h. The reaction mixture was diluted with ethyl acetate, washed with 0.1N sodium hydroxide and brine, dried ($MgSO_4$) and evaporated. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(piperazin-1-yl)nicotinamide. MS (Q1) 408.3 $(M)^+$.

Example 279 (*R*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(2-hydroxypropylamino)-2-methylnicotinamide



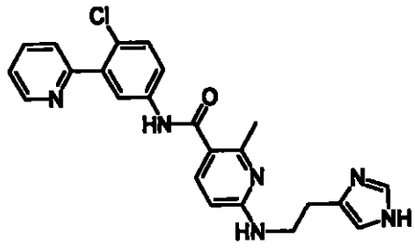
Procedure F was performed using 60 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 116 µL of R-(-)-1-amino-2-propanol in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield (*R*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(2-hydroxypropylamino)-2-methylnicotinamide. MS (Q1) 397.4 $(M)^+$.

Example 280 (*S*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(2-hydroxypropylamino)-2-methylnicotinamide



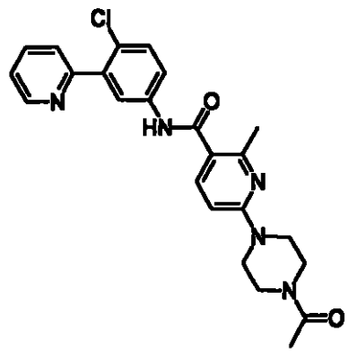
Procedure F was performed using 60 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 116 μL of S-(+)-1-amino-2-propanol in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield (*S*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(2-hydroxypropylamino)-2-methylnicotinamide. MS (Q1) 397.4 $(M)^+$.

Example 281. 6-(2-(1*H*-imidazol-4-yl)ethylamino)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide



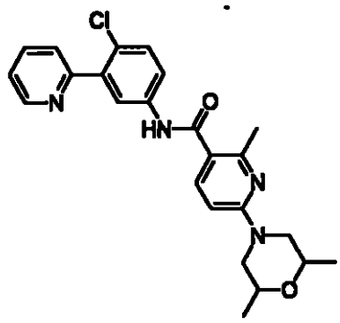
Procedure F was performed using 60 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 93 mg of histamine in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield 6-(2-(1*H*-imidazol-4-yl)ethylamino)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide. MS (Q1) 433.0 (M)

Example 282 6-(4-acetylpiperazin-1-yl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide



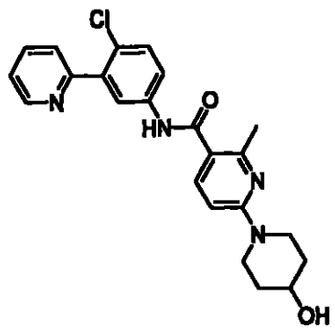
Procedure F was performed using 55 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 99 mg of 1-acetylpiperazine in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield 6-(4-acetylpiperazin-1-yl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide. MS (Q1) 450.4 $(M)^+$.

Example 283 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(2,6-dimethylmorpholino)-2-methylnicotinamide



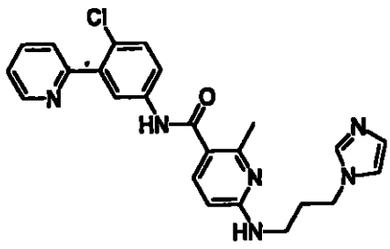
Procedure F was performed using 55 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 95 mg of 2,6-dimethylmorpholine in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(2,6-dimethylmorpholino)-2-methylnicotinamide. MS (Q1) 436.2 $(M)^+$.

Example 284 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(4-hydroxypiperidin-1-yl)-2-methylnicotinamide



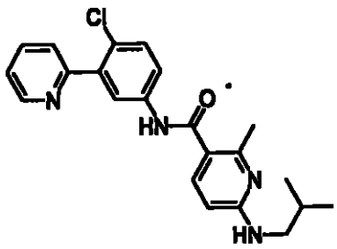
Procedure F was performed using 55 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 78 mg of 4-hydropiperidine in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(4-hydroxypiperidin-1-yl)-2-methylnicotinamide. MS (Q1) 422.1 $(M)^+$.

Example 285 6-(3-(1*H*-imidazol-1-yl)propylamino)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide



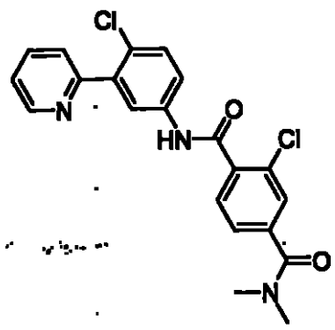
Procedure F was performed using 55 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 92 µL of 1-(3-aminopropyl)-imidazole in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield 6-(3-(1*H*-imidazol-1-yl)propylamino)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide. MS (Q1) 446.1 $(M)^+$.

Example 286 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(isobutylamino)-2-methylnicotinamide



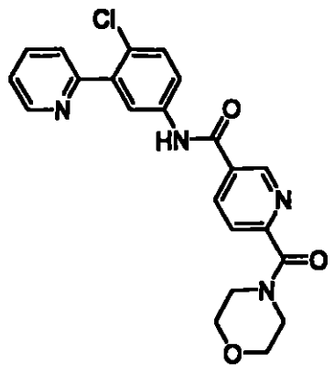
Procedure F was performed using 50 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 70 µL of isobutylamine in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(isobutylamino)-2-methylnicotinamide. MS (Q1) 395.4 $(M)^+$.

Example 287 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4,N^4-dimethylterephthalamide



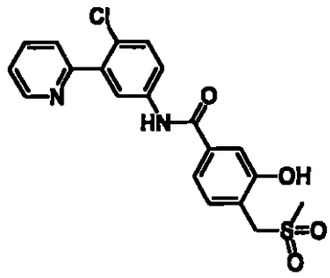
290 mg of dimethylamine hydrochloride was coupled to 1 g of 4-(*tert*-butoxycarbonyl)-3-chlorobenzoic acid via Procedure G. The reaction mixture was diluted with ethyl acetate, washed with 0.1 N HCl, 0.1 N NaOH and brine, dried ($MgSO_4$) and evaporated to afford tert-butyl 2-chloro-4-(dimethylcarbamoyl)benzoate. 1.1g of tert-butyl 2-chloro-4-(dimethylcarbamoyl)benzoate was treated with TFA (4 mL) containing trace amounts of H_2O for 2 h. The reaction mixture was evaporated, and then added 0.1 N HCl. The resulting solid was filtered and washed with H_2O to yield 2-chloro-4-(dimethylcarbamoyl)benzoic acid. 100 mg of 4-chloro-3-(pyridine-2-yl)aniline was coupled to 2-chloro-4-(dimethylcarbamoyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4,N^4-dimethylterephthalamide.
MS (Q1) 414.1 $(M)^+$.

Example 288 N-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(morpholine-4-carbonyl)nicotinamide



63 mg of morpholine was coupled to 120 mg of 5-(methoxycarbonyl)pyridine-2-carboxylic acid via Procedure G. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate and brine, dried ($MgSO_4$) and evaporated to afford methyl 6-(morpholine-4-carbonyl)nicotinate. 180 mg of methyl 6-(morpholine-4-carbonyl)nicotinate was hydrolyzed via Procedure M to give 6-(morpholine-4-carbonyl)nicotinic acid. 100 mg of 4-chloro-3-(pyridine-2-yl)aniline was coupled to 6-(morpholine-4-carbonyl)nicotinic acid via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro- N-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(morpholine-4-carbonyl)nicotinamide. MS (Q1) 423.4 $(M)^+$.

Example 289 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-3-hydroxy-4-(methylsulfonylmethyl)benzamide

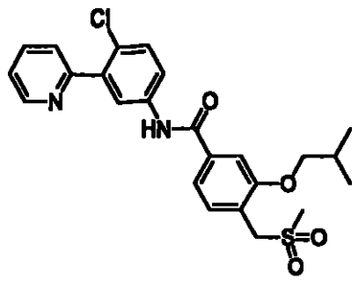


3-Hydroxy-4-methylbenzoic acid (6.86 g, 45.1 mmol) was dissolved in methanol (200 ml). 4N HCl in 1,4-dioxane (34 ml, 0.135 mmol HCl) was added and the solution heated to 55°C for 18 hours. The solvent was concentrated on a rotary evaporator, and then partitioned between water and ethyl acetate. The aqueous portion was extracted with ethyl acetate once, and the ethyl acetate extracts were combined and washed with water once, brine once, dried with $MgSO_4$, and evaporated to methyl 3-hydroxy-4-methylbenzoate as a crude tan solid (6.66 g) which was used without purification. Methyl 3-hydroxy-4-methylbenzoate (6.66 g, 40.1 mmol) was dissolved in

dichloromethane (200 ml), treated with pyridine (4.3 ml, 60.2 mmol), and cooled in an ice water bath. Acetyl chloride (3.6 ml, 50.1 mmol) was added dropwise. The solution was allowed to warm to room temperature, with stirring, over 18 hours. The solution was washed with 1 N aqueous HCl twice, water once, brine once, dried with $MgSO_4$, and evaporated to methyl 3-acetoxy-4-methylbenzoate as a crude tan oil (6.93 g) which was used without purification. Methyl 3-acetoxy-4-methylbenzoate (6.38 g, 30.6 mmol) was dissolved in carbon tetrachloride (130 ml) and treated with benzoic peroxyanhydride (200 mg, 0.83 mmol) and NBS (5.45 g, 30.6 mmol), then heated to 85°C for 3 hours. After cooling to room temperature, the solution was filtered through Celite 545 and evaporated to a crude yellow solid which was purified by silica gel flash chromatography (5% dichloromethane/hexanes increasing to 35% dichloromethane/hexanes) to yield methyl 3-acetoxy-4-(bromomethyl)benzoate as an off white solid (4.18 g). Methyl 3-acetoxy-4-(bromomethyl)benzoate (2.00 g, 6.97 mmol) was used in procedure O to afford methyl 3-acetoxy-4-(methylsulfonylmethyl)benzoate as a white solid (1.67 g) which was used without purification. Methyl 3-acetoxy-4-(methylsulfonylmethyl)benzoate (1.67 g, 5.83 mmol) was saponified via procedure M to afford 3-hydroxy-4-(methylsulfonylmethyl)benzoic acid as a white solid (1.05 g) which was used without purification. 3-Hydroxy-4-(methylsulfonylmethyl)benzoic acid (860 mg, 3.74 mmol) was dissolved in 1,4-dioxane (25 ml) and treated with thionyl chloride (8 ml) and DMF (5 drops), then heated to 50°C for 2 hours. The reaction was cooled and evaporated to an oil. The oil residue was dissolved in dichloromethane (40 ml), cooled in an ice water bath, and treated dropwise with a solution of 4-chloro-3-(pyridin-2-yl)aniline (767 mg, 3.74 mmol) in dichloromethane (30 ml). The reaction was stirred 18 hours, allowing to warm to room temperature. The reaction was diluted with dichloromethane (40 ml) and stirred vigorously with water (50 ml) while acidifying to pH 6 with 1 M citric acid. The dichloromethane portion was separated, and enough methanol was added to dissolve precipitating solids. The solution was washed with water once, brine once, dried with $MgSO_4$, and evaporated to a solid which was triturated with dichloromethane, filtered, and air dried to yield 909 mg of crude product. A portion (20 mg) was purified on reverse phase HPLC to yield 16 mg of purified *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-hydroxy-4-(methylsulfonylmethyl)benzamide as a white solid. MS (Q1) 417 $(M)^+$.

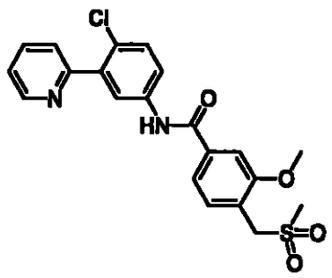
Example 290 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-3-isobutoxy-4-(methylsulfonylmethyl)benzamide

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N-(4-chloro-3-(pyridin-2-yl)phenyl)-3-hydroxy-4-(methylsulfonylmethyl)benzamide (50 mg, 0.12 mmol) was treated with 1-bromo-2-methylpropane (26 µl, 0.24 mmol) via procedure U to yield 19 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-isobutoxy-4-(methylsulfonylmethyl)benzamide. MS (Q1) 473 $(M)^+$.

Example 291 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-3-methoxy-4-(methylsulfonylmethyl)benzamide

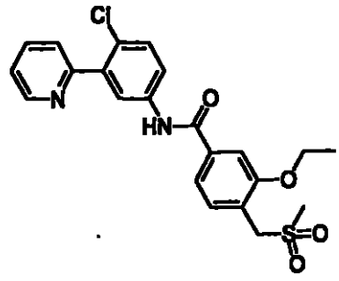


N-(4-Chloro-3-(pyridin-2-yl)phenyl)-3-hydroxy-4-(methylsulfonylmethyl)benzamide (50 mg, 0.12 mmol) was treated with iodomethane (7.5 µl, 0.12 mmol) via procedure U to yield 12 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-methoxy-4-(methylsulfonylmethyl)benzamide. MS (Q1) 431 $(M)^+$.

Example 292 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-3-ethoxy-4-(methylsulfonylmethyl)benzamide

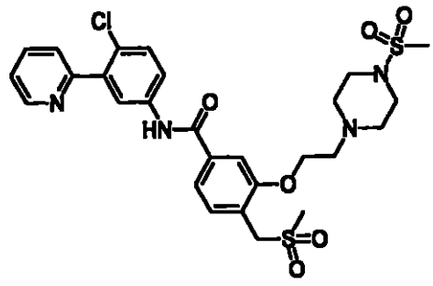
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N-(4-Chloro-3-(pyridin-2-yl)phenyl)-3-hydroxy-4-(methylsulfonylmethyl)benzamide (50 mg, 0.12 mmol) was treated with iodoethane (10 µl, 0.12 mmol) via procedure U to yield 22 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-ethoxy-4-(methylsulfonylmethyl)benzamide. MS (Q1) 445 $(M)^+$.

Example 293 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-3-(2-(4-(methylsulfonyl)piperazin-1-yl)ethoxy)-4-(methylsulfonylmethyl)benzamide

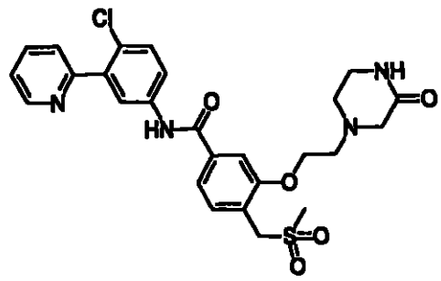


N-(4-Chloro-3-(pyridin-2-yl)phenyl)-3-hydroxy-4-(methylsulfonylmethyl)benzamide (1.00 g, 2.40 mmol) was dissolved in DMF (20 ml). Cesium carbonate (1.56 g, 4.8 mmol) and 1,2-dibromoethane (0.83 ml, 9.6 mmol) were added, and the reaction was stirred at 50°C for 18 hours. The reaction was quenched with water, basified with 10% aqueous NaOH, and extracted with ethyl acetate twice. The ethyl extracts were washed with water once, brine once, dried with $MgSO_4$, and evaporated to a crude oil which was purified by chromatography (25% hexanes in ethyl acetate) to yield 490 mg of 3-(2-bromoethoxy)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide as a yellow solid. 3-(2-Bromoethoxy)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide (100 mg, 0.19 mmol) was dissolved in DMF (2.0 ml), and potassium carbonate (32 mg, 0.23 mmol) and tert-butyl piperazine-1-carboxylate (38 mg, 0.21 mmol) were added. The reaction was stirred for 18 hours at room temperature, quenched in water, and extracted with ethyl acetate twice. The ethyl acetate extracts were washed with water once, brine once, dried with $MgSO_4$, and evaporated to a crude oil. The oil was dissolved in

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dichloromethane (1 ml) and treated with trifluoroacetic acid (3 ml) for 1 hour. The reaction was evaporated to dryness, and the crude solid was purified on reverse phase HPLC to yield 63 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)-3-(2-(piperazin-1-yl)ethoxy)benzamide as a white solid. *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)-3-(2-(piperazin-1-yl)ethoxy)benzamide (30 mg, 0.047 mmol) was dissolved in dichloromethane (1.5 ml) and THF (1.0 ml). *N*-ethyl-*N*-isopropylpropan-2-amine (18 µl, 0.10 mmol) and methanesulfonyl chloride (4 µl, 0.051 mmol) were added, and the reaction stirred at room temperature for 72 hours. Additional *N*-ethyl-*N*-isopropylpropan-2-amine (9 µl, 0.051 mmol) and methanesulfonyl chloride (4 µl, 0.051 mmol) were added and the reaction stirred for 2 hours. After a further addition of methanesulfonyl chloride (4 µl, 0.051 mmol), the reaction was stirred for 2 hours and evaporated to a crude solid which was purified on reverse phase HPLC to yield 8 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-(2-(4-(methylsulfonyl)piperazin-1-yl)ethoxy)-4-(methylsulfonylmethyl)benzamide. MS (Q1) 607 $(M)^+$.

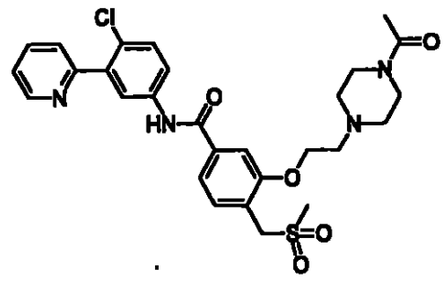
Example 294 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)-3-(2-(3-oxopiperazin-1-yl)ethoxy)benzamide



3-(2-Bromoethoxy)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide (50 mg, 0.095 mmol) was dissolved in DMF (1.0 ml) and treated with potassium carbonate (18 mg, 0.13 mmol) and piperazin-2-one (11 mg, 0.11 mmol) for 18 hours. The reaction was heated for 2.0 hours at 50°C, then additional potassium carbonate (18 mg, 0.13 mmol) and piperazin-2-one (11 mg, 0.11 mmol) was added. After 2 hours, the reaction was quenched in 5% NaOH and extracted with ethyl acetate twice. The ethyl acetate extracts were washed with water once, brine once, dried with $MgSO_4$, and purified by reverse phase HPLC to yield 16 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)-3-(2-(3-oxopiperazin-1-yl)ethoxy)benzamide. MS (Q1) 558 $(M)^+$.

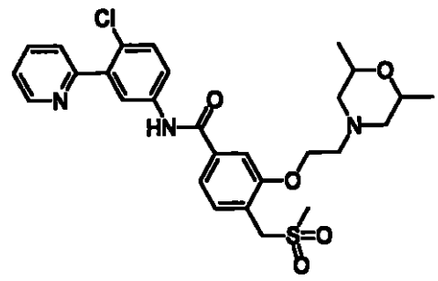
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Example 295 3-(2-(4-Acetylpiperazin-1-yl)ethoxy)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide



3-(2-Bromoethoxy)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide (50 mg, 0.095 mmol) was dissolved in DMF (1.0 ml) and treated with potassium carbonate (18 mg, 0.13 mmol) and 1-(piperazin-1-yl)ethanone (15 mg, 0.11 mmol) for 18 hours. The reaction was heated for 2.0 hours at 50°C, then additional potassium carbonate (18 mg, 0.13 mmol) and 1-(piperazin-1-yl)ethanone (15 mg, 0.11 mmol) was added. After 2 hours, the reaction was quenched in 5% NaOH and extracted with ethyl acetate twice. The ethyl acetate extracts were washed with water once, brine once, dried with $MgSO_4$, and purified by reverse phase HPLC to yield 18 mg of 3-(2-(4-acetylpiperazin-1-yl)ethoxy)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide. MS (Q1) 543 $(M)^+$.

Example 296 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-3-(2-(2,6-dimethylmorpholino)ethoxy)-4-(methylsulfonylmethyl)benzamide

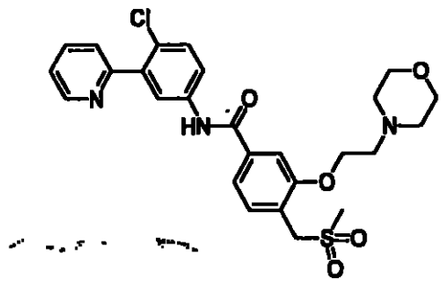


3-(2-Bromoethoxy)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide (50 mg, 0.095 mmol) was dissolved in DMF (1.0 ml) and treated with potassium carbonate (18 mg, 0.13 mmol) and 2,6-dimethylmorpholine (14 µl, 0.11 mmol), and stirred at room temperature for 18 hours. The reaction was quenched in 5% NaOH and extracted with ethyl acetate twice. The

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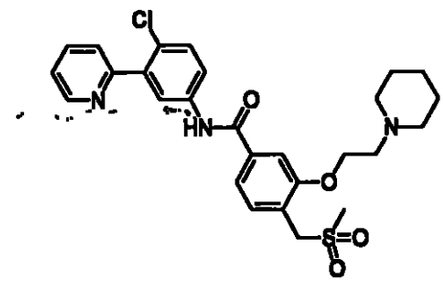
ethyl acetate extracts were washed with water once, brine once, dried with $MgSO_4$, and purified by reverse phase HPLC to yield 20 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-(2-(2,6-dimethylmorpholino)ethoxy)-4-(methylsulfonylmethyl)benzamide. MS (Q1) 571 $(M)^+$.

Example 297 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)-3-(2-morpholinoethoxy)benzamide



3-(2-Bromoethoxy)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide (50 mg, 0.095 mmol) was dissolved in acetonitrile (1.0 ml) and DMF (1.0 ml), treated with potassium carbonate (16 mg, 0.12 mmol) and morpholine (10 µl, 0.11 mmol), and stirred 18 hours at room temperature. The reaction was heated to 50°C for 8 hours, and then was allowed to stir 18 hours at room temperature. The reaction was quenched in water and extracted with ethyl acetate twice. The ethyl acetate extracts were washed with water once, brine once, dried with $MgSO_4$, and evaporated to an oil which was purified by reverse phase HPLC to yield 30 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)-3-(2-morpholinoethoxy)benzamide. MS (Q1) 530 $(M)^+$.

Example 298 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)-3-(2-(piperidin-1-yl)ethoxy)benzamide

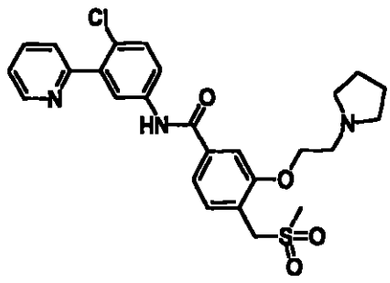


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3-(2-Bromoethoxy)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide (50 mg, 0.095 mmol) was dissolved in dichloromethane (1.0 ml), treated with triethylamine (20 µl, 0.15 mmol) and piperidine (11 µl, 0.11 mmol), and stirred 2.0 hours at room temperature. Acetonitrile (0.25 ml) and *N*-ethyl-*N*-isopropylpropan-2-amine (25 µl, 0.19 mmol) were added, and the reaction was stirred for an additional 45 hours. The reaction was quenched in water and extracted with dichloromethane twice. The dichloromethane extracts were washed with water once, brine once, dried with $MgSO_4$, and evaporated to an solid which was purified by reverse phase HPLC to yield 17 mg *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)-3-(2-(piperidin-1-yl)ethoxy)benzamide. MS (Q1) 528 $(M)^+$.

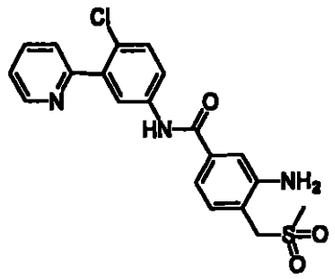
Example 299 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)-3-(2-(pyrrolidin-1-yl)ethoxy)benzamide



3-(2-Bromoethoxy)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide (40 mg, 0.076 mmol) was dissolved in acetonitrile (1.0 ml) and DMF (1.0 ml), treated with potassium carbonate (16 mg, 0.12 mmol) and pyrrolidine (7 µl, 0.084 mmol), and stirred 18 hours at room temperature. The reaction was quenched in water and extracted with ethyl acetate twice. The ethyl acetate extracts were washed with water once, brine once, dried with $MgSO_4$, and evaporated to an oil which was purified by reverse phase HPLC to yield 30 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)-3-(2-(pyrrolidin-1-yl)ethoxy)benzamide. MS (Q1) 514 $(M)^+$.

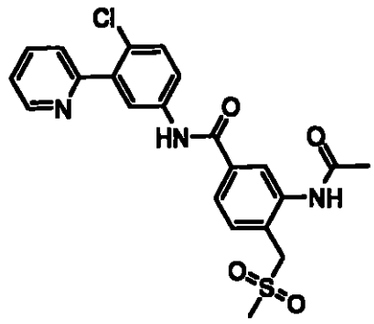
Example 300 3-Amino-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide

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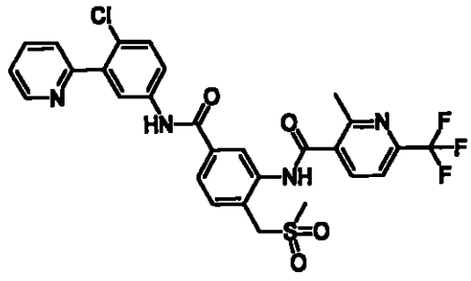
4-(Bromomethyl)-3-nitrobenzoic acid (2.00 g, 7.69 mmol) was dissolved in methanol (20 ml) and treated with 1 drop of concentrated sulfuric acid, then stirred 72 hours at room temperature. An additional 3 drops of concentrated sulfuric acid was added, and the reaction stirred at 50°C for 24 hours. The solvent was concentrated on a rotary evaporator, diluted with ethyl acetate, and washed with water twice, saturated $NaHCO_3$ once, water once, brine once, dried with $MgSO_4$, and evaporated to a 1.82 g of a yellow oil, methyl 4-(bromomethyl)-3-nitrobenzoate and used without purification. Methyl 4-(bromomethyl)-3-nitrobenzoate (1.82 g, 6.64 mmol) was used in procedure O to afford 1.66 g of methyl 4-(methylsulfonylmethyl)-3-nitrobenzoate as a solid which was used without purification. Methyl 4-(methylsulfonylmethyl)-3-nitrobenzoate (1.66 g, 6.07 mmol) was saponified via procedure M to afford 1.21 g of 4-(methylsulfonylmethyl)-3-nitrobenzoic acid as an orange solid, which was used without purification. 4-(Methylsulfonylmethyl)-3-nitrobenzoic acid (639 mg, 2.46 mmol) was dissolved in 1,4-dioxane (15 ml), treated with thionyl chloride (1.0 ml) and DMF (1 drop), and stirred at room temperature for 18 hours, then at 50°C for 8 hours, then at room temperature for 18 hours. After an additional 4.0 hours at 50°C, the solvents and excess thionyl chloride were removed via rotary evaporator, and the residue was dissolved dichloromethane (25.0 ml) and treated with *N*-ethyl-*N*-isopropylpropan-2-amine (1.7 ml, 9.8 mmol) and 4-chloro-3-(pyridin-2-yl)aniline (503 mg, 2.46 mmol) and stirred for 20 min at room temperature, over which time a solid precipitated. Water was added, and the mixture was filtered and air dried, to afford 797 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)-3-nitrobenzamide as a tan-yellow solid. *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)-3-nitrobenzamide (786 mg, 1.76 mmol) was dissolved in ethanol (74 ml) and concentrated HCl (12 ml). Tin(II) chloride dihydrate (1.31 g, 5.82 mmol) was added and the reaction was heated to 55°C for 2.5 hours. The reaction was cooled in an ice bath and triethylamine (10 ml) was added to basify the solution. The reaction was evaporated to a yellow solid which was slurried in ethyl acetate. The slurry was filtered through Celite 545, and the mother liquors were washed with water twice, brine once, dried with $MgSO_4$, and evaporated to 552 mg of as a crude yellow solid, 20 mg of which was purified by reverse phase HPLC to afford 13 mg of purified 3-amino-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide. MS (Q1) 416 $(M)^+$.

Example 301 3-Acetamido-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide



3-Amino-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide (30 mg, 0.072 mmol) was reacted with acetyl chloride (5.6 µl, 0.079 mol) via procedure V to afford 19 mg of 3-acetamido-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide as a white solid. MS (Q1) 458 $(M)^+$.

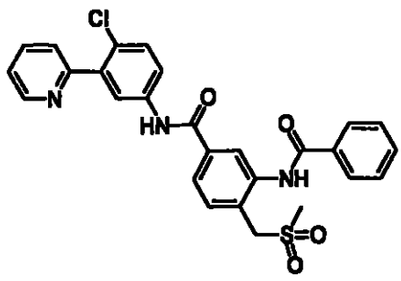
Example 302 *N*-(5-(4-Chloro-3-(pyridin-2-yl)phenylcarbamoyl)-2-(methylsulfonylmethyl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide



3-Amino-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide (30 mg, 0.072 mmol) was reacted with 2-methyl-6-(trifluoromethyl)nicotinoyl chloride (19 mg, 0.079 mmol) via procedure V to afford 16 mg of *N*-(5-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)-2-(methylsulfonylmethyl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide as a white solid. MS (Q1) 603 $(M)^+$.

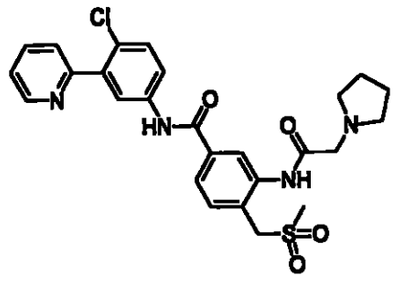
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Example 303 3-Benzamido-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide



3-Amino-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide (30 mg, 0.072 mmol) was reacted with benzoyl chloride (9 µl, 0.079 mmol) via procedure V to afford 17 mg of 3-benzamido-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide as a white solid. MS (Q1) 520 $(M)^+$.

Example 304 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)-3-(2-(pyrrolidin-1-yl)acetamido)benzamide

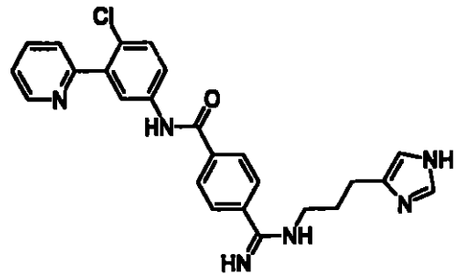


3-Amino-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide (100 mg, 0.24 mmol) was dissolved in 1,4-dioxane (5.0 ml), treated with triethylamine (274 µl, 1.97 mmol) and 2-bromoacetyl bromide (121 µl, 1.39 mmol). The reaction was heated to reflux for 10 minutes, and stirred at room temperature for 18 hours. The reaction was quenched with water, and extracted twice with ethyl acetate. The ethyl acetate extracts were filtered, washed with water once, brine once, dried with $MgSO_4$, evaporated to 158 mg of a crude brown oil, 3-(2-bromoacetamido)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide, which was used without further purification. Crude 3-(2-bromoacetamido)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl-methyl)benzamide (158 mg) was dissolved in DMF, treated with *N*-

~~251~~ 252

ethyl-*N*-isopropylpropan-2-amine (61 µl, 0.35 mmol) and pyrrolidine (27 µl, 0.32 mmol), and stirred at room temperature for 18 hours. The reaction was quenched with water and extracted with ethyl acetate twice. The ethyl acetate extracts were washed with water once, brine once, dried with $MgSO_4$, evaporated to a tan solid which was purified by reverse phase HPLC to afford 27 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)-3-(2-(pyrrolidin-1-yl)acetamido)benzamide as a white powder. MS (Q1) 527 $(M)^+$.

Example 305 4-(*N*-(3-(1*H*-Imidazol-4-yl)propyl)carbamimidoyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide



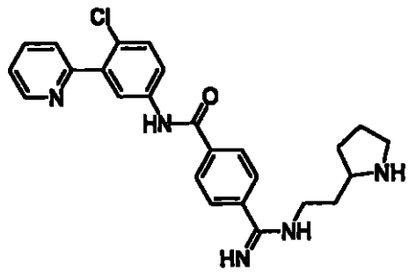
4-Chloro-3-(pyridin-2-yl)aniline (687 mg, 3.36 mmol) was dissolved in dichloromethane (8.0 ml) and THF (8.0 ml), treated with pyridine (0.33 ml, 4.0 mmol), and cooled to 0°C. 4-Cyanobenzoyl chloride (612 mg, 3.7 mmol) was added and the reaction was stirred for 1.0 hour. The reaction was diluted with dichloromethane and methanol was added to dissolve all solids. The solution was washed with water once, brine once, dried with $MgSO_4$, and evaporated to an orange solid which was purified by silica gel flash column chromatography (50% ethyl acetate/50% hexanes) to afford 908 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-cyanobenzamide as a yellow solid. *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-cyanobenzamide (500 mg, 1.5 mmol) was slurried in ethanol (75 ml) and heated until just dissolved. The solution was cooled in an ice bath, and saturated with HCl gas. The solution was heated briefly to 70°C to dissolve precipitated solids, cooled in an ice bath, and resaturated with HCl gas. The solution was then stored at 0°C for 18 hours. The solution was saturated again with HCl gas, heated to 70°C until all solids dissolved, cooled to 0°C, resaturated with HCl gas, and stored at 0°C for 18 hours. Finally, nitrogen gas was bubbled through the solution for 1.0 hour, and the solution was evaporated to dryness. The residue was dissolved in methanol, treated with MP-carbonate (2.57 g) and stirred 30 min. The solution was filtered to afford a neutral, methanolic solution of ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzimidate, which was diluted with enough methanol to make a 0.075 M solution.

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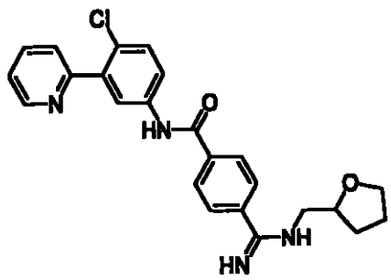
Ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzimidate (2.0 ml of a 0.075 M methanol solution, 0.15 mmol) was treated with 3-(1H-imidazol-4-yl)propan-1-amine (27 µl, 0.23 mmol) via procedure W to afford 83 mg of 4-(*N*-(3-(1*H*-imidazol-4-yl)propyl)carbamimidoyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide. MS (Q1) 459 $(M)^+$.

Example 306 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-(2-(pyrrolidin-2-yl)ethyl)carbamimidoyl)benzamide



Ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzimidate (2.0 ml of a 0.075 M methanol solution, 0.15 mmol) was treated with 2-(pyrrolidin-2-yl)ethanamine (28 µl, 0.23 mmol) via procedure W to afford 90 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-(2-(pyrrolidin-2-yl)ethyl)carbamimidoyl)benzamide. MS (Q1) 448 $(M)^+$.

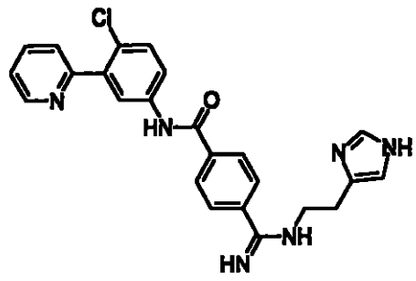
Example 307 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-((tetrahydrofuran-2-yl)methyl)carbamimidoyl)benzamide



Ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzimidate (2.0 ml of a 0.075 M methanol solution, 0.15 mmol) was treated with (tetrahydrofuran-2-yl)methanamine (23 µl, 0.23 mmol) via

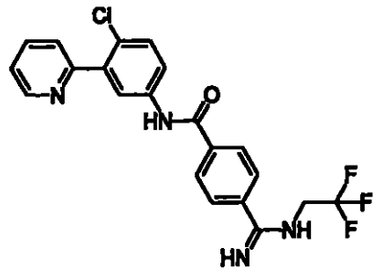
procedure W to afford 76 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-((tetrahydrofuran-2-yl)methyl)carbamimidoyl)benzamide. MS (Q1) 435 $(M)^+$.

Example 308 4-(*N*-(2-(1*H*-Imidazol-4-yl)ethyl)carbamimidoyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide



Ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzimidate (2.0 ml of a 0.075 M methanol solution, 0.15 mmol) was treated with 2-(1H-imidazol-4-yl)ethanamine (25 mg, 0.23 mmol) via procedure W to afford 90 mg of 4-(*N*-(2-(1*H*-imidazol-4-yl)ethyl)carbamimidoyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide. MS (Q1) 445 $(M)^+$.

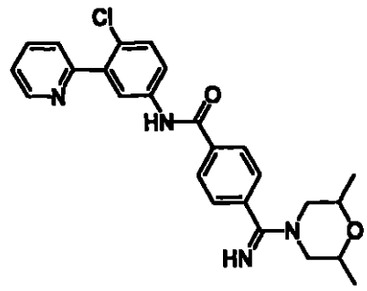
Example 309 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-(2,2,2-trifluoroethyl)carbamimidoyl)benzamide



Ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzimidate (2.0 ml of a 0.075 M methanol solution, 0.15 mmol) was treated with 2,2,2-trifluoroethanamine (18 µl, 0.23 mmol) via procedure W to afford 56 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-(2,2,2-trifluoroethyl)carbamimidoyl)benzamide. MS (Q1) 433 $(M)^+$.

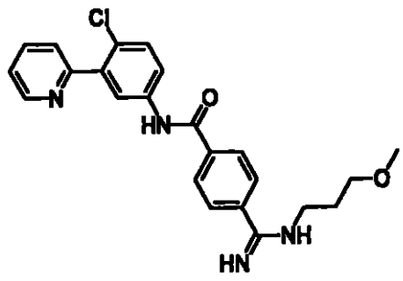
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Example 310 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-((2,6-dimethylmorpholino)(imino)methyl)-benzamide



Ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzimidate (2.0 ml of a 0.075 M methanol solution, 0.15 mmol) was treated with 2,6-dimethylmorpholine (28 µl, 0.23 mmol) via procedure W to afford 74 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((2,6-dimethylmorpholino)(imino)methyl)-benzamide. MS (Q1) 449 $(M)^+$.

Example 311 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-(3-methoxypropyl)carbamimidoyl)-benzamide

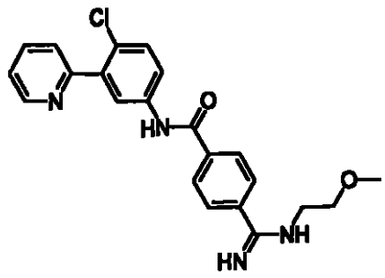


Ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzimidate (2.0 ml of a 0.075 M methanol solution, 0.15 mmol) was treated with 3-methoxypropan-1-amine (23 µl, 0.23 mmol) via procedure W to afford 68 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-(3-methoxypropyl)carbamimidoyl)-benzamide. MS (Q1) 423 $(M)^+$.

Example 312 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-(2-methoxyethyl)carbamimidoyl)benzamide

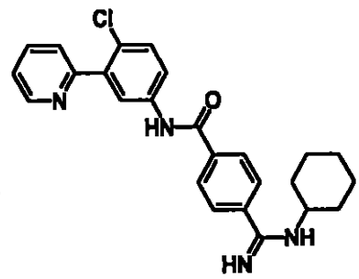
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Ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzimidate (2.0 ml of a 0.075 M methanol solution, 0.15 mmol) was treated with 2-methoxyethanamine (19 µl, 0.23 mmol) via procedure W to afford 50 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-(2-methoxyethyl)carbamimidoyl)benzamide. MS (Q1) 409 $(M)^+$.

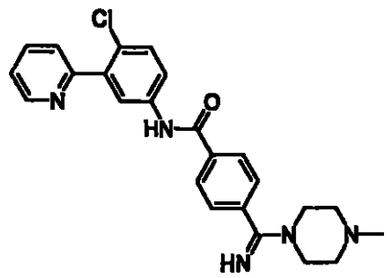
Example 313 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-cyclohexylcarbamimidoyl)benzamide



Ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzimidate (2.0 ml of a 0.075 M methanol solution, 0.15 mmol) was treated with cyclohexanamine (26 µl, 0.23 mmol) via procedure W to afford 30 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-cyclohexylcarbamimidoyl)benzamide. MS (Q1) 433 $(M)^+$.

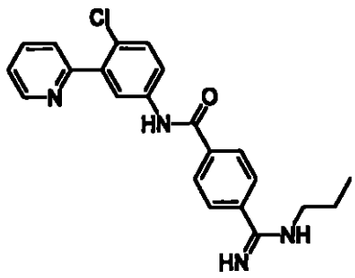
Example 314 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(imino(4-methylpiperazin-1-yl)methyl)benzamide

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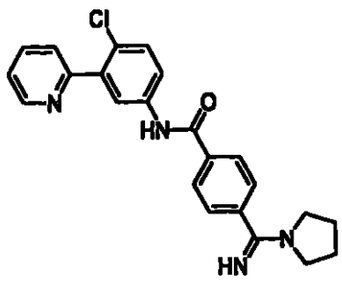
Ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzimidate (2.0 ml of a 0.075 M methanol solution, 0.15 mmol) was treated with 1-methylpiperazine (23 mg, 0.23 mmol) via procedure W to afford 35 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(imino(4-methylpiperazin-1-yl)methyl)benzamide. MS (Q1) 434 $(M)^+$.

Example 315 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-propylcarbamimidoyl)benzamide



Ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzimidate (2.0 ml of a 0.075 M methanol solution, 0.15 mmol) was treated with propan-1-amine (18 µl, 0.23 mmol) via procedure W to afford 39 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-propylcarbamimidoyl)benzamide. MS (Q1) 393 $(M)^+$.

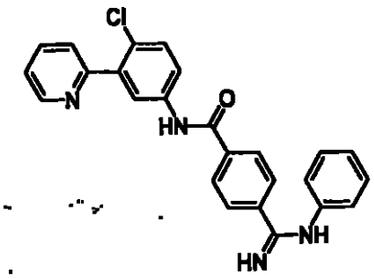
Example 316 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(imino(pyrrolidin-1-yl)methyl)benzamide



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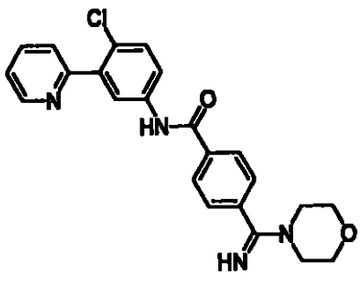
Ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzimidate (2.0 ml of a 0.075 M methanol solution, 0.15 mmol) was treated with pyrrolidine (19 µl, 0.23 mmol) via procedure W to afford 25 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(imino(pyrrolidin-1-yl)methyl)benzamide. MS (Q1) 405 $(M)^+$.

Example 317 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-phenylcarbamimidoyl)benzamide



Ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzimidate (2.0 ml of a 0.075 M methanol solution, 0.15 mmol) was treated with aniline (21 µl, 0.23 mmol) via procedure W to afford 7 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-phenylcarbamimidoyl)benzamide. MS (Q1) 427 $(M)^+$.

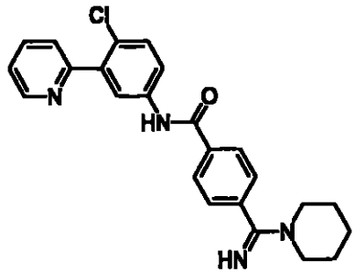
Example 318 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(imino(morpholino)methyl)benzamide



N-(4-chloro-3-(pyridin-2-yl)phenyl)-4-cyanobenzamide (300 mg, 0.899 mmol) was slurried in 45 ml ethanol and treated with 10 ml of ethanol saturated with HCl. The reaction was stored at 0°C for 3 days, then heated to 75°C for 3.0 hours, and cooled to room temperature for 18 hours. The reaction was cooled in an ice bath, and saturated with HCl gas. After storing at 0°C for an additional 3 days, N_2 gas was bubbled through the solution for 1.0 hour, and the solution was diluted with enough ethanol to make a 0.0155 M solution of ethyl 4-(4-chloro-3-(pyridin-2-

yl)phenylcarbamoyl)benzimidate. Ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzimidate (17.5 ml of a 0.0155 M ethanol solution, 0.27 mmol) was treated with morpholine (1.0 ml, 11.4 mmol) for 3 days. The ethanol was evaporated, and the residue purified by reverse phase HPLC to afford 30 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(imino(morpholino)methyl)benzamide. MS (Q1) 421 $(M)^+$.

Example 319 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(imino(piperidin-1-yl)methyl)benzamide



Ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzimidate (17.5 ml of a 0.0155 M solution, 0.27 mmol) was treated with piperidine (1.0 ml, 10.0 mmol) for 3 days. The ethanol was evaporated, and the residue purified by reverse phase HPLC to afford 26 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(imino(piperidin-1-yl)methyl)benzamide. MS (Q1) 419 $(M)^+$.

Example 320 Hedgehog signalling inhibition assays

Mouse Reporter Cell lines - 10T1/2-GliLuc [S12] cells (derived from cell line C3H10T1/2 ATCC #CCL-226); Mouse Embryonic Fibroblasts); Growth Medium: Dulbecco's modified Eagles' Medium (DMEM) supplemented with 10% Fetal Bovine Serum (FBS), 10 units/mL penicillin, 100 ug/mL streptomycin, 2mM glutamine, and 10mM HEPES.

Human Reporter Cell lines - HEPM-GliLuc [MZ24] - cells (derived from HEPM, Human Embryonic Palatal Mesenchyme ATCC #CRL-1486); Growth Medium: Minimum Essential Medium (MEM; with Earle's salts) supplemented with 10-20% Fetal Bovine Serium (FBS), 10 units/mL penicillin, 100ug/mL streptomycin, 2mM glutamine, and 10mM HEPES pH 7.2.

Sonic hedgehog - recombinant human SHh N-terminal octylated conjugate.

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Microtiter Plates (MTPs) - For the Luciferase assay cells are plated in 96-well MTPs (White, Flat-bottom, Clear-View).

Luciferase-Assay Medium - DMEM supplemented with 0.5% FBS, 10 units/mL penicillin, 100ug/mL streptomycin, 2mM glutamine, and 10mM HEPES pH 7.2.

PBS/Ca/Mg Mix - Phosphate Buffered Saline (PBS) supplemented with 0.5mM $CaCl_2$ and 1mM $MgCl_2$.

Assay Procedure

S12 and MZ24 cells genetically modified to contain a luciferase reporter gene driven by the hedgehog-reseponsive Gli promoter were maintained on tissue culture dishes in Growth Medium at 37°C and 5% CO_2. Cell cultures were passaged at sub-confluency at every 3-4 days. (1:20 to 1:40 for s12; 1:3 to 1:10 for MZ24). Cells were harvested and diluted in Growth Medium such that they could be plated in a microtitre plate at 10,000-20,000 cells (s12), or 20,000-30,000 cells (MZ24), per 100ul, per well. Cells were further incubated for ~24-48 hours at 37°C and 5% CO_2.

After ~24-48 hour incubation the Growth Medium in the microtitre plates was replaced by Luciferase-Assay Medium (100 ul per well), with and without Sonic hedgehog-octyl conjugate, at 0.1-0.3 ug/ml (S12) or 0.5-1.0 ug/ml (MZ24), and test compounds. Cells were then further incubated for and additional 24 hrs.

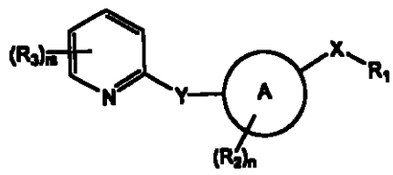
Microtitre plates were then subjected to the luciferase reporter gene assay kit (LucLite™), with modifications to the manufacturer's procedure wherein medium was removed and the substrate was reconstituted with 1:1 PBS/Ca/Mg : lysis buffer instead of straight lysis buffer. In brief, the PBS/Ca/Mg was mixed 1:1 with lysis buffer and 10mL were added to each substrate vial (of the 1000-assay kit). Then the assay media from the microtitre plate was discarded, and 100ul of this substrate mix was added to each well. Plates were incubated at room termperature for 20-30 minutes and then the Relative Light Units (RLUS) representing the relative expression level of the luciferase reporter gene were determined with a Topcount reader (Packard) or an Analyst reader (Molecular Devices). Compounds of the invention tested in the assays demonstrated reduced Gli expression in the reporter cell lines indicating hedgehog pathway signalling inhibition.

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WE CLAIM:

1. A compound of formula I:



I

wherein

A is a carbocycle or heterocycle;

X is alkylene, $NR_4C(O)$, $NR_4C(S)$, $N(C(O)R_1)C(O)$, NR_4SO, NR_4SO_2, $NR_4C(O)NH$, $NR_4C(S)NH$, $C(O)NR_4$, $C(S)NR_4$, NR_4PO or $NR_4PO(OH)$;

Y is absent, CHR_4, O, S, SO, SO_2 or NR_4;

R_1 is selected from the group consisting of alkyl, a carbocycle or a heterocycle each of which is optionally substituted with hydroxyl, halogen, amino, carboxyl, amidino, guanidino, carbonyl, nitro, cyano, acyl, alkyl, haloalkyl, sulfonyl, sulfinyl, alkoxy, alkylthio, carbamoyl, acylamino, sulfamoyl, sulfonamide, a carbocycle or a heterocycle; wherein said amino, amidino, alkyl, acyl, sulfonyl, sulfinyl, alkoxy, alkylthio, carbamoyl, acylamino, sulfamoyl, sulfonamide, carbocycle and heterocycle substituent is optionally substituted with, halogen, haloakyl, hydroxyl, carboxyl, carbonyl, or an amino, alkyl, alkoxy, acyl, sulfonyl, sulfinyl, phosphinate, carbocycle or heterocycle that is optionally substituted with hydroxyl, carboxyl, carbonyl, amino, halogen, haloalkyl, alkyl, alkoxy, alkylthio, sulfonyl, sulfinyl, acyl, a carbocycle or a heterocycle;

R_2 is halogen, hydroxyl, alkyl, acyl or alkoxy, wherein each alkyl, acyl and alkoxy is optionally substituted with hydroxyl, halogen, amino, nitro, alkyl, acyl, alkylsulfonyl or alkoxy;

R_3 is halogen, hydroxyl, carboxyl, alkyl, acyl, alkoxy, alkoxycarbonyl, carbamoyl, alkylsulfide, sulfinyl, sulfonyl, a carbocycle or a heterocycle wherein each alkyl, acyl, alkoxy, alkoxycarbonyl, carbamoyl, alkylsulfide, sulfinyl, sulfonyl, carbocycle and heterocycle is optionally substituted with hydroxyl, halogen, amino, nitro, alkyl, acyl, sulfonyl or alkoxy;

R_4 is H or alkyl;

m is 0-3;

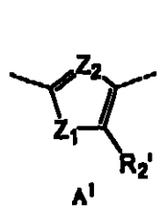
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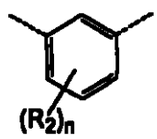
n is 0-3;

and salts and solvates thereof.

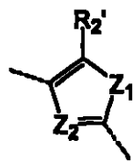
2. The compound of claim 1, wherein A is a ring selected from the group consisting of A^1, A^2, A^3, A^4 A^5, A^6 and A^7:



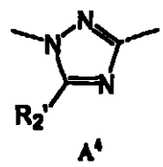
A^1



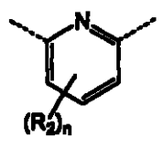
A^2



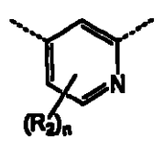
A^3



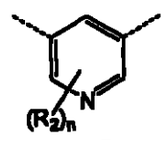
A^4



A^5



A^6



A^7

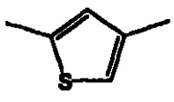
wherein Z_1 is O, S or NR_5 wherein R_5 is H or alkyl; Z_2 is CH, CR_2· or N; R_2 is halogen, hydroxyl, alkyl or alkoxy; R_2· is H, halogen, hydroxyl, alkyl or alkoxy; and n is 0-3.

3. The compound of claim 2, wherein A is ring A^1 wherein Z_1 is S and Z_2 is CH or N.

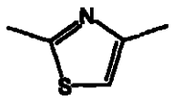
4. The compound of claim 2, wherein A is the ring A^2.

5. The compound of claim 2, wherein R_2 or R_2' is Cl.

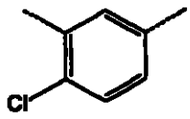
6. The compound of claim 1, wherein A is A^{1a}, A^{1b}, A^{2a}, A^{3a}, A^{3b}, A^{4a}, A^{5a}, A^{6a}, A^{7a},:



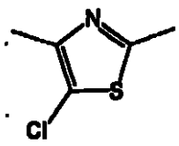
A^{1a}



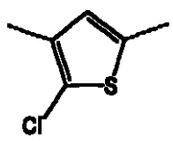
A^{1b}



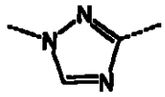
A^{2a}



A^{3a}



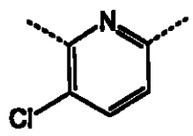
A^{3b}



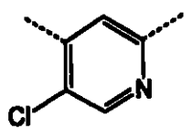
A^{4a}

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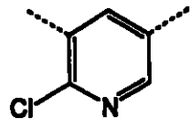
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A^{5a}



A^{6a}



A^{7a}

7. The compound of claim 1, wherein X is $NR_4C(O)$.

8. The compound of claim 1, wherein X is NR_4SO_2.

9. The compound of claim 7, wherein R_4 is H or Me.

10. The compound of claim 9, wherein R_4 is H.

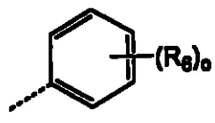
11. The compound of claim 1, wherein R_3 is Me or F.

12. The compound of claim 1, wherein R_3 is Me and m is 1 or 2.

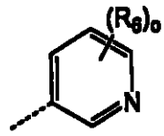
13. The compound of claim 1, wherein R_3 is F and m is 1 or 2.

14. The compound of claim 1, wherein m is 0.

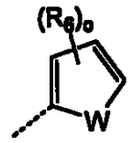
15. The compound claim 1, wherein R_1 is selected from the group consisting of formula IIa - IIo:



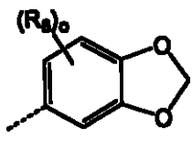
IIa



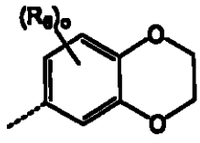
IIb



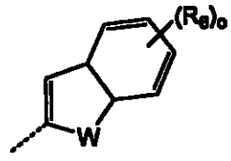
IIc



IId



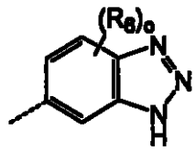
IIe



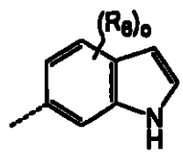
IIf

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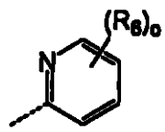
264



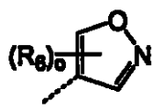
IIg



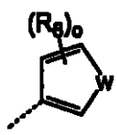
IIh



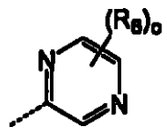
IIi



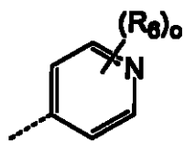
IIj



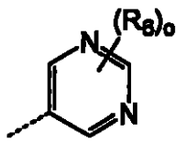
IIk



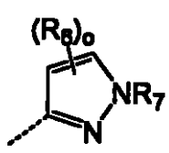
IIl



IIm



IIn



IIo

wherein

W is O, S or NR_7 wherein R_7 is H, alkyl, acyl, a carbocycle or a heterocycle wherein said alkyl carbocycle and heterocycle are each optionally substituted with 1-3 amino, halogen, hydroxyl and haloalkyl;

R_6 in each instance is independently hydroxyl, halogen, amino, carbonyl, nitro, cyano, acyl, alkyl, sulfonyl, alkylsulfonyl, alkylsulfinyl, alkoxy, alkylcarbamoyl, alkanoylamine, alkylsulfamoyl, alkylsulfonamide, a carbocycle or a heterocycle; wherein said amino, alkyl, carbonyl, acyl, sulfonyl, alkylsulfonyl, alkylsulfinyl, alkoxy, alkylcarbamoyl, alkanoylamine, alkylsulfamoyl, alkylsulfonamide, carbocycle and heterocycle substituent is optionally substituted with amino, halogen, hydroxyl, carbonyl, or a carbocycle or heterocycle that is optionally substituted with hydroxyl, amino, halogen, haloalkyl, alkyl, alkoxy or acyl; and

o is 0-3.

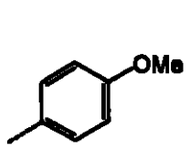
16. The compound of claim 15, wherein R_1 is the group of formula IIa.

17. The compound of claim 16, wherein R_6 is alkoxy and o is 1 or 2.

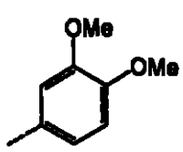
18. The compound of claim 16, wherein R_1 is selected from the group of formula IIa^1 - IIa^{28}:

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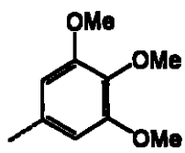
265



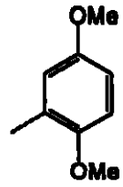
IIa[1]



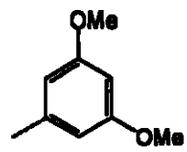
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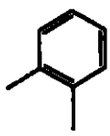
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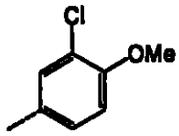
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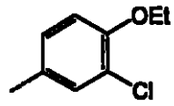
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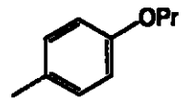
IIa[6]



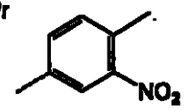
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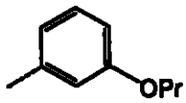
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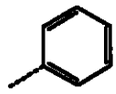
IIa[9]



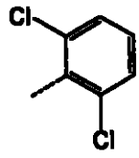
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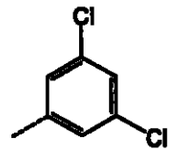
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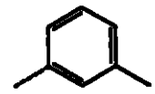
IIa[12]



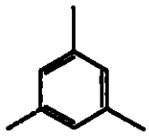
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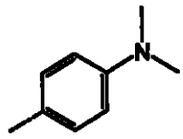
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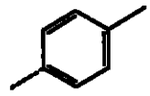
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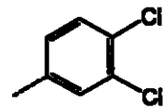
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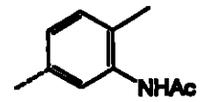
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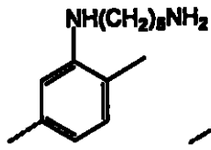
IIa[18]



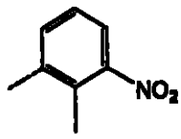
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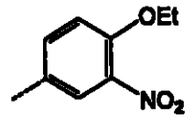
IIa[20]



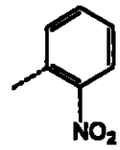
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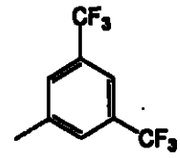
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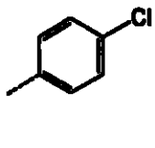
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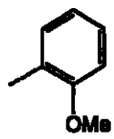
IIa[24]



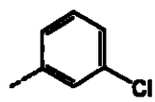
IIa[25]



IIa[26]



IIa[27]



IIa[28]

19. The compound of claim 16, wherein A is ring A^1 or A^2.

20. The compound of claim 16, wherein A is ring A^{2a}.

21. The compound of claim 16, wherein R_3 is Me or F.

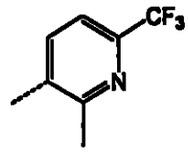
22. The compound of claim 3, wherein m is 0.

23. The compound of claim 3, wherein X is $NR_4C(O)$.

24. The compound of claim 15, wherein R_1 is the group of formula IIb.

25. The compound of claim 24, wherein R_6 is alkyl or haloalkyl.

26. The compound of claim 24, wherein R_1 is the group of formula IIb[1]



IIb[1]

27. The compound of claim 24, wherein A is ring A^1 or A^2.

28. The compound of claim 24, wherein A is ring $A^{2'}$.

29. The compound of claim 24, wherein R_3 is H, Me or F.

30. The compound of claim 24, wherein R_3 is H.

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31. The compound of claim 24, wherein X is $NR_4C(O)$.

32. A composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

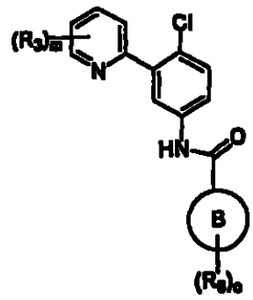
33. A method of treating cancer in a mammal, comprising administering to said mammal an effective amount of a compound of claim 1.

34. The method of claim 33, wherein said cancer is basal cell carcinoma, medullablastoma, pancreatic adenocarcinoma, small-cell lung carcinoma, breast carcinoma, rhabdomyosarcoma, oesophageal cancer, stomach cancer, biliary tract cancer.

35. A method of inhibiting angiogenesis in a mammal, comprising administering to said mammal an effective amount of a compound of claim 1.

36. A method of inhibiting hedgehog pathway signalling in a cell comprising contacting said cell with an effective amount of a compound of claim 1.

37. A process for preparing a compound of formula Ib''



Ib''

wherein

ring B is a carbocycle or heterocycle;

R_3 is halogen, hydroxyl, carboxyl, alkyl, acyl, alkoxy, alkoxycarbonyl, carbamoyl, alkylsulfide, alkylsulfinyl, alkylsulfonyl, a carbocycle or a heterocycle wherein each alkyl, acyl, alkoxy, alkoxycarbonyl, carbamoyl, alkylsulfide, alkylsulfinyl, alkylsulfonyl, carbocycle and heterocycle is optionally substituted with hydroxyl, halogen, amino, nitro, alkyl, acyl, alkylsulfonyl or alkoxy;

SUBSTITUTE SHEET (RULE 26)

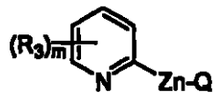
R_4 in each instance is independently hydroxyl, halogen, amino, carbonyl, nitro, cyano, acyl, alkyl, sulfonyl, alkylsulfonyl, alkylsulfinyl, alkoxy, alkylcarbamoyl, alkanoylamine, alkylsulfamoyl, alkylsulfonamide, a carbocycle or a heterocycle; wherein said amino, alkyl, carbonyl, acyl, sulfonyl, alkylsulfonyl, alkylsulfinyl, alkoxy, alkylcarbamoyl, alkanoylamine, alkylsulfamoyl, alkylsulfonamide, carbocycle and heterocycle substituent is optionally substituted with amino, halogen, hydroxyl, carbonyl, or a carbocycle or heterocycle that is optionally substituted with hydroxyl, amino, halogen, haloalkyl, alkyl, alkoxy or acyl;

o is 0-3; and

m is 0-3;

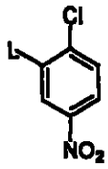
said process comprising

-reacting a compound of formula (a)



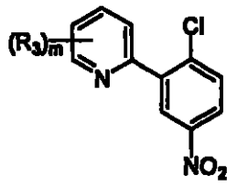
(a)

wherein Q is Cl, Br or I; with a compound of formula (b)



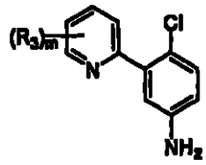
(b)

wherein L is Br, I or OTf; to yield a compound of formula (c);



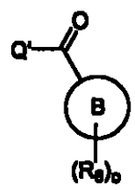
(c)

- reducing said compound of formula (c) to give a compound of formula (d)



(d)

- and reacting said compound of formula (d) with a compound of formula (e)



(c)

wherein Q' is halogen, OH, OR wherein R is an activating group; to yield said compound of formula Ib''.

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INHIBIDORES PIRIDILO DE SEÑALIZACION DE HEDGEHOG

Esta solicitud reivindica prioridad a la solicitud de patente provisional 60/607.367 presentada el 02 de septiembre de 2004.

CAMPO DE LA INVENCIÓN

La presente invención se relaciona con compuestos orgánicos útiles para terapia y/o profilaxis en un mamífero, en particular con compuestos de piridilo que inhiben la vía de señalización de hedgehog y son útiles en el tratamiento de enfermedades hiperproliferativas y de enfermedades mediadas por angiogénesis.

ANTECEDENTES DE LA INVENCIÓN

La proteína Hedgehog (Hh) se identificó por primera vez en *Drosophila melanogaster* como un gen control de la polaridad de los segmentos involucrado en la estructuración embrionaria (Nusslein-Volhard y col., Roux. Arch. Dev. Biol. 193: 267-282 (1984)). Más tarde se identificaron tres ortólogos de hedgehog de *Drosophila* (Sónico, Desierto e Indio) que se encuentran en todos los vertebrados incluso en peces, pájaros y mamíferos. El Hedgehog Desierto (DHh) se expresa principalmente en los testículos, en el desarrollo embrionario de ratón y en roedores adultos y humanos; hedgehog Indio (IHh) se encuentra involucrado en el desarrollo del hueso durante el embriogénesis y en la formación del hueso en el adulto; y, hedgehog Sónico (SHh) se expresa en altos niveles en la notocorda y placa del piso de los embriones vertebrados en desarrollo. Ensayos *in vitro* de transplante así como la expresión ectópica de SHh en los animales transgénicos mostraron que SHh posee un rol importante en la estructuración del tubo neuronal (Echelard y col., supra.; Ericson y col., Cell 81: 747-56 (1995); Marti y col., Nature 375: 322-5 (1995); Krauss y col.,

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Cell 75, 1432-44 (1993); Riddle y col., Cell 75: 1401-16 (1993); Roelink et al, Cell 81:445-55 (1995); Hynes y col., Neuron 19: 15-26 (1997)). Hh también tiene un rol en el desarrollo de extremidades (Krauss y col., Cell 75: 1431-44 (1993); Laufer y col., Cell 79, 993-1003 (1994)), somitas (Fan and Tessier-Lavigne, Cell 79, 1175-86 (1994); Johnson y col., Cell 79: 1165-73 (1994)), pulmones (Bellusci y col., Develop. 124: 53-63 (1997) y piel (Oro y col., Science 276: 817-21 (1997)). De la misma forma, IHh y DHh se encuentran involucrados en el desarrollo del hueso, intestino y de la célula germinal (Apelqvist y col., Curr. Biol. 7: 801-4 (1997); Bellusci y col., Dev. Suppl. 124: 53-63 (1997); Bitgood y col., Curr. Biol. 6: 298-304 (1996); Roberts y col., Development 121: 3163-74 (1995)).

La SHh humana se sintetiza como una proteína precursora de 45 kDa que por clivaje autocatalítico produce un fragmento N-terminal de 20 kDa que el es responsable de la actividad de señalización de hedgehog normal; y un fragmento C-terminal de 25 kDa que es responsable de la actividad de autoprocesamiento donde el fragmento N-terminal está conjugado con un grupo colesterol (Lee, J.J., y col. (1994) Science 266, 1528- 1536; Burncrot, D.A., y col. (1995), Mol. Cell Biol. 15, 2294-2303; Porter, J.A., y col. (1995) Nature 374, 363- 366). El fragmento N-terminal está compuesto por los residuos de aminoácidos 24-197 de la secuencia del precursor completo que permanece asociado a membrana a través del colesterol en su C-terminal (Porter, J.A., y col. (1996) Science 274, 255- 258; Porter, J.A., y col. (1995) Cell 86, 21-34). La conjugación con colesterol es responsable de la localización en tejido de señal hedgehog.

En la superficie celular, se piensa que la señal Hh se transmite por la

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proteína Patched de 12 dominios transmembrana (Ptc) (Hooper y Scott, Cell 59: 751-65 (1989); Nakano y col., Nature 341: 508-13 (1989)) y el receptor del tipo de los acoplado a proteína G Smoothened (Smo) (Alcedo y col., Cell 86: 221-232 (1996); van den Heuvel y Ingham, Nature 382: 547-551 (1996)). La evidencia genética y bioquímica apoyan un modelo de receptor donde Ptc y Smo son parte de un complejo receptor multicomponente (Chen y Struhl, Cell 87: 553-63 (1996); Marigo y col., Nature 384: 176-9 (1996); Stone y col., Nature 384: 129-34 (1996)). Con la unión de Hh a Ptc, se libera el efecto inhibitorio normal de Ptc sobre Smo, lo que permite que Smo traduzca la señal Hh a través de membrana plasmática. Sin embargo, el mecanismo exacto por el cual Ptc controla la actividad de Smo todavía tiene que ser aclarado.

La cascada de señalización iniciada por Smo resulta en la activación de los factores de transcripción Gli que se translocan al núcleo donde ellos controlan la transcripción de genes blanco. Se ha mostrado que Gli influencia la transcripción de inhibidores de la vía Hh tales como Ptc e Hip1 en un circuito de retroalimentación negativa lo que indica que se requiere el control severo de la actividad de la vía Hh para la adecuada diferenciación celular y formación del órgano. La activación descontrolada de la vía de señalización de Hh está asociada con malignidades en particular aquellas del cerebro, piel y músculo así como angiogénesis. Una explicación para esto es que se mostró que la vía Hh regula la proliferación celular en los adultos por activación de genes involucrados en la progresión del ciclo celular tal como ciclina D que está involucrada en la transición de G1-S. También, SHh bloquea la detención del ciclo celular mediado por p21, un inhibidor de quinasas dependientes de ciclinas. La señalización de Hh además está implicada con cáncer por

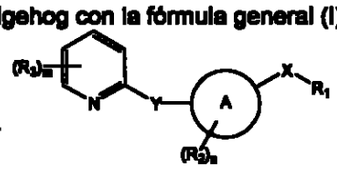
inducción de componentes de la vía EGFR (EGF, Her2) involucrados en la proliferación así como de los componentes de las vías PDGF (PDGFα) y VEGF involucradas en la angiogénesis. Se han identificado mutaciones con pérdida de la función en el gen Ptc en pacientes con el síndrome de nevus de células basales (BCNS), una enfermedad hereditaria caracterizada por carcinomas múltiples de célula basales (BCCs). Las mutaciones disfuncionales del gen Ptc también se han asociado con un gran porcentaje de tumores carcinomatosos de células basales esporádicos (Chidambaram y col., cáncer Research 56: 4599-601 (1996); Gailani y col., Nature Genet. 14: 78-81 (1996); Hahn y col., Cell 85: 841-51 (1996); Johnson y col., Science 272: 1668-71 (1996); Unden y col., cáncer Res. 56: 4562-5; Wicking y col., Am. J. Hum. Genet. 60: 21-6 (1997)). Se piensa que la pérdida de función de Ptc produce una señalización descontrolada de Smo en el carcinoma de células basales. De manera similar, se han identificado mutaciones activadoras de Smo en los tumores de BCC esporádicos (Xie y col., Nature 391: 90-2 (1998)), poniendo énfasis en el rol de Smo como la unidad de señalización en el complejo de receptor para SHh.

Se han investigado varios inhibidores de la señalización de hedgehog tal como Ciclopamina, un alcaloide natural que se ha mostrado que detiene el ciclo celular en G0-G1 e induce apoptosis en SCLC. Se cree que la Ciclopamina inhibe Smo por unión a su dominio de siete hélices. Se ha mostrado que Forskolin inhibe la vía de Hh corriente abajo de Smo por activación de la proteína quinasa A (PKA) que mantiene inactivos los factores de transcripción de Gli. A pesar de los avances con éstos y otros compuestos, allí continua una necesidad de potentes inhibidores de la vía de señalización de hedgehog.

RESUMEN DE LA INVENCIÓN

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En un aspecto de la presente invención se proveen nuevos inhibidores de hedgehog con la fórmula general (I)



I

en donde

A es un carbociclo o heterociclo;

X es alquileno, $NR_4C(O)$, $NR_4C(S)$, $N(C(O)R_1)C(O)$, NR_4SO, NR_4SO_2, $NR_4C(O)NH$, $NR_4C(S)NH$, $C(O)NR_4$, $C(S)NR_4$, NR_4PO o $NR_4PO(OH)$;

Y está ausente, CHR_4, O, S, SO, SO_2 o NR_4;

R_1 se selecciona entre el grupo formado por alquilo, un carbociclo o un heterociclo cada uno de los cuales está opcionalmente sustituido con hidroxilo, halógeno, amino, carbonilo, nitro, ciano, acilo, alquilo, haloalquilo, alquilsulfonilo, alquilsulfinilo, alcoxi, alquilcarbamoilo, alcanoilamina, alquilsulfamoilo, alquilsulfonamida, un carbociclo o a heterociclo; donde dicho sustituyente amino, alquilo, acilo, alquilsulfonilo, alquilsulfinilo, alcoxi, alquilcarbamoilo, alcanoilamina, alquilsulfamoilo, alquilsulfonamida, carbociclo y heterociclo está opcionalmente sustituido con amino, halógeno, hidroxilo, carbonilo, o un carbociclo o heterociclo que está opcionalmente sustituido con hidroxilo, amino, halógeno, haloalquilo, alquilo, alcoxi o acilo;

R_2 es halógeno, hidroxilo, alquilo, acilo o alcoxi cada uno opcionalmente sustituido con hidroxilo, halógeno, amino, nitro, alquilo, acilo, alquilsulfonilo o alcoxi;

R_3 es halógeno, hidroxilo, carboxilo, alquilo, acilo, alcoxi, alcoxicarbonilo, carbamoilo, alquilsulfuro, alquilsulfinilo, alquilsulfonilo, un carbociclo o un

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heterociclo donde dicho alquilo, acilo, alcoxi, alcoxicarbonilo, carbamoilo, alquilsulfuro, alquilsulfinilo, alquilsulfonilo, carbociclo y heterociclo está opcionalmente sustituido con hidroxilo, halógeno, amino, nitro, alquilo, acilo, alquilsulfonilo o alcoxi;

R_4 es H o alquilo;

m es 0-3;

n es 0-3;

y sus sales y solvatos.

En otro aspecto de la invención, se proveen composiciones que comprenden compuestos de fórmula I y un vehículo, diluyente o excipiente.

En otro aspecto de la invención, se provee un método para el tratamiento del cáncer que comprende la administración de una cantidad eficaz de un compuesto de fórmula I a un mamífero con esa necesidad.

En otro aspecto de la invención, se provee un método para inhibir la señalización de hedgehog en una célula que comprende poner en contacto la mencionada célula con un compuesto de fórmula I.

En otro aspecto de la invención, se provee un método para el tratamiento de una enfermedad o condición asociada con la señalización de hedgehog en un mamífero, que comprende la administración de una cantidad eficaz de un compuesto de fórmula I al mencionado mamífero.

En otro aspecto de la invención, se proveen los procesos para la preparación de los compuestos de la invención.

DESCRIPCIÓN DETALLADA DE LAS REALIZACIONES PREFERIDAS

"Acilo" se refiere a un sustituyente que contiene carbonilo representado por la fórmula -C(O)-R en el cual R es H, alquilo, un carbociclo, un heterociclo,

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alquilo carbocicio sustituido o alquilo heterocicio sustituido donde el alquilo, alcoxilo, carbocicio y heterocicio son como se los define en la presente documentación. Entre los grupos acilo se incluyen alcanoilo (por ejemplo acetilo), aroilo (por ejemplo benzoilo), y heteroaroilo.

"Alquilo" se refiere a un grupo hidrocarbonado alifático ramificado o no ramificado, saturado o no saturado (es decir alquinilo, alquinilo), que tiene hasta 12 átomos de carbono a menos que se especifique algo distinto. Cuando se utiliza como parte de otro término, por ejemplo "alquilamino", la porción alquil es preferentemente una cadena hidrocarbonada saturada, sin embargo también incluye cadenas de carbono hidrocarbonadas no saturadas tales como "alquenilamino" y "alquinilamino. "Alquilfosfinato" se refiere a un grupo –P(O)R-alquilo en el cual R es H, alquilo, carbocicio-alquilo o heterocicio-alquilo. Entre los ejemplos de grupos alquilo preferidos se incluyen metilo, etilo, n-propilo, isopropilo, n-butilo, iso-butilo, sec-butilo, tert-butilo, n-pentilo, 2-metilbutilo, 2,2-dimetilpropilo, n-hexilo, 2-metilpentilo, 2,2-dimetilbutilo, n-heptilo, 3-heptilo, 2-metilhexilo, y similares. Los términos "alquilo inferior" "alquilo C_1-C_4" y "alquilo de entre 1 y 4 átomos de carbono" son sinónimos y se usan de manera intercambiable para indicar metilo, etilo, 1-propilo, isopropilo, ciclopropilo, 1-butilo, sec-butilo o t-butilo. A menos que se especifique, los grupos alquilo, sustituidos, pueden contener uno (preferentemente), dos, tres o cuatro sustituyentes que pueden ser el mismo o diferentes. Entre los ejemplos de grupos alquilo sustituidos de más arriba se incluyen, pero no se limitan a; cianometilo, nitrometilo, hidroximetilo, tritiloximetilo, propioniloximetilo, aminometilo, carboximetilo, carboxietilo, carboxipropilo, alquiloxicarbonilmetilo, aliloxicarbonilaminometilo, carbamoiloximetilo, metoximetilo, etoximetilo, t-

butoximetilo, acetoximetilo, clorometilo, bromometilo, iodometilo, trifluorometilo, 6-hidroxihexilo, 2,4-dicloro(n-butilo), 2-amino(iso-propilo), 2-carbamoiloxietilo y similares. El grupo alquilo también se puede sustituir con un grupo carbocicio. Entre los ejemplos se incluyen ciclopropilmetilo, ciclobutilmetilo, ciclopentilmetilo, y ciclohexilmetilo, así como los correspondiente grupos -etilo, -propilo, -butilo, -pentilo, -hexilo, etc. Los alquilos sustituidos preferidos son los metilos sustituidos por ejemplo un grupo metilo sustituido con el mismo sustituyente como el grupo "alquilo sustituido C_n-C_m". Entre los ejemplos de grupos metilo sustituido se incluyen grupos tales como hidroximetilo, hidroximetilo protegido (por ejemplo tetrahidropiraniloximetilo), acetoximetilo, carbamoiloximetilo, trifluorometilo, clorometilo, carboximetilo, bromometilo e iodometilo.

"Amidina" o "amidino" se refiere al grupo -C(NH)-NRR donde cada R es independientemente H, OH, alquilo, alcoxi, un carbocicio, un heterocicio, un alquilo carbocicio sustituido o un alquilo heterocicio sustituido; o ambos grupos R forman juntos un heterocicio. Una amidina preferida es el grupo -C(NH)-NH_2.

"Amino" indica aminas primarias (es decir –NH_2), secundarias (es decir –NRH) y terciarias (es decir –NRR) donde R es independientemente alquilo, un carbocicio (por ejemplo arilo), un heterocicio (por ejemplo heteroarilo), alquilo carbocicio sustituido (por ejemplo bencilo) o un alquilo heterocicio sustituido o alternativamente dos grupos R junto con el átomo de nitrógeno del que ellos dependen forman un heterocicio. Las aminas primarias y secundarias particulares son alquilamina, dialquilamina, arilamina, diarilamina, aralquilamina y diaralquilamina. Las aminas primarias y secundarias particulares son metilamina, etilamina, propilamina, isopropilamina, fenilamina, dimetilamina,

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bencilamina, dietilamina, dipropilamina y diisopropilamina.

"Grupo amino protector" como se lo utiliza en la presente documentación se refiere a un derivado de los grupos normalmente empleados para bloquear o proteger un grupo amino a la vez que se llevan a cabo reacciones en otros grupos funcionales en el compuesto. Entre los ejemplos de tales grupos protectores se incluyen los carbamatos, amidas, grupos alquilo y arilo, iminas, así como muchos derivados de N-heteroátomos que se pueden quitar para regenerar el grupo amina deseado. Los grupos amino protectores son Boc, Fmoc y Cbz. Ejemplos adicionales de estos grupos se encuentran en T. W. Greene y P. G. M. Wuts, "*Protective Groups in Organic Synthesis*", 2da ed., John Wiley & Sons, Inc., New York, NY, 1991, capítulo 7; E. Haslam, "*Protective Groups in Organic Chemistry*", J. G. W. McOmie, Ed., Plenum Press, New York, NY, 1973, Capítulo 5, y T.W. Greene, "*Protective Groups in Organic Synthesis*", John Wiley and Sons, New York, NY, 1981. El término "amino protegido" se refiere a un grupo amino sustituido con uno de los grupos amino protectores de más arriba.

Cuando "arilo" se usa solo o como la parte de otro término se refiere a un grupo carbocíclico aromático fusionado o no fusionado que tiene el número de átomos de carbono designado o si no se designa ningún número, hasta 14 átomos de carbono. Entre los grupos arilo se incluyen fenilo, naftilo, bifenilo, fenantrenilo, naftacenilo y similares (véase por ejemplo *Lang's Handbook of Chemistry* (Dean, J. A., ed) 13va ed. Tabla 7-2 [1985]). En una realización particular arilo puede ser fenilo. Fenilo sustituido o arilo sustituido se refiere a un grupo fenilo o grupo arilo sustituido con uno, dos, tres, cuatro o cinco, tal como 1-2, 1-3 ó 1-4 sustituyentes seleccionados, a menos que se especifique

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de otro modo, entre halógeno (F, Cl, Br, I), hidroxi, hidroxi protegido, ciano, nitro, alquilo (por ejemplo alquilo C_1-C_8), alcoxi (por ejemplo alcoxi C_1-C_8), benciloxi, carboxi, carboxi protegido, carboximetilo, carboximetilo protegido, hidroximetilo, hidroximetilo protegido, aminometilo, aminometilo protegido, trifluorometilo, alquilsulfonilamino, arilsulfonilamino, heterociclilsulfonilamino, heterociclilo, arilo, u otros grupos especificado. Uno o más grupos metino (CH) y/o metileno (CH_2) en estos sustituyentes a su vez se pueden sustituir con un grupo similar como aquéllos indicados anteriormente. Entre los ejemplos del término "fenilo sustituido" se incluye pero no se limita a un grupo mono- o di(halo)fenilo tal como 2-clorofenilo, 2-bromofenilo, 4-clorofenilo, 2,6-diclorofenilo, 2,5-diclorofenilo, 3,4-diclorofenilo, 3-clorofenilo, 3-bromofenilo, 4-bromofenilo, 3,4-dibromofenilo, 3-cloro-4-fluorofenilo, 2-fluorofenilo y similares; un grupo mono- o di(hidroxi)fenilo tal como 4-hidroxifenilo, 3-hidroxifenilo, 2,4-dihidroxifenilo, los derivados hidroxi-protegidos de los mismos y similares; un grupo nitrofenilo tal como 3- ó 4-nitrofenilo; un grupo cianofenilo, por ejemplo, 4-cianofenilo; un grupo mono- o di(alquilo inferior)fenilo tal como 4-metilfenilo, 2,4-dimetilfenilo, 2-metilfenilo, 4-(iso-propil)fenilo, 4-etilfenilo, 3-(n-propil)fenilo y similares; un grupo mono o di(alcoxi)fenilo, por ejemplo, 3,4-dimetoxifenilo, 3-metoxi-4-benciloxifenilo, 3-metoxi-4-(1-clorometil)benciloxi-fenilo, 3-etoxifenilo, 4-(isopropoxi)fenilo, 4-(t-butoxi)fenilo, 3-etoxi-4-metoxifenilo y similares; 3- ó 4-trifluorometilfenilo; un grupo mono- o dicarboxifenilo o grupo (carboxi protegido)fenilo tal como 4-carboxifenilo; un grupo mono- o di(hidroximetil)fenilo o (hidroximetil protegido)fenilo tal como 3-(hidroximetil protegido)fenilo o 3,4-di(hidroximetil)fenilo; un mono- o di(aminometil)fenilo o (aminometil protegido)fenilo tal como 2-(aminometil)fenilo o 2,4-(aminometil

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protegido)fenilo; o un mono- o di(N-(metilsulfonilamino))fenilo tal como 3-(N-metilsulfonilamino))fenilo. Además, el término "fenil sustituido" representa grupos fenilo disustituidos donde los sustituyentes son diferentes, por ejemplo, 3-metil-4-hidroxifenilo, 3-cloro-4-hidroxifenilo, 2-metoxi-4-bromofenilo, 4-etil-2-hidroxifenilo, 3-hidroxi-4-nitrofenilo, 2-hidroxi-4-clorofenilo, y similares, así como los grupos fenilo trisustituidos donde los sustituyentes son diferentes, por ejemplo 3-metoxi-4-benciloxi-6-metil sulfonilamino, 3-metoxi-4-benciloxi-6-fenil sulfonilamino, y los grupos fenilo tetrasustituidos donde los sustituyentes son diferentes tal como 3-metoxi-4-benciloxi-5-metil-6-fenil sulfonilamino. Entre los grupos fenil sustituidos se incluyen grupos 2-clorofenilo, 2-aminofenilo, 2-bromofenilo, 3-metoxifenilo, 3-etoxi-fenilo, 4-benciloxifenilo, 4-metoxifenilo, 3-etoxi-4-benciloxifenilo, 3,4-dietoxifenilo, 3-metoxi-4-benciloxifenilo, 3-metoxi-4-(1-clorometil)benciloxi-fenilo, 3-metoxi-4-(1-clorometil)benciloxi-6-metilsulfonil aminofenilo. Los anillos arilo fusionados también pueden estar sustituidos con cualquier (por ejemplo 1, 2 ó 3) sustituyente especificado en la presente documentación de la misma manera que los grupos alquilo sustituidos.

"Carbamoilo" se refiere a un aminocarbonilo que contiene un sustituyente representado por la fórmula $-C(O)N(R)_2$ en el cual R es H, hidroxilo, alcoxi, alquilo, un carbociclo, un heterociclo, alquil carbociclo-sustituido o alcoxi, o alquil heterociclo sustituido o alcoxi donde el alquilo, alcoxi, carbociclo y heterociclo son como se los define en la presente documentación. Entre los grupos carbamoilo se incluyen alquilaminocarbonilo (por ejemplo etilaminocarbonilo, Et-NH-CO-), arilaminocarbonilo (por ejemplo fenilaminocarbonilo), aralquilaminocarbonilo (por ejemplo benzilaminocarbonilo) un heterocicloaminocarbonilo (por ejemplo

piperizinilaminocarbonilo), y en particular un heteroarilaminocarbonilo (por ejemplo piridilaminocarbonilo).

"Carbociclilo", "carbocíclico", y "carbociclo" solo y cuando se usa como una porción en un grupo complejo tal como un grupo carbocicloalquilo, se refiere a un anillo alifático mono-, bi-, o tricíclico que tiene entre 3 y 14 átomos de carbono y preferentemente entre 3 y 7 átomos de carbono que pueden ser saturado o no saturado, aromático o no aromático. Entre los grupos carbocíclicos saturados preferidos se incluyen los grupos ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo y más preferidos son ciclopropilo y ciclohexilo y el más preferido es ciclohexilo. Los carbociclos no saturados preferidos son aromáticos por ejemplo grupos arilo como se los definió previamente, el más preferido es fenilo. Los términos "carbociclilo sustituido" y "carbociclo sustituido", a menos que se especifique de otro modo, se refieren a estos grupos sustituidos por los mismos sustituyentes como el grupo "alquilo sustituido".

"Grupo carboxi protector" tal como se lo usa en la presente documentación se refiere a uno de los derivados éster del grupo ácido carboxílico que normalmente se emplea para bloquear o proteger el grupo ácido carboxílico a la vez que se llevan a cabo reacciones en otros grupos funcionales del compuesto. Entre los ejemplos de tal ácido carboxílico que protege los grupos se incluyen 4-nitrobencilo, 4-metoxibencilo, 3,4-dimetoxibencilo, 2,4-dimetoxibencilo, 2,4,6-trimetoxibencilo, 2,4,6-trimetilbencilo, pentametilbencilo, 3,4-metilenedioxibencilo, benzhidrilo, 4,4'-dimetoxibenzhidrilo, 2,2',4,4'-tetrametoxibenzhidrilo, alquilo tal como t-butilo o t-amilo, tritilo, 4-metoxitritilo, 4,4'-dimetoxitritilo, 4,4',4"-trimetoxitritilo, 2-feniliprop-

2-ilo, trimetilsililo, t-butildimetilsilil, fenacilo, 2,2,2-tricloroetilo, beta-(trimetilsilil)etilo, beta-(di(n-butil)metilsilil)etilo, p-toluensulfoniletilo, 4-nitrobencilsulfoniletilo, alilo, cinamilo, 1-(trimetilsililmetil)prop-1-en-3-ilo, y como grupos similares. Las especies de grupos carboxi protectores empleadas no es crítica con la condición que el ácido carboxílico derivatizado sea estable a la condición de la reacción(es) subsiguiente en otras posiciones de la molécula y se puede quitar en el punto adecuado sin desestabilizar el resto de la molécula. En particular, es importante no someter una molécula carboxi protegida a bases nucleofílicas fuertes, tales como hidróxido de litio o NaOH, o a condiciones reductoras que empleen hidruros metálicos altamente activados tal como $LiAlH_4$. (Tales condiciones de extracción severas también se deben evitar cuando se quitan los grupos amino protectores y grupos hidroxi protectores, como se discute más abajo.) Los grupos protectores de ácidos carboxílicos preferidos son los grupos alquilo (por ejemplo metilo, etilo, t-butilo), alilo, bencilo y p-nitrobencilo. Los grupos carboxi protectores similares a los que se usan en el arte de cefalosporina, penicilina y de péptidos también se pueden usar para proteger sustituyentes de grupo carboxi. Otros ejemplos de estos grupos se encuentran en T. W. Greene y P. G. M. Wuts, "*Protective Groups in Organic Synthesis*", 2da ed., John Wiley & Sons, Inc., New York, N.Y., 1991, capítulo 5; E. Haslam, "*Protective Groups in Organic Chemistry*", J. G. W. McOmie, Ed., Plenum Press, New York, N.Y., 1973, Capítulo 5, y T.W. Greene, "*Protective Groups in Organic Synthesis*", John Wiley and Sons, New York, NY, 1981, Capítulo 5. El término "carboxi protegido" se refiere a un grupo carboxi sustituido con uno de los grupos carboxi protectores anteriores.

"Guanidino" se refiere al grupo -NH-C(NH)-NHR donde R es H, alquilo,

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un carbociclo, un heterociclo, un alquilo carbociclo sustituido, o un alquilo heterociclo sustituido. Un grupo guanidino particular es -NH-C(NH)-NH_2.

"Grupo heterocíclico", "heterocíclico", "heterociclo", o "heterociclilo" solo y cuando se usa como una porción en un grupo complejo tal como un grupo heterocicloalquilo, se usa de manera intercambiable y se refiere a cualquier anillo mono-, bi-, o tricíclico, saturado o no saturado, aromático (heteroarilo) o no aromático que tiene el número de átomos designado, generalmente entre 5 y aproximadamente 14 átomos del anillo donde los átomos del anillo son carbono y al menos un heteroátomo (nitrógeno, azufre u oxígeno) y preferentemente entre 1 y 4 heteroátomos. "Heterociclosulfonilo" se refiere a un grupo –SO_2-heterociclo; "heterociclosulfinilo" se refiere a un grupo –SO-heterociclo. Típicamente, un anillo de 5 miembros tiene entre 0 y 2 uniones dobles y un anillo de 6 ó 7 miembros tiene entre 0 y 3 uniones dobles y los heteroátomos nitrógeno o azufre opcionalmente pueden estar oxidados (por ejemplo SO, SO_2), y cualquier heteroátomo nitrógeno opcionalmente puede ser cuaternizado. Entre los heterociclos no aromáticos preferidos se incluyen morfolinilo (morfolino), pirrolidinilo, oxiranilo, oxetanilo, tetrahidrofuranilo, 2,3-dihidrofuranilo, 2H-piranilo, tetrahidropiranilo, tiranilo, tietanilo, tetrahidrotietanilo, aziridinilo, azetidinilo, 1-metil-2-pirrolilo, piperazinilo y piperidinilo. Un grupo "heterocicloalquilo" es un grupo heterociclo como se lo definió más arriba unido de forma covalente a un grupo alquilo como se lo definió anteriormente. Entre los heterociclos de 5 miembros preferidos que contienen un átomo de azufre o de oxígeno y entre uno y tres átomos de nitrógeno se incluyen tiazolilo, en particular tiazol-2-ilo y N-óxido de tiazol-2-ilo, tiadiazolilo, en particular 1,3,4-tiadiazol-5-ilo y 1,2,4-tiadiazol-5-ilo, oxazolilo,

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preferentemente oxazol-2-ilo, y oxadiazolilo, tal como 1,3,4-oxadiazol-5-ilo, y 1,2,4-oxadiazol-5-ilo. Entre los heterocicios de anillos de 5 miembros preferidos que contienen entre 2 y 4 átomos de nitrógeno se incluyen imidazolilo, preferentemente imidazol-2-ilo; triazolilo, preferentemente 1,3,4-triazol-5-ilo; 1,2,3-triazol-5-ilo, 1,2,4-triazol-5-ilo, y tetrazolilo, preferentemente 1H-tetrazol-5-ilo. Los heterocicios de 5 miembros benzo-fusionados preferidos son benzoxazol-2-ilo, benztiazol-2-ilo y benzimidazol-2-ilo. Los heterocicios de 6 miembros preferidos contienen entre uno y tres átomos de nitrógeno y opcionalmente un átomo de azufre o de oxigeno, por ejemplo piridilo, tal como pirid-2-ilo, pirid-3-ilo, y pirid-4-ilo; pirimidilo, preferentemente pirimid-2-ilo y pirimid-4-ilo; triazinilo, preferentemente 1,3,4-triazin-2-ilo y 1,3,5-triazin-4-ilo; piridazinilo, en particular piridazin-3-ilo, y pirazinilo. Los N-óxidos de piridina y N-óxidos de piridazina y el piridilo, pirimid-2-ilo, pirimid-4-ilo, piridazinilo y los grupos 1,3,4-triazin-2-ilo, son un grupo preferido. Los sustituyentes para heterocicios opcionalmente sustituidos, y ejemplos adicionales de los sistemas de anillos de 5 y 6 miembros discutidos más arriba se pueden encontrar en W. Druckheimer y col., Patente de los EE.UU. No. 4.278.793.

"Heteroarilo" solo y cuando se usa como una porción en un grupo complejo tal como un grupo heteroaralquilo, se refiere a cualquier sistema de anillo aromático mono-, bi-, o tricíclico que tiene el número de átomos designado donde al menos un anillo es un anillo de 5, 6 ó 7 miembros que contiene entre uno y cuatro heteroátomos seleccionados entre el grupo nitrógeno, oxigeno, y azufre, y preferentemente al menos un heteroátomo es nitrógeno (*Lang's Handbook of Chemistry, supra*). Cualquier grupo bicíclico se encuentra incluido en la definición donde cualquiera de los anillos heteroarilo

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anteriores están fusionado a un anillo benceno. Se prefieren heteroarilos donde el heteroátomo es nitrógeno u oxígeno. Los siguientes sistemas de anillo son ejemplos de grupos heteroarilos (sustituidos o no sustituidos) indicados por el término "heteroarilo": tienilo, furilo, imidazolilo, pirazolilo, tiazolilo, isotiazolilo, oxazolilo, isoxazolilo, triazolilo, tiadiazolilo, oxadiazolilo, tetrazolilo, tiatriazolilo, oxatriazolilo, piridilo, pirimidilo, pirazinilo, piridazinilo, tiazinilo, oxazinilo, triazinilo, tiadiazinilo, oxadiazinilo, ditiazinilo, dioxazinilo, oxatiazinilo, tetrazinilo, tiatriazinilo, oxatriazinilo, ditiadiazinilo, imidazolinilo, dihidropirimidilo, tetrahidropirimidilo, tetrazolo[1,5-b]piridazinilo y purinilo, así como derivados benzo-fusionados, por ejemplo benzoxazolilo, benzofurilo, benzotiazolilo, benzotiadiazolilo, benzotriazolilo, benzoimidazolilo e indolilo. Un grupo particularmente preferido de "heteroarilo" incluye; 1,3-tiazol-2-ilo, 4-(carboximetil)-5-metil-1,3-tiazol-2-ilo, sal sódica de 4-(carboximetil)-5-metil-1,3-tiazol-2-ilo, 1,2,4-tiadiazol-5-ilo, 3-metil-1,2,4-tiadiazol-5-ilo, 1,3,4-triazol-5-ilo, 2-metil-1,3,4-triazol-5-ilo, 2-hidroxi-1,3,4-triazol-5-ilo, sal sódica de 2-carboxi-4-metil-1,3,4-triazol-5-ilo, 2-carboxi-4-metil-1,3,4-triazol-5-ilo, 1,3-oxazol-2-ilo, 1,3,4-oxadiazol-5-ilo, 2-metil-1,3,4-oxadiazol-5-ilo, 2-(hidroximetil)-1,3,4-oxadiazol-5-ilo, 1,2,4-oxadiazol-5-ilo, 1,3,4-tiadiazol-5-ilo, 2-tiol-1,3,4-tiadiazol-5-ilo, 2-(metiltio)-1,3,4-tiadiazol-5-ilo, 2-amino-1,3,4-tiadiazol-5-ilo, 1H-tetrazol-5-ilo, 1-metil-1H-tetrazol-5-ilo, 1-(1-(dimetilamino)et-2-il)-1H-tetrazol-5-ilo, 1-(carboximetil)-1H-tetrazol-5-ilo, sal sódica de 1-(carboximetil)-1H-tetrazol-5-ilo, 1-(ácido metilsulfónico)-1H-tetrazol-5-ilo, sal sódica de 1-(ácido metilsulfónico)-1H-tetrazol-5-ilo, 2-metil-1H-tetrazol-5-ilo, 1,2,3-triazol-5-ilo, 1-metil-1,2,3-triazol-5-ilo, 2-metil-1,2,3-triazol-5-ilo, 4-metil-1,2,3-triazol-5-ilo, N-óxido de pirid-2-ilo, 6-metoxi-2-(n-óxido)-piridaz-3-ilo, 6-hidroxipiridaz-3-ilo, 1-metilpirid-2-

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ilo, 1-metilpirid-4-ilo, 2-hidroxipirimid-4-ilo, 1,4,5,6-tetrahidro-5,6-dioxo-4-metil-as-triazin-3-ilo, 1,4,5,6-tetrahidro-4-(formilmetil)-5,6-dioxo-as-triazin-3-ilo, 2,5-dihidro-5-oxo-6-hidroxi-astriazin-3-ilo, sal sódica de 2,5-dihidro-5-oxo-6-hidroxi-as-triazin-3-ilo, sal sódica de 2,5-dihidro-5-oxo-6-hidroxi-2-metil-astriazin-3-ilo, 2,5-dihidro-5-oxo-6-hidroxi-2-metil-as-triazin-3-ilo, 2,5-dihidro-5-oxo-6-metoxi-2-metil-as-triazin-3-ilo, 2,5-dihidro-5-oxo-as-triazin-3-ilo, 2,5-dihidro-5-oxo-2-metil-as-triazin-3-ilo, 2,5-dihidro-5-oxo-2,6-dimetil-as-triazin-3-ilo, tetrazolo[1,5-b]piridazin-6-ilo y 8-aminotetrazolo[1,5-b]-piridazin-6-ilo. Un grupo alternativo de "heteroarilo" incluye; 4-(carboximetil)-5-metil-1,3-tiazol-2-ilo, sal sódica de 4-(carboximetil)-5-metil-1,3-tiazol-2-ilo, 1,3,4-triazol-5-ilo, 2-metil-1,3,4-triazol-5-ilo, 1H-tetrazol-5-ilo, 1-metil-1H-tetrazol-5-ilo, 1-(1-(dimetilamino)et-2-ilo)-1H-tetrazol-5-ilo, 1-(carboximetil)-1H-tetrazol-5-ilo, sal sódica de 1-(carboximetil)-1H-tetrazol-5-ilo, 1-(ácido metilsulfónico)-1H-tetrazol-5-ilo, sal sódica de 1-(ácido metilsulfónico)-1H-tetrazol-5-ilo, 1,2,3-triazol-5-ilo, 1,4,5,6-tetrahidro-5,6-dioxo-4-metil-as-triazin-3-ilo, 1,4,5,6-tetrahidro-4-(2-formilmetil)-5,6-dioxo-as-triazin-3-ilo, sal sódica de 2,5-dihidro-5-oxo-6-hidroxi-2-metil-as-triazin-3-ilo, 2,5-dihidro-5-oxo-6-hidroxi-2-metil-as-triazin-3-ilo, tetrazolo[1,5-b]piridazin-6-ilo, y 8-aminotetrazolo[1,5-b]piridazin-6-ilo.

"Grupo hidroxi protector" como se usa en la presente documentación se refiere a un derivado del grupo hidroxi normalmente empleado para bloquear o proteger el grupo hidroxi a la vez que se llevan a cabo reacciones en otros grupos funcionales en el compuesto. Entre los ejemplos de tales grupos protectores se incluyen tetrahidropiraniloxi, benzoilo, acetoxi, carbamoiloxi, bencilo, y grupos sililéteres (por ejemplo TBS, TBDPS). Ejemplos adicionales de estos grupos se encuentran en T. W. Greene y P. G. M. Wuts, "*Protective*

Groups in Organic Synthesis", 2da ed., John Wiley & Sons, Inc., New York, NY, 1991, capítulos 2-3; E. Haslam, "*Protective Groups in Organic Chemistry*", J. G. W. McOmie, Ed., Plenum Press, New York, NY, 1973, Capítulo 5, y T.W. Greene, "*Protective Groups in Organic Synthesis*", John Wiley and Sons, New York, NY, 1981. El término "hidroxi protegido" se refiere a un grupo hidroxi sustituido con uno de los grupos hidroxi protectores anteriores.

"Sales aceptables para uso farmacéutico" incluye sales de adición ácidas y básicas. "Sal de adición ácida aceptable para uso farmacéutico" se refiere a aquellas sales que retienen la eficacia biológica y las propiedades de las bases libres y que no son indeseables biológicamente o en cualquier otro aspecto, formada con ácidos inorgánicos tal como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico, ácido carbónico, ácido fosfórico y similares, y ácidos orgánicos que se pueden seleccionar entre clases de ácidos orgánicos alifáticos, cicloalifáticos, aromáticos, aralifáticos, heterocíclicos, carboxílicos, y sulfónicos tales como ácido fórmico, ácido acético, ácido propiónico, ácido glicólico, ácido glucónico, ácido láctico, ácido pirúvico, ácido oxálico, ácido málico, ácido maléico, ácido malonéico, ácido succínico, ácido fumárico, ácido tartárico, ácido cítrico, ácido aspártico, ácido ascórbico, ácido glutámico, ácido antranílico, ácido benzoico, ácido cinámico, ácido mandélico, ácido embónico, ácido fenilacético, ácido metanosulfónico, ácido etanosulfónico, ácido p-toluensulfónico, ácido salicílico y similares.

"Sales de adición básicas aceptables para uso farmacéutico" incluye aquéllas derivadas de bases inorgánicas tales como sales de sodio, potasio, litio, amonio, calcio, magnesio, hierro, zinc, cobre, manganeso, aluminio y similares. Las sales de amonio, potasio, sodio, calcio y magnesio son

particularmente preferidas. Entre las sales derivadas de bases orgánicas no tóxicas aceptables para uso farmacéutico se incluyen las sales de aminas primarias, secundarias, y terciarias, aminas sustituidas que incluye aminas sustituidas naturales, aminas cíclicas y resinas de intercambio de iónico básicas, tales como isopropilamina, trimetilamina, dietilamina, TEA, tripropilamina, etanolamina, 2-dietilaminoetanol, trimetamina, diciclohexilamina, lisina, arginina, histidina, cafeína, procaína, hidrabamina, colina, betaína, etilenediamina, glucosamina, metilglucamina, teobromina, purinas, piperizina, piperidina, N-etilpiperidina, las resinas de poliamina y similares. Las bases no tóxicas orgánicas particularmente preferidas son isopropilamina, dietilamina, etanolamina, trimetamina, diciclohexilamina, colina, y cafeína.

"Fosfinato" se refiere a –P(O)R-OR donde cada R es independientemente H, alquilo, carbociclo, heterociclo, carbocicloalquilo o heterocicloalquilo. Los grupos fosfinato particulares son alquilfosfinato (es decir –P(O)R-O-alquilo), por ejemplo –P(O)Me-OEt.

"Sulfamoilo" se refiere a $-SO_2-N(R)_2$ donde cada R es independientemente H, alquilo, carbociclo, heterociclo, carbocicloalquilo o heterocicloalquilo. Los grupos sulfamoilo particulares son alquilsulfamoilo, por ejemplo metilsulfamoilo ($-SO_2-NHMe$); arilsulfamoilo, por ejemplo fenilsulfamoilo; aralquilsulfamoilo, por ejemplo bencilsulfamoilo.

"Sulfinilo" se refiere a un grupo –SO-R donde R es alquilo, carbociclo, heterociclo, carbocicloalquilo o heterocicloalquilo. Los grupos sulfinilo particulares son alquilsulfinilo (es decir –SO-alquilo), por ejemplo metilsulfinilo; arilsulfinilo (es decir –SO-arilo) por ejemplo fenilsulfinilo; aralquilsulfinilo, por ejemplo bencilsulfinilo.

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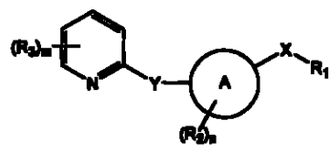
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"Sulfonamida" se refiere a $-NR-SO_2-R$ donde cada R es independientemente H, alquilo, carbociclo, heterociclo, carbociclolalquilo o heterociclolalquilo), un carbociclo o un heterociclo. Los grupos sulfonamida particulares son alquilsulfonamida (por ejemplo $-NH-SO_2-$alquilo), por ejemplo metilsulfonamida; arilsulfonamida (es decir $-NH-SO_2-$arilo) por ejemplo fenilsulfonamida; aralquilsulfonamida, por ejemplo bencilsulfonamida.

"Sulfonilo" se refiere a un grupo $-SO_2-R$ donde R es alquilo, carbociclo, heterociclo, carbociclolalquilo o heterociclolalquilo. Los grupos sulfonilo particulares son alquilsulfonilo (es decir $-SO_2-$alquilo), por ejemplo metilsulfonilo; arilsulfonilo, por ejemplo fenilsulfonilo; aralquilsulfonilo, por ejemplo bencilsulfonilo.

La frase "y sales y solvatos de los mismos" como se usa en la presente documentación se refiere a que compuestos de la invención pueden existir en una o mezcla de formas de sales y solvatos. Por ejemplo un compuesto de la invención puede ser sustancialmente puro en una forma particular de sal o solvato o bien puede ser mezcla de dos o más formas de sales o solvatos.

La presente invención provee nuevos compuestos con la fórmula general I:



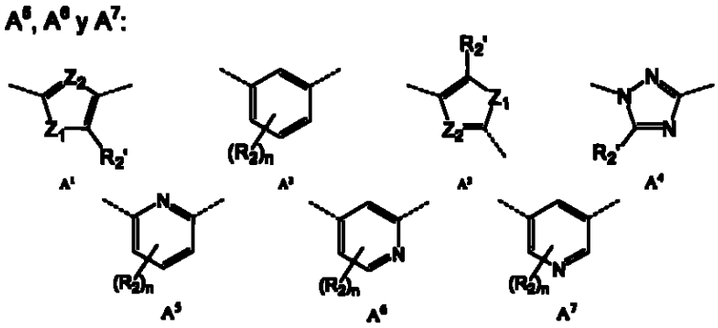
I

en donde A, X, Y, R_1, R_2, y R_3 tienen los valores que se definen en la presente.

A es un anillo carbociclo o heterociclo sustituido con entre 1 y 3 3 (por

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ejemplo n es 0-3) R_2 grupos seleccionados entre el grupo formado por halógeno, hidroxilo, alquilo, acilo o alcoxi cada uno opcionalmente sustituido con hidroxilo, halógeno, amino, nitro, alquilo, acilo, alquilsulfonilo o alcoxi. En una realización particular, A es arilo o heteroarilo opcionalmente sustituido. En la realización particular A es benceno, tiofeno, tiazol, imidazol, pirrol, N-alquilo pirrol, piridina, pirazol o N-alquilo pirazol opcionalmente sustituido. En una realización particular A es un anillo seleccionado entre el grupo formado por A^1, A^2, A^3, A^4 A^5, A^6 y A^7:



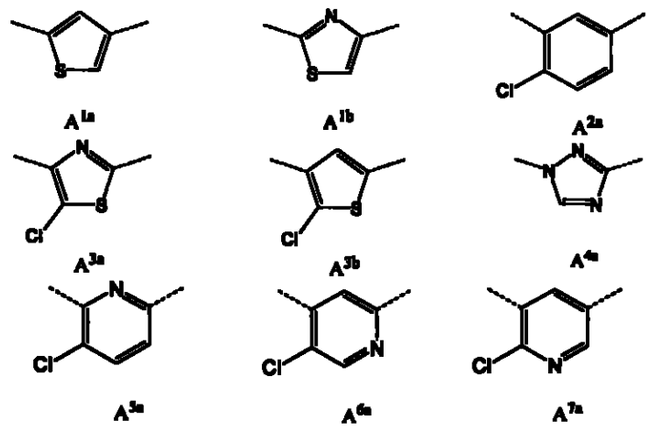
en donde Z_1 es O, S o NR_5 donde R_5 es H o alquilo; Z_2 es CH, $CR_{2'}$ o N; R_2 es halógeno, hidroxilo, alquilo, acilo o alcoxi cada uno opcionalmente sustituido con hidroxilo, halógeno, amino, nitro, alquilo, acilo, alquilsulfonilo o alcoxi; $R_{2'}$ es H, halógeno, hidroxilo, alquilo, acilo o alcoxi cada uno opcionalmente sustituido con hidroxilo, halógeno, amino, nitro, alquilo, acilo, alquilsulfonilo o alcoxi; y n es 0-3. En una realización particular A es el anillo de fórmula A^1. En una realización particular, A es el anillo de fórmula A^1 donde Z_1 es S y Z_2 es CH o N. En otra realización, A es el anillo de fórmula A^1 donde Z_1 es S y Z_2 es CH, i.e. tiofeno. En otra realización, A es el anillo de fórmula A^1 donde Z_1 es S y Z_2 es N, i.e. tiazol. En otra realización, A es el anillo de fórmula A^1 donde $R_{2'}$ es H. En una realización, A es el anillo de fórmula A^1 donde $R_{2'}$ es

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metilo. En otra realización, A es el anillo A^1 donde R_2' es metilo. En una realización particular A es el anillo A^2. En otra realización, A es el anillo de fórmula A^1 donde R_2 puede estar ausente, por ejemplo n es 0. En otra realización, n es 1 y R_2 es Cl. En otra realización particular A es el anillo de fórmula A^3. En una realización, A es un anillo de fórmula A^3 donde Z_1 es S y Z_2 es N, por ejemplo un tiazol. En otra realización, A es un anillo de fórmula A^3 donde Z_1 es S, Z_2 es N y R_2' es Cl. En otra realización, A es un anillo de fórmula A^3 donde Z_1 es S, Z_2 es CH (por ejemplo tiofeno) y R_2' es Cl.

En una realización particular A es el anillo A^{1a}, A^{1b}, A^{2a}, A^{3a}, A^{3b}, A^{4a}, A^{5a}, A^{6a}, A^{7a},:



En una realización particular A es el anillo de fórmula A^{1a}. En otra realización A es el anillo de fórmula A^{1b}. En otra realización A es el anillo de fórmula A^{2a}. En otra realización A es el anillo de fórmula A^{3a}. En otra realización A es el anillo de fórmula A^{3b}. En otra realización A es el anillo de fórmula A^{4a}.

X es alquileno, $NR_4C(O)$, $NR_4C(S)$, $N(C(O)R_1)C(O)$, NR_4SO, NR_4SO_2, $NR_4C(O)NH$, $NR_4C(S)NH$, $C(O)NR_4$, $C(S)NR_4$, NR_4PO o $NR_4PO(OH)$ donde R_4 es H o alquilo. En una realización particular X es $NR_4C(O)$ el cual forma una

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unión amida entre el anillo A y R_1. En otra realización, X es $N_4C(S)$, el cual forma una unión tioamida entre el anillo A y R_1. En otra realización, X es $NR_4C(O)NH$ el cual forma una unión urea entre el anillo A y R_1. En otra realización X es $NR_4C(S)NH$ el cual con NR_2 forma una unión tiourea entre el anillo A y R_1. En otra realización X es $N(C(O)R_1)C(O)$ por ejemplo un nitrógeno con dos grupos $-C(O)R_1$ pendientes del mismo.

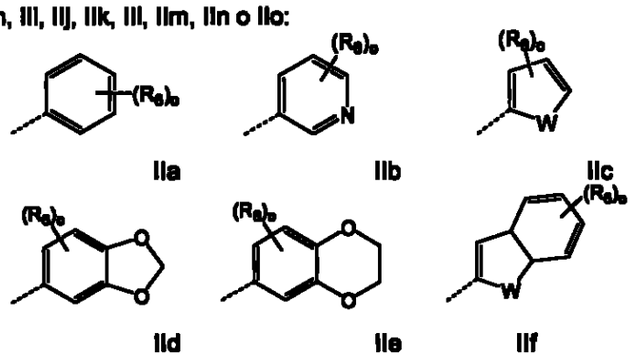
Y está ausente, CHR_4, O, S, SO, SO_2 o NR_4 donde R_4 es como se define aquí. En una realización particular Y es CHR_4. En una realización particular Y es NR_4. En una realización particular Y es O. En una realización particular Y es S. En una realización particular Y es SO. En una realización particular Y es SO_2. En otra realización Y está ausente por ejemplo el anillo A se encuentra unido directamente al anillo piridilo en la posición 2.

R_1 se selecciona entre el grupo formado por alquilo, un carbociclo o un heterociclo cada uno de los cuales está opcionalmente sustituido con hidroxilo, halógeno, amino, carboxilo, amidino, guanidino, carbonilo (por ejemplo =O), nitro, ciano, acilo, alquilo, haloalquilo, sulfonilo, sulfinilo, alcoxi, alquiltio, carbamoilo, acilamino, sulfamoilo, sulfonamida, un carbociclo o a heterociclo; donde dicho sustituyente amino, amidino, alquilo, acilo, sulfonilo, sulfinilo, alcoxi, alquiltio, carbamoilo, acilamino, sulfamoilo, sulfonamida, carbociclo y heterociclo se sustituye opcionalmente con, halógeno, haloalquilo, hidroxilo, carboxilo, carbonilo, o un amino, alquilo, alcoxi, acilo, sulfonilo, sulfinilo, fosfinato, carbociclo o heterociclo que está opcionalmente sustituido con hidroxilo, carboxilo, carbonilo, amino, halógeno, haloalquilo, alquilo, alcoxi, alquiltio, sulfonilo, sulfinilo, acilo, un carbociclo o a heterociclo.

En otra realización R_1 se selecciona entre el grupo formado por alquilo,

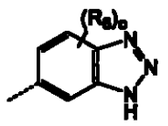
un carbociclo o un heterociclo cada uno de los cuales está opcionalmente sustituido con hidroxilo, halógeno, amino, carbonilo, nitro, ciano, acilo, alquilo, haloalquilo, alquilsulfonilo, alquilsulfinilo, alcoxi, alquilcarbamoilo (por ejemplo -CONR-alquilo donde R es H o alquilo), alcanoilamina (por ejemplo -NRCO-alquilo donde R es H o alquilo), alquilsulfamoilo (por ejemplo -SO_2NR-alquilo donde R es H o alquilo), alquilsulfonamida (por ejemplo -NR-SO_2-alquilo donde R es H o alquilo), un carbociclo o un heterociclo; donde dicho sustituyente amino, alquilo, acilo, alquilsulfonilo, alquilsulfinilo, alcoxi, alquilcarbamoilo, alcanoilamina, alquilsulfamoilo, alquilsulfonamida, carbociclo y heterociclo está opcionalmente sustituido con amino, halógeno, hidroxilo, carbonilo, o un carbociclo o heterociclo que está opcionalmente sustituido con hidroxilo, amino, halógeno, haloalquilo, alquilo, alcoxi o acilo.

En una realización particular R_1 es un arilo o heteroarilo opcionalmente sustituido. En una realización particular R_1 es un grupo fenilo opcionalmente sustituido. En otra realización particular R_1 es un grupo piridina opcionalmente sustituido. En una realización particular R_1 es de fórmula IIa, IIb, IIc, IId, IIe, IIf, IIg, IIh, III, IIj, IIk, III, IIm, IIn o IIo:

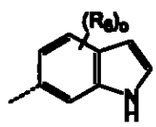


IIa IIb IIc

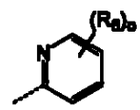
IId IIe IIf



IIg



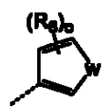
IIh



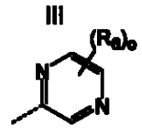
III



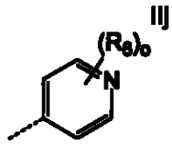
IIj



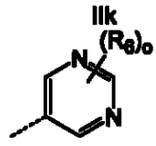
IIk



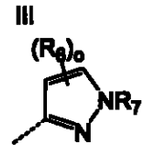
III



IIm



IIn



IIo

en donde W es O, S o NR_7 donde R_7 es H, alquilo, acilo, un carbociclo o un heterociclo donde dichos alquilo, acilo, carbociclo y heterociclo cada uno se sustituyen opcionalmente con 1-3 amino, halógeno, hidroxilo y haloalquilo; o es 0-3. En una realización particular W es S.

R_8 en cada instancia es en forma independiente hidroxilo, halógeno, amino, carboxilo, amidino, guanidino, carbonilo, nitro, ciano, acilo, alquilo, haloalquilo, sulfonilo, sulfinilo, alcoxi, alquiltio, carbamoilo, acilamino, sulfamoilo, sulfonamida, un carbociclo o un heterociclo; donde dicho sustituyente amino, amidino, alquilo, acilo, sulfonilo, sulfinilo, alcoxi, alquiltio, carbamoilo, acilamino, sulfamoilo, sulfonamida, carbociclo y heterociclo se sustituye opcionalmente con, halógeno, haloalquilo, hidroxilo, carboxilo, carbonilo, o an amino, alquilo, alcoxi, acilo, sulfonilo, sulfinilo, fosfinato, carbociclo o heterociclo que está opcionalmente sustituido con hidroxilo, carboxilo, carbonilo, amino, halógeno, haloalquilo, alquilo, alcoxi, alquiltio, sulfonilo, sulfinilo, acilo, un carbociclo o a heterociclo.

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En una realización particular R_6 en cada instancia es en forma independiente hidroxilo, halógeno, amino, carbonilo, nitro, ciano, acilo, alquilo, sulfonilo, alquilsulfonilo, alquilsulfinilo, alcoxi, alquilcarbamoilo, alcanolamina, alquilsulfamoilo, alquilsulfonamida, un carbociclo o a heterociclo; donde dicho sustituyente amino, alquilo, carbonilo, acilo, sulfonilo, alquilsulfonilo, alquilsulfinilo, alcoxi, alquilcarbamoilo, alcanolamina, alquilsulfamoilo, alquilsulfonamida, carbociclo y heterociclo está opcionalmente sustituido con amino, halógeno, hidroxilo, carbonilo, o un carbociclo o heterociclo que está opcionalmente sustituido con hidroxilo, amino, halógeno, haloalquilo, alquilo, alcoxi o acilo.

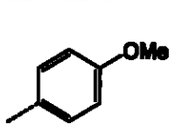
En una realización particular R_6 es en forma independiente en cada instancia opcionalmente alquilo sustituido (por ejemplo metilo, trifluorometilo, dimetilaminometilo, piperidinilmetilo, morfolinometilo, tiomorfolinometil); halógeno (por ejemplo cloro); alcoxi (por ejemplo metoxi); carbonilo (por ejemplo morfolinocarbonilo, acetil); un heterociclo (por ejemplo morfolino, N-metil-piperazin-4-ilo, N-acetil-piperazin-4-ilo, 1H-1,2,4-triazol); alquilamino (por ejemplo t-butilamino, bencilamino, hidroxietilamino, metoxietilamino, dimetilaminoetilamino, morfolinoetilamino, morfolinopropilamino, propilamino sustituido con pirrolidin-2-ona, imidazol-etilamino, imidazol-propilamino); arilamino (por ejemplo fenilamino); alquilcarbamoilo (por ejemplo dimetilcarbamoilo, t-butilaminocarbonilo); alquilsulfamoilo (por ejemplo propilaminosulfonilo, t-butilaminosulfonilo, dimetilaminosulfonilo, dimetilaminoetilo hidroxietilaminosulfonilo, metoxietilaminosulfonilo, metoxipropilaminosulfonilo, metilsulfoniletilaminosulfonilo, propilaminosulfonilo sustituido con imidazol, hidroxipropilaminosulfonilo, 2-

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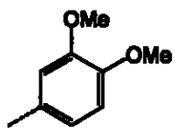
hidroxipropilaminosulfonilo); o sulfonilo (por ejemplo metilsulfonilo, etilsulfonilo, aminosulfonilo, dimetilaminopropilsulfonilo, N-metil-piperazin-4-il-sulfonilo, morfolino-4-il-sulfonilo, trifluorometilsulfonilo).

En una realización particular R_7 es H. En otra realización particular R_7 es opcionalmente acilo sustituido. En otra realización particular R_7 es opcionalmente alquilo sustituido (por ejemplo metilo). En otra realización particular R_7 es opcionalmente acilo sustituido (por ejemplo acetilo, benzoilo). En otra realización particular R_7 es un grupo arilo opcionalmente sustituido (por ejemplo fenilo, bencilo).

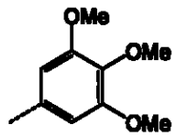
En una realización particular R_1 es el grupo de fórmula IIa. en una realización tal R_6 puede ser alcoxi y o es 1, 2 o 3. Grupos IIa particulares son IIa^1 - IIa^{28}:



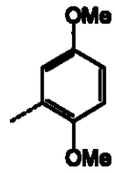
IIa^1



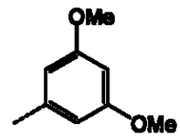
IIa^2



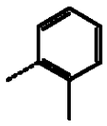
IIa^3



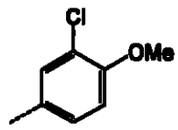
IIa^4



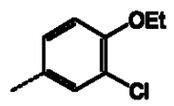
IIa^5



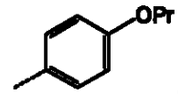
IIa^6



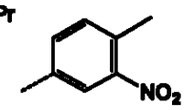
IIa^7



IIa^8

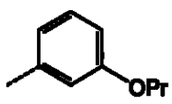


IIa^9

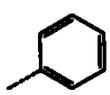


IIa^{10}

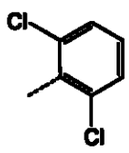
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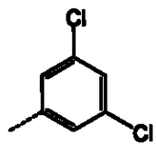
IIa[11]



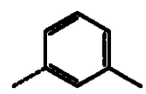
IIa[12]



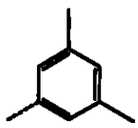
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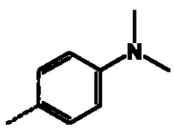
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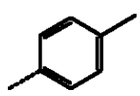
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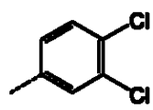
IIa[16]



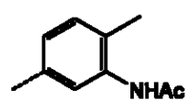
IIa[17]



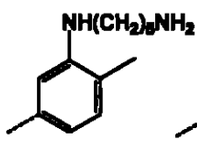
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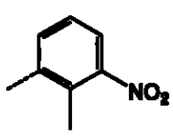
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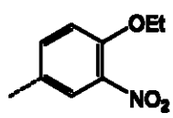
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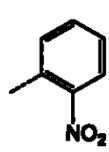
IIa[21]



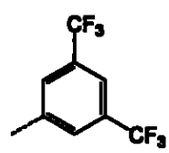
IIa[22]



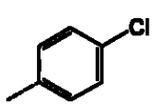
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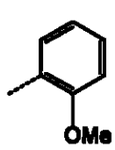
IIa[24]



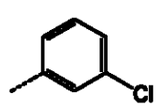
IIa[25]



IIa[26]

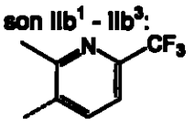


IIa[27]

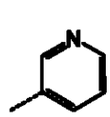


IIa[28]

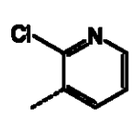
En otra realización particular R_1 es el grupo de fórmula IIb. En una realización tal R_6 puede ser alquilo o haloalquilo (por ejemplo CF_3). Grupos IIb particulares son IIb[1] - IIb[3]:



IIb[1]



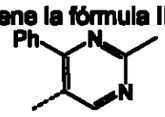
IIb[2]



IIb[3]

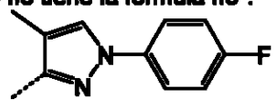
En una realización particular R_1 es el grupo de fórmula IIc. En una realización tal W puede ser S y o es 0. En otra realización particular R_1 es el grupo de fórmula IId. En una realización tal o puede ser 0. En otra realización particular R_1 es el grupo de fórmula IIe. En una realización tal o puede ser 0. En otra realización particular R_1 es el grupo de fórmula IIf. En una realización tal o puede ser 0.

En otra realización particular R_1 es el grupo de fórmula IIn. En una realización tal o puede ser 0 o 2 y R_6 puede ser alquilo o arilo. En una realización particular, el grupo IIn tiene la fórmula IIn^1:



IIn^1

En otra realización particular R_1 es el grupo de fórmula IIo. En una realización tal o puede ser 0 o 2 y R_6 puede ser alquilo o arilo. En una realización particular, el grupo IIo tiene la fórmula IIo^1:



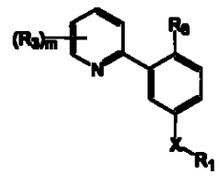
IIo^1

R_2 es halógeno, hidroxilo, alquilo, acilo o alcoxi cada uno opcionalmente sustituido con hidroxilo, halógeno, amino, nitro, alquilo, acilo, alquilsulfonilo o alcoxi. n es 0-3, por ejemplo 0 o 1. En una realización particular R_2 es hidroxilo. En una realización particular R_2 es alquilo o alquilo sustituido con halógeno, metilo o trifluorometilo. En una realización particular R_2 es acilo, por ejemplo alcanoilo por ejemplo acetilo. En una realización particular R_2 es halógeno, por ejemplo Cl o F. En otra realización particular R_2 es alcoxi, por ejemplo metoxi o etoxi.

298
299

R_3 es halógeno, hidroxilo, carboxilo, alquilo, acilo, alcoxi, alcoxicarbonilo, carbamoilo, alquilsulfuro, sulfinilo, sulfonilo, un carbociclo o un heterociclo donde cada alquilo, acilo, alcoxi, alcoxicarbonilo, carbamoilo, alquilsulfuro, sulfinilo, sulfonilo, carbociclo y heterociclo está opcionalmente sustituido con hidroxilo, halógeno, amino, nitro, alquilo, acilo, sulfonilo o alcoxi. En una realización particular R_3 es halógeno, hidroxilo, carboxilo, alquilo, acilo, alcoxi, alcoxicarbonilo, carbamoilo, alquilsulfuro, alquilsulfinilo, alquilsulfonilo, un carbociclo o un heterociclo donde cada alquilo, acilo, alcoxi, alcoxicarbonilo, carbamoilo, alquilsulfuro, alquilsulfinilo, alquilsulfonilo, carbociclo y heterociclo está opcionalmente sustituido con hidroxilo, halógeno, amino, nitro, alquilo, acilo, alquilsulfonilo o alcoxi; mientras m es entre 1 y 3 3. En una realización particular, R_3 es halógeno (por ejemplo F), carboxilo, o opcionalmente alquilo sustituido (por ejemplo metilo, hidroximetilo, dimetilaminometilo), alcoxicarbonilo (por ejemplo metoxicarbonil) o carbamoilo (por ejemplo dimetilaminocarbonilo). En una realización particular m es 0, por ejemplo R_3 está ausente. En otra realización particular m es 1-3.

En una realización particular, compuestos de la invención se representan con la fórmula general Ib:

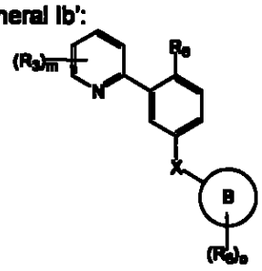


Ib

en donde X, R_1, R_3 y m tienen los valores que se definen en la presente y R_8 es halógeno. En una realización, compuestos de la invención tienen la fórmula general Ib y X es NR_4CO. En otra realización, los compuestos son de

fórmula Ib y R_3 es H o metilo.

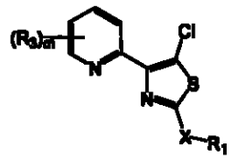
En otra realización particular, los compuestos de la invención se representan con la fórmula general Ib':



Ib'

en donde X, R_3, R_6, m y o tienen los valores que se definen en la presente; R_6 es un halógeno; y el anillo B es un carbocicio o heterocicio. En una realización particular R_6 es Cl. En una realización particular el anillo B es fenilo o piridilo. en una realización particular X es $NR_4C(O)$ y R_4 es como se lo define aquí.

En otra realización particular, compuestos de la invención tienen la fórmula general Ic:



Ic

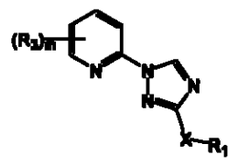
en donde X, R_1, R_3 y m tienen los valores que se definen en la presente. En una realización, compuestos de la invención tienen la fórmula general Ib y X es NR_4CO. En una realización adicional, compuestos are de fórmula Ic y R_3 es H o metilo y m es 0 o 1.

En otra realización particular, compuestos de la invención tienen la

300

301

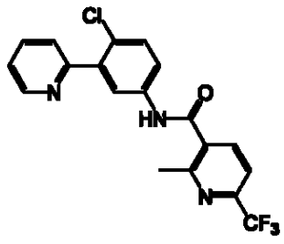
fórmula general Id:

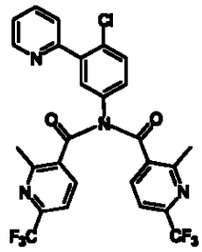


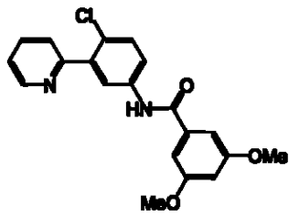
Id

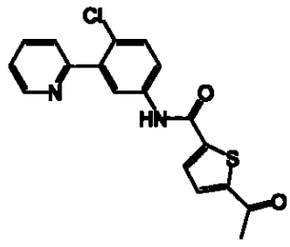
en donde X, R_1, R_3 y m tienen los valores que se definen en la presente. En una realización, compuestos de la invención tienen la fórmula general Ib y X es NR_4CO. En una realización adicional, compuestos son de fórmula Id y R_3 es H, Cl o trifluorometilo y m es 0 o 1.

Compuestos particulares de la invención incluyen, pero no se limitan a los siguientes:

1 

2 

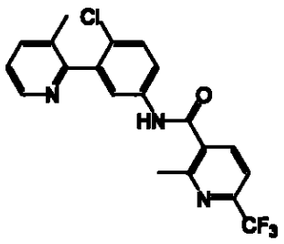
3 

4 

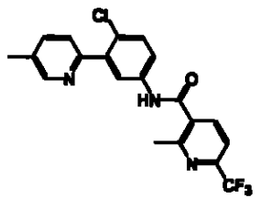
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302

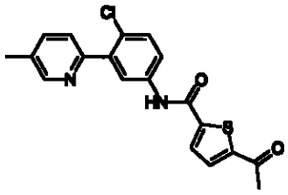
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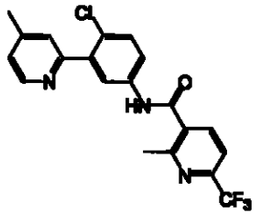
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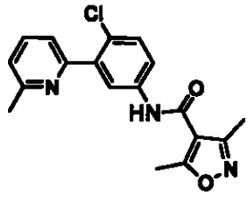
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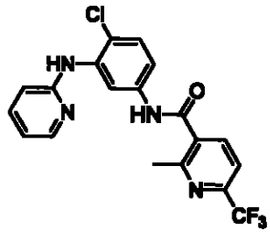
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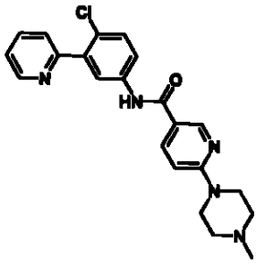
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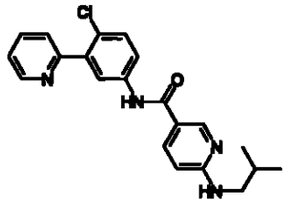
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11

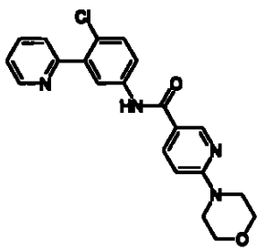


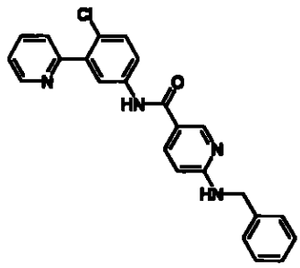
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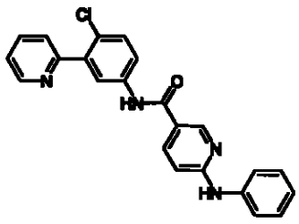


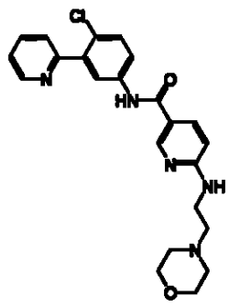
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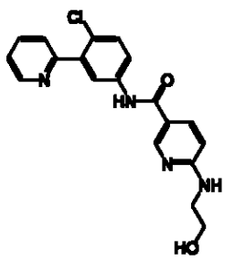
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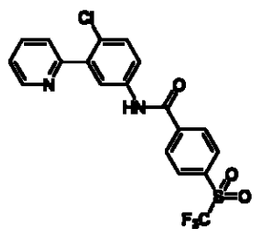
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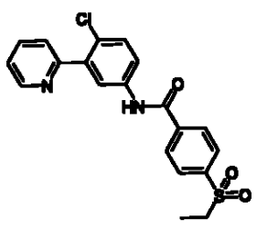
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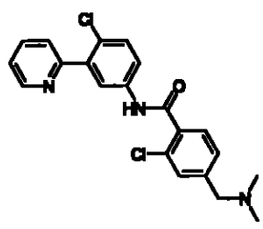
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16 

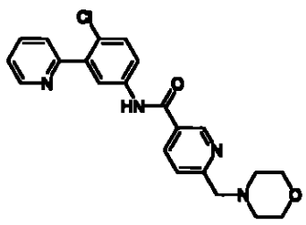
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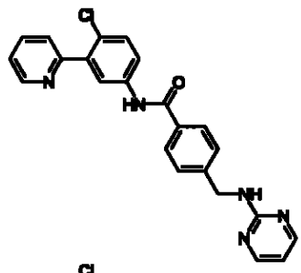
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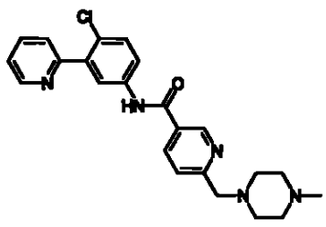
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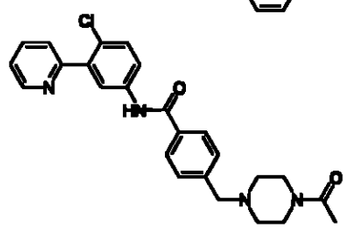
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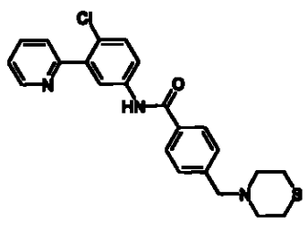
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304

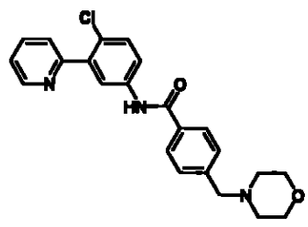
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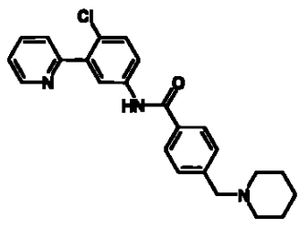
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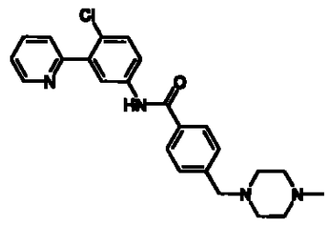
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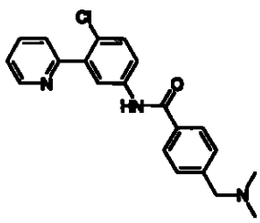
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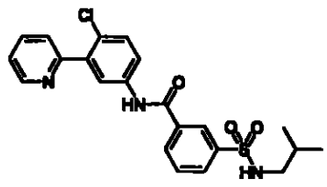
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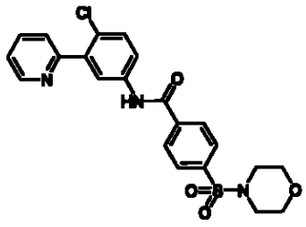
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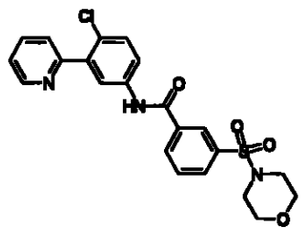
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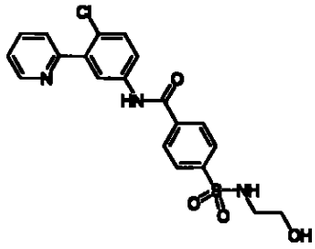
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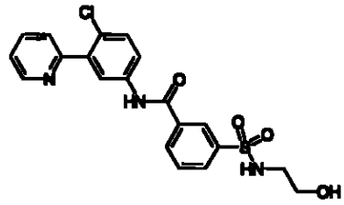
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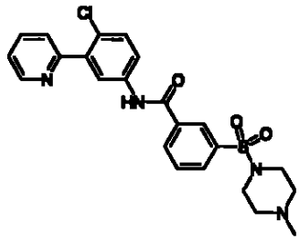
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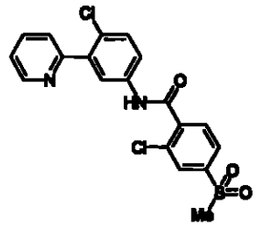
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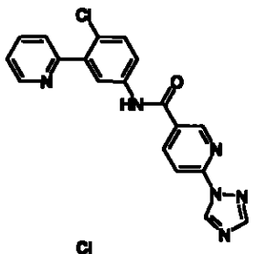
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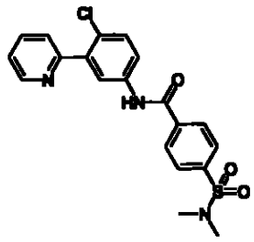
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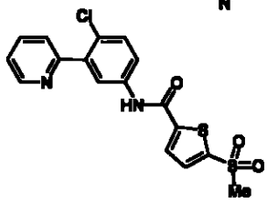
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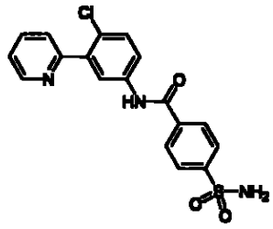
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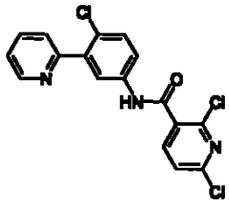
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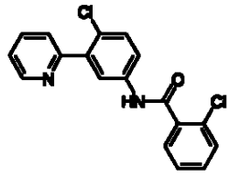
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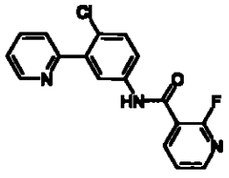
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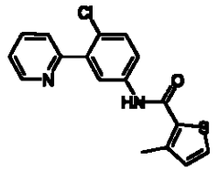
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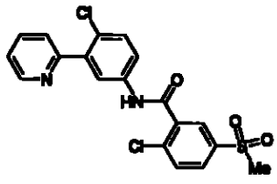
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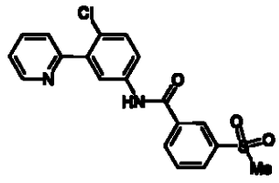
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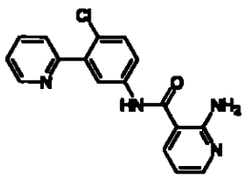
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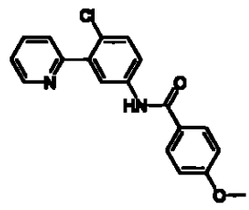
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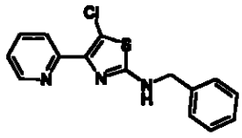
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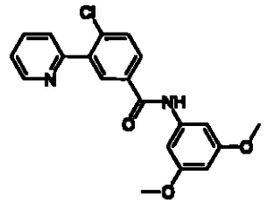
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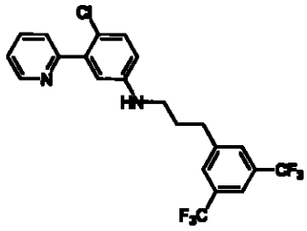
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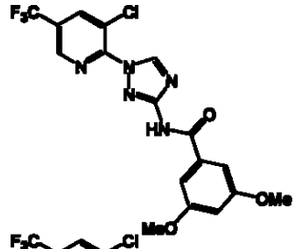
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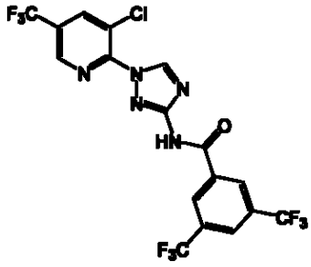
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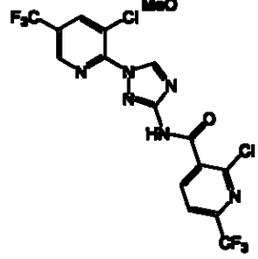
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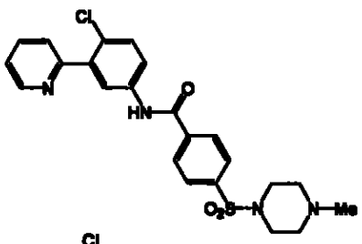
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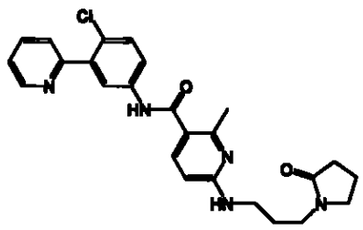
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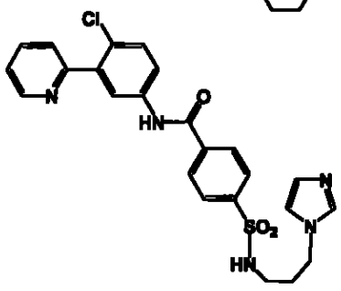
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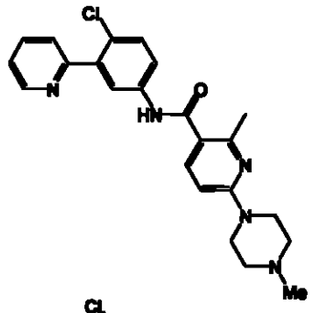
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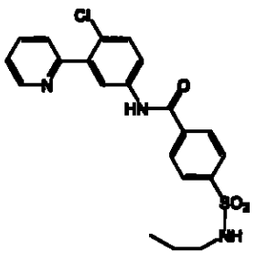
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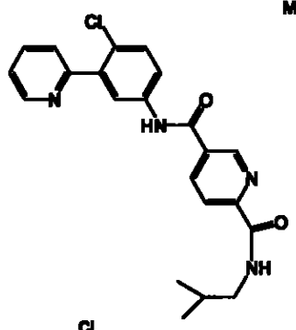
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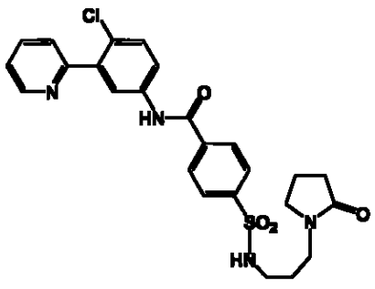
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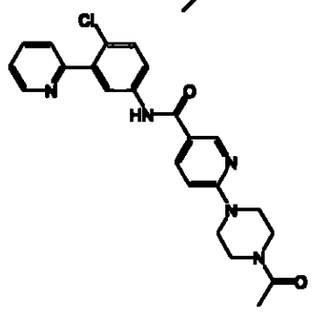
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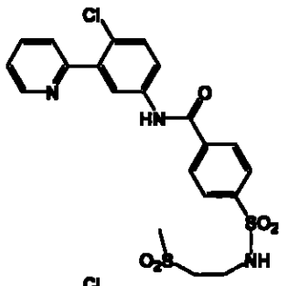


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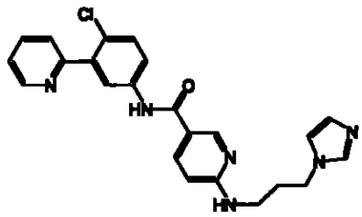


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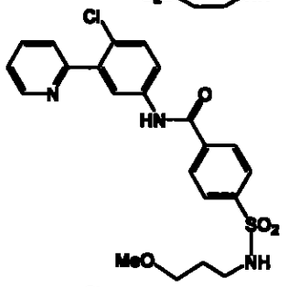
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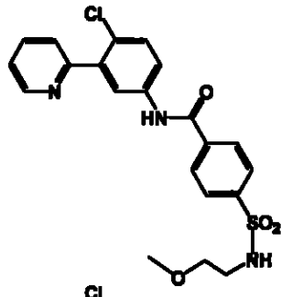
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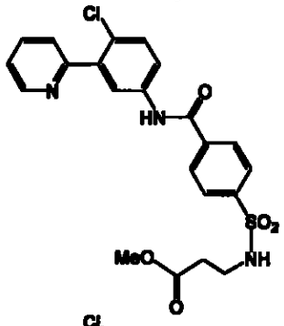
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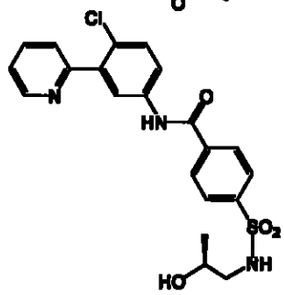
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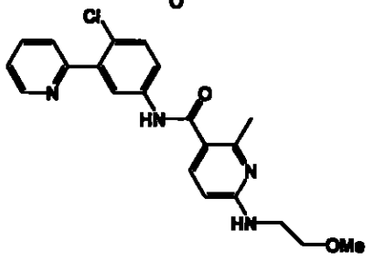
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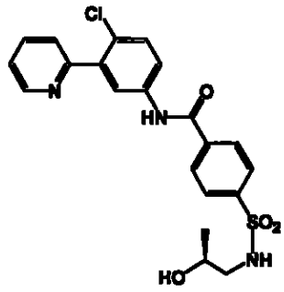
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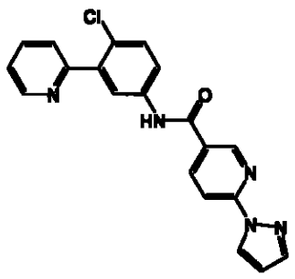


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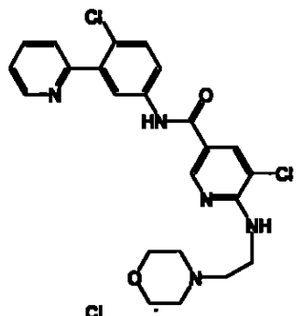


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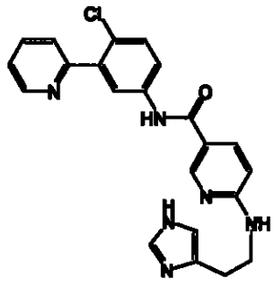
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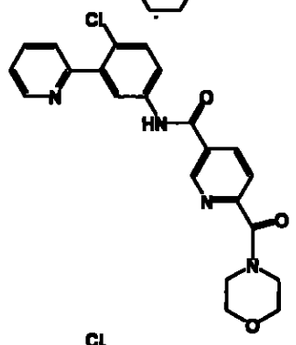
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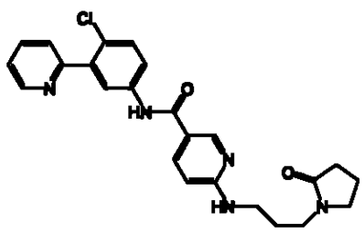
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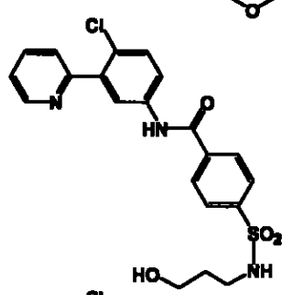
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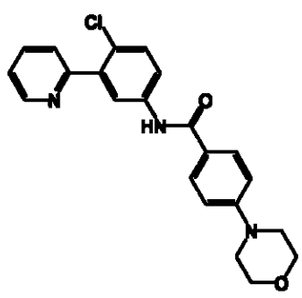
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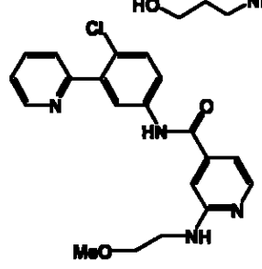
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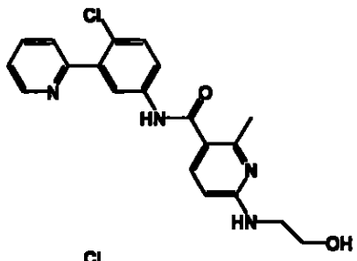
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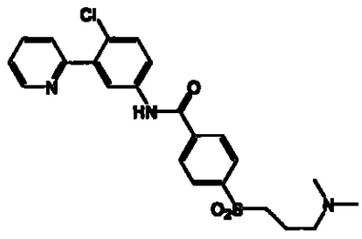


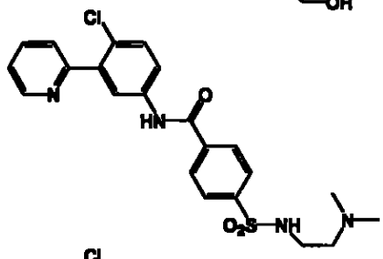
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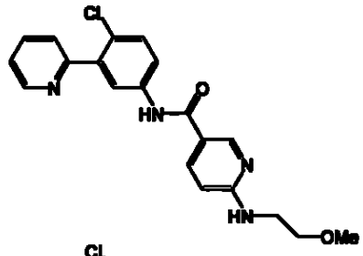


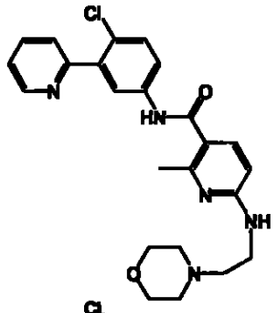
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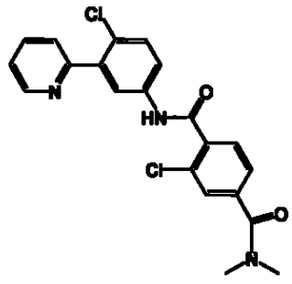
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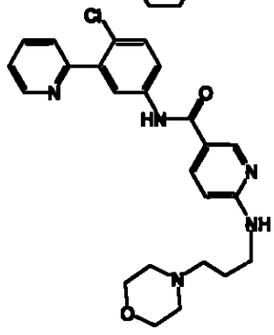
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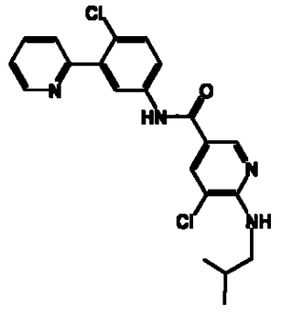
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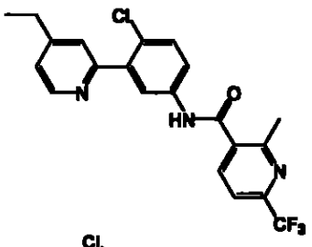
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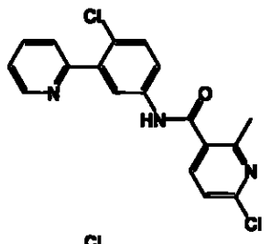
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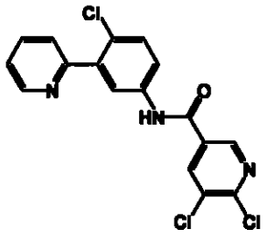
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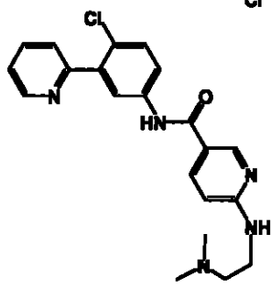
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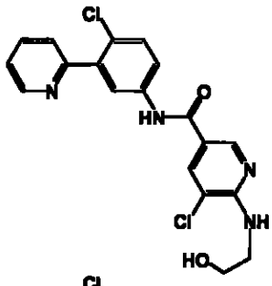
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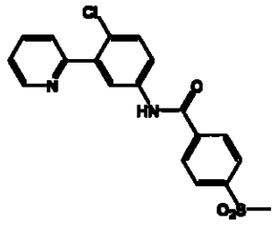
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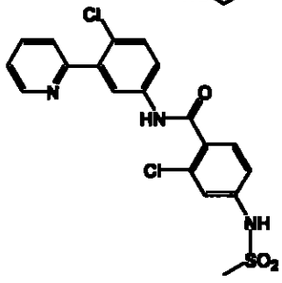
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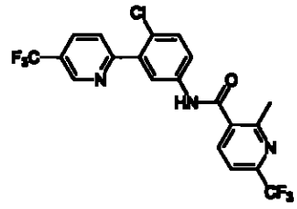
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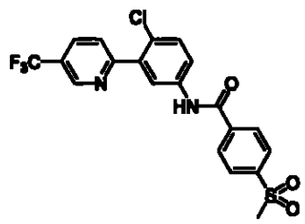
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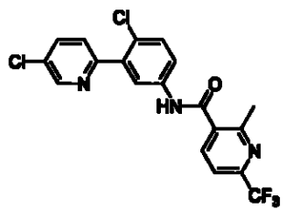
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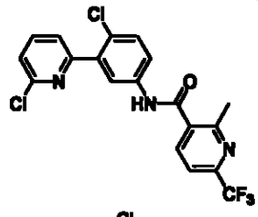
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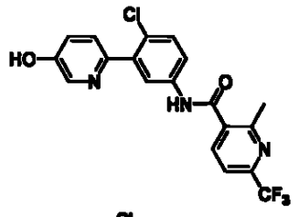
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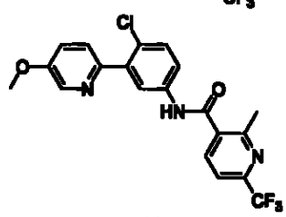
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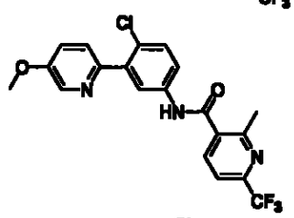
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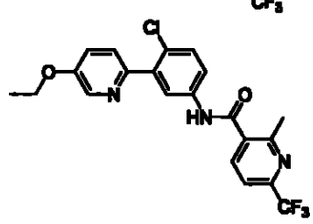
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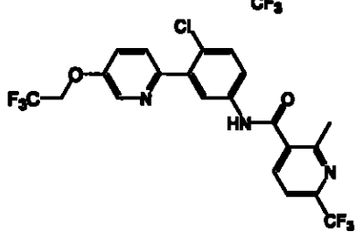
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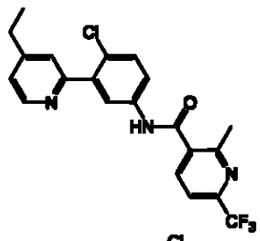
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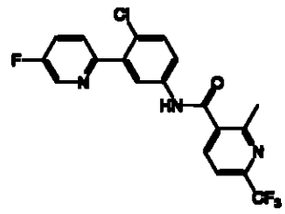
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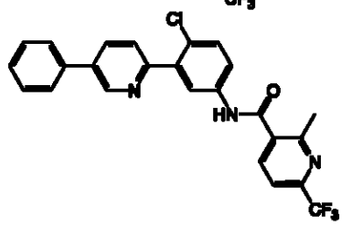
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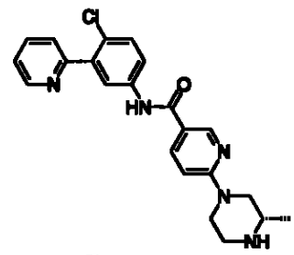
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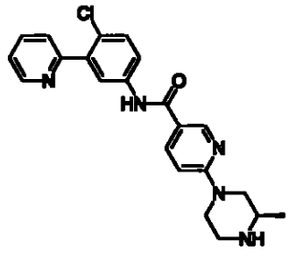
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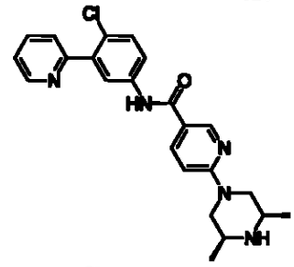


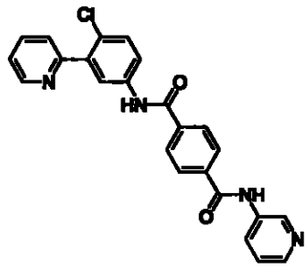


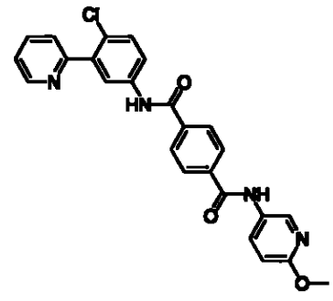




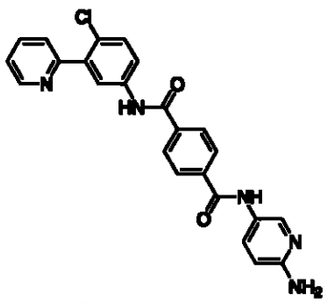


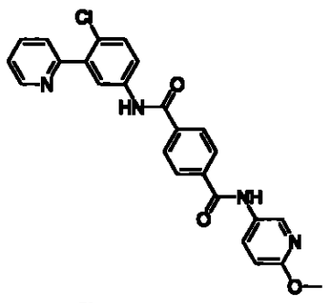


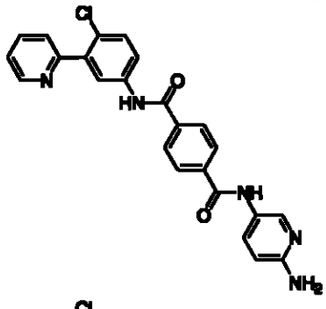


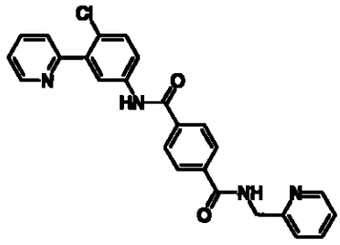


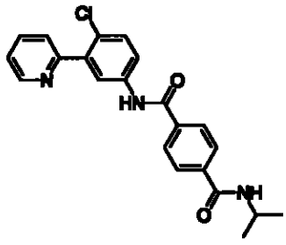
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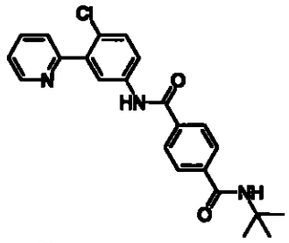


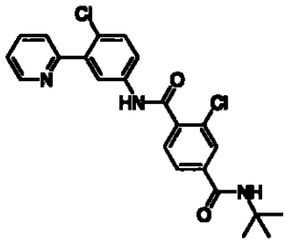


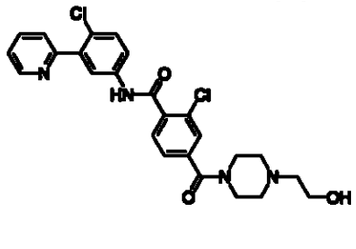




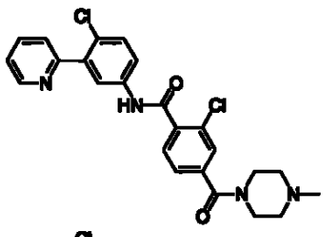


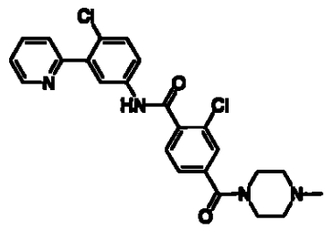


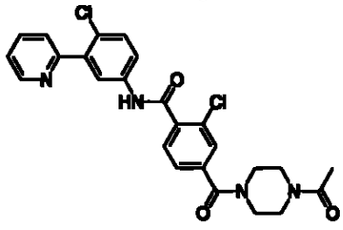


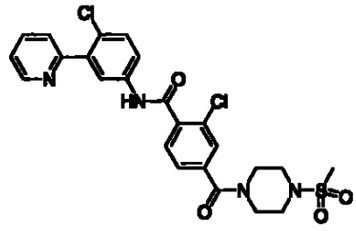


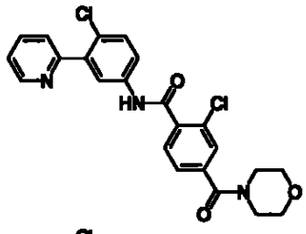
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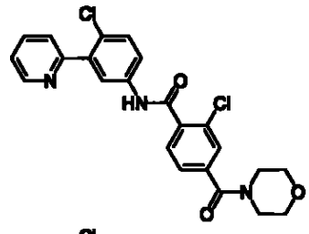


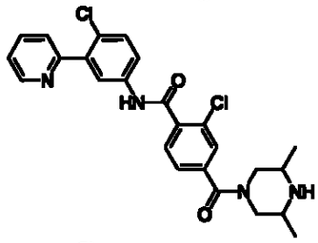


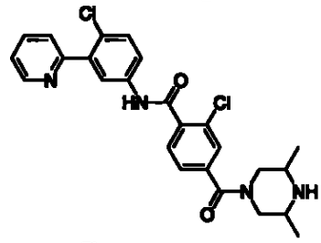


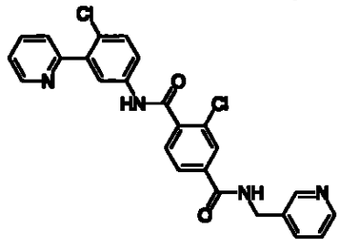


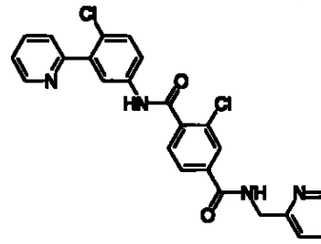




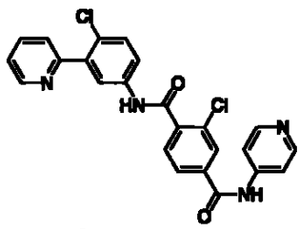


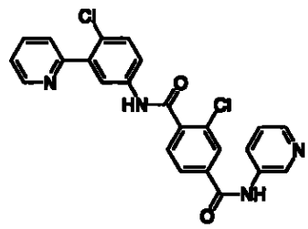


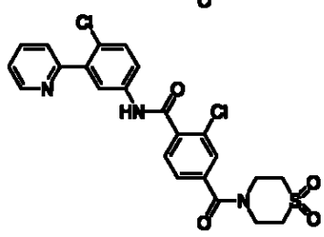


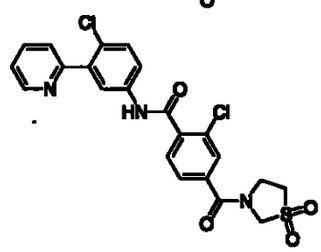


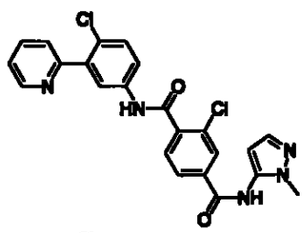
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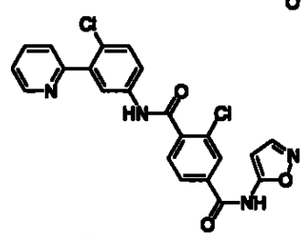


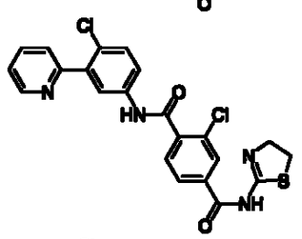


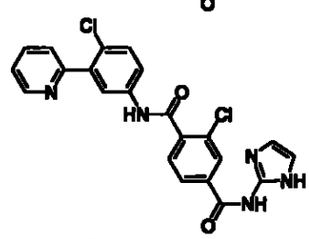


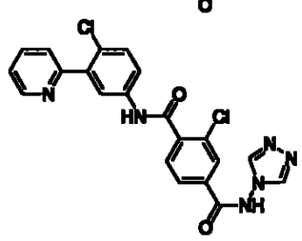


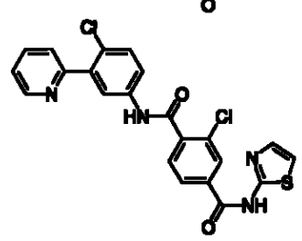




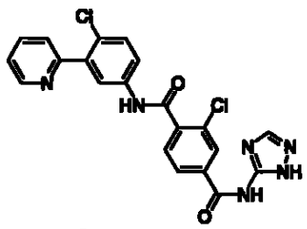


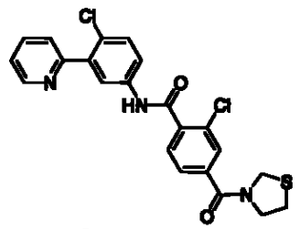


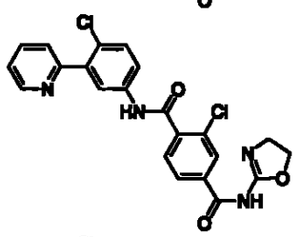


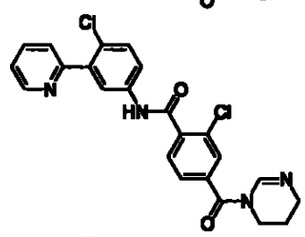


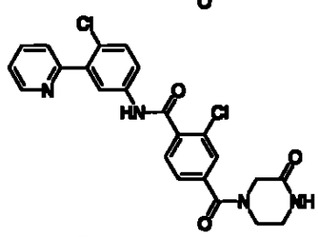
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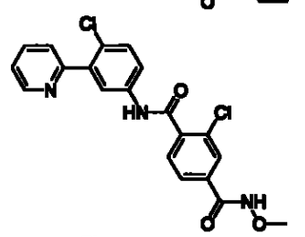


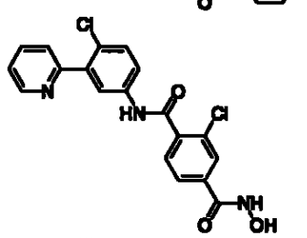


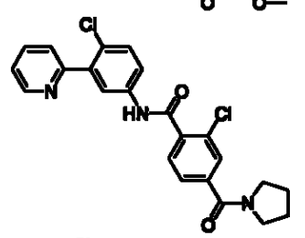


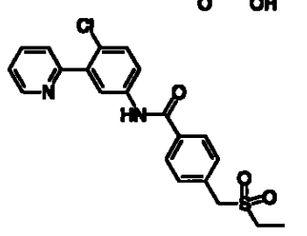


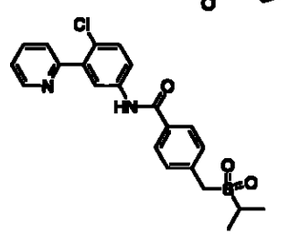




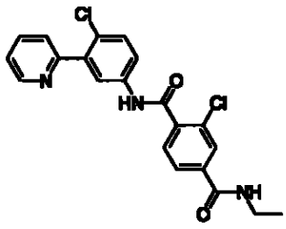


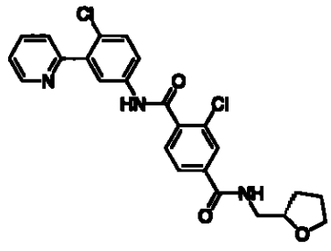


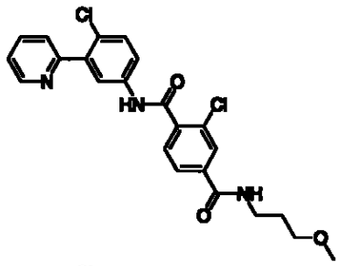


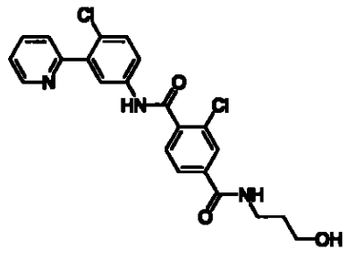


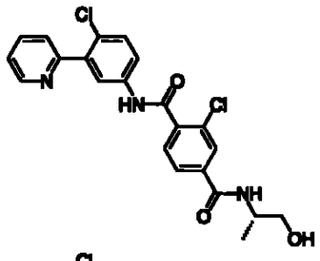
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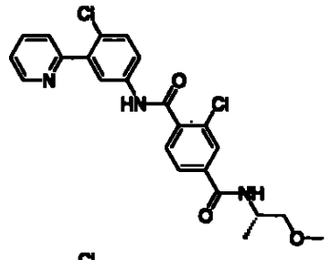


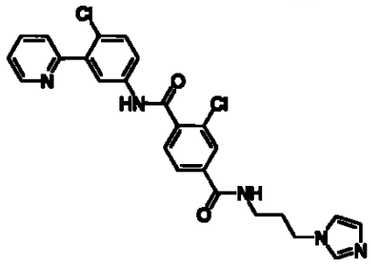


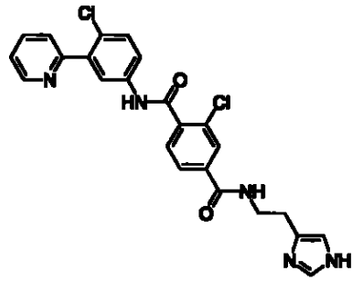




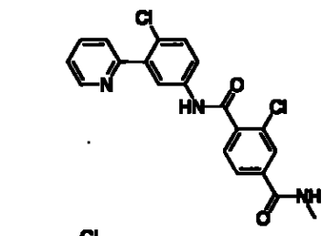


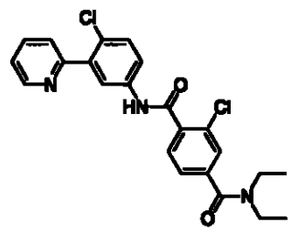


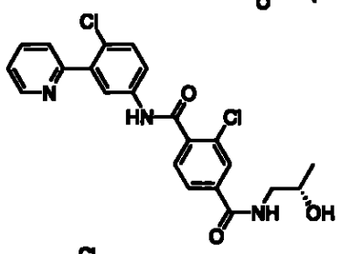


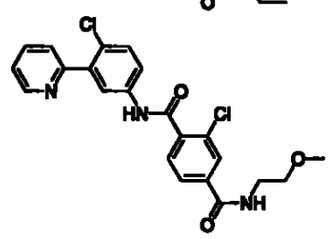


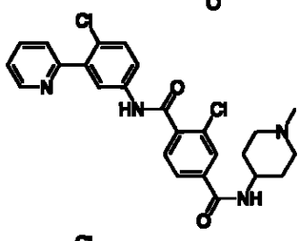
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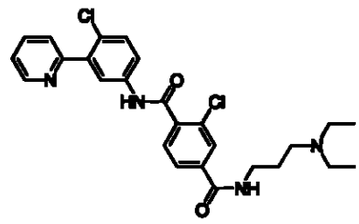


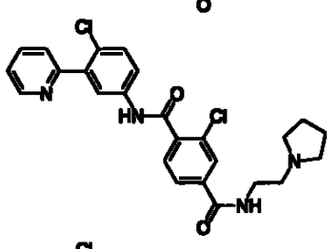


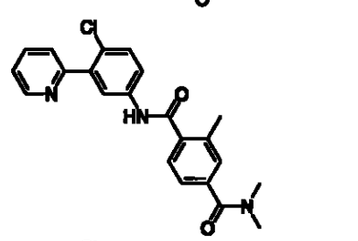


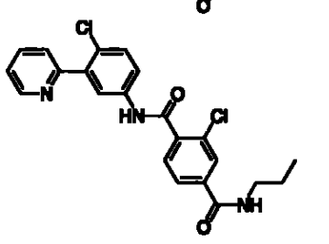


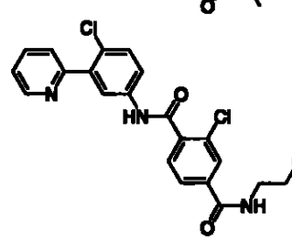




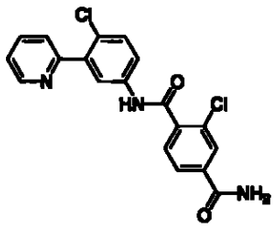


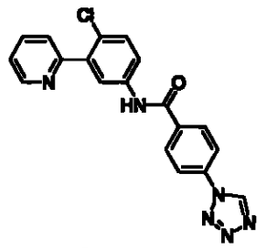


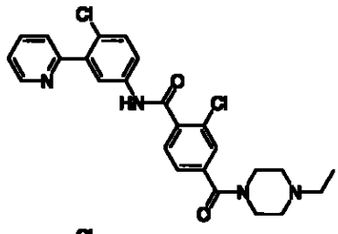


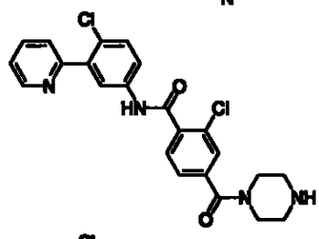


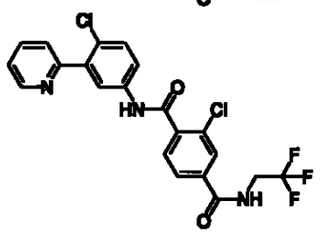
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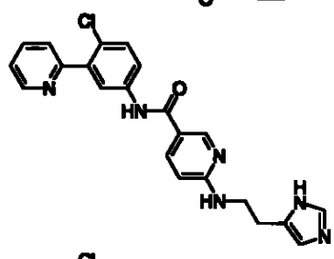


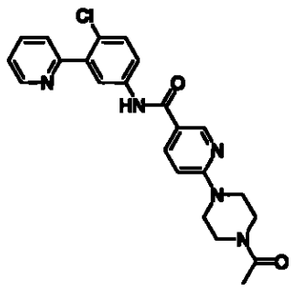


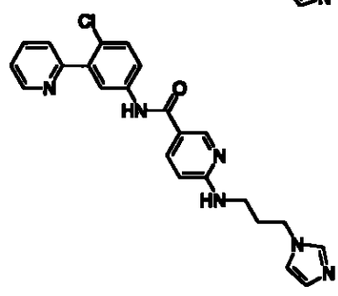






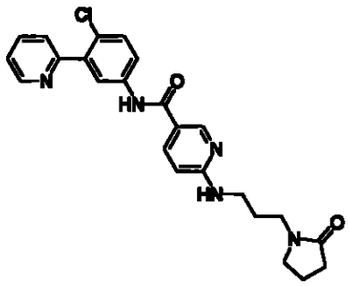


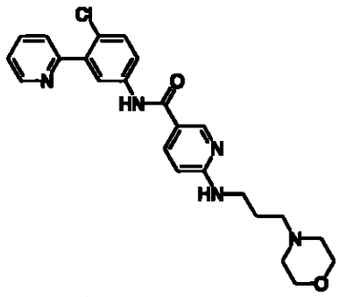


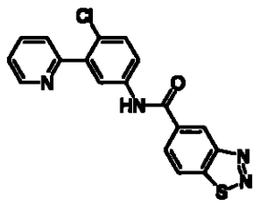


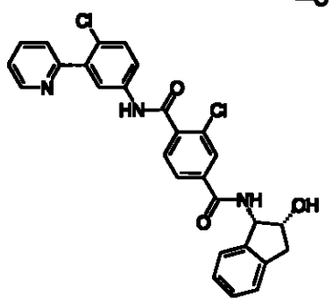
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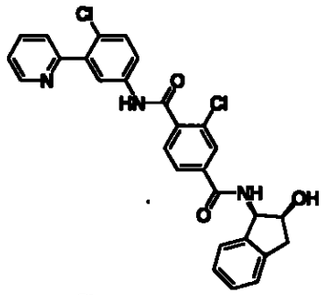
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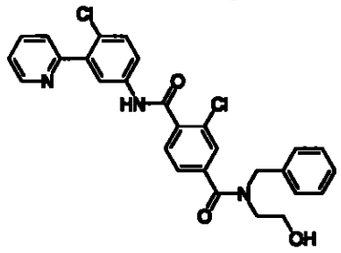


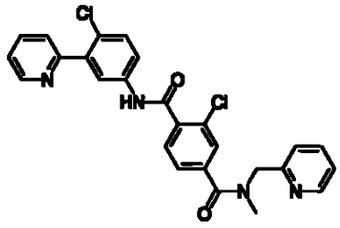


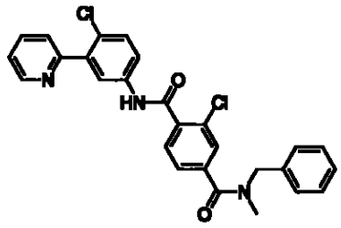




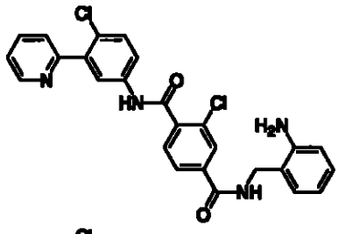


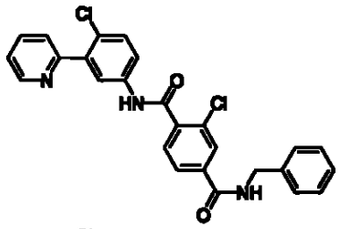


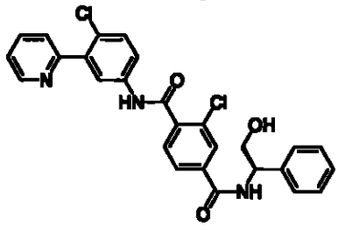


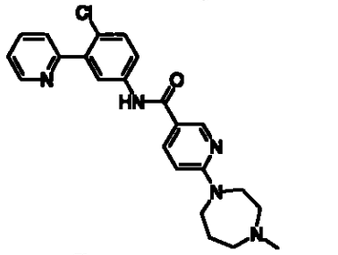


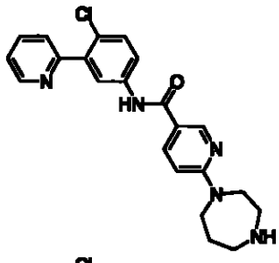
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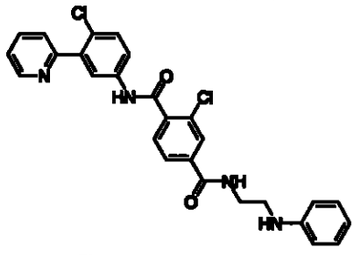


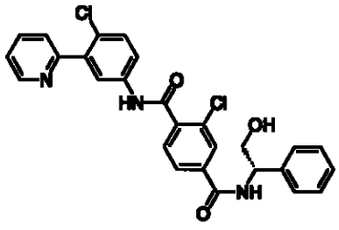


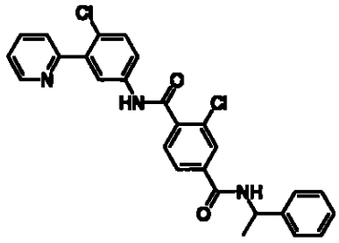


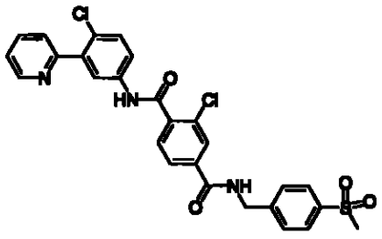


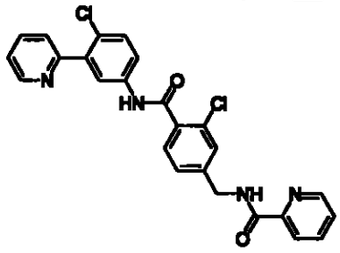






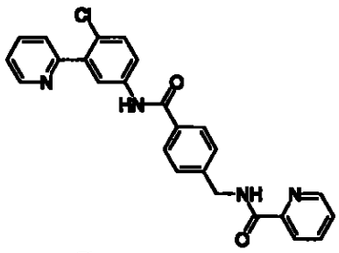


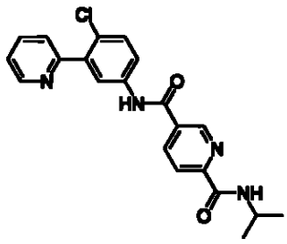


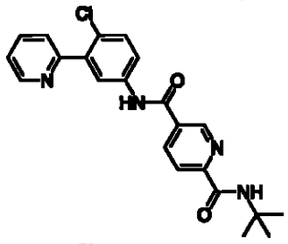


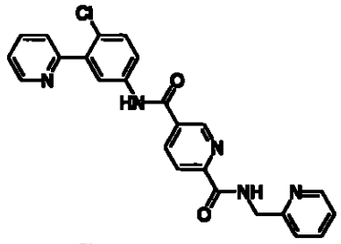
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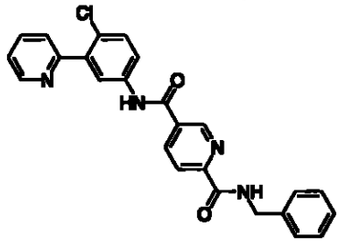
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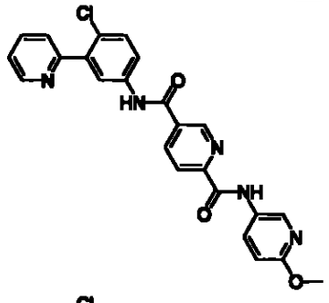


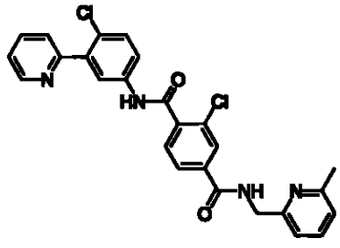


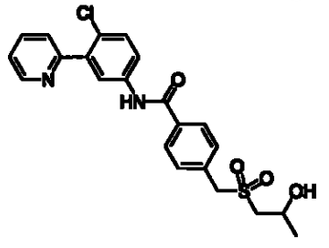




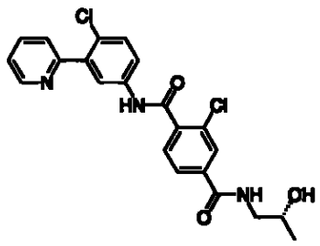


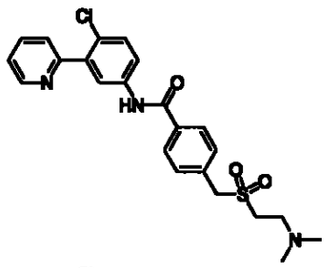


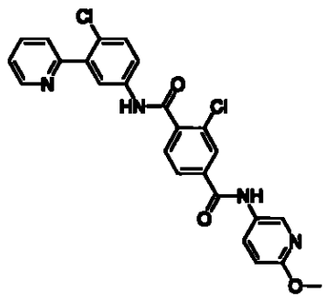


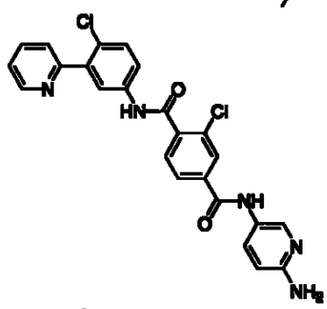


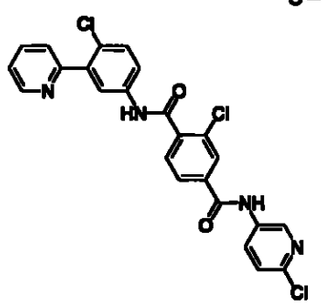
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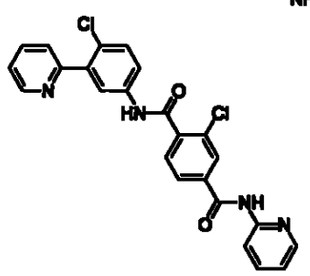


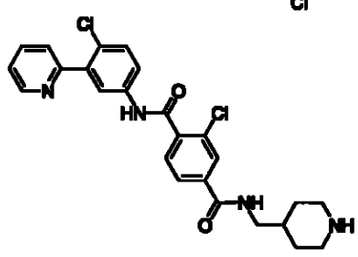


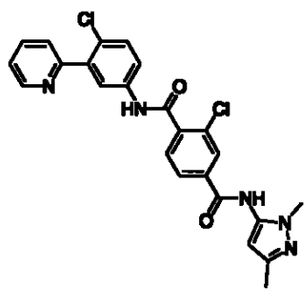






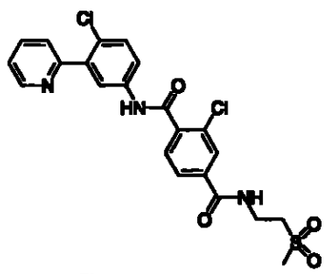


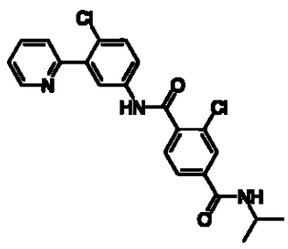


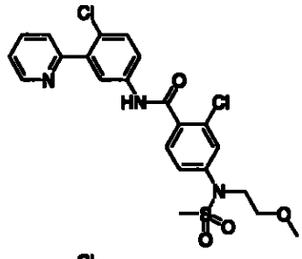


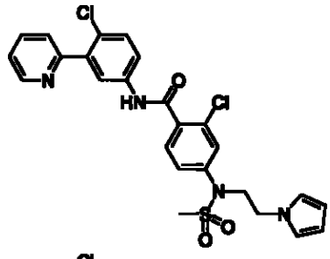
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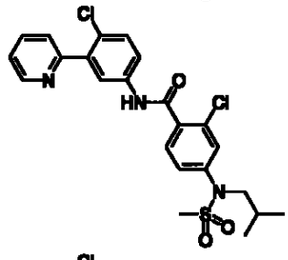
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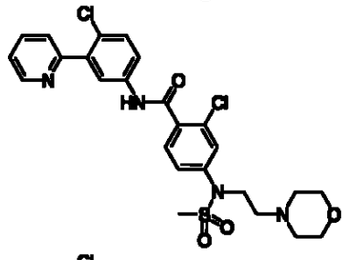


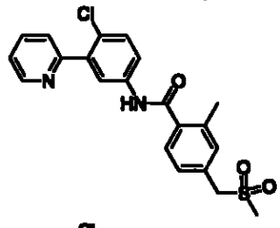


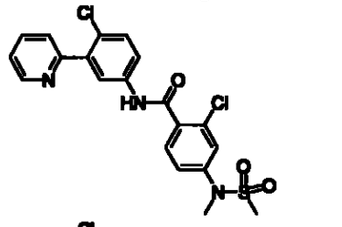


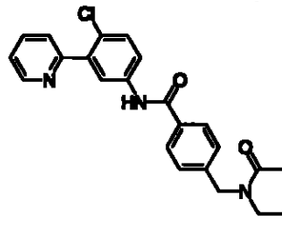


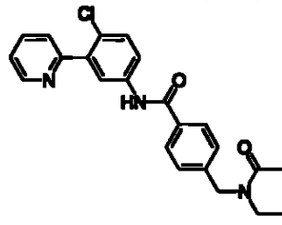






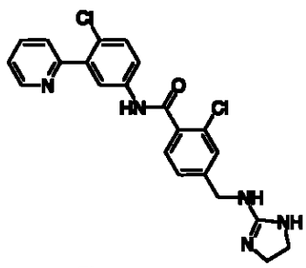


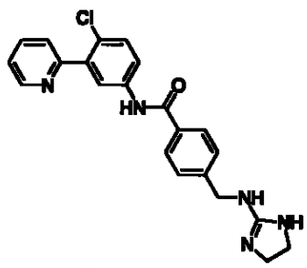


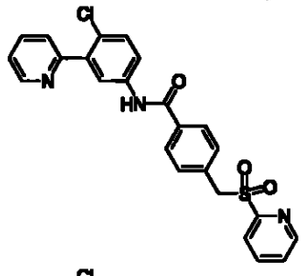


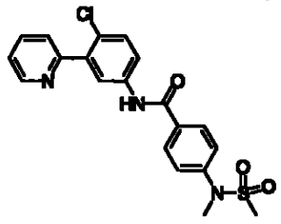
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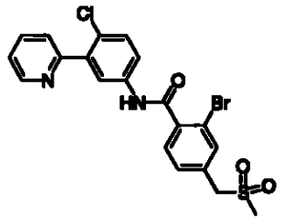
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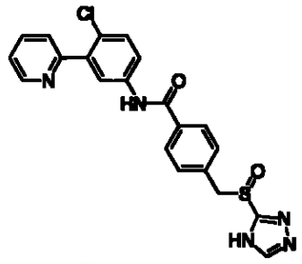


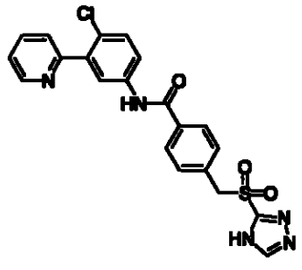


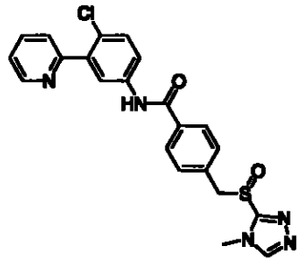




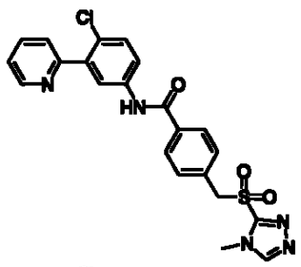


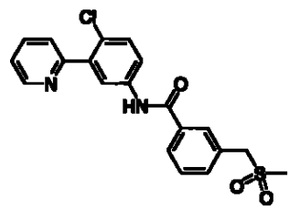


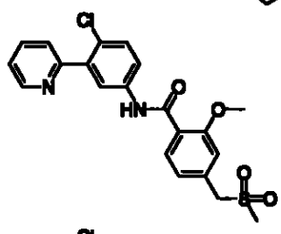


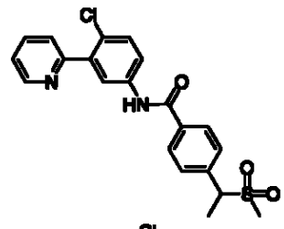


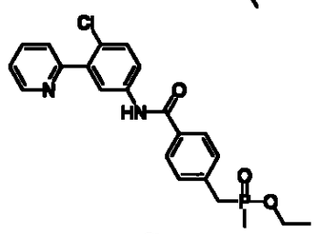
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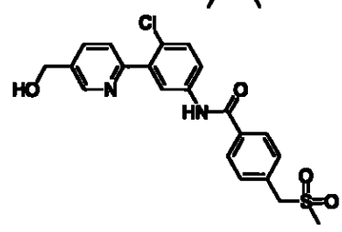


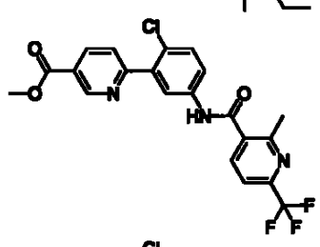


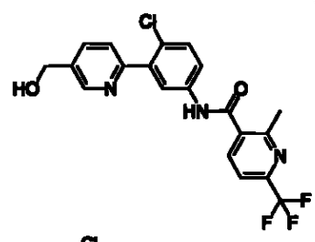


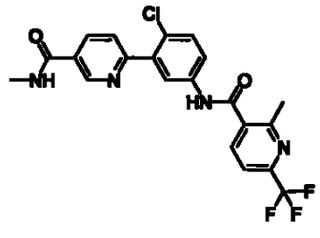


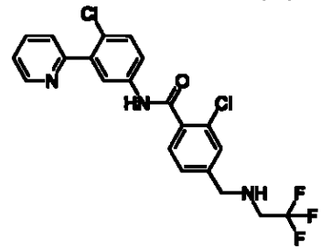






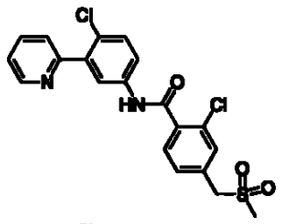


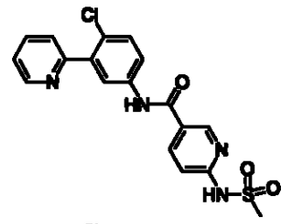


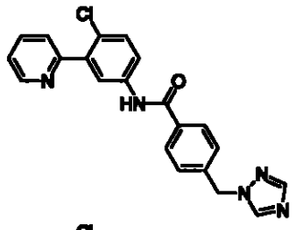


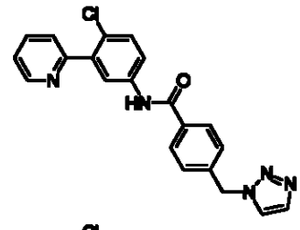
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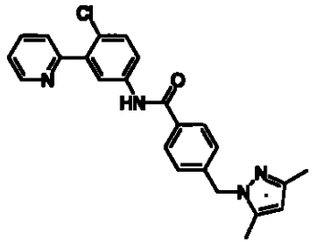
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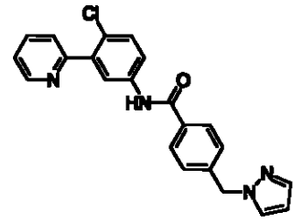


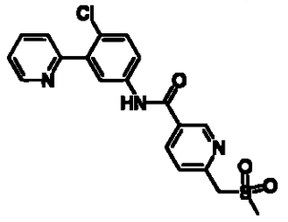


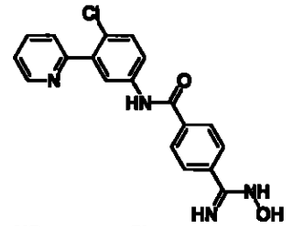


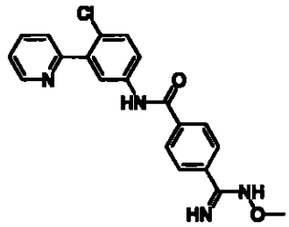






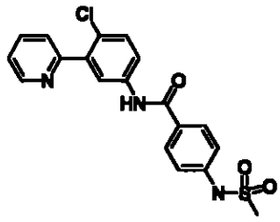


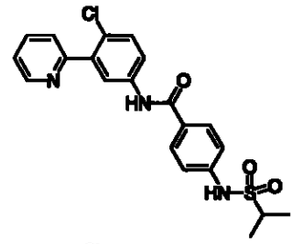


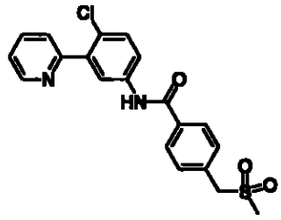


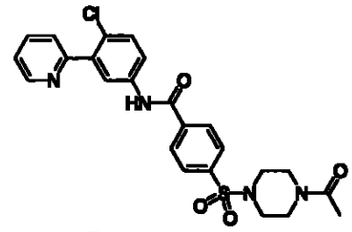
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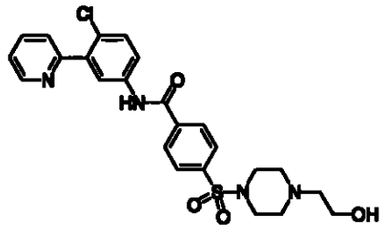
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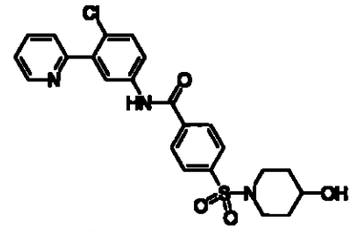


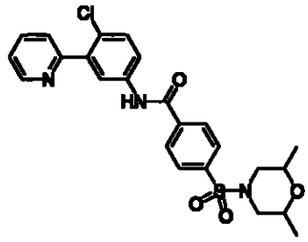


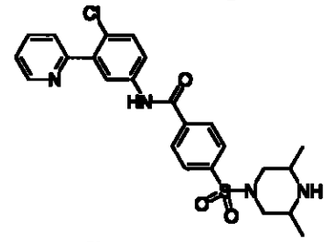


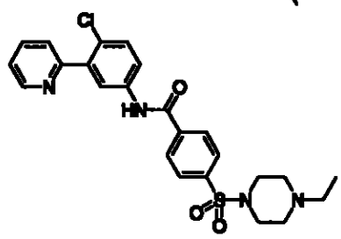






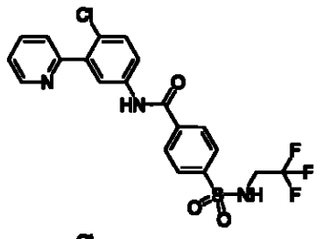


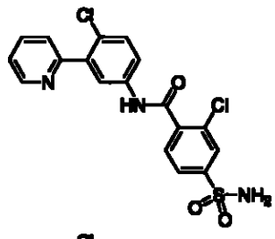


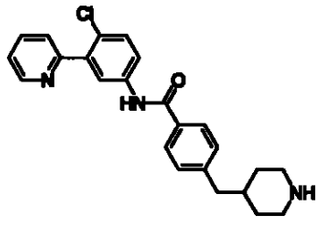


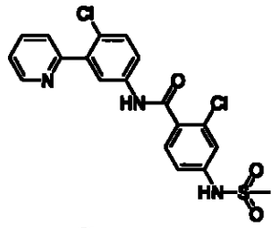
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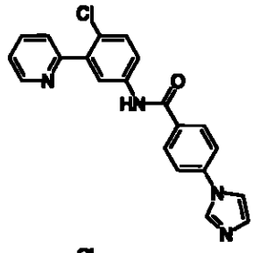
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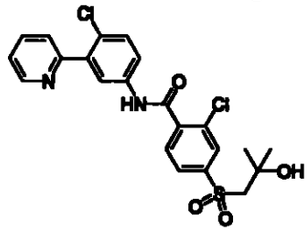


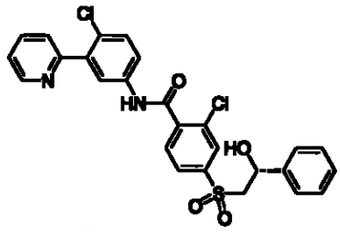


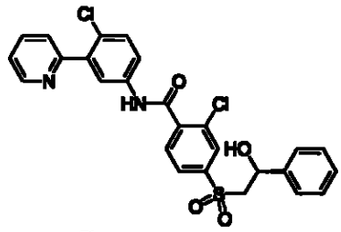


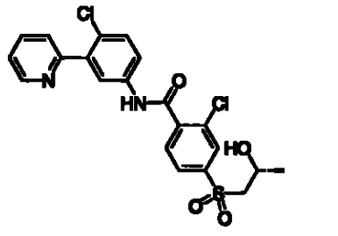


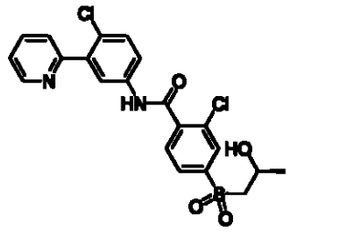






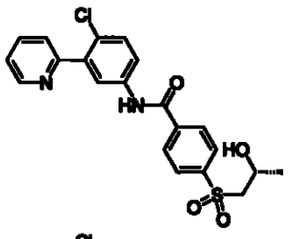


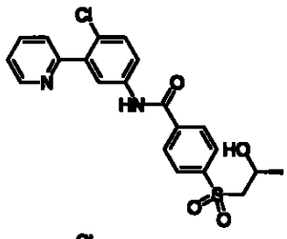


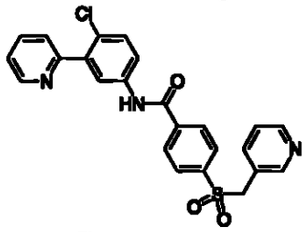


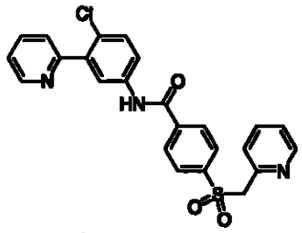
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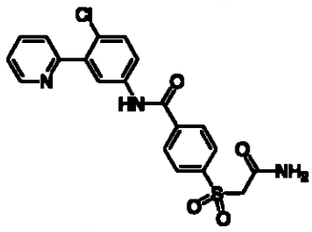
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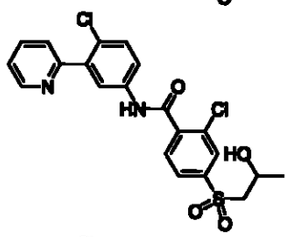


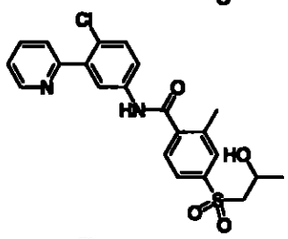


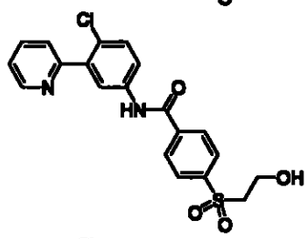


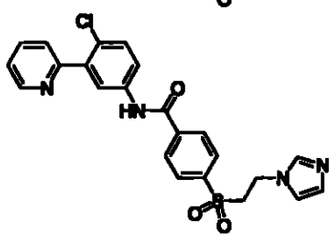


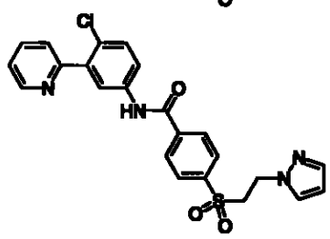




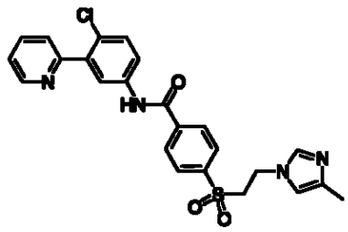


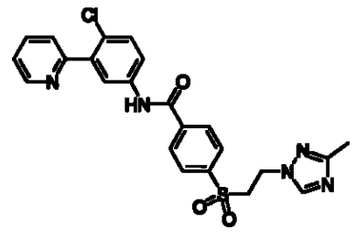


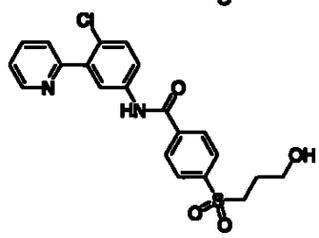


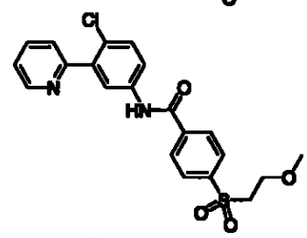


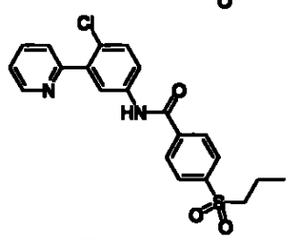
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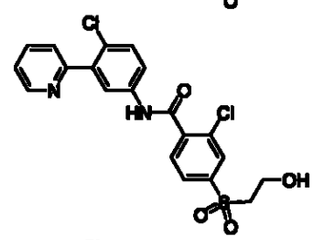


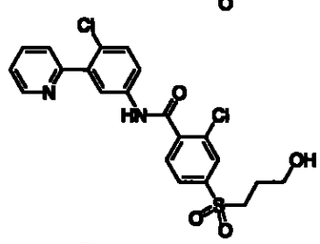


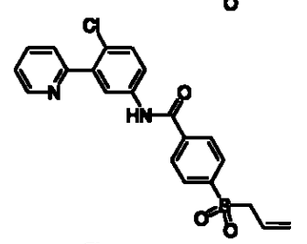


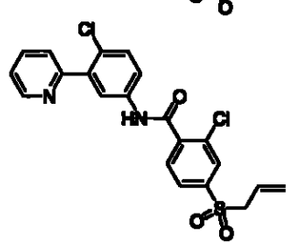


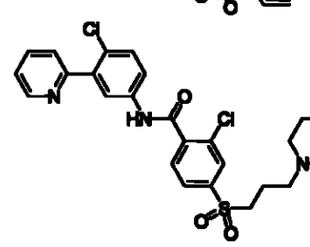




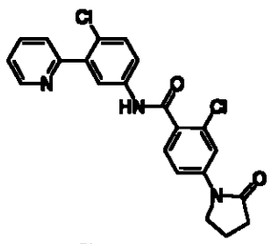


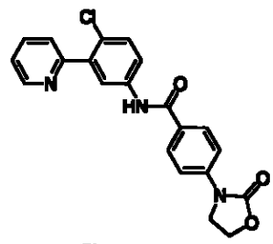


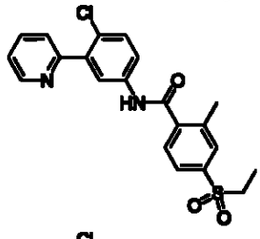


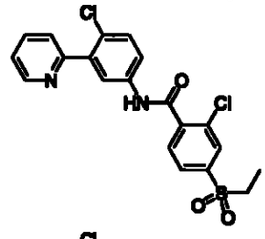


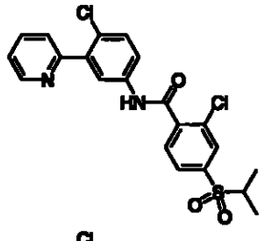
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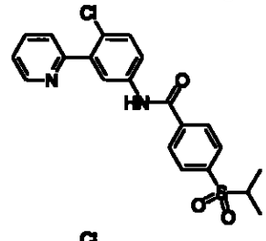


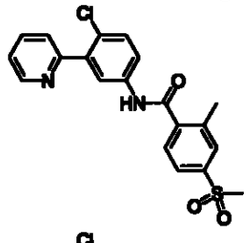


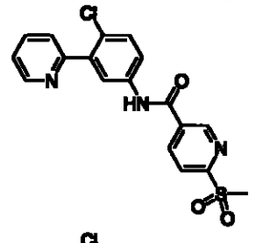


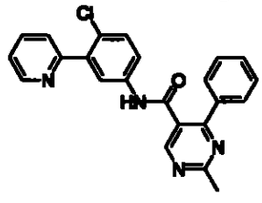


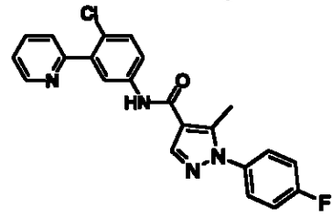




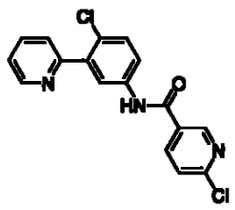


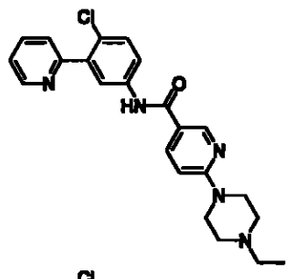


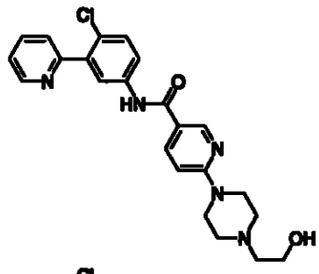


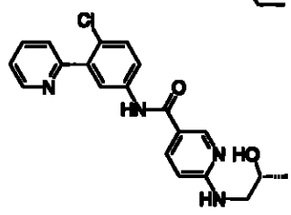


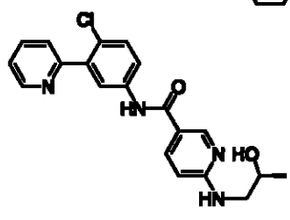
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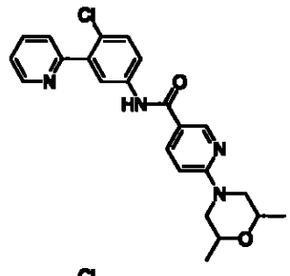


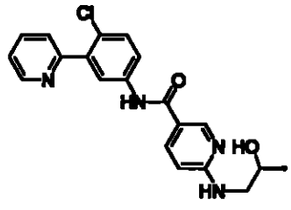


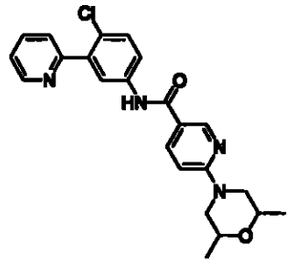






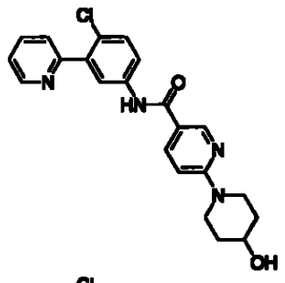


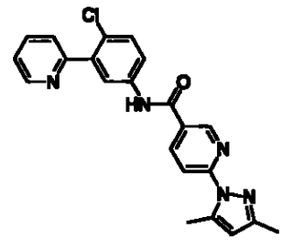


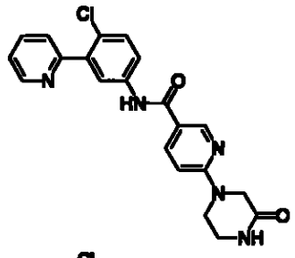


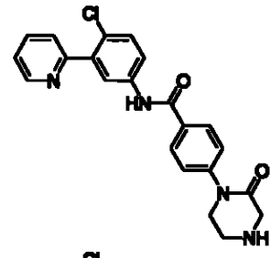
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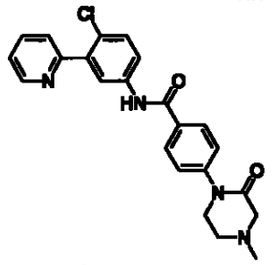
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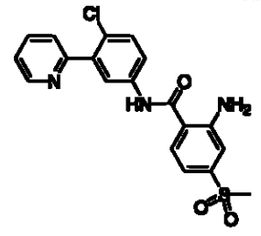


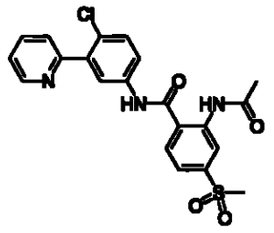


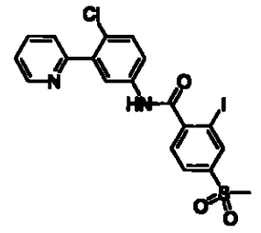




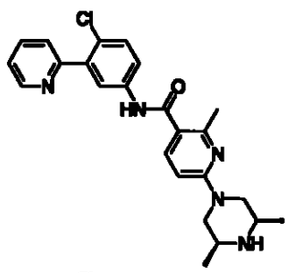


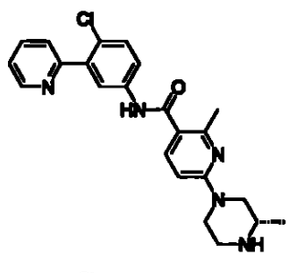


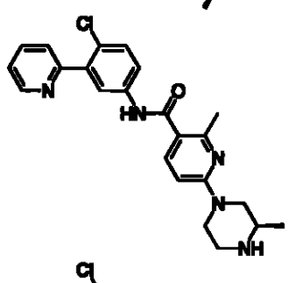


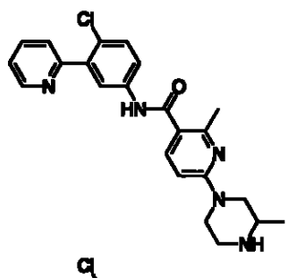


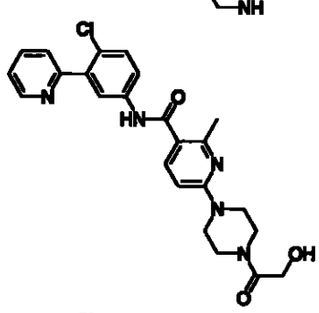
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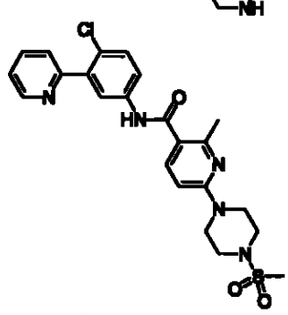


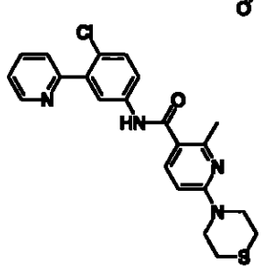


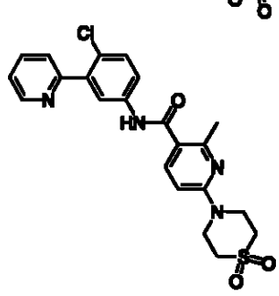






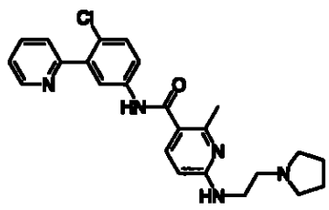


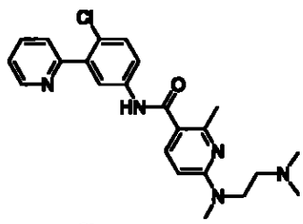


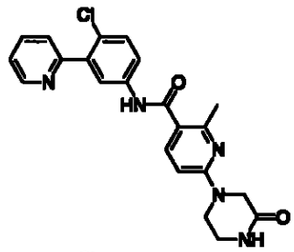


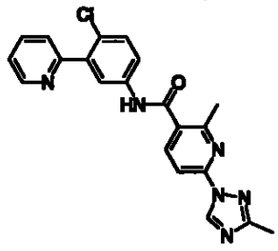
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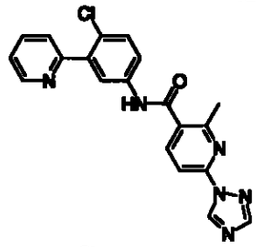
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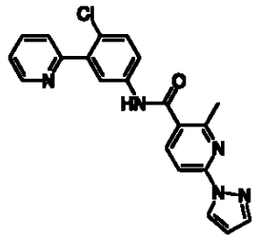


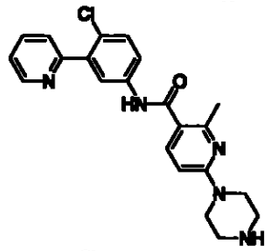


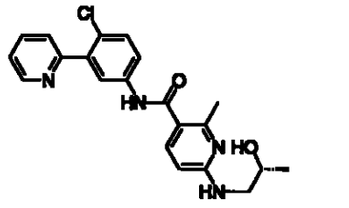


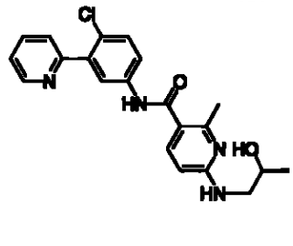


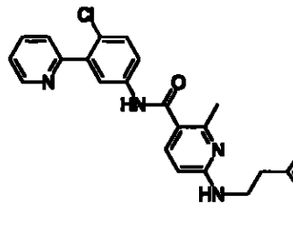






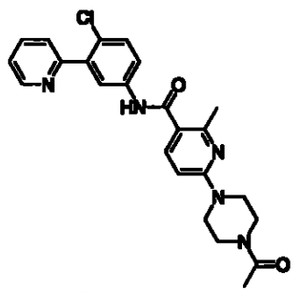


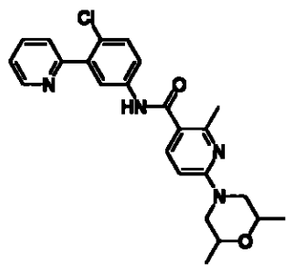


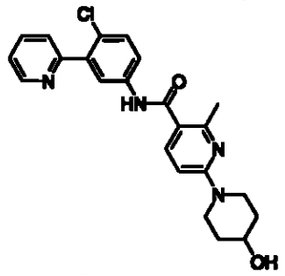


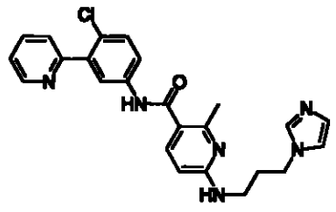
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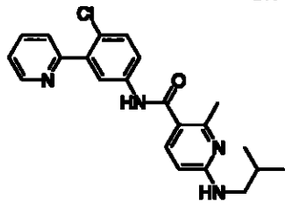
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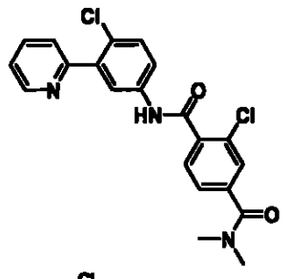


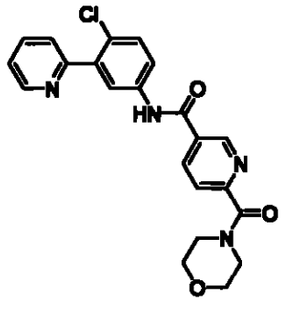


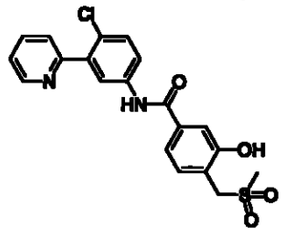




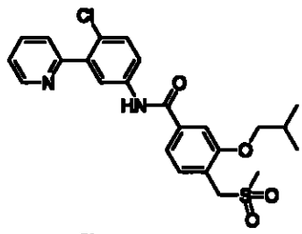


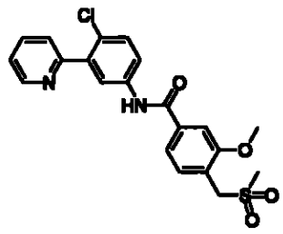


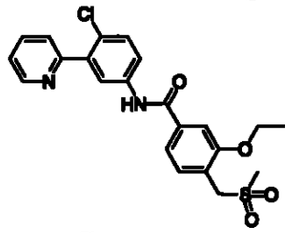


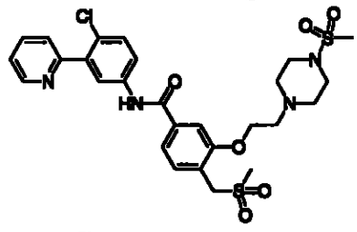


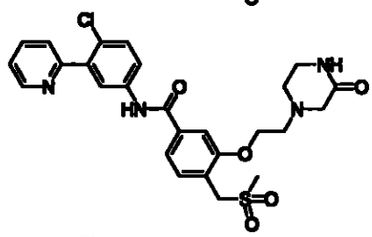
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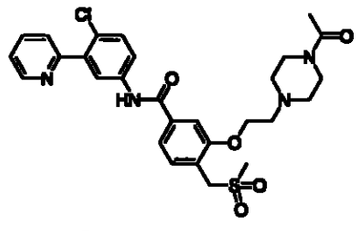


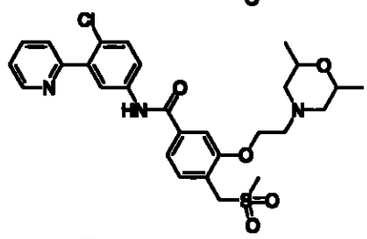


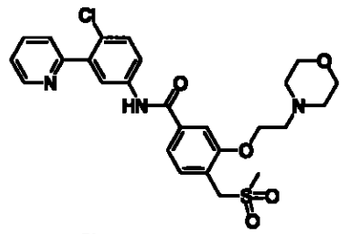


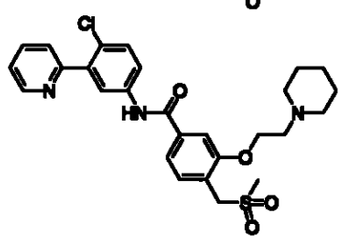






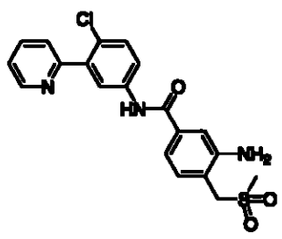


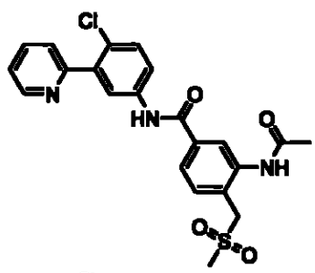


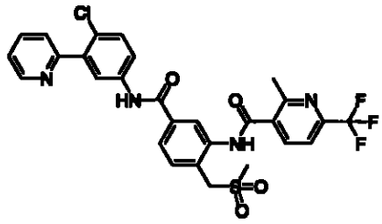


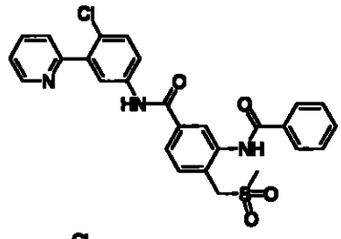
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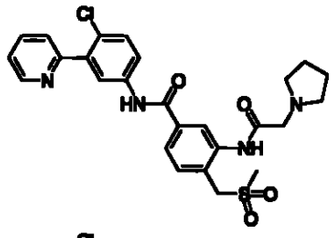
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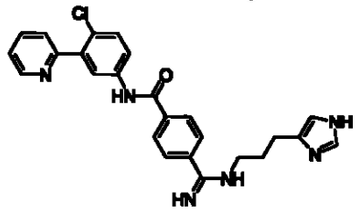


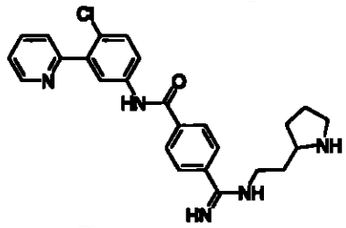


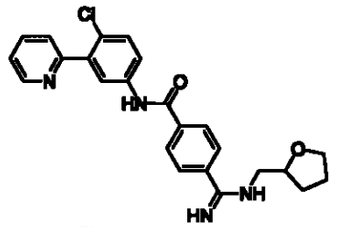


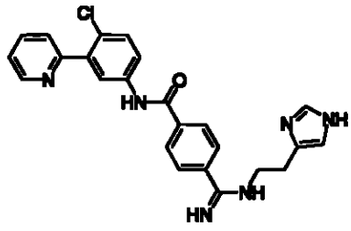


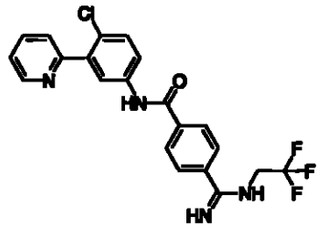






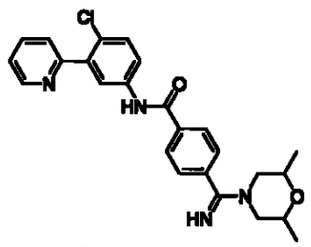


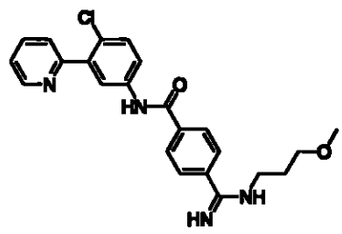


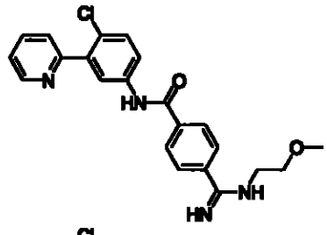


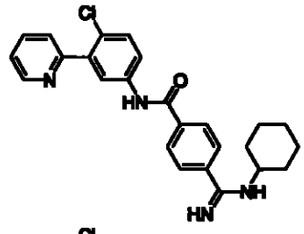
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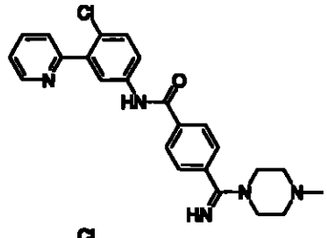
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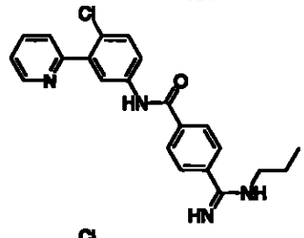


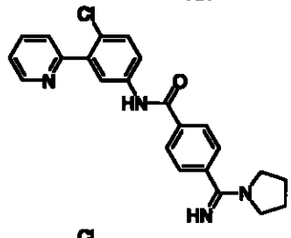


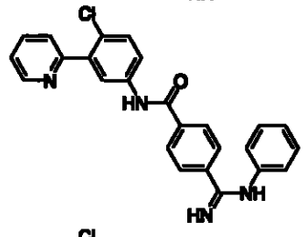


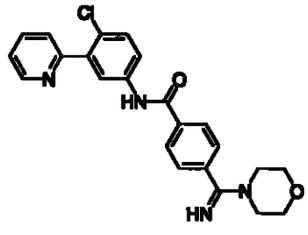












Los compuestos de la invención pueden contener uno o más átomos de

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carbono asimétricos. Por lo tanto, los compuestos pueden existir como diastereómeros, enantiómeros o mezclas de los mismos. Las síntesis de los compuestos pueden emplear racematos, diastereómeros o enantiómeros como materiales iniciales o como intermediarios. Los compuestos diastereoméricos se pueden separar por métodos cromatográficos o de cristalización. De manera similar, se pueden separar mezclas enantioméricas con el uso de las mismas técnicas u otras conocidas en la materia. Cada uno de los átomos de carbono asimétricos pueden estar en la configuración R ó S y ambas de estas dos configuraciones se encuentran dentro del alcance de la invención.

La invención también abarca prodrogas de los compuestos descriptos más arriba. Entre las prodrogas adecuadas se incluyen grupos amino protectores y carboxi protectores conocidos que se liberan, por ejemplo hidrolizados, para obtener el compuesto relacionado bajo condiciones fisiológicas. Una clase particular de prodrogas son los compuestos donde un átomo de nitrógeno en un grupo amino, amidino, aminoalquilenamino, iminoalquilenamino o guanidino se sustituye con un grupo hidroxi (OH), un grupo alquilcarbonilo (-CO-R), un alcoxicarbonilo (-CO-OR), un grupo aciloxialquil-alcoxicarbonilo (-CO-O-R-O-CO-R) donde R es un grupo monovalente o divalente y como se definió más arriba o un grupo que tiene la fórmula -C(O)-O-CP1P2-haloalquilo donde P1 y P2 son el mismo o diferentes y son H, alquilo inferior, alcoxi inferior, ciano, halo alquilo o arilo inferior. Los compuestos prodroga se pueden preparar por reacción de los compuestos de la invención descriptos más arriba con un compuesto acilo activado para unir un átomo de nitrógeno en el compuesto de la invención al carbonilo del compuesto acilo activado. Los compuestos carbonilo activado adecuados

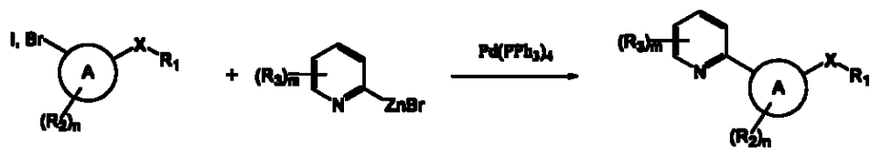
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contienen un buen grupo saliente unido al carbono del carbonilo e incluye haluros de acilo, acilaminas, sales de acilpiridinio, alcóxidos de acilo, en particular fenóxidos de acilo tal como p-nitrofenoxiacilo, dinitrofenoxiacilo, fluorofenoxiacilo, y difluorofenoxiacilo. Las reacciones son generalmente exotérmicas y se llevan a cabo en solventes inertes a temperaturas reducidas tal como entre -78 y aproximadamente 50 °C. Las reacciones normalmente también se llevan a cabo en presencia de una base inorgánica tal como carbonato de potasio o bicarbonato de sodio, o una base orgánica tal como un amina, incluso piridina, TEA, etc. Una manera de preparar prodrogas se describe en USSN 08/843.369 presentado el 15 de abril de 1997 (correspondiente a la publicación PCT WO9846576) cuyos contenidos se incorporan en su totalidad a la presente documentación a modo de referencia.

SÍNTESIS

Los compuestos de la invención se preparan con el uso de técnicas de síntesis orgánica estándar a partir de materiales iniciales y reactivos disponibles de manera comercial. Se apreciará que los procedimientos de síntesis empleados en la preparación de los compuestos de la invención van a depender de los sustituyentes particular presentes en un compuesto y que se pueden requerir varios procedimientos de protección y desprotección como ocurre en la síntesis orgánica estándar. Los compuestos de la invención en los cuales Y está ausente se pueden preparan por un procedimiento de acoplamiento de Negishi de acuerdo al siguiente esquema general 1:

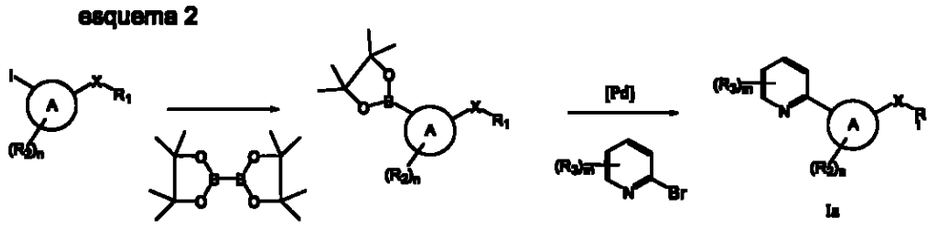
esquema 1



Ia

en donde el bromuro de piridilzinc (o alternativamente el cloruro de piridilzinc) se hace reaccionar con un anillo A sustituido con iodo o bromo para dar el compuesto final Ia. De manera alternativa, los compuestos Ia de la invención se pueden preparar con el uso de una reacción de acoplamiento de Suzuki de un anillo borilado A para proveer unión directa entre el piridilo adecuado y el anillo A de acuerdo con el esquema 2.

esquema 2



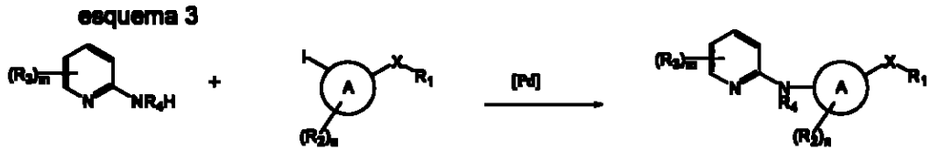
Ia

Un anillo A halógeno-sustituido se hace reaccionar con un éster de boro tal como diborano de pinacol en presencia de catalizador de paladio tal como $PdCl_2$(dppf) y el éster boronato resultante se calienta con un 2-halógeno-sustituido piridino y un catalizador de paladio para dar un compuesto final Ia de la invención.

Los compuestos de la invención en los cuales Y es NR_4 se pueden preparar por aminación catalizada por paladio de un anillo halógeno-sustituido A con la 2-aminopiridina deseada de acuerdo con el esquema 3.

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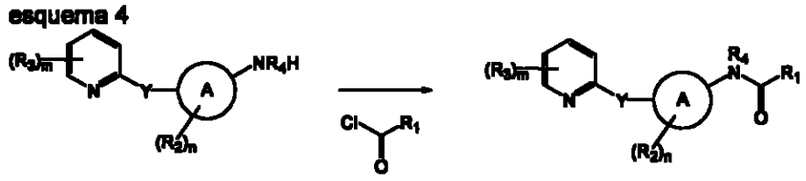
esquema 3



Ib

Los compuestos de la invención en los cuales X es NR_4CO se pueden preparar por el esquema general 4 en el cual el anillo A amino-sustituido se hace reaccionar con el cloruro de ácido deseado Cl-C(O)-R_1.

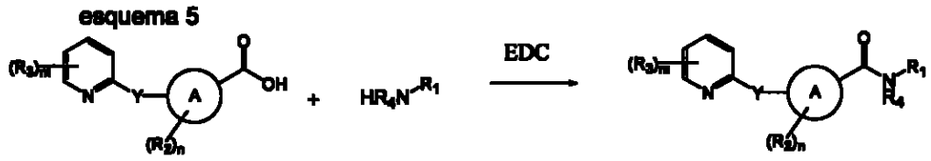
esquema 4



De manera alternativa, dichos compuestos se pueden preparar por acoplamiento catalizado por EDC de un anillo A carboxi-sustituido con un grupo R_1 amino-sustituido, es decir R_1-NR_4H. El mismo esquema se puede usar para preparar compuestos tioamida de la invención, es decir X es $NR_4C(S)$, por empleo de cloruro de tioácido adecuado Cl-C(S)-R_1 en el paso de acetilación.

Los compuestos de la invención en los cuales X es $C(O)NR_4$ se pueden preparar de modo similar por reacción de un anillo A amino-sustituido con un grupo R_1 carboxi-sustituido y catalizador de EDC de acuerdo con el esquema 5.

esquema 5



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Un esquema similar se puede usar para preparar compuestos tioamida de la invención, es decir X es $C(S)NR_4$, por empleo de un anillo A sustituido con ácido tióico adecuado (por ejemplo -C(S)OH) o por conversión de la amida con el reactivo de Lawesson.

Se pueden preparar compuestos de la invención en los cuales X es $NR_4C(O)NH$ de acuerdo con el esquema general 6 por reacción del anillo A amino-sustituido con el isocianato adecuado R_1-NCO.

esquema 6



El mismo esquema se puede usar para preparar compuestos tiourea de la invención, es decir X es $NR_4C(S)NH$, por empleo de un isotiocianato R_1-NCS adecuado en lugar de isocianato R_1-NCO.

Se pueden preparar compuestos de la invención en los cuales X es NR_4SO_2 de acuerdo con el esquema general 7 por reacción de un anillo A amino-sustituido con cloruro de sulfonilo R_1-$S(O_2)Cl$ adecuado en presencia de una base no nucleofílica tal como TEA o diisopropiletilamina para formar la sulfonamida deseada.

esquema 7

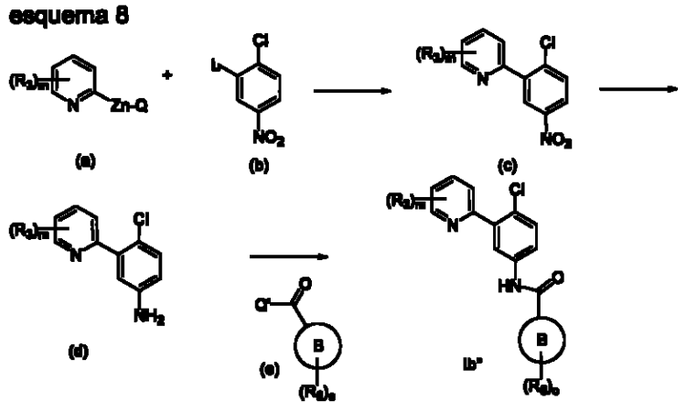


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Los compuestos de la invención en los cuales X es NR_4SO se preparan de modo similar con el uso de cloruro de sulfinilo R1-SO-Cl adecuado en lugar de cloruro de sulfonilo R1-$S(O_2)$Cl.

Los compuestos de la invención que tienen la estructura de fórmula Ib' en los cuales X es NHCO (es decir fórmula Ib") se pueden preparar de acuerdo con el esquema general 8 en el cual R_3, R_6, m y o son como se los define en la presente documentación y Q es Cl, Br ó I; Q' es halógeno, OH, OR donde R es un grupo activador; L es Br, I ó OTf (por ejemplo O-SO_2-CF_3):

esquema 8



El reactivo de haluro de piridinzinc (a) se hace reaccionar con el reactivo 2-cloro-5-nitro-benceno (b) en un reacción de acoplamiento Negishi en presencia de un catalizador adecuado tal como el complejo tetraquis(trifenilfosfina) de paladio ($Pd(PPh_3)_4$). En una realización particular, el catalizador tetraquis(trifenilfosfina) de paladio se estabiliza con trifenilfosfina (PPh_3). En una realización particular Q es Br. En una realización particular L es I. En una realización particular, la reacción de acoplamiento se realiza entre aproximadamente 50 °C y aproximadamente 60 °C.

El reactivo nitrobenceno (b) se puede obtener por activación de la amina

correspondiente (es decir 2-cloro-5-nitroanilina) en una solución de ácido sulfúrico acuoso con nitrito de sodio y por desplazamiento con un grupo L (por ejemplo con KI, KBr). En una realización particular, L es I. En una realización particular la reacción se realiza a menos de aproximadamente 15 °C.

El intermediario resultante (c) se reduce, por ejemplo con Fe, Zn o $SnCl_2$ en presencia de ácido para dar la amina intermediaria (d). En una realización particular, el intermediario (c) se reduce con Fe, por ejemplo, en presencia de AcOH en EtOH. En una realización particular, el intermediario (c) se reduce con Zn, por ejemplo en presencia de AcOH en EtOH. En una realización particular, el intermediario (c) se reduce con $SnCl_2$, por ejemplo en presencia de HCl en EtOH. En una realización particular la reacción de reducción se realiza a aproximadamente 60 °C.

Finalmente, el intermediario (d) se hace reaccionar con un ácido activado (e) para obtener el compuesto final Ib". En una realización particular, el ácido activado (e) es un haluro de ácido (por ejemplo Q' es cloruro) o éster activado (por ejemplo Q' es O-EDC). En una realización particular la última reacción se realiza a aproximadamente 0 °C.

Los compuestos de la invención inhiben la señalización de hedgehog y son útiles para el tratamiento de cánceres asociados con señalización de hedgehog aberrante, por ejemplo cuando Patched falla en, o de modo inadecuado, reprimir Smoothened (fenotipo de pérdida de función Ptc) y/o cuando Smoothened está activo a pesar de la represión Patched (fenotipo de ganancia de función Smo). Entre los ejemplos de dichos tipos de cáncer se incluyen carcinoma de células basales, tumores neuroectodérmicos tales como medulobiastoma, meningioma, hemangioma, glioblastoma, adenocarcinoma

pancreático, carcinoma escamoso de pulmón, carcinoma de células pequeñas de pulmón, carcinoma de células no pequeñas de pulmón, condrosarcoma, carcinoma de mama, rabdomiosarcoma, cáncer esofágico, cáncer de estómago, cáncer de tracto biliar, carcinoma renal, carcinoma tiroideo. Se pueden administrar los compuestos de la invención antes de, simultáneamente con, o luego de la administración de otros tratamientos anticáncer tales como terapia de radiación o quimioterapia. Entre los compuestos de quimioterapia citostáticos adecuados se incluyen, pero no se limita a (i) antimetabolitos, tales como citarabina, fludarabina, 5-fluoro-2'-deoxiuiridina, gemcitabina, hidroxiurea o metotrexato; (ii) agentes que fragmentan ADN, tal como bleomicina, (iii) agentes que entrecruzan ADN, tales como clorambucilo, cisplatino, ciclofosfamida o mostaza de nitrógeno; (iv) agentes intercalantes tales como adriamicina (doxorubicina) o mitoxantrona; (v) inhibidores de síntesis protéica, tales como L-asparaginasa, cicloheximida, puromicina o toxina diftérica; (vi) venenos de la topoisomerasa I, tales como camptotecina o topotecano; (vii) venenos de la topoisomerasa II, tales como etopósido (VP-16) o tenipósido; (viii) agentes dirigidos a microtúbulos, tales como colcemida, colchicina, paclitaxel, vinblastina o vincristina; (ix) inhibidores de quinasas tales como flavopiridol, estaurosporina, STI571 (CPG 57148B) o UCN-01 (7-hidroxiestaurosporina); (x) agentes en investigación variados tales como tioplatino, PS-341, fenilbutirato, ET-18-OCH_3, o inhibidores de farnesil transferasa (L-739749, L-744832); polifenoles tales como quercetina, resveratrol, piceatanol, galato de epigalocatecina, teaflavinas, flavanoles, procianidinas, ácido betulínico y derivados de los mismos; (xi) hormonas tales como glucocorticoides o fenretinida; (xii) antagonistas de hormonas, tales como

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tamoxifeno, finasterida o antagonistas de LHRH. En una realización particular, los compuestos de la presente invención se coadministran con un compuesto citostático seleccionado del grupo formado por cisplatino, doxorubicina, taxol, taxotere y mitomicina C.

Otra clase de compuestos activos que se pueden usar en la presente invención son aquéllos que pueden sensibilizar para o inducir apoptosis por unión a los receptores de muerte ("agonistas de receptor de muerte"). Entre dichos agonistas de los receptores de muerte se incluyen ligandos de receptor de muerte tales como el factor de necrosis tumoral α (TNF-α), factor de necrosis tumoral β (TNF-β, linfotoxina-α), LT-β (linfotoxina-β), TRAIL (Apo2L, ligando DR4), ligando CD95 (Fas, APO-1), ligando TRAMP (DR3, Apo-3), ligando DR6 así como fragmentos y derivados de cualquiera de los mencionados ligandos. En una realización particular, el ligando de receptor de muerte es TNF-α. En otra realización particular el ligando de receptor de muerte es Apo2L/TRAIL. Aún más, los agonistas de receptores de muerte comprenden los anticuerpos agonistas de los receptores de muerte tales como el anticuerpo anti-CD95, anticuerpo anti-TRAIL-R1 (DR4), anticuerpo anti-TRAIL-R2 (DR5), anticuerpo anti-TRAIL-R3, anticuerpo anti-TRAIL-R4, anticuerpo anti-DR6, anticuerpo anti-TNF-R1 y anticuerpo anti-TRAMP (DR3) así como fragmentos y derivados de cualquiera de los mencionados anticuerpos.

Con el propósito de sensibilizar las células para apoptosis, se pueden usar también los compuestos de la presente invención en combinación con terapia de radiación. La frase "terapia de radiación" se refiere al uso de radiación electromagnética o de partículas en el tratamiento de neoplasia. La

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terapia de radiación se basa en el principio que la administración de radiación en altas dosis a un área blanco producirá la muerte de las células en reproducción en el tejido tumoral y normal. El régimen de dosificación de radiación generalmente se define en términos de la dosis de radiación absorbida (rad), tiempo y fraccionamiento, y debe ser definido de modo cuidadoso por el oncólogo. La cantidad de radiación que un paciente recibe dependerá de varias consideraciones que incluyen la localización del tumor en relación a otros órganos del cuerpo, y con el grado en el cual el tumor se ha extendido. Los ejemplos de agentes radioterapéuticos se proveen en, pero no se limita a, terapia de radiación y son conocidos en la materia (Hellman, *Principles of Radiation Therapy, Cancer*, en *Principles I and Practice of Oncology*, 24875 (Devita y col., 4ta ed., vol 1, 1993). Entre los recientes adelantos en la terapia de radiación se incluyen la radiación conformal de haz externo en tres dimensiones, terapia de radiación de intensidad modulada (IMRT), radiocirugía estereotáxica y braquiterapia (terapia de radiación intersticial), con esta última se coloca la fuente de radiación directamente en el tumor como "semillas" implantadas. Estas modalidades más nuevas de tratamiento administran mayores dosis de radiación al tumor, que explican su aumentada eficacia cuando se compara con la terapia de radiación de haz externo estándar.

La radiación ionizante con radionucleidos emisores beta es considerada la más útil para las aplicaciones radioterapéuticas debido a la transferencia de energía lineal moderada (LET) de la partícula ionizante (electrón) y su rango intermedio (típicamente varios milímetros en el tejido). Los rayos gamma administran dosis a niveles más bajos por distancias más grandes. Las

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partículas alfa representan el otro extremo, éstas administran dosis de LET muy elevadas, pero tienen un rango extremadamente limitado y deben, por consiguiente, estar en contacto íntimo con las células del tejido a ser tratado. Además, los emisores alfa son generalmente metales pesados, lo cual limita la posible química y presenta riesgos excesivos de escape del radionucleido del área a ser tratada. De acuerdo al tumor a ser tratado, todos los tipos de emisores son concebibles dentro del alcance de la presente invención. Además, la presente invención abarca tipos de radiación no ionizante como por ejemplo radiación ultravioleta (UV), luz visible de alta energía, radiación microonda (terapia hipertérmica), radiación infrarroja (IR) y láseres. En una realización particular de la presente invención se aplica radiación UV.

Los compuestos de la invención inhiben la angiogénesis y por consiguiente son útiles en el tratamiento de enfermedades o condiciones mediadas por angiogénesis tal como los tumores, en particular los tumores sólidos como el de colon, pulmonar, pancreático, ovárico, de mama y glioma. Además, los compuestos de la invención son útiles para tratar la degeneración macular por ejemplo la degeneración macular húmeda relacionada con la edad. Los compuestos de la invención también son útiles para tratar las enfermedades inflamatorias/inmunes tales como la de Crohn, síndrome de colon irritable, el síndrome de Sjogren, asma, rechazo de trasplante de órgano, lupus eritematoso sistémico, artritis reumatoidea, artritis psoriásica, psoriasis y esclerosis múltiple. Los compuestos de la invención también son útiles como depilatorios.

La invención también incluye composiciones farmacéuticas o medicamentos que contienen los compuestos de la invención y un vehículo,

diluyente o excipiente terapéuticamente inerte, así como los métodos de uso de los compuestos de la invención para preparar tales composiciones y medicamentos. Típicamente, los compuestos de la invención que se usan en los métodos de la invención se formulan por mezclado a temperatura ambiente a pH adecuado, y con un grado de pureza deseado, con vehículos fisiológicamente aceptables, es decir, vehículos que no son tóxicos para los receptores a las dosis y concentraciones empleadas en la forma de administración galénica. El pH de la formulación depende principalmente del uso particular y la concentración del compuesto, pero puede ir entre aproximadamente 3 y aproximadamente 8. Una formulación particular es un buffer acetato a pH 5. Los compuestos para uso de la presente documentación pueden estar en una formulación estéril. El compuesto se puede guardar como una composición sólida, aunque las formulaciones liofilizadas o las soluciones acuosas son aceptables.

La composición de la invención se formulará, se dosificará, y se administrará de un modo consistente con las buenas prácticas médicas. Entre los factores para consideración en este contexto se incluyen el desorden tratado particular, el mamífero tratado particular, la condición clínica del paciente individual, la causa del desorden, el sitio de administración del agente, el método de administración, el programa de administración, y otros factores conocidos por el profesional médico. La "cantidad eficaz" del compuesto a ser administrada va a depender de tales consideraciones, y es la cantidad mínima necesaria para disminuir la vía de señalización de hedgehog o bien es la cantidad mínima necesaria para causar la reducción en el tamaño, volumen o masa de un tumor que es sensible a la señalización de hedgehog, o una

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reducción en el aumento de tamaño, volumen o masa de tal tumor en relación al aumento en ausencia de la administración del compuesto de la invención. De manera alternativa, "cantidad eficaz" de compuesto se refiere a la cantidad necesaria para reducir el número de células malignas o la velocidad de aumento del número de células malignas. De manera alternativa, "cantidad eficaz" es la cantidad del compuesto de la invención que se requiere para aumentar la sobrevida de pacientes enfermos con un tumor sensible a la vía anti-hedgehog. Dicha cantidad puede estar debajo de la cantidad que es tóxica para células normales, o el mamífero en conjunto. Con respecto a las indicaciones no malignas, "cantidad eficaz" se refiere a la cantidad de compuesto de la invención que se requiere para disminuir la severidad de la indicación particular o síntomas de la misma.

Generalmente, la cantidad inicial farmacéuticamente eficaz del compuesto de la invención administrada por vía parenteral por dosis estará en el rango entre aproximadamente 0,01 y aproximadamente 100 mg/kg, por ejemplo entre aproximadamente 0,1 y aproximadamente 20 mg/kg de peso corporal del paciente por día, por ejemplo entre aproximadamente 0,3 y aproximadamente 15 mg/kg/día. Las formas de dosificación de unidades oral, tal como pastillas y cápsulas, pueden contener entre aproximadamente 25 y aproximadamente 1000 mg del compuesto de la invención.

El compuesto de la invención se puede administrar por cualquier medio adecuado, que incluye oral, tópico, transdérmico, parenteral, hipodérmico, rectal, intraperitoneal, intrapulmonar, e intranasal, y, si se desea para tratamiento local, administración intralesión. Entre las infusiones parenterales se incluyen intramuscular, intravenosa, intraarterial, intraperitoneal, o la

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administración hipodérmica. Un ejemplo de una forma de dosificación oral adecuada es una pastilla que contiene aproximadamente 25mg, 50mg, 100mg, 250mg, o 500mg del compuesto de la invención compuesta con aproximadamente entre 90 y 30 mg de lactosa anhidra, aproximadamente 5-40 mg de croscarmelosa de sodio, aproximadamente entre 5 y 30 mg polivinilpirrolidona (PVP) K30, y aproximadamente entre 1 y 10 mg de estearato de magnesio. Los ingredientes en polvo primero se mezclan entre sí y luego se mezclan con una solución de PVP. La composición resultante se puede secar, granular, mezclar con estearato de magnesio y comprimirla en forma de pastilla con el uso de equipamiento convencional. Se puede preparar una formulación en aerosol por disolución del compuesto, por ejemplo entre 5 y 400 mg, de la invención en una solución buffer adecuada, por ejemplo un buffer fosfato, agregado de un tonificante, por ejemplo una sal tal como cloruro de sodio, si se desea. La solución típicamente se filtra, por ejemplo con el uso de un filtro de 0,2 micrones, para extraer impurezas y contaminantes. Entre las formulaciones tópicas se incluyen pomadas, cremas, lociones, polvos, soluciones, óvulos, rociadores, aerosoles y cápsulas. Se pueden formular pomadas y cremas con una base acuosa o aceitosa con el agregado de un espesante adecuado y/o agentes gelificantes y/o solventes. Dichas bases pueden incluir agua y/o un aceite tal como parafina líquida o un aceite vegetal tal como aceite de maní o aceite de castor o un solvente tal como un polietilenglicol. Entre los agentes espesantes que se pueden usar se incluyen parafina blanda, estearato de aluminio, alcohol cetoestearílico, polietilenglicoles, cera microcristalina y cera de abejas. Las lociones se pueden formular con una base acuosa o aceitosa y pueden contener uno o más de los agentes emulsificantes, agentes

estabilizantes, agentes dispersantes, agentes de suspensión o agentes espesantes. Se pueden formar polvos para aplicación externa con la ayuda de cualquier base de polvo adecuada por ejemplo talco, lactosa o almidón. Se pueden formular gotas con una base acuosa o no acuosa que también comprenda uno o más agentes de dispersión, agentes solubilizantes o agentes de suspensión.

EJEMPLOS

La invención se entenderá de modo más completo por referencia a los siguientes ejemplos. Ellos no se deben, sin embargo, interpretar como limitantes del alcance de la invención. Las abreviaciones utilizadas en la presente documentación son las siguientes:

BuOH: butanol;

DIPEA: diisopropiletilamina;

DMA: NN-dimetilacetamida;

DMAP: 4- dimetilaminopiridina;

DME: 1,2-dimetoxietano;

DMF: dimetilformamida;

EDC: 1-etil-3-(3-dimetilaminopropil)carbodiimida;

HATU: hexafluorofosfato de O-(7-Azobenzotriazol-1-il)-1,1,3,3-tetrametiluronio;

HPLC: cromatografía líquida de alta presión

MPLC: cromatografía líquida de media presión

NBS: N-Bromosuccinimida;

TEA: Trietilamina;

TASF: difluorotrimetilsilicato de tris(dimetilamino)sulfonio;

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THF: tetrahidrofurano;

EtOH: Etanol;

MeOH: Metanol;

µL: microlitro

Todos los reactivos se obtuvieron de modo comercial a menos que se indique de otro modo. Se realizaron las reacciones con el uso de material de vidrio secado en estufa bajo una atmósfera de nitrógeno. Los líquidos y soluciones sensibles al aire y humedad se transfirieron a través de una jeringa o cánula de acero inoxidable. Las soluciones orgánicas se concentraron bajo presión reducida (aproximadamente 15 mmHg) por evaporación rotatoria. A menos que se indique de otro modo, todos los solventes utilizados se obtuvieron de modo comercial. La purificación por cromatografía de los productos se llevó a cabo con el uso de un equipo *Isco CombiFlash Companion* y medio. Los tiempos de reacción se dan solo a modo de ilustración. El curso de las reacciones se siguió por cromatografía en capa fina (TLC) y cromatografía líquida acoplada a espectrometría de masa (LC-MS). La cromatografía en capa fina (TLC) se realizó en placas de sílica gel 60 F_{254} EM (250 µm). La visualización del cromatograma desarrollado se realizó por inhibición de fluorescencia. LC-MS se obtuvo con un equipo Shimadzu 10AD LC sobre una columna Phenomenex (50 x 4,6 mm, 5 µm) con operación a 3 mL/min. Se utilizó un detector Shimadzu SPD-10A con detección a 214 y 254 nm. Se realizó espectroscopia de masa cuadrupolar simple en un espectrómetro de masa Applied Biosystems. Los espectros de resonancia magnética nuclear (NMR) se adquirieron en un espectrómetro Varian Inova con operación a 400 MHz para ^1H y referenciado internamente a tetrametilsilano

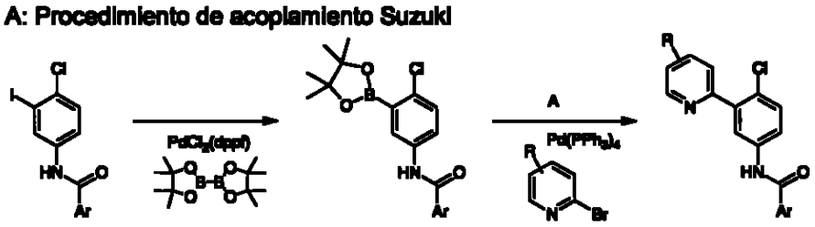
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(TMS) en partes por millón (ppm). Los datos para ^{1}H NMR se graban como sigue: desplazamiento químico (δ, ppm), multiplicidad (s, singlete; bs, singlete ancho; d, doblete; t, triplete; q, cuarteto; quint, quinteto; sext, sexteto; hept, septeto; m, multiplete; bm, multiplete ancho), e integración. La estructura y pureza de todos los productos finales se evaluó por al menos una de las siguientes técnicas: LC-MS, NMR, TLC.

Ejemplo 1 Procedimiento general

Compuestos de ejemplos 2-51 se prepararon de acuerdo con los siguientes procedimientos generales.

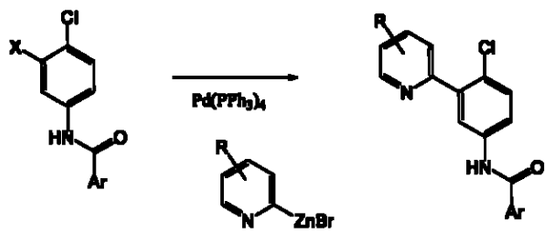
A: Procedimiento de acoplamiento Suzuki



Se agregaron carbonato de potasio acuoso 2 M (5,0 eq) y mezcla 4:1 de tolueno:etanol (2,5 mL) a un recipiente de microondas cargado con el éster boronato apropiado éster (2,6 eq), halogenuro de arilo (0,35 mmol, 1,0 eq), y $Pd(PPh_3)_4$ (0,04 eq). El recipiente se selló y se calentó con agitación en el microondas a 160 °C durante diez minutos. La solución se vertió en hidróxido de sodio acuoso 2 M (20 mL), se extrajo con acetato de etilo (2 x 20 mL), se secó ($MgSO_4$), y se concentró. La purificación del producto sin tratar por cromatografía en gel de sílice (condiciones dadas a continuación) dio el producto deseado.

B: Procedimiento de acoplamiento Negishi

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X = I o Br

R = H, 3-Me, 4-Me, 5-Me, 6-Me

Se agregó bromuro de aril-zinc (0,5 M en THF, 2,5 eq) a un recipiente de microondas calentado en horno cargado con el halogenuro de arilo apropiado (1,0 eq) y $Pd(PPh_3)_4$ (0,04 eq). El recipiente se selló y se calentó con agitación en el microondas a 140 °C durante 10 minutos. La mezcla de mezcla de reacción sin tratar se concentró y se purificó por cromatografía en gel de sílice (condiciones dadas a continuación) para dar el producto deseado.

C: Reducción con hierro del grupo nitro arilo

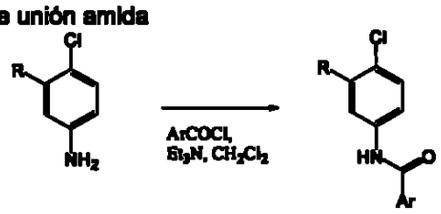


R = I o piridin-2-ilo

El nitro arilo apropiado (1 mmol, 1 eq) en AcOH/EtOH (1:1, 0,42 M) se agregó lentamente a una solución de polvo de hierro (6,0 eq) en AcOH/EtOH (1:2, 2 M) a 60 °C. La solución se agitó a 70 °C durante 30-60 minutos. La mezcla de reacción se enfrió a 23 °C, se filtró a través de celite, se lavó con acetato de etilo, y se concentró. El residuo oleoso se disolvió en acetato de etilo (30 mL), se lavó con $NaHCO_3$ acuoso saturado (2 x 15 mL) y agua (2 x 10 mL), se secó ($MgSO_4$), y se concentró. El residuo oleoso se usó sin purificación subsiguiente.

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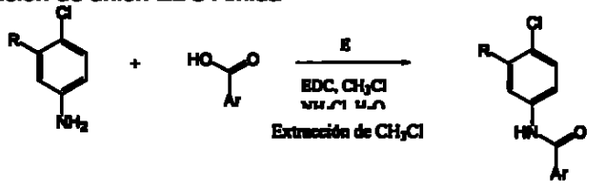
D: Formación de unión amida



R = I o piridin-2-ilo

Se agregó cloruro de ácido (1,05-1,1 eq) a una solución de abilina (1,0 eq) y TEA (1,1-1,5 eq) en cloruro de metileno a la temperatura indicada. La solución se agitó por 0,5-3 horas, se vertió en $NaHCO_3$ acuoso saturado, se extrajo dos veces con cloruro de metileno, se secó ($MgSO_4$), y se concentró. La purificación del producto sin tratar por cromatografía en gel de sílice (condiciones dadas a continuación) dio el producto deseado.

E: Formación de unión EDC Amida

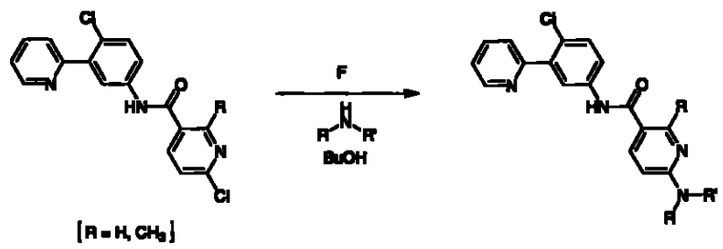


R = I o piridin-2-ilo

Se agregó ácido carboxílico (1,1 eq) a una solución de abilina (1,0 eq) y EDC (1,4 eq) en cloruro de metileno (0,7 M en anilina). La solución se agitó a 23 °C durante 2 horas, se vertió en una mezcla 1:1 de NH_4 acuoso saturado y agua, se extrajo dos veces con cloruro de metileno, se secó ($MgSO_4$), y se concentró. La purificación del producto sin tratar por cromatografía en gel de sílice (condiciones dadas a continuación) dio el producto deseado.

F: adición de aminas a 2-cloropiridina

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NHRR' = etanolamina, analina, bencilamina, 2-metilpropilamina, N-metilpiperazina, morfolina, 2-morfolinoetilamina

Se calentó amina primaria o secundaria (5 eq) en tanto BuOH como una mezcla de BuOH/etilenglicol a 170 a 220 °C durante 20 min en un tubo sellado. El BuOH se eliminó bajo presión reducida. En los casos donde se utilizó en etilenglicol, la reacción se diluyó con agua, y el producto se extrajo en acetato de etilo, se secó ($MgSO_4$), y se concentró. El residuo sin tratar se purificó por HPLC de fase inversa para dar el producto deseado.

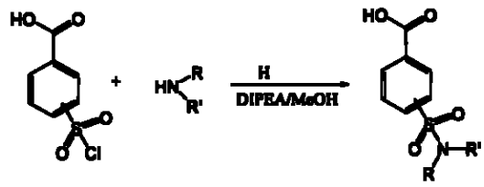
G: Acoplamiento de unión amida con HATU



Se agregó abilina (1,0 eq) a una mezcla de ácido carboxílico (1,1 eq), HATU (1,1 eq) y DIPEA (2 eq) en DMF (0,1 - 0,2 M). Luego de agitar durante la noche, la mezcla de reacción se diluyó con hidróxido de sodio 0,1 N o $NaHCO_3$ saturado, se extrajo en acetato de etilo y las capas orgánicas combinadas se lavaron con salmuera. La capa orgánica se secó ($MgSO_4$), se concentró y la mezcla cruda se purificó por HPLC de fase inversa.

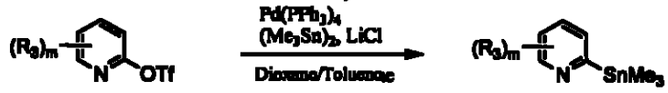
H: Preparación de ácidos sulfonamida benzoicos

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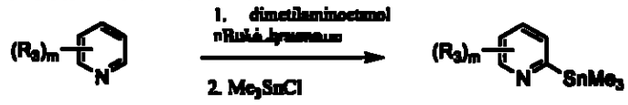
Se agregó ácido clorosulfonilbenzoico (1,0 eq) a una solución de amina (1,1 eq) en 10-20% DIPEA/metanol (1 M) a 4 °C. Luego de 1 h, la mezcla de reacción se concentró, y el residuo sin tratar se purificó por HPLC de fase inversa.

I : Estanilación de triflatos de 2-piridilo



Se agregó una solución de tetrakis-trifenilfosfinapaladio (0,04 eq.) en tolueno (1 mL) a una solución desgasificada de ariltriflato (1 eq), bis-trialquiltina (1,05 eq), y cloruro de litio (3 eq) en dioxano. Se calentó a reflujo por 2 horas, se enfrió a 23 °C, se diluyó con acetato de etilo, se lavó con $NH_4OH_{(aq)}$ 10% y salmuera, se secó ($MgSO_4$) y se concentró. El material sin tratar se usó sin purificación subsiguiente.

J: Estanilación de piridinas sustituidas



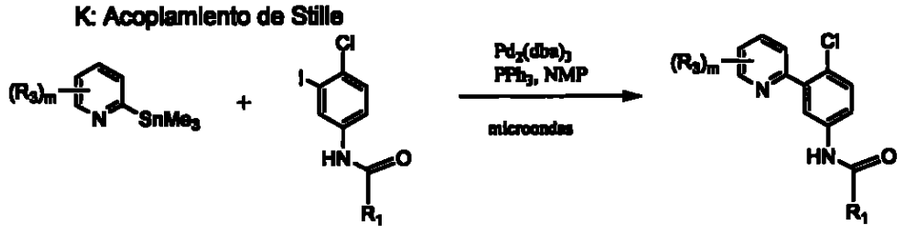
Se agregó n-Butillitio (6 eq, 2,5 M en hexanos) por goteo a una solución de dimetilaminoetanol (3 eq) en hexano a 0 °C. La solución se agitó a 0 °C durante treinta minutos antes de la adición por goteo de la piridina sustituida (1 eq). La solución se agitó a 0 °C durante otra hora, luego se enfrió a –78 °C. Se agregó una solución de trialquiltina en hexano por goteo. La solución se agitó a –78 °C durante treinta minutos, se calentó a 0 °C, se fraguó con agua, se

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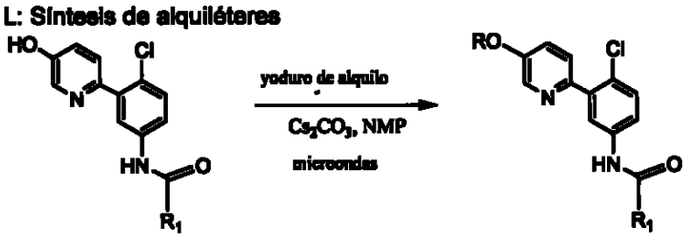
extrajo dos veces con éter, se secó ($MgSO_4$), y se concentró.

K: Acoplamiento de Stille



Se agregó catalizador paladio (0,02 eq) a una solución desgasificada de arilyoduro (1 eq), arilestanano (2 eq), y trifenilfosfina (0,16 eq) en NMP. Se calentó en el microondas a 130 °C durante 15 minutos. La mezcla de reacción se diluyó con etilacetato, se lavó con $NH_4OH_{(aq)}$ 10% y salmuera, se secó ($MgSO_4$), se concentró y se purificó mediante cromatografía en gel de sílice.

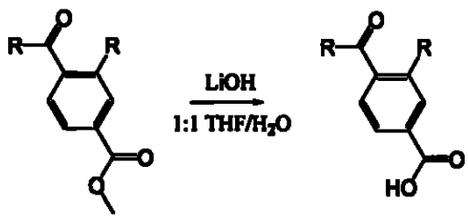
L: Síntesis de alquiléteres



Una solución de hidroxipiridina (1 eq), alquilyoduro (exceso), y carbonato de cesio en NMP se calentó en el microondas a 100 °C durante diez minutos. La mezcla de reacción se diluyó con etilacetato, se lavó con $NH_4OH_{(aq)}$ 10% y salmuera, se secó ($MgSO_4$), se concentró y se purificó mediante cromatografía en gel de sílice.

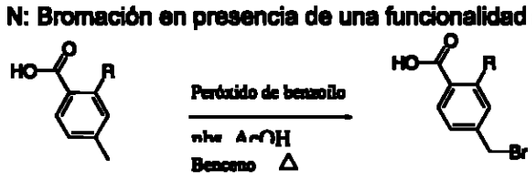
M: Saponificación de metiléster

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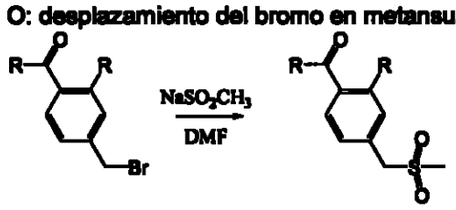
El metiléster (1eq) se hidrolizó con LIOH (2eq) en una mezcla 50/50 de THF/agua. Al completarse la reacción el THF se evaporó bajo presión reducida y la solución se acidificó con HCl a pH 2. El sólido resultante se filtró y se secó para dar el ácido puro.

N: Bromación en presencia de una funcionalidad ácida libre



El ácido parametilbenzoico (1eq) se combinó con peróxido de benzoilo (0,1eq) y N-Bromosuccinimida (0,9eq) en una solución de 5%AcOH en Benceno y se calentó en el microondas a 120°C durante 5-15minutos. El producto se separó del material inicial y del producto di-bromado mediante cromatografía rápida ISCO con un sistema de solventes de acetato de etilo (con 1% de AcOH) y hexanos.

O: desplazamiento del bromo en metansulfinato de sodio

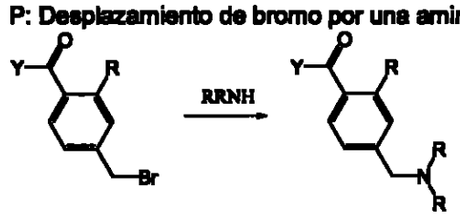


Se agregó metansulfinato de sodio (2eq) en DMF al material inicial bromo (1eq) y se calentó a 120°C en el microondas por 5 minutos. En forma

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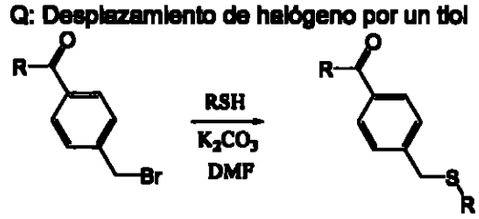
alternativa, la reacción se calentó a 60°C en un baño de aceite por varias horas hasta completarse. La mezcla de reacción se concentró bajo presión reducida y se extrajo en acetato de etilo y agua. La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró al vacío para dar metilsulfona genérica.

P: Desplazamiento de bromo por una amina



Se agregó la amina apropiada (3eq) en tanto DMSO como BuOH al material inicial bromo (1eq) y se agitó a temperatura ambiente hasta completarse. Para menos aminas o anilinas nucleofílicas, las reacciones fueron forzadas a completarse usando condiciones de microondas con un rango de 150°-170°C durante 15 minutos. Las reacciones crudas se concentraron a sequedad y se extrajo con acetato de etilo y bicarbonato saturado si la reacción resultó en un intermediario o se purificó mediante HPLC si la reacción resultó en un producto final.

Q: Desplazamiento de halógeno por un tiol

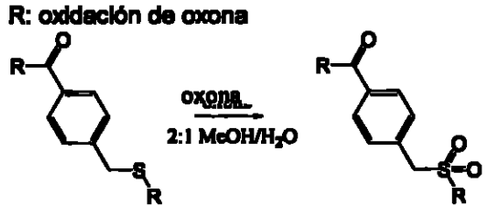


El benzoato de parametilbromo (1eq) se trató con carbonato de potasio (o cesio) (1,5eq) y el derivado tiol apropiado (1,1eq) en DMF (o CH_3CN) y se agitó durante la noche a temperatura ambiente. El DMF se evaporó al vacío y la reacción se extrajo con acetato de etilo y agua. La capa orgánica se secó

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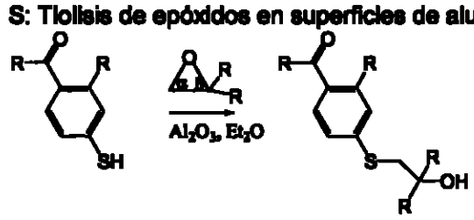
sobre sulfato de magnesio, se filtró y se concentró para dar el compuesto tiol o tiol derivatizado.

R: oxidación de oxona



Se disolvió tiol derivatizado (1eq) en MeOH mientras Oxona (2eq) se disolvió en forma separada en la mitad de cantidad de agua. Al disolverse toda la Oxona, la solución se agregó al tiol en solución de MeOH de una vez y se agitó hasta completarse. El MeOH se evaporó al vacío y el agua se extrajo dos veces con acetato de etilo. La capa orgánica se secó sobre sulfato de magnesio y se concentró para dar la sulfona.

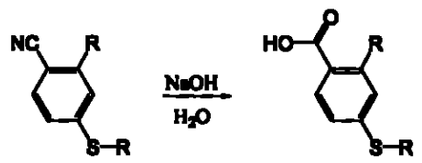
S: Tiolisis de epóxidos en superficies de alumina



Una mezcla de epóxidos (1,0 eq), tiofenol (1,5 eq) y óxido de aluminio neutral (~70 eq) en dietiléter se agitó por 3 h a temperatura ambiente mientras se monitoreaba con TLC. La mezcla de reacción se filtró a través de Celite, se lavó con acetato de etilo y se concentró. Se purificó mediante cromatografía en gel de sílice (0-40% acetato de etilo/hexano) para dar producto β - hidroxisulfuro.

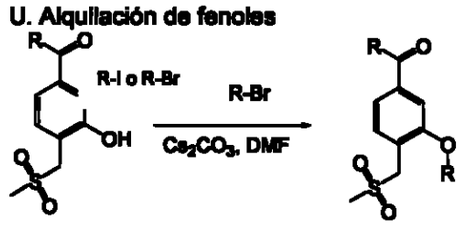
T: Conversión de grupo nitrilo a ácido carboxílico

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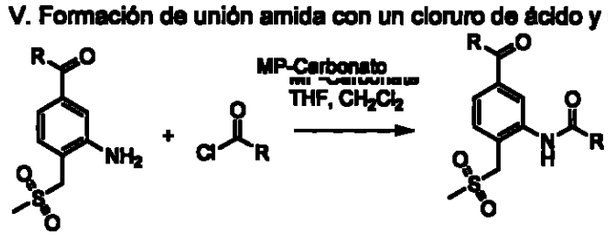
Una solución de benzonitrilo (1,0 eq) e hidróxido de sodio (2,0 eq) en H_2O se calentó a 120°C durante 2h. La mezcla de reacción se enfrió a temperatura ambiente y se acidificó con HCl a pH 2. El sólido resultante se filtró para dar el producto ácido puro.

U. Alquilación de fenoles



El fenol se disolvió en DMF (1,0 ml). Se agregaron carbonato de cesio (1,0 eq.) y un bromuro de alquilo o yoduro de alquilo (1,0 a 2,0 eq.), y la reacción se agitó a temperatura ambiente durante 18 hrs o 50°C durante 1 a 24 horas. La reacción se detuvo en agua, y se extrajo con acetato de etilo dos veces. Los extractos orgánicos se lavaron con agua una vez, salmuera una vez, se secó con $MgSO_4$, y se evaporó para dar un aceite sin tratar el cual se purificó en HPLC de fase inversa.

V. Formación de unión amida con un cloruro de ácido y una anilina

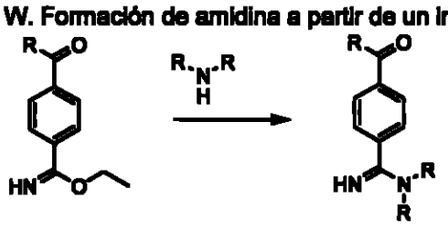


La abilina se disolvió en THF (1,5 ml) y diclorometano (1,5 ml). Se

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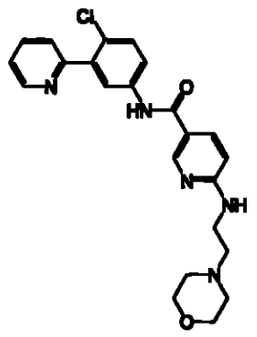
agregaron MP-Carbonato (1,5 eq.) y un cloruro de ácido (1,1 eq.), y la solución se agitó a temperatura ambiente durante 18 horas. La reacción se diluyó con metanol y diclorometano, y se filtró para eliminar el MP-Carbonato. Los licores madre se evaporaron para dar un sólido y se purificó por HPLC de fase inversa.

W. Formación de amidina a partir de un imidato



Se trató una solución de imidato en metanol recién formada con una amina primaria o secundaria (1,5 eq.) a temperatura ambiente durante 18 horas. El metanol se eliminó en un evaporador rotatorio y el residuo se purificó por HPLC de fase inversa.

Ejemplo 2 6-(2-morfolinoetilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil)piridin-3-carboxamida

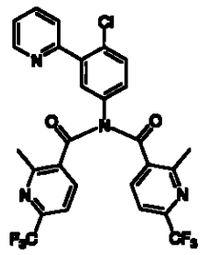


El procedimiento F se realizó usando *N*-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (50 mg) y 2-morfolinoetilamina en butanol (0,5 mL). La mezcla de reacción sin tratar se purificó por HPLC de fase inversa para dar 6-(2-morfolinoetilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil)piridin-3-carboxamida como

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un sólido blanco. MS (Q1) 438,3 $(M)^+$.

Ejemplo 3 *N,N*-(4-Cloro-3-(piridin-2-il)fenil)-bis[6-(trifluorometil)-2-metilpiridin-3]-carboxamida

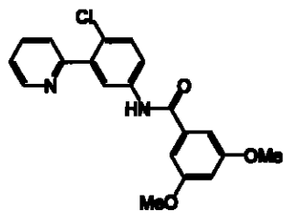


El procedimiento B se realizó con bromuro de 2-piridilzinc (4 mL, 2,0 mmol, 0,5 M en THF) y 3-bromo-4-cloro-nitrobenceno (236 mg, 1,0 mmol). Se purificó por cromatografía en gel de sílice (10% acetato de etilo/hexanos) para dar 2-(2-cloro-5-nitrofenil)piridina como un sólido amarillo claro.

El procedimiento C se realizó con 2-(2-cloro-5-nitrofenil)piridina (122 mg, 0,52 mmol) para dar 4-cloro-3-(piridin-2-il)abilina como un sólido amarillo claro, el cual se usó sin purificación subsiguiente.

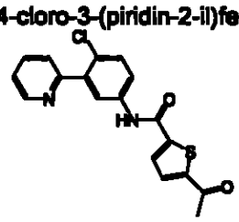
El procedimiento D se realizó usando 4-cloro-3-(piridin-2-il)abilina (40 mg, 0,2 mmol). El residuo sin tratar se purificó por cromatografía en gel de sílice (15-60% acetato de etilo/hexanos) para dar *N,N*-(4-Cloro-3-(piridin-2-il)fenil)-bis[6-(trifluorometil)-2-metilpiridin-3]-carboxamida como un residuo oleoso: TLC R_f = 0,42 (35% acetato de etilo/hexanos); ^1H NMR ($CDCl_3$, 400 MHz) δ 8,72 (m, 1H), 7,84 (d, 2H0, 7,77 (dd, 1H), 7,68 (m, 1H), 7,57 (d, 1H), 7,51 (m, 3H), 7,33 (m, 1H), 7,12 (dd, 1H), 2,78 (s, 6H); MS (Q1) 579 $(M)^+$.

Ejemplo 4 *N*-(4-Cloro-3-(piridin-3-il)fenil)-3,5-dimetoxibenzamida



Se usó 4-Cloro-3-(piridin-2-il)abilina (40 mg, 0,2 mmol) en el Procedimiento D con cloruro de 3,5-dimetoxibenzoilo (43 mg, 0,216 mmol) a 23 °C durante 2 horas. El residuo sin tratar se purificó por cristalización (CH_2Cl_2/hexanos) para dar *N*-(4-cloro-3-(piridin-3-il)fenil)-3,5-dimetoxibenzamida como un sólido blancuzco: TLC R_f = 0,30 (15% acetato de etilo/hexanos); ^1H NMR ($CDCl_3$, 400 MHz) δ 8,72 (m, 1H), 7,91 (m, 1H), 7,88 (dd, 1H), 7,78 (m, 2H), 7,74 (dd, 1H), 748 (d, 1H), 7,35 (m, 1H), 6,96 (d, 2H), 6,62 (t, 1H), 3,82 (s, 6H); MS (Q1) 369 $(M)^+$.

Ejemplo 5 5-Acetil-*N*-(4-cloro-3-(piridin-2-il)fenil)tiofeno-2-carboxamida

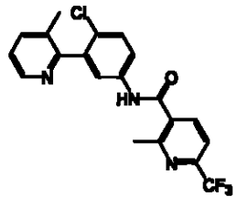


Se usó 4-Cloro-3-iodoabilina (2,5 g, 9,88 mmol) en el Procedimiento E con ácido 5-acetiltiofeno-2-carboxílico (1,85 g, 10,8 mmol) a 23 °C durante 2 horas. El material sin tratar se purificó por cromatografía en gel de sílice (20-100% acetato de etilo/hexanos) para dar 5-Acetil-*N*-(4-cloro-3-iodofenil)tiofeno-2-carboxamida como un sólido de color amarillo.

Se usó 5-Acetil-*N*-(4-cloro-3-iodofenil)tiofeno-2-carboxamida (202 mg, 0,5 mmol) en el Procedimiento B con 2-piridilzincbromuro (2,5 mL, 1,25 mmol, 0,5 M en THF). Se purificó mediante cromatografía en gel de sílice (10-100%

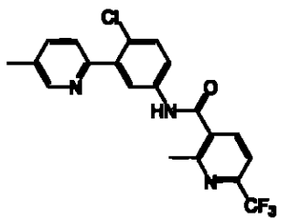
acetato de etilo/hexanos) para dar 5-acetil-*N*-(4-cloro-3-(piridin-2-il)fenil)tiofeno-2-carboxamida como un sólido amarillo: TLC R_f = 0,19 (50% acetato de etilo/hexanos); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8,96 (bs, 1H), 8,67 (d, 1H), 7,79 (dt, 1H), 7,68 (m, 3H), 7,61 (d, 1H), 7,58 (d, 1H), 7,37 (d, 1H), 7,32 (m, 1H), 2,58 (s, 3H); MS (Q1) 357,0 $(M)^+$.

Ejemplo 6 *N*-(4-Cloro-3-(3-metilpiridin-2-il)fenil)-6-(trifluorometil)-2-metilpiridin-3-carboxamida



Se usó *N*-(4-Cloro-3-iodofenil)-6-(trifluorometil)-2-metilpiridin-3-carboxamida (142 mg, 0,32 mmol) en el Procedimiento B con bromuro de 6-metil-2-piridilzinc (1,75 mL, de a 0,5 M en THF). Se purificó mediante cromatografía en gel de sílice (5-100% Acetato de etilo/Hexanos) para dar *N*-(4-cloro-3-(3-metilpiridin-2-il)fenil)-6-(trifluorometil)-2-metilpiridin-3-carboxamida como un sólido blanco: TLC R_f = 0,23 (30% acetato de etilo/hexanos); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8,81 (bs, 1H), 7,95 (dd, 1H), 7,67 (m, 3H), 7,53 (t, 2H), 7,38 (d, 1H), 7,07 (d, 1H), 2,71 (s, 3H), 2,43 (s, 3H); MS (Q1) 406,1 $(M)^+$.

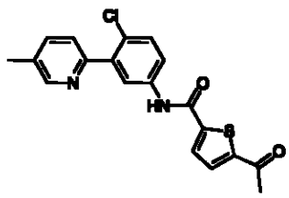
Ejemplo 7 *N*-(4-Cloro-3-(5-metilpiridin-2-il)fenil)-6-(trifluorometil)-2-metilpiridin-3-carboxamida



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Se usó *N*-(4-Cloro-3-iodofenil)-6-(trifluorometil)-2-metilpiridin-3-carboxamida (150 mg, 0,34 mmol) en el Procedimiento B con bromuro de 4-metil-2-piridilzinc (1,7 mL de una solución 0,5 M en THF). Se purificó mediante cromatografía en gel de sílice (5-75% Acetato de etilo/Hexanos) para dar *N*-(4-cloro-3-(5-metilpiridin-2-il)fenil)-6-(trifluorometil)-2-metilpiridin-3-carboxamida como un sólido blanco: TLC R_f = 0,23 (35% acetato de etilo/hexanos); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10,62 (bs, 1H), 8,12 (dd, 1H), 7,89 (d, 1H), 7,58 (d, 1H), 7,47 (m, 3H), 7,18 (d, 1H), 6,89 (d, 1H), 2,62 (s, 3H), 2,38 (s, 3H); MS (Q1) 406,3 $(M)^+$.

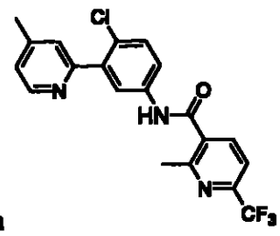
Ejemplo 8 5-Acetil-*N*-(4-cloro-3-(5-metilpiridin-2-il)fenil)tiofeno-2-carboxamida



Se usó 5-Acetil-*N*-(4-cloro-3-iodofenil)tiofeno-2-carboxamida (203 mg, 0,5 mmol) en el Procedimiento B con bromuro de 4-metil-2-piridilzinc (2,5 mL, 1,25 mmol, 0,5 M en THF). Se purificó mediante cromatografía en gel de sílice (30-100% acetato de etilo/hexanos) para dar 5-acetil-*N*-(4-cloro-3-(5-metilpiridin-2-il)fenil)tiofeno-2-carboxamida como un sólido de color amarillo: TLC R_f = 0,25 (50% acetato de etilo/hexanos); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9,52 (bs, 1H), 8,51 (d, 1H), 7,80 (m, 4H), 7,39 (s, 1H), 7,29 (d, 1H), 7,14 (d, 1H), 2,55 (s, 3H), 2,42 (s, 3H); MS (Q1) 371 $(M)^+$.

Ejemplo 9 *N*-(4-Cloro-3-(4-metilpiridin-2-il)fenil)-6-(trifluorometil)-2-

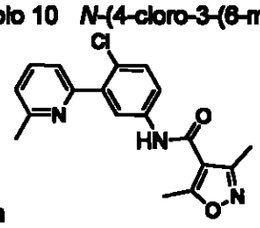
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metilpiridin-3-carboxamida

El procedimiento B se realizó con *N*-(4-Cloro-3-iodofenil)-6-(trifluorometil)-2-metilpiridin-3-carboxamida (440 mg, 1,0 mmol) y bromuro de 4-metil-2-piridilzinc (5 mL de una solución 0,5 M en THF). El residuo sin tratar se purificó cromatografía en gel de sílice (5-100% Acetato de etilo/Hexanos) para dar *N*-(4-cloro-3-(4-metilpiridin-2-il)fenil)-6-(trifluorometil)-2-metilpiridin-3-carboxamida como un sólido blanco: TLC R_f = 0,43 (35% acetato de etilo/hexanos); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10,39 (bs, 1H), 8,11 (dd, 1H), 7,87 (s, 1H), 7,61 (d, 1H), 7,59 (d, 1H), 7,49 (m, 3H), 2,66 (s, 3H), 2,21 (s, 3H); MS (Q1) 406,1 $(M)^+$.

Ejemplo 10 *N*-(4-cloro-3-(6-metilpiridin-2-il)fenil)-3,5-dimetilisoxazole-4-



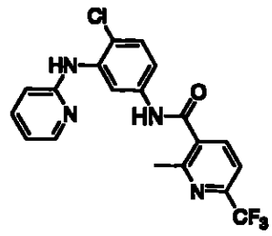
carboxamida

Se usó 4-Cloro-3-iodoanilina (1,01 g, 4 mmol) en el Procedimiento E con ácido 3,5-dimetil-4-isoxazolcarboxílico (0,565 g, 4 mmol), EDC (1,32 g, 6,8 mmol), TEA (0,5 mL), DMAP (50 mg, 0,4 mmol) a 23 °C durante la noche. La mezcla de reacción sin tratar se purificó por cromatografía en gel de sílice (0-15% acetato de etilo/CH_2Cl_2) para dar 3,5-dimetil-*N*-(4-cloro-3-iodofenil)isoxazole-4-carboxamida como un sólido blanco.

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El procedimiento B se realizó con 3,5-dimetil-*N*-(4-cloro-3-iodofenil)isoxazol-4-carboxamida (190 mg, 0,5 mmol) y bromuro de 3-metil-2-piridilzinc (2,5 mL de una solución 0,5 M en THF). La mezcla de reacción sin tratar se purificó por cromatografía en gel de sílice (5-100% Acetato de etilo/Hexanos) para dar *N*-(4-cloro-3-(6-metilpiridin-2-il)fenil)-3,5-dimetilisoxazol-4-carboxamida como un sólido blanco: TLC R_f = 0,43 (50% acetato de etilo/hexanos); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8,52 (bs, 1H), 7,68 (m, 2H), 7,48 (m, 3H), 2,70 (s, 3H), 2,49 (s, 3H), 2,21 (s, 3H); MS (Q1) 342,3 $(M)^+$.

Ejemplo 11 *N*-(4-cloro-3-(piridin-2-ilamino)fenil)-6-(trifluorometil)-2-metilpiridin-3-carboxamida

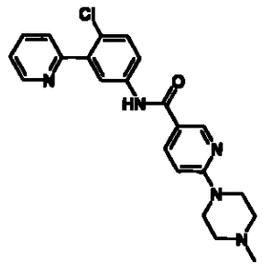


Se calentaron *N*-(4-Cloro-3-iodofenil)-6-(trifluorometil)-2-metilpiridin-3-carboxamida (220 mg, 0,5 mmol), 2-aminopiridina (40 mg, 0,42 mmol), *t*-butóxido de potasio (66 mg, 0,59 mmol), $Pd_2(dba)_3$ (20 mg, 0,21 mmol), dppf (24 mg, 0,042 mmol) en tolueno (2,1 mL) a 100 °C por 1,5 días. La solución se enfrió a 23 °C, se diluyó con éter, se filtró a través de celite, se lavó con acetato de etilo, y se concentró. Se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-ilamino)fenil)-6-(trifluorometil)-2-metilpiridin-3-carboxamida como un sólido blanco: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11,53 (s, 1H), 9,68 (s, 1H), 8,05 (m, 2H), 7,85 (m, 2H), 7,55 (d, 1H), 7,26 (d, 1H), 7,13 (dd, 1H), 6,91 (t, 1H), 6,88 (d, 1H), 2,75 (s, 3H); MS (Q1) 407,0 $(M)^+$.

Ejemplo 12 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(4-metilpiperazin-1-il)piridin-

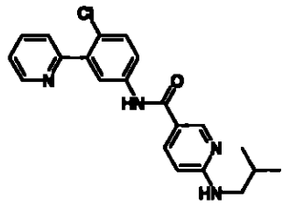
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3-carboxamida



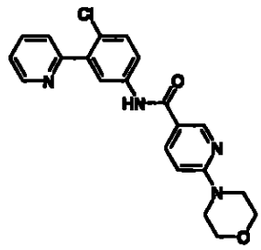
El procedimiento F se realizó usando *N*-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (50 mg) y *N*-metilpiperazina en butanol (0,5 mL). La mezcla de reacción sin tratar se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(4-metilpiperazin-1-il)piridin-3-carboxamida como un sólido blanco. MS (Q1) 408,4 $(M)^+$.

Ejemplo 13 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(isobutilamino)piridin-3-carboxamida



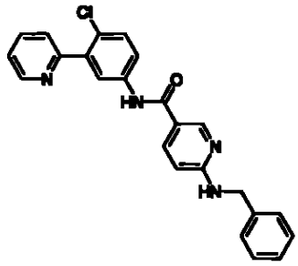
El procedimiento F se realizó usando *N*-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (50 mg) y 2-metilpropilamina en butanol (0,5 mL). La mezcla de reacción sin tratar se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(isobutilamino)piridin-3-carboxamida como un sólido blanco. MS (Q1) 381,1 $(M)^+$.

Ejemplo 14 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-morfolinopiridin-3-carboxamida



El procedimiento F se realizó usando *N*-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (50 mg) y morfolina en butanol (0,5 mL). La mezcla de reacción sin tratar se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-6-morfolinopiridin-3-carboxamida como un sólido blanco. MS (Q1) 401,3 $(M)^+$.

Ejemplo 15 6-(bencilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil)piridin-3-carboxamida

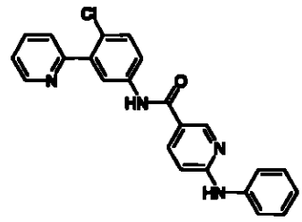


El procedimiento F se realizó usando *N*-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (50 mg) y bencilamina en butanol (0,5 mL). La mezcla de reacción sin tratar se purificó por HPLC de fase inversa para dar 6-(bencilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil)piridin-3-carboxamida como un sólido blanco. MS (Q1) 415,1 $(M)^+$.

Ejemplo 16 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(fenilamino)piridin-3-carboxamida

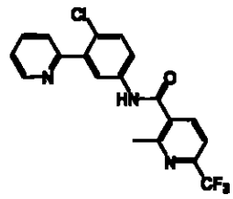
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El procedimiento F se realizó usando *N*-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (50 mg) y anilina en butanol (0,5 mL). La mezcla de reacción sin tratar se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(fenilamino)piridin-3-carboxamida como un sólido blanco. MS (Q1) 401,0 $(M)^+$.

Ejemplo 17 *N*-(4-Cloro-3-(piridin-2-il)fenil)-6-(trifluorometil)-2-metilpiridin-3-carboxamida



El procedimiento C se realizó con 1-cloro-2-iodo-4-nitrobenceno (283 mg, 1 mmol) para producir 4-cloro-3-iodoanilina el cual se usó sin purificación subsiguiente.

El procedimiento D se realizó con 4-cloro-3-iodoanilina (225 mg, 0,889 mmol) y cloruro de 6-(trifluorometil)-2-metilpiridin-3-carbonilo (237 mg, 0/93 mmol, 1,05 eq) a 0 °C durante 30 minutos. El residuo sin tratar se purificó por cromatografía en gel de sílice (2-50% acetato de etilo/hexanos) para dar *N*-(4-cloro-3-iodofenil)-6-(trifluorometil)-2-metilpiridin-3-carboxamida como un sólido blanco.

El procedimiento B se realizó usando *N*-(4-Cloro-3-iodofenil)-6-

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(trifluorometil)-2-metilpiridin-3-carboxamida (88 mg, 0,2 mmol) con bromuro de 2-piridilzinc (1 mL, 0,5 mmol, 0,5 M en THF). Se purificó mediante cromatografía en gel de sílice (10-80% acetato de etilo/hexanos) para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(trifluorometil)-2-metilpiridin-3-carboxamida como un sólido de color amarillo: TLC R_f = 0,28 (35% acetato de etilo/hexanos); TLC R_f = 0,28 (35% acetato de etilo/hexanos); ^{1}H NMR ($CDCl_3$, 400 MHz) 8,88 (bs, 1H), 8,41 (d, 1H), 7,96 (dd, 1H), 7,74 (m, 4H), 7,52 (d, 1H), 7,22 (m, 1H), 2,75 (s, 3H); MS (Q1) 392 $(M)^+$.

Un procedimiento sintético alternativo es de la siguiente manera. Se agregó 75g (435 mmol) de 2-cloro-5-nitroanilina a una solución de agua (600 mL) y ácido sulfúrico concentrado(60 mL) en un recipiente de 3 cuellos de 3L equipado para agitación mecánica. La solución se enfrió a 0 °C y una solución de nitrito de sodio (34,2 g, 496 mmol) en agua (130 mL) se agregó lentamente. La mezcla se agitó por ½ hr. y luego se agregó una solución de yoduro de potasio (130 g, 783 mmol) en agua (520 mL) por goteo durante ½ hr manteniendo la temperatura por debajo de 15°C. La solución se agitó por 2 hr, luego se extrajo con EtOAc (3 x 500 mL). Los extractos orgánicos combinados se lavaron con $Na_2S_2O_3$ saturado (2x 500 mL), se secó (Na_2SO_4), y se concentró. El yoduro sin tratar se disolvió en iPrOH caliente (500 mL) y se agregaron hexanos (200 mL). La reacción se dejó enfriar con agitación y el producto se recogió mediante filtración por succión luego de agitar a 0°C durante 2hr dando 90g (318 mmol, 73%) de 2-cloro-5-nitro-iodobenceno como un sólido cristalino color tostado claro.

El 2-cloro-5-nitro-yodobenceno (5g, 17,6 mmol) se disolvió en 5 mL DMA en un recipiente secado en un horno y se agregó una solución 0,5M de 2-

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piridilzincbromuro (53 mL, 26,5 mmol, 0,5 M en THF). La solución se desgasificó con N_2 por ½ hr., se agregaron el PPh_3 (0,185g, 0,7 mmol) y $Pd(PPh_3)_4$ (0,825g, 0,7 mmol), se enjuagó con varios mLs de THF y la solución se desgasificó por otros 10 min antes de calentar a 60°C bajo N_2. La reacción mostró estar completa por TLC en ~8h, se enfrió a temperatura ambiente, y se volcó en una mezcla 1:1 de EtOAc/2,5N NaOH (500 mL). Esta solución se agitó por 10 min, se pasó a través de un filtro de vidrio fritado grueso que contenía celite para eliminar el sólido, y luego se extrajo. Los orgánicos se lavaron con salmuera y se concentró para dar un sólido marrón. Las capas acuosas combinadas se re-extrajeron con Et_2O (1 x 200 mL). Esto se usó para suspender el producto crudo, el cual se extrajo con HCl 1N (1 x 200 mL, 3 x 100 mL). Los extractos acuosos combinados se enfriaron a 0°C, se diluyó con EtOAc (250 mL), y se basificó con NaOH 10N (100 mL). Esta solución se separó, la capa acuosa se extrajo con EtOAc, y los orgánicos combinados se secaron sobre Na_2SO_4 y carbón vegetal con agitación. Esta solución se filtró a través de celite y se concentró para dar 4-cloro-3-(piridin-2-il)nitrobenceno puro (2,47g, 10,5 mmol, rendimiento 60%) el cual se usó en la próxima reacción sin purificación subsiguiente.

Se suspendió 4-cloro-3-(piridin-2-il)nitrobenceno (1,47g, 6,26 mmol) en EtOH (35 mL), y se agregaron el $SnCl_2$ (3,87g; 20,4 mmol) y HCl concentrado (5 mL) y se enjuagó con otros 5 mLs de EtOH. La solución se colocó en un baño de aceite a 40°C y se calentó a 60°C. La solución se agitó a 60°C durante 1 ½ hr., se enfrió a temperatura ambiente y se diluyó con HCl 1 N (100 mL). Esta solución se vertió en una solución de Et_2O/ HCl 1 N (100 mL:150 mL) y se extrajo. La capa acuosa se diluyó con EtOAc (250 mL), se enfrió a 0°C, y se

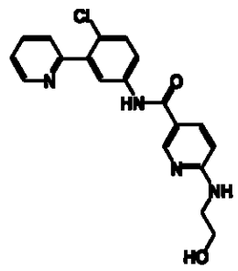
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basificó con NaOH 10 N (50 mL). Esta solución se extrajo (EtOAc, 2x), y los orgánicos combinados se lavaron con salmuera y se secó sobre Na_2SO_4 y carbón vegetal. La filtración por succión a través de celite dio una solución traslúcida incolora la cual se concentró para dar 4-cloro-3-(piridin-2-il)abilina (1,21g, 5,93 mmol, rendimiento 94%) como un sólido cristalino color crema el cual se usó en la próxima reacción sin purificación subsiguiente.

Se agregó cloruro de 6-(trifluorometil)-2-metilpiridin-3-carbonilo (1,68g, 7,51 mmol) en 3 mL THF por goteo a una solución de 4-cloro-3-(piridin-2-il)abilina (1,21g, 5,93 mmol) en THF (15 mL) a 0°C. La solución se agitó por 10 min., se vertió en EtOAc y se lavó con $NaHCO_3$ acuoso saturado (2x), y salmuera. Los orgánicos se secaron (Na_2SO_4) y se concentró. El producto sin tratar se suspendió en iPrOAc/Et_2O (10 mL, 1:1), se agitó a 0°C durante ½ hr, y se recogió mediante filtración por succión para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(trifluorometil)-2-metilpiridin-3-carboxamida (2,04g, 5,21 mmol, rendimiento 88%) como un sólido blanco: TLC R_f = 0,28 (35% EtOAc/Hex); ^1H NMR ($CDCl_3$, 400 MHz) δ 8,88 (bs, 1H), 8,41 (d, 1H), 7,96 (dd, 1H), 7,74 (m, 4H), 7,52 (d, 1H), 7,22 (m, 1H), 2,75 (s, 3H); MS (Q1) 392 $(M)^+$.

Ejemplo 18 6-(2-hidroxietilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil)piridin-3-carboxamida

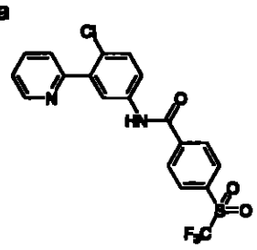


El procedimiento F se realizó usando *N*-(4-cloro-3-(piridin-2-il)fenil)-6-

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cloro-3-carboxamida (50 mg) y etanolamina en butanol (0,5 mL). La mezcla de reacción sin tratar se purificó por HPLC de fase inversa para dar 6-(2-hidroxetilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil)piridin-3-carboxamida como un sólido blanco. MS (Q1) 369,0 $(M)^+$.

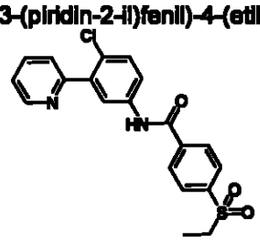
Ejemplo 19 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(trifluorometilsulfonil)benzamida



Se disolvió ácido 4-(trifluorometiltio)benzoico (200 mg, 0,9 mmol) en agua (2 mL) y ácido acético (4 mL) y se trató con permanganato de potasio (711 mg, 4,5 mmol) a temperatura ambiente. La reacción se dejó en agitación por 16 h, se diluyó con acetato de etilo y se lavó con agua. La capa orgánica se secó ($MgSO_4$) y se concentró para dar ácido 4-(trifluorometilsulfona)benzoico.

El Procedimiento general G se realizó usando ácido 4-(trifluorometilsulfona)benzoico y 4-cloro-3-(piridin-2-il)anilina. La mezcla de mezcla de reacción sin tratar se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(trifluorometilsulfonil)benzamida. MS (Q1) 440,95 $(M)^+$.

Ejemplo 20 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(etilsulfonil)benzamida



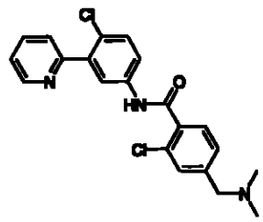
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El Procedimiento general G se realizó usando ácido 4-(etiltio)benzoico y 4-cloro-3-(piridin-2-il)abilina para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(etiltio)benzamida.

Se enfrió una solución de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(etiltio)benzamida (40 mg, 0,11 mmol) en MeOH (3 mL) a 0° C se trató con Oxona (133 mg, 0,22 mmol), y el baño de hielo se retiró. Luego de agitar por 1h, la mezcla de reacción se concentró, y el residuo se disolvió en acetato de etilo. La solución orgánica se lavó con agua, se secó ($MgSO_4$) y se concentró. La mezcla de mezcla de reacción sin tratar se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(etilsulfonil)benzamida. MS (Q1) 401,0 $(M)^+$.

Ejemplo 21 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-((dimetilamino)metil) benzamida



El Procedimiento general G se usó para acoplar ácido 4-(BOC-aminometil)-2-cloro-benzoico y 4-cloro-3-(piridin-2-il)abilina para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)-fenil)-4-(BOC-aminometil)benzamida con. La mezcla de mezcla de reacción sin tratar se trató con TFA y trazas de agua por 1 h antes de concentrar a sequedad para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)-fenil)-4-(aminometil)benzamida.

Comentario [C.U.1]: No es, está en el original

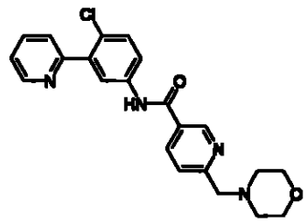
Se disolvió 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(aminometil)benzamida (60 mg, 0,20 mmol) en DMF (5 mL) y se trató con

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AcOH (10 uL), paraformaldehido (43 mg, 0,47 mmol), y triacetoxiborohidruro de sodio (125 mg, 0,59 mmol). Luego de agitar por 16 h, el solvente se evaporó y el residuo se disolvió en acetato de etilo. La capa orgánica se lavó con hidróxido de sodio 1 N, se secó ($MgSO_4$) y se concentró. El producto sin tratar se purificó por HPLC de fase inversa para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-((dimetilamino)metil) benzamida. MS (Q1) 400,0 $(M)^+$.

Ejemplo 22 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(morfolinometil)piridin-3-carboxamida



Se disolvió ácido 6-metilnicotínico (100 mg 0,14 mmol) en AcOH/benceno 10% (1 mL) y se trató con NBS (117 mg, 0,18 mmol) y benzoilperóxido (18 mg, 0,07 mmol). La mezcla de reacción se calentó en un reactor de microondas sellado a 120° C durante 1 min. La mezcla de reacción se diluyó con acetato de etilo, se lavó con $NaHCO_3$ acuoso saturado, se secó ($MgSO_4$), se concentró y se purificó mediante cromatografía en gel de sílice para dar ácido 6-(bromometil)piridin-3-carboxílico.

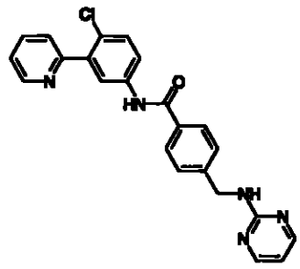
Se acopló ácido 6-(bromometil)piridin-3-carboxílico a 4-cloro-3-(piridin-2-il)abilina como se describe en procedimiento general E para dar 6-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)piridin-3-carboxamida.

Se disolvió 6-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)piridin-3-carboxamida en DMSO (1 mL) tratado con morfolina (33 uL) por 1 h. La reacción se concentró, y el residuo sin tratar se purificó por HPLC de fase

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inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(morfolinometil)piridin-3-carboxamida. MS (Q1) 409,3 $(M)^+$.

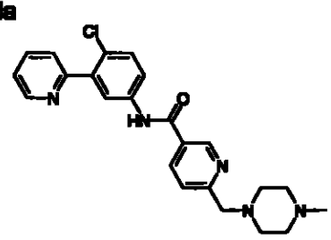
Ejemplo 23 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((pirimidin-2-ilamino)metil)benzamida



Se acopló ácido 4-(bromometil)benzoico a 4-cloro-3-(piridin-2-il)abilina como se describe en procedimiento general E para dar 4-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida.

Se disolvió 4-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida (85 mg) en DMSO (0,5 mL) y se trató con 2-aminopiridina (59 mg) a 150° C en un reactor de microondas sellado por 5 min. La mezcla de reacción se concentró, y el residuo sin tratar se purificó por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((pirimidin-2-ilamino)metil)benzamida pura. MS (Q1) 416,3 $(M)^+$.

Ejemplo 24 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-((4-metilpiperazin-1-il)metil)piridin-3-carboxamida

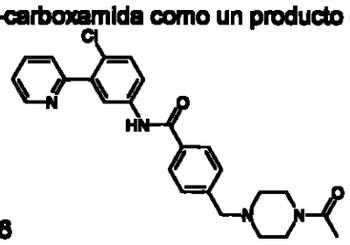


Se disolvió 6-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)piridin-3-

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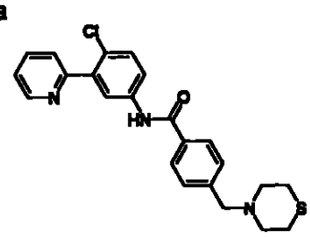
carboxamida en 1 mL de DMSO y se agitó por 1 h con *N*-metilpiperazina. La reacción se concentró, y el residuo sin tratar se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-6-((4-metilpiperazin-1-il)metil)piridin-3-carboxamida como un producto crudo. MS (Q1) 422,3 $(M)^+$.



G-025956

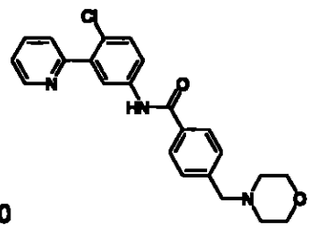
Se disolvió 6-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)piridin-3-carboxamida (85 mg) en DMSO (1 mL) y se agitó por 1 h con N-acetilpiperazina. La mezcla de reacción se concentró, y el residuo sin tratar se purificó por HPLC de fase inversa para dar 4-((4-acetilpiperazin-1-il)metil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida. MS (Q1) 449,1 $(M)^+$.

Ejemplo 26 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(tiomorfolinometil)benzamida



Se disolvió 4-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida (85 mg) en DMSO (1 mL) y se agitó por 1 h con tiomorfolina. La mezcla de reacción se concentró, y el residuo sin tratar se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(tiomorfolinometil)benzamida. MS (Q1) 424,0 $(M)^+$.

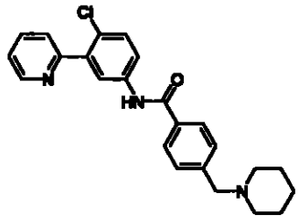
386
387



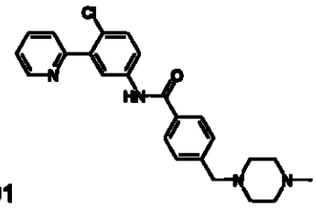
G-025790

Se disolvió 4-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida (85 mg) en DMSO (1 mL) y se agitó por 1 h con morfolina. La mezcla de reacción se concentró, y el residuo sin tratar se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(morfolinometil)benzamida. MS (Q1) 408,4 $(M)^+$.

Ejemplo 28 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((piperidin-1-il)metil)benzamida



Se disolvió 4-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida (85 mg) en DMSO (1 mL) y se agitó por 1 h con piperdina. La mezcla de reacción se concentró, y el residuo sin tratar se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((piperidin-1-il)metil)benzamida. MS (Q1) 408,4 $(M)^+$.



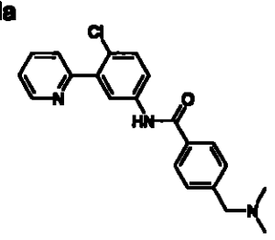
G-025791

387

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Se disolvió 4-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida (85 mg) en DMSO (1 mL) y se agitó por 1 h con metilpiperazina. La mezcla de reacción se concentró, y el residuo sin tratar se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((4-metilpiperazin-1-il)metil) benzamida. MS (Q1) 421,3 $(M)^+$.

Ejemplo 30 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((dimetilamino)metil)benzamida



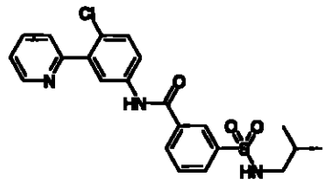
El procedimiento G se usó para acoplar ácido BOC-4-(aminometil)benzoico (48 mg) con 4-cloro-3-(piridin-2-il)abilina (35 mg). La mezcla de mezcla de reacción sin tratar se trató con TFA (1 mL) con rastros de agua por 1 h. La mezcla de reacción se concentró para dar 4-(aminometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida.

Se disolvió 4-(aminometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida (80 mg) en DMF (5 mL) y se trató con AcOH (10 µL), paraformaldehído (48 mg), y triacetoxiborhidruro de sodio (125 mg) por 16 h. La mezcla de reacción se concentró, y el residuo sin tratar se disolvió en acetato de etilo y se lavó con hidróxido de sodio 1 N, se secó ($MgSO_4$) y se concentró. El producto sin tratar se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((dimetilamino)metil)benzamida. MS (Q1) 365,0 $(M)^+$.

G-025909

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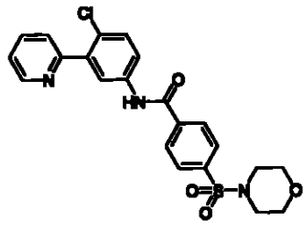
389



El procedimiento H se realizó para acoplar ácido 3-(clorosulfonil)benzoico con *sec*-butilamina para producir ácido 3-(sec-butilsulfamoil)benzoico el cual se purificó por HPLC de fase inversa.

El procedimiento G se usó para acoplar ácido 3-(sec-butilsulfamoil)benzoico con 4-cloro-3-(piridin-2-il)abilina (28 mg) para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-3-[(2-metilpropil)aminosulfonil]benzamida. MS (Q1) 444,0 $(M)^+$.

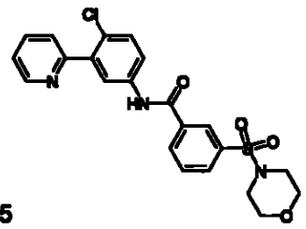
Ejemplo 32 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-morfolinilsulfonil)benzamida



El procedimiento H se realizó para acoplar ácido 4-(clorosulfonil)benzoico con morfolina para producir ácido 4-(morfolinosulfamoil)benzoico el cual se purificó por HPLC de fase inversa.

El procedimiento G se usó para acoplar ácido 4-(morfolinosulfamoil)benzoico con 4-cloro-3-(piridin-2-il)abilina (34 mg) para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-morfolinilsulfonil)benzamida. MS (Q1) 458,1 $(M)^+$.

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390

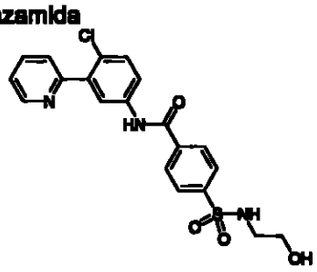


G-025905

El procedimiento H se realizó para acoplar ácido 3-(clorosulfonil)benzoico con morfolina para producir ácido 3-(morfolinosulfamoil)benzoico el cual se purificó por HPLC de fase inversa.

El procedimiento G se usó para acoplar ácido 3-(morfolinosulfamoil)benzoico con 4-cloro-3-(piridin-2-il)abilina (25 mg) para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-3-(4-morfolinilsulfonil)benzamida. MS (Q1) 458,1 $(M)^+$.

Ejemplo 34 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-[(2-hidroxietil)amino]sulfonil]benzamida

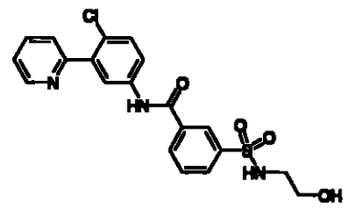


El procedimiento H se realizó para acoplar ácido 4-(clorosulfonil)benzoico con etanolamina para producir ácido 4-(2-hidroxietilsulfamoil)benzoico el cual se purificó por HPLC de fase inversa.

El procedimiento G se usó para acoplar ácido 4-(2-hidroxietilsulfamoil)benzoico con 4-cloro-3-(piridin-2-il)abilina (42 mg) para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-[(2-hidroxietil)amino]sulfonil]benzamida. MS (Q1) 431,9 $(M)^+$.

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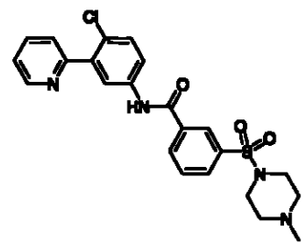
G-025907



El procedimiento H se realizó para acoplar ácido 3-(clorosulfonil)benzoico con etanolamina para producir ácido 3-(2-hidroxietilsulfamoil)benzoico el cual se purificó por HPLC de fase inversa.

El procedimiento G se usó para acoplar ácido 3-(2-hidroxietilsulfamoil)benzoico con 4-cloro-3-(piridin-2-il)abilina (42 mg) para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-3-[(2-hidroxietil)amino]sulfonil]benzamida. MS (Q1) 432,0 $(M)^+$.

Ejemplo 36 *N*-(4-cloro-3-(piridin-2-il)fenil)-3-(4-morfolinilsulfonil)benzamida

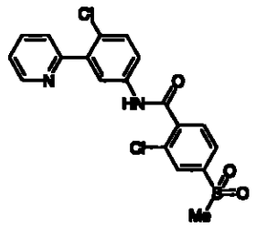


El procedimiento H se realizó para acoplar ácido 3-(clorosulfonil)benzoico con piperazina para producir ácido 3-(N-metilpiperazinosulfamoil)benzoico el cual se purificó por HPLC de fase inversa.

El procedimiento G se usó para acoplar ácido 3-(N-metilpiperazinosulfamoil)benzoico con 4-cloro-3-(piridin-2-il)abilina (50 mg) para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-3-(4-morfolinilsulfonil)benzamida. MS (Q1) 471,0 $(M)^+$.

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392

G-025897

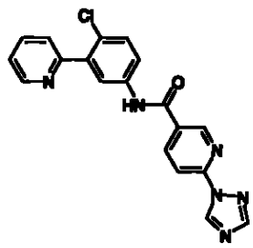


El procedimiento G se usó para acoplar 4-cloro-3-(piridin-2-il)abilina (50 mg) y ácido 2-cloro-4-metilsulfonilbenzoico para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonil)benzamida. MS (Q1) 421,0 $(M)^+$. El producto luego se disolvió en solución 1 N de HCl seguido por liberación de bases con solución 0,5 N de NaOH (pH a 11). El precipitado resultante se filtró y se secó al vacío.

El procedimiento D también se puede utilizar para acoplar 4-cloro-3-(piridin-2-il)abilina y cloruro de 2-cloro-4-(metilsulfonil)benzoilo para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonil)benzamida la cual se recoge por filtración por succión y la sal HCl se lava con Et_2O (o en forma alternativa con MTBE). Este material se libera de bases usando EtOAc/$NaHCO_3$ acuoso y los orgánicos se secan y se concentran para dar el sólido libre de bases. Este material luego se cristaliza a partir de acetona:EtOAc (80:20, aprox 10mL/g) el cual luego finalmente se recristaliza a partir de una lechada caliente de iPrOAc. También se puede disolver sal HCl de 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonil)benzamida en agua destilada seguida por liberación de bases con solución 0,5 N de NaOH (pH a 11) y filtrado y secado al vacío del precipitado.

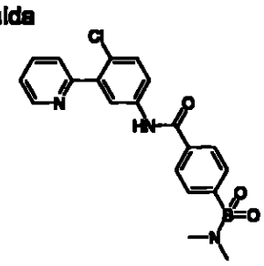
Ejemplo 38 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(1*H*-1,2,4-triazol-1-il)piridin-3-carboxamida

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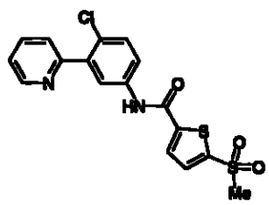
El procedimiento G se usó para acoplar 4-cloro-3-(piridin-2-il)abilina (40 mg) y ácido 6-(1*H*-1,2,4-triazol-1-il)piridin-3- carboxílico para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(1*H*-1,2,4-triazol-1-il)piridin-3-carboxamida. MS (Q1) 377,0 $(M)^+$.

Ejemplo 39 N-(4-cloro-3-(piridin-2-il)fenil)-4-[(dimetilamino)sulfonil]benzamida



El procedimiento G se usó para acoplar 4-cloro-3-(piridin-2-il)abilina (50 mg) y ácido 4-[(dimetilamino)sulfonil]benzoico para producir N-(4-cloro-3-(piridin-2-il)fenil)-4-[(dimetilamino)sulfonil]benzamida. MS (Q1) 416,0 $(M)^+$.

Ejemplo 40 *N*-(4-cloro-3-(piridin-2-il)fenil)-5-(metilsulfonil)tiofeno-2-carboxamida



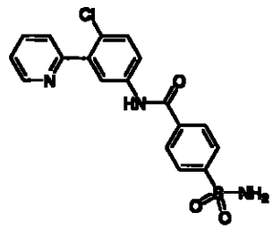
El procedimiento G se usó para acoplar 4-cloro-3-(piridin-2-il)abilina (40

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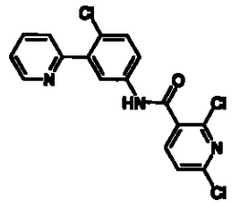
mg) y ácido 5-(metilsulfonil)tiofeno-2-carboxílico para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-5-(metilsulfonil)tiofeno-2-carboxamida. MS (Q1) 393,0 $(M)^+$.

G-025814



El procedimiento G se usó para acoplar 4-cloro-3-(piridin-2-il)abilina (30 mg) y 4-carboxibencenosulfonamida para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(aminosulfonil)benzamida. MS (Q1) 388,0 $(M)^+$.

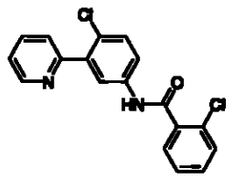
Ejemplo 42 2,6-dicloro-*N*-(4-cloro-3-(piridin-2-il)fenil)piridin-3-carboxamida



El procedimiento G se usó para acoplar 4-cloro-3-(piridin-2-il)abilina (50 mg) y ácido 2,6-dicloronicotínico para producir 2,6-dicloro-*N*-(4-cloro-3-(piridin-2-il)fenil)piridin-3-carboxamida. MS (Q1) 378,1 $(M)^+$.

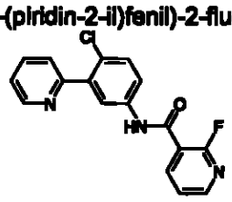
G-025721

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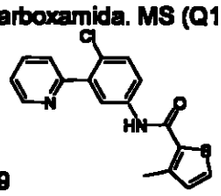


El procedimiento G se usó para acoplar 4-cloro-3-(piridin-2-il)abilina (50 mg) y ácido 2-clorobenzoico para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida. MS (Q1) 343,1 $(M)^+$.

Ejemplo 44 *N*-(4-cloro-3-(piridin-2-il)fenil)-2-fluoropiridin-3-carboxamida



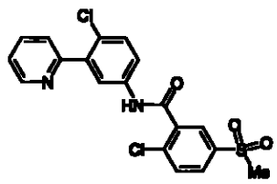
El procedimiento G se usó para acoplar 4-cloro-3-(piridin-2-il)abilina (50 mg) y ácido 2-fluoronicotínico para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-2-fluoropiridin-3-carboxamida. MS (Q1) 328,1 $(M)^+$.



G-025709

El procedimiento G se usó para acoplar 4-cloro-3-(piridin-2-il)abilina (50 mg) y ácido 3-metil-2-tiofencarboxílico para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-3-metiltiofeno-2-carboxamida. MS (Q1) 329,0 $(M)^+$.

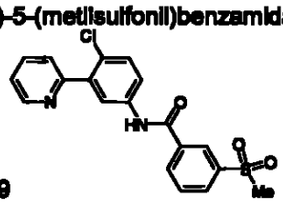
Ejemplo 46 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-5-(metilsulfonil)benzamida



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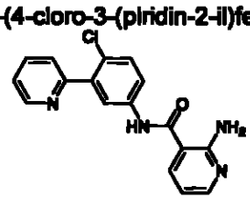
El procedimiento G se usó para acoplar 4-cloro-3-(piridin-2-il)abilina y ácido 2-cloro-5-(metanosulfonil)benzoico para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-5-(metilsulfonil)benzamida. MS (Q1) 420,95 $(M)^+$.



G-025639

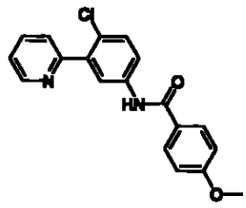
El procedimiento G se usó para acoplar 4-cloro-3-(piridin-2-il)abilina y ácido 3-(metanosulfonil)benzoico para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-3-(metilsulfonil)benzamida. MS (Q1) 387,2 $(M)^+$.

Ejemplo 48 2-amino-*N*-(4-cloro-3-(piridin-2-il)fenil)piridin-3-carboxamida



El procedimiento G se usó para acoplar 4-cloro-3-(piridin-2-il)abilina (50 mg) y ácido 2-aminonicotínico para producir 2-amino-*N*-(4-cloro-3-(piridin-2-il)fenil)piridin-3-carboxamida. MS (Q1) 325,2 $(M)^+$.

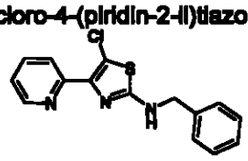
G-025733



El procedimiento G se usó para acoplar 4-cloro-3-(piridin-2-il)abilina y ácido 4-metoxilbenzoico para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-metoxibenzamida. MS (Q1) 341,2 $(M)^+$.

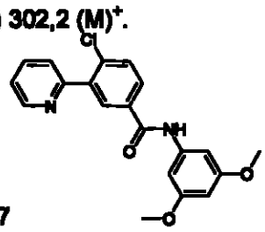
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Ejemplo 50 *N*-bencil-5-cloro-4-(piridin-2-il)tiazol-2-amina



Se trató una solución de hidrobromuro de 2-(Bromoacetil)piridina (100 mg, 0,36 mmol) en etanol (2 mL) con 1-bencil-2-tiourea (90 mg, 0,54 mmol). La solución amarilla resultante se concentró, y el residuo sin tratar se purificó en HPLC de fase inversa para producir *N*-bencil-4-(piridin-2-il)tiazol-2-amina.

Se enfrió una solución de *N*-bencil-4-(piridin-2-il)tiazol-2-amina (60 mg, 0,23 mmol) en DMF (2 mL) a 0 °C y se trató con *N*-clorosuccinimida (33 mg, 0,25 mmol), y la mezcla de reacción se dejó subir la temperatura hasta la temperatura ambiente. El solvente se evaporó, y el producto se purificó en HPLC de fase inversa para producir *N*-bencil-5-cloro-4-(piridin-2-il)tiazol-2-amina. MS (Q1) 302,2 $(M)^+$.



G-025257

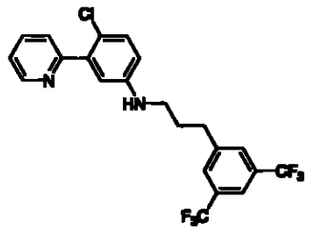
Se trató una solución de ácido 3-bromo-4-clorobenzoico (250 mg, 1,1 mmol) en DMF (2 mL) con PyBop (550 mg, 1,1 mmol) y DIPEA (370 uL, 2,1 mmol). Luego de agitar la mezcla de reacción por 5 min. Se agregó 3,5-dimetoxi analina (105 mg, 0,69 mmol) y la reacción se agitó por 16 h. La mezcla de reacción se diluyó con acetato de etilo y se lavó con 0,1 N HCl, hidróxido de sodio 0,1 N y Salmuera, sucesivamente. La capa orgánica se secó ($MgSO_4$) y se concentró, y sin tratar 3-bromo-4-cloro-*N*-(3,5-dimetoxifenil)benzamida se usó sin purificación subsiguiente.

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Se disolvió 3-bromo-4-cloro-*N*-(3,5-dimetoxifenil)benzamida en 2-piridilzincbromuro 0,5 M (2,5 mL) y se trató con $Pd(PPh_3)_4$ (20 mg, 0,02 mmol). La mezcla de reacción se calentó a 155° C en un tubo sellado por 20 min. en un reactor de microondas. La solución resultante se diluyó con acetato de etilo y se lavó con hidróxido de sodio 0,1 N y luego salmuera. La capa orgánica se secó ($MgSO_4$) y se concentró, y el residuo sin tratar se purificó parcialmente mediante cromatografía en gel de sílice. Se obtuvo 4-cloro-*N*-(3,5-dimetoxifenil)-3-(piridin-2-il)benzamida pura por una segunda purificación en HPLC de fase inversa. MS (Q1) 369,1 $(M)^+$.

Ejemplo 52 *N*-(3-(3,5-bis(trifluorometil)fenil)propil)-4-cloro-3-(piridin-2-il)bencenamina



Una solución de ácido 3,5-bis(trifluorometil)hidrocinámico (1,0 g, 3,5 mmol) y TEA (0,46 g, 4,5 mmol) en THF (16 mL) se enfrió a –40°C (etanol-agua/baño de hielo seco). A esta mezcla se agregó por goteo cloroformiato de isobutilo (0,56 g, 4,1 mmol) y la agitación se continuó por otras 1,5 horas mientras se mantenía la temperatura del baño de frío entre –40 °C y –20 °C. Se agregó $NaBH_4$ sólido (0,53 g, 14 mmol), seguido por H_2O (1,3 mL). La mezcla turbia se agitó durante la noche mientras se calentaba a temperatura ambiente. Luego de concentrar al vacío, el residuo se particionó entre acetato de etilo y agua. La capa acuosa se acidificó a pH 1 con 37% HCl y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron secuencialmente con

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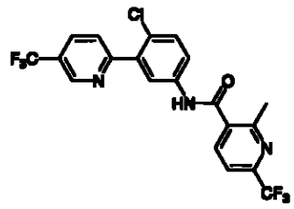
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$NaHCO_3$ saturado, y salmuera, luego se secó ($MgSO_4$) y se concentró. El aceite resultante se purificó por cromatografía rápida en gel de sílice (6:4 etiléter-hexano) para dar 3-[3',5'-bis(trifluorometil)fenil]-1-propanol.

Se disolvieron 3-[3',5'-bis(trifluorometil)fenil]-1-propanol (0,88 g, 3,2 mmol) y CBr_4 (1,3 g, 4,0 mmol) en CH_2Cl_2 (5 mL) y se enfrió a 0°C. Se agregó trifenilfosfina (1,3 g, 4,8 mmol) en tres porciones durante 0,5 h. La mezcla se agitó a 0 °C durante 10 min., luego se diluyó con pentano (30 mL) y $NaHCO_3$ saturado (30 mL). La capa acuosa se separó y se lavó con etiléter, y las capas orgánicas combinadas se secaron ($MgSO_4$) y se concentró. El residuo se purificó por gel de sílice cromatografía rápida (99:1 etiléter-hexano) para dar 0,8 g, (74%) del 3-[3',5'-bis(trifluorometil)fenil]-1-bromopropano.

Se agitó 4-cloro-3-(2'-piridil)abilina (10 mg, 0,05 mmol), 3-[3',5'-bis(trifluorometil)fenil]-1-bromopropano (34 mg, 0,1 mmol) y K_2CO_3 (14 mg, 0,1 mmol) en DMF (1 mL) a 100°C durante la noche. La mezcla de reacción se acidificó con HCl 1N (acuoso) y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera, se secó ($MgSO_4$) y se concentró. El producto sin tratar se purificó por HPLC preparativa para dar *N*-(3-(3,5-bis(trifluorometil)fenil)propil)-4-cloro-3-(piridin-2-il)bencenamina.

Ejemplo 53 *N*-(4-cloro-3-(5-(trifluorometil)piridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida



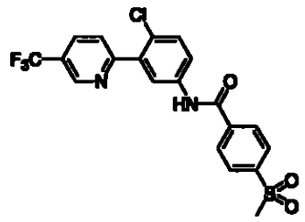
Se usó *N*-(4-cloro-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-2-

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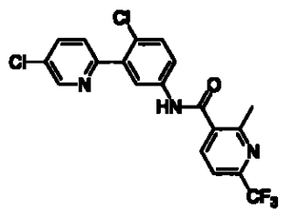
metil-6-(trifluorometil)nicotinamida (~ 0,5 mmol) en el Procedimiento A con 5-trifluorometil-2-bromopiridina (113 mg, 0,5 mmol). Se purificó mediante cromatografía en gel de sílice (5-50% acetato de etilo/hexanos) para dar *N*-(4-cloro-3-(5-(trifluorometil)piridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida como una espuma blanca: TLC R_f = 0,30 (15% acetato de etilo/hexanos); MS (Q1) 460 $(M)^+$.

Ejemplo 54 *N*-(4-cloro-3-(5-(trifluorometil)piridin-2-il)fenil)-4-(metilsulfonil)benzamida



Se usó N-(4-cloro-3-(4,4,5,5-tetrametil.1,3,2-dioxaborolan-2-il)fenil)-4-(metilsulfonil)benzamida (~ 1,0 mmol) en el Procedimiento A con 5-trifluorometil-2-bromopiridina (226 mg, 1 mmol). Se purificó mediante cromatografía en gel de sílice (0-10% acetona/diclorometano) para dar *N*-(4-cloro-3-(5-(trifluorometil)piridin-2-il)fenil)-4-(metilsulfonil)benzamida como un sólido blanco: MS (Q1) 455 $(M)^+$.

Ejemplo 55 *N*-(4-cloro-3-(5-cloropiridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida



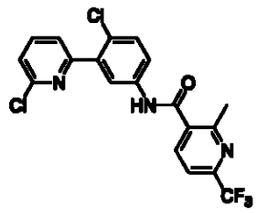
Se usó trifluorometanosulfonato de 5-cloropiridin-2-ilo (4,12 mmol) en el

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Procedimiento I con cloruro de trimetilestaño para dar 5-cloro-2-(trimetilstannil)piridina. El material sin tratar (~4 mmol) se usó en el Procedimiento K con *N*-(4-cloro-3-iodofenil)-2-metil-6-(trifluorometil)nicotinamida (2 mmol). Se purificó mediante cromatografía en gel de sílice (0-50% acetato de etilo/hexano) para dar *N*-(4-cloro-3-(5-cloropiridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida como un sólido blanco: TLC R_f = 0,48 (25% acetato de etilo/hexanos); MS (Q1) 427 $(M)^+$.

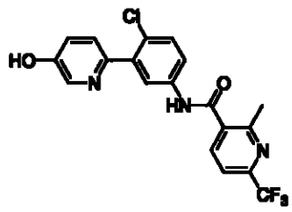
Ejemplo 56 *N*-(4-cloro-3-(6-cloropiridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida



Se usó trifluorometanosulfonato de 6-cloropiridin-2-ilo (4,12 mmol) en el Procedimiento I con cloruro de trimetilestaño para dar 2-cloro-6-(trimetilstannil)piridina. El material sin tratar (~4 mmol) se usó en el Procedimiento K con *N*-(4-cloro-3-iodofenil)-2-metil-6-(trifluorometil)nicotinamida (2 mmol). Se purificó mediante cromatografía en gel de sílice (5-45% acetato de etilo/hexano) para dar *N*-(4-cloro-3-(6-cloropiridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida como un sólido blanco: TLC R_f = 0,45 (25% acetato de etilo/hexanos); MS (Q1) 426 $(M)^+$.

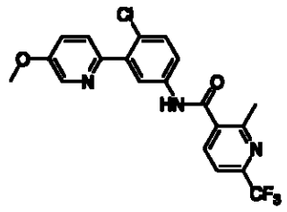
Ejemplo 57 *N*-(4-cloro-3-(5-hidroxipiridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida

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Se usó 3-(triisopropilsililoxi)piridina (2,66 mmol) en el Procedimiento J con hexametildiestaño para dar 5-(triisopropilsililoxi)-2-(trimetilstannil)piridina. El material sin tratar (~0,55 mmol) se usó en el Procedimiento K con *N*-(4-cloro-3-iodofenil)-2-metil-6-(trifluorometil)nicotinamida (0,17 mmol). Se purificó mediante cromatografía en gel de sílice (0-40% acetato de etilo/hexano) para dar *N*-(4-cloro-3-(5-(triisopropilsililoxi)piridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida como un aceite amarillo. *N*-(4-cloro-3-(5-(triisopropilsililoxi)piridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida (1 mmol) se trató con TBAF (2 mL, 1 M en THF) en THF (1 mL) a 23 °C durante treinta minutos, se concentró, se redisolvió en acetato de etilo, se lavó con salmuera, se secó ($MgSO_4$), y se concentró. El sólido sin tratar se purificó por cromatografía en gel de sílice (0-10 % isopropanol/diclorometano) para dar *N*-(4-cloro-3-(5-hidroxipiridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida como un sólido blanco: TLC R_f = 0,59 (10% acetato de etilo/hexanos); MS (Q1) 408 $(M)^+$.

Ejemplo 58 *N*-(4-cloro-3-(5-metoxipiridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida

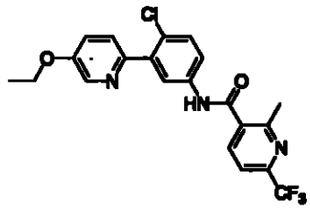


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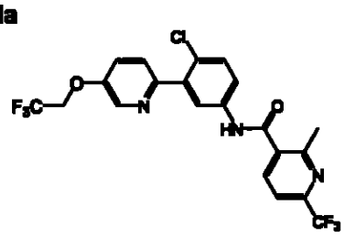
N-(4-cloro-3-(5-hidroxipiridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida (0,12 mmol) se usó en el Procedimiento L con exceso de yodometano. Se purificó mediante cromatografía en gel de sílice (0-100% acetato de etilo/hexano) para dar *N*-(4-cloro-3-(5-metoxipiridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida como un sólido blanco: TLC R_f = 0,57 (50% acetato de etilo/hexanos); MS (Q1) 423(M)$^+$.

Ejemplo 59 *N*-(4-cloro-3-(5-etoxipiridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida



Se usó *N*-(4-cloro-3-(5-hidroxipiridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida (0,05 mmol) en el Procedimiento L con exceso de yodoetano. Se purificó mediante cromatografía en gel de sílice (0-100% acetato de etilo/hexano) para dar *N*-(4-cloro-3-(5-etoxipiridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida como un sólido blanco: TLC R_f = 0,64 (50% acetato de etilo/hexanos); MS (Q1) 436 (M)$^+$.

Ejemplo 60 *N*-(4-cloro-3-(5-(2,2,2-trifluoroetoxi)piridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida

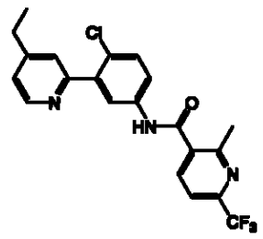


Se usó *N*-(4-cloro-3-(5-hidroxipiridin-2-il)fenil)-2-metil-6-

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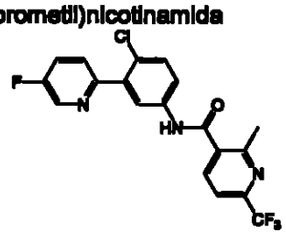
(trifluorometil)nicotinamida (0,12 mmol) en el Procedimiento L con exceso de yoduro de trifluoroetilo. Se purificó mediante cromatografía en gel de sílice (0-40% acetato de etilo/hexano) para dar *N*-(4-cloro-3-(5-(2,2,2-trifluoroetoxi)piridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida como un sólido blanco: TLC R_f = 0,64 (40% acetato de etilo/hexanos); MS (Q1) 490 $(M)^+$.

Ejemplo 61 *N*-(4-cloro-3-(4-etilpiridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida



Se usó *N*-(4-cloro-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida (~ 1 mmol) en el Procedimiento A con 4-etil-2-bromopiridina (1 mmol). Se purificó mediante cromatografía en gel de sílice (0-60% acetato de etilo/hexanos) para dar *N*-(4-cloro-3-(4-etilpiridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida como un sólido color tostado: MS (Q1) 419 $(M)^+$.

Ejemplo 62 *N*-(4-cloro-3-(5-fluoropiridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida

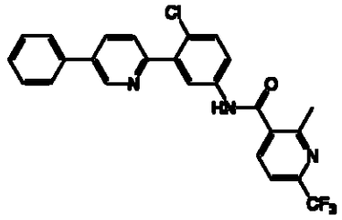


Se usó *N*-(4-cloro-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-2-

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metil-6-(trifluorometil)nicotinamida (~ 1 mmol) en el Procedimiento A con 5-fluoro-2-bromopiridina (1 mmol). Se purificó mediante cromatografía en gel de sílice (5-45% acetato de etilo/hexanos) para dar *N*-(4-cloro-3-(5-fluoropiridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida como un sólido color tostado: MS (Q1) 409 $(M)^+$.

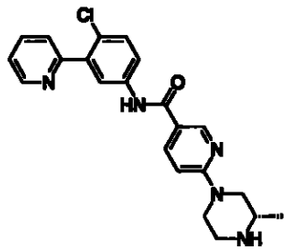
Ejemplo 63 *N*-(4-cloro-3-(5-fenilpiridin-2-il)fenil)-2-metil-6-(trifluorometil)-nicotinamida



Se usó trifluorometanosulfonato de 5-fenilpiridin-2-ilo (1,5 mmol) en el Procedimiento J con cloruro de trimetilestaño para dar 5-fenil-2-(trimetilstannil)piridina. El material sin tratar (~1,25 mmol) se usó en el Procedimiento K con *N*-(4-cloro-3-iodofenil)-2-metil-6-(trifluorometil)nicotinamida (1 mmol). Se purificó mediante cromatografía en gel de sílice (1% acetona/cloruro de metileno) para dar *N*-(4-cloro-3-(5-fenilpiridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida como un sólido color tostado: TLC R_f = 0,15 (1% acetona/cloruro de metileno); MS (Q1) 467 $(M)^+$.

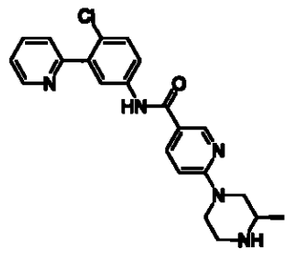
Ejemplo 64 (*S*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-6-(3-metilpiperazin-1-il)nicotinamida

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El procedimiento F se realizó usando N-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (50 mg) y 75 mg de (S)-2-metilpiperazina en 0,75 mL de butanol a 160°C durante 60 min. La purificación por HPLC de fase inversa dio (*S*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-6-(3-metilpiperazin-1-il)nicotinamida. MS (Q1) 408 $(M)^+$.

Ejemplo 65 (*R*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-6-(3-metilpiperazin-1-il)nicotinamida

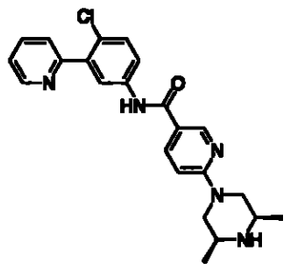


El procedimiento F se realizó usando N-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (50 mg) y 75 mg de (R)-2-metilpiperazina en 0,75 mL de butanol a 160°C durante 60 min. La purificación por HPLC de fase inversa dio (*R*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-6-(3-metilpiperazin-1-il)nicotinamida. MS (Q1) 408 $(M)^+$.

Ejemplo 66 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-((3*S*,5*R*)-3,5-dimetilpiperazin-1-il)nicotinamida

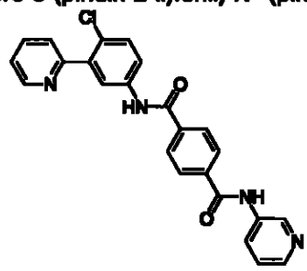
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El procedimiento F se realizó usando N-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (75 mg) y 114 mg de 2,6-dimetilpiperazina en 1 mL de butanol a 160°C durante 60 min. La purificación por HPLC de fase inversa dio *N*-(4-cloro-3-(piridin-2-il)fenil)-6-((3*S*,5*R*)-3,5-dimetilpiperazin-1-il)nicotinamida. MS (Q1) 422,1 $(M)^+$.

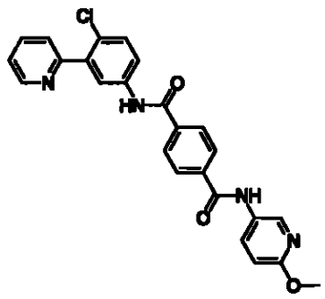
Ejemplo 67 N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(piridin-3-il)tereftalamida



Se acopló 320 mg de 4-cloro-3-(piridin-2-il)abilina a 400 mg de ácido 4-(metoxicarbonil)benzoico por medio del procedimiento G para dar 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoato de metilo. Luego se hidrolizó 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoato de metilo mediante el procedimiento M para dar 550 mg de ácido 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico. Se acopló ácido 50 mg de 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 3-aminopiridina por medio del procedimiento G. La capa orgánica se evaporó a sequedad y se purificó en HPLC de fase inversa para dar N^1-(4-cloro-3-(piridin-

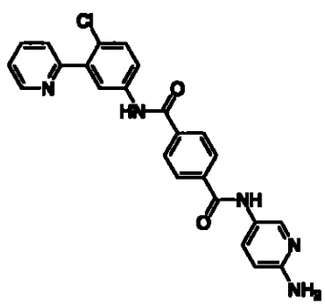
2-il)fenil)-N^4-(piridin-3-il)tereftalamida. MS (Q1) 429 $(M)^+$.

Ejemplo 68 N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(6-metoxipiridin-3-il)tereftalamida



Se acopló 50 mg de ácido 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 2-metoxi-5-aminopiridina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(6-metoxipiridin-3-il)tereftalamida. MS (Q1) 459 $(M)^+$.

Ejemplo 69 N^1-(6-aminopiridin-3-il)-N^4-(4-cloro-3-(piridin-2-il)fenil)tereftalamida

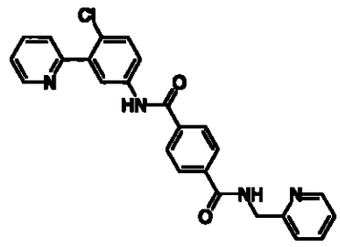


Se acopló 50 mg de ácido 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 2,5-diaminopiridina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar N^1-(6-aminopiridin-3-

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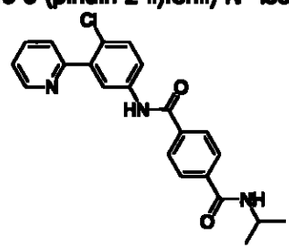
il)-N^4-(4-cloro-3-(piridin-2-il)fenil)tereftalamida. MS (Q1) 444 $(M)^+$.

Ejemplo 70 N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(piridin-2-ilmetil)tereftalamida



Se acopló 50 mg de ácido 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 2-(aminometil)piridina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(piridin-2-ilmetil)tereftalamida. MS (Q1) 443 $(M)^+$.

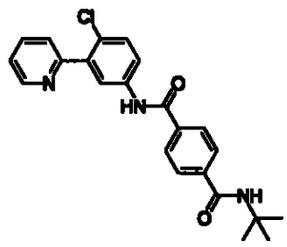
Ejemplo 71 N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-isopropiltereftalamida



Se acopló 50 mg de ácido 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a isopropilamina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-isopropiltereftalamida. MS (Q1) 394 $(M)^+$.

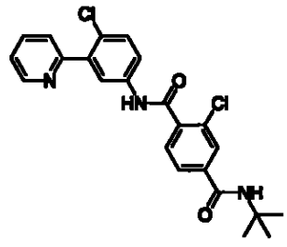
Ejemplo 72 N^1-*ter*-butil-N^4-(4-cloro-3-(piridin-2-il)fenil)tereftalamida

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Se acopló 50 mg de ácido 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a *ter*-butilamina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar N^1-*ter*-butil-N^4-(4-cloro-3-(piridin-2-il)fenil)tereftalamida. MS (Q1) 408 $(M)^+$.

Ejemplo 73 N^4-*ter*-butil-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)tereftalamida

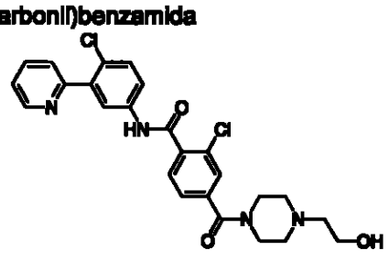


Se sometieron 67 mL de 2-cloro-1,4-dimetilbenceno y 356 g de Permanganato de potasio a reflujo en 1,5 L de H_2O por varias horas y y se verificó si el material de partida había desaparecido por TLC. El Permanganato de potasio se filtró y la mezcla de reacción se acidificó y se filtró para dar ácido 2-cloroteréftálico. 46,8 g de ácido 2-cloroteréftálico se trató con una solución saturada de gas HCl en MeOH durante la noche a temperatura ambiente. La mezcla de reacción se concentró, se sometió a trabajo básico y se secó para dar el 2-cloroteréftalato de dimetilo. 20 g de 2-cloroteréftalato de dimetilo se enfrió a 0°C en DCM y se agregaron 87 mL de una solución 1M en DCM de

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BBr_3 por goteo durante varias horas. La mezcla de reacción se calentó subsiguientemente a temperatura ambiente y se agitó hasta completarse. Luego del trabajo básico, se purificó ácido 2-cloro-4-(metoxicarbonil)benzoico por ISCO Combi-Flash. Se acopló 959 mg de ácido 2-cloro-4-(metoxicarbonil)benzoico a 750 mg de 4-cloro-3-(piridin-2-il)abilina por medio del procedimiento G. Se hidrolizó 1 g de 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoato de metilo por medio del procedimiento M para dar ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico. Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a *ter*-butilamina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar *N*^{4}-*ter*-butil-2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)tereftalamida. MS (Q1) 443,2 $(M)^+$.

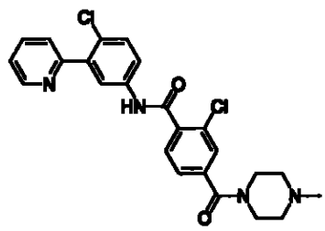
Ejemplo 74 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-(2-hidroxietil)piperazina-1-carbonil)benzamida



Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a N-(2-hidroxietil)piperazina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-(2-hidroxietil)piperazina-1-carbonil)benzamida. MS (Q1) 499 $(M)^+$.

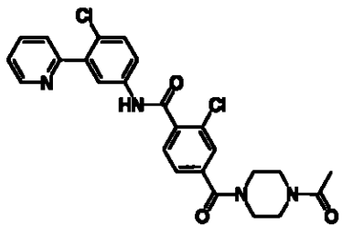
Ejemplo 75 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-metilpiperazina-1-carbonil)benzamida

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Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 1-metilpiperazina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-metilpiperazina-1-carbonil)benzamida. MS (Q1) 469 $(M)^+$.

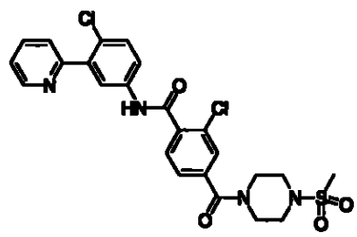
Ejemplo 76 4-(4-acetilpiperazina-1-carbonil)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida



Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 1-acetilpiperazina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 4-(4-acetilpiperazina-1-carbonil)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida. MS (Q1) 497 $(M)^+$.

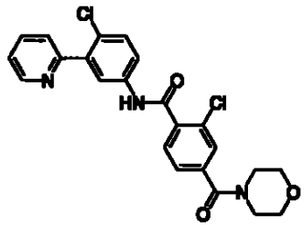
Ejemplo 77 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-(metilsulfonil)piperazina-1-carbonil)benzamida

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Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 1-sulfonilpiperazina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-(metilsulfonil)piperazina-1-carbonil)benzamida. MS (Q1) 533 $(M)^+$.

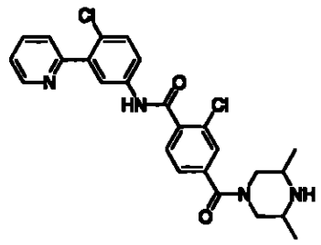
Ejemplo 78 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(morfolin-4-carbonil)benzamida



Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a morfolina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(morfolin-4-carbonil)benzamida. MS (Q1) 456 $(M)^+$.

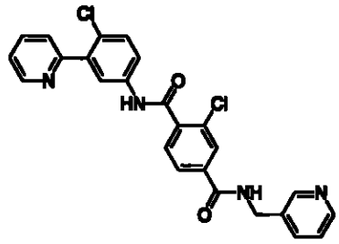
Ejemplo 79 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(3,5-dimetilpiperazina-1-carbonil)benzamida

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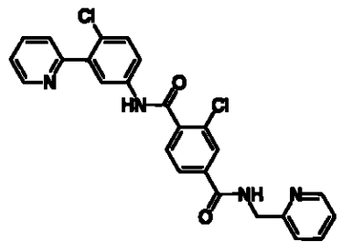
Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 2,6-dimetilpiperazina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(3,5-dimetilpiperazina-1-carbonil)benzamida. MS (Q1) 483 $(M)^+$.

Ejemplo 80 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(piridin-3-ilmetil)tereftalamida



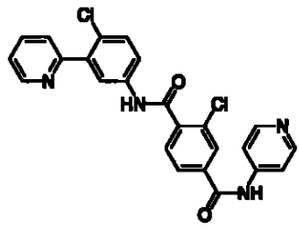
Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 3-(aminometil)piridina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(piridin-3-ilmetil)tereftalamida. MS (Q1) 477 $(M)^+$.

Ejemplo 81 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(piridin-2-ilmetil)tereftalamida



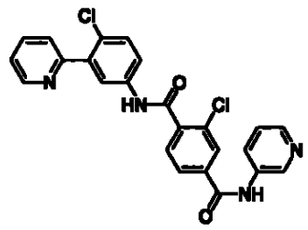
Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 2-(aminometil)piridina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(piridin-2-ilmetil)tereftalamida. MS (Q1) 477 $(M)^+$.

Ejemplo 82 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(piridin-4-il)tereftalamida



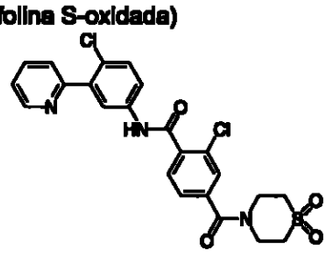
Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 4-aminopiridina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(piridin-4-il)tereftalamida. MS (Q1) 463 $(M)^+$.

Ejemplo 83 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(piridin-3-il)tereftalamida



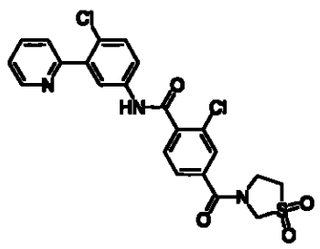
Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 3-aminopiridina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-(piridin-3-il)tereftalamida. MS (Q1) 463 (M)$^+$.

Ejemplo 84 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(tiomorfolin-4-carbonil)benzamida (tiomorfolina S-oxidada)



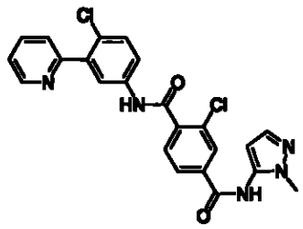
Se acopló 100 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a tiomorfolina por medio del procedimiento G. 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(tiomorfolin-4-carbonil)benzamida cruda se hizo reaccionar por medio del procedimiento R para oxidar el azufre de la tiomorfolina y se purificó por HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(tiomorfolin-4-carbonil)benzamida (en la cual el azufre de la tiomorfolina se oxida a SO_2). MS (Q1) 504 (M)$^+$.

Ejemplo 85 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(tiazolidin-3-carbonil)benzamida (tiazolidina S-oxidada)



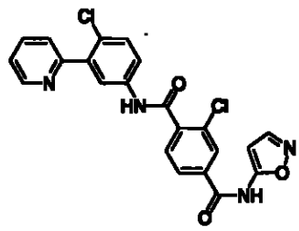
Se acopló 100 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a tiazolidina por medio del procedimiento G. Se hizo reaccionar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(tiazolidin-3-carbonil)benzamida cruda por medio del procedimiento R y se purificó vía HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(tiazolidin-3-carbonil)benzamida (en el cual el azufre de la tiazolidina se oxida a SO_2). MS (Q1) 490 $(M)^+$.

Ejemplo 86 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(1-metil-1*H*-pirazol-5-il)tereftalamida



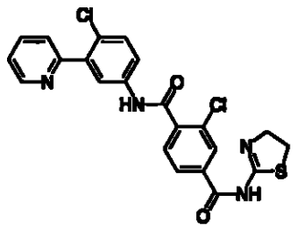
Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 5-amino-1-metilpirazol por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(1-metil-1*H*-pirazol-5-il)tereftalamida. MS (Q1) 466 $(M)^+$.

Ejemplo 87 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(isoxazol-5-il)tereftalamida



Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 5-aminoisoxazol por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(isoxazol-5-il)tereftalamida. MS (Q1) 463 $(M)^+$.

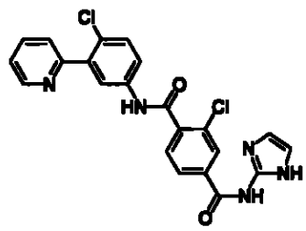
Ejemplo 88 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(4,5-dihidrotiazol-2-il)tereftalamida



Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 2-amino-4,5-dihidrotiazol por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(4,5-dihidrotiazol-2-il)tereftalamida. MS (Q1) 471 $(M)^+$.

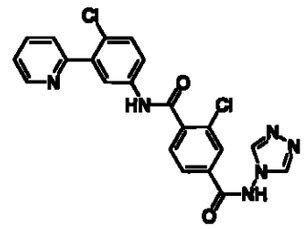
Ejemplo 89 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(1*H*-imidazol-2-il)tereftalamida

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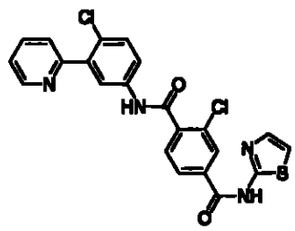
Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 2-aminoimidazol por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-(1*H*-imidazol-2-il)tereftalamida. MS (Q1) 452 (M)$^+$.

Ejemplo 90 2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-(4*H*-1,2,4-triazol-4-il)tereftalamida



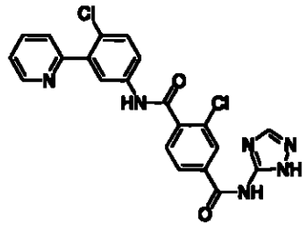
Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 4-amino-1,2,4-triazol por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-(4*H*-1,2,4-triazol-4-il)tereftalamida. MS (Q1) 453 (M)$^+$.

Ejemplo 91 2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-(tiazol-2-il)tereftalamida



Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 2-aminotiazol por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-(tiazol-2-il)tereftalamida. MS (Q1) 469 $(M)^+$.

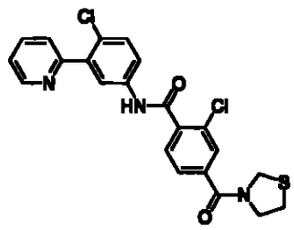
Ejemplo 92 2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-(1*H*-1,2,4-triazol-5-il)tereftalamida



Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 3-amino-1,2,4-triazol por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-(1*H*-1,2,4-triazol-5-il)tereftalamida. MS (Q1) 453 $(M)^+$.

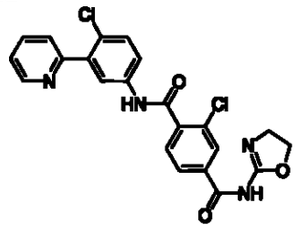
Ejemplo 93 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(tiazolidin-3-carbonil)benzamida

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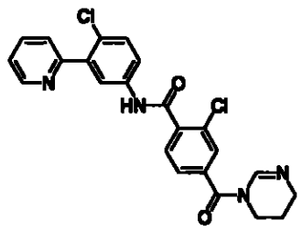
Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a tiazolina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(tiazolidin-3-carbonil)benzamida. MS (Q1) 459 $(M)^+$.

Ejemplo 94 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(4,5-dihidrooxazol-2-il)tereftalamida



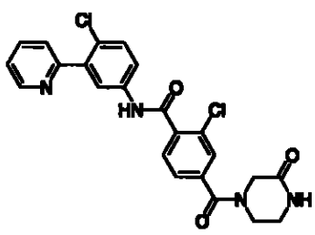
Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 2-amino-4,5-dihidrooxazol por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(4,5-dihidrooxazol-2-il)tereftalamida. MS (Q1) 456 $(M)^+$.

Ejemplo 95 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(1,4,5,6-tetrahidropirimidin-1-carbonil)benzamida



Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 1,4,5,6-tetrahidropirimidina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(1,4,5,6-tetrahidropirimidin-1-carbonil)benzamida. MS (Q1) 454 $(M)^+$.

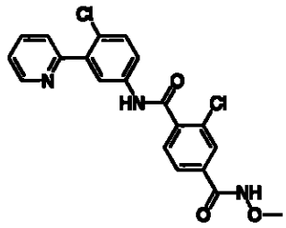
Ejemplo 96 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(3-oxopiperazina-1-carbonil)benzamida



Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 3-oxopiperazina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(3-oxopiperazina-1-carbonil)benzamida. MS (Q1) 470 $(M)^+$.

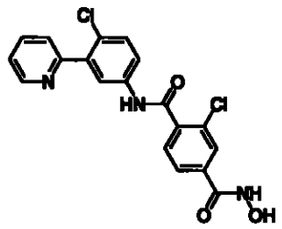
Ejemplo 97 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-metoxitereftalamida

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Se acopló 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a clorhidrato de *N*-metilhidroxilamina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-metoxitereftalamida. MS (Q1) 417 $(M)^+$.

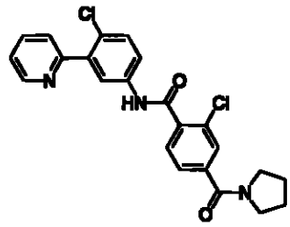
Ejemplo 98 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-hidroxitereftalamida



Se acopló 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a clorhidrato de hidroxilamina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-hidroxitereftalamida. MS (Q1) 403 $(M)^+$.

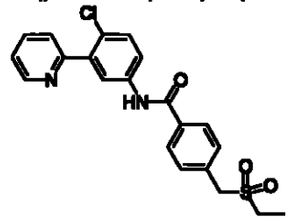
Ejemplo 99 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(pirrolidin-1-carbonil)benzamida

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Se acopló 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a pirrolidina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(pirrolidin-1-carbonil)benzamida. MS (Q1) 441 $(M)^+$.

Ejemplo 100 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(etilsulfonilmetil)benzamida



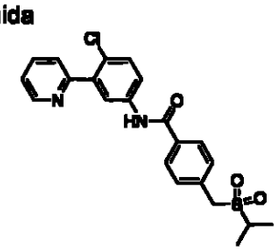
Se redujo cloruro de etansulfonilo a etansulfinato de sodio de acuerdo con el procedimiento en J. Med. Chem. 1989, vol. 32, no. 11, p2436. Brevemente, se agregó 2,5 ml de cloruro de etansulfonilo por goteo a una solución de 3,67 g de carbonato de sodio y 5,51 g de sulfato de sodio en 13 mL de agua. Al completarse la reacción el agua se evaporó y los sólidos se suspendieron en etanol y se calentó a 80° C durante 1 h antes de filtrar los sólidos. El filtrado luego se evaporó para dar 2,5 gramos del etansulfinato de sodio. 293 mg del etansulfinato de sodio se combinó con 230 mg de (4-bromoetil)benzoato de metilo en 2 mL de DMF y se calentó a 120 C durante 5 min en un reactor de microondas. La reacción luego se extrajo con acetato de etilo y salmuera para dar 250 mg de 4-(etilsulfonilmetil)benzoato de metilo

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luego de la evaporación de la capa orgánica. Se hidrolizó 200 mg de 4-(etilsulfonilmetil)benzoato de metilo por medio del procedimiento M para dar 119 mg de ácido 4-(etilsulfonilmetil)benzoico.

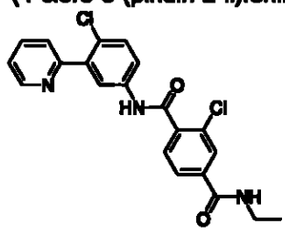
Se acopló 50 mg de ácido 4-(etilsulfonilmetil)benzoico con 67mg de 4-cloro-3-(piridin-2-il)abilina por medio del procedimiento G. Este producto se recristalizó a partir de metanol para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(etilsulfonilmetil)benzamida. MS (Q1) 415 $(M)^+$.

Ejemplo 101 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(isopropilsulfonilmetil)benzamida



Se preparó *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(isopropilsulfonilmetil)benzamida usando el mismo procedimiento que *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(etilsulfonilmetil)benzamida excepto que se sustituyó cloruro de propan-2-sulfonilo por cloruro de etansulfonilo. El producto se purificó en HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(isopropilsulfonilmetil)benzamida. MS (Q1) 429 $(M)^+$.

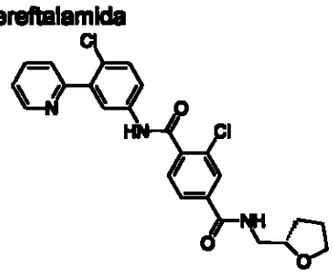
Ejemplo 102 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-etiltereftalamida



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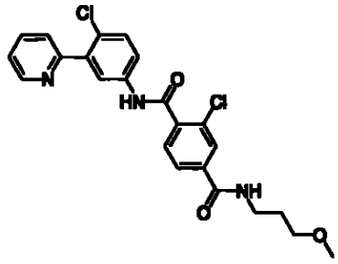
Se acopló 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a etilamina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-etiltereftalamida. MS (Q1) 415 $(M)^+$.

Ejemplo 103 (*S*)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-((tetrahidrofuran-2-il)metil)tereftalamida



Se acopló 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a (S)-(+)-tetrahidrofurilamina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar (*S*)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-((tetrahidrofuran-2-il)metil)tereftalamida. MS (Q1) 471 $(M)^+$.

Ejemplo 104 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(3-metoxipropil)tereftalamida

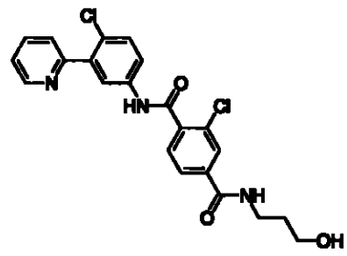


Se acopló 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 3-metoxipropilamina por medio del procedimiento

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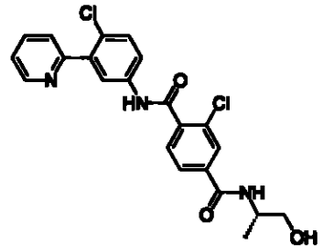
G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(3-metoxipropil)tereftalamida. MS (Q1) 459 $(M)^+$.

Ejemplo 105 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(3-hidroxipropil)tereftalamida



Se acopló 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 3-hidroxipropilamina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(3-hidroxipropil)tereftalamida. MS (Q1) 445 $(M)^+$.

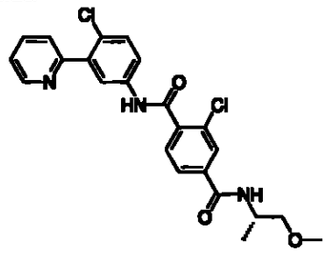
Ejemplo 106 (*S*)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(1-hidroxipropan-2-il)tereftalamida



Se acopló 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a (S)-2-amino-1-propanol por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar (*S*)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(1-hidroxipropan-2-il)tereftalamida. MS (Q1) 445 $(M)^+$.

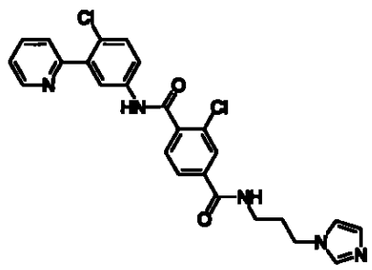
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Ejemplo 107 (*S*)-2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-(1-metoxipropan-2-il)tereftalamida



Se acopló 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a (S)-1-metoxi-2-propilamina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar (*S*)-2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-(1-metoxipropan-2-il)tereftalamida.
MS (Q1) 459 $(M)^+$.

Ejemplo 108 *N*^{4}-(3-(1*H*-imidazol-1-il)propil)-2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)tereftalamida

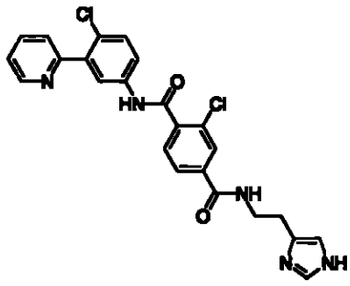


Se acopló 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 1-(3-aminopropil)imidazol por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar *N*^{4}-(3-(1*H*-imidazol-1-il)propil)-2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)tereftalamida.
MS (Q1) 495 $(M)^+$.

Ejemplo 109 *N*^{4}-(2-(1*H*-imidazol-4-il)etil)-2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-

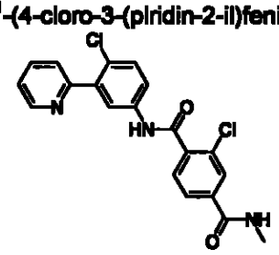
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il)fenil)tereftalamida



Se acopló 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a histamina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar *N*^{4}-(2-(1*H*-imidazol-4-il)etil)-2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)tereftalamida. MS (Q1) 481 (M)$^+$.

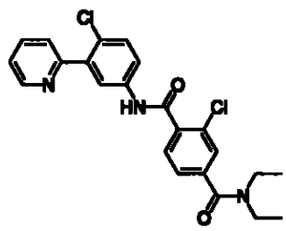
Ejemplo 110 2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-metiltereftalamida



Se acopló 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a clorhidrato de metilamina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-metiltereftalamida. MS (Q1) 401 (M)$^+$.

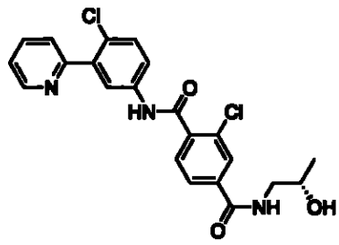
Ejemplo 111 2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4},*N*^{4}-dietiltereftalamida

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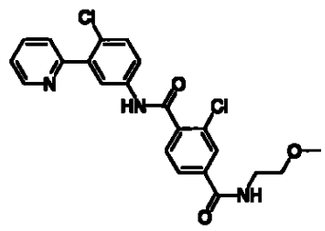
Se acopló 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a clorhidrato de dietilamina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4},*N*^{4}-dietiltereftalamida. MS (Q1) 443 $(M)^+$

Ejemplo 112 (*S*)-2-cloro-*N*1-(4-cloro-3-(piridin-2-il)fenil)-*N*4-(2-hidroxipropil)-tereftalamida



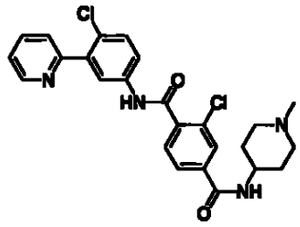
Se acopló 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a (S)-1-amino-2-propanol por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar (*S*)-2-cloro-*N*1-(4-cloro-3-(piridin-2-il)fenil)-*N*4-(2-hidroxipropil)tereftalamida. MS (Q1) 444 $(M)^+$.

Ejemplo 113 2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-(2-metoxietil)tereftalamida



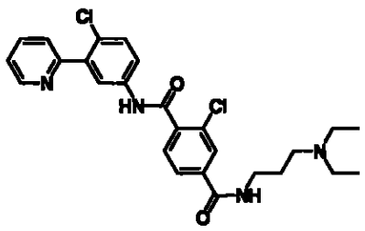
Se acopló 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 2-metoxietanamina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-metoxietil)tereftalamida. MS (Q1) 444 $(M)^+$.

Ejemplo 114 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(1-metilpiperidin-4-il)tereftalamida



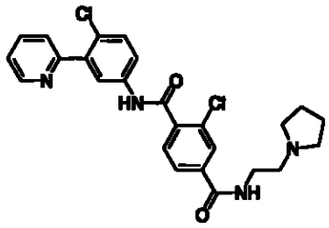
Se acopló 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 4-amino-1-metilpiperidina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(1-metilpiperidin-4-il)tereftalamida. MS (Q1) 483 $(M)^+$.

Ejemplo 115 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(3-(dietilamino)propil)tereftalamida



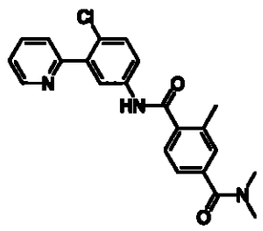
Se acopló 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a N,N-dietilpropilenediamina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(3-(dietilamino)propil)tereftalamida. MS (Q1) 499 $(M)^+$.

Ejemplo 116 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-(pirrolidin-1-il)etil)tereftalamida



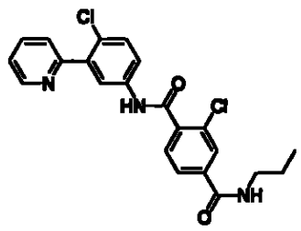
Se acopló 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a N-(2-aminoetil)pirrolidina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-(pirrolidin-1-il)etil)tereftalamida. MS (Q1) 483 $(M)^+$.

Ejemplo 117 N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4,N^4,2-trimetiltereftalamida



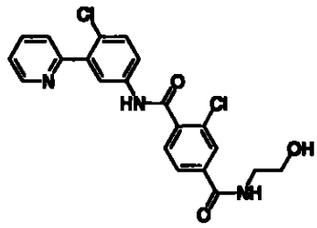
En un tubo sellado, se disolvió 1,94 g de 2-bromotereftalato de dimetilo en 4 mL de HMPA y se desgasificó con nitrógeno antes de agregar 1,1 mL de tetrametil estaño y 0,077 g de tetrakistrifenilfosfenpaladio. Luego de sellar el tubo, la reacción se calentó a 65° C durante 16 h. La reacción luego se particionó en etiléter y agua y se extrajo. Las capas orgánicas se lavaron con hidróxido de amonio 5%, HCl 1N, nuevamente con hidróxido de amonio 5%, y finalmente con agua. La filtración del solvente a través de sulfato de sodio y evaporación dio 1,44 g de 2-metiltereftalato de dimetilo crudo. 210 mg de 2-metiltereftalato de dimetilo se hidrolizó por medio del procedimiento M para dar ácido 4-(metoxicarbonil)-3-metilbenzoico. Se realizó cromatografía en gel de sílice (gradiente 0% a 70% de EtOAc en Hexanos) para dar 115 mg de ácido 4-(metoxicarbonil)-3-metilbenzoico. Luego se acopló ácido 4-(metoxicarbonil)-3-metilbenzoico a clorhidrato de dimetilamina por medio del procedimiento G. Luego se hidrolizó el 4-(dimetilcarbamoil)-2-metilbenzoato de metilo sin tratar por medio del procedimiento M para dar 110 mg de ácido 4-(dimetilcarbamoil)-2-metilbenzoico. Se acopló 4-cloro-3-(piridin-2-il)abilina a 110 mg de ácido 4-(dimetilcarbamoil)-2-metilbenzoico por medio del procedimiento G para dar N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4,N^4,2-trimetiltereftalamida. MS (Q1) 394 $(M)^+$.

Ejemplo 118 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-propiltereftalamida



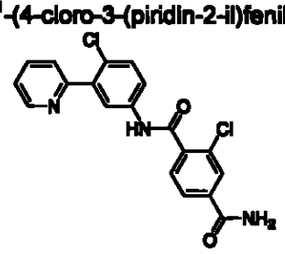
Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a propilamina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-propiltereftalamida. MS (Q1) 430 $(M)^+$.

Ejemplo 119 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-hidroxietil)tereftalamida



Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a propanolamina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-hidroxietil)tereftalamida. MS (Q1) 428 $(M)^+$.

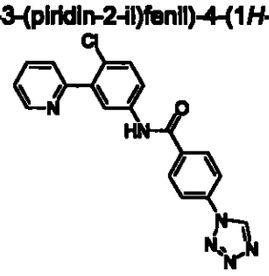
Ejemplo 120 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)tereftalamida



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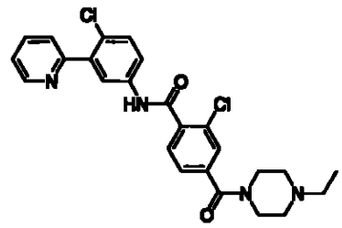
Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a cloruro de amonio por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)tereftalamida. MS (Q1) 366 (M)$^+$.

Ejemplo 121 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(1*H*-tetrazol-1-il)benzamida



El procedimiento G se usó para acoplar 4-cloro-3-(piridin-2-il)abilina (50 mg) y ácido 4-(1*H*-tetrazol-1-il)benzoico para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(1*H*-tetrazol-1-il)benzamida. MS (Q1) 421,0 (M)$^+$.

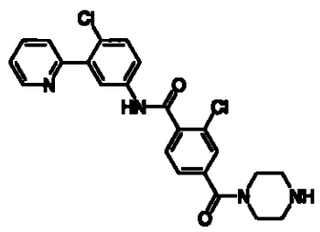
Ejemplo 122 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-etilpiperazina-1-carbonil)benzamida



Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 1-etilpiperazina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-etilpiperazina-1-carbonil)benzamida. MS (Q1) 483 (M)$^+$.

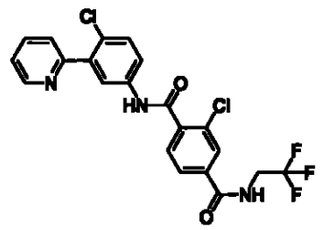
Ejemplo 123 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(piperazina-1-carbonil)benzamida

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Se acopló 50 mg ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a Boc-piperazina por medio del procedimiento G. La capa orgánica se evaporó a sequedad y se trató con TFA. 1 h después el TFA se eliminó y el producto sin tratar se purificó en HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(piperazina-1-carbonil)benzamida. MS (Q1) 455 $(M)^+$.

Ejemplo 124 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2,2,2-trifluoroetil)tereftalamida

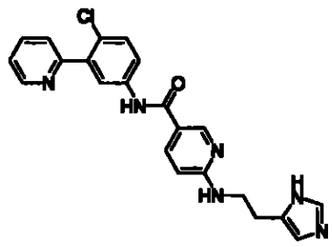


Se acopló 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 2,2,2-trifluoroetilamina por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2,2,2-trifluoroetil)tereftalamida. MS (Q1) 469 $(M)^+$.

Ejemplo 125 6-(2-(1*H*-imidazol-5-il)etilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil)nicotinamida

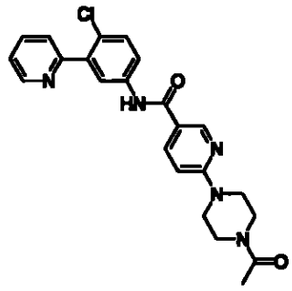
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El procedimiento F se realizó usando *N*-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (50 mg) y 100 mg de histamina en butanol (0,5 mL). La mezcla de reacción sin tratar se purificó por HPLC de fase inversa para dar 6-(2-(1*H*-imidazol-5-il)etilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil)nicotinamida. MS (Q1) 419 $(M)^+$.

Ejemplo 126 6-(4-acetilpiperazin-1-il)-*N*-(4-cloro-3-(piridin-2-il)fenil)nicotinamida

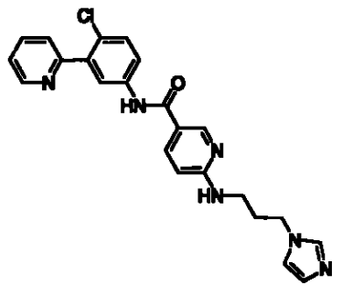


El procedimiento F se realizó usando *N*-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (50 mg) y 0,12 mL de acetilpiperazina en butanol (0,5 mL). La mezcla de reacción sin tratar se purificó por HPLC de fase inversa para dar 6-(4-acetilpiperazin-1-il)-*N*-(4-cloro-3-(piridin-2-il)fenil)nicotinamida. MS (Q1) 436 $(M)^+$.

Ejemplo 127 6-(3-(1*H*-imidazol-1-il)propilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil)nicotinamida

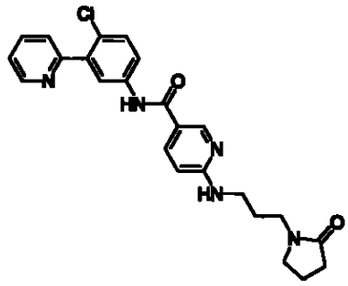
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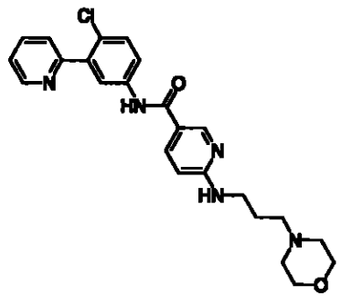
El procedimiento F se realizó usando *N*-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (50 mg) y 125 mg de 1-(3-aminopropil)imidazol en butanol (0,5 mL). La mezcla de reacción sin tratar se purificó por HPLC de fase inversa para dar 6-(3-(1*H*-imidazol-1-il)propilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil)nicotinamida. MS (Q1) 433 $(M)^+$.

Ejemplo 128 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(3-(2-oxopirrolidin-1-il)propilamino)nicotinamida



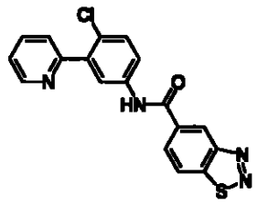
El procedimiento F se realizó usando *N*-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (50 mg) y 0,42 mL de 1-(3-aminopropil)-2-pirrolidinona en butanol (0,5 mL). La mezcla de reacción sin tratar se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(3-(2-oxopirrolidin-1-il)propilamino)nicotinamida. MS (Q1) 450 $(M)^+$.

Ejemplo 129 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(3-morfolinopropilamino)nicotinamida



El procedimiento F se realizó usando *N*-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (50 mg) y 0,14 mL de N-(3-aminopropil)morfolina en butanol (0,5 mL). La mezcla de reacción sin tratar se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(3-morfolinopropilamino)nicotinamida. MS (Q1) 452 $(M)^+$.

Ejemplo 130 *N*-(4-cloro-3-(piridin-2-il)fenil)benzo[d][1,2,3]tiadiazol-5-carboxamida

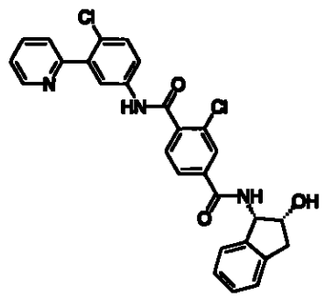


Se acopló 50 mg de 4-cloro-3-(piridin-2-il)abilina a ácido benzo-1,2,3-tiadiazol-5-carboxílico por medio del procedimiento G. El producto sin tratar se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)benzo[d][1,2,3]tiadiazol-5-carboxamida. MS (Q1) 367 $(M)^+$.

Ejemplo 131 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-((1*S*,2*R*)-2-hidroxi-2,3-dihidro-1*H*-inden-1-il)tereftalamida

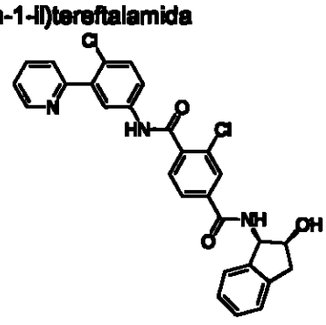
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Se acopló 60 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a (1*S*,2*R*)-1-amino-2,3-dihidro-1*H*-inden-2-ol por medio del procedimiento G. El producto sin tratar se purificó en HPLC de fase inversa para dar 2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-((1*S*,2*R*)-2-hidroxi-2,3-dihidro-1*H*-inden-1-il)tereftalamida. MS (Q1) 518,2 $(M)^+$.

Ejemplo 132 2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-((1*R*,2*S*)-2-hidroxi-2,3-dihidro-1*H*-inden-1-il)tereftalamida

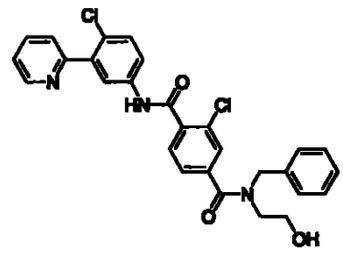


Se acopló 60 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a (1*R*,2*S*)-1-amino-2,3-dihidro-1*H*-inden-2-ol por medio del procedimiento G. El producto sin tratar se purificó en HPLC de fase inversa para dar 2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-((1*R*,2*S*)-2-hidroxi-2,3-dihidro-1*H*-inden-1-il)tereftalamida. MS (Q1) 518,2 $(M)^+$.

Ejemplo 133 *N*^{4}-bencil-2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-(2-

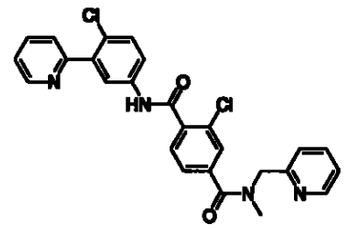
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hidroxietil)-tereftalamida



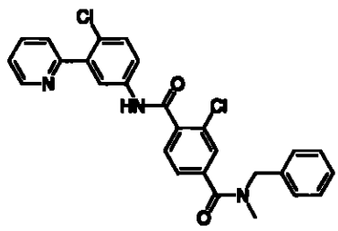
Se acopló 40 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 2-(bencilamino)etanol por medio del procedimiento G. El producto sin tratar se purificó en HPLC de fase inversa para dar N^4-bencil-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-hidroxietil)tereftalamida. MS (Q1) 520 $(M)^+$.

Ejemplo 134 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-metil-N^4-(piridin-2-ilmetil)tereftalamida



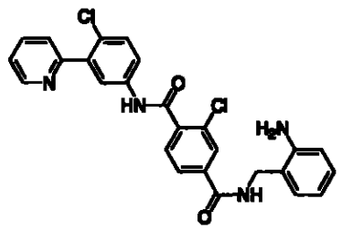
Se acopló 40 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a *N*-metil-1-(piridin-2-il)metanamina por medio del procedimiento G. El producto sin tratar se purificó en HPLC de fase inversa para dar 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-metil-N^4-(piridin-2-ilmetil)tereftalamida. MS (Q1) 491 $(M)^+$.

Ejemplo 135 N^4-bencil-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-metiltereftalamida



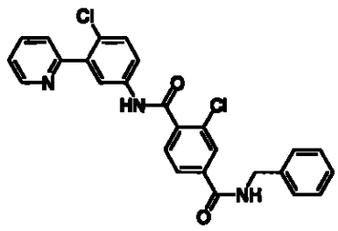
Se acopló 40 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a *N*-metil-1-fenilmetanamina por medio del procedimiento G. El producto sin tratar se purificó en HPLC de fase inversa para dar N^4-bencil-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-metiltereftalamida. MS (Q1) 490,1 $(M)^+$.

Ejemplo 136 N^4-(2-aminobencil)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)tereftalamida



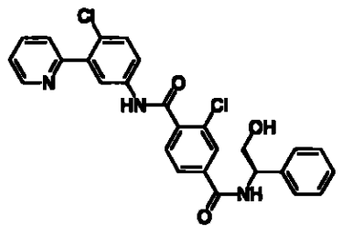
Se acopló 60 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a N^1-feniletan-1,2-diamina por medio del procedimiento G. El producto sin tratar se purificó en HPLC de fase inversa para dar N^4-(2-aminobencil)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)tereftalamida. MS (Q1) 491 $(M)^+$.

Ejemplo 137 N^4-bencil-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)tereftalamida



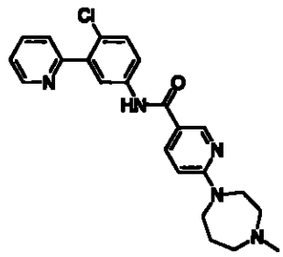
Se acopló 60 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a bencilamina por medio del procedimiento G. El producto sin tratar se purificó en HPLC de fase inversa para dar *N*^{4}-bencil-2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)tereftalamida. MS (Q1) 476 (M)$^+$.

Ejemplo 138 (*R*)-2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-(2-hidroxi-1-feniletil)tereftalamida



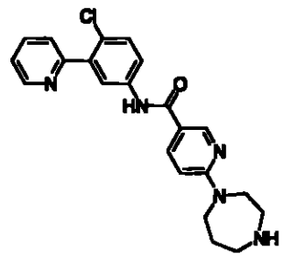
Se acopló 60 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a (*R*)-2-amino-2-feniletanol por medio del procedimiento G. El producto sin tratar se purificó en HPLC de fase inversa para dar (*R*)-2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-(2-hidroxi-1-feniletil)tereftalamida. MS (Q1) 506 (M)$^+$.

Ejemplo 139 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(4-metil-1,4-diazepan-1-il)nicotinamida



Se hizo reaccionar 50 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)nicotinamida con 1-metil-1,4-diazepan por medio del procedimiento F. La reacción se evaporó a sequedad y se purificó en HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(4-metil-1,4-diazepan-1-il)nicotinamida. MS (Q1) 422 $(M)^+$.

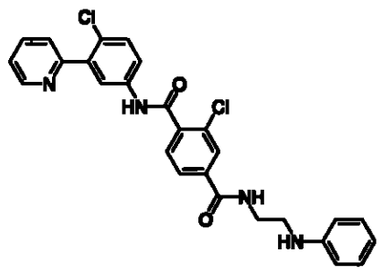
Ejemplo 140 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(1,4-diazepan-1-il)nicotinamida



Se hizo reaccionar 50 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)nicotinamida con 1,4-diazepan por medio del procedimiento F. La reacción se evaporó a sequedad y se purificó en HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(1,4-diazepan-1-il)nicotinamida. MS (Q1) 408 $(M)^+$.

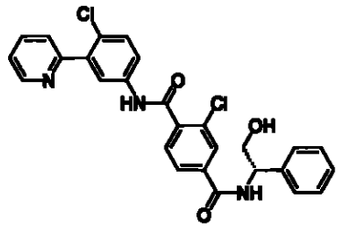
Ejemplo 141 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-(fenilamino)etil)tereftalamida

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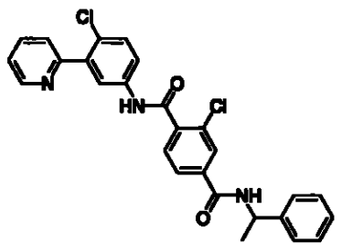
Se acopló 62 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a N^1-feniletan-1,2-diamina por medio del procedimiento G. El producto sin tratar se purificó en HPLC de fase inversa para dar 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-(feniamino)etil)tereftalamida. MS (Q1) 505,1 $(M)^+$.

Ejemplo 142 (*S*)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-hidroxi-1-feniletil)tereftalamida



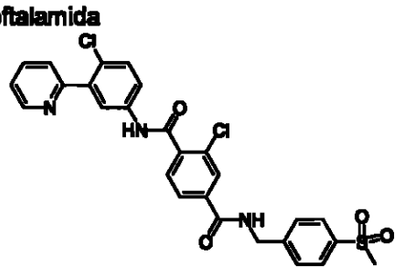
Se acopló 62 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a (*S*)-2-amino-2-feniletanol por medio del procedimiento G. El producto sin tratar se purificó en HPLC de fase inversa para dar (*S*)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-hidroxi-1-feniletil)tereftalamida. MS (Q1) 506 $(M)^+$.

Ejemplo 143 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(1-feniletil)tereftalamida



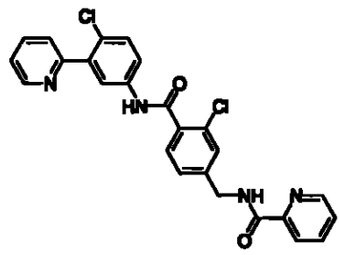
Se acopló 62 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 1-feniletanamina por medio del procedimiento G. El producto sin tratar se purificó en HPLC de fase inversa para dar 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(1-feniletil)tereftalamida. MS (Q1) 490,1 $(M)^+$.

Ejemplo 144 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(4-(metilsulfonil)bencil)-tereftalamida



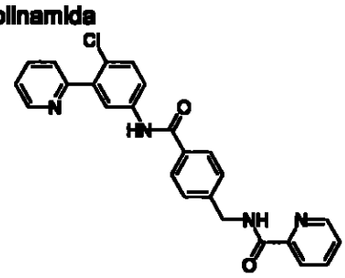
Se acopló 62 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a (4-(metilsulfonil)fenil)metanamina por medio del procedimiento G. El producto sin tratar se purificó en HPLC de fase inversa para dar 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(4-(metilsulfonil)bencil)tereftalamida. MS (Q1) 554 $(M)^+$.

Ejemplo 145 *N*-(3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencil)picolinamida



Se acopló 75 mg de 4-cloro-3-(piridin-2-il)abilina a ácido 4-((*ter*-butoxicarbonilamino)metil)-2-clorobenzoico por medio del procedimiento G para dar 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencilcarbamato de *ter*-butilo. 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencilcarbamato de *ter*-butilo se trató subsiguientemente con HCl 4N en Dioxano para eliminar el grupo Boc protector y formar la sal de HCl de 4-(aminometil)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida. 54 mg de la sal de HCl cruda de 4-(aminometil)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida se acopló a ácido picolínico por medio del procedimiento G. El producto sin tratar se purificó por HPLC de fase inversa para dar *N*-(3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencil)picolinamida. MS (Q1) 477,3 $(M)^+$.

Ejemplo 148 *N*-(4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencil)picolinamida

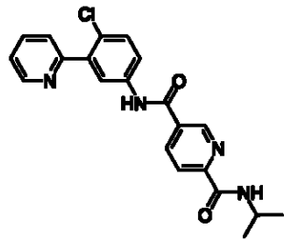


Se acopló 75 mg de 4-cloro-3-(piridin-2-il)abilina a ácido 4-((*ter*-butoxicarbonilamino)metil)benzoico por medio del procedimiento G para dar 4-

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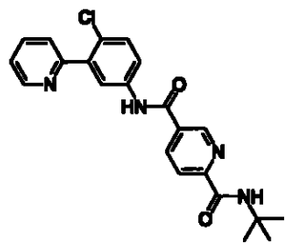
(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencilcarbamato de *ter*-butilo. 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencilcarbamato de *ter*-butilo se trató subsiguientemente con HCl 4N en Dioxano para eliminar el grupo Boc protector y formar la sal de HCl de 4-(aminometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida. 50 mg de la sal de HCl cruda de 4-(aminometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida se acopló a ácido picolínico por medio del procedimiento G. El producto sin tratar se purificó por HPLC de fase inversa para dar *N*-(4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencil)picolinamida. MS (Q1) 443,3 $(M)^+$.

Ejemplo 147 N^5-(4-cloro-3-(piridin-2-il)fenil)-N^2-isopropilpiridin-2,5-dicarboxamida



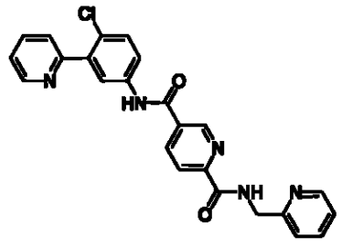
Se acopló 250 mg de ácido 5-(metoxicarbonil)picolínico a isopropilamina por medio del procedimiento G. 6-(isopropilcarbamoil)nicotinato de metilo sin tratar se hidrolizó por medio del procedimiento M para dar 227 mg de ácido 6-(isopropilcarbamoil)nicotínico. 60 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 6-(isopropilcarbamoil)nicotínico por medio del procedimiento G. El producto sin tratar se purificó por HPLC de fase inversa para dar N^5-(4-cloro-3-(piridin-2-il)fenil)-N^2-isopropilpiridin-2,5-dicarboxamida. MS (Q1) 395,1 $(M)^+$.

Ejemplo 148 N^2-*ter*-butil-N^5-(4-cloro-3-(piridin-2-il)fenil)piridin-2,5-dicarboxamida



Se acopló 250 mg de ácido 5-(metoxicarbonil)picolínico a *ter*-butilamina por medio del procedimiento G. 6-(*ter*-butilcarbamoil)nicotinato de metilo sin tratar se hidrolizó por medio del procedimiento M para dar 250 mg de ácido 6-(*ter*-butilcarbamoil)nicotínico. 60 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 6-(*ter*-butilcarbamoil)nicotínico por medio del procedimiento G. El producto sin tratar se purificó por HPLC de fase inversa para dar N^2-*ter*-butil-N^5-(4-cloro-3-(piridin-2-il)fenil)piridin-2,5-dicarboxamida. MS (Q1) 409 $(M)^+$.

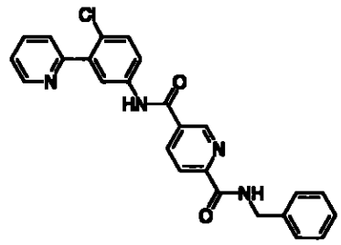
Ejemplo 149 N^5-(4-cloro-3-(piridin-2-il)fenil)-N^2-(piridin-2-ilmetil)piridin-2,5-dicarboxamida



Se acopló 250 mg de ácido 5-(metoxicarbonil)picolínico a piridin-2-ilmetanamina por medio del procedimiento G. 6-(piridin-2-ilmetilcarbamoil)nicotinato de metilo sin tratar se hidrolizó por medio del procedimiento M para dar 250 mg de ácido 6-(piridin-2-ilmetilcarbamoil)nicotínico. 60 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 6-(piridin-2-ilmetilcarbamoil)nicotínico por medio del procedimiento G. El

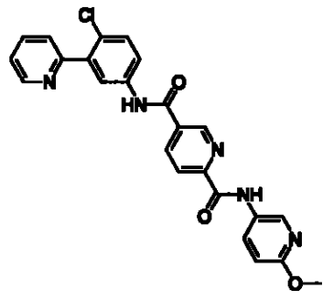
producto sin tratar se purificó por HPLC de fase inversa para dar N^5-(4-cloro-3-(piridin-2-il)fenil)-N^2-(piridin-2-ilmetil)piridin-2,5-dicarboxamida. MS (Q1) 444,1 $(M)^+$.

Ejemplo 150 N^2-bencil-N^5-(4-cloro-3-(piridin-2-il)fenil)piridin-2,5-dicarboxamida



Se acopló 250 mg de ácido 5-(metoxicarbonil)picolínico a bencilamina por medio del procedimiento G. 6-(bencilcarbamoil)nicotinato de metilo sin tratar se hidrolizó por medio del procedimiento M para dar 300 mg de ácido 6-(bencilcarbamoil)nicotínico. 60 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 6-(bencilcarbamoil)nicotínico por medio del procedimiento G. El producto sin tratar se purificó por HPLC de fase inversa para dar N^2-bencil-N^5-(4-cloro-3-(piridin-2-il)fenil)piridin-2,5-dicarboxamida. MS (Q1) 443,1 $(M)^+$.

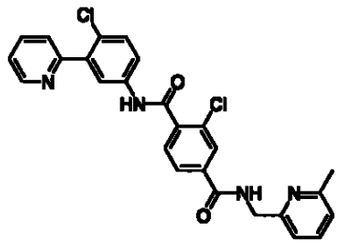
Ejemplo 151 N^5-(4-cloro-3-(piridin-2-il)fenil)-N^2-(6-metoxipiridin-3-il)piridin-2,5-dicarboxamida



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Se acopló 250 mg de ácido 5-(metoxicarbonil)picolínico a 6-metoxipiridin-3-amina por medio del procedimiento G. 6-(6-metoxipiridin-3-ilcarbamoil)nicotinato de metilo sin tratar se hidrolizó por medio del procedimiento M para dar 196 mg de ácido 6-(6-metoxipiridin-3-ilcarbamoil)nicotínico. 60 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 6-(6-metoxipiridin-3-ilcarbamoil)nicotínico por medio del procedimiento G. El producto sin tratar se recristalizó para dar N^5-(4-cloro-3-(piridin-2-il)fenil)-N^2-(6-metoxipiridin-3-il)piridin-2,5-dicarboxamida pura. MS (Q1) 460 $(M)^+$.

Ejemplo 152 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-((6-metilpiridin-2-il)metil)-tereftalamida

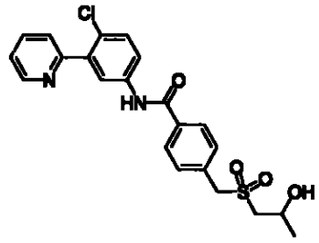


Se agregó 2,5 mL de Diisopropilazodicarboxilato en 1,5mL de THF por goteo a una solución de 250 mg de (6-metilpiridin-2-il)metanol, 2,8g de Trifenilfosfina y 1,6 g de isoindolin-1,3-diona en THF anhidro a temperatura ambiente. La reacción se agitó por 2 horas y se monitoreó por TLC. El completarse, el solvente se concentró, el material sin tratar se extrajo en agua y cloroformo 3 veces y se secó sobre Sulfato de magnesio. El material sin tratar se purificó mediante ISCO Combi-Flash para dar 2-((6-metilpiridin-2-il)metil)isoindolin-1,3-diona. 350 mg de 2-((6-metilpiridin-2-il)metil)isoindolin-1,3-diona se trató con 440 µL de monohidrato de hidrazina en EtOH y se sometió a reflujo por varias horas para dar (6-metilpiridin-2-il)metanamina. La (6-

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metilpiridin-2-il)metanamina cruda se evaporó y se acopló directamente a 50mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico por medio del procedimiento G. El producto sin tratar se purificó en HPLC de fase inversa para dar 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-((6-metilpiridin-2-il)metil)tereftalamida. MS (Q1) 491,1 $(M)^+$.

Ejemplo 153 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((2-hidroxipropilsulfonil)metil)benzamida

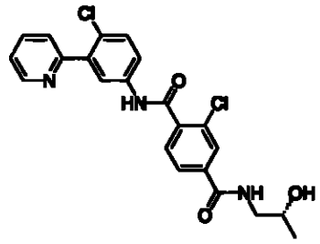


Se hizo reaccionar 1 g de 4-(bromometil)benzoato de metilo con 1-mercaptopropan-2-ol por medio del procedimiento Q. 1 g de 4-((2-hidroxipropiltio)metil)benzoato de metilo se oxidó con 2g de MCPBA en DCM a –78°C para formar 4-((2-hidroxipropilsulfonil)metil)benzoato de metilo crudo. La reacción se evaporó y se purificó mediante ISCO Combi-Flash para dar 567 mg de 4-((2-hidroxipropilsulfonil)metil)benzoato de metilo puro el cual subsiguientemente se hidrolizó por medio del procedimiento M para dar 328 mg de ácido 4-((2-hidroxipropilsulfonil)metil)benzoico. 50 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 4-((2-hidroxipropilsulfonil)metil)benzoico por medio del procedimiento G. El producto sin tratar se purificó en HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((2-hidroxipropilsulfonil)metil)benzamida. MS (Q1) 445,3 $(M)^+$.

Ejemplo 154 (*R*)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-

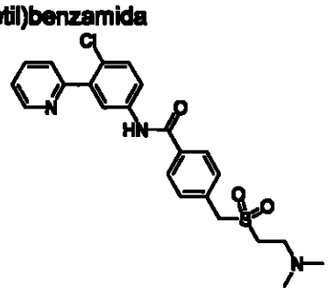
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hidroxipropil)tereftalamida



Se acopló 100 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a (*R*)-2-amino-2-feniletanol por medio del procedimiento G. El producto sin tratar se purificó en HPLC de fase inversa para dar (*R*)-2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-(2-hidroxipropil)tereftalamida. MS (Q1) 444,3 $(M)^+$.

Ejemplo 155 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((2-(dimetilamino)etilsulfonil)metil)benzamida

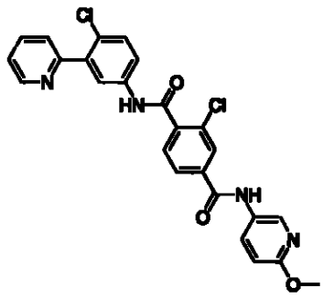


Se acopló 500 mg de ácido 4-cloro-3-(piridin-2-il)abilina a 4-(bromometil)benzoico por medio del procedimiento E. 170 mg de 4-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida se hizo reaccionar con clorhidrato de 2-(dimetilamino)etantiol por medio del procedimiento Q. 140mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((2-(dimetilamino)etiltio)metil)benzamida cruda se hizo reaccionar con Oxona por medio del procedimiento R. El producto sin tratar se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-

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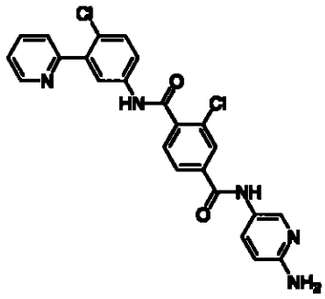
(piridin-2-il)fenil)-4-((2-(dimetilamino)etilsulfonil)metil)benzamida. MS (Q1) 458,3 $(M)^+$.

Ejemplo 156 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(6-metoxipiridin-3-il)tereftalamida



Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 6-metoxipiridin-3-amina por medio del procedimiento G. El producto sin tratar se purificó en HPLC de fase inversa para dar 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(6-metoxipiridin-3-il)tereftalamida. MS (Q1) 493 $(M)^+$.

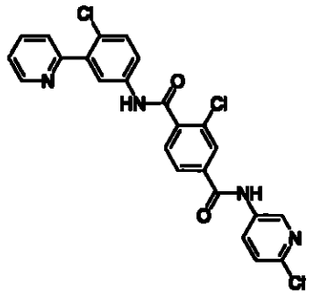
Ejemplo 157 N^4-(6-aminopiridin-3-il)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-tereftalamida



Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a piridin-2,5-diamina por medio del procedimiento G.

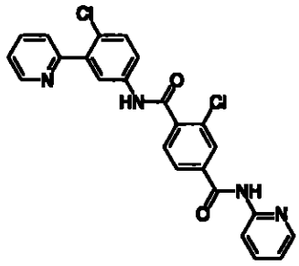
El producto sin tratar se purificó en HPLC de fase inversa para dar N^4-(6-aminopiridin-3-il)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)tereftalamida. MS (Q1) 478 $(M)^+$.

Ejemplo 158 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(6-cloropiridin-3-il)tereftalamida



Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 6-cloropiridin-3-amina por medio del procedimiento G. El producto sin tratar se purificó en HPLC de fase inversa para dar 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(6-cloropiridin-3-il)tereftalamida. MS (Q1) 497 $(M)^+$.

Ejemplo 159 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(piridin-2-il)tereftalamida

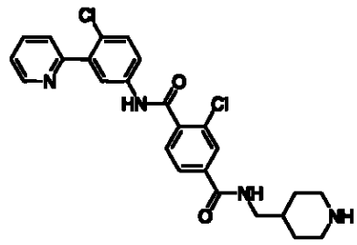


Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a piridin-2-amina por medio del procedimiento G. El

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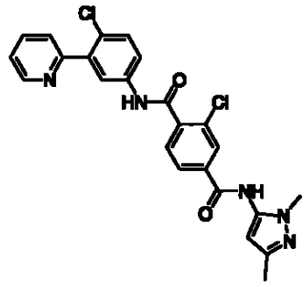
producto sin tratar se purificó en HPLC de fase inversa para dar 2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-(piridin-2-il)tereftalamida. MS (Q1) 483 (M)$^+$.

Ejemplo 160 2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-(piperidin-4-ilmetil)tereftalamida



Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a piperidin-4-ilmetanamina por medio del procedimiento G. El producto sin tratar se purificó en HPLC de fase inversa para dar 2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-(piperidin-4-ilmetil)tereftalamida. MS (Q1) 483 (M)$^+$.

Ejemplo 161 2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-(1,3-dimetil-1*H*-pirazol-5-il)tereftalamida

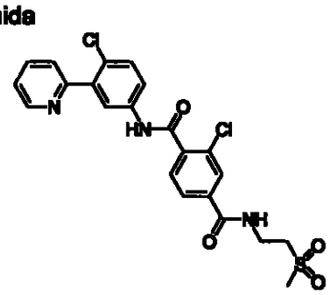


Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 1,3-dimetil-1*H*-pirazol-5-amina por medio del procedimiento G. El producto sin tratar se purificó en HPLC de fase inversa para dar 2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-(1,3-dimetil-1*H*-pirazol-5-

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457

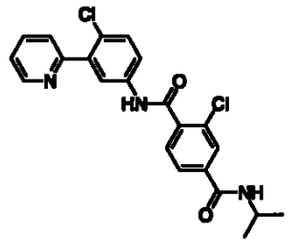
il)tereftalamida. MS (Q1) 480 $(M)^+$.

Ejemplo162 2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-(2-(metilsulfonil)etil)-tereftalamida



Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a 2-(metilsulfonil)etanamina por medio del procedimiento G. El producto sin tratar se purificó en HPLC de fase inversa para dar 2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-(2-(metilsulfonil)etil)tereftalamida. MS (Q1) 492 $(M)^+$.

Ejemplo 163 2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-isopropiltereftalamida

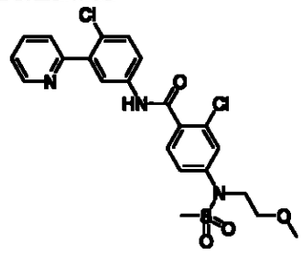


Se acopló 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)benzoico a isopropilamina por medio del procedimiento G. El producto sin tratar se purificó en HPLC de fase inversa para dar 2-cloro-*N*^{1}-(4-cloro-3-(piridin-2-il)fenil)-*N*^{4}-isopropiltereftalamida. MS (Q1) 428 $(M)^+$.

Ejemplo 164 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-(2-

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metoxietil)metil-sulfonamido)benzamida

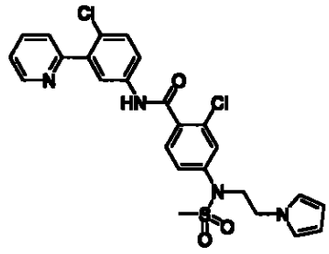


Se agregó a 5 g de 2-cloro-4-nitrobenzoato de metilo en 100 mL de EtOH 20 g de cloruro de estaño (II) en porciones. La reacción se calentó a 55°C y se monitoreó por TLC hasta completarse. El solvente se concentró y la extracción se realizó en acetato de etilo y agua con TEA para reducir las emulsiones. La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró para dar 3,9 g de 4-amino-2-clorobenzoato de metilo. 1 g de 4-amino-2-clorobenzoato de metilo se enfrió a 0°C en DCM con 485 µL de Piridina antes de agregar cloruro de Metanosulfonilo por goteo. La reacción se dejó subir la temperatura hasta la temperatura ambiente y agitar durante la noche. El solvente se concentró y el material sin tratar se disolvió en acetato de etilo y se extrajo con solución saturada de bicarbonato y luego salmuera. El material sin tratar se secó sobre sulfato de magnesio, se filtró y se concentró para dar 1,54 g de 2-cloro-4-(metilsulfonamido)benzoato de metilo. Se agregaron 107 µL de 1-bromo-2-metoxietano y 556 mg de carbonato de cesio a 150 mg de 2-cloro-4-(metilsulfonamido)benzoato de metilo en DMF y se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se extrajo en acetato de etilo dos veces con bicarbonato saturado y una vez con salmuera, se secó sobre sulfato de magnesio, se filtró y se concentró para dar 2-cloro-4-(*N*-(2-metoxietil)metilsulfonamido)benzoato de metilo. 182 mg de 2-cloro-4-(*N*-

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(2-metoxietil)metilsulfonamido)benzoato de metilo se hidrolizó por medio del procedimiento M para dar 169 mg de ácido 2-cloro-4-(*N*-(2-metoxietil)metilsulfonamido)benzoico crudo. 65 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 2-cloro-4-(*N*-(2-metoxietil)metilsulfonamido)benzoico por medio del procedimiento G. El producto sin tratar se purificó por HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-(2-metoxietil)metilsulfonamido)benzamida. MS (Q1) 494 $(M)^+$.

Ejemplo 165 4-(*N*-(2-(1*H*-pirrol-1-il)etil)metilsulfonamido)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida



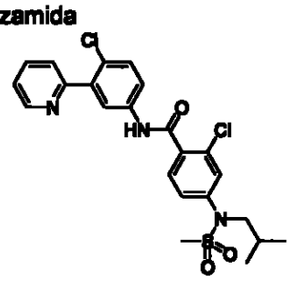
Se agregaron 200 µL de 1-(2-bromoetil)-1*H*-pirrol y 556 mg de Carbonato de cesio a 150 mg de 2-cloro-4-(metilsulfonamido)benzoato de metilo en DMF y se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se extrajo en acetato de etilo dos veces con bicarbonato saturado y una vez con salmuera, se secó sobre Sulfato de magnesio, se filtró y se concentró para dar 4-(*N*-(2-(1*H*-pirrol-1-il)etil)metilsulfonamido)-2-clorobenzoato de metilo. 230 mg de 4-(*N*-(2-(1*H*-pirrol-1-il)etil)metilsulfonamido)-2-clorobenzoato de metilo se hidrolizó por medio del procedimiento M para dar 221 mg de ácido 4-(*N*-(2-(1*H*-pirrol-1-il)etil)metilsulfonamido)-2-clorobenzoico crudo.

Se acopló 64 mg de 4-cloro-3-(piridin-2-il)abilina a ácido 4-(*N*-(2-(1*H*-

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pirrol-1-il)etil)metilsulfonamido)-2-clorobenzoico por medio del procedimiento G. El producto sin tratar se purificó por HPLC de fase inversa para dar 4-(*N*-(2-(1*H*-pirrol-1-il)etil)metilsulfonamido)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida. MS (Q1) 529 $(M)^+$.

Ejemplo 166 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-isobutilmetilsulfonamido)-benzamida

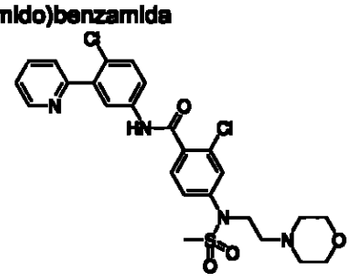


Se agregaron 175 µL de 1-yodo-2-metilpropano y 740 mg de carbonato de cesio a 200 mg de 2-cloro-4-(metilsulfonamido)benzoato de metilo en 2 mL de DMF y se agitó en el microondas a 140°C durante 30 minutos. La mezcla de reacción se extrajo en acetato de etilo dos veces con agua, se secó sobre sulfato de magnesio, se filtró, se concentró y se purificó en ISCO Combi-Flash para dar 2-cloro-4-(*N*-isobutilmetilsulfonamido)benzoato de metilo. 120 mg de 2-cloro-4-(*N*-isobutilmetilsulfonamido)benzoato de metilo se hidrolizó por medio del procedimiento M para dar 110 mg de ácido 2-cloro-4-(*N*-isobutilmetilsulfonamido)benzoico crudo. 75 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 2-cloro-4-(*N*-isobutilmetilsulfonamido)benzoico por medio del procedimiento G. El producto sin tratar se purificó por HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-isobutilmetilsulfonamido)benzamida. MS (Q1) 492 $(M)^+$.

Ejemplo 167 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-(2-

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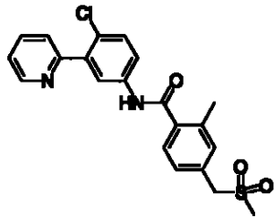
morfolinoetil)metil-sulfonamido)benzamida



Se agregaron 1,2 g de 4-(2-cloroetil)morfolina y 2,5 g de Carbonato de cesio a 334 mg de 2-cloro-4-(metilsulfonamido)benzoato de metilo en 7 mL de DMF y se agitó en el microondas a 150°C durante 30 minutos. La mezcla de reacción se extrajo en acetato de etilo dos veces con agua, se secó sobre Sulfato de magnesio, se filtró, se concentró para dar 2-cloro-4-(*N*-(2-morfolinoetil)metilsulfonamido)benzoato de metilo crudo. 476 mg de 2-cloro-4-(*N*-(2-morfolinoetil)metilsulfonamido)benzoato de metilo se hidrolizó por medio del procedimiento M y se purificó por HPLC de fase inversa para dar 460 mg de ácido 2-cloro-4-(*N*-(2-morfolinoetil)metilsulfonamido)benzoico crudo. 100 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 2-cloro-4-(*N*-(2-morfolinoetil)metilsulfonamido)benzoico por medio del procedimiento G. El producto sin tratar se purificó por HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-(2-morfolinoetil)metilsulfonamido)benzamida. MS (Q1) 549 $(M)^+$.

Ejemplo 168 *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-4-(metilsulfonilmetil)benzamida

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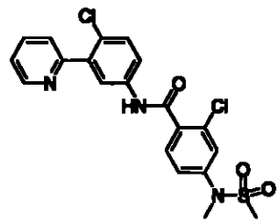


Se hidrolizó 410 mg de 2-metiltereftalato de dimetilo por medio del procedimiento M y se purificó mediante ISCO Combi-Flash para dar ácido 4-(metoxicarbonil)-3-metilbenzoico. 255 mg de ácido 4-(metoxdcarbonil)-3-metilbenzoico se enfrió a 0°C en 2 mL de THF antes de agregarse una solución de 2,6 mL de complejo BH_3-THF 1M en THF por goteo. El baño de hielo subsiguientemente se retiró y la reacción se agitó a temperatura ambiente hasta que la reacción se detuvo a ~50% de completarse por TLC. La reacción se reenfrió a 0°C y se agregaron otros 2,6 mL de BH_3-THF por goteo antes de retirar el baño de hielo. Al completarse, la reacción se reenfrió a 0°C y se detuvo con HCl 3N por goteo. La capa acuosa se extrajo 2 veces con acetato de etilo y la capa orgánica luego se extrajo una vez con solución de bicarbonato y salmuera, se secó sobre sulfato de magnesio, se filtró y se concentró para dar 4-(hidroxdmetil)-2-metilbenzoato de metilo. 220 mg de 4-(hidroxdmetil)-2-metilbenzoato de metilo se enfrió a 0°C en 5 mL de DCM antes de agregar 260 mg de Trifenilfosfina y 395 mg de NBS. La reacción se concentró y directamente se purificó mediante ISCO Combi-Flash para dar 4-(bromometil)-2-metilbenzoato de metilo puro. 255 mg de 4-(bromometil)-2-metilbenzoato de metilo se hizo reaccionar por medio del procedimiento O para dar 2-metil-4-(metilsulfonilmetil)benzoato de metilo. 250 mg de 2-metil-4-(metilsulfonilmetil)benzoato de metilo luego se hidrolizó al calentar a 45°C durante 1 hora por medio del procedimiento M para dar ácido 2-metil-4-

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(metilsulfonilmetil)benzoico. 202 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 2-metil-4-(metilsulfonilmetil)benzoico por medio del procedimiento G. El producto sin tratar se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-4-(metilsulfonilmetil)benzamida. MS (Q1) 415 $(M)^+$.

Ejemplo 169 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-metilmetil-sulfonamido)benzamida

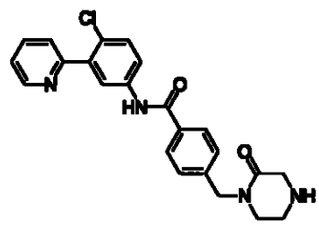


Se agregaron 78 µL de yodometano y 447 mg de carbonato de cesio a 300 mg de 2-cloro-4-(metilsulfonamido)benzoato de metilo en 3 mL de DMF y se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se extrajo en acetato de etilo dos veces con bicarbonato saturado y una vez con salmuera, se secó sobre sulfato de magnesio, se filtró y se concentró para dar 2-cloro-4-(*N*-metilmetilsulfonamido)benzoato de metilo crudo. 295 mg de 2-cloro-4-(*N*-metilmetilsulfonamido)benzoato de metilo se hidrolizó por medio del procedimiento M para dar 249 mg de ácido 2-cloro-4-(*N*-metilmetilsulfonamido)benzoico.

Se acopló 100 mg de 4-cloro-3-(piridin-2-il)abilina a ácido 2-cloro-4-(*N*-metilmetilsulfonamido)benzoico por medio del procedimiento G. El producto sin tratar se purificó por HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-metilmetilsulfonamido)benzamida. MS (Q1) 450 $(M)^+$.

Ejemplo 170 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((2-oxopiperazin-1-il)metil)benzamida

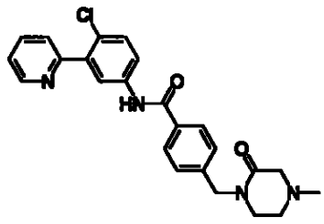
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Se hizo reaccionar 500 mg de 4-(bromometil)benzoato de metilo con 480 mg de 3-oxopiperazina-1-carboxilato de *ter*-butilo y 1 g de carbonato de cesio en 9 mL de DMF a 45°C. Al completarse, la reacción se extrajo en acetato de etilo 2 veces bicarbonato saturado, se secó sobre sulfato de magnesio, se filtró y se concentró para dar 4-(4-(metoxicarbonil)bencil)-3-oxopiperazina-1-carboxilato de *ter*-butilo. Se hidrolizaron 613 mg de 4-(4-(metoxicarbonil)bencil)-3-oxopiperazina-1-carboxilato de *ter*-butilo por medio del procedimiento M para dar ácido 4-((4-(*ter*-butoxicarbonil)-2-oxopiperazin-1-il)metil)benzoico. 200 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 4-((4-(*ter*-butoxicarbonil)-2-oxopiperazin-1-il)metil)benzoico por medio del procedimiento G. El producto sin tratar se extrajo dos veces con bicarbonato saturado en acetato de etilo, se secó sobre sulfato de magnesio, se filtró y se concentró para dar 4-(4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencil)-3-oxopiperazina-1-carboxilato de *ter*-butilo crudo. Subsiguientemente se agregó HCl 4N a 4-(4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencil)-3-oxopiperazina-1-carboxilato de *ter*-butilo sin tratar y se concentró para dar la sal de HCl de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((2-oxopiperazin-1-il)metil)benzamida. La reacción se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((2-oxopiperazin-1-il)metil)benzamida pura. MS (Q1) 421,3 $(M)^+$.

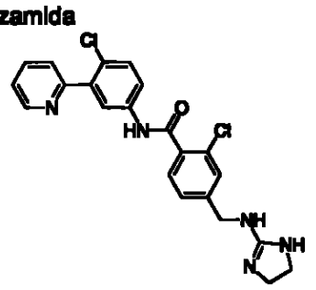
Ejemplo 171 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((4-metil-2-oxopiperazin-1-il)metil)benzamida

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Se agregó 55 mg de Paraformaldehido y 185 mg de Triacetoxiborhidruro de sodio en 1 mL de 2% AcOH en DMF a 200 mg de la sal de HCl de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((2-oxopiperazin-1-il)metil)benzamida. Luego de completarse, la reacción se extrajo una vez con bicarbonato y salmuera en Acetato de etilo, se secó sobre Sulfato de magnesio, se concentró y se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((4-metil-2-oxopiperazin-1-il)metil)benzamida pura. MS (Q1) 435,3 $(M)^+$.

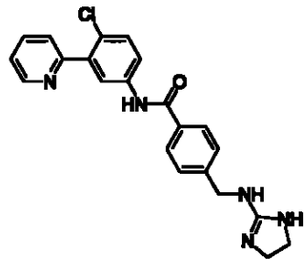
Ejemplo 172 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-((4,5-dihidro-1*H*-imidazol-2-ilamino)metil)benzamida



Se hizo reaccionar 100 mg de la sal de HCl cruda de 4-(aminometil)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida con 72 mg de 1-(4,5-dihidro-1*H*-imidazol-2-il)-3,5-dimetil-1*H*-pirazol y 100 µL de DIPEA en 500 µL de DMF en el microondas a 150°C durante 5 minutos. El producto sin tratar se concentró a sequedad y se purificó por HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-((4,5-dihidro-1*H*-imidazol-2-ilamino)metil)benzamida. MS

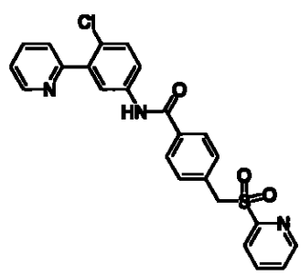
(Q1) 440 $(M)^+$.

Ejemplo 173 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((4,5-dihidro-1*H*-imidazol-2-ilamino)metil)benzamida



Se hizo reaccionar 100 mg de la sal de HCl cruda de 4-(aminometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida con 80 mg de 1-(4,5-dihidro-1*H*-imidazol-2-il)-3,5-dimetil-1*H*-pirazol y 110 µL de DIPEA en 1 mL de DMF en el microondas a 150°C durante 5 minutos. El producto sin tratar se concentró a sequedad y se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((4,5-dihidro-1*H*-imidazol-2-ilamino)metil)benzamida. MS (Q1) 406 $(M)^+$.

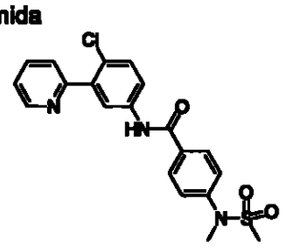
Ejemplo 174 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((piridin-2-ilsulfonil)metil)benzamida



Se hizo reaccionar 500 mg de 4-(bromometil)benzoato de metilo con piridin-2-tiol por medio del procedimiento Q. 260 mg de 4-((piridin-2-iltio)metil)benzoato de metilo se hizo reaccionar por medio del procedimiento R

para dar 4-((piridin-2-ilsulfonil)metil)benzoato de metilo. 275 mg de 4-((piridin-2-ilsulfonil)metil)benzoato de metilo se hidrolizó por medio del procedimiento M para dar ácido 4-((piridin-2-ilsulfonil)metil)benzoico. 75 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 4-((piridin-2-ilsulfonil)metil)benzoico por medio del procedimiento G. El producto sin tratar se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((piridin-2-ilsulfonil)metil)benzamida pura. MS (Q1) 464,1 $(M)^+$.

Ejemplo 175 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-metilmetilsulfonamido)benzamida

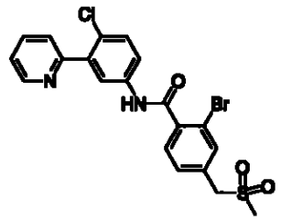


Se enfrió 500 mg de 4-(metilamino)benzoato de metilo a 0°C en DCM con 270 µL de Piridina antes de agregar 260 µL de cloruro de Metansulfonilo se agregó por goteo. La reacción se dejó subir la temperatura hasta la temperatura ambiente y agitar durante la noche. El solvente se concentró y el material sin tratar se disolvió en acetato de etilo y se extrajo con una solución 0,1N de NaOH dos veces. El material sin tratar se secó sobre Sulfato de magnesio, se filtró y se concentró para dar 4-(*N*-metilmetilsulfonamido)benzoato de metilo. 698 mg de 4-(*N*-metilmetilsulfonamido)benzoato de metilo se hidrolizó por medio del procedimiento M para dar ácido 4-(*N*-metilmetilsulfonamido)benzoico. 100 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 4-(*N*-metilmetilsulfonamido)benzoico por medio del procedimiento G. El producto sin

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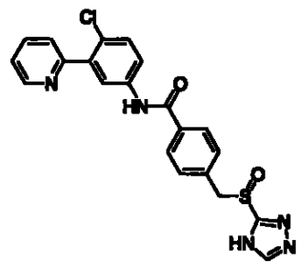
tratar se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-metilmetilsulfonamido)benzamida pura. MS (Q1) 416,3 $(M)^+$.

Ejemplo 176 2-bromo-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida



Se bromó 1,2 g de ácido 2-bromo-4-metilbenzoico por medio del procedimiento N. 100 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a 160 mg de ácido 2-bromo-4-(bromometil)benzoico por medio del procedimiento E. 213 mg de 2-bromo-4-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida se hizo reaccionar por medio del procedimiento O para dar 2-bromo-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida la cual se purificó por HPLC de fase inversa para dar 2-bromo-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida pura. MS (Q1) 481,2 $(M)^+$.

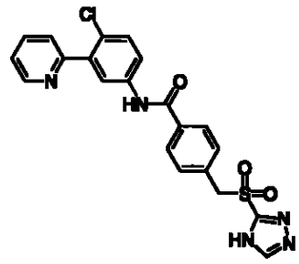
Ejemplo 177 4-((4*H*-1,2,4-triazol-3-ilsulfinil)metil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida



Se hizo reaccionar 500 mg de 4-(bromometil)benzoato de metilo con 4*H*-

1,2,4-triazol-3-tiol por medio del procedimiento Q. 542 mg de 4-((4*H*-1,2,4-triazol-3-iltio)metil)benzoato de metilo subsiguientemente se hizo reaccionar por medio del procedimiento R para dar una mezcla aproximadamente 1:9 de 4-((4*H*-1,2,4-triazol-3-ilsulfinil)metil)benzoato de metilo y 4-((4*H*-1,2,4-triazol-3-ilsulfonil)metil)benzoato de metilo. La mezcla de 467 mg se hidrolizó por medio del procedimiento M para dar ácido 4-((4*H*-1,2,4-triazol-3-ilsulfinil)metil)benzoico y ácido 4-((4*H*-1,2,4-triazol-3-ilsulfonil)metil)benzoico. 107 mg de la mezcla de ácido 4-((4*H*-1,2,4-triazol-3-ilsulfinil)metil)benzoico y ácido 4-((4*H*-1,2,4-triazol-3-ilsulfonil)metil)benzoico se acopló a 75 mg de 4-cloro-3-(piridin-2-il)abilina por medio del procedimiento G. La mezcla se separó en HPLC de fase inversa para dar 4-((4*H*-1,2,4-triazol-3-ilsulfinil)metil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida. MS (Q1) 438,1 $(M)^+$.

Ejemplo 178 4-((4*H*-1,2,4-triazol-3-ilsulfonil)metil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida

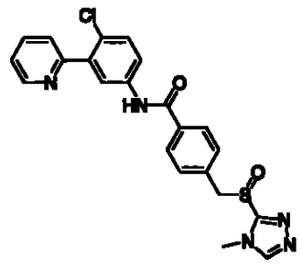


Se acopló 107 mg de una mezcla de ácido 4-((4*H*-1,2,4-triazol-3-ilsulfinil)metil)benzoico y ácido 4-((4*H*-1,2,4-triazol-3-ilsulfonil)metil)benzoico a 75 mg de 4-cloro-3-(piridin-2-il)abilina por medio del procedimiento G. La mezcla se separó en HPLC de fase inversa para dar 4-((4*H*-1,2,4-triazol-3-ilsulfonil)metil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida. MS (Q1) 454,3 $(M)^+$.

Ejemplo 179 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((4-metil-4*H*-1,2,4-triazol-3-

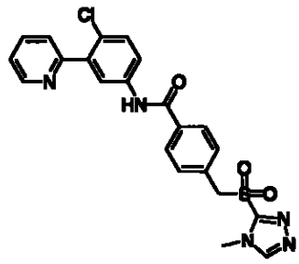
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ilsulfinil)-metil)benzamida



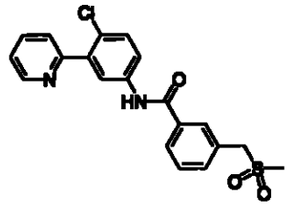
Se hizo reaccionar 500 mg de 4-(bromometil)benzoato de metilo con 4-metil-4*H*-1,2,4-triazol-3-tiol por medio del procedimiento Q. 804 mg de 4-((4-metil-4*H*-1,2,4-triazol-3-iltio)metil)benzoato de metilo subsiguientemente se hizo reaccionar por medio del procedimiento R para dar una mezcla aproximadamente 1:9 de 4-((4-metil-4*H*-1,2,4-triazol-3-ilsulfinil)metil)benzoato de metilo y 4-((4-metil-4*H*-1,2,4-triazol-3-ilsulfonil)metil)benzoato de metilo. La mezcla de 740 mg se hidrolizó por medio del procedimiento M para dar ácido 4-((4-metil-4*H*-1,2,4-triazol-3-ilsulfinil)metil)benzoico y ácido 4-((4-metil-4*H*-1,2,4-triazol-3-ilsulfonil)metil)benzoico. 114 mg de la mezcla de ácido 4-((4-metil-4*H*-1,2,4-triazol-3-ilsulfinil)metil)benzoico y ácido 4-((4-metil-4*H*-1,2,4-triazol-3-ilsulfonil)metil)benzoico se acopló a 75 mg de 4-cloro-3-(piridin-2-il)abilina por medio del procedimiento G. La mezcla se separó en HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((4-metil-4*H*-1,2,4-triazol-3-ilsulfinil)metil)benzamida. MS (Q1) 452,3 $(M)^+$.

Ejemplo 180 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((4-metil-4*H*-1,2,4-triazol-3-ilsulfonil)-metil)benzamida



Se acopló 114 mg de la mezcla de ácido 4-((4-metil-4*H*-1,2,4-triazol-3-ilsulfinil)metil)benzoico y ácido 4-((4-metil-4*H*-1,2,4-triazol-3-ilsulfonil)metil)benzoico a 75 mg de 4-cloro-3-(piridin-2-il)abilina por medio del procedimiento G. La mezcla se separó en HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((4-metil-4*H*-1,2,4-triazol-3-ilsulfonil)metil)benzamida. MS (Q1) 468,1 $(M)^+$.

Ejemplo 181 *N*-(4-cloro-3-(piridin-2-il)fenil)-3-(metilsulfonilmetil)benzamida

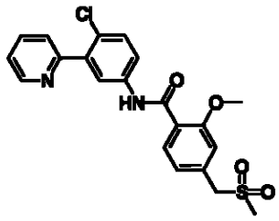


300 mg de 3-(bromometil)benzoato de metilo se hizo reaccionar por medio del procedimiento O para dar 3-(metilsulfonilmetil)benzoato de metilo. 230 mg de 3-(metilsulfonilmetil)benzoato de metilo se hizo reaccionar por medio del procedimiento M para dar ácido 3-(metilsulfonilmetil)benzoico.

75 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 3-(metilsulfonilmetil)benzoico por medio del procedimiento G. El producto sin tratar se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-3-(metilsulfonilmetil)benzamida pura. MS (Q1) 401 $(M)^+$.

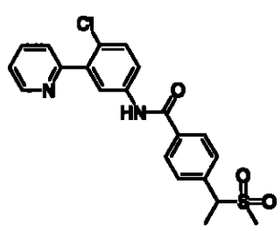
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Ejemplo 182 *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metoxi-4-(metilsulfonilmetil)benzamida



Se bromó 900 mg de ácido 2-metoxi-4-metilbenzoico por medio del procedimiento N para dar ácido 4-(bromometil)-2-metoxibenzoico. 100 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a 132 mg de ácido 4-(bromometil)-2-metoxibenzoico por medio del procedimiento E. 211 mg de 4-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metoxibenzamida se hizo reaccionar por medio del procedimiento O y se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metoxi-4-(metilsulfonilmetil)benzamida pura. MS (Q1) 431 $(M)^+$.

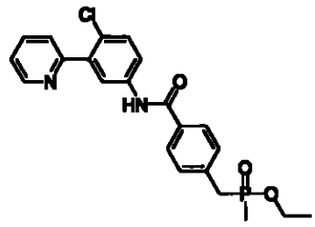
Ejemplo 183 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(1-(metilsulfonil)etil)benzamida



Se acopló 75 mg de 4-cloro-3-(piridin-2-il)abilina a 93 mg de ácido 4-(1-bromoetil)benzoico por medio del procedimiento E. 153 mg de 4-(1-bromoetil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida se hizo reaccionar por medio del procedimiento O y se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-

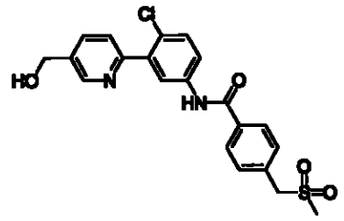
(piridin-2-il)fenil)-4-(1-(metilsulfonil)etil)benzamida pura. MS (Q1) 415,3 $(M)^+$.

Ejemplo 184 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencil(metil)fosfinato de etilo



Se hizo reaccionar 90 mg de 4-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida con 45 µL de metilfosfonito de dietilo en el microondas a 120°C durante 5 minutos. La reacción se evaporó a sequedad y se purificó por HPLC de fase inversa para dar 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencil(metil)fosfinato de etilo puro. MS (Q1) 429 $(M)^+$.

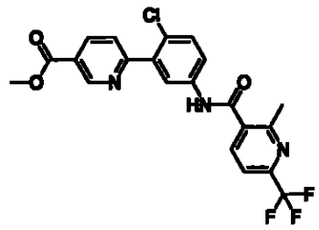
Ejemplo 185 *N*-(4-cloro-3-(5-(hidroximetil)piridin-2-il)fenil)-4-(metilsulfonil-metil)benzamida



Se hizo reaccionar 75 mL de bromuro de (5-metilpiridin-2-il)zinc(II) con 4 g de 1-cloro-2-iodo-4-nitrobenceno por medio del procedimiento B. A 935 mg de 2-(2-cloro-5-nitrofenil)-5-metilpiridina en 5 mL de ácido sulfúrico se agregó lentamente 2,25 g de óxido de cromo (III) y la reacción se agitó por varias horas a temperatura ambiente hasta completarse. Se agregó agua helada para diluir la reacción y la capa acuosa se extrajo 3 veces con Acetato de etilo. Las capas

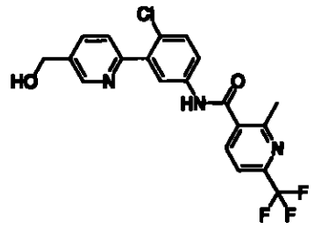
orgánicas se combinaron, se secó sobre Sulfato de magnesio, se filtró y se concentró para dar ácido 6-(2-cloro-5-nitrofenil)nicotínico. 704 mg de ácido 6-(2-cloro-5-nitrofenil)nicotínico se esterificó con 3,1 mL de HCl 4N en Dioxano en 20 mL de MeOH. La reacción se concentró y se sometió a trabajo básico, se secó sobre Sulfato de magnesio, se filtró y se concentró para dar 6-(2-cloro-5-nitrofenil)nicotinato de metilo. 681 mg de 6-(2-cloro-5-nitrofenil)nicotinato de metilo se trató con 2,1 g de Cloruro de estaño (II) y 1 mL de HCl en 25 mL de EtOH. Al completarse, EtOH se concentró y la reacción se extrajo con acetato de etilo y agua con TEA para disminuir las emulsiones. La capa orgánica se secó sobre Sulfato de magnesio, se filtró y se concentró para dar 6-(5-amino-2-clorofenil)nicotinato de metilo crudo. 296 mg de 6-(5-amino-2-clorofenil)nicotinato de metilo se acopló a 266 mg de ácido 4-(metilsulfonilmetil)benzoico por medio del procedimiento G. A 518 mg de 6-(2-cloro-5-(4-(metilsulfonilmetil)benzamido)fenil)nicotinato de metilo a 0°C en 20 mL de EtOH se agregó lentamente 640 mg de Borhidruro de sodio. La reacción subsiguientemente se reflujó por 1 hora hasta completarse, se fraguó con agua y se extrajo con Acetato de etilo. La capa orgánica se secó sobre Sulfato de magnesio, se filtró, se concentró y se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(5-(hidroxdmetil)piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida pura. MS (Q1) 431,1 $(M)^+$.

Ejemplo 186 6-(2-cloro-5-(2-metil-6-(trifluorometil)nicotinamido)fenil)nicotinato



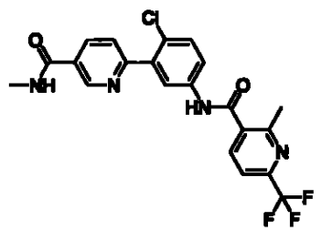
Se trató 200 mg de 6-(5-amino-2-clorofenil)nicotinato de metilo con 255 µL de cloruro de 2-metil-6-(trifluorometil)nicotinoilo por medio del procedimiento D y se purificó por HPLC de fase inversa para dar 6-(2-cloro-5-(2-metil-6-(trifluorometil)nicotinamido)fenil)nicotinato puro. MS (Q1) 450 $(M)^+$.

Ejemplo 187 *N*-(4-cloro-3-(5-(hidroximetil)piridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida



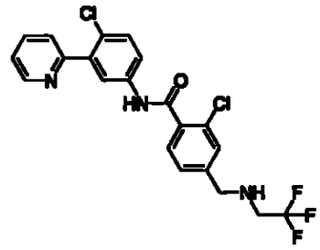
A 110 mg de 6-(2-cloro-5-(2-metil-6-(trifluorometil)nicotinamido)fenil)nicotinato de metilo a 0°C en 5 mL de EtOH se agregó lentamente 148 mg de Borhidruro de sodio. La reacción subsiguientemente se reflujó por 1 hora hasta completarse, se fraguó con agua y se extrajo con Acetato de etilo. La capa orgánica se secó sobre Sulfato de magnesio, se filtró, se concentró y se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(5-(hidroximetil)piridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida puro. MS (Q1) 422,1 $(M)^+$.

Ejemplo 188 *N*-(4-cloro-3-(5-(metilcarbamoil)piridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida



Se hidrolizó 120 mg de 6-(2-cloro-5-(2-metil-6-(trifluorometil)nicotinamido)fenil)nicotinato por medio del procedimiento M. 112 mg de ácido 6-(2-cloro-5-(2-metil-6-(trifluorometil)nicotinamido)fenil)nicotínico se acopló a Clorhidrato de metilamina por medio del procedimiento G y se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(5-(metilcarbamoil)piridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida pura. MS (Q1) 449 $(M)^+$.

Ejemplo 189 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-((2,2,2-trifluoroetilamino)metil)benzamida.



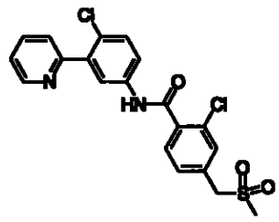
A 24,9 g de ácido 2-cloro-4-(metoxicarbonil)benzoico y 2 mL de ácido sulfúrico en 350 mL de DCM se agregó gas isobutileno a –78°C hasta que el solvente se saturó y se destapó en forma segura. Se dejó estar varios días a temperatura ambiente y se reenfrió a –78°C antes de retirar la tapa. Se concentró el solvente, se extrajo con acetato de etilo y bicarbonato, se secó con sulfato de magnesio, se filtró y se concentró para dar 31,4 g de 2-clorotereftalato de 1-*ter*-butilo 4-metilo. 3,35 g de 2-clorotereftalato de 1-*ter*-

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butilo 4-metilo se hidrolizó por medio del procedimiento M. 2,5 g de ácido 4-(*ter*-butoxicarbonil)-3-clorobenzoico se enfrió a 0°C en 25 mL de THF antes de agregar una solución de 19,5 mL de complejo BH_3-THF 1M en THF por goteo. El baño de hielo subsiguientemente se retiró y la reacción se agitó a temperatura ambiente hasta que la reacción se detuvo a ~50% de completarse por TLC. La reacción se reenfrió a 0°C y se agregaron otros 19,5 mL de BH_3-THF por goteo antes de retirar el baño de hielo. Al completarse, la reacción se reenfrió a 0°C y se fraguó con HCl 3N por goteo. La capa acuosa se extrajo dos veces con acetato de etilo y la capa orgánica luego se extrajo una vez con solución de bicarbonato y salmuera, se secó sobre Sulfato de magnesio, se filtró y se concentró para dar 2-cloro-4-(hidroximetil)benzoato de *ter*-butilo. 564 mg de 2-cloro-4-(hidroximetil)benzoato de *ter*-butilo se enfrió a 0°C en 5 mL de DCM antes de agregar 665 mg de Trifenilfosfina y 417 mg de NBS. La reacción se concentró y se purificó directamente mediante ISCO Combi-Flash para dar 2-cloro-4-(hidroximetil)benzoato de *ter*-butilo puro. 147 mg de 4-(bromometil)-2-clorobenzoato de *ter*-butilo se hizo reaccionar con 2,2,2-trifluoroetanamina en DMSO por medio del procedimiento P. 141 mg de 2-cloro-4-((2,2,2-trifluoroetilamino)metil)benzoato de *ter*-butilo se trató con HCl 4N en Dioxano a 45°C y se concentró para dar ácido 2-cloro-4-((2,2,2-trifluoroetilamino)metil)benzoico. 50 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a 75 mg de ácido 2-cloro-4-((2,2,2-trifluoroetilamino)metil)benzoico por medio del procedimiento G. El producto sin tratar se purificó por HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-((2,2,2-trifluoroetilamino)metil)benzamida pura. MS (Q1) 454,8 $(M)^+$.

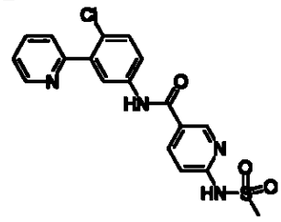
Ejemplo 190 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-

(metilsulfonilmetil)benzamida



Se hizo reaccionar 3,01 g de 4-(bromometil)-2-clorobenzoato de *ter*-butilo por medio del procedimiento O para dar 2-cloro-4-(metilsulfonilmetil)benzoato de *ter*-butilo. 1,2 g de 2-cloro-4-(metilsulfonilmetil)benzoato de *ter*-butilo se trató con 10 mL de HCl 4N en Dioxano a 45°C y se concentró al completarse para dar ácido 2-cloro-4-(metilsulfonilmetil)benzoico crudo. 775 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a 1 g de ácido 2-cloro-4-(metilsulfonilmetil)benzoico por medio del procedimiento G. El producto sin tratar se purificó por HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida pura. MS (Q1) 435 $(M)^+$.

Ejemplo 191 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(metilsulfonamido)nicotinamida



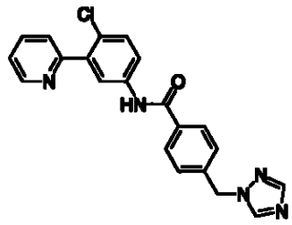
Se hizo reaccionar 100 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)nicotinamida con metanosulfonamida y 108 µL de 2-*ter*-Butilimino-2-dietilamino-1,3-dimetil-perhidro-1,3,2-diazafosforina por medio del

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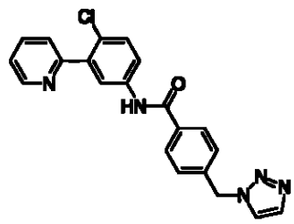
procedimiento F. La mezcla de reacción sin tratar se concentró a sequedad y se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(metilsulfonamido)nicotinamida pura. MS (Q1) 403 $(M)^+$.

Ejemplo 192 4-((1*H*-1,2,4-triazol-1-il)metil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida



Se acopló 88 mg de 4-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida a 45 mg de 1*H*-1,2,4-triazol por medio del procedimiento P. La reacción se evaporó a sequedad y se purificó por HPLC de fase inversa para dar 4-((1*H*-1,2,4-triazol-1-il)metil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida. MS (Q1) 390 $(M)^+$.

Ejemplo 193 4-((1*H*-1,2,3-triazol-1-il)metil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida

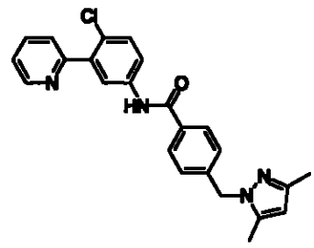


Se acopló 88 mg de 4-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida a 40 µL de 1*H*-1,2,3-triazol por medio del procedimiento P. La reacción se evaporó a sequedad y se purificó por HPLC de fase inversa para dar 4-((1*H*-1,2,3-triazol-1-il)metil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida.

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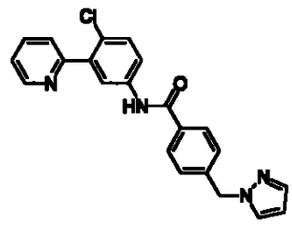
MS (Q1) 390,1 $(M)^+$.

Ejemplo 194 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((3,5-dimetil-1*H*-pirazol-1-il)metil)benzamida



Se acopló 70 mg de 4-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida a 50 mg de 3,5-dimetil-1*H*-pirazol por medio del procedimiento P. La reacción se evaporó a sequedad y se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((3,5-dimetil-1*H*-pirazol-1-il)metil)benzamida. MS (Q1) 417,3 $(M)^+$.

Ejemplo 195 4-((1*H*-pirazol-1-il)metil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida

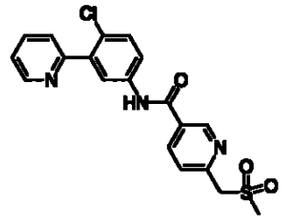


Se acopló 70 mg de 4-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida a 36 mg de 1*H*-pirazol por medio del procedimiento P. La reacción se evaporó a sequedad y se purificó por HPLC de fase inversa para dar 4-((1*H*-pirazol-1-il)metil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida. MS (Q1) 389,3 $(M)^+$.

Ejemplo 196 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-

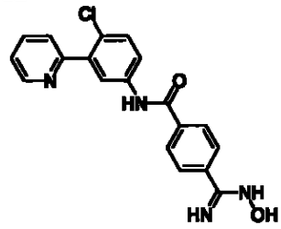
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(metilsulfonilmetil)nicotinamida



Se bromó 1,2 g de ácido 6-metilnicotínico por medio del procedimiento N para dar ácido 6-(bromometil)nicotínico. 75 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a 87 mg de ácido 6-(bromometil)nicotínico por medio del procedimiento E. 145 mg de 6-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)nicotinamida se hizo reaccionar por medio del procedimiento O y se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(metilsulfonilmetil)nicotinamida pura. MS (Q1) 402 $(M)^+$.

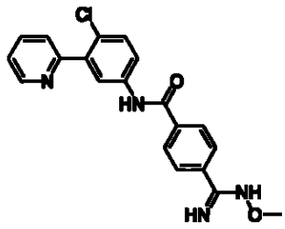
Ejemplo 197 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-hidroxicarbamimidoil)benzamida



Se acopló 240 mg de 4-cloro-3-(piridin-2-il)abilina a 207 mg de ácido 4-cianobenzoico por medio del procedimiento G. A 445 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-cianobenzamida y 2,5 mL de DIPEA en 10 mL de EtOH se agregó 793 mg de clorhidrato de hidroxilamina y se calentó a 60°C hasta completarse la reacción. El solvente subsiguientemente se evaporó, se extrajo dos veces con agua en Acetato de etilo, se secó con Sulfato de magnesio, se

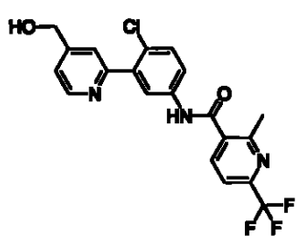
filtró y se concentró. El producto sin tratar se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-hidroxicarbamimidoil)benzamida pura. MS (Q1) 367,4 $(M)^+$.

Ejemplo 198 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-metoxicarbamimidoil)benzamida



Se enfrió 100 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-hidroxicarbamimidoil)benzamida a 0°C en 1,5 mL de Dioxano. 5 mL de NaOH 2N se agregó lentamente seguido por la adición por goteo de 33 µL de dimetilsulfato. El baño de hielo se eliminó y la reacción se agitó a temperatura ambiente durante 1 hora. La reacción subsiguientemente se evaporó y se extrajo con agua dos veces en acetato de etilo, se secó con Sulfato de magnesio, se filtró y se concentró para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-metoxicarbamimidoil)benzamida pura. MS (Q1) 381 $(M)^+$.

Ejemplo 199 *N*-(4-cloro-3-(4-(hidroximetil)piridin-2-il)fenil)-2-metil-6-(trifluorometil)nicotinamida



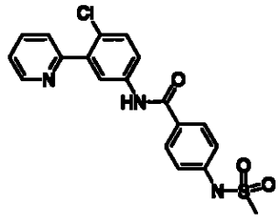
Se hizo reaccionar 75 mL de bromuro de (4-metilpiridin-2-il)zinc(II) con 4

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g de 1-cloro-2-iodo-4-nitrobenceno por medio del procedimiento B. A 300 mg de 2-(2-cloro-5-nitrofenil)-4-metilpiridina en 1,5 mL de ácido sulfúrico se agregó lentamente 362 mg de óxido de cromo (III) y la reacción se agitó por varias horas a temperatura ambiente hasta completarse. Se agregó agua helada para diluir la reacción y la capa acuosa se extrajo 3 veces con acetato de etilo. Las capas orgánicas se combinaron, se secó sobre Sulfato de magnesio, se filtró y se concentró para dar ácido 2-(2-cloro-5-nitrofenil)isonicotínico. 300 mg de ácido 2-(2-cloro-5-nitrofenil)isonicotínico se esterificó con 750 µL de HCl 4N en Dioxano en 10 mL de MeOH a 55°C durante 16 horas. La reacción se concentró y se sometió a trabajo básico, se secó sobre Sulfato de magnesio, se filtró y se concentró para dar 2-(2-cloro-5-nitrofenil)isonicotinato de metilo. 259 mg de 2-(2-cloro-5-nitrofenil)isonicotinato de metilo se trató con 200 mg de cloruro de estaño (II) y 500 µL de HCl en 10 mL de EtOH. Al completarse, EtOH se concentró y la reacción se extrajo con acetato de etilo y agua con TEA para disminuir las emulsiones. La capa orgánica se secó sobre Sulfato de magnesio, se filtró y se concentró para dar 2-(5-amino-2-clorofenil)isonicotinato de metilo crudo. 240 mg de 2-(5-amino-2-clorofenil)isonicotinato de metilo se trató con 204 µL de cloruro de 2-metil-6-(trifluorometil)nicotinoilo por medio del procedimiento D. A 100 mg de 2-(2-cloro-5-(2-metil-6-(trifluorometil)nicotinamido)fenil)isonicotinato de metilo a 0°C en 5 mL de EtOH se agregó lentamente 135 mg de borhidruro de sodio. La reacción subsiguientemente se refluió por 1 hora hasta completarse, se fraguó con agua y se extrajo con Acetato de etilo. La capa orgánica se secó sobre Sulfato de magnesio, se filtró, se concentró y se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(4-(hidroximetil)piridin-2-il)fenil)-2-metil-6-

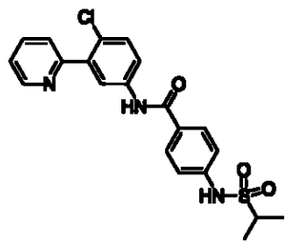
(trifluorometil)nicotinamida pura. MS (Q1) 422,1 $(M)^+$.

Ejemplo 200 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilamida)benzamida



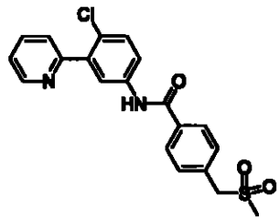
Se acopló 300 mg de 4-cloro-3-(piridin-2-il)abilina a 270 mg de ácido 4-nitrobenzoico por medio del procedimiento G. A 520 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-nitrobenzamida en 2,5 mL de HCl en 10 mL de EtOH se agregó 1,3 g de cloruro de estaño (II) y se agitó a 55°C. Al completarse, la reacción se concentró y se extrajo con acetato de etilo en agua con TEA para reducir las emulsiones. La capa orgánica se secó sobre Sulfato de magnesio, se filtró y se concentró para dar 4-amino-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida. 100 mg de 4-amino-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida se hizo reaccionar con 30 µL de cloruro de metansulfonilo y 90 µL DIPEA en 500 µL DCM. La mezcla de reacción se evaporó, se sometió a condiciones básicas de purificación y se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilamida)benzamida. MS (Q1) 402 $(M)^+$.

Ejemplo 201 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(1-metiletilsulfonamido)benzamida



Se hizo reaccionar 151 mg de 4-amino-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida con 105 µL de cloruro de propan-2-sulfonilo y 205 µL DIPEA en 500 µL DCM. La mezcla de reacción se evaporó, se sometió a condiciones básicas de purificación y se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(1-metiletilsulfonamido)benzamida. MS (Q1) 430 $(M)^+$.

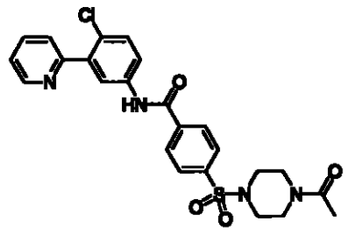
Ejemplo 202 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida



Se hizo reaccionar 1 g de 4-(bromometil)benzoato de metilo por medio del procedimiento O. 2,77 g de 4-(metilsulfonilmetil)benzoato de metilo se hidrolizó por medio del procedimiento M. 1g de 4-cloro-3-(piridin-2-il)abilina se acopló a 1,15 g de ácido 4-(metilsulfonilmetil)benzoico por medio del procedimiento G. El producto sin tratar se sometió a purificación básica y se recristalizó con una proporción 1:1 de isopropilacetato y éter para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida. MS (Q1) 401 $(M)^+$.

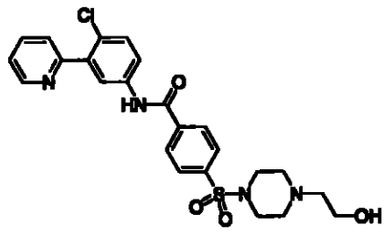
Ejemplo 203 4-(4-acetilpiperazin-1-ilsulfonil)-*N*-(4-cloro-3-(piridin-2-

il)fenil)benzamida



Se hizo reaccionar 1 g de ácido 4-(clorosulfonil)benzoico con 648 µL de 1-(piperazin-1-il)etanona por medio del procedimiento H. 75 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a 125 mg de ácido 4-(4-acetilpiperazin-1-ilsulfonil)benzoico por medio del procedimiento G y se purificó por HPLC de fase inversa para dar 4-(4-acetilpiperazin-1-ilsulfonil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida. MS (Q1) 499,4 $(M)^+$.

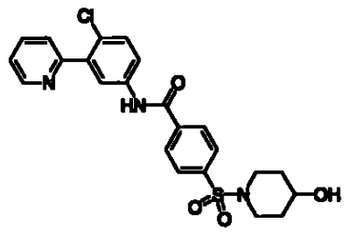
Ejemplo 204 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-(2-hidroxietil)piperazin-1-ilsulfonil)benzamida



Se hizo reaccionar 1 g de ácido 4-(clorosulfonil)benzoico con 615 µL de 2-(piperazin-1-il)etanol por medio del procedimiento H. 75 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a 125 mg de ácido 4-(4-(3-hidroxdpropil)piperazin-1-ilsulfonil)benzoico mediante el procedimiento G y se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-(2-hidroxietil)piperazin-1-ilsulfonil)benzamida. MS (Q1) 501,3 $(M)^+$.

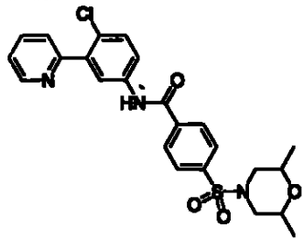
Ejemplo 205 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-hidroxdpiperidin-1-

ilsulfonil)benzamida



Se hizo reaccionar 1 g de ácido 4-(clorosulfonil)benzoico con 506 µL de piperidin-4-ol por medio del procedimiento H. 75 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a 114 mg de ácido 4-(4-hidroxipiperidin-1-ilsulfonil)benzoico por medio del procedimiento G y se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-hidroxipiperidin-1-ilsulfonil)benzamida. MS (Q1) 472,3 $(M)^+$.

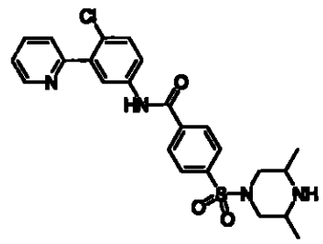
Ejemplo 206 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2,6-dimetilmorfolinosulfonil)benzamida



Se hizo reaccionar 1 g de ácido 4-(clorosulfonil)benzoico con 616 µL de 2,6-dimetilmorfolina por medio del procedimiento H. 75 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a 120 mg de ácido 4-(2,6-dimetilmorfolinosulfonil)benzoico por medio del procedimiento G y se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2,6-dimetilmorfolinosulfonil)benzamida. MS (Q1) 486,3 $(M)^+$.

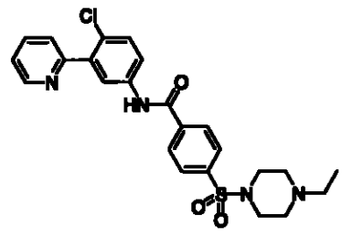
Ejemplo 207 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(3,5-dimetilpiperazin-1-

ilsulfonil)benzamida



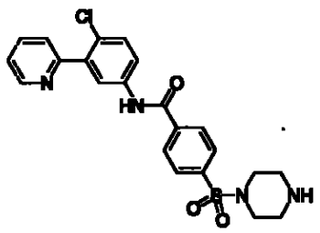
Se hizo reaccionar 1 g de ácido 4-(clorosulfonil)benzoico con 570 mg de 2,6-dimetilpiperazina por medio del procedimiento H. 75 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a 119 mg de ácido 4-(3,5-dimetilpiperazin-1-ilsulfonil)benzoico por medio del procedimiento G y se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(3,5-dimetilpiperazin-1-ilsulfonil)benzamida. MS (Q1) 485,4 $(M)^+$.

Ejemplo 208 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-etilpiperazin-1-ilsulfonil)benzamida



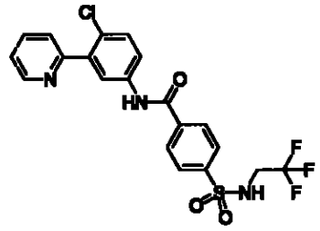
Se hizo reaccionar 1 g de ácido 4-(clorosulfonil)benzoico con 570 mg de 1-etilpiperazina por medio del procedimiento H. 75 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 4-(4-etilpiperazin-1-ilsulfonil)benzoico por medio del procedimiento G y se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-etilpiperazin-1-ilsulfonil). MS (Q1) 485 $(M)^+$.

Ejemplo 209 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(piperazin-1-ilsulfonil)benzamida



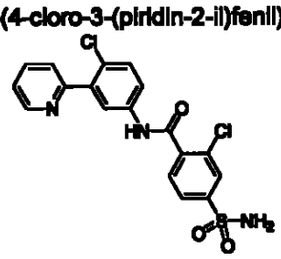
Se hizo reaccionar 1 g de ácido 4-(clorosulfonil)benzoico con 931 mg de piperazina-1-carboxilato de *ter*-butilo por medio del procedimiento H. 75 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a 150 mg de ácido 4-(4-(*ter*-butoxicarbonil)piperazin-1-ilsulfonil)benzoico por medio del procedimiento G. El producto sin tratar se sometió a condiciones de purificación básica, se trató con TFA para eliminar el grupo Boc y se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(piperazin-1-ilsulfonil)benzamida. MS (Q1) 457,1 $(M)^+$.

Ejemplo 210 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-(2,2,2-trifluoroetil)sulfamoil)benzamida



Se hizo reaccionar 1 g de ácido 4-(clorosulfonil)benzoico con 500 µL de 2,2,2-trifluoroetanamina por medio del procedimiento H. 60 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a 92 mg de ácido 4-(*N*-(2,2,2-trifluoroetil)sulfamoil)benzoico mediante el procedimiento G y se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-(2,2,2-trifluoroetil)sulfamoil)benzamida. MS (Q1) 470 $(M)^+$.

Ejemplo 211 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-sulfamoilbenzamida

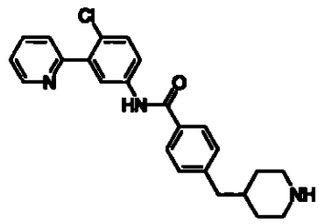


Se agregó por goteo una solución de 818 mg de nitrito de sodio en 13 mL de agua a una solución de 2g de 4-amino-2-clorobenzoato de metilo en 5 mL de HCl y 15 mL de AcOH a 0°C. La reacción se eliminó del baño de hielo y se agitó a temperatura ambiente por 15 minutos. Simultáneamente una solución de 460 mg de cloruro cobre II dihidratado en 1 mL de agua se agregó a una solución saturada de gas dióxido de azufre en 10 mL de AcOH a 0°C. La solución enfriada que contenía cloruro de cobre II y gas dióxido de azufre se agregó lentamente a la solución inicial reenfriada que contenía nitrito de sodio. La reacción se calentó a temperatura ambiente y se agitó hasta que cesó la evolución de gas. La reacción se filtró a través de celite y se volcó en un vaso de precipitado con agua helada agitada hasta que se separó un sólido amarillo-anaranjado. La solución de agua helada se filtró a través de un embudo Buchner para recoger el 2-cloro-4-(clorosulfonil)benzoato de metilo precipitado y se secó por 24 horas bajo vacío. Se agregó 1g de 2-cloro-4-(clorosulfonil)benzoato de metilo a una solución de 2 mL de solución 2M de amoníaco en MeOH y 970 µL DIPEA en 5 mL de MeOH. Al completarse la reacción se concentró, se extrajo dos veces con bicarbonato saturado, se secó con Sulfato de magnesio, se filtró y se concentró para dar 2-cloro-4-sulfamoilbenzoato de metilo. 777 mg de 2-cloro-4-sulfamoilbenzoato de metilo se hidrolizó por medio del procedimiento M para dar ácido 2-cloro-4-

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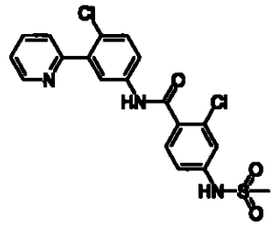
sulfamoilbenzoico crudo. 75 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a 91 mg de ácido 2-cloro-4-sulfamoilbenzoico sin tratar por medio del procedimiento G. El producto sin tratar se purificó por HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-sulfamoilbenzamida. MS (Q1) 422 $(M)^+$.

Ejemplo 212 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(piperidin-4-ilmetil)benzamida



Se acopló 75 mg de 4-cloro-3-(piridin-2-il)abilina a 125 mg de ácido 4-((1-(*ter*-butoxicarbonil)piperidin-4-il)metil)benzoico por medio del procedimiento G. El producto sin tratar se trató con HCl 4N en Dioxano, se evaporó y se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(piperidin-4-ilmetil)benzamida. MS (Q1) 406,1 $(M)^+$.

Ejemplo 213 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonamido)benzamida

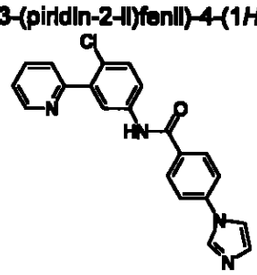


Se hidrolizó 4,2 g de 2-cloro-4-(metilsulfonamido)benzoato de metilo por medio del procedimiento M. 1 g de 4-cloro-3-(piridin-2-il)abilina se acopló a 1,35 g de ácido 2-cloro-4-(metilsulfonamido)benzoico por medio del procedimiento

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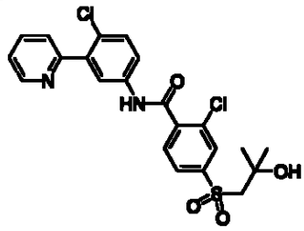
G. El producto sin tratar se purificó por HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonamido)benzamida. MS (Q1) 436,1 $(M)^+$.

Ejemplo 214 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(1*H*-imidazol-1-il)benzamida



Se acopló 75 mg de 4-cloro-3-(piridin-2-il)abilina a 78 mg de ácido 4-(1*H*-imidazol-1-il)benzoico por medio del procedimiento G. El producto sin tratar se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(1*H*-imidazol-1-il)benzamida. MS (Q1) 375,3 $(M)^+$.

Ejemplo 215 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxi-2-metilpropilsulfonil)benzamida



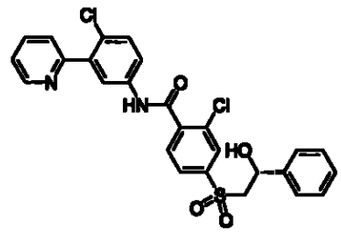
Se disolvió 8 g de 4-amino-2-clorobenzoato de metilo en 16 mL de MeOH, 8 mL de H_2O y 8 mL de ácido clorhídrico concentrado y luego se enfrió a 0 $^{\circ}$C. Se agregó una solución de 3,9 g de nitrito de sodio en 15 mL de H_2O por goteo durante 30 min. La reacción se agitó a 0 $^{\circ}$C durante otra 1h. La mezcla de diazotación fría se agregó a una solución de 13,8 g de etil xantato de potasio en 10 mL de H_2O a 50-60 $^{\circ}$C. La reacción se calentó a 65 $^{\circ}$C durante

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2h y se monitoreó por TLC hasta completarse. La mezcla se enfrió a 25 °C y se extrajo con acetato de etilo. Los extractos orgánicos combinados se lavaron con salmuera, se secó ($MgSO_4$), y se concentró. Se purificó mediante cromatografía en gel de sílice (0-10% acetato de etilo/hexano) para dar 2-cloro-4-(etoxicarbonotioiltio)benzoato de metilo. Se agregó una solución de 2,6 g de hidróxido de sodio en 20 mL de H_2O a 5,9 g de 2-cloro-4-(etoxicarbonotioiltio)benzoato de metilo en 40 mL de EtOH La mezcla de reacción se calentó a 70 °C durante 1h. Al completarse, la mezcla se enfrió a 25 °C, y luego se acidificó a pH 3 mediante la adición de HCl 10 N. El sólido se filtró y se lavó con H_2O para dar ácido 2-cloro-4-mercaptobenzonico. 3,8 g de ácido 2-cloro-4-mercaptobenzonico en 40 mL de ácido sulfúrico-metanol 5% se refluió bajo una atmósfera de nitrógeno por 3h. Luego de la concentración de la mezcla de reacción, se agregó 10 mL de H_2O y la mezcla resultante se hizo alcalina con carbonato ácido de sodio, y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó ($MgSO_4$), y se evaporó para dar 2-cloro-4-mercaptobenzoato de metilo. Se hizo reaccionar 80 mg de óxido de isobutileno con 2-cloro-4-mercaptobenzoato de metilo por medio del procedimiento S para dar 2-cloro-4-(2-hidroxi-2-metilpropiltio)benzoato de metilo. 190 mg de 2-cloro-4-(2-hidroxi-2-metilpropiltio)benzoato de metilo se hidrolizó por medio del procedimiento M para dar ácido 2-cloro-4-(2-hidroxi-2-metilpropiltio)benzoico. 160 mg de ácido 2-cloro-4-(2-hidroxi-2-metilpropiltio)benzoico se hizo reaccionar por medio del procedimiento R para dar ácido 2-cloro-4-(2-hidroxi-2-metilpropilsulfonil)benzoico. 60 mg de 4-cloro-3-(piridin-2-il)abilina se acopió a ácido 2-cloro-4- (2-hidroxi-2-metilpropilsulfonil)benzoico por medio del procedimiento G. El producto se

purificó en HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxi-2-metilpropilsulfonil)benzamida. MS (Q1) 479,1 $(M)^+$.

Ejemplo 216 (*R*)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxi-2-feniletilsulfonil)benzamida

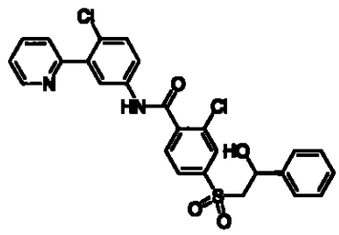


Se hizo reaccionar 150 mg de óxido de (*R*)-estireno con 2-cloro-4-mercaptobenzoato de metilo por medio del procedimiento S para dar 2-cloro-4-(2-hidroxi-2-feniletiltio)benzoato de (*R*)-metilo. 190 mg de 2-cloro-4-(2-hidroxi-2-feniletiltio)benzoato de (*R*)-metilo se hidrolizó por medio del procedimiento M para dar ácido (*R*)-2-cloro-4-(2-hidroxi-2-feniletiltio)benzoico. 170 mg de ácido (*R*)-2-cloro-4-(2-hidroxi-2-feniletiltio)benzoico se hizo reaccionar por medio del procedimiento R para dar ácido (*R*)-2-cloro-4-(2-hidroxi-2-feniletilsulfonil)benzoico. 60 mg de 4-cloro-3-(piridin-2-il)abilna se acopló a ácido (*R*)-2-cloro-4-(2-hidroxi-2-feniletilsulfonil)benzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar (*R*)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxi-2-feniletilsulfonil)benzamida. MS (Q1) 527,2 $(M)^+$.

Ejemplo 217 (*S*)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxi-2-feniletil-sulfonil)benzamida

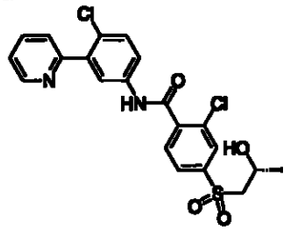
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Se hizo reaccionar 119 mg de óxido de (S)-estireno con 2-cloro-4-mercaptobenzoato de metilo por medio del procedimiento S para dar 2-cloro-4-(2-hidroxi-2-feniletiltio)benzoato de (*S*)-metilo. 230 mg de (*S*)-metil-2-cloro-4-(2-hidroxi-2-feniletiltio)benzoato se hidrolizó por medio del procedimiento M para dar ácido (*S*)-2-cloro-4-(2-hidroxi-2-feniletiltio)benzoico. 180 mg de ácido (*S*)-2-cloro-4-(2-hidroxi-2-feniletiltio)benzoico se hizo reaccionar por medio del procedimiento R para dar ácido (*S*)-2-cloro-4-(2-hidroxi-2-feniletilsulfonil)benzoico. 60 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido (*S*)-2-cloro-4-(2-hidroxi-2-feniletilsulfonil)benzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar (*S*)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxi-2-feniletilsulfonil)benzamida. MS (Q1) 527,0 $(M)^+$.

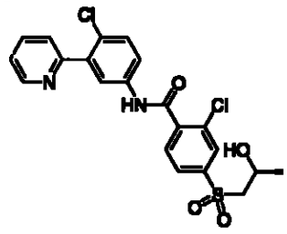
Ejemplo 218 (*R*)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxdpropilsulfonil)benzamida



Se hizo reaccionar 140 mg de óxido de (*R*)-propileno con 2-cloro-4-mercaptobenzoato de metilo por medio del procedimiento S para dar 2-cloro-4-

(2-hidroxipropiltio)benzoato de (*R*)-metilo. 435 mg de (*R*)-metil-2-cloro-4-(2-hidroxipropiltio)benzoato se hidrolizó por medio del procedimiento M para dar ácido (*R*)-2-cloro-4-(2-hidroxipropiltio)benzoico. 403 mg de ácido (*R*)-2-cloro-4-(2-hidroxipropiltio)benzoico se hizo reaccionar por medio del procedimiento R para dar ácido (*R*)-2-cloro-4-(2-hidroxipropilsulfonil)benzoico. 298 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido (*R*)-2-cloro-4-(2-hidroxipropilsulfonil)benzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar (*R*)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxipropilsulfonil)benzamida. MS (Q1) 485,1 $(M)^+$.

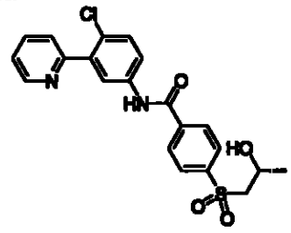
Ejemplo 219 (*S*)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxipropilsulfonil)benzamida



Se hizo reaccionar 86 mg de óxido de (S)-propileno con 2-cloro-4-mercaptobenzoato de metilo por medio del procedimiento S para dar 2-cloro-4-(2-hidroxipropiltio)benzoato de (*S*)-metilo. 275 mg de (*S*)-metil-2-cloro-4-(2-hidroxipropiltio)benzoato se hidrolizó por medio del procedimiento M para dar ácido (*S*)-2-cloro-4-(2-hidroxipropiltio)benzoico. 220 mg de ácido (*S*)-2-cloro-4-(2-hidroxipropiltio)benzoico se hizo reaccionar por medio del procedimiento R para dar ácido (*S*)-2-cloro-4-(2-hidroxipropilsulfonil)benzoico. 70 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido (*S*)-2-cloro-4-(2-hidroxipropilsulfonil)benzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar (*S*)-2-cloro-*N*-(4-cloro-3-(piridin-2-

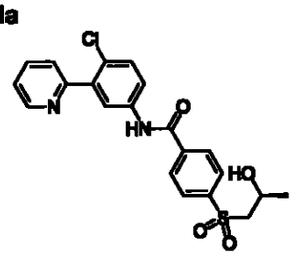
il)fenil)-4-(2-hidroxipropilsulfonil)benzamida. MS (Q1) 465,0 $(M)^+$

Ejemplo 220 (*R*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxipropilsulfonil)benzamida



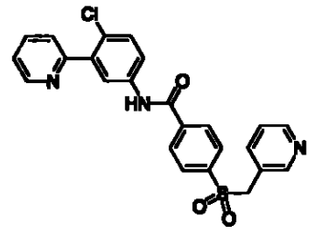
Se hizo reaccionar 100 mg de óxido de (*R*)-propileno con metilo 4-mercaptobenzoato de metilo por medio del procedimiento S para dar 4-(2-hidroxipropiltio)benzoato de (*R*)-metilo. 169 mg de (*R*)-metilo 4-(2-hidroxipropiltio)benzoato se hizo reaccionar por medio del procedimiento R para dar 4-(2-hidroxipropilsulfonil)benzoato de (*R*)-metilo. 179 mg de 4-(2-hidroxipropilsulfonil)benzoato de (*R*)-metilo se hidrolizó por medio del procedimiento M para dar ácido (*R*)-4-(2-hidroxipropilsulfonil)benzoico. 45 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido (*R*)-4-(2-hidroxipropilsulfonil)benzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar (*R*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxipropilsulfonil)benzamida. MS (Q1) 431,2 $(M)^+$.

Ejemplo 221 (*S*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxipropilsulfonil)benzamida



Se hizo reaccionar 150 mg de óxido de (S)-propileno con 4-mercaptobenzoato de metilo por medio del procedimiento S para dar (*S*)-metilo 4-(2-hidroxipropiltio)benzoato de (*S*)-metilo. Se hizo reaccionar 650 mg de 4-(2-hidroxipropiltio)benzoato de (*S*)-metilo por medio del procedimiento R para dar 4-(2-hidroxipropilsulfonil)benzoato de (*S*)-metilo. Se hidrolizó 350 mg de 4-(2-hidroxipropilsulfonil)benzoato de (*S*)-metilo por medio del procedimiento M para dar ácido (*S*)-4-(2-hidroxipropilsulfonil)benzoico. 45 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido (*S*)-4-(2-hidroxipropilsulfonil)benzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar (*S*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxipropilsulfonil)benzamida. MS (Q1) 431,3 $(M)^+$.

Ejemplo 222 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(piridin-3-ilmetilsulfonil)benzamida



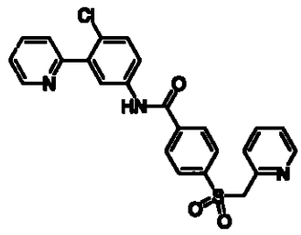
Se hizo reaccionar 1g de hidrobromuro de 3-(bromometil)piridina con 4-mercaptobenzoato de metilo por medio del procedimiento Q para dar 4-(piridin-3-ilmetiltio)benzoato de metilo. 980 mg de 4-(piridin-3-ilmetiltio)benzoato de metilo se hizo reaccionar por medio del procedimiento R para dar 4-(piridin-3-ilmetilsulfonil)benzoato de metilo. 760 mg de 4-(piridin-3-ilmetilsulfonil)benzoato de metilo se hidrolizó por medio del procedimiento M para dar ácido 4-(piridin-3-ilmetilsulfonil)benzoico. 60 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 4-(piridin-3-ilmetilsulfonil)benzoico por medio del procedimiento G. El

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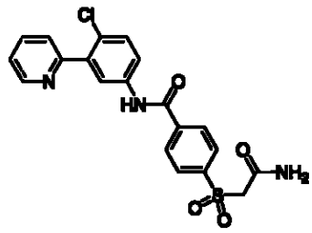
producto se purificó en HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(piridin-3-ilmetilsulfonil)benzamida. MS (Q1) 464,1 $(M)^+$.

Ejemplo 223 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(piridin-2-ilmetilsulfonil)benzamida



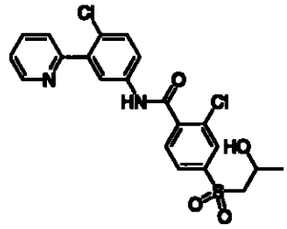
Se hizo reaccionar 1g de hidrobromuro de 2-(bromometil)piridina con 4-mercaptobenzoato de metilo por medio del procedimiento Q para dar 4-(piridin-2-ilmetiltio)benzoato de metilo. Se hizo reaccionar 500 mg de 4-(piridin-2-ilmetiltio)benzoato de metilo por medio del procedimiento R para dar 4-(piridin-2-ilmetilsulfonil)benzoato de metilo. 470 mg de 4-(piridin-2-ilmetilsulfonil)benzoato de metilo se hidrolizó por medio del procedimiento M para dar ácido 4-(piridin-2-ilmetilsulfonil)benzoico. 70 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 4-(piridin-2-ilmetilsulfonil)benzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(piridin-2-ilmetilsulfonil)benzamida. MS (Q1) 464,1 $(M)^+$.

Ejemplo 224 4-(2-amino-2-oxoetilsulfonil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida



Se hizo reaccionar 2,5 g de 2-bromoacetamida con 4-mercaptobenzoato de metilo por medio del procedimiento Q para dar 4-(2-amino-2-oxoetiltio)benzoato de metilo. Se hizo reaccionar 2,6 g de 4-(2-amino-2-oxoetiltio)benzoato de metilo por medio del procedimiento R para dar 4-(2-amino-2-oxoetilsulfonil)benzoato de metilo. 1 g de 4-(2-amino-2-oxoetilsulfonil)benzoato de metilo se hidrolizó por medio del procedimiento M para dar ácido 4-(2-amino-2-oxoetilsulfonil)benzoico. 150 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 4-(2-amino-2-oxoetilsulfonil)benzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 4-(2-amino-2-oxoetilsulfonil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida. MS (Q1) 430,2 $(M)^+$.

Ejemplo 225 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxipropilsulfonil)benzamida

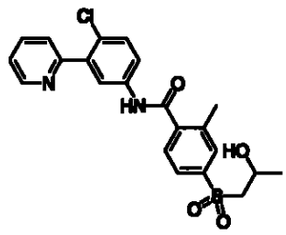


Se hizo reaccionar 2 g de 2-cloro-4-fluorobenzonitrilo con 1-mercapto-2-propanol por medio del procedimiento Q para dar 2-cloro-4-(2-hidroxipropiltio)benzonitrilo. Se hizo reaccionar 2,5 g de 2-cloro-4-(2-

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hidroxipropiltio)benzonitrilo por medio del procedimiento T para dar ácido 2-cloro-4-(2-hidroxipropiltio)benzoico. Se hizo reaccionar 2,1 g de ácido 2-cloro-4-(2-hidroxipropiltio)benzoico por medio del procedimiento R para dar ácido 2-cloro-4-(2-hidroxipropilsulfonil)benzoico. 70 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 2-cloro-4-(2-hidroxipropilsulfonil)benzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxipropilsulfonil)benzamida. MS (Q1) 485,2 $(M)^+$.

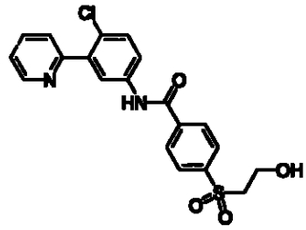
Ejemplo 226 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxipropilsulfonil)-2-metilbenzamida



Se hizo reaccionar 2 g de 4-bromo-2-metilbenzonitrilo con 1-mercapto-2-propanol por medio del procedimiento Q para dar 4-(2-hidroxipropiltio)-2-metilbenzonitrilo. Se hizo reaccionar 950 mg de 4-(2-hidroxipropiltio)-2-metilbenzonitrilo por medio del procedimiento T para dar ácido 4-(2-hidroxipropiltio)-2-metilbenzoico. Se hizo reaccionar 1,0 g de ácido 4-(2-hidroxipropiltio)-2-metilbenzoico por medio del procedimiento R para dar ácido 4-(2-hidroxipropilsulfonil)-2-metilbenzoico. 100 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 4-(2-hidroxipropilsulfonil)-2-metilbenzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxipropilsulfonil)-2-metilbenzamida. MS (Q1) 445,3 $(M)^+$.

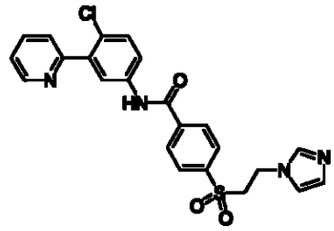
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Ejemplo 227 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxietilsulfonil)benzamida



Se usó 5 g de 4-fluorobenzonitrilo en el Procedimiento Q con 2-mercaptoetanol para dar 4-(2-hidroxietiltio)benzonitrilo. Se hizo reaccionar 900 mg de 4-(2-hidroxietiltio)benzonitrilo por medio del procedimiento T para dar ácido 4-(2-hidroxietiltio)benzoico. Se hizo reaccionar 1,0 g de ácido 4-(2-hidroxietiltio)benzoico por medio del procedimiento R para dar ácido 4-(2-hidroxietilsulfonil)benzoico. 80 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 4-(2-hidroxietilsulfonil)benzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxietilsulfonil)benzamida. MS (Q1) 417,0 $(M)^+$.

Ejemplo 228 4-(2-(1*H*-imidazol-1-il)etilsulfonil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida

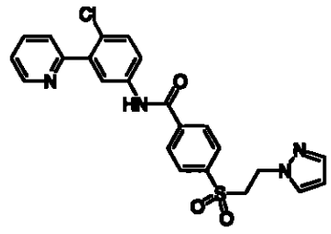


Se hizo reaccionar 4 g de 4-(2-hidroxietiltio)benzonitrilo por medio del procedimiento R para dar 4-(2-hidroxietilsulfonil)benzonitrilo. Se agregó 3,0 g de trifenilfosfina a una solución de 2 g de 4-(2-hidroxietilsulfonil)benzonitrilo y

4,7 g de tetrabromuro de carbono en diclorometano a 0 °C. La mezcla de reacción se dejó subir la temperatura hasta la temperatura ambiente y se agitó por 1h. La mezcla se diluyó con diclorometano, se lavó con H_2O, se secó ($MgSO_4$) y se evaporó. Se purificó mediante cromatografía en gel de sílice (0-70% acetato de etilo/hexano) para dar 4-(2-bromoetilsulfonil)benzonitrilo. 250 mg de 4-(2-bromoetilsulfonil)benzonitrilo se usó en el Procedimiento P con imidazol para dar 4-(2-(1*H*-imidazol-1-il)etilsulfonil)benzonitrilo. Se hizo reaccionar 300 mg de 4-(2-(1*H*-imidazol-1-il)etilsulfonil)benzonitrilo por medio del procedimiento T para dar ácido 4-(2-(1*H*-imidazol-1-il)etilsulfonil)benzoico.

60 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 4-(2-(1*H*-imidazol-1-il)etilsulfonil)benzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 4-(2-(1*H*-imidazol-1-il)etilsulfonil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida. MS (Q1) 467,1 $(M)^+$.

Ejemplo 229 4-(2-(1*H*-pirazol-1-il)etilsulfonil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida



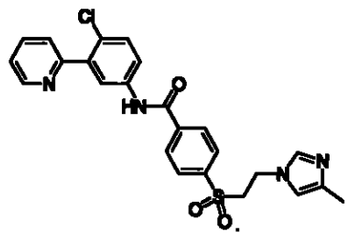
Se usó 250 mg de 4-(2-bromoetilsulfonil)benzonitrilo en el Procedimiento P con pirazol para dar 4-(2-(1*H*-pirazol-1-il)etilsulfonil)benzonitrilo. Se hizo reaccionar 300 mg de 4-(2-(1*H*-pirazol-1-il)etilsulfonil)benzonitrilo por medio del procedimiento T para dar ácido 4-(2-(1*H*-pirazol-1-il)etilsulfonil)benzoico. 75 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 4-(2-(1*H*-pirazol-1-il)etilsulfonil)benzoico por medio del procedimiento G. El producto se purificó en

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HPLC de fase inversa para dar 4-(2-(1*H*-pirazol-1-il)etilsulfonil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida. MS (Q1) 467,0 $(M)^+$.

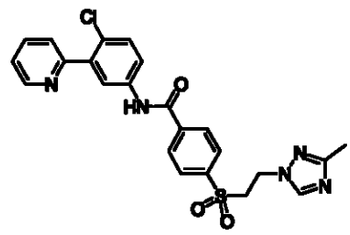
Ejemplo 230 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-(4-metil-1*H*-imidazol-1-il)etilsulfonil)benzamida



Se usó 270 mg de 4-(2-bromoetilsulfonil)benzonitrilo en el Procedimiento P con 4-metilimidazol para dar 4-(2-(4-metil-1*H*-imidazol-1-il)etilsulfonil)benzonitrilo. 320 mg de 4-(2-(4-metil-1*H*-imidazol-1-il)etilsulfonil)benzonitrilo se hizo reaccionar por medio del procedimiento T para dar ácido 4-(2-(4-metil-1*H*-imidazol-1-il)etilsulfonil)benzoico.

70 mg de ácido 4-cloro-3-(piridin-2-il)abilina se acopló a 4-(2-(4-metil-1*H*-imidazol-1-il)etilsulfonil)benzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-(4-metil-1*H*-imidazol-1-il)etilsulfonil)benzamida. MS (Q1) 481,0 $(M)^+$.

Ejemplo 231 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-(3-metil-1*H*-1,2,4-triazol-1-il)etilsulfonil)benzamida.



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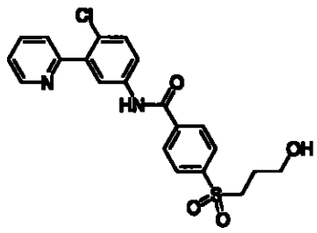
A una suspensión agitada de 10 g de tiosemicarbazida en 100 mL de piridina se agregó lentamente 7,8 ml de cloruro de acetilo a 0 °C. La temperatura se mantuvo durante la adición (0 °C - 4 °C). La mezcla de reacción se dejó subir la temperatura hasta la temperatura ambiente y se agitó por 16 h. La evaporación dio tiosemicarbazida de 1-acetilo. La tiosemicarbazido de 1-acetilo cruda se disolvió en 70 mL de MeOH y 12 g de metóxido de sodio, y se refluió por 10 h. El solvente se eliminó y el residuo se disolvió en H_2O, luego se acidificó a pH 2 mediante la adición de HCl 1N. El sólido resultante se filtró y se lavó con H_2O para dar 3-metil-1,2,4-triazol-5-tiol. Se agregó 1 g de 3-metil-1,2,4-triazol-5-tiol a una solución de 61 mg de nitrito de sodio en 3 ml de ácido nítrico y 6 mL de H_2O a 0 °C. La mezcla de reacción se agitó por 1h a 0 °C, y se basificó con carbonato de sodio saturado y se concentró. El residuo se disolvió con MeOH y se filtró. El filtrado se evaporó para dar 3-metil-1,2,4-triazol. 230 mg de 4-(2-bromoetilsulfonil)benzonitrilo se usó en el Procedimiento P con 3-metil-1,2,4-triazol para dar 4-(2-(3-metil-1*H*-1,2,4-triazol-1-il)etilsulfonil)benzonitrilo. 310 mg de 4-(2-(3-metil-1*H*-1,2,4-triazol-1-il)etilsulfonil)benzonitrilo se hizo reaccionar por medio del procedimiento T para dar ácido 4-(2-(3-metil-1*H*-1,2,4-triazol-1-il)etilsulfonil)benzoico.

Se acopló 60 mg de ácido 4-cloro-3-(piridin-2-il)abilina a 4-(2-(3-metil-1*H*-1,2,4-triazol-1-il)etilsulfonil)benzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-(3-metil-1*H*-1,2,4-triazol-1-il)etilsulfonil)benzamida. MS (Q1) 482,1 $(M)^+$.

Ejemplo 232 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(3-hidroxipropilsulfonil)benzamida

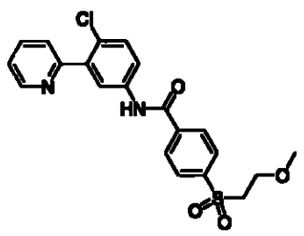
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Se usó 5 g de 4-fluorobenzonitrilo en el Procedimiento Q con 3-mercapto-1-propanol para dar 4-(3-hidroxipropiltio)benzonitrilo. Se hizo reaccionar 1,8 g de 4-(3-hidroxipropiltio)benzonitrilo por medio del procedimiento T para dar ácido 4-(3-hidroxipropiltio)benzoico. Se hizo reaccionar 1,2 g de ácido 4-(3-hidroxipropiltio)benzoico por medio del procedimiento R para dar ácido 4-(3-hidroxipropilsulfonil)benzoico. 50 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 4-(3-hidroxipropilsulfonil)benzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(3-hidroxipropilsulfonil)benzamida. MS (Q1) 431,3 $(M)^+$.

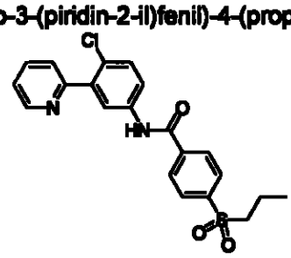
Ejemplo 233 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-metoxietilsulfonil)benzamida



Se refluió una mezcla de 500 mg de 4-mercaptobenzoato de metilo, 1,6 g de carbonato de potasio, 1,2 g de 2-bromoetilmetiléter y 329 mg de yoduro de tetrabutilamonio en 10 mL de acetona por 16 h. Se diluyó la mezcla de reacción con acetato de etilo, se lavó con H_2O y se concentró. Se purificó mediante

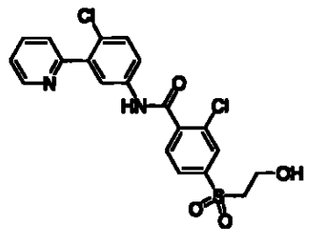
cromatografía en gel de sílice (0-50% acetato de etilo/ hexano) para dar 4-(2-metoxietiltio)benzoato. 240 mg de 4-(2-metoxietiltio)benzoato se hizo reaccionar por medio del procedimiento R para dar 4-(2-metoxietilsulfonil)benzoato. 120 mg de 4-(2-metoxietilsulfonil)benzoato se hidrolizó por medio del procedimiento M para dar ácido 4-(2-metoxietilsulfonil)benzoico. 50 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 4-(2-metoxietilsulfonil)benzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-metoxietilsulfonil)benzamida. MS (Q1) 431,0 $(M)^+$.

Ejemplo 234 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(propilsulfonil)benzamida



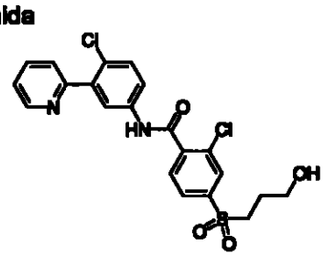
Se usó 1 g de 4-fluorobenzonitrilo en el Procedimiento Q con 1-propantiol para dar 4-(propiltio)benzonitrilo. Se hizo reaccionar 860 mg de 4-(propiltio)benzonitrilo por medio del procedimiento T para dar ácido 4-(propiltio)benzoico. Se hizo reaccionar 700 mg de ácido 4-(propiltio)benzoico por medio del procedimiento R para dar ácido 4-(propilsulfonil)benzoico. 60 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 4-(propilsulfonil)benzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(propilsulfonil)benzamida. MS (Q1) 415,0 $(M)^+$.

Ejemplo 235 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxietilsulfonil)benzamida



Se usó 4 g de 2-cloro-4-fluorobenzonitrilo en el Procedimiento Q con 2-mercaptoetanol para dar 2-cloro-4-(2-hidroxietiltio)benzonitrilo. Se hizo reaccionar 1 g de 2-cloro-4-(2-hidroxietiltio)benzonitrilo por medio del procedimiento T para dar ácido 2-cloro-4-(2-hidroxietiltio)benzoico. Se hizo reaccionar 1 g de ácido 2-cloro-4-(2-hidroxietiltio)benzoico por medio del procedimiento R para dar ácido 2-cloro-4-(2-hidroxietilsulfonil)benzoico. 50 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 2-cloro-4-(2-hidroxietilsulfonil)benzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxietilsulfonil)benzamida. MS (Q1) 451,0(M)$^+$.

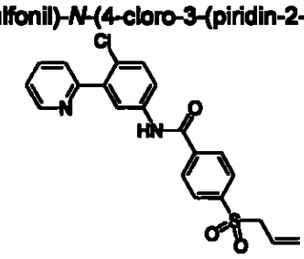
Ejemplo 236 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(3-hidroxipropilsulfonil)benzamida



Se usó 4 g de 2-cloro-4-fluorobenzonitrilo en el Procedimiento Q con 3-mercapto-1-propanol para dar 2-cloro-4-(3-hidroxipropiltio)benzonitrilo. Se hizo reaccionar 1 g de 2-cloro-4-(3-hidroxipropiltio)benzonitrilo por medio del procedimiento T para dar ácido 2-cloro-4-(3-hidroxipropiltio)benzoico. Se hizo

reaccionar 1,2 g de ácido 2-cloro-4-(3-hidroxipropiltio)benzoico por medio del procedimiento R para dar ácido 2-cloro-4-(2-hidroxipropilsulfonil)benzoico. 75 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 2-cloro-4-(2-hidroxipropilsulfonil)benzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(3-hidroxipropilsulfonil)benzamida. MS (Q1) 465,0 $(M)^+$.

Ejemplo 237 4-(alilsulfonil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida

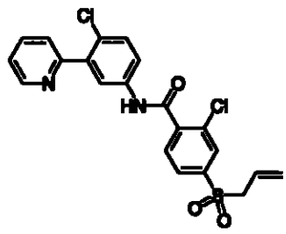


Se hizo reaccionar 7,3 g de 4-(3-hidroxipropiltio)benzonitrilo por medio del procedimiento R para dar 4-(3-hidroxipropilsulfonil)benzonitrilo. 1,9 g de NBS se agregó a una solución de 2 g de 4-(3-hidroxipropilsulfonil)benzonitrilo y 2,8 g de trifenilfosfina en 10 mL de diclorometano a 0 °C. La mezcla de reacción se agitó a 0 ~5 °C durante 1h. La mezcla se diluyó con diclorometano, se lavó con H_2O, se secó ($MgSO_4$) y se evaporó. Se purificó mediante cromatografía en gel de sílice (10-70% acetato de etilo/hexano) para dar 4-(3-bromopropilsulfonil)benzonitrilo. 300 mg de 4-(3-bromopropilsulfonil)benzonitrilo se hizo reaccionar por medio del procedimiento T para dar ácido 4-(alilsulfonil)benzoico. 40 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 4-(alilsulfonil)benzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 4-(alilsulfonil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida. MS (Q1) 413,2 $(M)^+$.

Ejemplo 238 4-(alilsulfonil)-2-cloro-*N*-(4-cloro-3-(piridin-2-

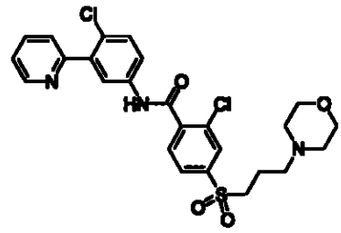
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il)fenil)benzamida



Se agregó 115 mg de NBS a una solución de 200 mg de 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(3-hidroxipropilsulfonil)benzamida y 169 mg de trifenilfosfina en 3 mL de diclorometano a 0 °C. La mezcla de reacción se agitó a 0 ~5 °C durante 1h. La mezcla se diluyó con diclorometano, se lavó con H_2O, se secó ($MgSO_4$) y se evaporó. Se purificó mediante TLC preparativa en placa (60% acetato de etilo/hexano) para dar 4-(3-bromopropilsulfonil)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida. 60 mg de 4-(3-bromopropilsulfonil)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida y 111 mg de carbonato de cesio en 0,5 mL de DMF se calentaron a 100 °C en un reactor de microondas sellado por 20 min. La mezcla de reacción se evaporó, y el producto se purificó en HPLC de fase inversa para dar 4-(alilsulfonil)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida. MS (Q1) 448,0 $(M)^+$.

Ejemplo 239 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(3-morfolinopropilsulfonil)benzamida



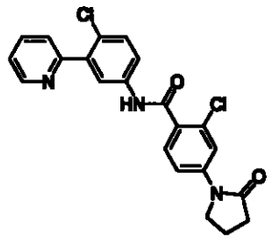
Se usó 120 mg de 4-(3-bromopropilsulfonil)-2-cloro-*N*-(4-cloro-3-(piridin-

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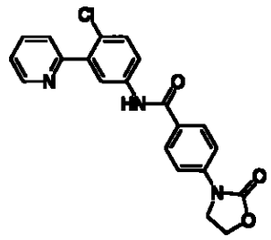
2-il)fenil)benzamida en el Procedimiento P con morfolina para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(3-morfolinopropilsulfonil)benzamida. MS (Q1) 534,0 $(M)^+$.

Ejemplo 240 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-oxopirrolidin-1-il)benzamida



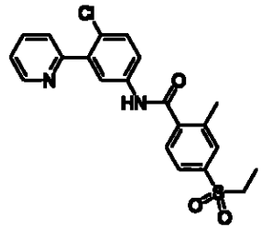
Se calentó una mezcla de 500 mg de 2-cloro-4-florobenzonitrilo, 821 mg de 2-pirrolidinona y 3 g de carbonato de cesio en 5 mL de DMF a 100 °C en un reactor de microondas sellado por 15 min. La mezcla de reacción se diluyó con acetato de etilo, se lavó con H_2O, se secó ($MgSO_4$) y se evaporó. Se purificó mediante cromatografía en gel de sílice (20-80% acetato de etilo/hexano) para dar 2-cloro-4-(2-oxopirrolidin-1-il)benzonitrilo. 890 mg de 2-cloro-4-(2-oxopirrolidin-1-il)benzonitrilo se hizo reaccionar por medio del procedimiento T para dar ácido 2-cloro-4-(2-oxopirrolidin-1-il)benzoico. 80 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 2-cloro-4-(2-oxopirrolidin-1-il)benzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-oxopirrolidin-1-il)benzamida. MS (Q1) 426,2 $(M)^+$.

Ejemplo 241 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-oxooxazolidin-3-il)benzamida



Se calentó una mezcla de 1 g de 4-iodobenzoato de metilo, 399 mg de 2-oxazolidona, 1,1 g de carbonato de potasio, 34 mg de N, N'-dimetiletilendiamina y 73 mg de yoduro de cobre en 10 mL de tolueno a 150 °C en un reactor de microondas sellado por 2h. La mezcla de reacción se diluyó con acetato de etilo, se lavó con H_2O, se secó ($MgSO_4$) y se evaporó. Se purificó mediante cromatografía en gel de sílice (20-70% acetato de etilo/hexano) para dar 4-(2-oxooxazolidin-3-il)benzoato de metilo. 530 mg de 4-(2-oxooxazolidin-3-il)benzoato de metilo se hidrolizó por medio del procedimiento M para dar ácido 4-(2-oxooxazolidin-3-il)benzoico. 70 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 4-(2-oxooxazolidin-3-il)benzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-oxooxazolidin-3-il)benzamida. MS (Q1) 394,2 $(M)^+$.

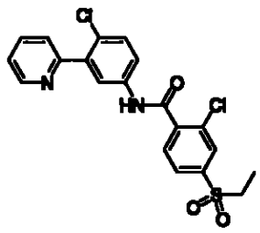
Ejemplo 242 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(etilsulfonil)-2-metilbenzamida



Se usó 4 g de 4-bromo-2-metilbenzonitrilo en el Procedimiento Q con

etantiol para dar 4-(etiltio)-2-metilbenzonitrilo. Se hizo reaccionar 2 g de 4-(etiltio)-2-metilbenzonitrilo por medio del procedimiento R para dar 4-(etilsulfonil)-2-metilbenzonitrilo. Se hizo reaccionar 2,5 g de 4-(etilsulfonil)-2-metilbenzonitrilo por medio del procedimiento T para dar ácido 4-(etilsulfonil)-2-metilbenzoico. Se acopló 75 mg de 4-cloro-3-(piridin-2-il)abilina a ácido 4-(etilsulfonil)-2-metilbenzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(etilsulfonil)-2-metilbenzamida. MS (Q1) 415,0 $(M)^+$.

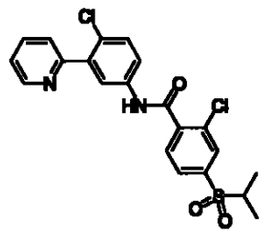
Ejemplo 243 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(etilsulfonil)benzamida



Se usó 4 g de 2-cloro-4-fluorobenzonitrilo en el Procedimiento Q con etantiol para dar 2-cloro-4-(etiltio)benzonitrilo. Se hizo reaccionar 2 g de 2-cloro-4-(etiltio)benzonitrilo por medio del procedimiento T para dar ácido 2-cloro-4-(etiltio)benzoico. 1,5 g de ácido 2-cloro-4-(etiltio)benzoico se hizo reaccionar por medio del procedimiento R para dar ácido 2-cloro-4-(etilsulfonil)benzoico. 75 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 2-cloro-4-(etilsulfonil)benzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(etilsulfonil)benzamida. MS (Q1) 435,1 $(M)^+$.

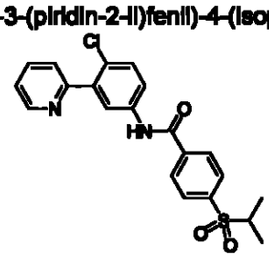
Ejemplo 244 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(isopropilsulfonil)benzamida

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Se usó 2 g de 2-cloro-4-fluorobenzonitrilo en el Procedimiento Q con 2-propantiol para dar 2-cloro-4-(isopropiltio)benzonitrilo. 1,6 g de 2-cloro-4-(isopropiltio)benzonitrilo se hizo reaccionar por medio del procedimiento T para dar ácido 2-cloro-4-(isopropiltio)benzoico. 1 g de ácido 2-cloro-4-(isopropiltio)benzoico se hizo reaccionar por medio del procedimiento R para dar ácido 2-cloro-4-(isopropilsulfonil)benzoico. 75 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 2-cloro-4-(isopropilsulfonil)benzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(isopropilsulfonil)benzamida. MS (Q1) 449,1 $(M)^+$.

Ejemplo 245 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(isopropilsulfonil)benzamida



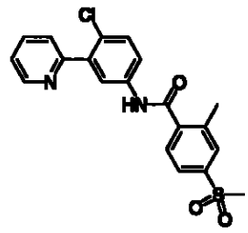
Se usó 2 g de 4-fluorobenzonitrilo en el Procedimiento Q con 2-propantiol para dar 4-(isopropiltio)benzonitrilo. 900 mg de 4-(isopropiltio)benzonitrilo se hizo reaccionar por medio del procedimiento T para dar ácido 4-(isopropiltio)benzoico. 730 mg de ácido 4-(isopropiltio)benzoico se hizo reaccionar por medio del procedimiento R para dar ácido 4-

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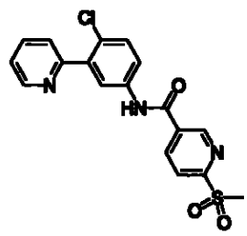
(isopropilsulfonil)benzoico.75 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 4-(isopropilsulfonil)benzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(isopropilsulfonil)benzamida. MS (Q1) 415,0 (M)

Ejemplo 246 *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-4-(metilsulfonil)benzamida



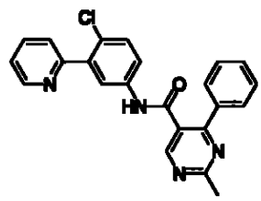
Se agitó una solución de 500 mg de 4-bromo-2-metilbenzonitrilo y 268 mg de tiometóxido de sodio en 3 mL de DMF durante 1h. Se diluyó la mezcla de reacción con acetato de etilo, se lavó con H_2O, se secó ($MgSO_4$) y se evaporó para dar 2-metil-4-(metiltio)benzonitrilo. 400 mg de 2-metil-4-(metiltio)benzonitrilo se hizo reaccionar por medio del procedimiento T para dar ácido 2-metil-4-(metiltio)benzoico. 430 mg de ácido 2-metil-4-(metiltio)benzoico se hizo reaccionar por medio del procedimiento R para dar ácido 2-metil-4-(metilsulfonil)benzoico. 60 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 2-metil-4-(metilsulfonil)benzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-4-(metilsulfonil)benzamida. MS (Q1) 401,0 $(M)^+$.

Ejemplo 247 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(metilsulfonil)nicotinamida



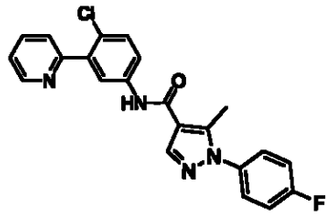
Se hizo reaccionar 1 g de 6-cloronicotinato de metilo por medio del procedimiento O para dar 6-(metilsulfonil)nicotinato de metilo. 1 g de 6-(metilsulfonil)nicotinato de metilo se hidrolizó por medio del procedimiento M para dar ácido 6-(metilsulfonil)nicotínico. 100 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 6-(metilsulfonil)nicotínico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(metilsulfonil)nicotinamida. MS (Q1) 388,1 $(M)^+$.

Ejemplo 248 *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-4-fenilpirimidin-5-carboxamida



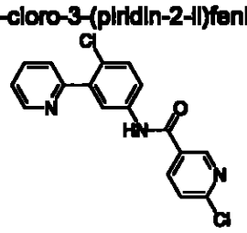
Se acopló 50 mg de 4-cloro-3-(piridin-2-il)abilina a ácido 4-metil-2-fenil-5-pirimidincarboxílico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-4-fenilpirimidin-5-carboxamida. MS (Q1) 401,1 $(M)^+$.

Ejemplo 249 *N*-(4-cloro-3-(piridin-2-il)fenil)-1-(4-fluorofenil)-5-metil-1*H*-pirazol-4-carboxamida



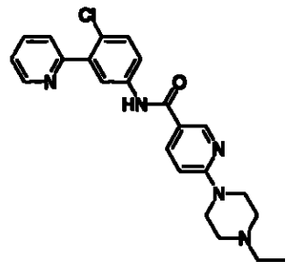
Se acopló 50 mg de 4-cloro-3-(piridin-2-il)abilina a ácido 1-(4-fluorofenil)-5-metil-1*H*-pirazol-4-carboxílico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-1-(4-fluorofenil)-5-metil-1*H*-pirazol-4-carboxamida. MS (Q1) 407,0 $(M)^+$.

Ejemplo 250 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)nicotinamida



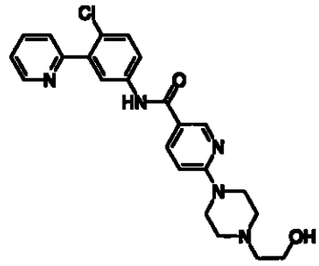
Una mezcla de 450 mg de 4-cloro-3-(piridin-2-il)anilina, 427 mg de cloruro de 6-cloronicotinilo y 1,9 g de PS-DIEA en 10 mL de diclorometano se agitó en el agitador por 3h. La mezcla de reacción se filtró y se lavó con diclorometano. El filtrado se concentró para dar 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)nicotinamida. MS (Q1) 344,2 $(M)^+$.

Ejemplo 251 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(4-etilpiperazin-1-il)nicotinamida



El procedimiento F se realizó usando 50 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)nicotinamida y 93 µL de 1-etilpiperazina en 0,5 mL de BuOH. Se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(4-etilpiperazin-1-il)nicotinamida. MS (Q1) 422,0 $(M)^+$.

Ejemplo 252 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(4-(2-hidroxietil)piperazin-1-il)nicotinamida

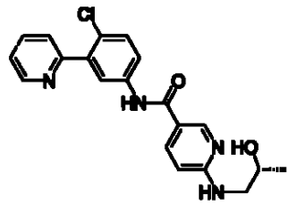


Se realizó el procedimiento F usando 50 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)nicotinamida y 90 µL de 1-(2-hidroxietil)piperazina en 0,5 mL de BuOH. Se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(4-(2-hidroxietil)piperazin-1-il)nicotinamida. MS (Q1) 438,0 $(M)^+$.

Ejemplo 253 (*R*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-6-(2-hidroxipropilamino)nicotinamida.

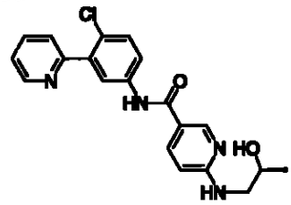
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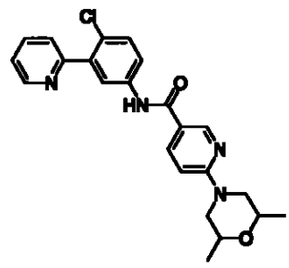
Se realizó el procedimiento F usando 50 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)nicotinamida y 57 µL de R-1-Amino-2–propanol en 0,5 mL de BuOH. Se purificó por HPLC de fase inversa para dar (*R*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-6-(2-hidroxipropilamino)nicotinamida. MS (Q1) 383,4 $(M)^+$.

Ejemplo 254 (*S*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-6-(2-hidroxipropilamino)nicotinamida



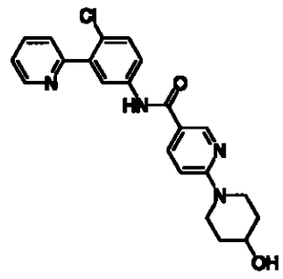
Se realizó el procedimiento F usando 50 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)nicotinamida y 57 µL de S-1-Amino-2–propanol en 0,5 mL de BuOH. Se purificó por HPLC de fase inversa para dar (*S*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-6-(2-hidroxipropilamino)nicotinamida. MS (Q1) 383,4 $(M)^+$.

Ejemplo 255 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(2,6-dimetilmorfolino)nicotinamida



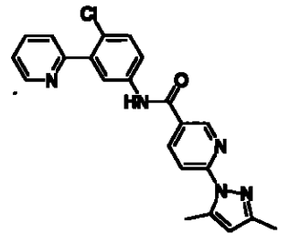
Se realizó el procedimiento F usando 50 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)nicotinamida y 90 µL de 2,6-dimetilmorfolina en 0,5 mL de BuOH. Se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(2,6-dimetilmorfolino)nicotinamida. MS (Q1) 423,4 $(M)^+$.

Ejemplo 256 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(4-hidroxipiperidin-1-il)nicotinamida



Se realizó el procedimiento F usando 50 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)nicotinamida y 74 mg de 4-hidroxipiperidina en 0,5 mL de BuOH. Se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(4-hidroxipiperidin-1-il)nicotinamida. MS (Q1) 409,3 $(M)^+$.

Ejemplo 257 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(3,5-dimetil-1*H*-pirazol-1-il)nicotinamida

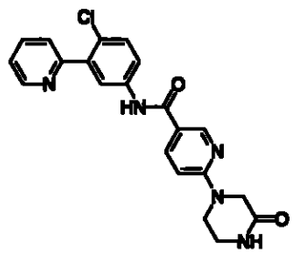


Se agregó 21 mg de hidruro de sodio a una solución de 84 mg de 3,5-dimetilpirazol en 2 mL de DMF. La mezcla de reacción se agitó por 10 min, y luego se agregó 100 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)nicotinamida.

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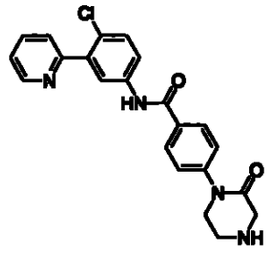
La reacción se calentó a 140 °C durante 16h. La mezcla se fraguó con MeOH y se evaporó. El producto se purificó en HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(3,5-dimetil-1*H*-pirazol-1-il)nicotinamida. MS (Q1) 404,3 $(M)^+$.

Ejemplo 258 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(3-oxopiperidin-1-il)nicotinamida



Se realizó el procedimiento F usando 50 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)nicotinamida y 29 mg de piperazin-2-ona en 0,5 mL de BuOH. Se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(3-oxopiperidin-1-il)nicotinamida. MS (Q1) 408,3 $(M)^+$.

Ejemplo 259 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-oxopiperazin-1-il)benzamida

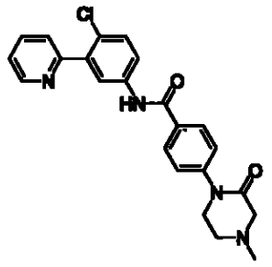


Se calentó una mezcla de 1 g de 4-yodobenzoato de metilo, 920 mg de 4-Boc-piperazinona, 1,1 g de carbonato de potasio, 32 mg de N, N'-dimetiletilenediamina y 70 mg de yoduro de cobre en 10 mL de tolueno a 150

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°C en un reactor de microondas sellado por 3h. La mezcla de reacción se diluyó con acetato de etilo, se lavó con H_2O, se secó ($MgSO_4$) y se evaporó. Se purificó mediante cromatografía en gel de sílice (20-80% acetato de etilo/hexano) para dar 4-(4-(metoxicarbonil)fenil)-3-oxopiperazina-1-carboxilato de ter-butilo. 500 mg de 4-(4-(metoxicarbonil)fenil)-3-oxopiperazina-1-carboxilato de ter-butilo se hidrolizó por medio del procedimiento M para dar ácido 4-(4-(ter-butoxicarbonil)-2-oxopiperazin-1-il)benzoico. 100 mg de 4-cloro-3-(piridin-2-il)anilina se acopló a ácido 4-(4-(ter-butoxicarbonil)-2-oxopiperazin-1-il)benzoico por medio del procedimiento G. La mezcla de reacción se diluyó con acetato de etilo, se lavó con hidróxido de sodio 0,1 N y salmuera, se secó ($MgSO_4$) y se evaporó para dar 4-(4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)fenil)-3-oxopiperazina-1-carboxilato de ter-butilo. 300 mg de 4-(4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)fenil)-3-oxopiperazina-1-carboxilato de ter-butilo sin tratar se trató con TFA (2 mL) que contenía trazas de H_2O por 1h. La mezcla de reacción se evaporó y el producto sin tratar se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-oxopiperazin-1-il)benzamida. MS (Q1) 407,3 $(M)^+$.

Ejemplo 280 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-metil-2-oxopiperazin-1-il)benzamida

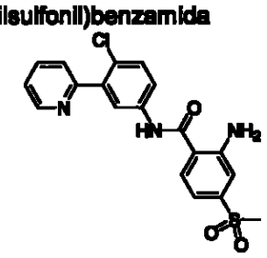


Se disolvió 120 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-oxopiperazin-1-

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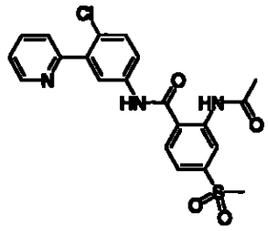
il)benzamida en 2 mL de DMF y luego se trató con 53 mg de paraformaldehído, 187 mg de triacetoxiborhidruro de sodio y 0,2 mL de AcOH. Luego de agitar 16 h, la mezcla de reacción se evaporó y el producto sin tratar se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-metil-2-oxopiperazin-1-il)benzamida. MS (Q1) 421,3 $(M)^+$.

Ejemplo 261 2-amino-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonil)benzamida



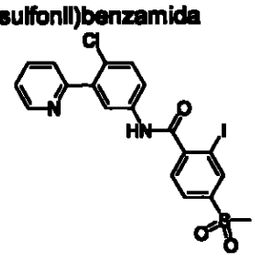
Se hizo reaccionar 2,2 g de 4-(metilsulfonil)-2-nitrobenzoato de metilo por medio del procedimiento C para dar 2-amino-4-(metilsulfonil)benzoato de metilo. Se hidrolizó 500 mg de 2-amino-4-(metilsulfonil)benzoato de metilo por medio del procedimiento M para dar ácido 2-amino-4-(metilsulfonil)benzoico. 100 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 2-amino-4-(metilsulfonil)benzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-amino-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonil)benzamida. MS (Q1) 402,0 $(M)^+$.

Ejemplo 262 2-acetamido-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonil)benzamida



Se agregó 20 µL de cloruro de acetilo a una solución de 90 mg de 2-amino-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonil)benzamida en 2 mL de piridina a 0 °C. La mezcla de reacción se dejó subir la temperatura hasta la temperatura ambiente y se agitó por 2h. La reacción se detuvo con MeOH y se evaporó. El producto se purificó en HPLC de fase inversa para dar 2-acetamido-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonil)benzamida. MS (Q1) 444,0 $(M)^+$.

Ejemplo 263 *N*-(4-cloro-3-(piridin-2-il)fenil)-2-iodo-4-(metilsulfonil)benzamida



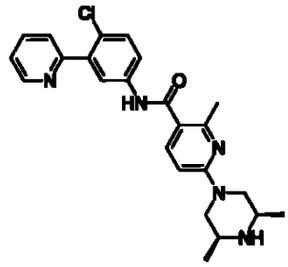
Se agregó 600 mg de 2-amino-4-(metilsulfonil)benzoato de metilo a una solución de 4 mL de H_2O y 1 mL de ácido sulfúrico concentrado. La solución se enfrió a 0 °C y se agregó lentamente una solución de 208 mg de nitrito de sodio en 1 mL de H_2O. La mezcla de reacción se agitó por 2 h y luego una solución de 782 mg de yoduro de potasio en 2 mL de H_2O se agregó por goteo a 0 °C. La reacción se dejó subir la temperatura hasta la temperatura ambiente y se agitó por 5 h. La mezcla se extrajo con acetato de etilo. Los extractos orgánicos

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combinados se lavaron con $Na_2S_2O_3$ saturado, se secó ($MgSO_4$) y se evaporó. Se purificó mediante cromatografía en gel de sílice (5-50% acetato de etilo/hexano) para dar 2-yodo-4-(metilsulfonil)benzoato de metilo. 160 mg de 2-Iodo-4-(metilsulfonil)benzoato de metilo se hidrolizó por medio del procedimiento M para dar ácido 2-Iodo-4-(metilsulfonil)benzoico. 60 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 2-Iodo-4-(metilsulfonil)benzoico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-2-Iodo-4-(metilsulfonil)benzamida. MS (Q1) 513,0 $(M)^+$.

Ejemplo 264 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-((3*S*,5*R*)-3,5-dimetilpiperazin-1-il)-2-metilnicotinamida

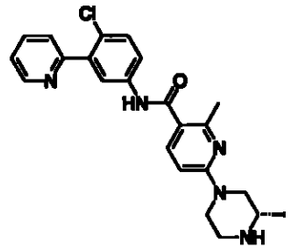


Se calentaron cantidades estequiométricas (0,04 mol) de propiolato de metilo y 3-aminocrotonato de etilo a 140 °C durante 1h. 1 g del (2E,4Z)-metil-4-(1-aminoetiliden)-5-oxooct-2-enoato sin tratar en 4 mL de DMF se calentó a 230 °C en un reactor de microondas sellado por 40 min. La mezcla de reacción se diluyó con acetato de etilo, se lavó con H_2O, se secó ($MgSO_4$) y se evaporó para dar 6-hidroxi-2-metilnicotinato de etilo crudo. una mezcla de 800 mg de 6-hidroxi-2-metilnicotinato de etilo sin tratar en 4 mL de oxicloruro de fósforo se calentó a 150 °C en un reactor de microondas sellado por 15 min. La mezcla de reacción se vertió en hielo/agua, se extrajo con dietiléter. Las capas orgánicas

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combinadas se secaron ($MgSO_4$) y se evaporó. Se purificó mediante cromatografía en gel de sílice (0-20% acetato de etilo/hexano) para dar 6-cloro-2-metilnicotinato de etilo. 400 mg de 6-cloro-2-metilnicotinato de etilo se hidrolizó por medio del procedimiento M para dar ácido 6-cloro-2-metilnicotínico. 300 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 6-cloro-2-metilnicotínico por medio del procedimiento G. La mezcla de reacción se diluyó con acetato de etilo, se lavó con hidróxido de sodio 0,1 N y salmuera, se secó ($MgSO_4$) y se evaporó para dar 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metilnicotinamida. El procedimiento F se realizó usando 100 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metilnicotinamida y 128 mg de 2,6-dimetilpiperazina en 1 mL de BuOH. Se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-6-((3*S*,5*R*)-3,5-dimetilpiperazin-1-il)-2-metilnicotinamida. MS (Q1) 436,3 $(M)^+$.

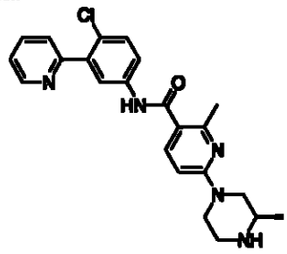
Ejemplo 285 (*S*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(3-metilpiperazin-1-il)nicotinamida



Se realizó el procedimiento F usando 100 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metilnicotinamida y 112 mg de S-(-)-2-metilpiperizina en 1 mL de BuOH. Se purificó por HPLC de fase inversa para dar (*S*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(3-metilpiperazin-1-il)nicotinamida. MS (Q1) 422,3 $(M)^+$.

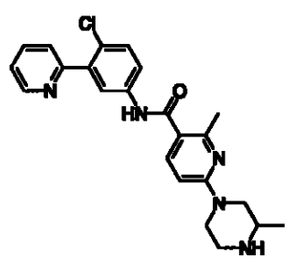
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Ejemplo 266 (*R*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(3-metilpiperazin-1-il)nicotinamida.



Se realizó el procedimiento F usando 100 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metilnicotinamida y 112 mg de R-(+)-2-metilpiperizina en 1 mL de BuOH. Se purificó por HPLC de fase inversa para dar (*R*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(3-metilpiperazin-1-il)nicotinamida. MS (Q1) 422,3 $(M)^+$.

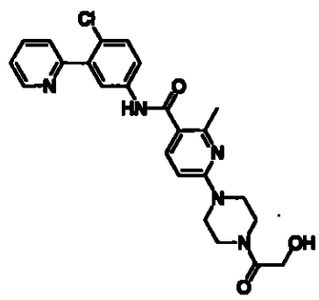
Ejemplo 267 *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(3-metilpiperazin-1-il)nicotinamida



Se realizó el procedimiento F usando 100 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metilnicotinamida y 112 mg de 2-metilpiperizina en 1 mL de BuOH. Se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(3-metilpiperazin-1-il)nicotinamida. MS (Q1) 422,3 $(M)^+$.

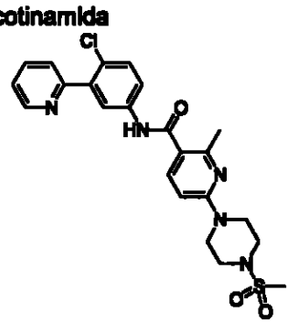
Ejemplo 268 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(4-(2-hidroxiacetil)piperazin-1-il)-2-metilnicotinamida

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Se acopló 100 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(piperazin-1-il)nicotinamida a ácido glicólico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(4-(2-hidroxiacetil)piperazin-1-il)-2-metilnicotinamida. MS (Q1) 466,3 $(M)^+$.

Ejemplo 269 *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(4-(metilsulfonil)piperazin-1-il)nicotinamida

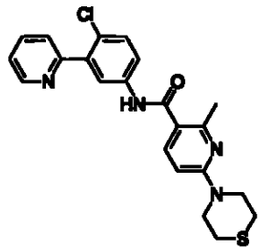


Se agregó 1,3 mL de cloruro de metansulfonilo a una solución de 2 g de 1-Boc–piperazina y 1,3 mL de piridina en 6 mL de diclorometano lentamente a 0°C. La mezcla de reacción se dejó subir la temperatura hasta la temperatura ambiente y se agitó por 2h mientras se monitoreaba con TLC. Al completarse, la mezcla se diluyó con diclorometano, se lavó con H_2O, se secó ($MgSO_4$) y se evaporó. Se purificó mediante cromatografía en gel de sílice (20-100% acetato de etilo/hexano) para dar ter-butil-4-(metilsulfonil)piperazina-1-carboxilato. 930

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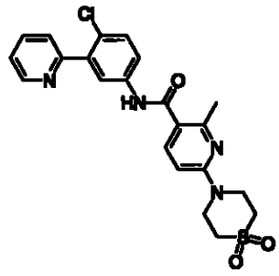
mg de ter-butil-4-(metilsulfonil)piperazina-1-carboxilato se trató con HCl 4N en dioxano por 2h. La mezcla de reacción se evaporó para dar la sal de HCl de 1-(metilsulfonil)piperazina. El procedimiento F se realizó usando 50 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metilnicotinamida, 69 mg de 1-(metilsulfonil)piperazina y DIEPA(1 eq) en 0,5 mL de BuOH. Se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(4-(metilsulfonil)piperazin-1-il)nicotinamida. MS (Q1) 486,3 $(M)^+$.

Ejemplo 270 *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-tiomorfolinonicotinamida



Se realizó el procedimiento F usando 90 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metilnicotinamida y 78 µL de tiomorfolina en 1 mL de BuOH. Se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-tiomorfolinonicotinamida. MS (Q1) 425,3 $(M)^+$.

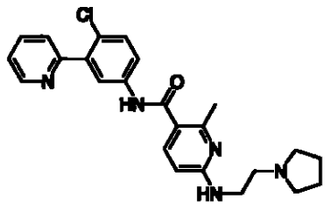
Ejemplo 271 *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-sulfonilmorfolinonicotinamida



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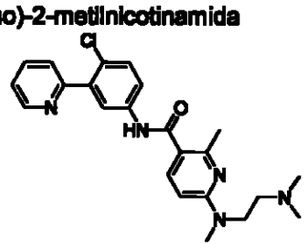
Se hizo reaccionar 100 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-tiomorfolinonicotinamida con el producto R. El producto se purificó en HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-sulfonilmorfolinonicotinamida. MS (Q1) 457,3 $(M)^+$.

Ejemplo 272 *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(2-(pirrolidin-1-il)etilamino)-nicotinamida



El procedimiento F se realizó usando 100 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metilnicotinamida y 70 µL de 1-(2-aminoetil)pirrolidina en 1 mL de BuOH. Se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(2-(pirrolidin-1-il)etilamino)nicotinamida. MS (Q1) 436,0 $(M)^+$.

Ejemplo 273 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-((2-(dimetilamino)etil)(metil)amino)-2-metilnicotinamida



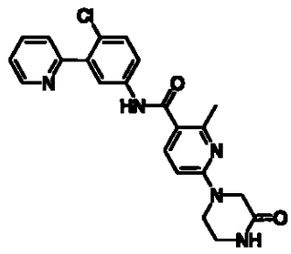
El procedimiento F se realizó usando 60 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metilnicotinamida y 66 µL de N,N,N'-trimetiletilendiamina en 0,5 mL de BuOH. Se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-6-((2-(dimetilamino)etil)(metil)amino)-2-metilnicotinamida. MS

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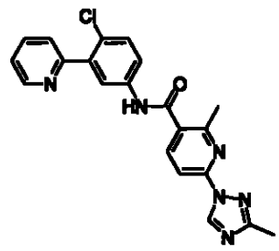
(Q1) 424,0 $(M)^+$.

Ejemplo 274 *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(3-oxopiperazin-1-il)nicotinamida



El procedimiento F se realizó usando 100 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metilnicotinamida y 84 mg de piperazina-2-ona en 1 mL de BuOH. Se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(3-oxopiperazin-1-il)nicotinamida. MS (Q1) 422,3 $(M)^+$.

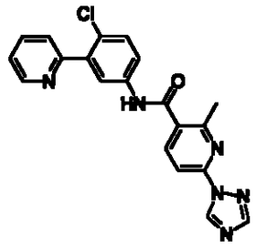
Ejemplo 275 *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(3-metil-1*H*-1,2,4-triazol-1-il)nicotinamida



Una mezcla de 57 mg de 3-metil-1,2,4-triazol y 16 mg de hidruro de sodio en 2 mL de DMF se agitó por 10 min. Se agregaron 80 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metilnicotinamida. La reacción se calentó a 140 °C durante 16h. La mezcla de la reacción se detuvo con MeOH y se evaporó. Se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(3-metil-1*H*-1,2,4-triazol-1-il)nicotinamida. MS (Q1) 405,3 $(M)^+$.

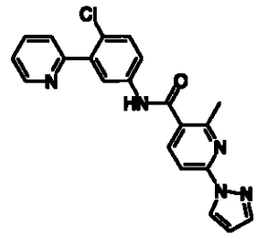
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Ejemplo 276 *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(1*H*-1,2,4-triazol-1-il)nicotinamida



Una mezcla de 41 mg de 1,2,4-triazol y 14 mg de hidruro de sodio en 2 mL de DMF se agitó por 10 min. Se agregó 70 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metilnicotinamida. La reacción se calentó a 140 °C durante 6h. La mezcla de la reacción se detuvo con MeOH y se evaporó. Se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(1*H*-1,2,4-triazol-1-il)nicotinamida. MS (Q1) 391,4 $(M)^+$.

Ejemplo 277 *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(1*H*-pirazol-1-il)nicotinamida



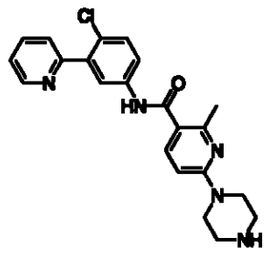
Una mezcla de 52 mg de pirazol y 18 mg de hidruro de sodio en 2 mL de DMF se agitaron por 10 min. Se agregaron 90 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metilnicotinamida. La reacción se calentó a 140 °C durante 5h. La mezcla de la reacción se detuvo con MeOH y se evaporó. Se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(1*H*-

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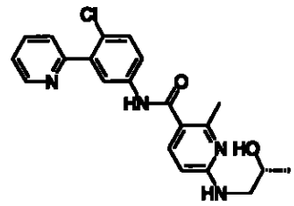
pirazol-1-il)nicotinamida. MS (Q1) 390,0 $(M)^+$.

Ejemplo 278 *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(piperazin-1-il)nicotinamida



El procedimiento F se realizó usando 80 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metilnicotinamida y 209 mg de 1-Boc-piperizina en 1 mL de BuOH. La mezcla de reacción se evaporó para dar 4-(5-(4-cloro-3-(piridin-2-il)fenilcarbamoil)-6-metilpiridin-2-il)piperazina-1-carboxilato de ter-butilo. 150 mg de 4-(5-(4-cloro-3-(piridin-2-il)fenilcarbamoil)-6-metilpiridin-2-il)piperazina-1-carboxilato de ter-butilo se trató con TFA (1 mL) que contenía trazas de H_2O por 2 h. La mezcla de reacción se diluyó con acetato de etilo, se lavó con hidróxido de sodio 0,1N y salmuera, se secó ($MgSO_4$) y se evaporó. Se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(piperazin-1-il)nicotinamida. MS (Q1) 408,3 $(M)^+$.

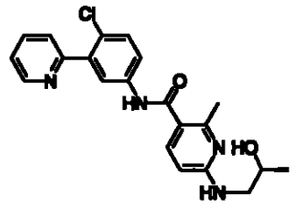
Ejemplo 279 (*R*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-6-(2-hidroxipropilamino)-2-metilnicotinamida



El procedimiento F se realizó usando 80 mg de 6-cloro-*N*-(4-cloro-3-

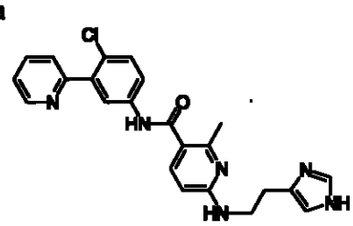
(piridin-2-il)fenil)-2-metilnicotinamida y 116 µL de R-(-)-1-amino-2-propanol en 0,5 mL de BuOH. Se purificó por HPLC de fase inversa para dar (*R*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-6-(2-hidroxipropilamino)-2-metilnicotinamida. MS (Q1) 397,4 $(M)^+$.

Ejemplo 280 (*S*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-6-(2-hidroxipropilamino)-2-metilnicotinamida



El procedimiento F se realizó usando 60 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metilnicotinamida y 116 µL de S-(+)-1-amino-2-propanol en 0,5 mL de BuOH. Se purificó por HPLC de fase inversa para dar (*S*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-6-(2-hidroxipropilamino)-2-metilnicotinamida. MS (Q1) 397,4 $(M)^+$.

Ejemplo 281 6-(2-(1*H*-imidazol-4-il)etilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metilnicotinamida

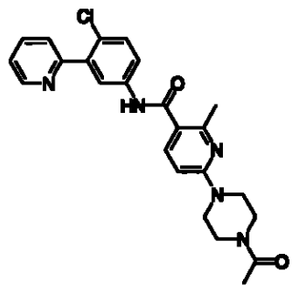


El procedimiento F se realizó usando 60 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metilnicotinamida y 93 mg de histamina en 0,5 mL de BuOH. Se purificó por HPLC de fase inversa para dar 6-(2-(1*H*-imidazol-4-il)etilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metilnicotinamida. MS (Q1) 433,0 (M)

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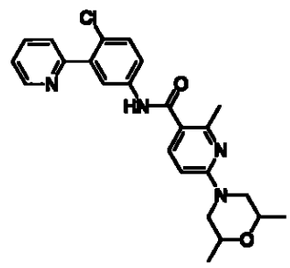
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Ejemplo 282 6-(4-acetilpiperazin-1-il)-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metilnicotinamida



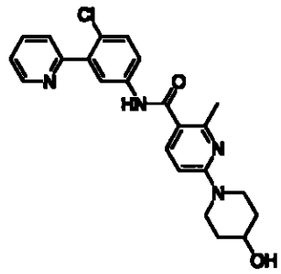
El procedimiento F se realizó usando 55 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metilnicotinamida y 99 mg de 1-acetilpiperazina en 0,5 mL de BuOH. Se purificó por HPLC de fase inversa para dar 6-(4-acetilpiperazin-1-il)-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metilnicotinamida. MS (Q1) 450,4 $(M)^+$.

Ejemplo 283 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(2,6-dimetilmorfolino)-2-metilnicotinamida



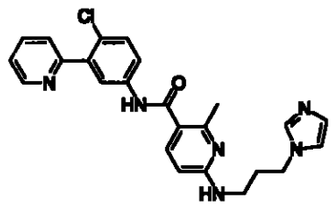
El procedimiento F se realizó usando 55 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metilnicotinamida y 95 mg de 2,6-dimetilmorfolina en 0,5 mL de BuOH. Se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(2,6-dimetilmorfolino)-2-metilnicotinamida. MS (Q1) 436,2 $(M)^+$.

Ejemplo 284 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(4-hidroxipiperidin-1-il)-2-metilnicotinamida



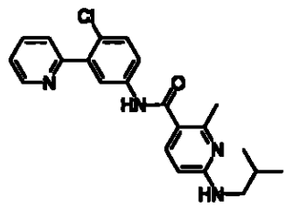
El procedimiento F se realizó usando 55 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metilnicotinamida y 78 mg de 4-hidropiperidina en 0,5 mL de BuOH. Se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(4-hidroxipiperidin-1-il)-2-metilnicotinamida. MS (Q1) 422,1 $(M)^+$.

Ejemplo 285 6-(3-(1*H*-imidazol-1-il)propilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metilnicotinamida



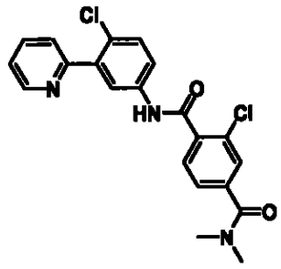
El procedimiento F se realizó usando 55 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metilnicotinamida y 92 µL de 1-(3-aminopropil)-imidazol en 0,5 mL de BuOH. Se purificó por HPLC de fase inversa para dar 6-(3-(1*H*-imidazol-1-il)propilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metilnicotinamida. MS (Q1) 446,1 $(M)^+$.

Ejemplo 286 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(isobutilamino)-2-metilnicotinamida



El procedimiento F se realizó usando 50 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metilnicotinamida y 70 µL de isobutilamina en 0,5 mL de BuOH. Se purificó por HPLC de fase inversa para dar *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(isobutilamino)-2-metilnicotinamida. MS (Q1) 395,4 $(M)^+$.

Ejemplo 287 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4,N^4-dimetiltereftalamida



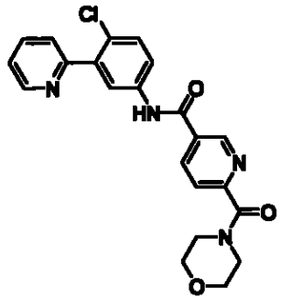
Se acopló 290 mg de clorhidrato de dimetilamina a 1 g de ácido 4-(*ter*-butoxicarbonil)-3-clorobenzoico por medio del procedimiento G. La mezcla de reacción se diluyó con acetato de etilo, se lavó con HCl 0,1 N, NaOH 0,1 N y salmuera, se secó ($MgSO_4$) y se evaporó para dar 2-cloro-4-(dimetilcarbamoil)benzoato de ter-butilo. 1,1g de 2-cloro-4-(dimetilcarbamoil)benzoato de ter-butilo se trató con TFA (4 mL) que contenía trazas de de H_2O por 2 h. La mezcla de reacción se evaporó, y luego se agregó HCl 0,1 N. El sólido resultante se filtró y se lavó con H_2O para dar ácido 2-cloro-4-(dimetilcarbamoil)benzoico. 100 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 2-cloro-4-(dimetilcarbamoil)benzoico por medio del

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procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4,N^4-dimetiltereftalamida.

MS (Q1) 414,1 $(M)^+$.

Ejemplo 288 N-(4-cloro-3-(piridin-2-il)fenil)-6-(morfolin-4-carbonil)nicotinamida

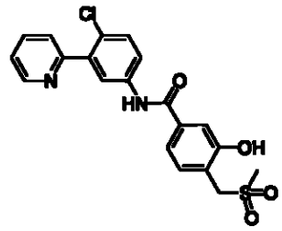


Se acopló 63 mg de morfolina a 120 mg de ácido 5-(metoxicarbonil)piridin-2- carboxílico por medio del procedimiento G. La mezcla de reacción se diluyó con acetato de etilo, se lavó con bicarbonato de sodio saturado y salmuera, se secó ($MgSO_4$) y se evaporó para dar 6-(morfolin-4-carbonil)nicotinato de metilo. 180 mg de 6-(morfolin-4-carbonil)nicotinato de metilo se hidrolizó por medio del procedimiento M para dar ácido 6-(morfolin-4-carbonil)nicotínico. 100 mg de 4-cloro-3-(piridin-2-il)abilina se acopló a ácido 6-(morfolin-4-carbonil)nicotínico por medio del procedimiento G. El producto se purificó en HPLC de fase inversa para dar 2-cloro- N-(4-cloro-3-(piridin-2-il)fenil)-6-(morfolin-4-carbonil)nicotinamida. MS (Q1) 423,4 $(M)^+$.

Ejemplo 289 *N*-(4-Cloro-3-(piridin-2-il)fenil)-3-hidroxi-4-(metilsulfonilmetil)benzamida

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Se disolvió ácido 3-Hidroxi-4-metilbenzoico (6,86 g, 45,1 mmol) en metanol (200 ml). Se agregó HCl 4N en 1,4-dioxano (34 ml, 0,135 mmol HCl) y la solución se calentó a 55°C durante 18 horas. El solvente se concentró en un evaporador rotatorio, y luego se particionó entre agua y acetato de etilo. La porción acuosa se extrajo con acetato de etilo una vez, y los extractos de acetato de etilo se combinaron y se lavó con agua una vez, salmuera una vez, se secó con $MgSO_4$, y se evaporó a 3-hidroxi-4-metilbenzoato de metilo como un sólido sin tratar color tostado (6,66 g) el cual se usó sin purificación. 3-hidroxi-4-metilbenzoato de metilo (6,66 g, 40,1 mmol) se disolvió en diclorometano (200 ml), se trató con piridina (4,3 ml, 60,2 mmol), y se enfrió en un baño de hielo y aguas. Se agregó cloruro de acetilo (3,6 ml, 50,1 mmol) por goteo. La solución se dejó subir la temperatura hasta la temperatura ambiente, con agitación, durante 18 horas. La solución se lavó con HCl acuoso 1 N dos veces, agua una vez, salmuera una vez, se secó con $MgSO_4$, y se evaporó a 3-acetoxi-4-metilbenzoato de metilo como un aceite sin tratar color tostado (6,93 g) el cual se usó sin purificación. 3-acetoxi-4-metilbenzoato de metilo (6,38 g, 30,6 mmol) se disolvió en tetracloruro de carbono (130 ml) y se trató con peroxdanhidruro benzoico (200 mg, 0,83 mmol) y NBS (5,45 g, 30,6 mmol), luego se calentó a 85°C durante 3 horas. Luego de enfriar a temperatura ambiente, la solución se filtró a través de Celite 545 y se evaporó a un sólido sin tratar amarillo el cual se purificó por gel de sílice cromatografía rápida (5%

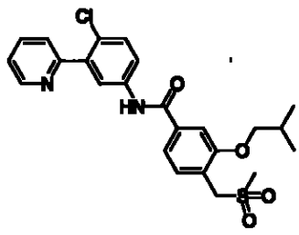
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diclorometano/hexanos incrementando a 35% diclorometano/hexanos) para dar 3-acetoxi-4-(bromometil)benzoato de metilo como un sólido blancuzco (4,18 g). 3-acetoxi-4-(bromometil)benzoato de metilo (2,00 g, 6,97 mmol) se usó en el Procedimiento O para dar 3-acetoxi-4-(metilsulfonilmetil)benzoato de metilo como un sólido blanco (1,67 g) el cual se usó sin purificación. 3-acetoxi-4-(metilsulfonilmetil)benzoato de metilo (1,67 g, 5,83 mmol) se saponificó por medio del procedimiento M para dar ácido 3-hidroxi-4-(metilsulfonilmetil)benzoico como un sólido blanco (1,05 g) el cual se usó sin purificación. Ácido 3-Hidroxi-4-(metilsulfonilmetil)benzoico (860 mg, 3,74 mmol) se disolvió en 1,4-dioxano (25 ml) y se trató con cloruro de tionilo (8 ml) y DMF (5 gotas), luego se calentó a 50°C durante 2 horas. La reacción se enfrió y se evaporó para dar un aceite. El residuo oleoso se disolvió en diclorometano (40 ml), se enfrió en un baño de agua y hielo, y se trató por goteo con una solución de 4-cloro-3-(piridin-2-il)abilina (767 mg, 3,74 mmol) en diclorometano (30 ml). La reacción se agitó 18 horas, dejando calentar a temperatura ambiente. La reacción se diluyó con diclorometano (40 ml) y se agitó fuertemente con agua (50 ml) mientras se acidificaba a pH 6 con ácido cítrico 1 M. La porción diclorometano se separó, y se agregó suficiente metanol se agregó para disolver los sólidos precipitados. La solución se lavó con agua una vez, salmuera una vez, se secó con $MgSO_4$, y se evaporó para dar un sólido el cual se trituró con diclorometano, se filtró, y se secó con aire para dar 909 mg de producto crudo. Una porción (20 mg) se purificó en HPLC de fase inversa para dar 16 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-3-hidroxi-4-(metilsulfonilmetil)benzamida purificada como un sólido blanco. MS (Q1) 417 $(M)^+$.

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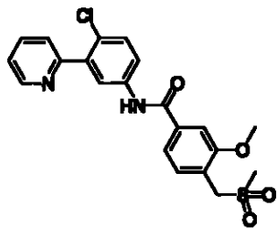
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Ejemplo 290 *N*-(4-Cloro-3-(piridin-2-il)fenil)-3-isobutoxi-4-(metilsulfonilmetil)benzamida



Se trató *N*-(4-cloro-3-(piridin-2-il)fenil)-3-hidroxi-4-(metilsulfonilmetil)benzamida (50 mg, 0,12 mmol) con 1-bromo-2-metilpropano (26 µl, 0,24 mmol) por medio del procedimiento U para dar 19 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-3-isobutoxi-4-(metilsulfonilmetil)benzamida. MS (Q1) 473 $(M)^+$.

Ejemplo 291 *N*-(4-Cloro-3-(piridin-2-il)fenil)-3-metoxi-4-(metilsulfonilmetil)benzamida

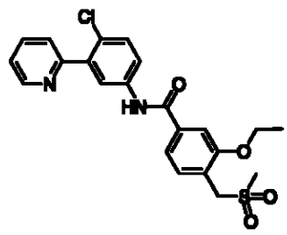


Se trató *N*-(4-Cloro-3-(piridin-2-il)fenil)-3-hidroxi-4-(metilsulfonilmetil)benzamida (50 mg, 0,12 mmol) con yodometano (7,5 µl, 0,12 mmol) por medio del procedimiento U para dar 12 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-3-metoxi-4-(metilsulfonilmetil)benzamida. MS (Q1) 431 $(M)^+$.

Ejemplo 292 *N*-(4-Cloro-3-(piridin-2-il)fenil)-3-etoxi-4-(metilsulfonilmetil)benzamida

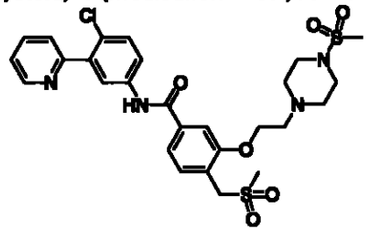
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Se trató *N*-(4-Cloro-3-(piridin-2-il)fenil)-3-hidroxi-4-(metilsulfonilmetil)benzamida (50 mg, 0,12 mmol) con yodoetano (10 µl, 0,12 mmol) por medio del procedimiento U para dar 22 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-3-etoxi-4-(metilsulfonilmetil)benzamida. MS (Q1) 445 $(M)^+$.

Ejemplo 293 *N*-(4-Cloro-3-(piridin-2-il)fenil)-3-(2-(4-(metilsulfonil)piperazin-1-il)etoxi)-4-(metilsulfonilmetil)benzamida

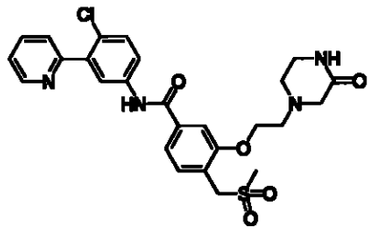


Se disolvió *N*-(4-Cloro-3-(piridin-2-il)fenil)-3-hidroxi-4-(metilsulfonilmetil)benzamida (1,00 g, 2,40 mmol) en DMF (20 ml). Se agregaron carbonato de cesio (1,56 g, 4,8 mmol) y 1,2-dibromoetano (0,83 ml, 9,6 mmol), y la reacción se agitó a 50°C durante 18 horas. La reacción se detuvo con agua, se basificó con NaOH acuoso 10%, y se extrajo con acetato de etilo dos veces. Los extractos de etilo se lavaron con agua una vez, salmuera una vez, se secaron con $MgSO_4$, y se evaporó para dar un aceite sin tratar el cual se purificó por cromatografía (25% hexanos en acetato de etilo) para dar 490 mg de 3-(2-bromoetoxi)-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida como un sólido de color amarillo. 3-(2-

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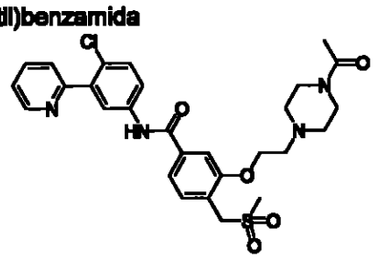
Bromoetoxi)-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida (100 mg, 0,19 mmol) se disolvió en DMF (2,0 ml), y se agregaron carbonato de potasio (32 mg, 0,23 mmol) y piperazina-1-carboxilato de ter-butilo (38 mg, 0,21 mmol). La reacción se agitó por 18 horas a temperatura ambiente, se fraguó en agua, y se extrajo con acetato de etilo dos veces. Los extractos de acetato de etilo se lavaron con agua una vez, salmuera una vez, se secó con $MgSO_4$, y se evaporó para dar un aceite crudo. El aceite se disolvió en diclorometano (1 ml) y se trató con ácido trifluoroacético (3 ml) por 1 hora. La reacción se evaporó a sequedad, y el sólido sin tratar se purificó en HPLC de fase inversa para dar 63 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)-3-(2-(piperazin-1-il)etoxi)benzamida como un sólido blanco. *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)-3-(2-(piperazin-1-il)etoxi)benzamida (30 mg, 0,047 mmol) se disolvió en diclorometano (1,5 ml) y THF (1,0 ml). Se agregaron *N*-etil-*N*-isopropilpropan-2-amina (18 µl, 0,10 mmol) y cloruro de metansulfonilo (4 µl, 0,051 mmol), y la reacción se agitó a temperatura ambiente durante 72 horas. Se agregaron más *N*-etil-*N*-isopropilpropan-2-amina (9 µl, 0,051 mmol) y cloruro de metansulfonilo (4 µl, 0,051 mmol) y la reacción se agitó por 2 horas. Luego de otra adición de cloruro de metansulfonilo (4 µl, 0,051 mmol), la reacción se agitó por 2 horas y se evaporó para dar un sólido sin tratar el cual se purificó en HPLC de fase inversa para dar 8 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-3-(2-(4-(metilsulfonil)piperazin-1-il)etoxi)-4-(metilsulfonilmetil)benzamida. MS (Q1) 607 $(M)^+$.

Ejemplo 294 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)-3-(2-(3-oxopiperazin-1-il)etoxi)benzamida



Se disolvió 3-(2-Bromoetoxi)-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida (50 mg, 0,095 mmol) en DMF (1,0 ml) y se trató con carbonato de potasio (18 mg, 0,13 mmol) y piperazin-2-ona (11 mg, 0,11 mmol) por 18 horas. La reacción se calentó por 2,0 horas a 50°C, luego se agregó más carbonato de potasio (18 mg, 0,13 mmol) y piperazin-2-ona (11 mg, 0,11 mmol). 2 horas después, la reacción se detuvo en NaOH 5% y se extrajo con acetato de etilo dos veces. Los extractos de acetato de etilo se lavaron con agua una vez, salmuera una vez, se secó con $MgSO_4$, y se purificó por HPLC de fase inversa para dar 16 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)-3-(2-(3-oxopiperazin-1-il)etoxi)benzamida. MS (Q1) 558 $(M)^+$.

Ejemplo 295 3-(2-(4-Acetilpiperazin-1-il)etoxi)-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida

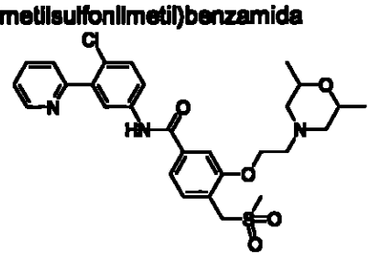


Se disolvió 3-(2-Bromoetoxi)-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida (50 mg, 0,095 mmol) en DMF (1,0 ml) y se trató con carbonato de potasio (18 mg, 0,13 mmol) y 1-(piperazin-1-il)etanona (15 mg, 0,11 mmol) por 18 horas. La reacción se calentó por 2,0 horas a 50°C,

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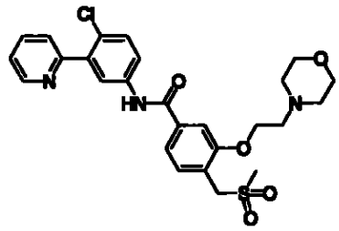
luego se agregó más carbonato de potasio (18 mg, 0,13 mmol) y 1-(piperazin-1-il)etanona (15 mg, 0,11 mmol). 2 horas después, la reacción se detuvo en NaOH 5% y se extrajo con acetato de etilo dos veces. Los extractos de acetato de etilo se lavaron con agua una vez, salmuera una vez, se secó con $MgSO_4$, y se purificó por HPLC de fase inversa para dar 18 mg de 3-(2-(4-acetilpiperazin-1-il)etoxi)-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida. MS (Q1) 543 $(M)^+$.

Ejemplo 296 *N*-(4-Cloro-3-(piridin-2-il)fenil)-3-(2-(2,6-dimetilmorfolino)etoxi)-4-(metilsulfonilmetil)benzamida



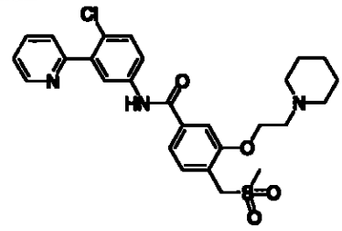
Se disolvió 3-(2-Bromoetoxi)-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida (50 mg, 0,095 mmol) en DMF (1,0 ml) y se trató con carbonato de potasio (18 mg, 0,13 mmol) y 2,6-dimetilmorfolina (14 µl, 0,11 mmol), y se agitó a temperatura ambiente durante 18 horas. La reacción se detuvo en 5% NaOH y se extrajo con acetato de etilo dos veces. Los extractos de acetato de etilo se lavaron con agua una vez, salmuera una vez, se secó con $MgSO_4$, y se purificó por HPLC de fase inversa para dar 20 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-3-(2-(2,6-dimetilmorfolino)etoxi)-4-(metilsulfonilmetil)benzamida. MS (Q1) 571 $(M)^+$.

Ejemplo 297 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)-3-(2-morfolinoetoxi)benzamida



Se disolvió 3-(2-Bromoetoxi)-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida (50 mg, 0,095 mmol) en acetonitrilo (1,0 ml) y DMF (1,0 ml), se trató con carbonato de potasio (16 mg, 0,12 mmol) y morfolina (10 µl, 0,11 mmol), y se agitó 18 horas a temperatura ambiente. La reacción se calentó a 50°C durante 8 horas, y luego se dejó en agitación 18 horas a temperatura ambiente. La reacción se detuvo en agua y se extrajo con acetato de etilo dos veces. Los extractos de acetato de etilo se lavaron con agua una vez, salmuera una vez, se secó con $MgSO_4$, y se evaporó para dar un aceite el cual se purificó por HPLC de fase inversa para dar 30 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)-3-(2-morfolinoetoxi)benzamida. MS (Q1) 530 $(M)^+$.

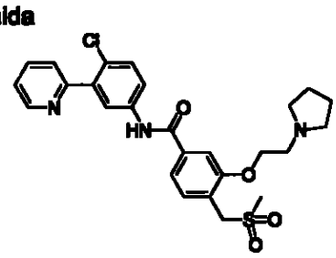
Ejemplo 298 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)-3-(2-(piperidin-1-il)etoxi)benzamida



Se disolvió 3-(2-Bromoetoxi)-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida (50 mg, 0,095 mmol) en diclorometano (1,0 ml), se trató con trietilamina (20 µl, 0,15 mmol) y piperidina (11 µl, 0,11 mmol), y se

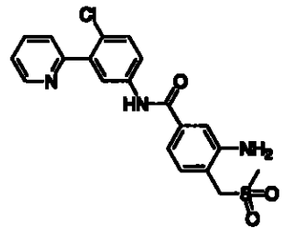
agitó 2,0 horas a temperatura ambiente. Se agregaron acetonitrilo (0,25 ml) y *N*-etil-*N*-isopropilpropan-2-amina (25 µl, 0,19 mmol), y la reacción se agitó por otras 45 horas. La reacción se detuvo en agua y se extrajo con diclorometano dos veces. Los extractos de diclorometano se lavaron con agua una vez, salmuera una vez, se secó con $MgSO_4$, y se evaporó para dar un sólido el cual se purificó por HPLC de fase inversa para dar 17 mg *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)-3-(2-(piperidin-1-il)etoxi)benzamida. MS (Q1) 528 $(M)^+$.

Ejemplo 299 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)-3-(2-(pirrolidin-1-il)etoxi)benzamida



Se disolvió 3-(2-Bromoetoxi)-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida (40 mg, 0,076 mmol) en acetonitrilo (1,0 ml) y DMF (1,0 ml), se trató con carbonato de potasio (16 mg, 0,12 mmol) y pirrolidina (7 µl, 0,084 mmol), y se agitó 18 horas a temperatura ambiente. La la reacción se detuvo en agua y se extrajo con acetato de etilo dos veces. Los extractos de acetato de etilo se lavaron con agua una vez, salmuera una vez, se secó con $MgSO_4$, y se evaporó para dar un aceite el cual se purificó por HPLC de fase inversa para dar 30 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)-3-(2-(pirrolidin-1-il)etoxi)benzamida. MS (Q1) 514 $(M)^+$.

Ejemplo 300 3-Amino-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida



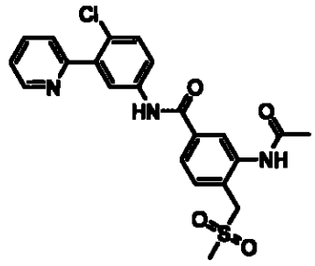
Se disolvió ácido 4-(bromometil)-3-nitrobenzoico (2,00 g, 7,69 mmol) en metanol (20 ml) y se trató con 1 gota de ácido sulfúrico concentrado, luego se agitó por 72 horas a temperatura ambiente. Se agregaron 3 gotas más de ácido sulfúrico concentrado, y la reacción se agitó a 50°C durante 24 horas. El solvente se concentró en un evaporador rotatorio, se diluyó con acetato de etilo, y se lavó con agua dos veces, $NaHCO_3$ saturado una vez, agua una vez, salmuera una vez, se secó con $MgSO_4$, y se evaporó para dar 1,82 g de un aceite amarillo, 4-(bromometil)-3-nitrobenzoato de metilo y se utilizó sin purificación. 4-(bromometil)-3-nitrobenzoato de metilo (1,82 g, 6,64 mmol) se usó en el Procedimiento O para dar 1,66 g de 4-(metilsulfonilmetil)-3-nitrobenzoato de metilo como un sólido el cual se usó sin purificación. 4-(metilsulfonilmetil)-3-nitrobenzoato de metilo (1,66 g, 6,07 mmol) se saponificó por medio del procedimiento M para dar 1,21 g de ácido 4-(metilsulfonilmetil)-3-nitrobenzoico como un sólido anaranjado, el cual se usó sin purificación. Ácido 4-(Metilsulfonilmetil)-3-nitrobenzoico (639 mg, 2,46 mmol) se disolvió en 1,4-dioxano (15 ml), se trató con cloruro de tionilo (1,0 ml) y DMF (1 gota), y se agitó a temperatura ambiente durante 18 horas, luego a 50°C durante 6 horas, luego a temperatura ambiente durante 18 horas. Luego de otras 4,0 horas a 50°C, los solventes y exceso de cloruro de tionilo se eliminaron mediante evaporador rotatorio, y el residuo se disolvió diclorometano (25,0 ml) y se trató con *N*-etil-*N*-isopropilpropan-2-amina (1,7 ml, 9,8 mmol) y 4-cloro-3-(piridin-2-

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il)abilina (503 mg, 2,46 mmol) y se agitó por 20 min a temperatura ambiente, durante los cuales un sólido precipitó. Se agregó agua, y la mezcla se filtró y se secó con aire, para dar 797 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)-3-nitrobenzamida como un sólido color tostado-amarillo. *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)-3-nitrobenzamida (786 mg, 1,76 mmol) se disolvió en etanol (74 ml) y se concentró HCl (12 ml). Se agregó cloruro de estaño (II) dihidratado (1,31 g, 5,82 mmol) y la reacción se calentó a 55°C durante 2,5 horas. La reacción se enfrió en un baño de hielo y se agregó trietilamina (10 ml) para basificar la solución. La reacción se evaporó para dar un sólido amarillo el cual se suspendió en acetato de etilo. La lechada se filtró a través de Celite 545, y los licores madre se lavaron con agua dos veces, salmuera una vez, se secó con $MgSO_4$, y se evaporó para dar 552 mg de un sólido sin tratar amarillo, 20 mg del cual se purificó por HPLC de fase inversa para dar 13 mg de 3-amino-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida purificada. MS (Q1) 416 $(M)^+$.

Ejemplo 301 3-Acetamido-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida



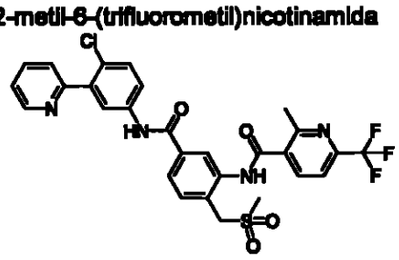
Se hizo reaccionar 3-Amino-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida (30 mg, 0,072 mmol) con cloruro de acetilo (5,6 µl, 0,079 mol) por medio del procedimiento V para dar 19 mg de 3-acetamido-

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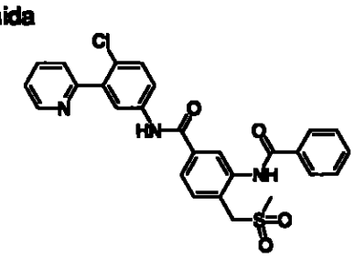
N-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida como un sólido blanco. MS (Q1) 458 $(M)^+$.

Ejemplo 302 *N*-(5-(4-Cloro-3-(piridin-2-il)fenilcarbamoil)-2-(metilsulfonilmetil)fenil)-2-metil-6-(trifluorometil)nicotinamida



Se hizo reaccionar 3-Amino-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida (30 mg, 0,072 mmol) con cloruro de 2-metil-6-(trifluorometil)nicotinoilo (19 mg, 0,079 mmol) por medio del procedimiento V para dar 16 mg de *N*-(5-(4-cloro-3-(piridin-2-il)fenilcarbamoil)-2-(metilsulfonilmetil)fenil)-2-metil-6-(trifluorometil)nicotinamida como un sólido blanco. MS (Q1) 603 $(M)^+$.

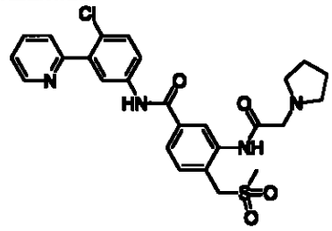
Ejemplo 303 3-Benzamido-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida



Se hizo reaccionar 3-Amino-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida (30 mg, 0,072 mmol) con cloruro de benzoilo (9 µl, 0,079 mmol) por medio del procedimiento V para dar 17 mg de 3-benzamido-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida como

un sólido blanco. MS (Q1) 520 $(M)^+$.

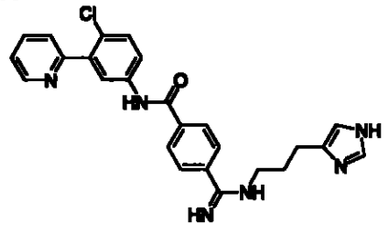
Ejemplo 304 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)-3-(2-(pirrolidin-1-il)acetamido)benzamida



Se disolvió 3-Amino-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida (100 mg, 0,24 mmol) en 1,4-dioxano (5,0 ml), se trató con trietilamina (274 µl, 1,97 mmol) y bromuro de 2-bromoacetilo (121 µl, 1,39 mmol). La reacción se calentó a reflujo por 10 minutos, y se agitó a temperatura ambiente durante 18 horas. La reacción se detuvo con agua, y se extrajo dos veces con acetato de etilo. Los extractos de acetato de etilo se filtraron, se lavó con agua una vez, salmuera una vez, se secó con $MgSO_4$, se evaporó para dar 158 mg de un aceite sin tratar marrón, 3-(2-bromoacetamido)-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)benzamida, el cual se usó sin purificación subsiguiente. 3-(2-bromoacetamido)-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonil-metil)benzamida cruda (158 mg) se disolvió en DMF, se trató con *N*-etil-*N*-isopropilpropan-2-amina (81 µl, 0,35 mmol) y pirrolidina (27 µl, 0,32 mmol), y se agitó a temperatura ambiente durante 18 horas. La reacción se detuvo con agua y se extrajo con acetato de etilo dos veces. Los extractos de acetato de etilo se lavaron con agua una vez, salmuera una vez, se secó con $MgSO_4$, se evaporó para dar un sólido tostado el cual se purificó por HPLC de fase inversa para dar 27 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)-3-(2-(pirrolidin-1-il)acetamido)benzamida como un polvo

blanco. MS (Q1) 527 $(M)^+$.

Ejemplo 305 4-(*N*-(3-(1*H*-Imidazol-4-il)propil)carbamimidoil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida

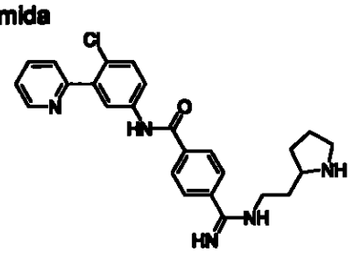


Se disolvió 4-Cloro-3-(piridin-2-il)abilina (687 mg, 3,36 mmol) en diclorometano (8,0 ml) y THF (8,0 ml), se trató con piridina (0,33 ml, 4,0 mmol), y se enfrió a 0°C. Se agregó cloruro de 4-cianobenzoilo (612 mg, 3,7 mmol) y la reacción se agitó por 1,0 hora. La reacción se diluyó con diclorometano y se agregó metanol para disolver todos los sólidos. La solución se lavó con agua una vez, salmuera una vez, se secó con $MgSO_4$, y se evaporó para dar un sólido anaranjado el cual se purificó por cromatografía de columna flash en gel de sílice (50% acetato de etilo/50% hexanos) para dar 908 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-cianobenzamida como un sólido de color amarillo. *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-cianobenzamida (500 mg, 1,5 mmol) se suspendió en etanol (75 ml) y se calentó hasta disolver. La solución se enfrió en un baño de hielo, y se saturó con HCl gaseoso. La solución se calentó brevemente a 70°C para disolver los sólidos precipitados, se enfrió en un baño de hielo, y se volvió a saturar con HCl gaseoso. La solución luego se guardó a 0°C durante 18 horas. La solución se saturó nuevamente con HCl gaseoso, se calentó a 70°C hasta que se disolvieron todos los sólidos, se enfrió a 0°C, se volvió a saturar con HCl gaseoso, y se guardó a 0°C durante 18 horas. Finalmente, se burbujeó gas nitrógeno a través de la solución por 1,0 hora, y la solución se

evaporó a sequedad. El residuo se disolvió en metanol, se trató con MP-carbonate (2,57 g) y se agitó 30 min. La solución se filtró para dar una solución metanólica neutra de 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencimidato de etilo, la cual se diluyó con suficiente metanol para lograr una solución 0,075 M.

4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencimidato de etilo (2,0 ml de una solución 0,075 M en metanol, 0,15 mmol) se trató con 3-(1H-imidazol-4-il)propan-1-amina (27 µl, 0,23 mmol) por medio del procedimiento W para dar 83 mg de 4-(*N*-(3-(1*H*-imidazol-4-il)propil)carbamimidoil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida. MS (Q1) 459 $(M)^+$.

Ejemplo 306 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(*N*-(2-(pirrolidin-2-il)etil)carbamimidoil)benzamida

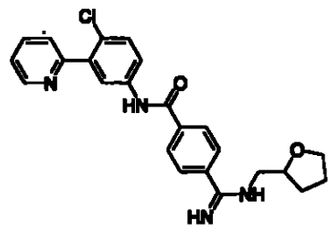


Se trató 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencimidato de etilo (2,0 ml de una solución 0,075 M en metanol, 0,15 mmol) con 2-(pirrolidin-2-il)etanamina (28 µl, 0,23 mmol) por medio del procedimiento W para dar 90 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-(2-(pirrolidin-2-il)etil)carbamimidoil)benzamida. MS (Q1) 448 $(M)^+$.

Ejemplo 307 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(*N*-((tetrahidrofuran-2-il)metil)carbamimidoil)benzamida

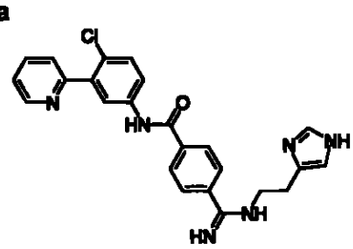
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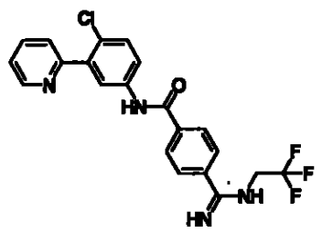
Se trató 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencimidato de etilo (2,0 ml de una solución 0,075 M en metanol, 0,15 mmol) con (tetrahidrofuran-2-il)metanamina (23 µl, 0,23 mmol) por medio del procedimiento W para dar 76 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-((tetrahidrofuran-2-il)metil)carbamimidoil)benzamida. MS (Q1) 435 $(M)^+$.

Ejemplo 308 4-(*N*-(2-(1*H*-Imidazol-4-il)etil)carbamimidoil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida



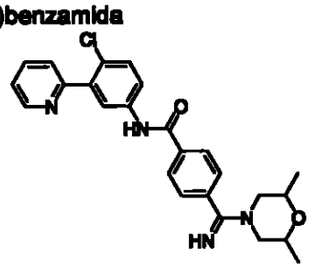
Se trató 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencimidato de etilo (2,0 ml de una solución 0,075 M en metanol, 0,15 mmol) con 2-(1H-imidazol-4-il)etanamina (25 mg, 0,23 mmol) por medio del procedimiento W para dar 90 mg de 4-(*N*-(2-(1*H*-Imidazol-4-il)etil)carbamimidoil)-*N*-(4-cloro-3-(piridin-2-il)fenil)benzamida. MS (Q1) 445 $(M)^+$.

Ejemplo 309 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(*N*-(2,2,2-trifluoroetil)carbamimidoil)benzamida



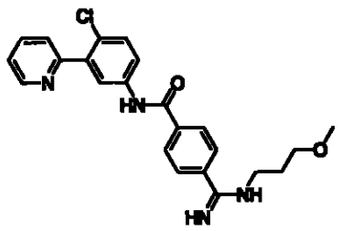
Se trató 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencimidato de etilo (2,0 ml de una solución 0,075 M en metanol, 0,15 mmol) con 2,2,2-trifluoroetanamina (18 µl, 0,23 mmol) por medio del procedimiento W para dar 56 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-(2,2,2-trifluoroetil)carbamimidoil)benzamida. MS (Q1) 433 $(M)^+$.

Ejemplo 310 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-((2,6-dimetilmorfolino)(imino)metil)benzamida



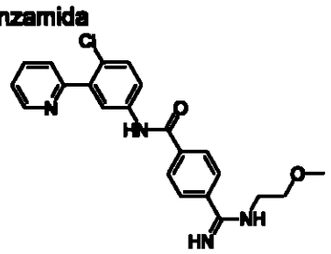
Se trató 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencimidato de etilo (2,0 ml de una solución 0,075 M en metanol, 0,15 mmol) con 2,6-dimetilmorfolina (28 µl, 0,23 mmol) por medio del procedimiento W para dar 74 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((2,6-dimetilmorfolino)(imino)metil)benzamida. MS (Q1) 449 $(M)^+$.

Ejemplo 311 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(*N*-(3-metoxdpropil)carbamimidoil)benzamida



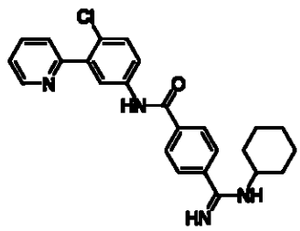
Se trató 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencimidato de etilo (2,0 ml de una solución 0,075 M en metanol, 0,15 mmol) con 3-metoxipropan-1-amina (23 µl, 0,23 mmol) por medio del procedimiento W para dar 68 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-(3-metoxipropil)carbamimidoil)benzamida. MS (Q1) 423 $(M)^+$.

Ejemplo 312 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(*N*-(2-metoxietil)carbamimidoil)benzamida



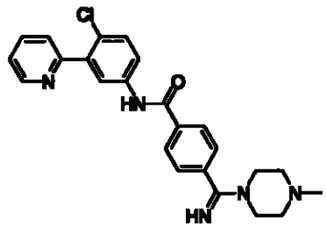
Se trató 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencimidato de etilo (2,0 ml de una solución 0,075 M en metanol, 0,15 mmol) con 2-metoxietanamina (19 µl, 0,23 mmol) por medio del procedimiento W para dar 50 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-(2-metoxietil)carbamimidoil)benzamida. MS (Q1) 409 $(M)^+$.

Ejemplo 313 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(*N*-ciclohexilcarbamimidoil)benzamida



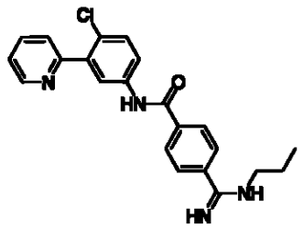
Se trató 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencimidato de etilo (2,0 ml de una solución 0,075 M en metanol, 0,15 mmol) con ciclohexanamina (26 µl, 0,23 mmol) por medio del procedimiento W para dar 30 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-ciclohexilcarbamimidoil)benzamida. MS (Q1) 433 $(M)^+$.

Ejemplo 314 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(imino(4-metilpiperazin-1-il)metil)benzamida



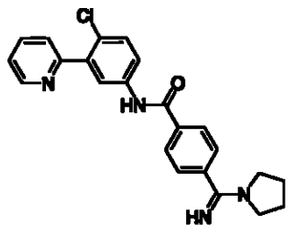
Se trató 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencimidato de etilo (2,0 ml de una solución 0,075 M en metanol, 0,15 mmol) con 1-metilpiperazina (23 mg, 0,23 mmol) por medio del procedimiento W para dar 35 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(imino(4-metilpiperazin-1-il)metil)benzamida. MS (Q1) 434 $(M)^+$.

Ejemplo 315 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(*N*-propilcarbamimidoil)benzamida



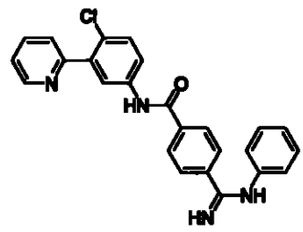
Se trató 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencimidato de etilo (2,0 ml de una solución 0,075 M en metanol, 0,15 mmol) con propan-1-amina (18 µl, 0,23 mmol) por medio del procedimiento W para dar 39 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-propilcarbamimidoil)benzamida. MS (Q1) 393 $(M)^+$.

Ejemplo 316 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(imino(pirrolidin-1-il)metil)benzamida



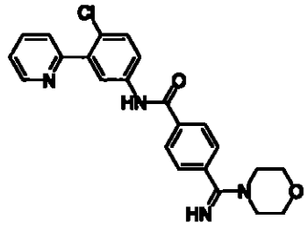
Se trató 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencimidato de etilo (2,0 ml de una solución 0,075 M en metanol, 0,15 mmol) con pirrolidina (19 µl, 0,23 mmol) por medio del procedimiento W para dar 25 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(imino(pirrolidin-1-il)metil)benzamida. MS (Q1) 405 $(M)^+$.

Ejemplo 317 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(*N*-fenilcarbamimidoil)benzamida



Se trató 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencimidato de etilo (2,0 ml de una solución 0,075 M en metanol, 0,15 mmol) con abilina (21 µl, 0,23 mmol) por medio del procedimiento W para dar 7 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-fenilcarbamimidoil)benzamida. MS (Q1) 427 $(M)^+$.

Ejemplo 318 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(imino(morfolino)metil)benzamida

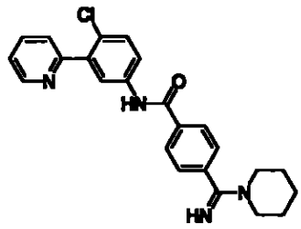


Se suspendió *N*-(4-cloro-3-(piridin-2-il)fenil)-4-cianobenzamida (300 mg, 0,899 mmol) en 45 ml de etanol y se trató con 10 ml de etanol saturado con HCl. La reacción se guardó a 0°C durante 3 días, luego se calentó a 75°C durante 3,0 horas, y se enfrió a temperatura ambiente por 18 horas. La reacción se enfrió en un baño de hielo, y se saturó con HCl gaseoso. Luego de guardar a 0°C durante otros 3 días, se burbujeó N_2 gaseoso a través de la solución por 1,0 hora, y la solución se diluyó con suficiente etanol para hacer una solución 0,0155 M de 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencimidato de etilo. 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencimidato de etilo (17,5 ml de una solución 0,0155 M en etanol, 0,27 mmol) se trató con morfolina (1,0 ml,

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11,4 mmol) por 3 días. El etanol se evaporó, y el residuo se purificó por HPLC de fase inversa para dar 30 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(imino(morfolino)metil)benzamida. MS (Q1) 421 $(M)^+$.

Ejemplo 319 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(imino(piperidin-1-il)metil)benzamida



Se trató 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencimidato de etilo (17,5 ml de una solución 0,0155 M, 0,27 mmol) con piperidina (1,0 ml, 10,0 mmol) por 3 días. El etanol se evaporó, y el residuo se purificó por HPLC de fase inversa para dar 26 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(imino(piperidin-1-il)metil)benzamida. MS (Q1) 419 $(M)^+$.

Ejemplo 320 Ensayos de inhibición de señalización de Hedgehog

Líneas celulares reporteras de ratón – células 10T1/2-GliLuc [S12] (derivadas de la línea celular C3H10T1/2 ATCC #CCL-226); fibroblastos embrionarios de ratón); Medio de Crecimiento: medio Eagle modificado de Dulbecco (DMEM) suplementado con 10% de Suero Fetal Bovino (FBS), 10 unidades/mL de penicilina, 100 ug/mL de estreptomicina, 2 mM glutamina, y 10 mM HEPES.

Líneas celulares reporteras de humano – células HEPM-GliLuc [MZ24] (derivadas de HEPM, células preosteoblásticas mesenquimales humanas ATCC #CRL-1486); Medio de Crecimiento: Medio Esencial Mínimo (MEM; con sales de Earle) suplementado con 10-20% Suero Fetal Bovino (FBS), 10

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unidades/mL de penicilina, 100 ug/mL de estreptomicina, 2 mM glutamina, y 10 mM HEPES pH 7.2.

Conjugado N-terminal octilado Hedgehog Sónico - SHh recombinante humano.

Placas de microtitulación (MTPs) - Para el ensayo de Luciferasa se plaquean células en MTPs de 96-fosas (blancas, de fondo plano, transparentes).

Medio de ensayo de Luciferasa - DMEM suplementado con 0,5% FBS, 10 unidades/mL de penicilina, 100 ug/mL de estreptomicina, 2 mM glutamina, y 10 mM HEPES pH 7,2.

Mezcla PBS/Ca/Mg – buffer fosfato salino (PBS) suplementado con 0,5 mM $CaCl_2$ y 1 mM $MgCl_2$.

Procedimiento del Ensayo

Se mantuvieron células S12 y MZ24 genéticamente modificadas para contener un gen reportero de luciferasa controlado por el promotor Gli sensible a hedgehog en placas de cultivo de tejido en Medio de Crecimiento a 37 °C y 5% de CO_2. Los cultivos celulares en sub-confluencia se replicaron cada 3-4 días. (entre 1:20 y 1:40 para s12; entre 1:3 y 1:10 para MZ24). Las células se colectaron y se diluyeron en Medio de Crecimiento de modo que se pudieran plaquear en una placa de microtitulación a 10.000-20.000 células (s12), o 20.000-30.000 células (MZ24), por 100 µl, por fosa. Las células luego se incubaron durante ~24-48 horas a 37 °C y 5% de CO_2.

Luego de 24-48 de incubación, el medio de crecimiento en las placas de microtitulación se reemplazó por el Medio de ensayo de Luciferasa (100 µl por fosa), con y sin conjugado octilado hedgehog Sónico, entre 0,1 y 0,3 µg/ml

(S12) o entre 0,5 y 1,0 µg/ml (MZ24), y compuestos de ensayo. Las células se incubaron entonces adicionalmente durante otras 24 horas adicionales.

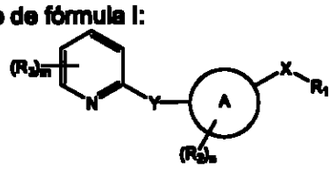
Luego las placas de microtitulación se sometieron al conjunto de elementos del ensayo del gen reportero de luciferasa (LucLite™), con modificaciones al procedimiento del fabricante donde se quitó el medio y el sustrato se reconstituyó con 1:1 PBS/Ca/Mg : buffer de lisis en lugar de directamente buffer de lisis. En resumen, el PBS/Ca/Mg se mezció 1:1 con buffer de lisis y se agregaron 10 mL a cada vial de sustrato (del conjunto de elementos de 1000 ensayos). Luego se descartó el medio de ensayo de la placa de microtitulación, y se agregaron 100 µl de esta mezcla de sustrato a cada fosa. Las placas se incubaron a temperatura ambiente durante entre 20 y 30 minutos y luego se determinaron las Unidades de Luz Relativa (RLUS) que representan el nivel de expresión relativo del gen reportero de luciferasa con un lector Topcount (Packard) o un lector Analyst (Molecular Devices). Los compuestos de la invención examinados en los ensayos demostraron una expresión de Gli reducida en las líneas celulares reporteras lo que indica la inhibición de la vía de señalización de hedgehog.

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REIVINDICACIONES

1. Un compuesto de fórmula I:



I

en donde

A es un carbocicio o heterocicio;

X es alquileno, $NR_4C(O)$, $NR_4C(S)$, $N(C(O)R_1)C(O)$, NR_4SO, NR_4SO_2, $NR_4C(O)NH$, $NR_4C(S)NH$, $C(O)NR_4$, $C(S)NR_4$, NR_4PO o $NR_4PO(OH)$;

Y está ausente, CHR_4, O, S, SO, SO_2 o NR_4;

R_1 se selecciona entre el grupo formado por alquilo, un carbocicio o un heterocicio cada uno de los cuales está opcionalmente sustituido con hidroxilo, halógeno, amino, carboxilo, amidino, guanidino, carbonilo, nitro, ciano, acilo, alquilo, haloalquilo, sulfonilo, sulfinilo, alcoxi, alquiltio, carbamoilo, acilamino, sulfamoilo, sulfonamida, un carbocicio o a heterocicio; donde dicho amino, amidino, alquilo, acilo, sulfonilo, sulfinilo, alcoxi, alquiltio, carbamoilo, acilamino, sulfamoilo, sulfonamida, carbocicio y sustituyente heterocicio se sustituye opcionalmente con, halógeno, haloalquilo, hidroxilo, carboxilo, carbonilo, o un amino, alquilo, alcoxi, acilo, sulfonilo, sulfinilo, fosfinato, carbocicio o heterocicio que está opcionalmente sustituido con hidroxilo, carboxilo, carbonilo, amino, halógeno, haloalquilo, alquilo, alcoxi, alquiltio, sulfonilo, sulfinilo, acilo, un carbocicio o a heterocicio;

R_2 es halógeno, hidroxilo, alquilo, acilo o alcoxi, donde cada alquilo, acilo y alcoxi está opcionalmente sustituido con hidroxilo, halógeno, amino, nitro, alquilo, acilo, alquilsulfonilo o alcoxi;

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R_3 es halógeno, hidroxilo, carboxilo, alquilo, acilo, alcoxi, alcoxicarbonilo, carbamoilo, alquilsulfuro, sulfinilo, sulfonilo, un carbociclo o un heterociclo donde cada alquilo, acilo, alcoxi, alcoxicarbonilo, carbamoilo, alquilsulfuro, sulfinilo, sulfonilo, carbociclo y heterociclo está opcionalmente sustituido con hidroxilo, halógeno, amino, nitro, alquilo, acilo, sulfonilo o alcoxi;

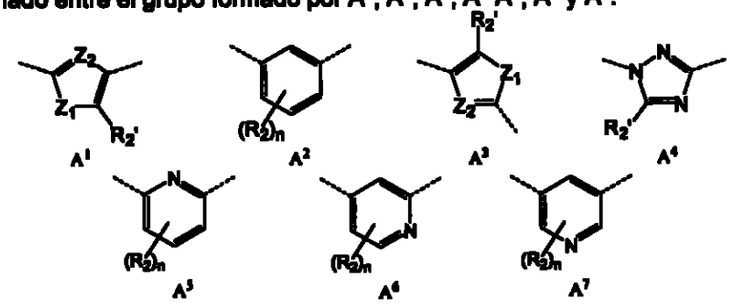
R_4 es H o alquilo;

m es 0-3;

n es 0-3;

y sus sales y solvatos.

2. El compuesto de la reivindicación 1, donde A es un anillo seleccionado entre el grupo formado por A^1, A^2, A^3, A^4 A^5, A^6 y A^7:



en donde Z_1 es O, S o NR_8 donde R_8 es H o alquilo; Z_2 es CH, CR_2 o N; R_2 es halógeno, hidroxilo, alquilo o alcoxi; $R_{2'}$ es H, halógeno, hidroxilo, alquilo o alcoxi; y n es 0-3.

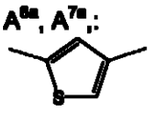
3. El compuesto de la reivindicación 2, donde A es el anillo A^1 donde Z_1 es S y Z_2 es CH o N.

4. El compuesto de la reivindicación 2, donde A es el anillo A^2.

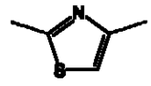
5. El compuesto de la reivindicación 2, donde R_2 o R_2' es Cl.

6. El compuesto de la reivindicación 1, donde A es A^{1a}, A^{1b}, A^{2a}, A^{3a},

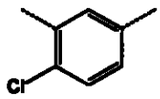
A^{3b}, A^{4a}, A^{5a}, A^{6a}, A^{7a},:



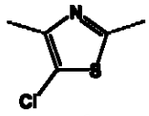
A^{1a}



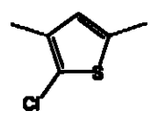
A^{1b}



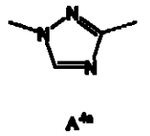
A^{2a}



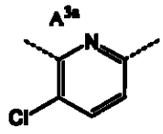
A^{3a}



A^{3b}



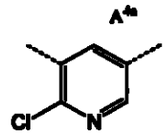
A^{4a}



A^{5a}

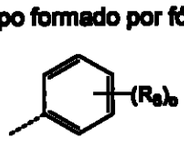


A^{6a}

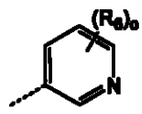


A^{7a}

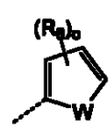
7. El compuesto de la reivindicación 1, donde X es $NR_4C(O)$.
8. El compuesto de la reivindicación 1, donde X es NR_4SO_2.
9. El compuesto de la reivindicación 7, donde R_4 es H o Me.
10. El compuesto de la reivindicación 9, donde R_4 es H.
11. El compuesto de la reivindicación 1, donde R_3 es Me o F.
12. El compuesto de la reivindicación 1, donde R_3 es Me y m es 1 o 2.
13. El compuesto de la reivindicación 1, donde R_3 es F y m es 1 o 2.
14. El compuesto de la reivindicación 1, donde m es 0.
15. El compuesto de la reivindicación 1, donde R_1 se selecciona entre el grupo formado por fórmula IIa - IIc:



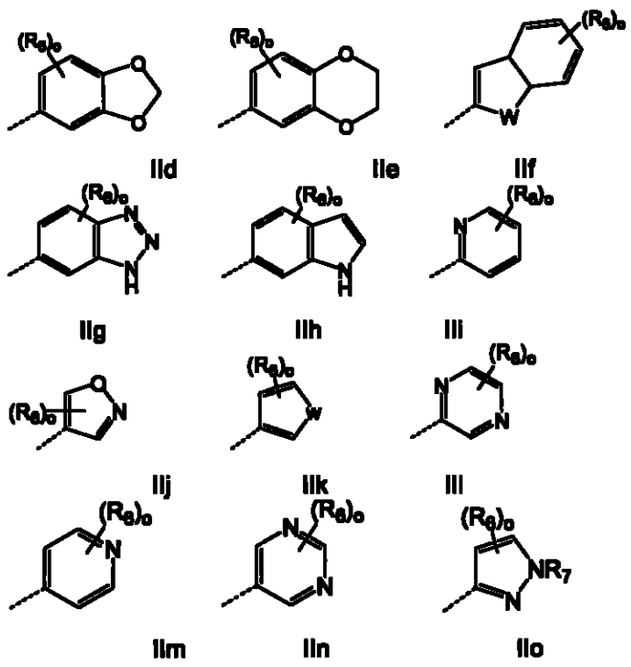
IIa



IIb



IIc



IId IIe IIf

IIg IIh III

IIj IIk III

IIm IIn IIo

en donde

W es O, S o NR_7 donde R_7 es H, alquilo, acilo, un carbociclo o un heterociclo donde dichos alquilo carbociclo y heterociclo se sustituyen cada uno opcionalmente con 1-3 amino, halógeno, hidroxilo y haloalquilo;

R_8 en cada instancia es en forma independiente hidroxilo, halógeno, amino, carbonilo, nitro, ciano, acilo, alquilo, sulfonilo, alquilsulfonilo, alquilsulfinilo, alcoxi, alquilcarbamoilo, alcanolamina, alquilsulfamoilo, alquilsulfonamida, un carbociclo o a heterociclo; donde dicho sustituyente amino, alquilo, carbonilo, acilo, sulfonilo, alquilsulfonilo, alquilsulfinilo, alcoxi, alquilcarbamoilo, alcanolamina, alquilsulfamoilo, alquilsulfonamida, carbociclo y heterociclo está opcionalmente sustituido con amino, halógeno, hidroxilo, carbonilo, o un carbociclo o heterociclo que está opcionalmente sustituido con

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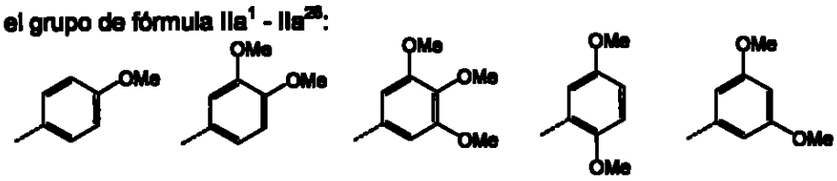
hidroxilo, amino, halógeno, haloalquilo, alquilo, alcoxi o acilo; y

o es 0-3.

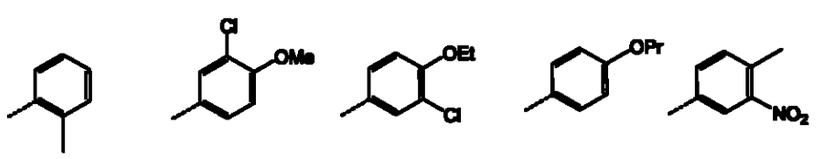
16. El compuesto de la reivindicación 15, donde R_1 es el grupo de fórmula IIa.

17. El compuesto de la reivindicación 16, donde R_6 es alcoxi y o es 1 o 2.

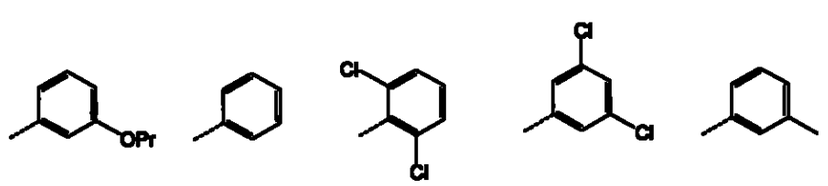
18. El compuesto de la reivindicación 16, donde R_1 se selecciona entre el grupo de fórmula IIa^1 - IIa^{28}:



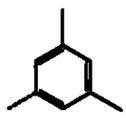
IIa^1 IIa^2 IIa^3 IIa^4 IIa^5



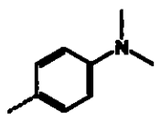
IIa^6 IIa^7 IIa^8 IIa^9 IIa^{10}



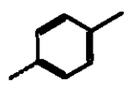
IIa^{11} IIa^{12} IIa^{13} IIa^{14} IIa^{15}



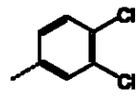
IIa[16]



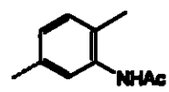
IIa[17]



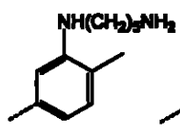
IIa[18]



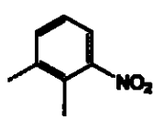
IIa[19]



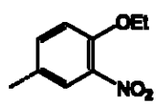
IIa[20]



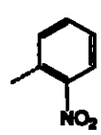
IIa[21]



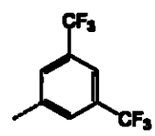
IIa[22]



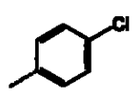
IIa[23]



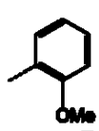
IIa[24]



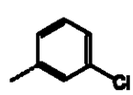
IIa[25]



IIa[26]



IIa[27]



IIa[28]

19. El compuesto de la reivindicación 16, donde A es el anillo A^1 o A^2.

20. El compuesto de la reivindicación 16, donde A es el anillo A^{2a}.

21. El compuesto de la reivindicación 16, donde R_3 es Me o F.

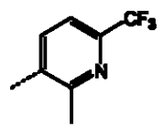
22. El compuesto de la reivindicación 3, donde m es 0.

23. El compuesto de la reivindicación 3, donde X es $NR_4C(O)$.

24. El compuesto de la reivindicación 15, donde R_1 es el grupo de fórmula IIb.

25. El compuesto de la reivindicación 24, donde R_8 es alquilo o haloalquilo.

26. El compuesto de la reivindicación 24, donde R_1 es el grupo de fórmula IIb^1



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IIb[1].

27. El compuesto de la reivindicación 24, donde A es el anillo A^1 o A^2.

28. El compuesto de la reivindicación 24, donde A es el anillo A^2.

29. El compuesto de la reivindicación 24, donde R_3 es H, Me o F.

30. El compuesto de la reivindicación 24, donde R_3 es H.

31. El compuesto de la reivindicación 24, donde X es $NR_4C(O)$.

32. Una composición que comprende un compuesto de la reivindicación 1 y un vehículo aceptable para uso farmacéutico.

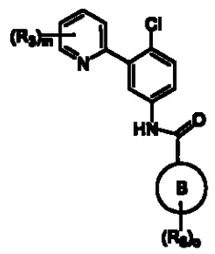
33. Un método de tratar el cáncer en un mamífero, que comprende administrar a dicho mamífero una cantidad efectiva de un compuesto de la reivindicación 1.

34. El método de la reivindicación 33, donde dicho cáncer es carcinoma de células basales, blastoma de médula, adenocarcinoma pancreático, carcinoma de pulmón de células pequeñas, carcinoma de mama, rabdomiosarcoma, cáncer de esófago, cáncer de estómago, cáncer del tracto biliar.

35. Un método de inhibir la angiogénesis en un mamífero, que comprende administrar a dicho mamífero una cantidad efectiva de un compuesto de la reivindicación 1.

36. Un método de inhibir señalización de la vía metabólica Hedgehog en una célula que comprende contactar dicha célula con una cantidad efectiva de un compuesto de la reivindicación 1.

37. Un proceso para preparar un compuesto de fórmula Ib"



Ib"

donde

el anillo B es un carbociclo o heterociclo;

R_3 es halógeno, hidroxilo, carboxilo, alquilo, acilo, alcoxi, alcoxicarbonilo, carbamoilo, alquilsulfuro, alquilsulfinilo, alquilsulfonilo, un carbociclo o un heterociclo donde cada alquilo, acilo, alcoxi, alcoxicarbonilo, carbamoilo, alquilsulfuro, alquilsulfinilo, alquilsulfonilo, carbociclo y heterociclo está opcionalmente sustituido con hidroxilo, halógeno, amino, nitro, alquilo, acilo, alquilsulfonilo o alcoxi;

R_6 en cada instancia es en forma independiente hidroxilo, halógeno, amino, carbonilo, nitro, ciano, acilo, alquilo, sulfonilo, alquilsulfonilo, alquilsulfinilo, alcoxi, alquilcarbamoilo, alcanolamina, alquilsulfamoilo, alquilsulfonamida, un carbociclo o a heterociclo; donde dicho sustituyente amino, alquilo, carbonilo, acilo, sulfonilo, alquilsulfonilo, alquilsulfinilo, alcoxi, alquilcarbamoilo, alcanoilamina, alquilsulfamoilo, alquilsulfonamida, carbociclo y heterociclo está opcionalmente sustituido con amino, halógeno, hidroxilo, carbonilo, o un carbociclo o heterociclo que está opcionalmente sustituido con hidroxilo, amino, halógeno, haloalquilo, alquilo, alcoxi o acilo;

o es 0-3; y

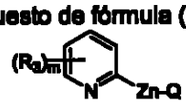
m es 0-3;

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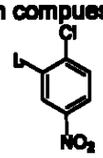
dicho proceso comprende

-hacer reaccionar un compuesto de fórmula (a)



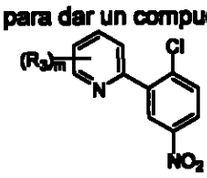
(a)

en donde Q es Cl, Br o I; con un compuesto de fórmula (b)



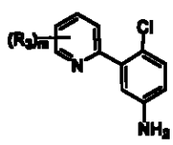
(b)

en donde L es Br, I o OTf; para dar un compuesto de fórmula (c);



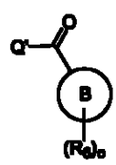
(c)

- reducir dicho compuesto de fórmula (c) para dar un compuesto de fórmula (d)



(d)

- y hacer reaccionar dicho compuesto de fórmula (d) con un compuesto de fórmula (e)



(e)

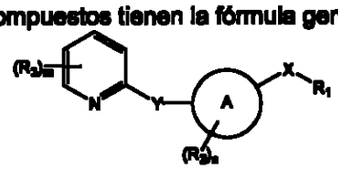
en donde Q' es halógeno, OH, OR donde R es un grupo activador; para dar dicho compuesto de fórmula Ib".

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RESUMEN

La invención provee nuevos inhibidores de señalización Hedgehog que son útiles como agentes terapéuticos para el tratamiento de malignidades donde los compuestos tienen la fórmula general I:



I

en donde A, X, Y R_1, R_2, R_3, R_4, m y n tienen los valores definidos en la memoria descriptiva.

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Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
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(71)Solicitante(s) GENENTECH, INC. y
CURIS INCORPORATION

(72) Inventor(es) JANET GUNZNER, DANIEL SUTHERLIN, MARK STANLEY, LIANG BAO, GEORGETTE CASTANEDO, REBECCA LALONDE, SHUMEI WANG, MARK REYNOLDS, SCOTT SAVAGE, KIMBERLY MALESKY, MICHAEL DINA

(74) Apoderado: DRA. MARGARITA CASTELLANOS A.

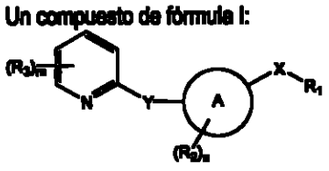
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(54) Título: **INHIBIDORES PIRIDILO DE SEÑALIZACION DE HEDGEHOG**

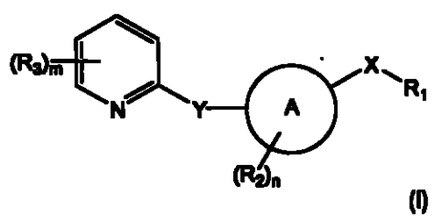
Reivindicación(es):

Un compuesto de fórmula I:



(I)

en donde
A es un carbociclo o heterociclo;
X es alquileno, $NR_4C(O)$, $NR_4C(S)$, $N(C(O)R_1)C(O)$, NR_4SO, NR_4SO_2, $NR_4C(O)NH$, $NR_4C(S)NH$, $C(O)NR_4$, $C(S)NR_4$, NR_4PO o $NR_4PO(OH)$;
Y está ausente, CHR_4, O, S, SO, SO_2 o NR_4;
R_1 se selecciona entre el grupo formado por alquilo, un carbociclo o un heterociclo cada uno de los cuales está opcionalmente sustituido con hidroxilo, halógeno, amino, carboxilo, amidino, guanidino, carbonilo, nitro, ciano, acilo, alquilo, haloalquilo, sulfonilo, sulfinilo, alcoxi, alquiltio, carbamoilo, acilamino, sulfamoilo, sulfonamida, un carbociclo o a heterociclo; donde dicho amino, amidino, alquilo, acilo, sulfonilo, sulfinilo, alcoxi, alquiltio, carbamoilo, acilamino, sulfamoilo, sulfonamida, carbociclo y sustituyente heterociclo se sustituye opcionalmente con, halógeno, haloalquilo, hidroxilo, carboxilo, carbonilo, o un amino, alquilo, alcoxi, acilo, sulfonilo, sulfinilo, fosfinato, carbociclo o heterociclo que está opcionalmente sustituido con hidroxilo, carboxilo, carbonilo, amino, halógeno, haloalquilo, alquilo, alcoxi, alquiltio, sulfonilo, sulfinilo, acilo, un carbociclo o a heterociclo;
R_2 es halógeno, hidroxilo, alquilo, acilo o alcoxi, donde cada alquilo, acilo y alcoxi está opcionalmente sustituido con hidroxilo, halógeno, amino, nitro, alquilo, acilo, alquilsulfonilo o alcoxi;
R_3 es halógeno, hidroxilo, carboxilo, alquilo, acilo, alcoxi, alcoxicarbonilo, carbamoilo, alquilsulfuro, sulfinilo, sulfonilo, un carbociclo o un heterociclo donde cada alquilo, acilo, alcoxi, alcoxicarbonilo, carbamoilo, alquilsulfuro, sulfinilo, sulfonilo, carbociclo y heterociclo está opcionalmente sustituido con hidroxilo, halógeno, amino, nitro, alquilo, acilo, sulfonilo o alcoxi;
R_4 es H o alquilo;
m es 0-3;
n es 0-3;
y sus sales y solvatos.



(I)

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCI

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Bogotá,
2020

Doctor(a)
CASTELLANOS ABONDANO MARGARITA

REFERENCIA	Radicación No.	7 33168
	Solicitud internacional	PCT/US2005/031284
	Fecha inicio fase nacional	02/04/2007
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	5038

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

2. La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 04 MAYO 2007
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