10 - 140789 PCT 1/2

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

PROPIEDAD INDUSTRIAL

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

10-140789

SOLICITUD DE

PATENTE DE INVENCION
PCT ENTRADA EN FASE NACIONAL

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-140789- -00000-0000
Fecha: 2010-11-10 13:53:59 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 535

21. EXPEDIENTE No. _

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

52. CLASIFICACION INTERNACIONAL: **C07D 403/14, C07D 403/06, C07D 213/06**

71. SOLICITANTE: **GENENTECH, INC.**
CURIS, INC.

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

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

22. BOGOTA, D.C., 10 NOV. 2010

11-11-2010

Industria y Comercio
SUPERINTENDENCIA

A

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-140789- -00000-0000

Fecha: 2010-11-10 13:53:59 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 535

PATENTE DE INVENCION [ ] **MODELO DE UTILIDAD** [ ] **Art. 33 Decisión 486/00**

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

Completa [ ] Incompleta [ ]

PATENTE DE INVENCION PCT [X] **MODELO DE UTILIDAD PCT** [ ] **Art. 33 Decisión 486/00 Circular Única**

- [X] Indicación que se solicita una PCT
- [X] Datos de identificación del solicitante o de la persona que presenta la solicitud
- [X] Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- [ ] Dibujos de ser estos pertinentes
- [X] Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa [X] Incompleta [ ]

DISEÑO INDUSTRIAL [ ] **(Art. 119 Decisión 486/00)**

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

Completa [ ] Incompleta [ ]

ESQUEMA DE TRAZADO [ ] **(Art. 92 Decisión 486/00)**

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

Completa [ ] Incompleta [ ]

D000001

Industria y Comercio
SUPERINTENDENCIA

PETITOR

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-140789- -00000-0000
Fecha: 2010-11-10 13:53:59 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 535

cación

FORMULARIO UNICO DE SOLICITUD DE PATENTES
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: **1. GENENTECH, INC.**
2. CURIS INC.
Dirección: **1. 1 DNA Way**
South San Francisco, CA 94080-4990
ESTADOS UNIDOS DE AMERICA
2. 45 Moulton Street
Cambridge, MA 02138
ESTADOS UNIDOS DE AMERICA
Nacionalidad o Domicilio:
1. South San Francisco, CA
ESTADOS UNIDOS DE AMERICA
2. 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**

Nombre: **MARGARITA CASTELLANOS A.**
Dirección: **CALLE 94A No. 7A-09**
Teléfono: **756 0770** Fax: **755 0158**
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)**

VER ANEXO # 1

(5) **PCT (86)**

Solicitud Internacional No. **PCT/US2009/040165** Fecha **10/04/2009**

Publicación Internacional No. **WO 2009/126863 A2** Fecha **15/10/2009**

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

(7) **Clasificación Internacional (51)** **C07D 403/14, C07D 403/06, C07D 213/06**

(8) **Prioridad** SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	11/04/2008	61/044.451

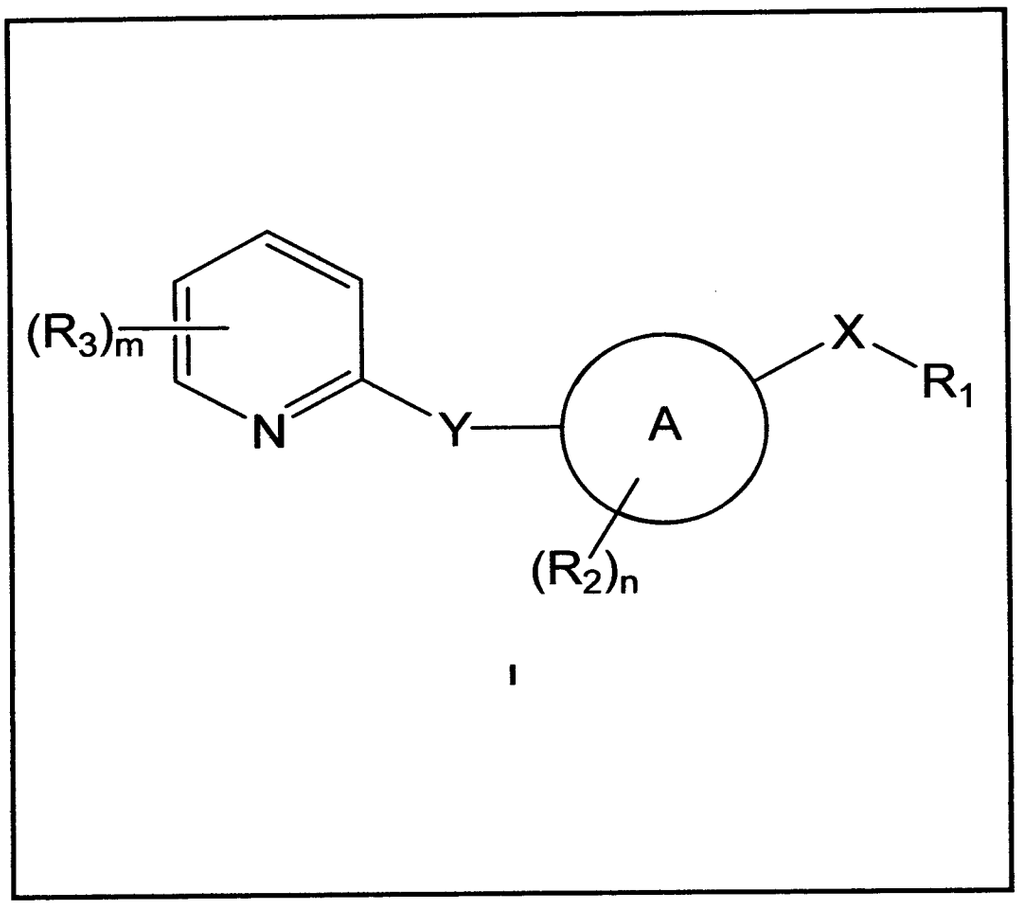
(9) **Comprobante de pago No.** **10-94,704 y 10-** 91523 **Fecha** **Noviembre 8 de 2010**
Noviembre 10 de 2010

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.

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página. - MCA/gcb - P2067

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

ANEXO # 1
INVENTORES

1. **JANET GUNZNER**
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   ESTADOS UNIDOS DE AMERICA

2. **DANIEL P. SUTHERLIN**
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   Burlingame, CA 94010
   ESTADOS UNIDOS DE AMERICA

3. **MARK S. STANLEY**
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   Pacifica, CA 94044
   ESTADOS UNIDOS DE AMERICA

4. **LIANG BAO**
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   Daly City, CA 94015
   ESTADOS UNIDOS DE AMERICA

5. **GEORGETTE CASTANEDO**
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   Redwood City, CA 94061
   ESTADOS UNIDOS DE AMERICA

6. **REBECCA L. LALONDE**
   1907 Center Street, Apt. # 12
   Berkeley, CA 94704
   ESTADOS UNIDOS DE AMERICA

7. **SHUMEI WANG**
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   Foster City, CA 94404
   ESTADOS UNIDOS DE AMERICA

8. **MARK E. REYNOLDS**
   175 Linda Vista
   Milbrae, CA 94030
   ESTADOS UNIDOS DE AMERICA

9. **SCOTT J. SAVAGE**
   3901 Lick Mill Boulevard, # 454
   Santa Clara, CA 95054
   ESTADOS UNIDOS DE AMERICA

10. **KIMBERLY MALESKY**
360 Green Street, Apt. 7
San Francisco, CA 94133
ESTADOS UNIDOS DE AMERICA

11. **MICHAEL S. DINA**
1003 San Antonio Circle, # 205
Daly City, CA 94014
ESTADOS UNIDOS DE AMERICA

000005

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 asuntos 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 OF 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, recordation of assignments, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rigths; b) For de obtention 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 us or against us; and that in all the above matters they may substitute this Power of Attorney, compromise, desist, cancel, receive, renounce actions, 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)

Esta copia coincide con el original que tuvo a la vista
Bogotá, D.C.
04 NOV 2010
JUANITA LALINDE GAITAN
NOTARIA CUARENTA Y UNO (41) C

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

000006

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
~~s~~toy
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 origen.

*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 ~~Mr~~ 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 ~~xx~~ 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, D.C.
04 NOV 2010
JUANITA LALINDE GARCIA
NOTARIA CUARENTA Y UNO (E.N.C.)

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

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04 NOV 2010
JUANITA LALINDE GARCIA
NOTARIA CUARENTA Y UNO (41)

000003

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:*

Dicho copia coincide con el que tuvo a la vista
Bogotá, D.C.
04 NOV 2003
JUANITA LALIN
SANTA CLARA COUNTY

10. *Signature*

Kevin Shelley
KEVIN SHELLEY
Secretary of State

BY

NP-24 A (REV. 1-03)

----------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

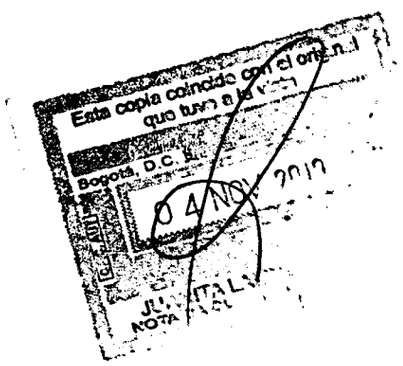
(Sello): TERI RENSHAW

Comisión No. 1272761

Notario Público – California

Condado de San Mateo

Mi comisión vence Agosto 3, 2004



DORA DUQUE DE BERNAL
TRADUCTORA E INTERPRETE OFICIAL
RES. 02755/68 Y 01144/97 - MINJUSTICIA
REP. DE COLOMBIA

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

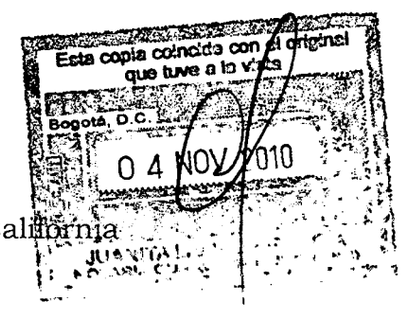
(Convención de La Haya del 5 de Octubre 1961)

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

DORA DUQUE DE BERNAL
TRADUCTORA E INTERPRETE OFICIAL
RES. 02755/93 - 01[illegible]/97 - MINJUSTICIA

9. Sello: (sello)

10. Firma

(fdo) Kevin Shelley

KEVIN SHELLEY

Secretario de Estado

Por (fdo) ilegible

ES TRADUCCION FIEL Y COMPLETA, A LA CUAL ME REMITO,

Bogotá, Septiembre 16, 2003.

DORA DUQUE DE BERNAL
TRADUCTORA E INTERPRETE OFICIAL
RES. 02755/03 Y 01144/97 - MINJUSTICIA
REP. DE COLOMBIA

Esta copia coincide con el original que tuve a la vista
Bogotá, D.C.
04 NOV 2010
JUANITA LALINDE GARCIA
NOTARIA CUARENTA Y UNO (E.D.)

COLOMBIA

PODER

El (los)

CURIS, INC.

Domiciliados en 45 Moulton Street, Cambridge, MA 02138, ESTADOS UNIDOS DE AMERICA

Nombran por el presente a **XIMENA CASTELLANOS A. y/o MARGARITA CASTELLANOS A.** abogadas con oficinas en la Calle 94 A No. 7 A-09, Bogotá-Colombia 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 fabrica, 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 mencionados sustituir éste mandato, transigir, desistir, recibir, cancelar, renunciar, aceptar notificaciones y nombrar apoderados judiciales y extrajudiciales.

Finalmente, este poder ratifica la validez de todos los actos y solicitudes que, a nombre de la poderdante hubieren realizado los apoderados en relación con las facultades anteriormente enumeradas, antes de la suscripción del presente poder

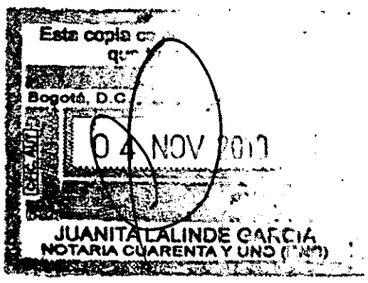
Dado y firmado hoy 26 DE Junio de 2007

en Cambridge, Massachusetts, ESTADOS UNIDOS DE AMERICA

por CURTIS, INC.
Mark Noel - Vice-Presidente

(El notario debe suscribir el documento en la pagina siguiente)

(Se requiere legalización consular o mediante apostilla)



POWER OF ATTORNEY

I (we) the undersigned

CURIS, INC.

Of
45 Moulton Street
Cambridge, MA 02138
United States of America

hereby grant(s) Power of Attorney to **XIMENA CASTELLANOS A. and /or MARGARITA CASTELLANOS** a. attorneys residing at Calle 94 A No. 7 A-09, Bogotá-Colombia, 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) Obtainment of patents, models and designs, registration of trademarks, service, collective and defensive marks, and of designations of origin; the deposit of trade names and ensigns; its renewal, extension, recordal of assignments, change of name or domicile, voluntary cancellation, and the registration of licenses of use of the above rights;
b) For the obtainment 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 rights; actions and suits instituted by us or against us;

In all the above matters they may substitute this power of attorney, compromise, desist, cancel, receive, renounce, accept notifications and appoint attorneys in fact, in or out of court.

Finally, this power of attorney ratifies the validity of all acts and applications made by the representatives in the name of the signatory of this power of attorney, with regard to the faculties above given, before the execution of the present power of attorney.

Given and signed this 26 day of June , 2007

in Cambridge, Massachusetts USA

by

Mark Noel
Vice President, Curis Inc.

Date: June 26 2007

(Notary shall execute on the next page)

(Consular legalization or apostille is required)

CERTIFICADO NOTARIAL (Sociedad)

Hoy 26de Junio del año 2007
compareció (eron) personalmente
MARK NOEL

a quienes conozco como la(s) personas que firma(n) en representación de la Sociedad (Compañía) denominada

CURIS, INC.
Certifico :

a) Que CURIS, INC.

es una sociedad/Compañía legalmente constituida y existente de acuerdo con las leyes de Delaware

b) Que el domicilio de dicha Sociedad/Compañía es
45 Moulton Street, Cambridge, MA 02138
ESTADOS UNIDOS DE AMERICA

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. MARK NOEL
esta autorizado para otorgar el presente poder. Lo anterior esta probado por medio de los siguientes documentos, que certifico he visto*

Acta de la Junta Directiva de CURIS, INC., de Junio 12 de 2002

(Ciudad) Boston

(Estado) Massachusetts

Hoy 26del Junio de 2007

(Notario Público)

*Los documentos debe identificarse con fecha y origen.

Esta copia coincide con el que tuvo a la vista
Bogotá, D.C.
04 NOV 2013
JUANITA LALINDE GARZÓN
NOTARIA CUARENTA Y UNO (E)

NOTARIAL CERTIFICATION (Corporation)

On this 26th day of June of 2007
personally appeared
MARK NOEL

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

CURIS, INC.

I certify:

a) that **CURIS, INC.**

is a corporation (Company legally constituted and in existence in accordance with the laws of Delaware

b) That the domicile of said Corporation/Company is

45 Moulton Street
Cambridge, MA 02138
United States of America

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 Mr. MARK NOEL
(is)(are) authorized to grant the present Power of Attorney. The aforementioned was duly proven through the following documents and I duly certify having seen them*:

June 12, 2002 Minutes of the CURIS, INC. Board of Directors Meeting

(City) Boston

(State) Massachusetts

this 26th day of June of the year 2007

MAURA C. KELLEHER
Notary Public
Commonwealth of Massachusetts
My Commission Expires
May 27, 2012

MARK NOEL personally appeared before me, and proved his/her identification through satisfactory evidence, which were his Massachusetts drivers license to be the person whose name is signed on the preceding or attached document in my presence on this 26 day of June, 2007.

Maura C. Kelleher
Notary Public
Commonwealth of Massachusetts
My Commission Expires May 27, 2012

(Notary Public)

*Documents must be identified with date and origin

* June 26, 2007 Columbian Power of Attorney document

The Commonwealth of Massachusetts

William Francis Galvin
Secretary of the Commonwealth

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. *Country:* United States of America

This public document

2. *has been signed by:* Maura C. Kelleher
3. *acting in the capacity of:* Notary Public
4. *bears the seal/stamp of:* the State of Massachusetts

whose commission expires on: May 25, 2012

Certified

5. *at:* Boston, Massachusetts
6. *the:* 4 September, 2007
7. *by:* the Secretary of the Commonwealth
8. *No.:* 1253561
9. *Seal/stamp:* *Great Seal of the Commonwealth*

10. *Signature:*

William Francis Galvin
Secretary of the Commonwealth

prepared by DGittens

Esta copia coincide
que reposa en
Bogotá, D.C.
04 NOV
JUANITA LA
NOTARIA CUA

----------TRADUCCION OFICIAL No. 07-1001----------

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.----------

(Anexo a un poder otorgado por Curis, Inc.)

Junio 12, 2002 Acta de CURIS, INC. Reunión de Junta Directiva

Boston, Massachussets

Hybui 26, año de 2007

MAURA C. KELLEHER

Notario Público – Estado de Massachussets

Mi comisión vence en Mayo 25, 2012

MARK NOEL compareció personalmente ante mí y probó su identificación a través de evidencia satisfactoria, esto es con su licencia de Massachussets, que es la persona cuyo nombre está firmado en el documento precedente o adjunto en mi presencia, hoy dia 26 de Junio de 2007.

Maura C. Kelleher Estado de Massachussets

Notario Pùblico – Mi comisiòn vence Mayo 27, 2012

(Notario Público)

- Los documento deben ser identificados con fecha y origen

Junio 26, 2007 – Poder para Colombia

APOSTILLA

(Convención de La Haya del 5 de octubre de 1961)

Esta copia coincide con el que tuvo a la vista
Bogotá, D.C.
04 NOV 2012
JUANITA LALINDE
NOTARIA CUARENTA

DORA DUQUE DE BERNAL
TRADUCTORA E INTERPRETE OFICIAL
RES. 02755/68 Y 01144/97 - MINJUSTICIA
REP. DE COLOMBIA

1. País: Estados Unidos de América

Este documento público

2. ha sido firmado por Maura C. Kelleher

3. actuando en su carácter de Notario Público

4. lleva el sello del Estado de Massachusetts

Cuya comisión vence en Mayo 25, 2012

Certificado

5. En Boston, Massachuesetts

6. el día 4 de Septiembre de 2007

7. por el Secretario del Estado

8 No. 1253561

Gran sello del Estado

9. Sello

10. Firma:

(fdo) illegible

William Francis Galvin

Secretario del Estado

(Sello en oblea dorada fijando Cintas)

ES TRADUCCION FIEL Y COMPLETA, a la cual me remito,

Bogotá, D. C., Octubre 4, 2007.

DORA DUQUE DE BERNAL
TRADUCTORA E INTERPRETE OFICIAL
RES. 02755/68 Y 01144/97 - MINJUSTICIA
REP. DE COLOMBIA

2

Esta copia coincide con el original que tuvo a la vista
Bogotá, D.C.
04 NOV 2010
JUANITA LALINDE C.
NOTARIA CUARENTA Y UNO

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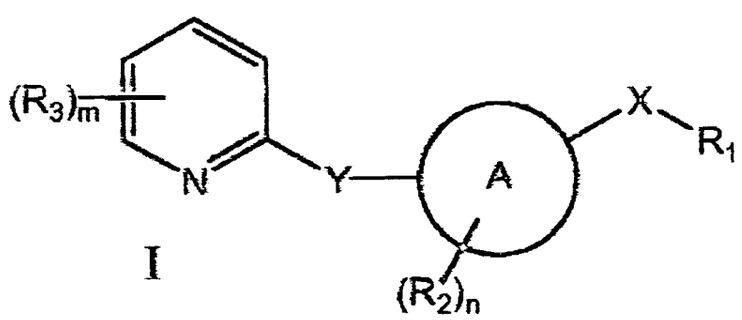
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(54) Title: PYRIDYL INHIBITORS OF HEDGEHOG SIGNALLING



I

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

WO 2009/126863 A2

PYRIDYL INHIBITORS OF HEDGEHOG SIGNALLING

PRIORITY CLAIM

This application claims priority to provisional United States application 61/044451 filed on 11 April 2008.

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.

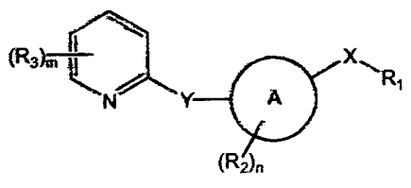
The signaling cascade initiated by Smo results in activation of Gli transcription factors that translocate into the nucleus where they control transcription of target genes. Gli has been shown to influence transcription of Hh pathway inhibitors such as Ptc and Hip1 in a negative feedback loop indicating 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 heterocyclcaminocarbonyl (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.

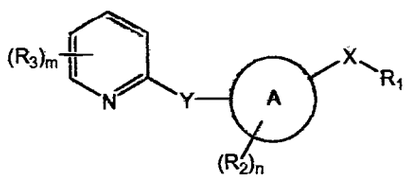
"Sulfonamide" means $-NR-SO_2-R$ wherein each R is independently H, alkyl, carbocycle, heterocycle, carbocycloalkyl or heterocycloalkyl), a carbocycle or a heterocycle. Particular sulfonamide groups are alkylsulfonamide (e.g. $-NH-SO_2-alkyl$), for example methylsulfonamide;

arylsulfonamdie (i.e. –NH-SO_2-aryl) for example phenylsulfonamide; aralkylsulfonamide, for example benzylsulfonamide.

"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.

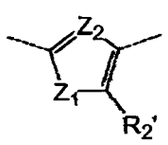
The present invention provides novel compounds having the general formula I:



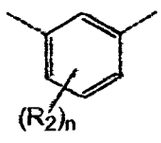
I

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

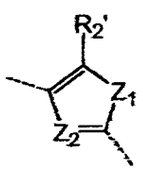
A is a carbocycle or heterocycle ring substituted with 0 to 3 (e.g. n is 0-3) R_2 groups selected from the group consisting of halogen, hydroxyl, alkyl, acyl or alkoxy each optionally substituted with hydroxyl, halogen, amino, nitro, alkyl, acyl, alkylsulfonyl or alkoxy;. In a particular embodiment, 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:



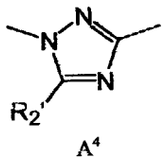
A1



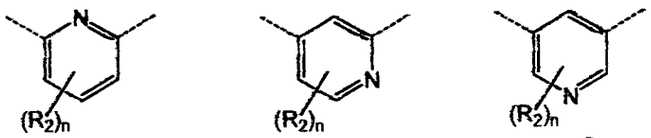
A2



A3



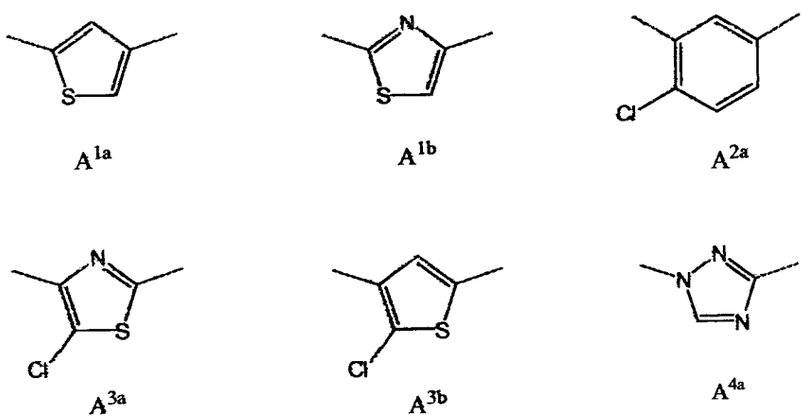
A4



A^5 A^6 A^7

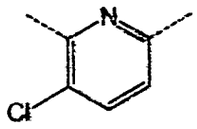
wherein Z_1 is O, S or NR_5 wherein R_5 is H or alkyl; Z_2 is CH, $CR_{2'}$ or N; R_2 is halogen, hydroxyl, alkyl, acyl or alkoxy each optionally substituted with hydroxyl, halogen, amino, nitro, alkyl, acyl, alkylsulfonyl or alkoxy; $R_{2'}$ is H, halogen, hydroxyl, alkyl, acyl or alkoxy each optionally 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},:

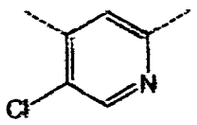


A^{1a} A^{1b} A^{2a}

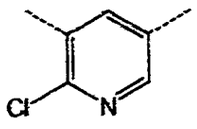
A^{3a} A^{3b} A^{4a}



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}.

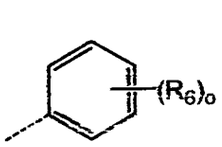
X is alkylene, $NR_4C(O)$, $NR_4C(S)$, $N(C(O)R_1)C(O)$, NR_4SO, NR_4SO_2, $NR_4C(O)NH$, $NR_4C(S)NH$, $C(O)NR_4$, $C(S)NR_4$, NR_4PO or $NR_4PO(OH)$ wherein R_4 is H or alkyl. In a particular embodiment X is $NR_4C(O)$ which forms an amide linkage between ring A and R_1. In another embodiment, X is $N_4C(S)$, 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.

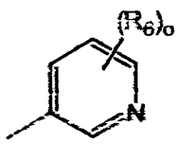
R_1 is selected from the group consisting of alkyl, a carbocycle or a heterocycle each of which is optionally substituted with hydroxyl, halogen, amino, carboxyl, amidino, guanidino, carbonyl (i.e. =O), nitro, cyano, acyl, alkyl, haloalkyl, sulfonyl, sulfinyl, alkoxy, alkylthio, carbamoyl, acylamino, 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 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.

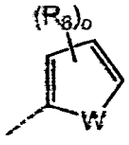
In a particular embodiment R_1 is an optionally substituted aryl or heteroaryl. In a particular embodiment R_1 is an optionally substituted phenyl group. In another particular embodiment R_1 is an optionally substituted pyridine group. In a particular embodiment R_1 is of formula IIa, IIb, IIc, IId,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



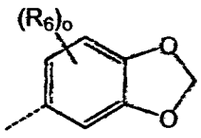
IIa



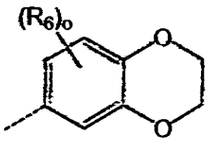
IIb



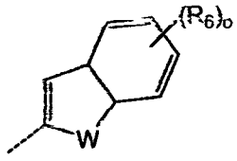
IIc



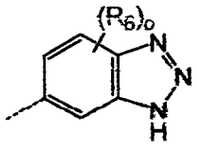
IId



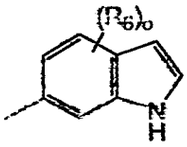
IIe



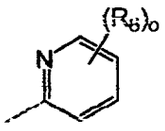
IIf



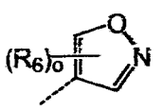
IIg



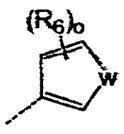
IIh



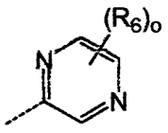
IIi



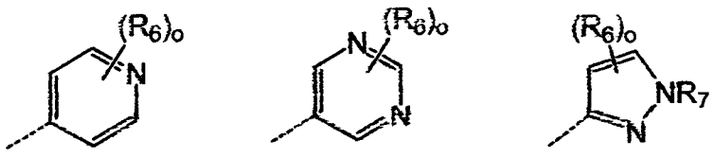
IIj



IIk



III



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, 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.

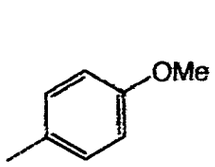
In a particular embodiment R_6 in each instance is independently hydroxyl, halogen, amino, carbonyl, nitro, cyano, acyl, alkyl, sulfonyl, alkylsulfonyl, alkylsulfinyl, alkoxy, alkylcarbamoyl, alkanoylamine, alkylsulfamoyl, alkylsulfonamide, a carbocycle or a heterocycle; wherein said amino, alkyl, carbonyl,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

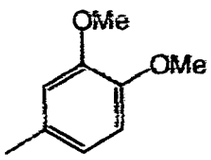
i-butylaminocarbonyl); alkylsulfamoyl (e.g. propylaminosulfonyl, i-butylaminosulfonyl, dimethylaminosulfonyl, dimethylaminoethyl hydroxyethylaminosulfonyl, methoxyethylaminosulfonyl, methoxypropylaminosulfonyl, methylsulfonylethylaminosulfonyl, imidazole substituted propylaminosulfonyl, hydroxypropylaminosulfonyl, 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).

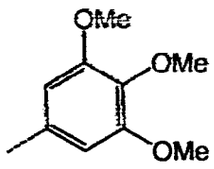
In a particular embodiment R_1 is the group of formula IIa. In such embodiment R_6 may be alkoxy and o is 1, 2 or 3. Particular IIa groups are IIa^1 - IIa^{28}:



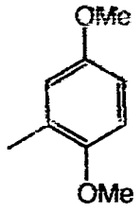
IIa^1



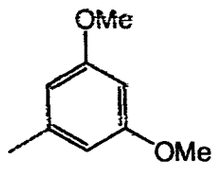
IIa^2



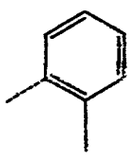
IIa^3



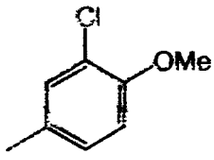
IIa^4



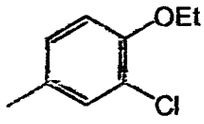
IIa^5



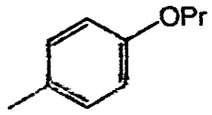
IIa^6



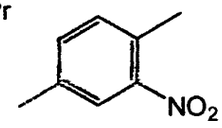
IIa^7



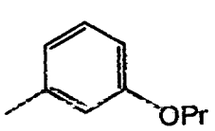
IIa^8



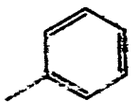
IIa^9



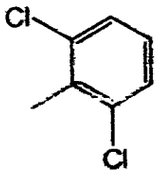
IIa^{10}



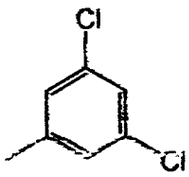
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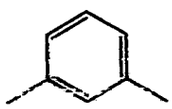
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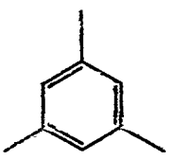
IIa[13]



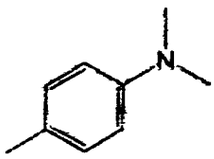
IIa[14]



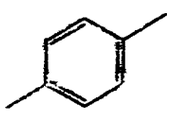
IIa[15]



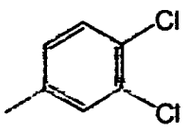
IIa[16]



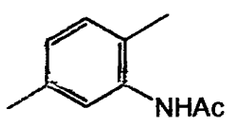
IIa[17]



IIa[18]

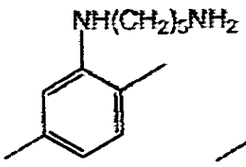


IIa[19]

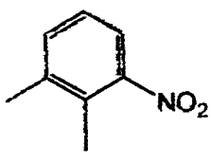


IIa[20]

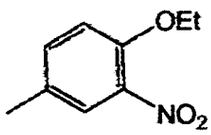
5



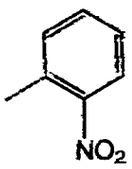
IIa[21]



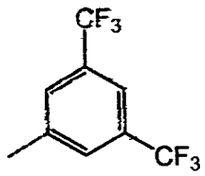
IIa[22]



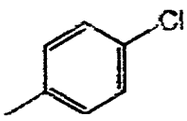
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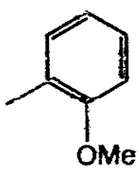
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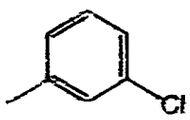
IIa[25]



IIa[26]



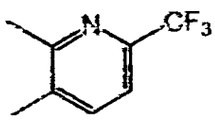
IIa[27]



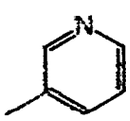
IIa[28]

10

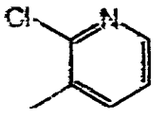
In another particular embodiment R_1 is the group of formula IIb. In such embodiment R_6 may be alkyl or haloalkyl (e.g. CF_3). Particular IIb groups are IIb[1] - IIb[3]:



IIb[1]



IIb[2]

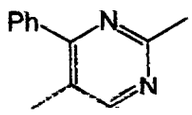


IIb[3]

15

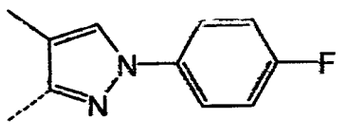
In a particular embodiment R_1 is the group of formula IIc. In such embodiment W may be S and o is 0. In another particular embodiment R_1 is the group of formula IId. In such embodiment o may be 0. In another particular embodiment R_1 is the group of formula IIe. In such embodiment o may be 0. In another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



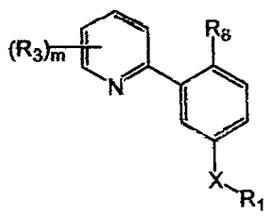
IIo^1

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.

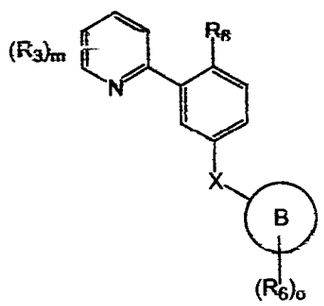
In a particular embodiment, compounds of the invention are represented by the general formula Ib:



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.

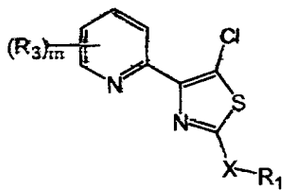
In another particular embodiment, compounds of the invention are represented by the general formula Ib':



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.

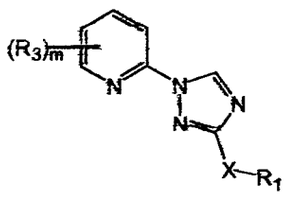
In another particular embodiment, compounds of the invention have the general formula Ic:



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:

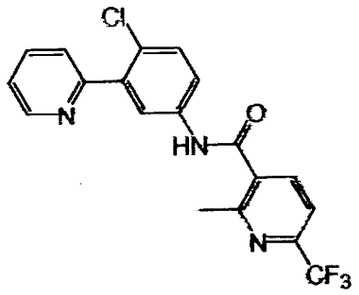


Id

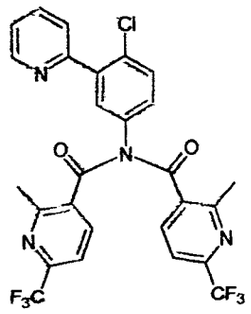
wherein X, R_1, R_3 and m are as defined herein. In an embodiment, compounds of the invention have the general formula Ib and X is NR_4CO. In a further embodiment, compounds are of formula Id and R_3 is H, Cl or trifluoromethyl and m is 0 or 1.

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

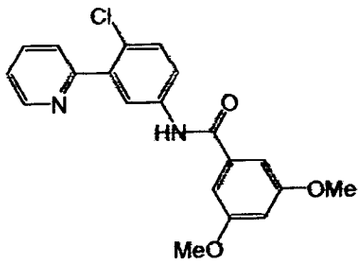
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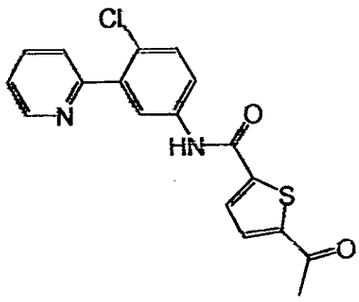
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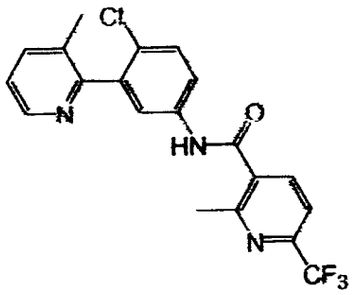
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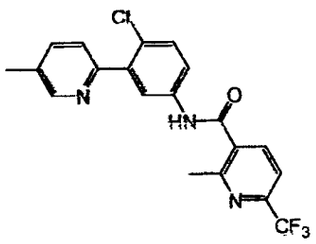
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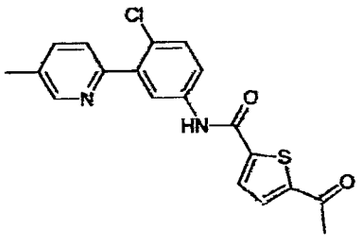
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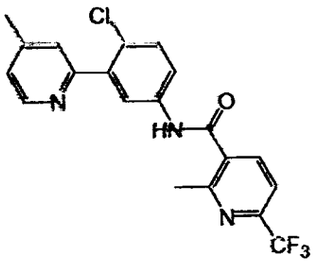
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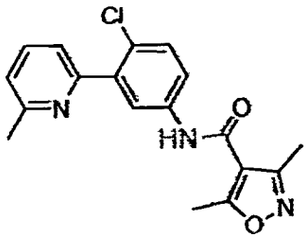
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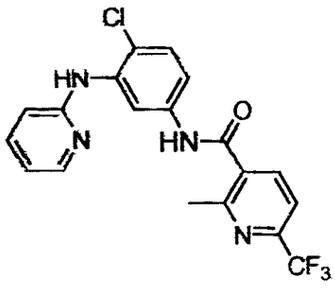
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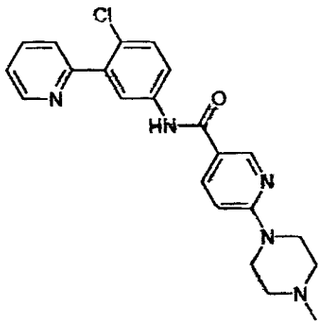
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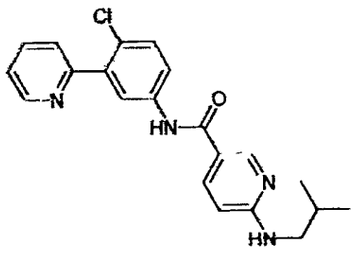
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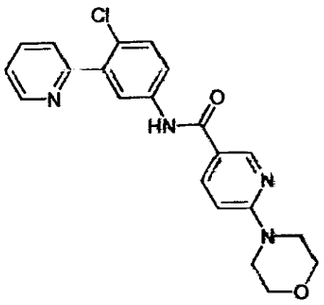
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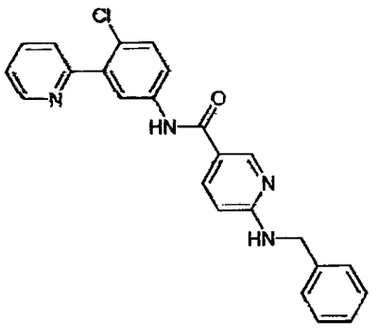
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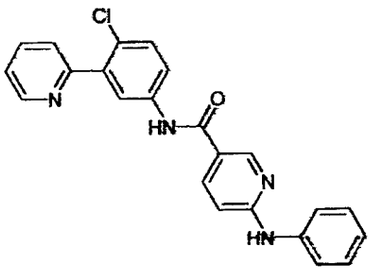
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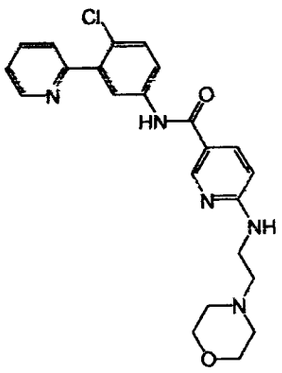
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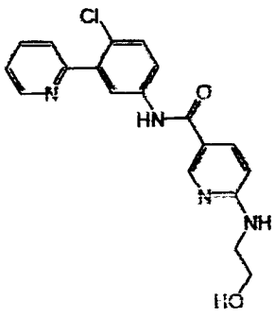
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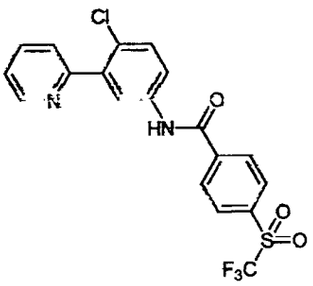
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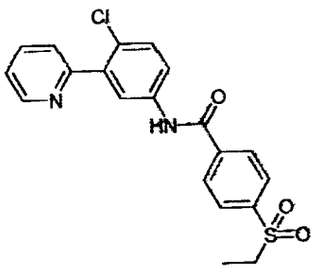
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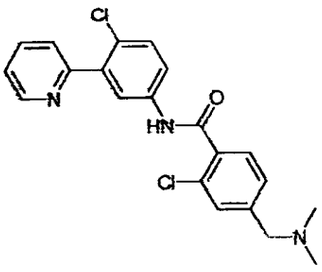
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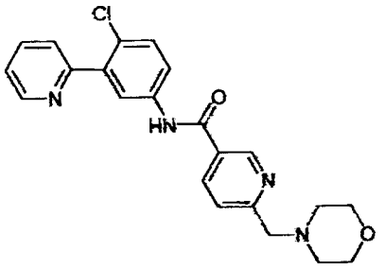
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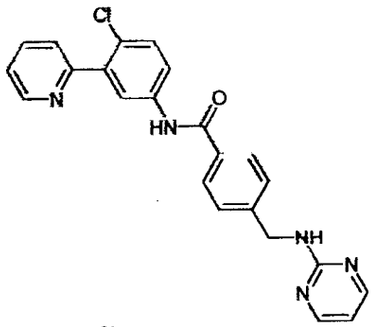
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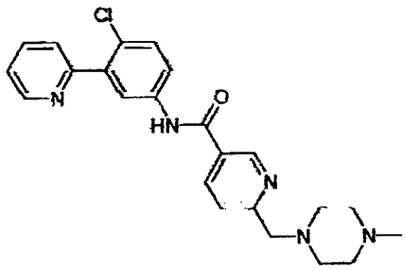
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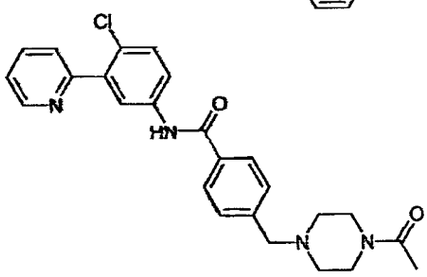
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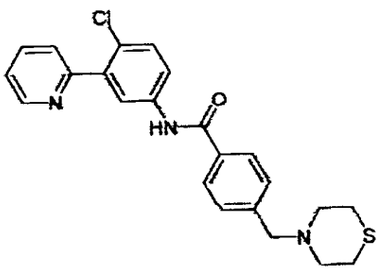
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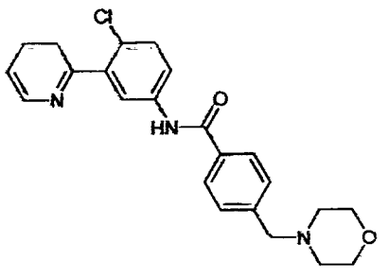
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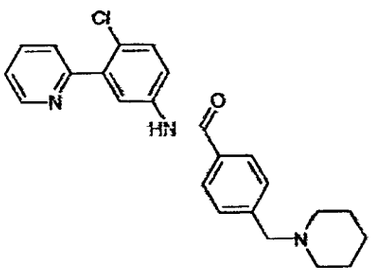
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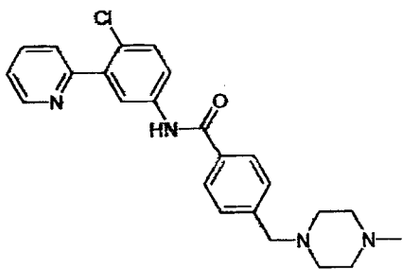
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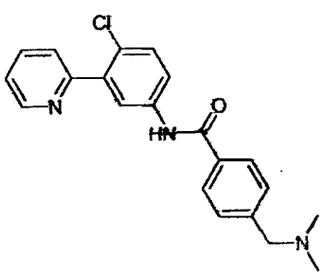
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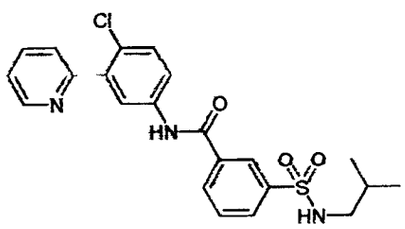
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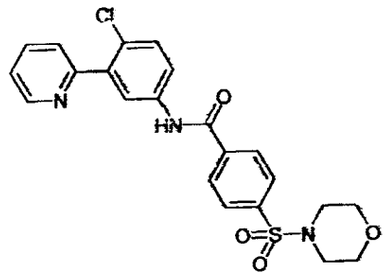
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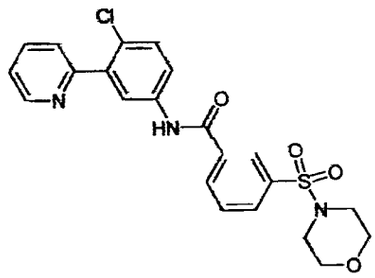
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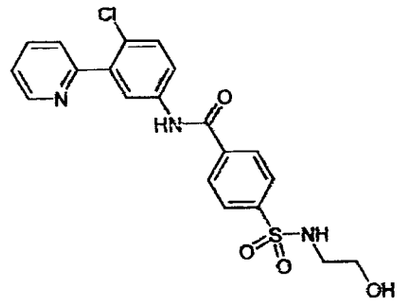
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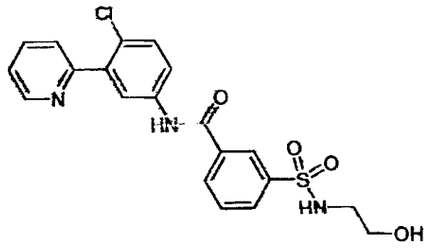
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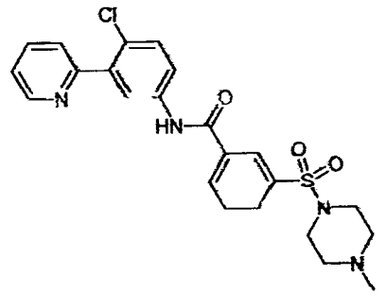
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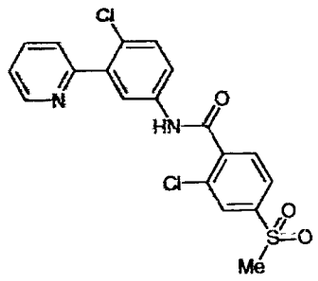
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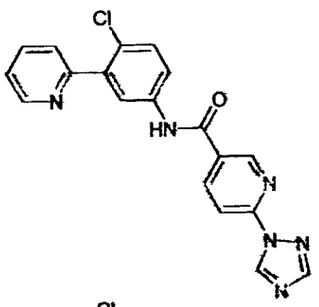
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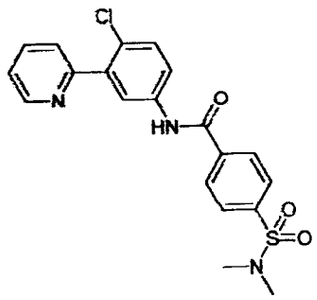
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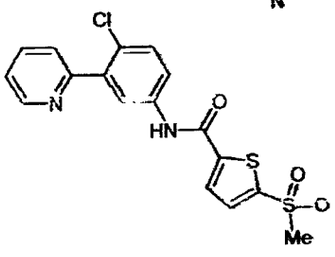
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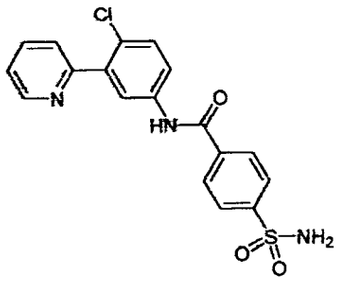
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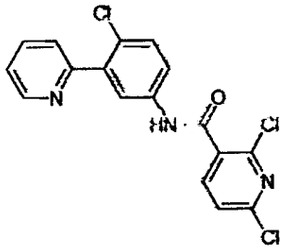
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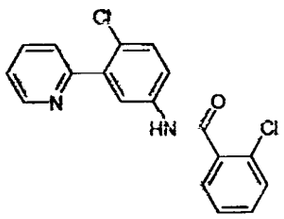
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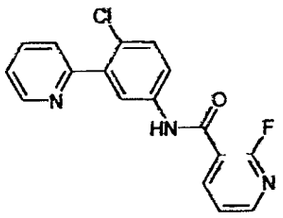
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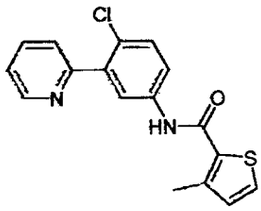
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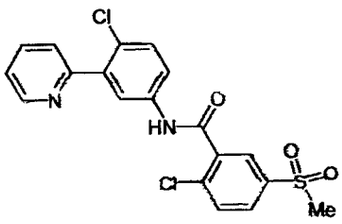
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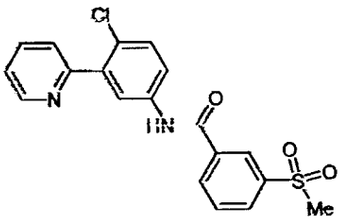
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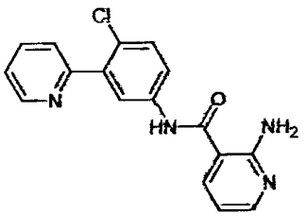
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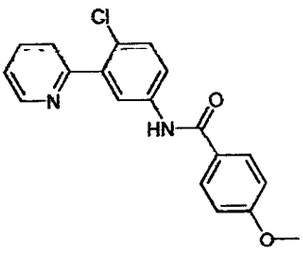
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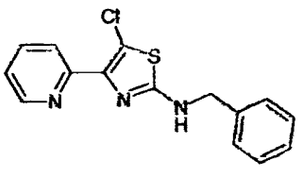
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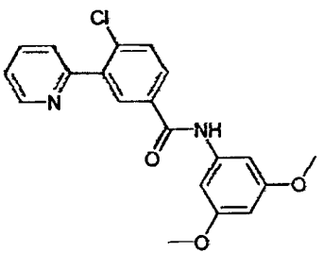
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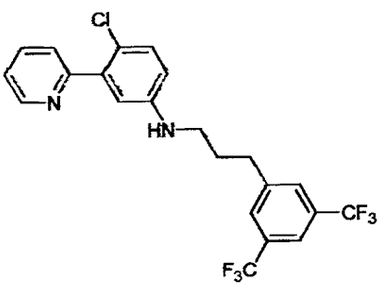
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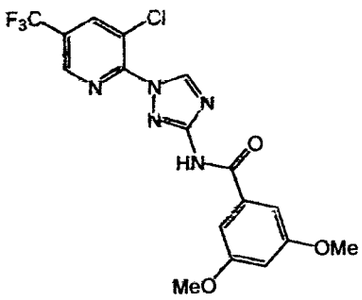
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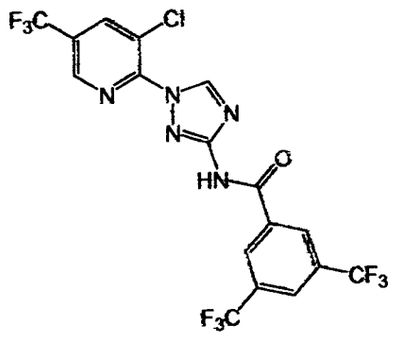


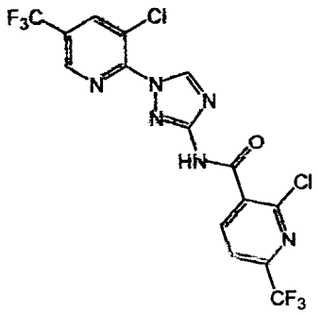
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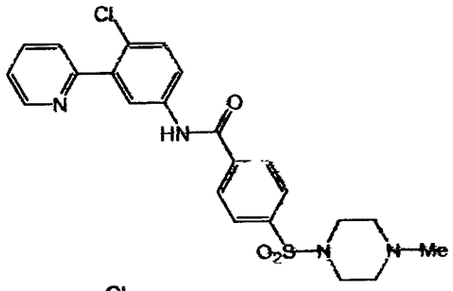


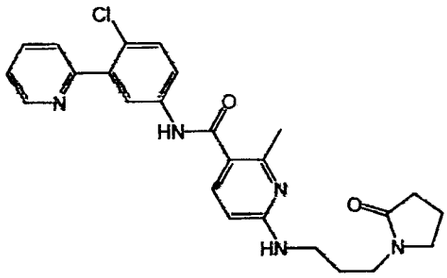
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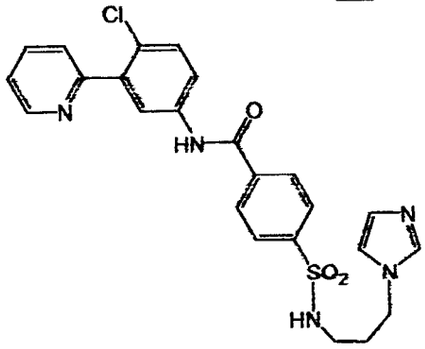


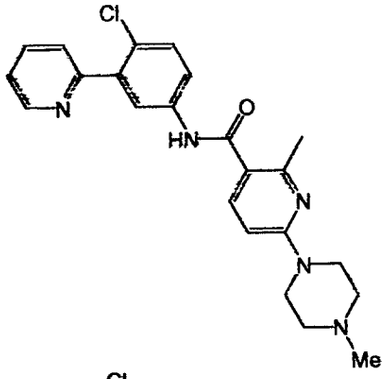
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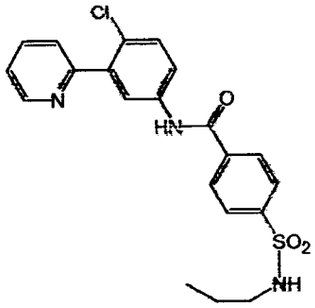
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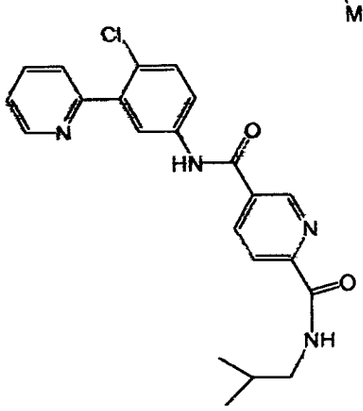
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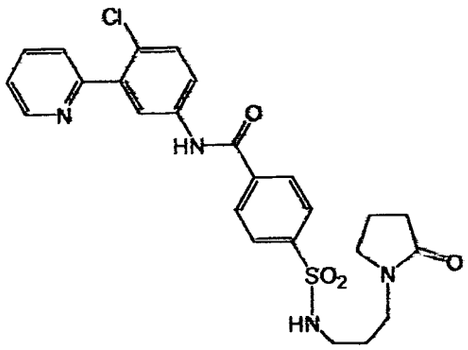
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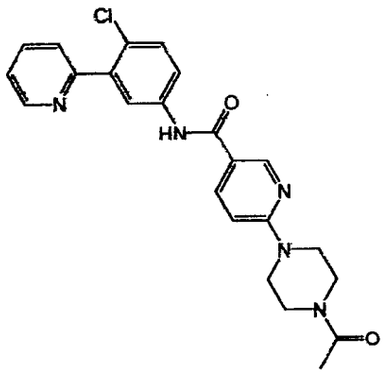
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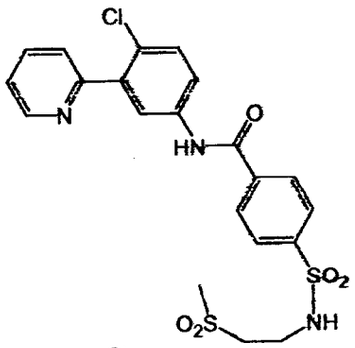
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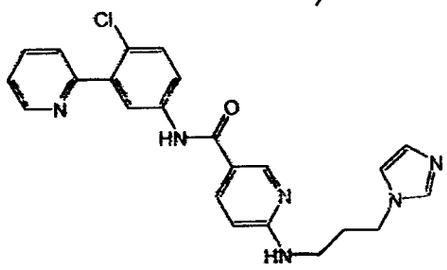
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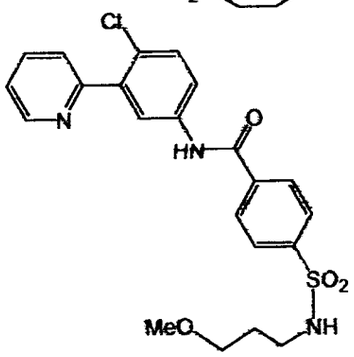
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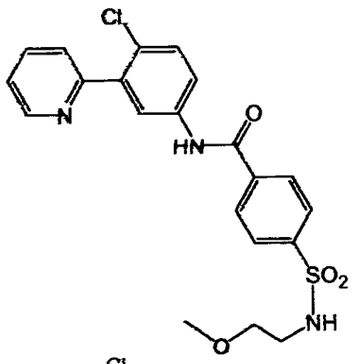
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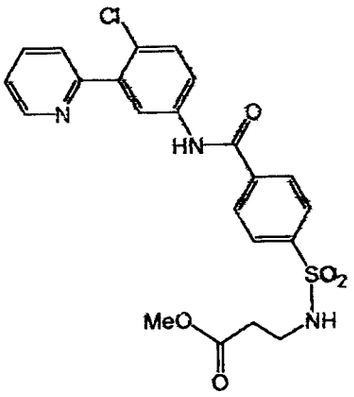
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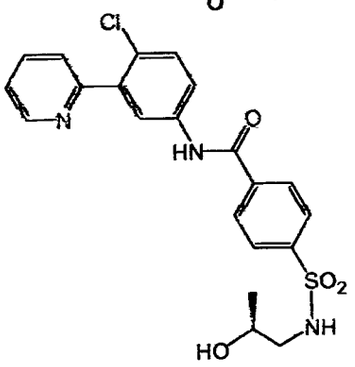
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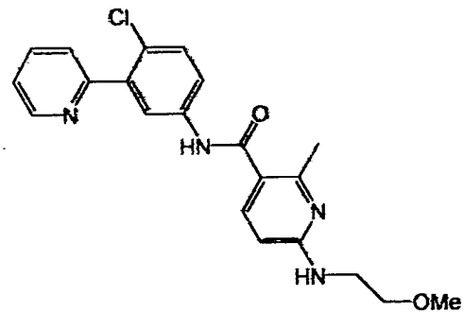
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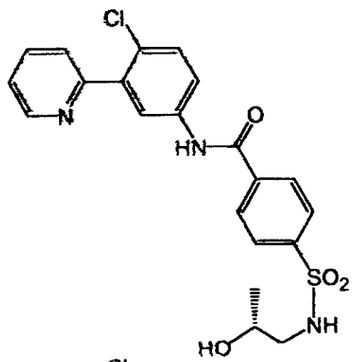
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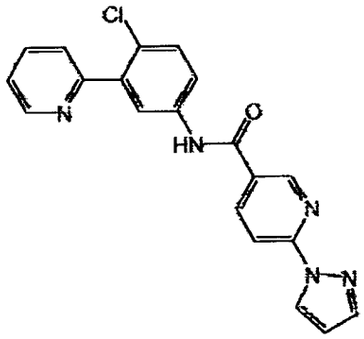
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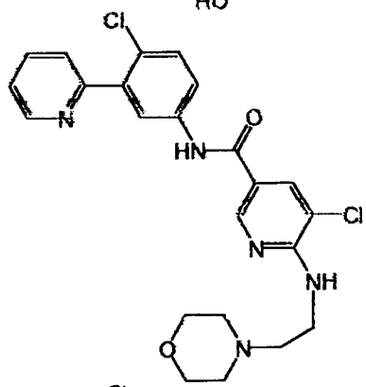
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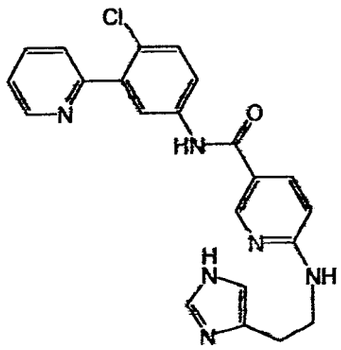
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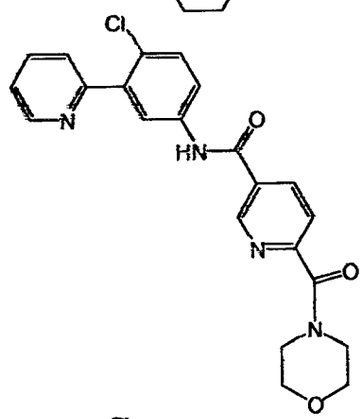
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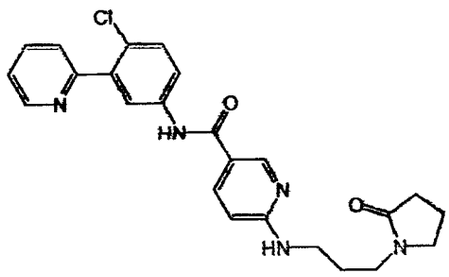
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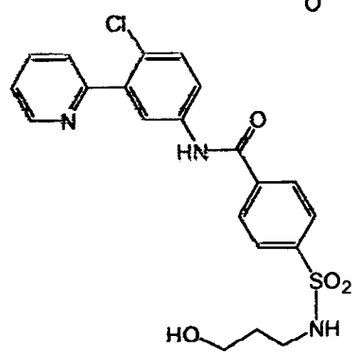
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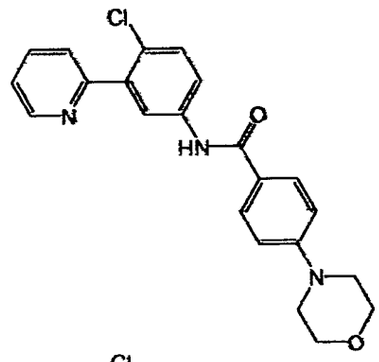
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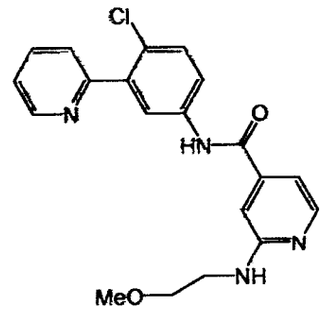
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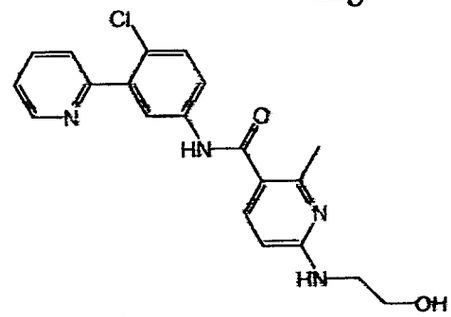
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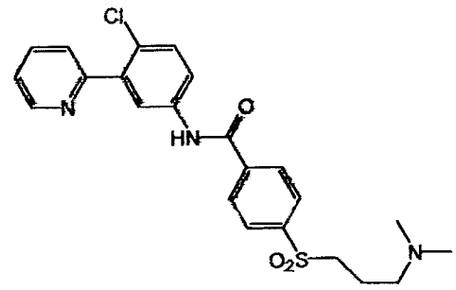
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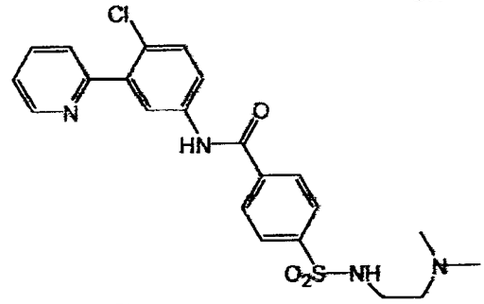
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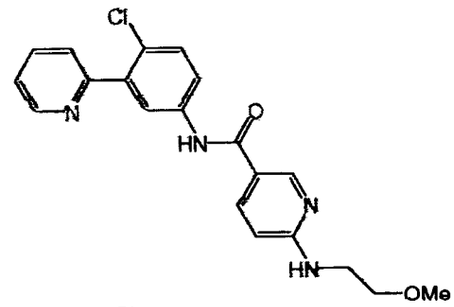
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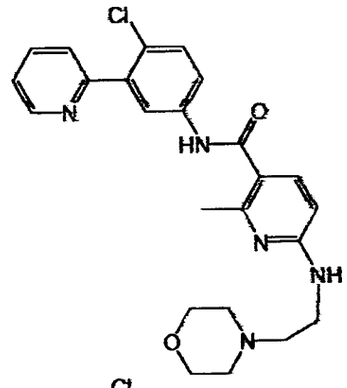
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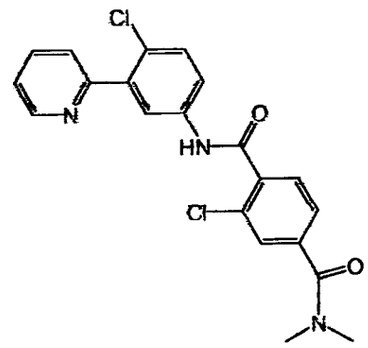
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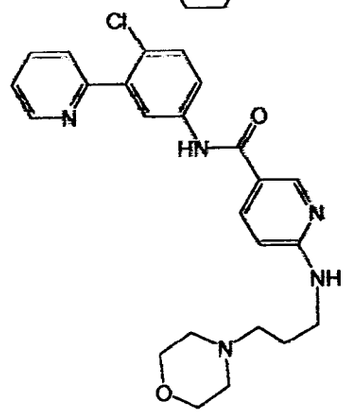
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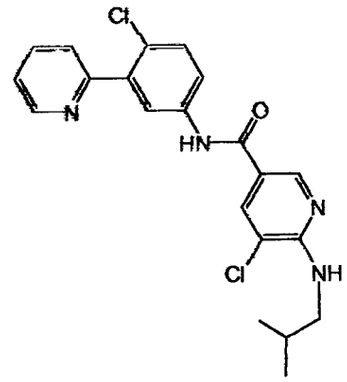
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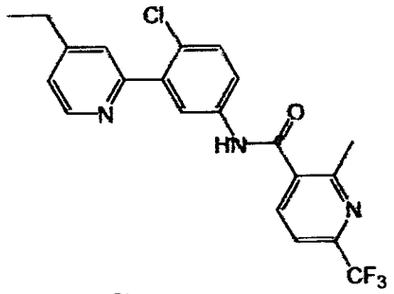


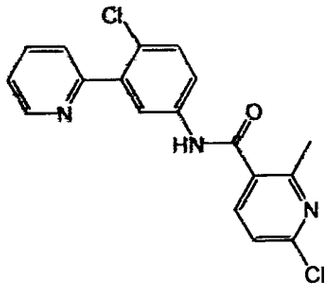
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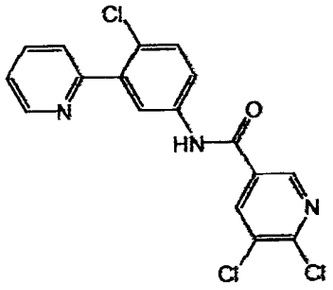


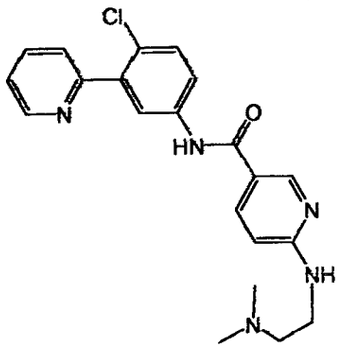
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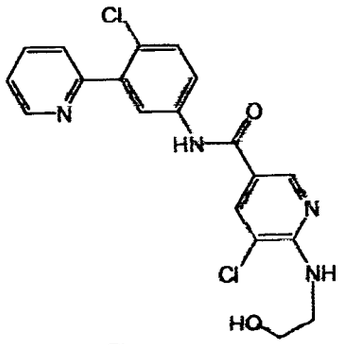


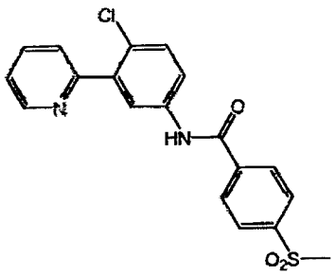
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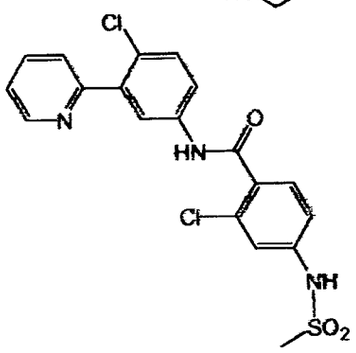
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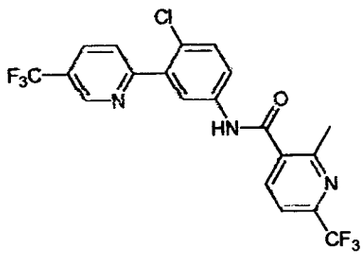
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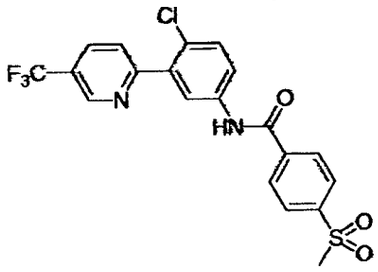
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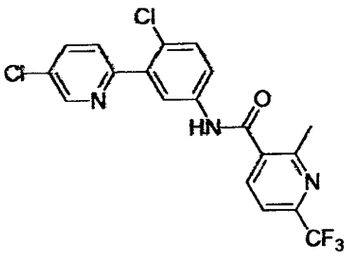
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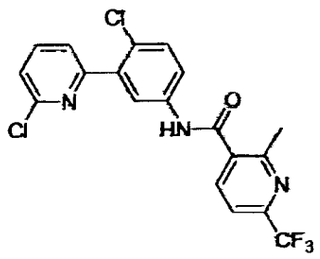
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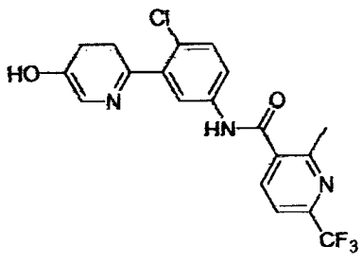
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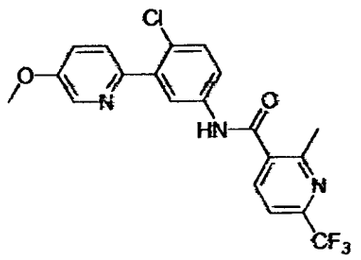
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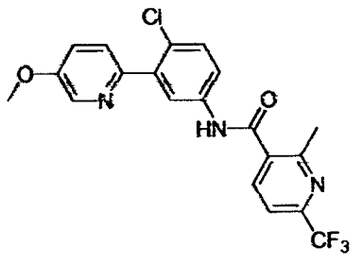
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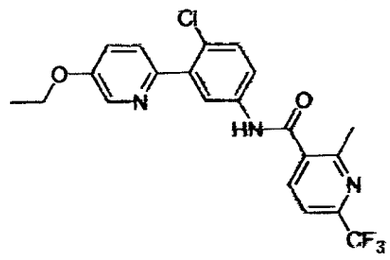
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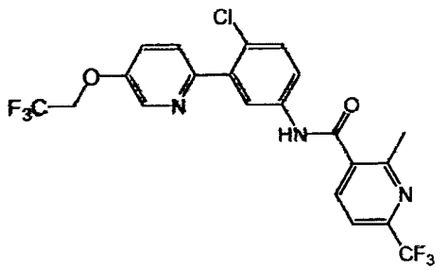
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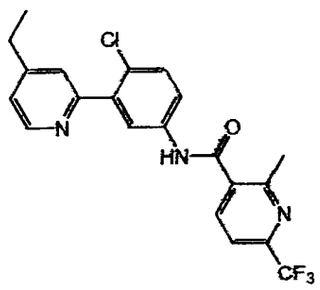
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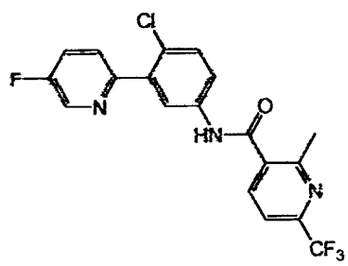
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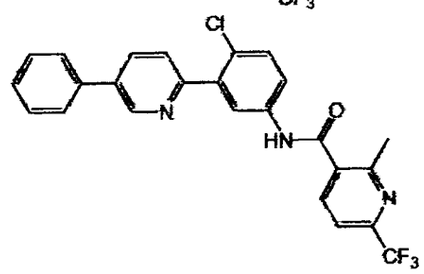
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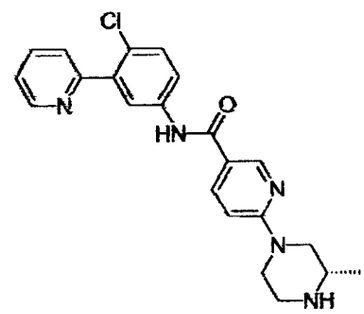
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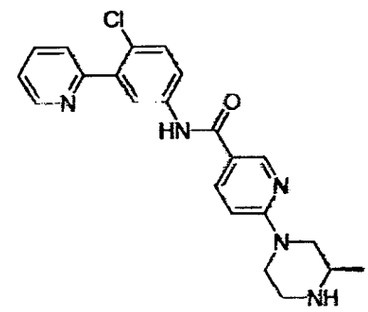
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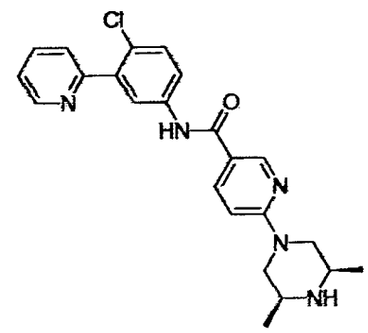
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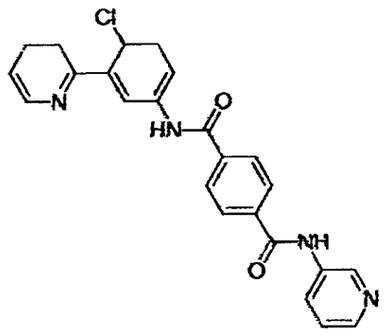
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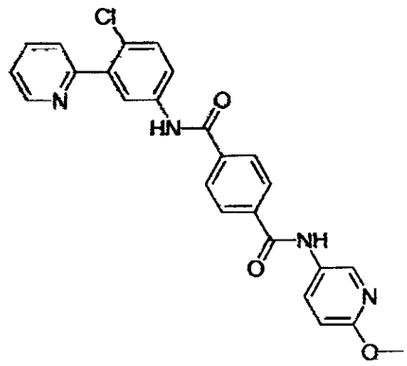
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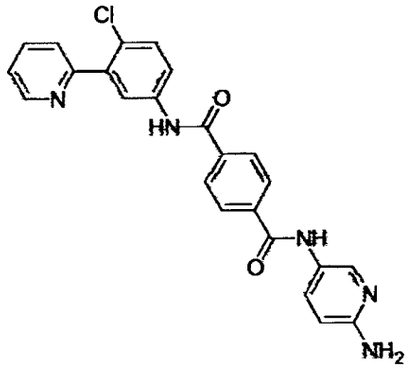
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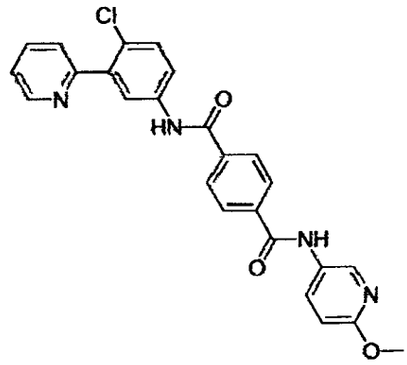
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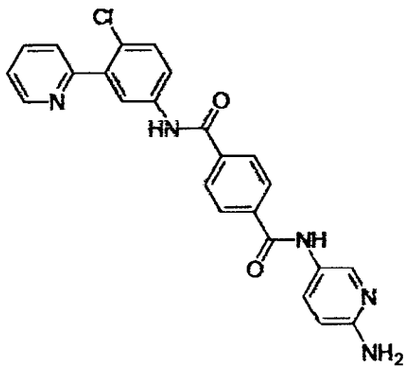
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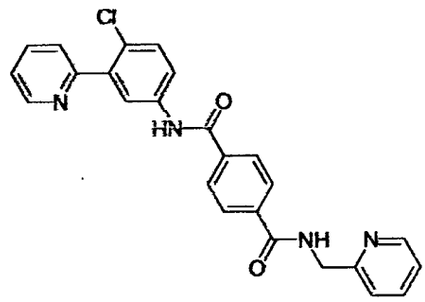
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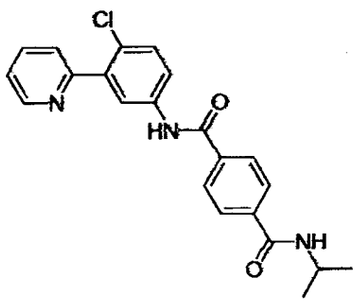
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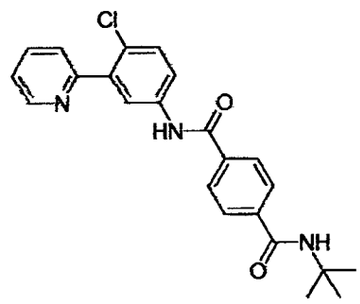
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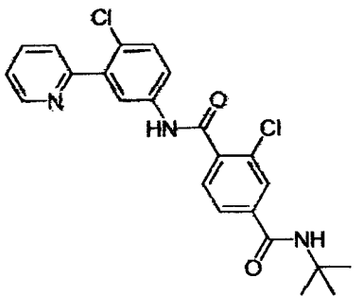
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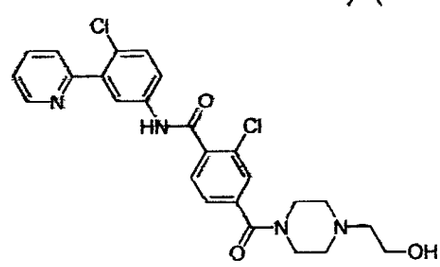
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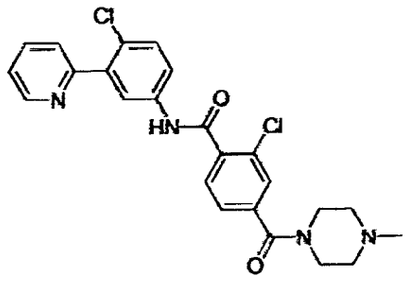
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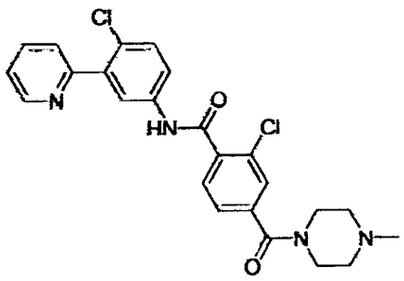
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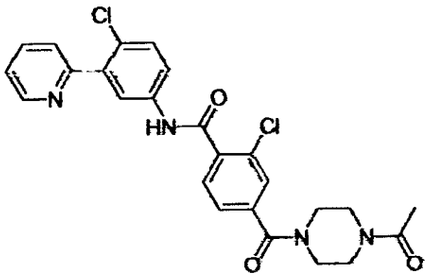
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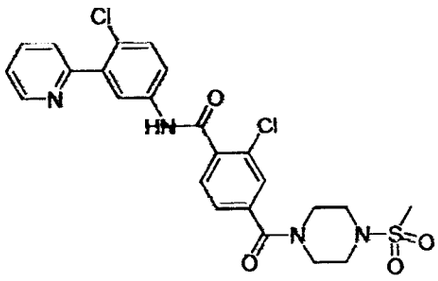
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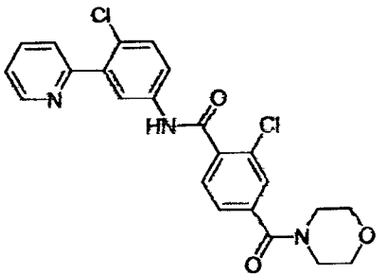
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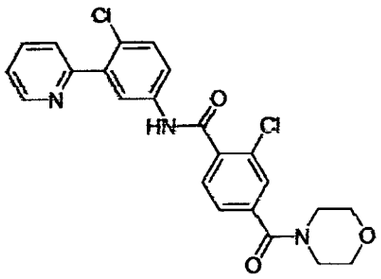
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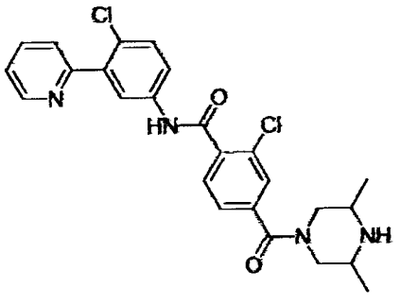
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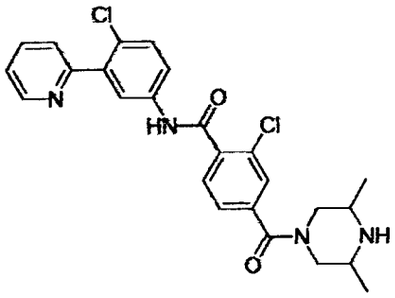
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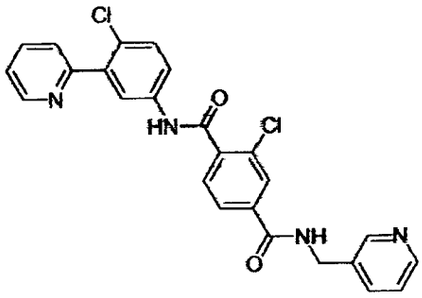
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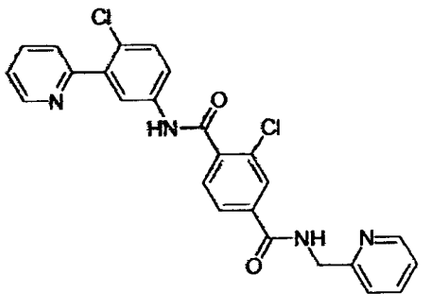
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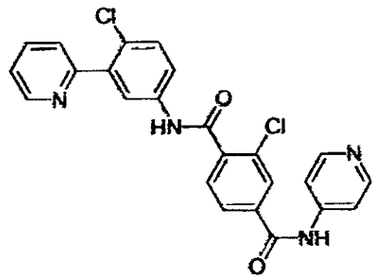
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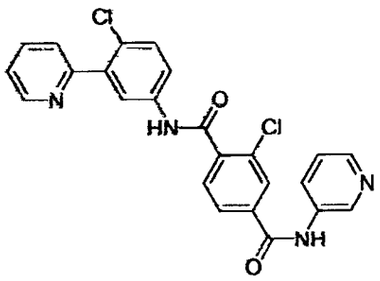
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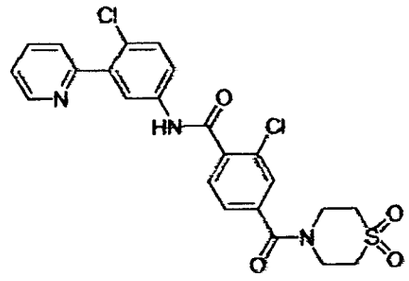
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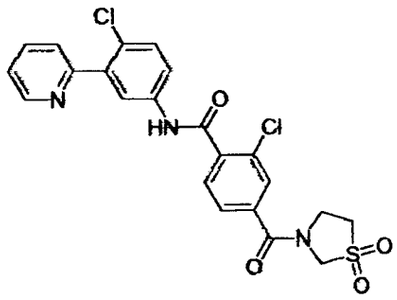
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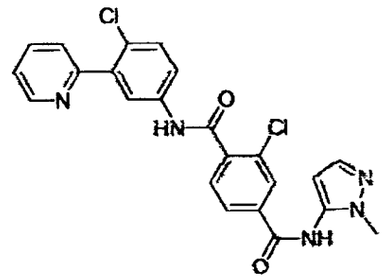
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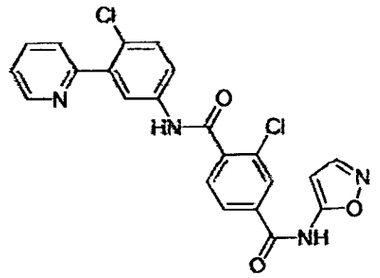
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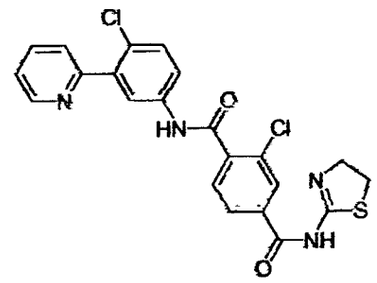
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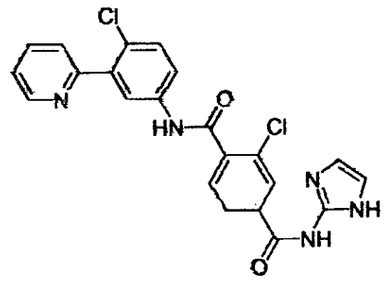
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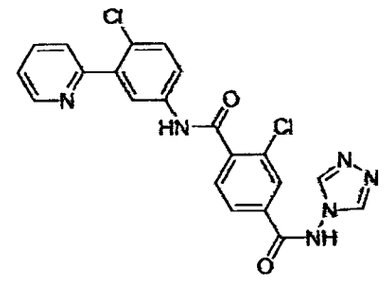
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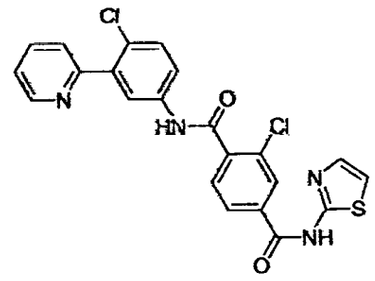
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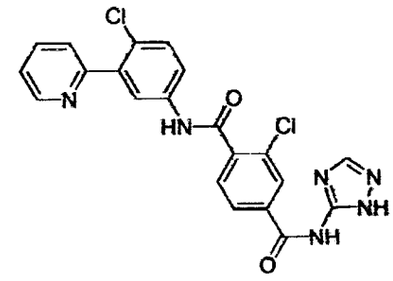
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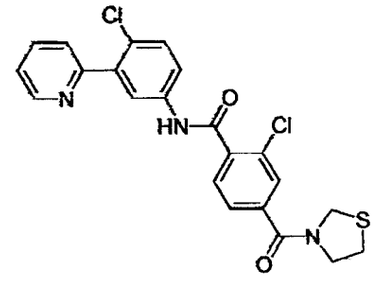
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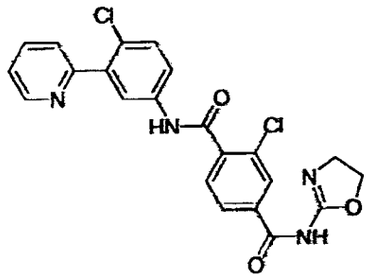
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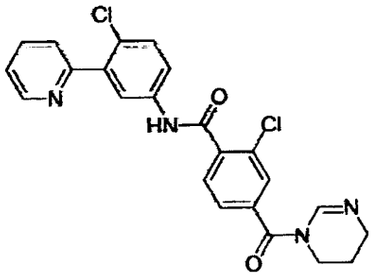
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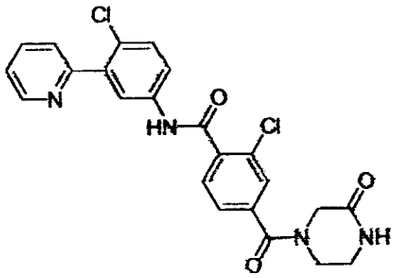
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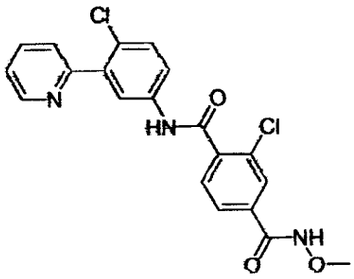
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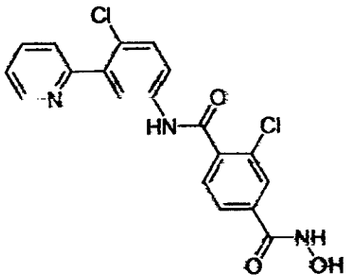
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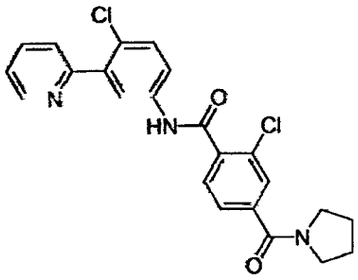
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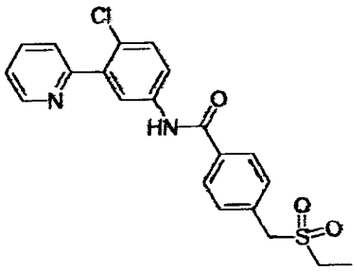
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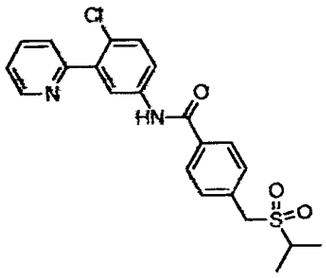
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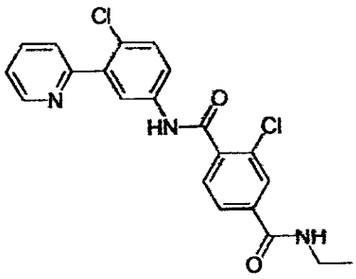
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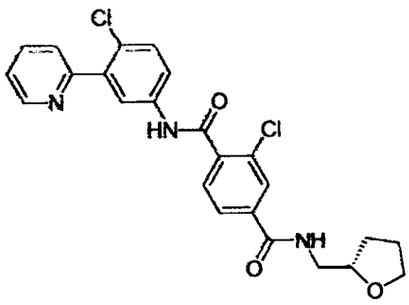
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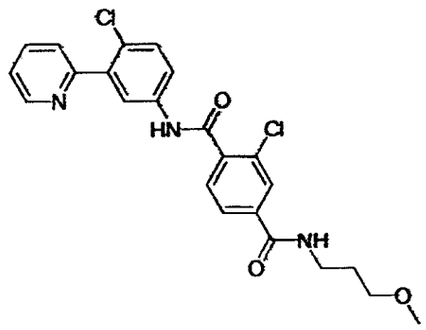
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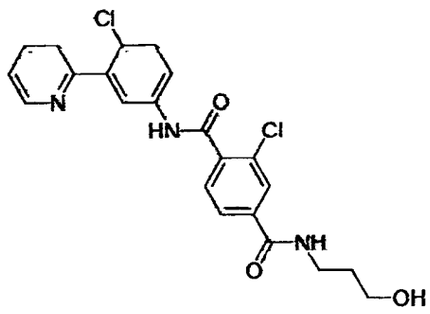
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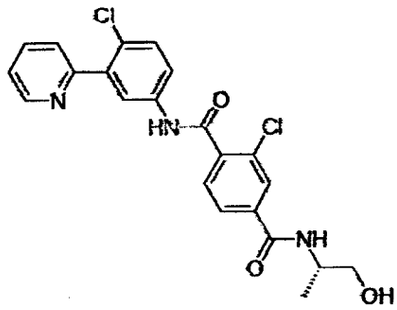
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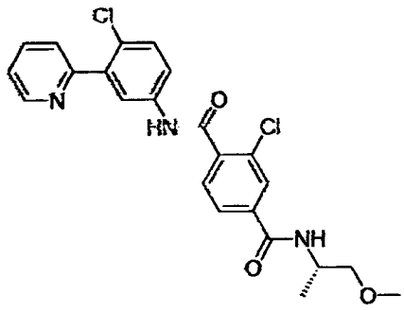
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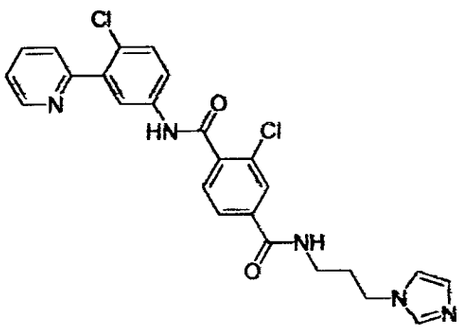
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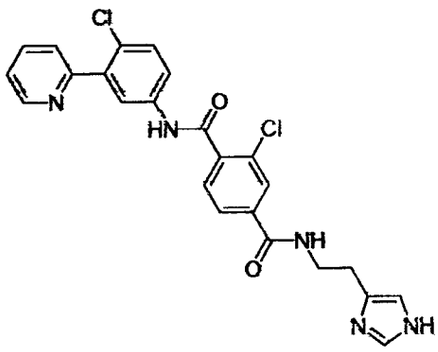
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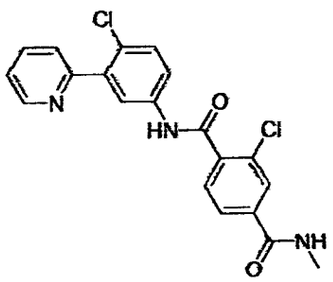
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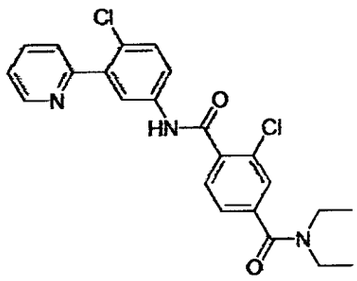
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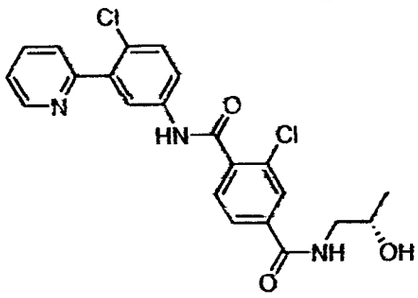
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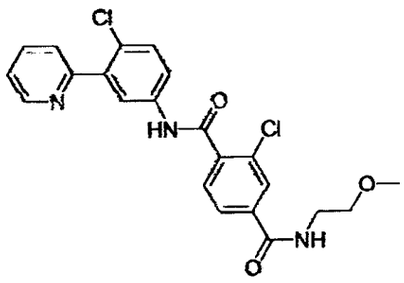
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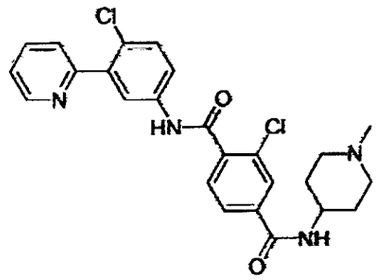
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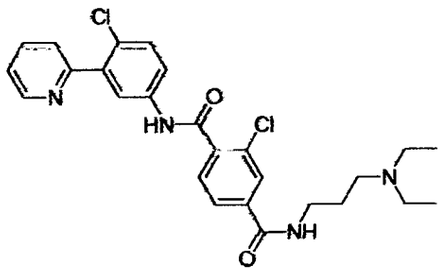
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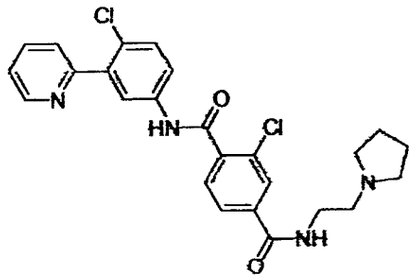
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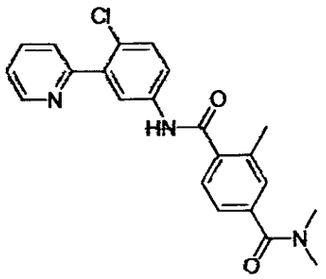
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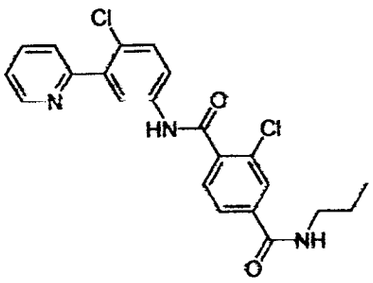
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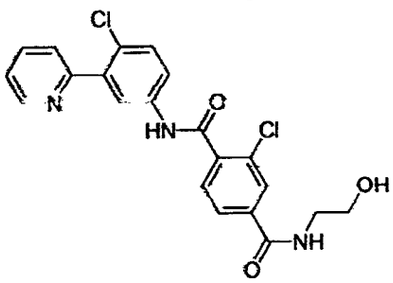
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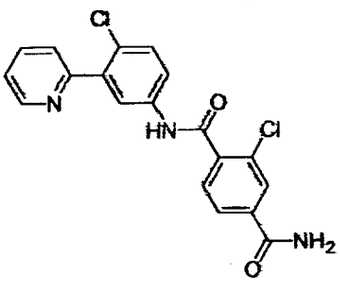
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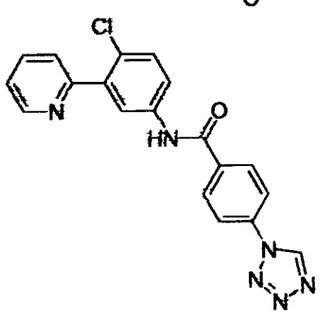
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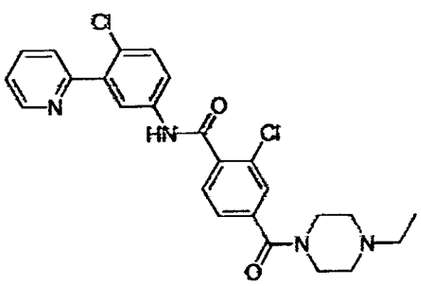
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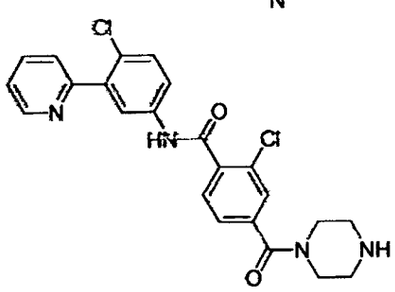
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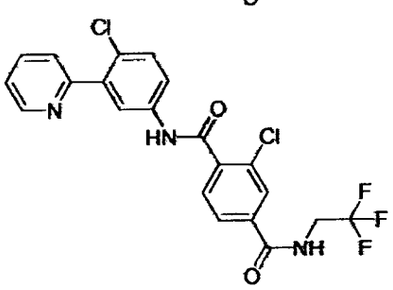
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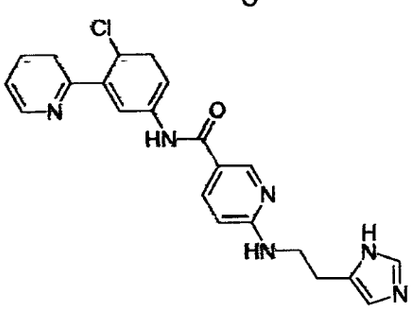
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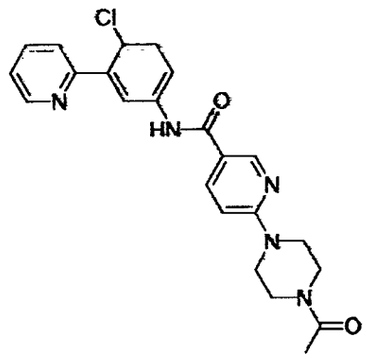
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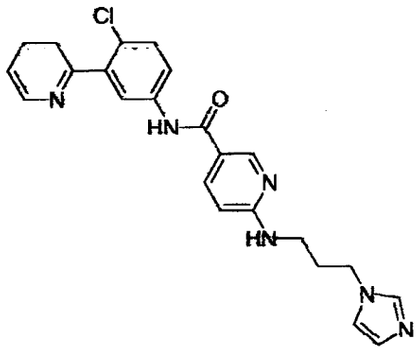
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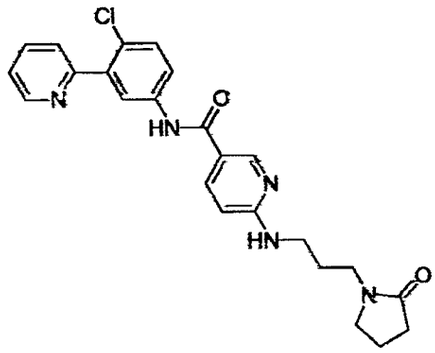
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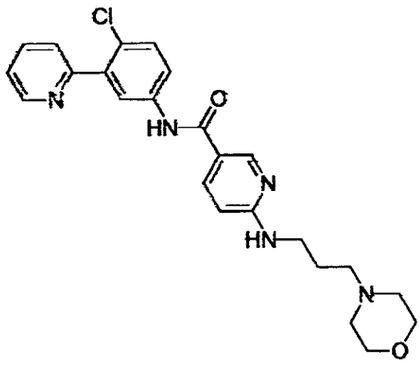
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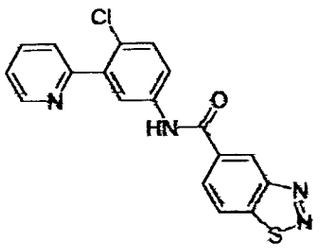
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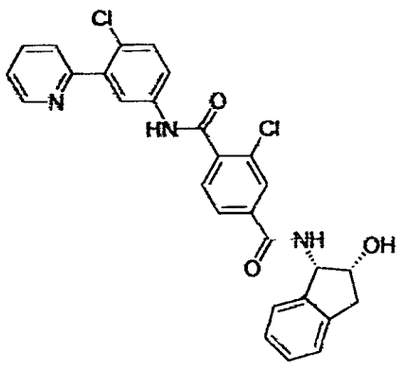
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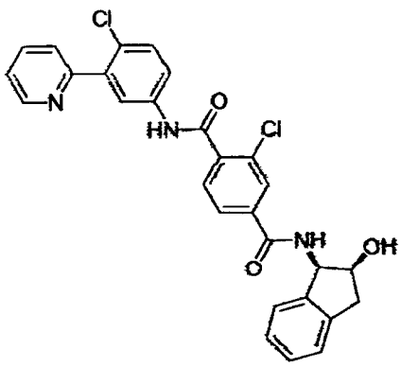
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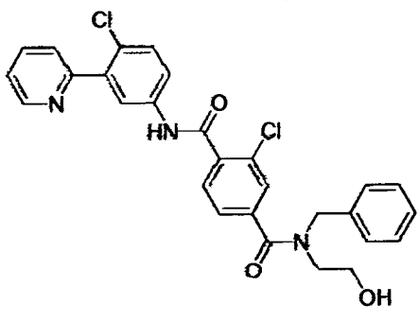
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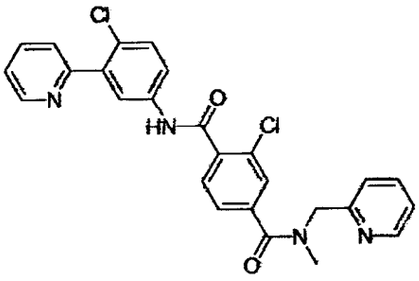
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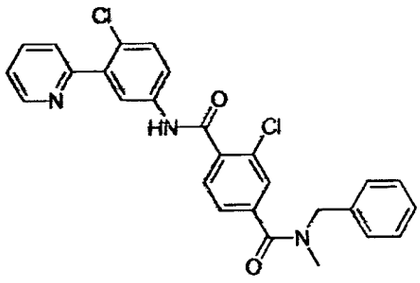
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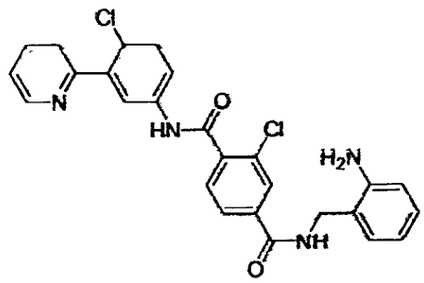
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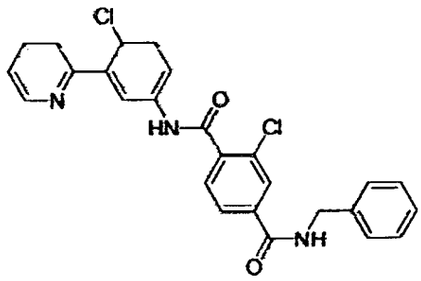
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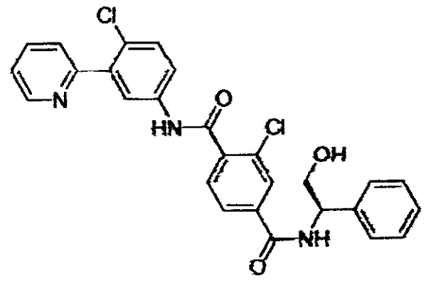
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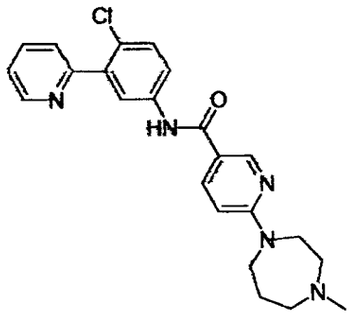
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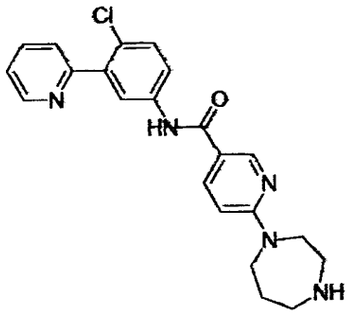
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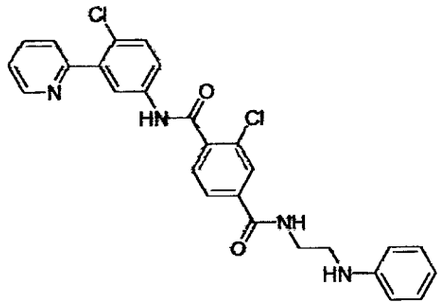
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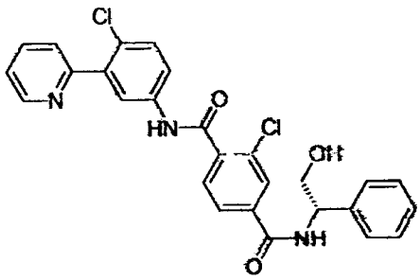
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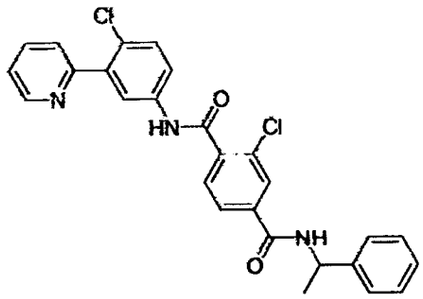
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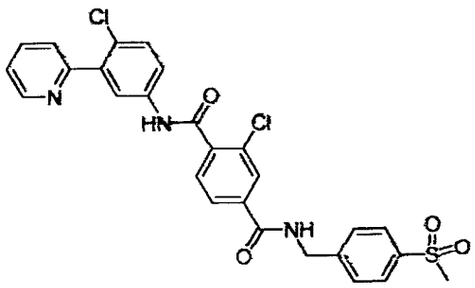
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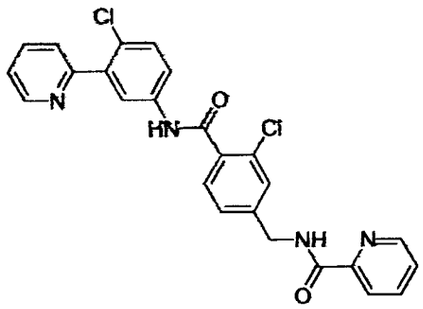
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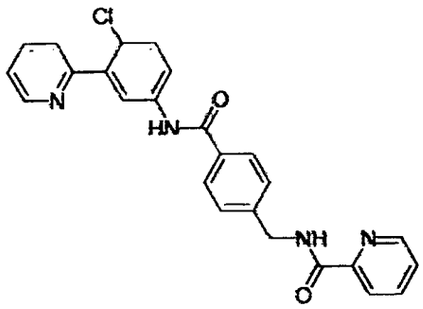
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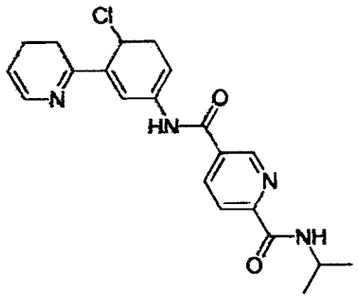
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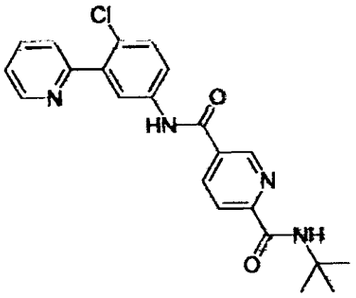
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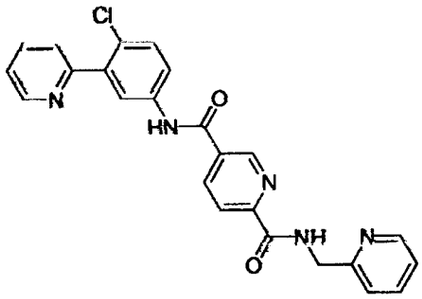
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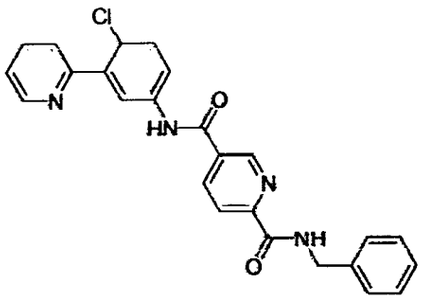
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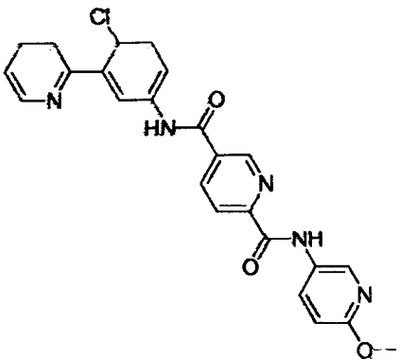
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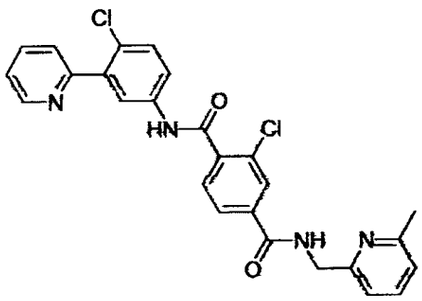
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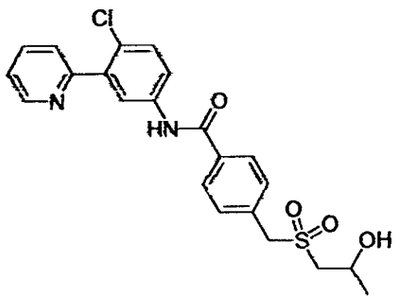
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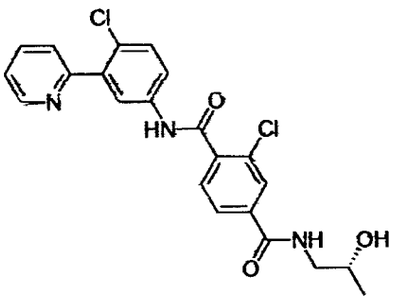
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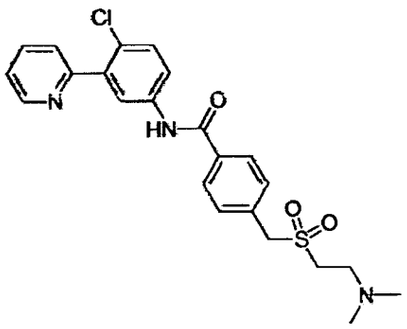
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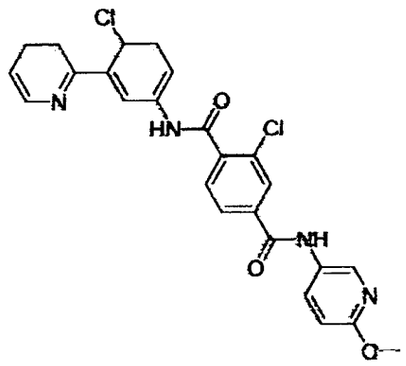
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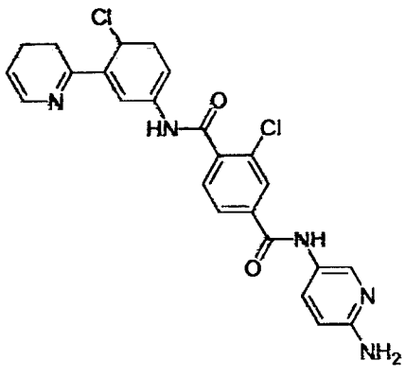
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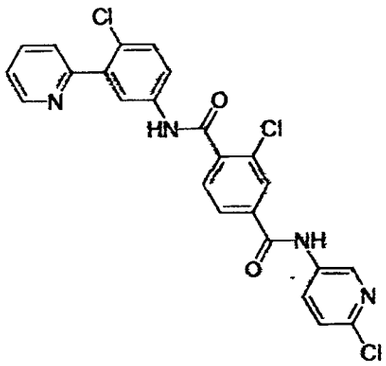
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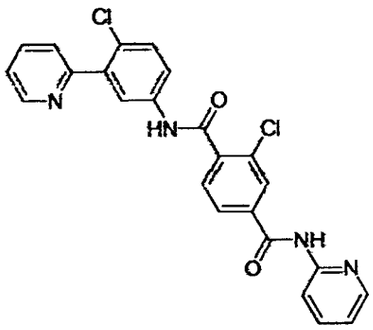
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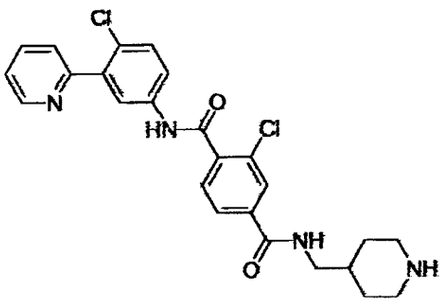
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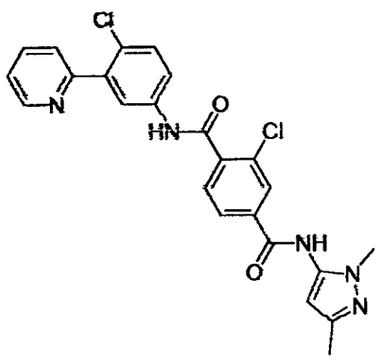
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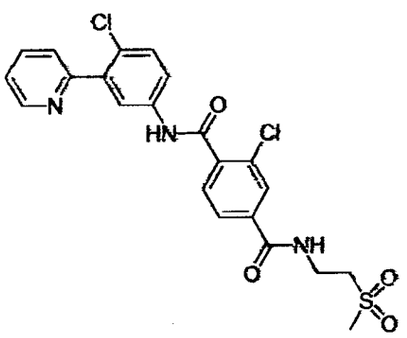
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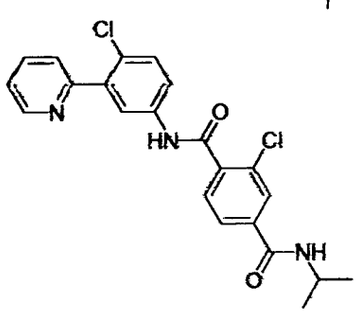
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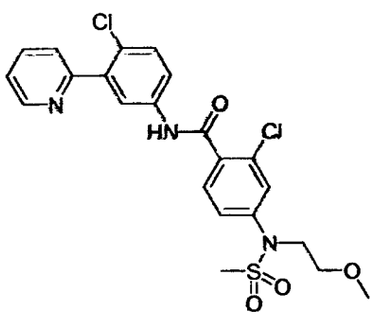
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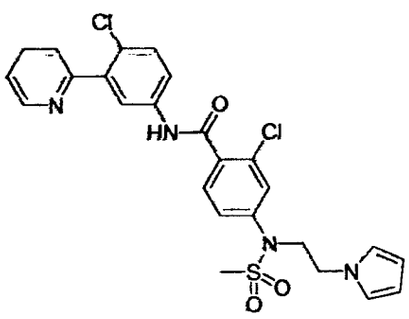
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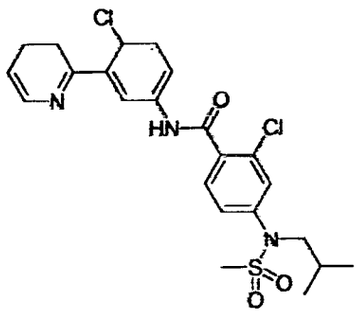
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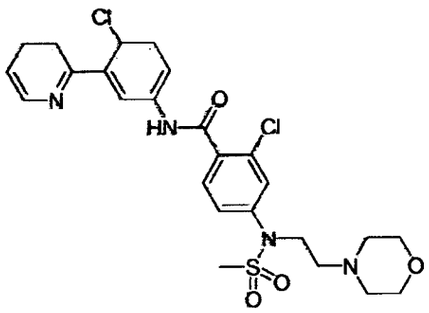
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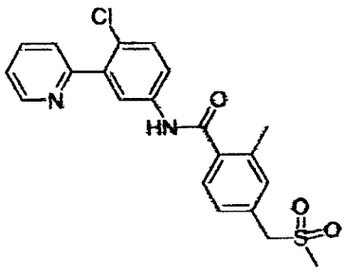
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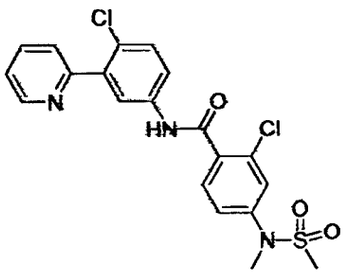
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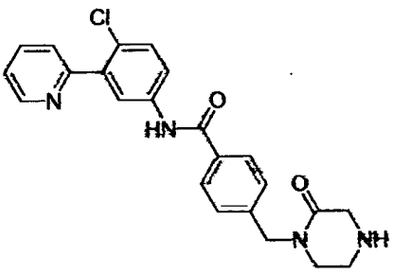
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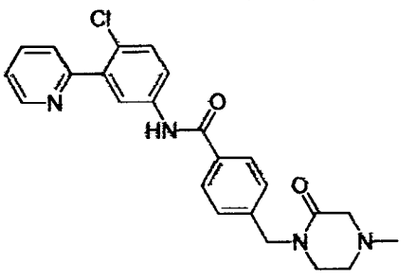
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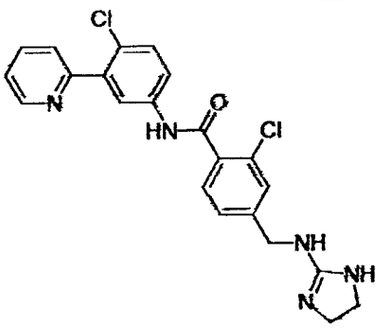
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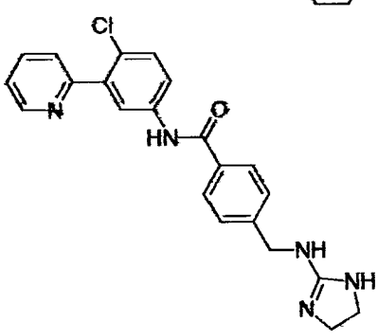
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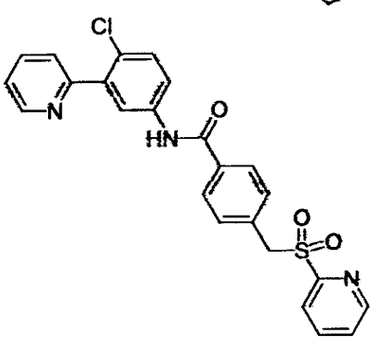
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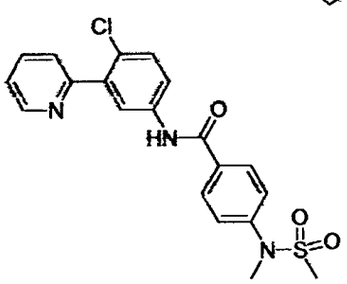
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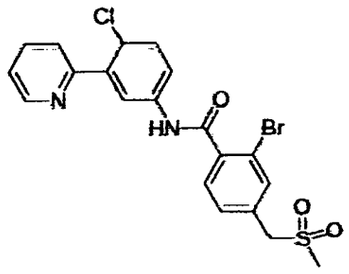
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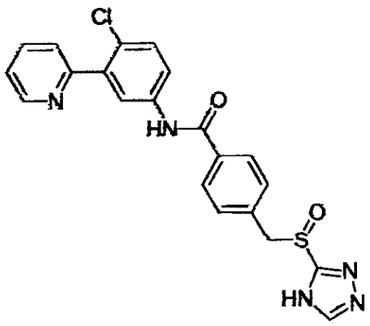
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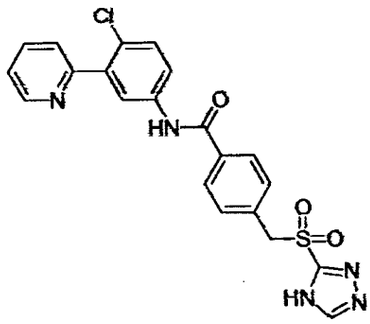
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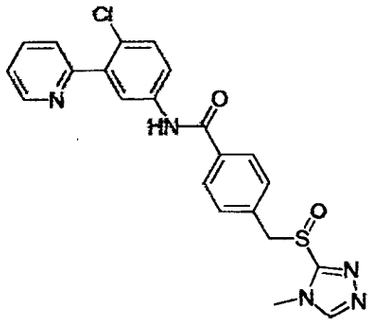
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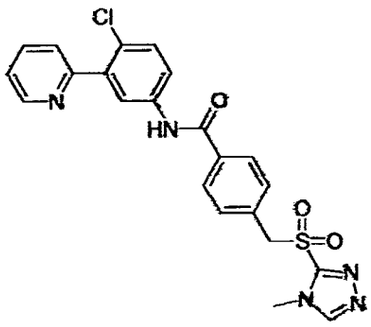
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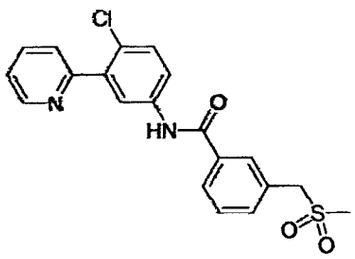
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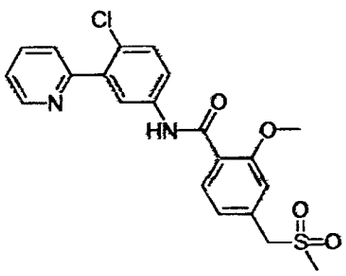
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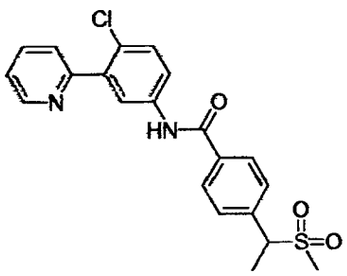
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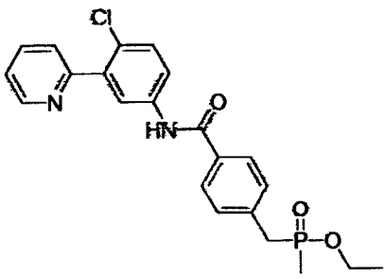
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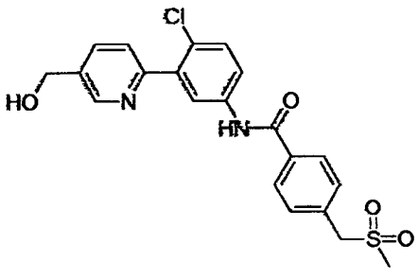
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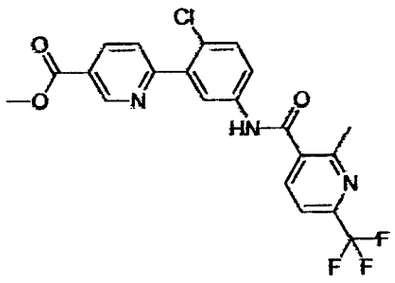
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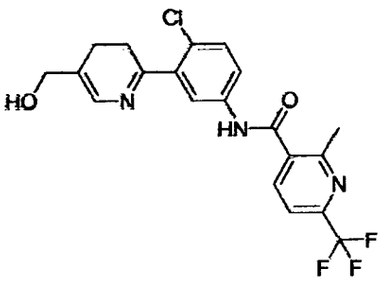
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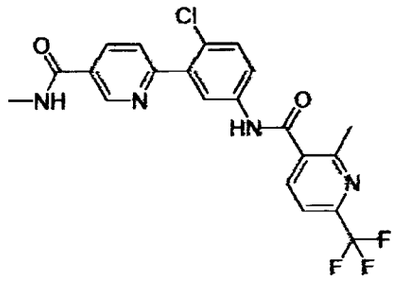
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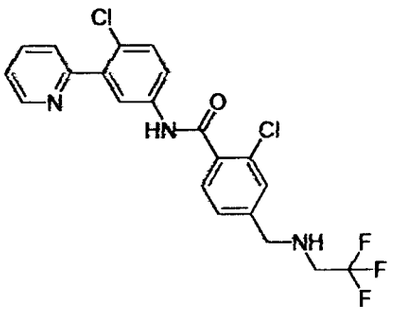
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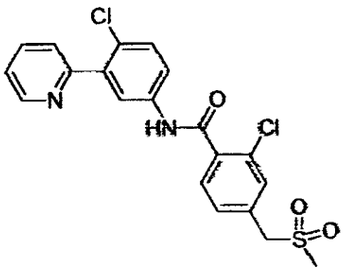
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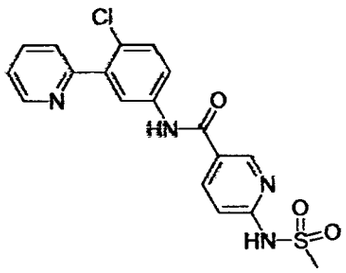
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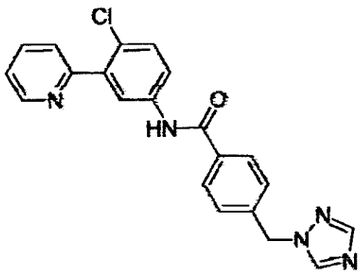
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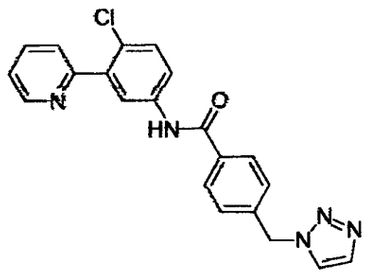
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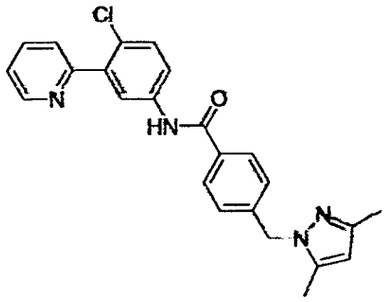
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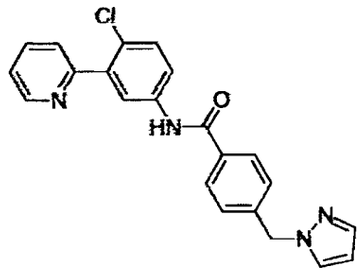
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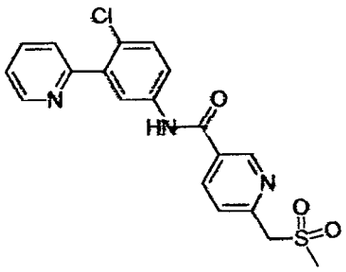
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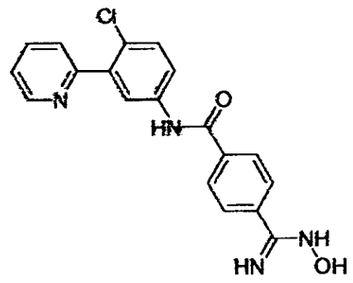
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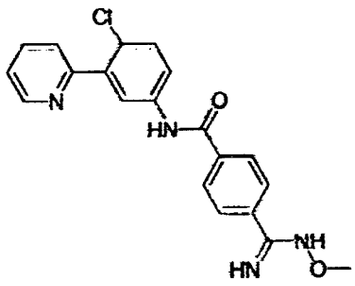
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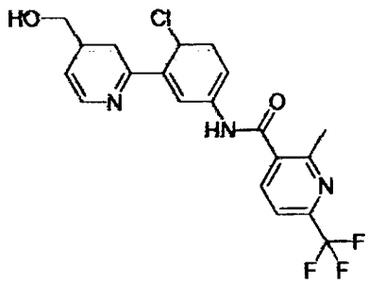
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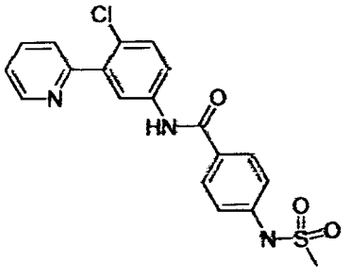
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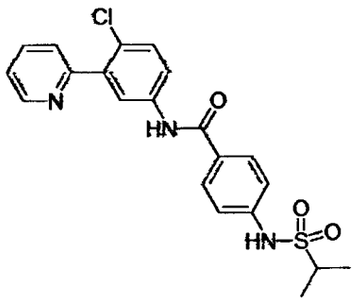
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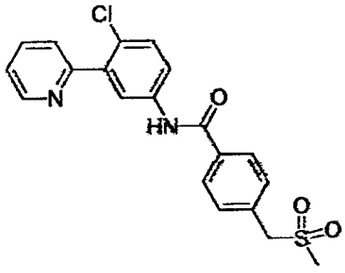
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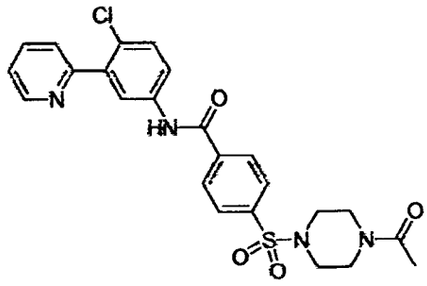
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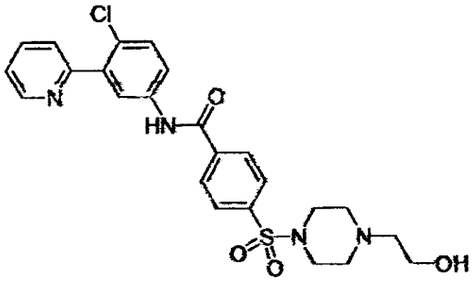
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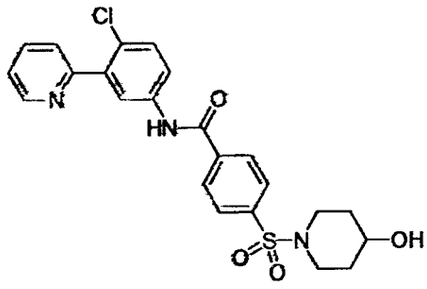
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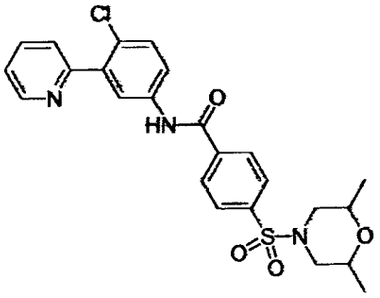
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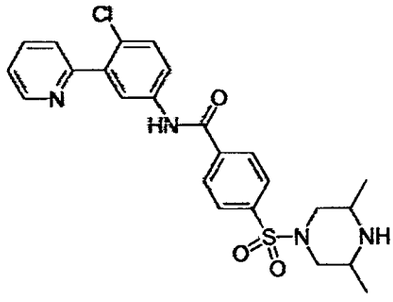
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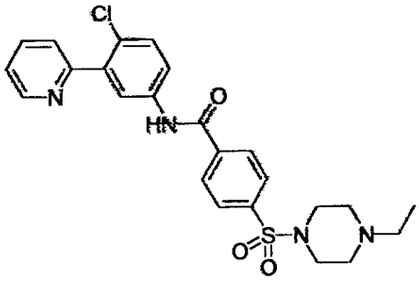
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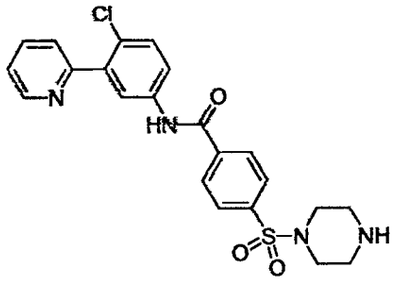
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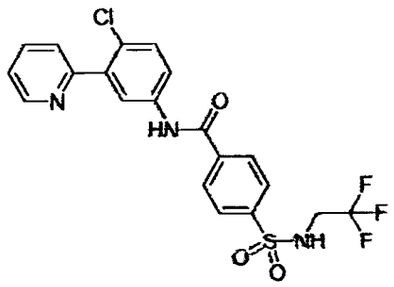
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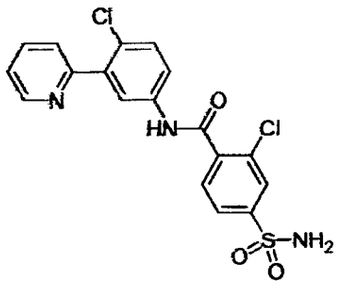
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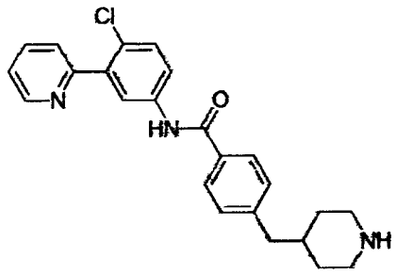
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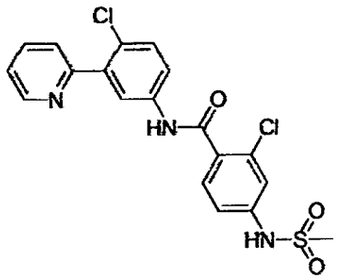
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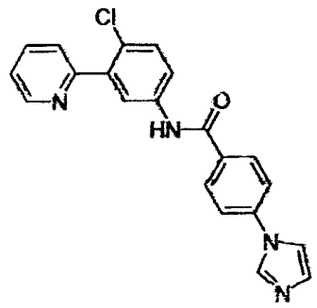
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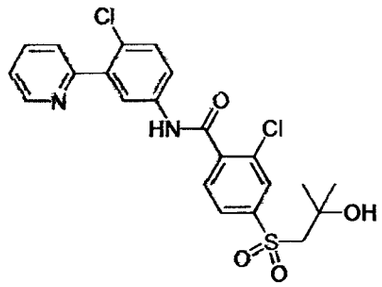
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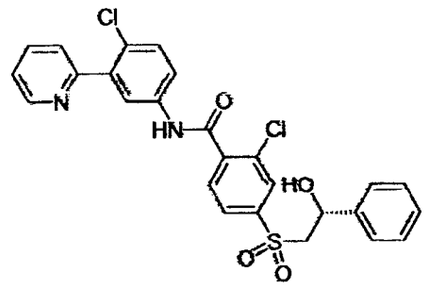
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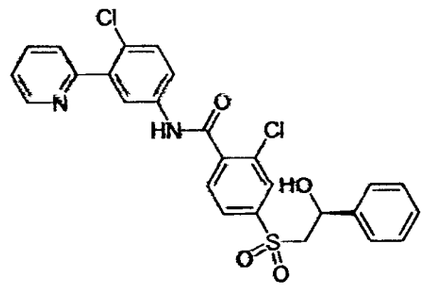
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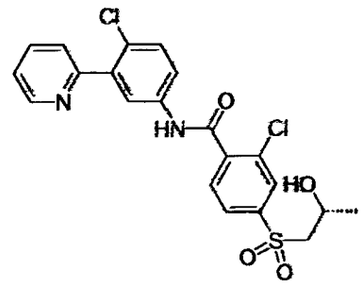
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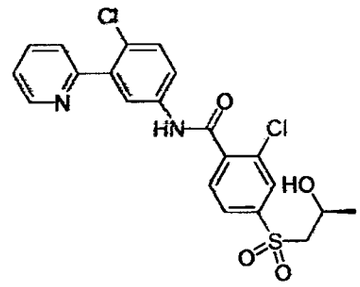
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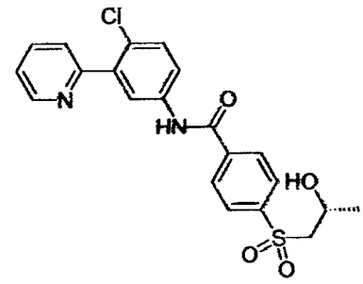
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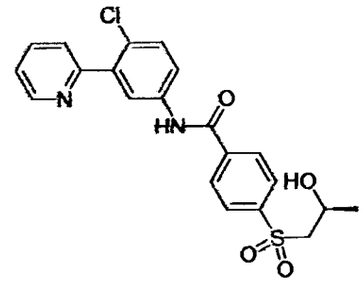
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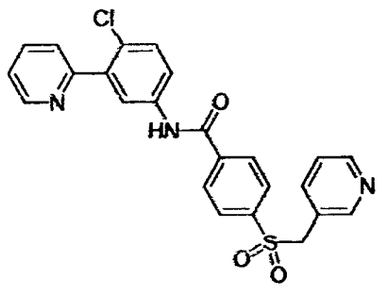
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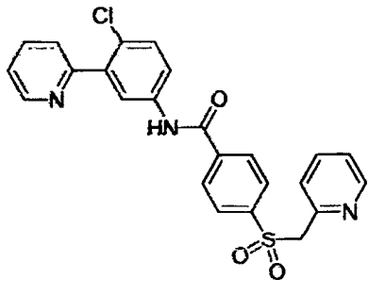
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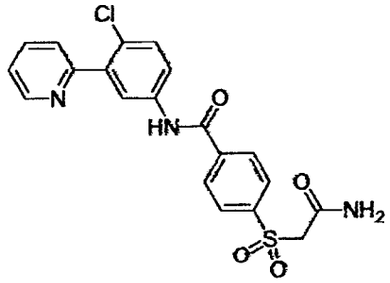
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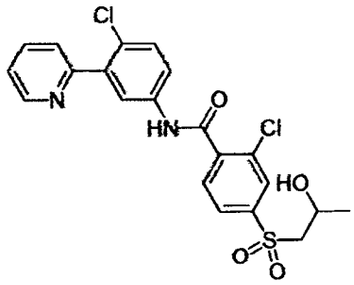
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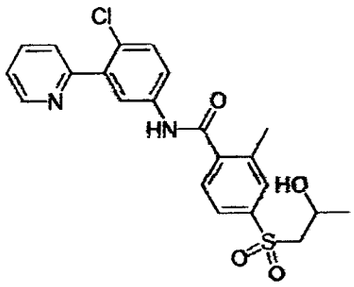
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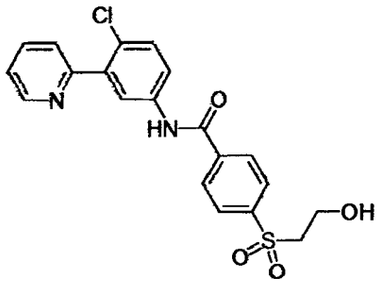
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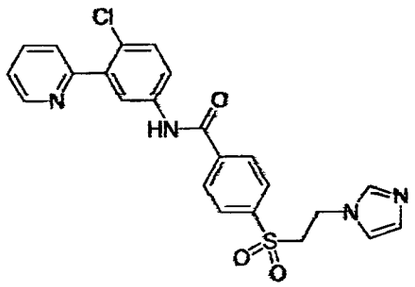
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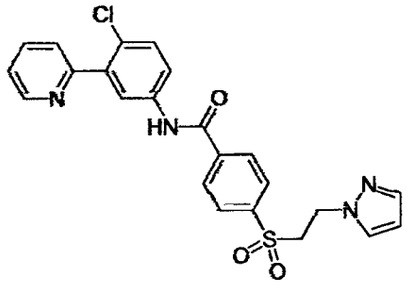
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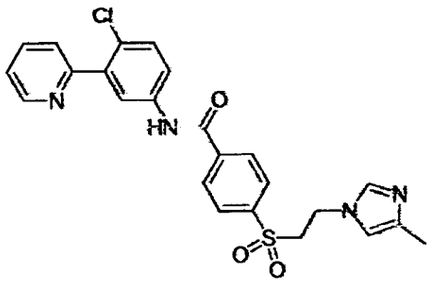
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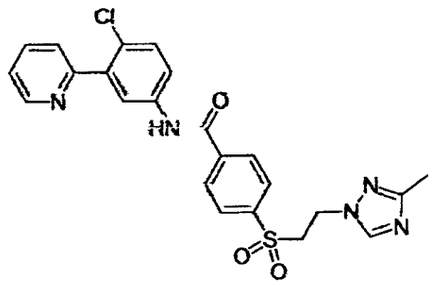
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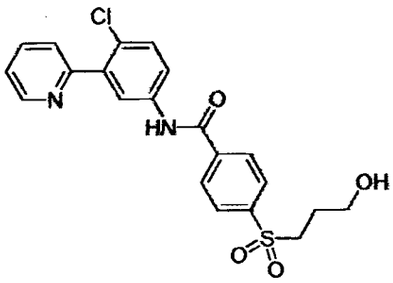
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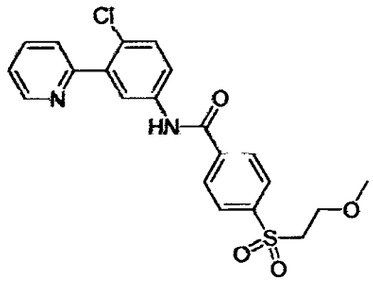
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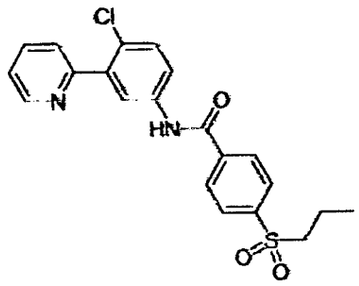
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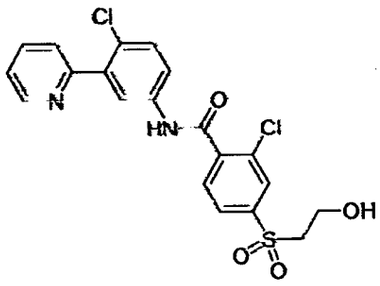
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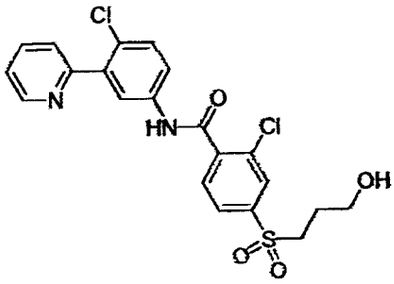
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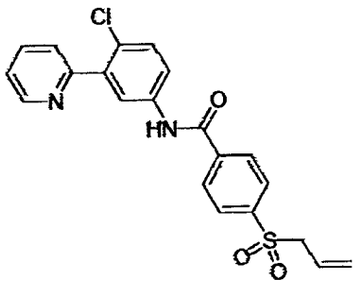
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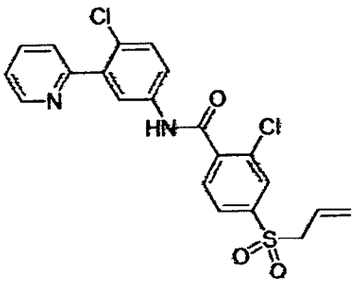
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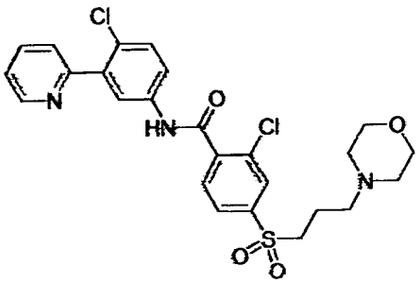
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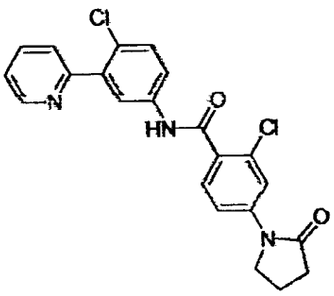
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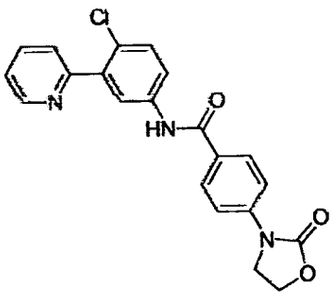
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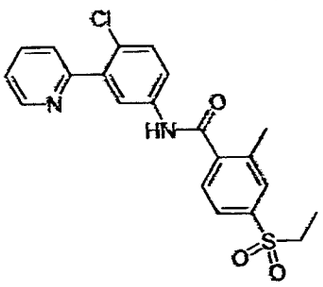
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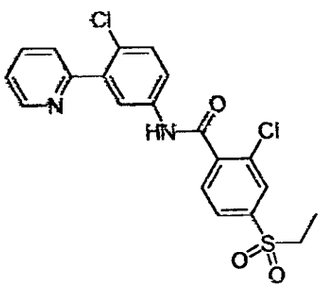
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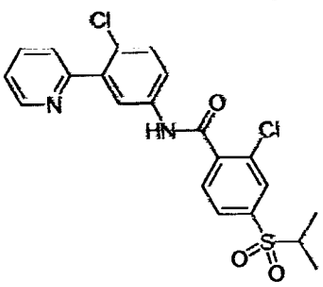
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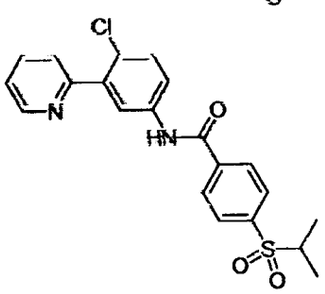
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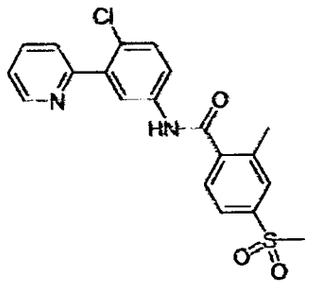
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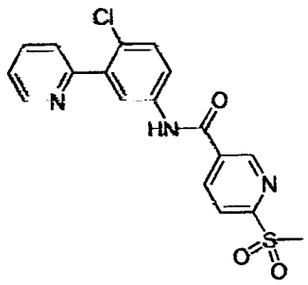
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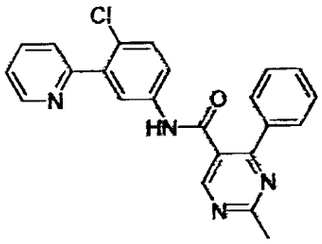
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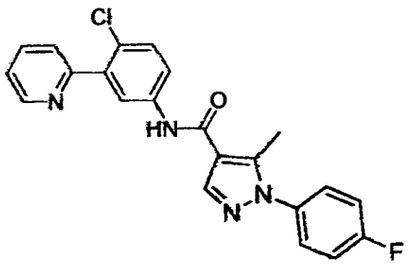
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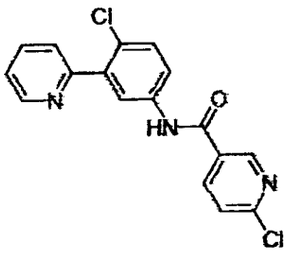
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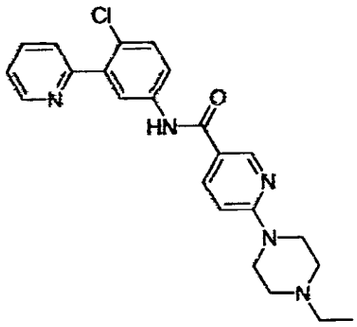
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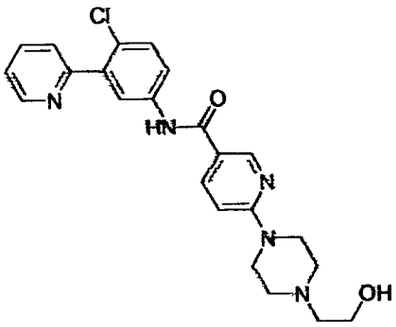
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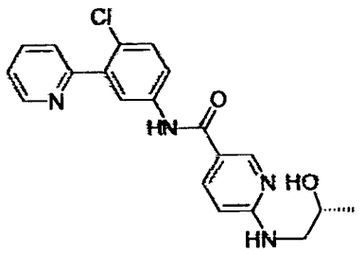
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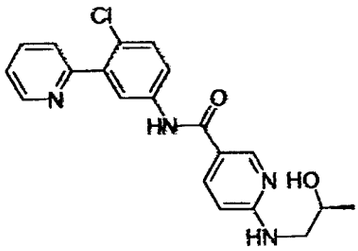
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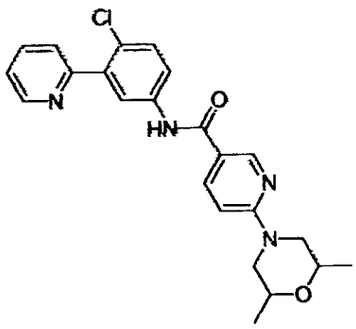
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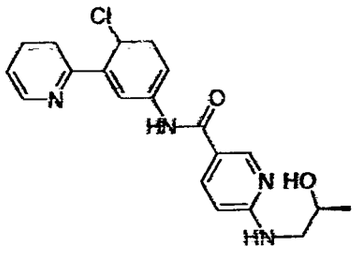
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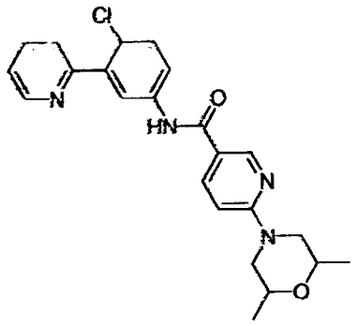
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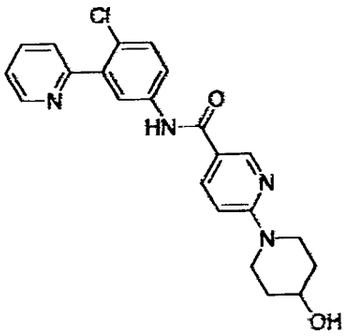
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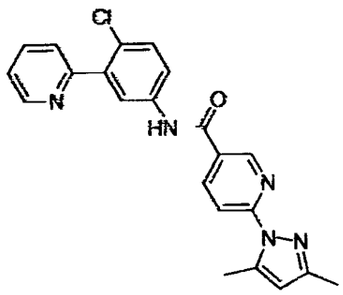
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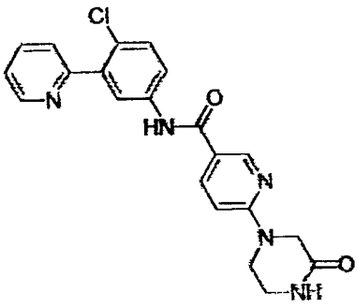
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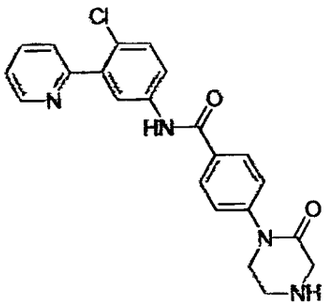
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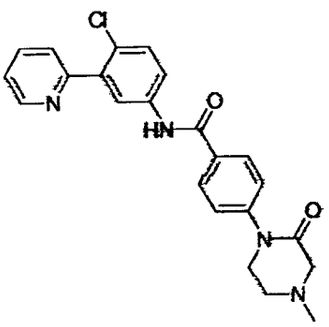
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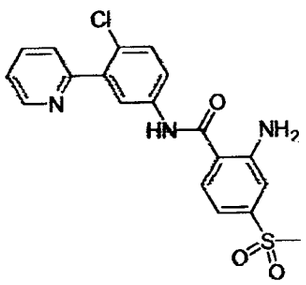
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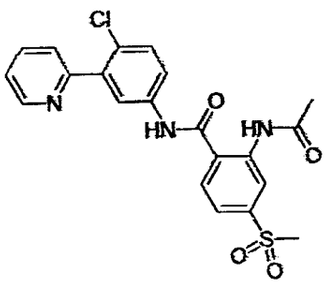
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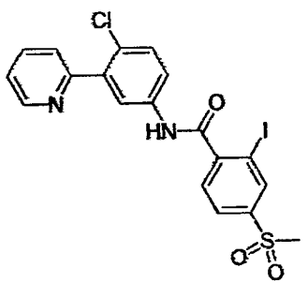
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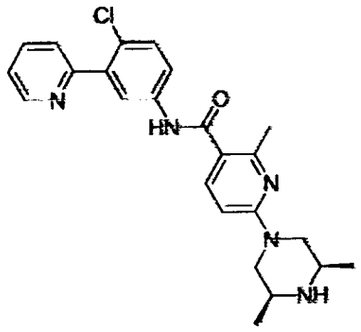
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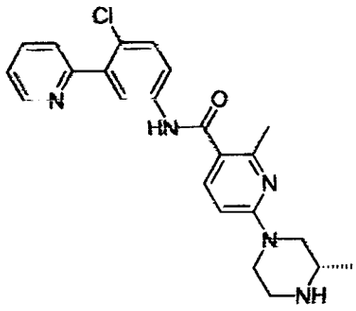
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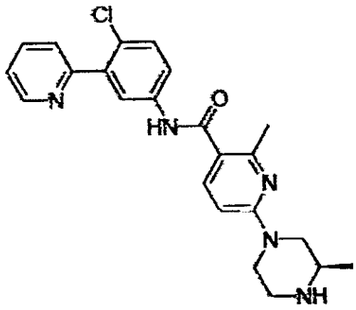
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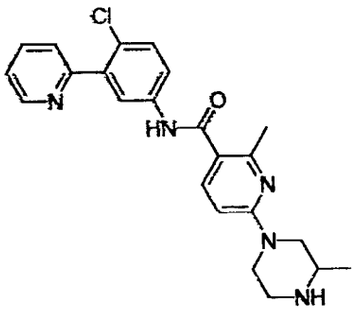
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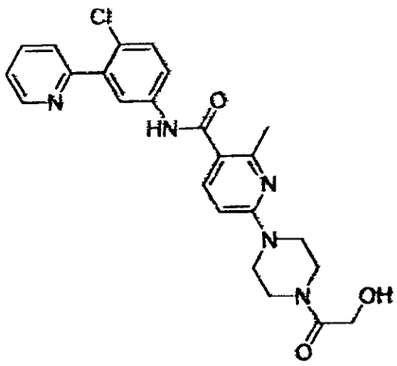
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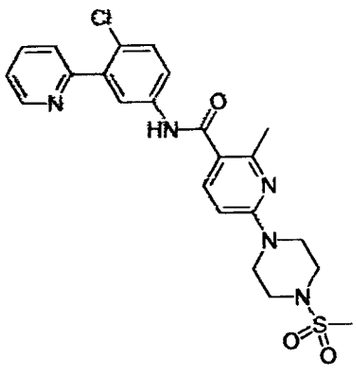
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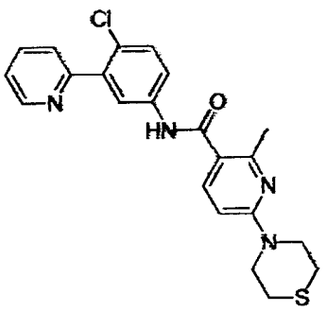
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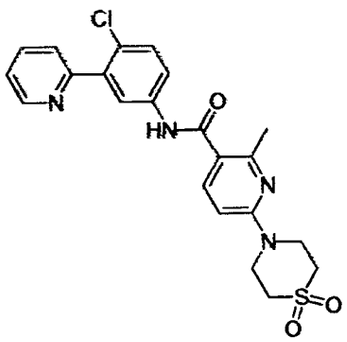
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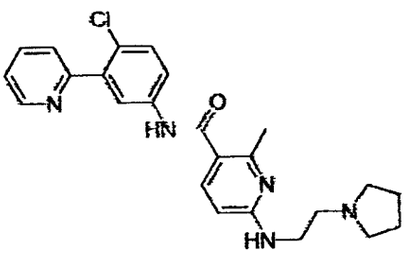
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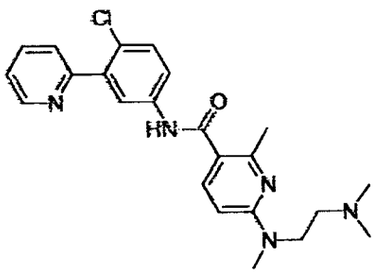
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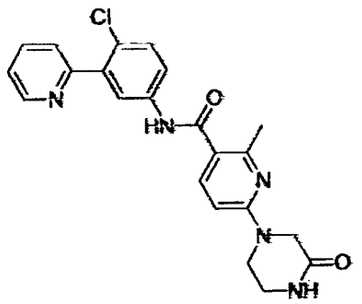
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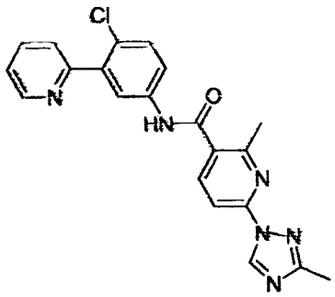
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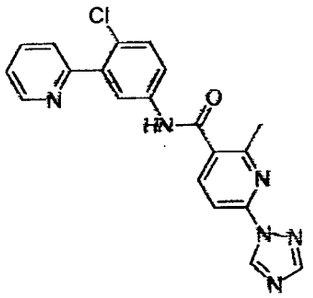
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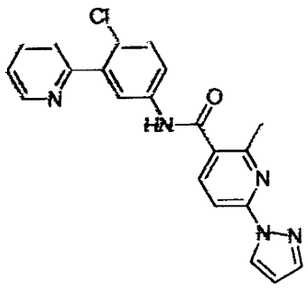
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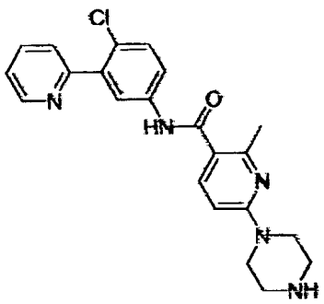
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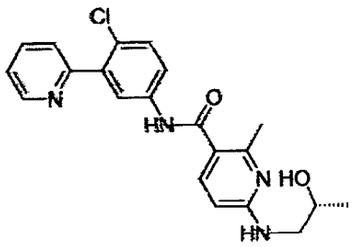
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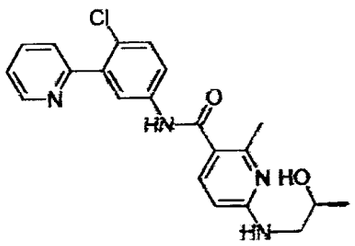
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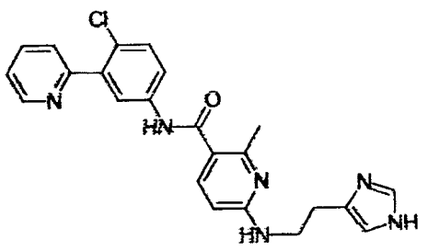
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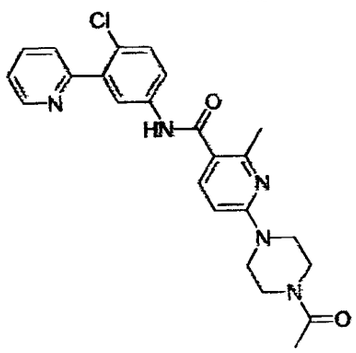
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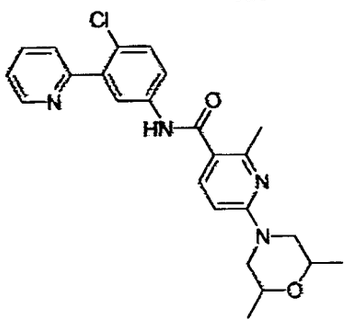
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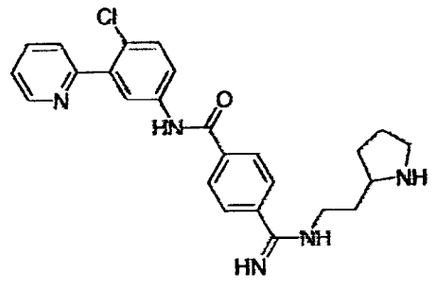
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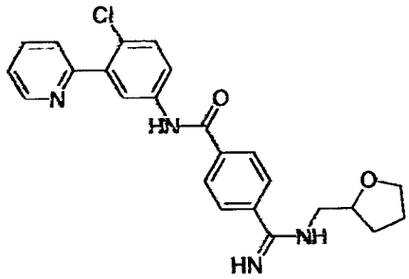
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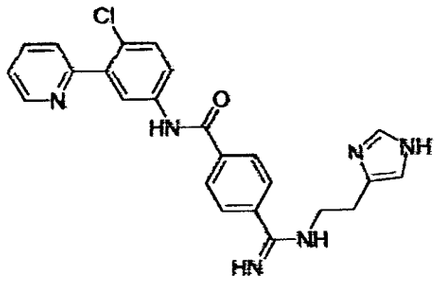
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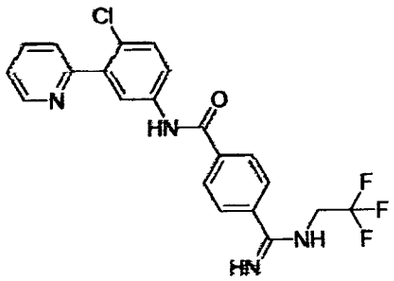
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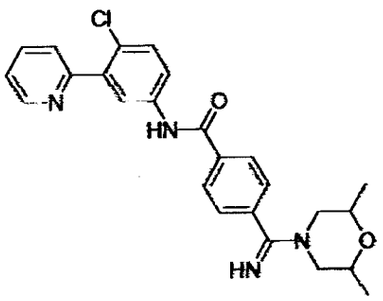
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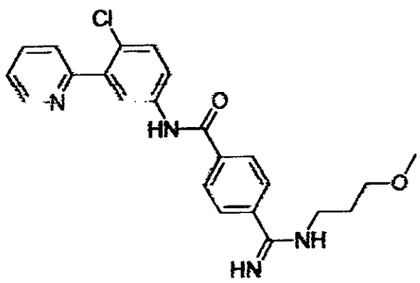
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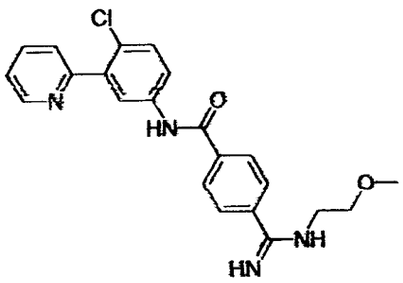
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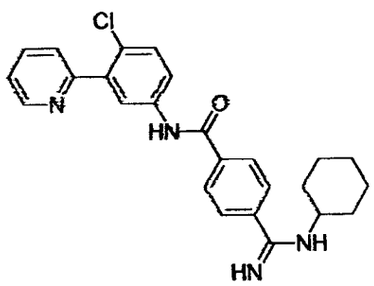
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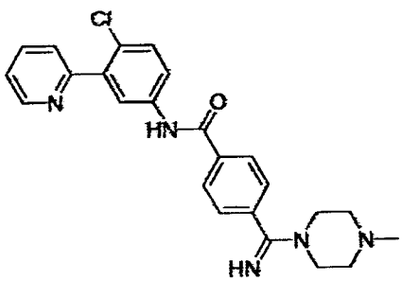
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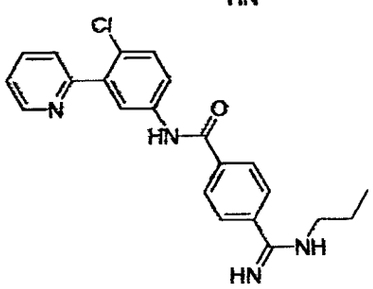
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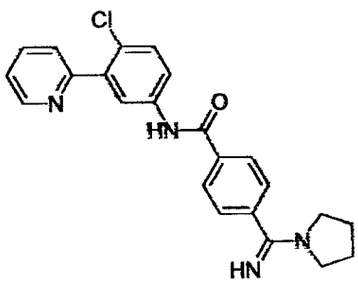
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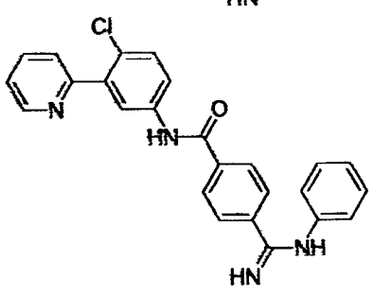
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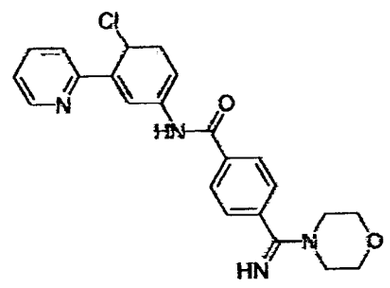
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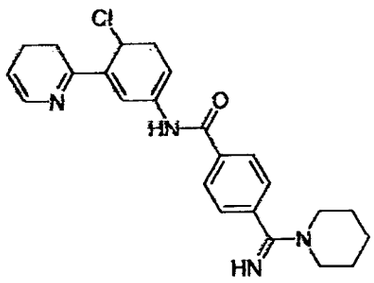
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Compounds of the invention may contain one or more asymmetric carbon atoms. Accordingly, the compounds may exist as diastereomers, enantiomers or mixtures thereof. The syntheses of the compounds may employ racemates, diastereomers or enantiomers as 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.

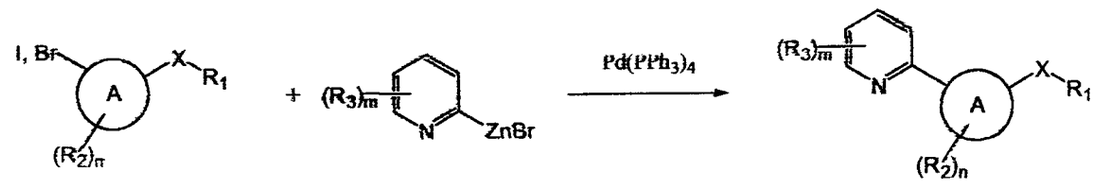
The invention also encompasses prodrugs of the compounds described above. Suitable prodrugs include known amino-protecting and carboxy-protecting groups which are released, for example hydrolyzed, to yield the parent compound under physiologic conditions. A particular class of prodrugs are compounds 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

(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:

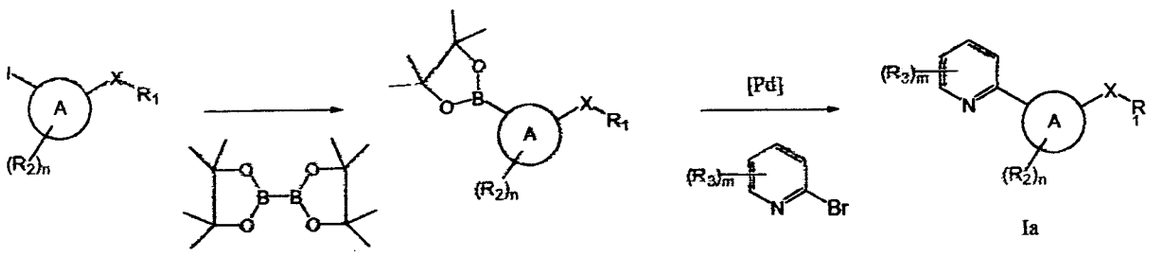
scheme 1



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.

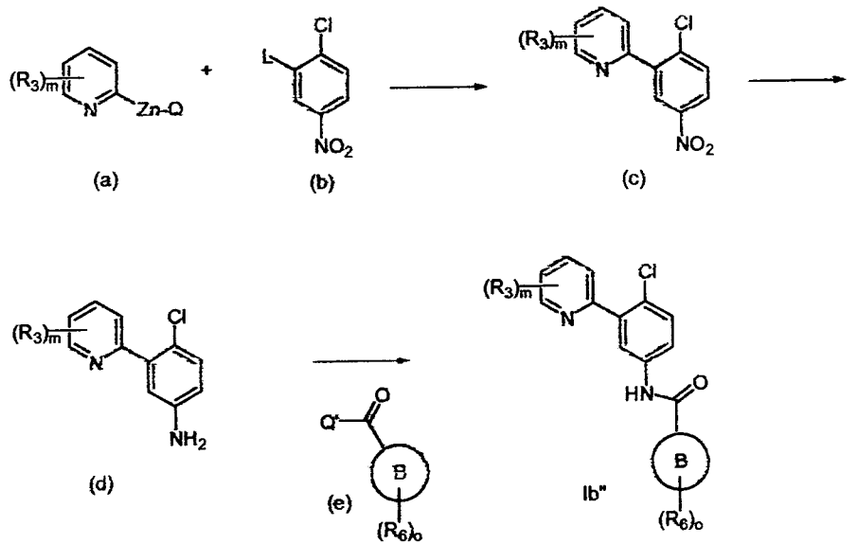
scheme 2



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.

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, 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-R1 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

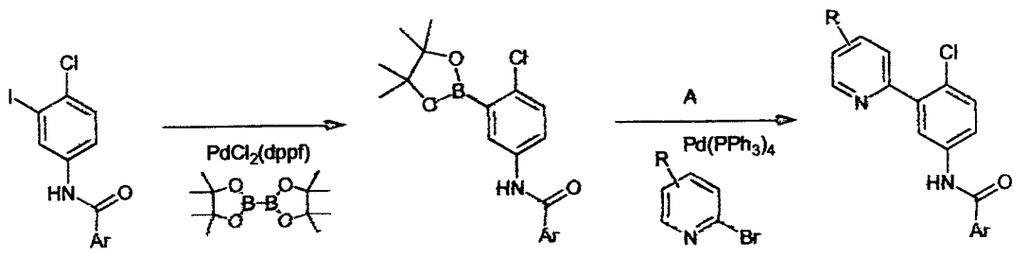
All reagents were obtained commercially unless otherwise noted. Reactions were performed using oven-dried glassware under an atmosphere of nitrogen. Air and moisture sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were

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 ^{1}H and are referenced internally to tetramethylsilane (TMS) in parts per million (ppm). Data for ^{1}H 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 Procedures

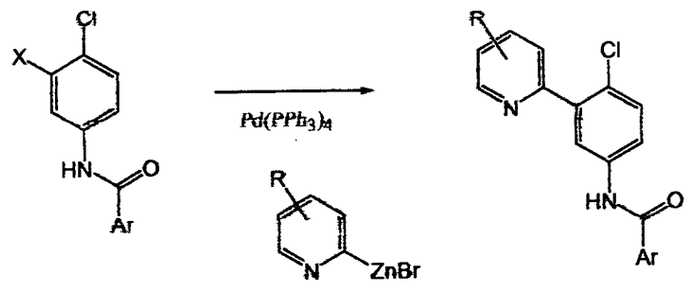
Compounds of examples 2-51 were prepared according to the following general procedures.

A: Suzuki Coupling Procedure



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.

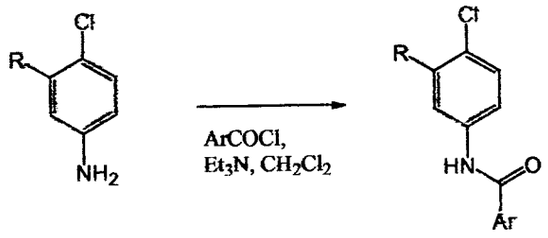
C: Iron Reduction of Aryl Nitro Group



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 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.

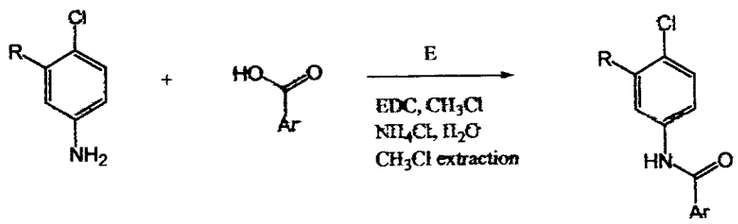
D: Amide Bond Formation



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.

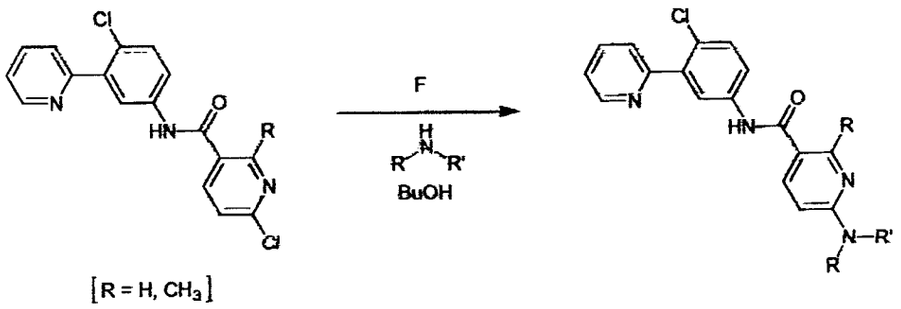
E: EDC Amide Bond Formation



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.

F: addition of amines to 2-chloropyridine

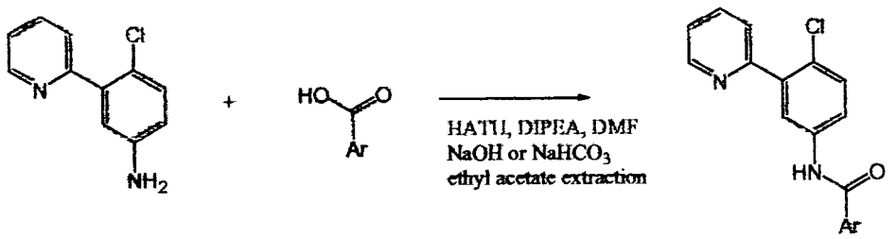


[R = H, CH_3]

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

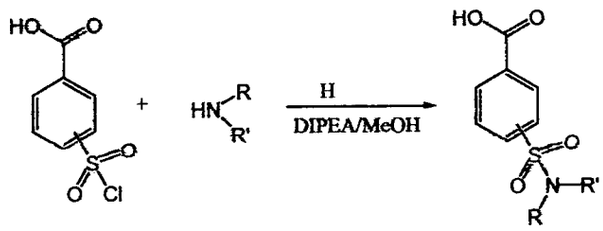
Primary or secondary amine (5 eq) in either BuOH or a mixture of BuOH/ethylene gylcol was heated to 170 to 220 °C for 20 min in a sealed tube. The BuOH was removed under reduced pressure. In cases where ethylene glycol was used, the reaction was diluted with water, and the product was extracted into 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



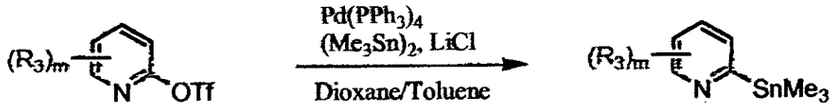
Aniline (1.0 eq) was added to a mixture of carboxylic acid (1.1 eq), HATU (1.1 eq) and DIPEA (2 eq) in DMF (0.1 - 0.2 M). After stirring overnight, the reaction mixture was diluted with 0.1 N sodium hydroxide or saturated $NaHCO_3$, extracted into ethyl acetate and the combined organic layers were washed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

H: Preparation of sulfonamide benzoic acids



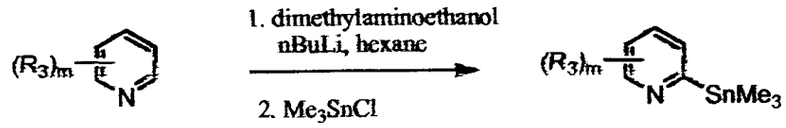
Chlorosulfonylbenzoic acid (1.0 eq) was added to a solution of amine (1.1 eq) in 10-20% DIPEA/methanol (1 M) at 4 °C. After 1 h, the reaction mixture was concentrated, and the crude residue was purified by reverse phase HPLC.

I: Stannylation of 2-pyridyl triflates



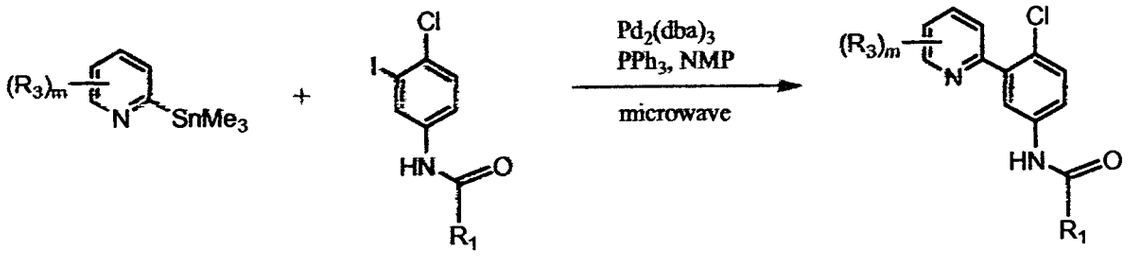
A solution of tetrakis-triphenylphosphinepalladium (0.04 eq.) in toluene (1 mL) was added to degassed solution of aryltriflate (1 eq), bis-trialkyltin (1.05 eq), and lithium chloride (3 eq) in dioxane. Heated to reflux for 2 hours, cooled to 23 °C, diluted with ethyl acetate, washed with 10% $NH_4OH_{(aq)}$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

J: Stannylation of substituted pyridines



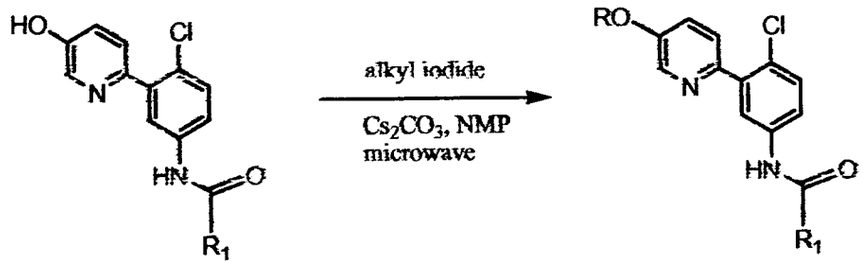
n-Butyl lithium (6 eq, 2.5 M in hexanes) was added dropwise to a solution of dimethylaminoethanol (3 eq) in hexane at 0 °C. The solution was stirred at 0 °C for thirty minutes before dropwise addition of the substituted pyridine (1 eq). The solution was stirred at 0 °C for an additional hour, then cooled 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.

K: Stille Coupling



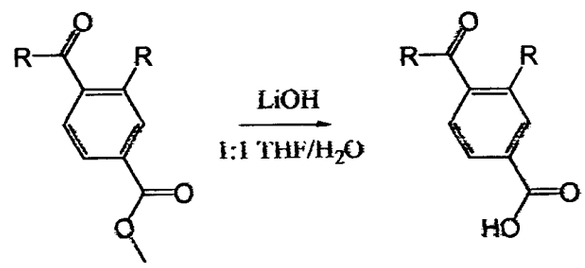
Palladium catalyst (0.02 eq) was added to a degassed solution of aryliodide (1 eq), arylstannane (2 eq), and triphenylphosphine (0.16 eq) in NMP. Heated in the microwave to 130 °C for 15 minutes. The reaction mixture was diluted with ethylacetate, washed with 10% $NH_4OH_{(aq)}$ and brine, dried ($MgSO_4$),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

L: Synthesis of alkylethers



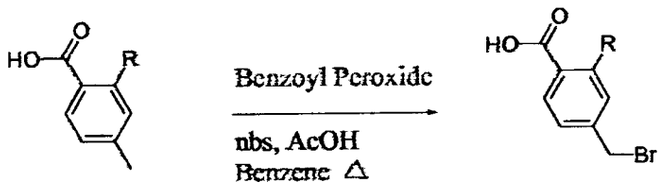
A solution of hydroxypyridine (1 eq), alkyliodide (excess), and cesium carbonate in NMP was heated in the microwave to 100 °C for ten minutes. The reaction mixture was diluted with ethylacetate, washed with 10% $NH_4OH_{(aq)}$ and brine, dried ($MgSO_4$), concentrated and purified by silica gel chromatography.

M: *Methyl Ester Saponification*



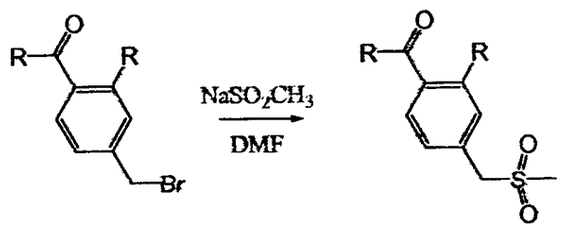
The methyl ester (1eq) was hydrolyzed with LiOH (2eq) in 50/50 THF/water mix. Upon completion of the reaction the THF was evaporated under reduced pressure and the solution is acidified with HCl to pH 2. The resultant solid was filtered and dried to give the pure acid.

N: Bromination in the presence of a free acid functionality



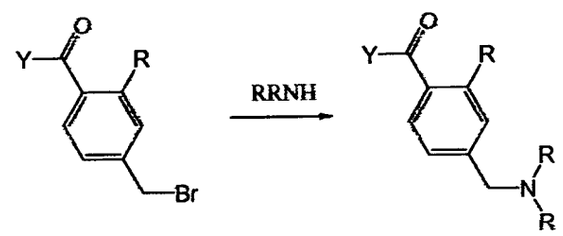
The paramethylbenzoic acid (1eq) was combined with Benzoyl Peroxide (0.1eq) and N-Bromosuccinimde (0.9eq) in a solution of 5%AcOH in Benzene and heated in the microwave at 120°C for 5-15minutes. The product was separated from the starting material and di-bromo product via ISCO flash chromatography with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

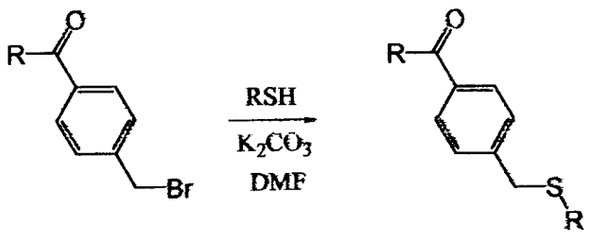
P: Amine displacement of Bromine



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

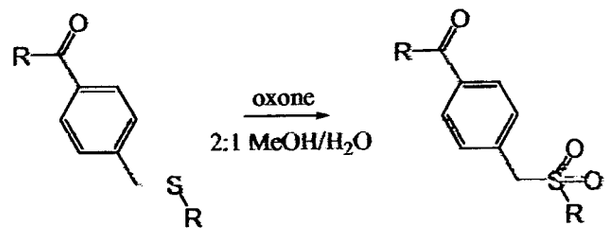
minutes. Crude reactions were concentrated to dryness and either extracted with ethyl acetate and saturated bicarbonate if the reaction resulted in an intermediate or purified via HPLC if the reaction resulted in a final product.

Q: Thiol displacement of halogen



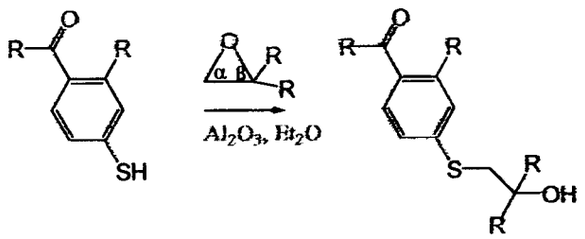
The paramethylbromo benzoate (1eq) was treated with Potassium (or Cesium) Carbonate (1.5eq) *and appropriate thiol derivative (1,1eq) in DMF (or CH_3CN) and stirred overnight* at room temperature. The DMF was evaporated in vacuo and the reaction was extracted with ethyl acetate and water. The organic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

R: Oxone Oxidation



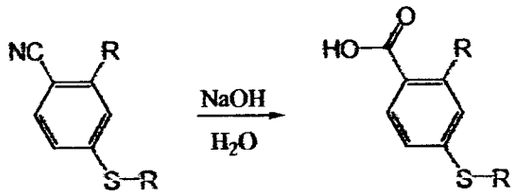
Derivatized thiol (1eq) was dissolved in MeOH while Oxone (2eq) was seperately dissolved in half the amount of water. Once all the oxone was dissolved, the solution was added to the thiol in MeOH solution at once and stirred until complete. The MeOH was evaporated in vacuo and the remaining water was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



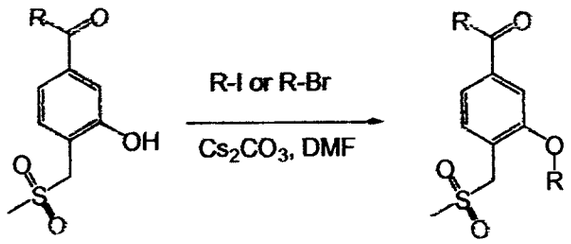
A mixture of epoxides (1.0 eq), thiophenol (1.5 eq) and neutral aluminum oxide (~70 eq) in diethyl ether was stirred for 3 h at room temperature while being monitored by TLC. The reaction mixture was filtered through Celite, washed with ethyl acetate and concentrated. Purified by silica gel chromatography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

T: Conversion of nitrile group to carboxylic acid



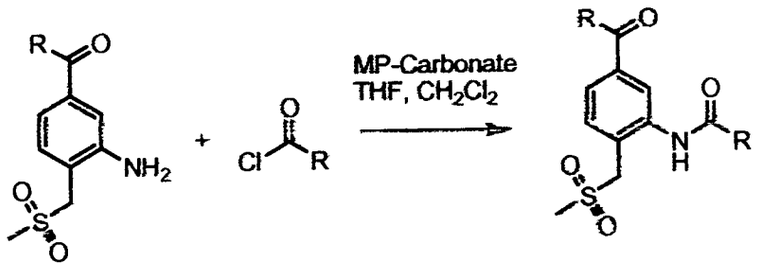
A solution of benzonitrile (1.0 eq) and sodium hydroxide (2.0 eq) in H_2O was heated to 120 °C for 2h. The reaction mixture was cooled to room temperature and acidified with HCl to pH 2. The resulting solid was filtered to afford the pure acid product.

U. Alkylation of phenols



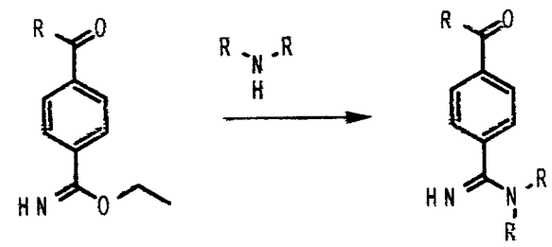
The phenol was dissolved in DMF (1.0 ml). Cesium carbonate (1.0 eq.) and an alkyl bromide or alkyl iodide (1.0 to 2.0 eq.) were added, and the reaction was stirred at room temperature for 18 hrs or 50°C for 1 to 24 hours. The reaction was quenched in water, and extracted with ethyl acetate twice. The 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



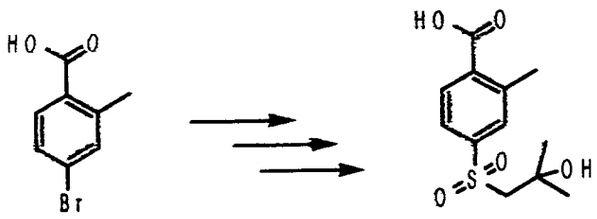
The aniline was dissolved in THF (1.5 ml) and dichloromethane (1.5 ml). MP-Carbonate (1.5 eq.) and an acid chloride (1.1 eq.) were added, and the solution was stirred at room temperature for 18 hours. The reaction was diluted with methanol and dichloromethane, and filtered to remove the MP-Carbonate.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

X. 4-(2-hydroxy-2-methylpropylsulfonyl)-2-methylbenzoic acid



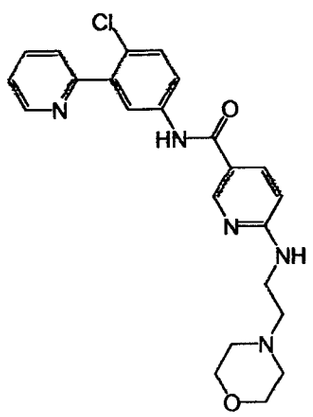
Step1. Preparation of methyl 4-bromo-2-methylbenzoate - A 1L 3 neck flask with mechanical stirrer, reflux condenser, internal temperature probe and a nitrogen bubbler was charged with 4-bromo-2-methylbenzoic acid (50.35 g, 1eq., Hongda) and methanol (350 mL). and the reactor contents were cooled to 0 °C. Acetyl chloride (27.6g, 1eq.) was slowly added at a rate which maintained an internal temperature of less than 30 °C. The reaction mixture was heated to reflux for 16 hours, until starting material was no longer detected by LC. Once reaction was complete, the reactor contents were cooled to room temperature and the reaction mixture was concentrated to an oil via rotary evaporator. The oil was then diluted with dichloromethane (100 mL) and washed with saturated sodium bicarbonate solution (100 mL). The organic layer was concentrated via rotary evaporator to afford methyl 4-bromo-2-methylbenzoate (51.22g, 95.5 %) as a yellow oil.

Step 2. 4-(2-hydroxy-2-methylpropylthio)-2-methylbenzoic acid - A 12 L 3 neck round bottom flask with mechanical stirrer, reflux condenser, internal temperature probe and a nitrogen bubbler was charge with methyl 4-bromo-2-methylbenzoate (500 g), toluene (4,000 mL), 2-ethylhexyl 3-mercaptopropanoate (715 g), and diisopropylethylamine (564 g). Reactor contents were degassed by repeating a cycle of vacuum/nitrogen 3 times. The reactor was then charged with $Pd_2(dba)_3$ (59.97 g), and Xantphos (63.15 g) and degassed by repeating a cycle of vacuum/nitrogen 1 time. Reactor contents were then heated to 95-100 °C for 16 hours, until starting material was no longer detected by LC. Once the reaction was complete, the reactor contents were cooled to 45 °C. The reactor was then charged with Florisil (1000 g) and the contents of reactor were stirred at 50 °C for 2 hours, until intermediate material was no longer detected by LC. Once reaction was complete, reactor contents were cooled to room temperature and filtered over celite pad. The filter cake was washed with ethyl acetate (4000 mL) and the filtrate was concentrated to an oil via rotary evaporator. The oil was then transferred back to the reactor with methanol (9000 mL) and the reactor was charged with sodium methoxide (327 g). (exothermic addition, ΔT~ 10 °C). Reactor contents were then heated to 50 °C for 1 hour, until intermediate material was no longer detected by LC. Reactor was then charged with 2,2-dimethyloxirane (236 g), (exothermic addition, ΔT~ 10 °C) and contents were continued heating at 50 °C for 1 hour, until intermediate material was no

longer detected by LC. Reactor was then charged with water (500 mL) and lithium hydroxide monohydrate (91 g) and then heated to 60 °C for 12 hours, until intermediate material was no longer detected by LC. Once reaction was complete, reactor contents were cooled to room temperature and concentrated to an oil via rotary evaporator followed by dilution with water (18 L), extraction with dichloromethane (2 x 4 L), washing aqueous fraction with heptane (2 x 4 L), acidifying aqueous fraction with conc. HCl (maintaining a temperature of less than 35 °C, and extracting with dichloromethane (2 x 16 L). Each organic fraction was washed with water (1 x 8L) and concentrated to dryness to obtain 4-(2-hydroxy-2-methylpropylthio)-2-methylbenzoic acid (472 g, 90 % yield) as a yellow solid.

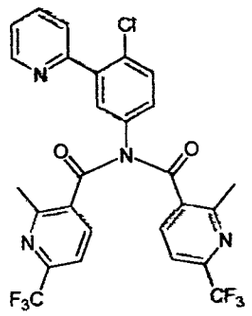
Step 3. Synthesis of 4-(2-hydroxy-2-methylpropylsulfonyl)-2-methylbenzoic acid - A 2000 mL reactor with mechanical stirrer, internal temperature probe and a nitrogen bubbler was charged with 4-(2-hydroxy-2-methylpropylthio)-2-methylbenzoic acid (52 g), methanol (370 mL), water (370 mL) and Oxone (146 g). (slight exotherm observed, ΔT ~15 °C) and stirred at room temperature for 18 hrs, until starting material was no longer present by LC. Methanol was removed via rotary evaporator and reactor contents were dissolved in 5% sodium bicarbonate solution (3L) and ethyl acetate (2L) was added followed by acidification with conc. HCl to pH 1. Organics were concentrated to dryness via rotary evaporator to obtain 4-(2-hydroxy-2-methylpropylsulfonyl)-2-methylbenzoic acid (52 g, 88 % yield, 96.47 area % by LC) as a white solid.

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

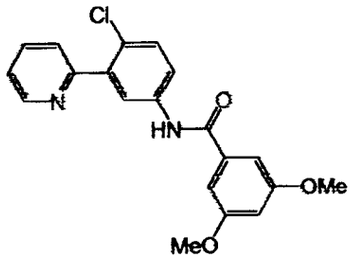


Procedure B was performed with 2-pyridylzinc bromide (4 mL, 2.0 mmol, 0.5 M in THF) and 3-bromo-4-chloro-nitrobenzene (236 mg, 1.0 mmol). Purified by chromatography on silica gel (10% ethyl acetate/hexanes) to yield 2-(2-chloro-5-nitrophenyl)pyridine as a light yellow solid.

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.

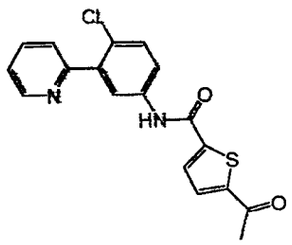
Procedure D was performed using 4-chloro-3-(pyridin-2-yl)aniline (40 mg, 0.2 mmol). The crude residue was purified by silica gel chromatography (15-60% ethyl acetate/hexanes) to yield *N,N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-bis[6-(trifluoromethyl)-2-methylpyridine-3]-carboxamide as an oily residue: TLC 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); ^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 $(M)^+$.

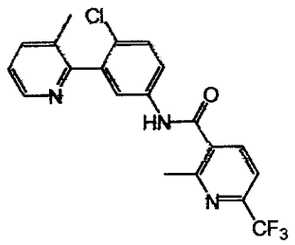
Example 5 5-Acetyl-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)thiophene-2-carboxamide



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.

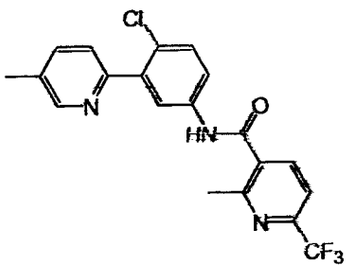
5-Acetyl-*N*-(4-chloro-3-iodophenyl)thiophene-2-carboxamide (202 mg, 0.5 mmol) was used in Procedure B with 2-pyridylzincbromide (2.5 mL, 1.25 mmol, 0.5 M in THF). Purified by silica gel chromatography (10-100% ethyl acetate/hexanes) to yield 5-acetyl-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)thiophene-2-carboxamide as a yellow solid: TLC R_f = 0.19 (50% ethyl acetate/hexanes); ^1H 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



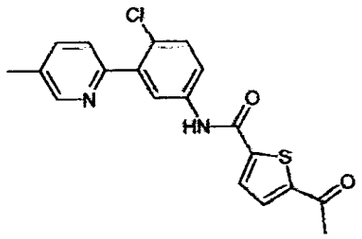
N-(4-Chloro-3-iodophenyl)-6-(trifluoromethyl)-2-methylpyridine-3-carboxamide (142 mg, 0.32 mmol) was used in Procedure B with 6-methyl-2-pyridylzinc bromide (1.75 mL, of a 0.5 M in THF). Purified by silica gel chromatography (5-100% Ethyl acetate/Hexanes) to yield *N*-(4-chloro-3-(3-methylpyridin-2-yl)phenyl)-6-(trifluoromethyl)-2-methylpyridine-3-carboxamide 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 $(M)^+$.

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



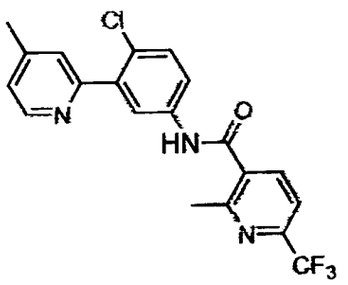
N-(4-Chloro-3-iodophenyl)-6-(trifluoromethyl)-2-methylpyridine-3-carboxamide (150 mg, 0.34 mmol) was used in Procedure B with 4-methyl-2-pyridylzinc bromide (1.7 mL of a 0.5 M in THF). Purified by silica gel chromatography (5-75% Ethyl acetate/Hexanes) to yield *N*-(4-chloro-3-(5-methylpyridin-2-yl)phenyl)-6-(trifluoromethyl)-2-methylpyridine-3-carboxamide 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



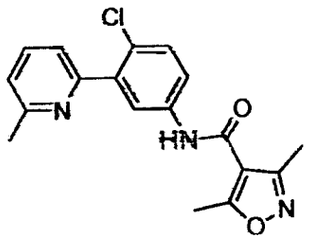
5-Acetyl-*N*-(4-chloro-3-iodophenyl)thiophene-2-carboxamide (203 mg, 0.5 mmol), was used in Procedure B with 4-methyl-2-pyridylzinc bromide (2.5 mL, 1.25 mmol, 0.5 M in THF). Purified by silica gel chromatography (30-100% ethyl acetate/hexanes) to yield 5-acetyl-*N*-(4-chloro-3-(5-methylpyridin-2-yl)phenyl)thiophene-2-carboxamide 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 $(M)^+$.

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 $(M)^+$.

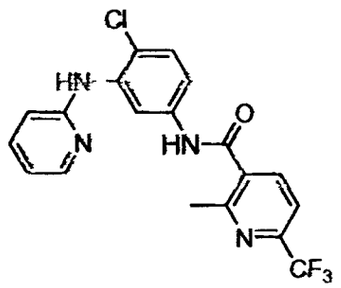
Example 10 *N*-(4-chloro-3-(6-methylpyridin-2-yl)phenyl)-3,5-dimethylisoxazole-4-carboxamide



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.

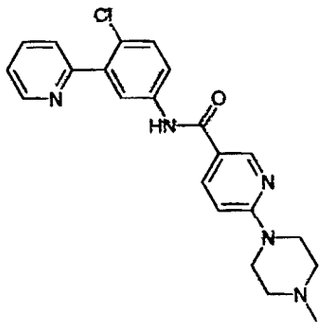
Procedure B was performed with 3,5-dimethyl-*N*-(4-chloro-3-iodophenyl)isoxazole-4-carboxamide (190 mg, 0.5 mmol) and 3-methyl-2-pyridylzinc bromide (2.5 mL of a 0.5 M solution in THF). The crude reaction was purified by silica gel chromatography (5-100% Ethyl acetate/Hexanes) to yield *N*-(4-chloro-3-(6-methylpyridin-2-yl)phenyl)-3,5-dimethylisoxazole-4-carboxamide 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 $(M)^+$.

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



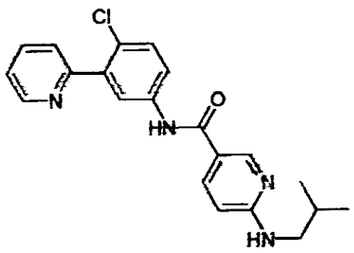
N-(4-Chloro-3-iodophenyl)-6-(trifluoromethyl)-2-methylpyridine-3-carboxamide (220 mg, 0.5 mmol), 2-aminopyridine (40 mg, 0.42 mmol), potassium *t*-butoxide (66 mg, 0.59 mmol), $Pd_2(dba)_3$ (20 mg, 0.21 mmol), dppf (24 mg, 0.042 mmol) in toluene (2.1 mL) were heated to 100 °C for 1.5 days. The solution 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



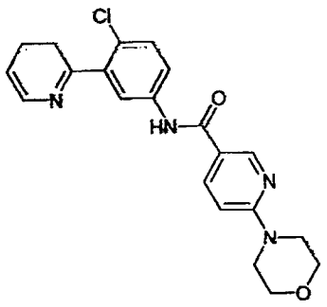
Procedure F was performed using *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-chloro-3-carboxamide (50 mg) and *N*-methylpiperazine in butanol (0.5 mL). The crude reaction was purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(4-methylpiperazin-1-yl)pyridine-3-carboxamide as a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

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



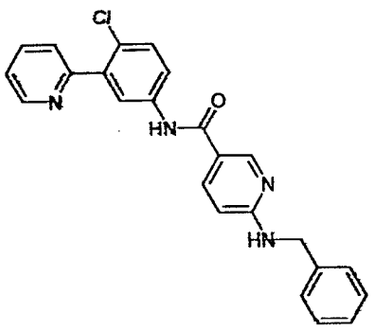
Procedure F was performed using *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-chloro-3-carboxamide (50 mg) and 2-methylpropylamine in butanol (0.5 mL). The crude reaction was purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(isobutylamino)pyridine-3-carboxamide as a white solid.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

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



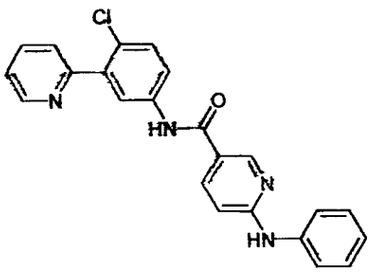
Procedure F was performed using *N* (1 chloro-3 (pyridin-2 yl)phenyl)-6-chloro-3-carboxamide (50 mg) and morpholine in butanol (0.5 mL). The crude reaction was purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-morpholinopyridine-3-carboxamide as a white solid. MS (Q1) 401.3 $(M)^+$.

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



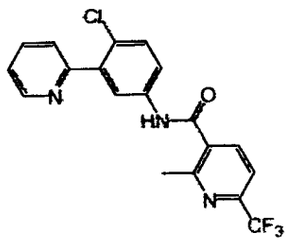
Procedure F was performed using *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-chloro-3-carboxamide (50 mg) and benzylamine in butanol (0.5 mL). The crude reaction was purified by reverse phase HPLC to yield 6-(benzylamino)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)pyridine-3-carboxamide as a white solid. MS (Q1)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

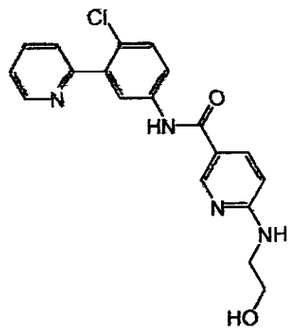
½ hr keeping the temperature below 15°C. The solution was stirred for 2 hr, then extracted with EtOAc (3 x 500 mL). The combined organic extracts were washed with sat. $Na_2S_2O_3$ (2x 500 mL), dried (Na_2SO_4), and concentrated. The crude iodide was dissolved in hot iPrOH (500 mL) and hexanes (200 mL) 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.

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.

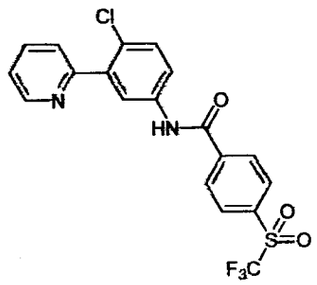
6-(trifluoromethyl)-2-methylpyridine-3-carbonyl chloride (1.68g, 7.51 mmol) in 3 mL THF was added dropwise to a solution of 4-chloro-3-(pyridine-2-yl)aniline (1.21g, 5.93 mmol) in THF (15 mL) at 0°C. The solution was stirred for 10 min., poured into EtOAc and washed with saturated aq. $NaHCO_3$ (2x), 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); ^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 $(M)^+$.

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 $(M)^+$.

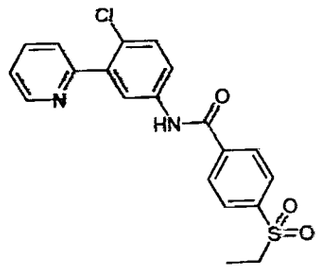
Example 19 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(trifluoromethylsulfonyl)benzamide



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 $(M)^+$.

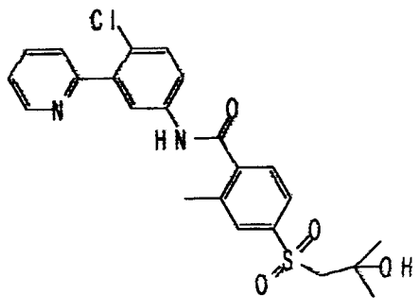
Example 20 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(ethylsulfonyl)benzamide



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 $(M)^+$.

N-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxy-2-methylpropylsulfonyl)-2-methylbenzamide



2-Chloro-5-nitroiodobenzene: The reactor used was purged with nitrogen and kept under nitrogen throughout the synthesis. Reactor was charged with USP purified water (400.0 L), agitated and charged with 2-chloro-5-nitroaniline (50.0 kg) and then the contents were cooled to 0 - 5 °C. To the stirring reactor was charged concentrated sulfuric acid (40.0 L), maintaining the temperature at

≤10 °C (addition time ~3-4 hr) and the contents were stirred at 0 - 5 °C for at least 15 minutes. In a separate vessel a solution of sodium nitrite (25.0 kg) and USP purified water (100.0L) was prepared. The sodium nitrite solution was slowly charged to the stirred reactor maintaining the temperature at ≤ 5 °C (exotherm and caused gas evolution, addition time ~2 hours) and then the contents were stirred at ≤ 5 °C for at least 1 hour. In a separate vessel a solution of potassium iodide (60.0 kg) and USP purified water (240.0 L) was prepared and slowly charged to the stirred reactor maintaining the temperature at ≤5 °C (exotherm, caused gas evolution and foaming, addition time ~7 hr). Cooling was turned off gradually allowing reaction to reach room temperature (~20 °C) and then the contents were stirred for at least 18 hours at 15 – 25 °C, and then sampled reaction mass by HPLC analysis (dissolved sample in acetonitrile), when ≤ 5% of 2-chloro-5-nitroaniline remained then continued to next step, however when the level of starting material was ≥ 5% then sampled every hour until the reaction was complete. In a separate vessel a solution of sodium thiosulfate (30.0 kg) and USP purified water (600.0 L) was prepared and slowly charged ~1/2 of the sodium thiosulfate solution to the stirred reactor, maintaining the temperature at 20 - 30 °C and then stirred reactor contents at 20 - 30 °C for at least 20 minutes. Cyclohexane (300.0 L) was charged to the reactor and the contents were heated to 55 - 60 °C and stirred for at least 20 minutes at 55 - 60 °C. Agitation was stopped to allow the layers to settle for at least 10 minutes and then were separated (setting aside organic layer) and returned the aqueous layer back into reactor. Cyclohexane (200.0 L) was charged to the reactor and stirred at 55 - 60 °C for at least 20 minutes and then agitation was stopped to allow the layers to settle for at least 10 minutes and then separating the layers (held aqueous layer for yield check) and combined both the organic layers from previous steps back into the reactor. The remaining ~1/2 of the sodium thiosulfate solution was charged to the stirred reactor, maintaining temperature at 55 - 60 °C and stirred for at least 20 minutes at 55 - 60 °C. Agitation was stopped to allow the layers to settle for at least 10 minutes and the the aqueous layer was drained from the reactor. USP purified water (300.0 L) was then charged to the reactor and stirred for at least 20 minutes at 55 - 60 °C and then agitation was stopped to allow the layers to settle for at least 10 minutes and the aqueous layer was drained to waste. The reactor contents were heated at ~45 °C and removed ~65% of the solvent by vacuum distillation. Reactor contents were then cooled to 0 - 5 °C and allowed to stir for at least 5 hours and then the solids were filtered and the product was washed with cold cyclohexane (100.0 L). The product was collected and dried in a hot air drier at 45 +/- 5 °C until LOD was ≤ 1.0%. The process yielded 50.0 kg (61 % yield) of 2-chloro-5-nitroiodobenzene as a yellow solid.

Crude 2-(2-pyridyl)-4-nitrochlorobenzene: Reactor was purged with nitrogen and kept under nitrogen throughout the synthesis. Toluene (375.0 L) was charged to the reactor and agitation was

begun and zinc chloride (19.56 kg) was charged to the reactor. Using atmospheric distillation reactor contents was stripped to ~50% of the original volume and then cooled to ≤ 30 °C. THF (100.0 L) was slowly charged to the reactor (addition was exothermic).

Preparation of Grignard reagent in reactor 2: Reactor was purged with nitrogen and kept under nitrogen throughout the synthesis. Agitation was begun and THF (50.0 L) was charged to reactor. Isopropyl magnesium chloride (89.0 kg, adjusted after titration) was drum rolled to mix and then was slowly added, maintaining the temperature at ≤ 30 (exothermic, addition time 30-40 min). 2-bromopyridine (22.3 kg) was slowly charged to the reactor maintaining the temperature at ≤ 30 oC (exothermic, addition time 50-60 min). The reactor contents were then heated to 50 +/- 5 °C and maintained for at least 1 hour. The Grignard solution (from Reactor 2) was slowly charged to the reactor (from earlier step) maintaining the temperature at ≤ 55 °C (exothermic addition caused foaming, addition time ~20 min). The reactor was then stirred at 50 +/- 5 °C at least 1 hour while maintaining the temperature. Dichlorobistriphenylphosphine palladium (2.0 kg) was charged to the reactor and stirred for ~15 minutes. Triphenylphosphine (2.75 kg) was charged to the reactor and stirred for ~15 minutes. 2-chloro-5-nitroiodobenzene (25.0 kg) was slowly charged to the stirred reactor (15 minute addition time). The reactor contents were heated to 60 +/- 5 °C and stirred for at least 14 hours at 60 +/- 5 °C, then sampled the reaction mass for HPLC analysis. When amount of starting material was ≥ 4% continued heating and sampled again every hour until the level of starting material fell below 4%. The reaction mixture was cooled to ~55 °C and then the reactor contents were heated to reflux under vacuum and 75-90 L of solvent was removed. Toluene (120.0 L) was charged to the reactor while stirring. In a separate tank, the ammonium chloride (25.0 kg) was dissolved in USP purified water (250.0 L) and the solution was slowly charged into the reactor and stir for at least 30 minutes. The mixture was filtered through a Nutsche filter (prepared with Celite (6.25 kg) and USP purified water (12.5 L)) and the filter cake was washed with toluene (75.0 L) and the filtrate was added and washed into a clean reactor. The layers were allowed to settle for at least 10 minutes and then separated (organic layer contained product) and returned the aqueous layer to the reactor. Toluene (75.0 L) was charged to the reactor and stirred for at least 15 minutes and then the layers were allowed to settle for at least 10 minutes before separating (organic layer contained product). The organic layers from previous steps were charged to a clean reactor. USP purified water (125.0 L) was charged to the reactor and stir for at least 15 minutes and then the layers were allowed to settle for at least 10 minutes before draining the aqueous layer and holding for yield check.

In a separate tank, a 3N hydrochloric acid solution was prepared by mixing concentrated hydrochloric acid (127.5 L) and USP purified water (272.5 L). Approximately 1/3 of the 3N

hydrochloric acid (133.3 L) was charged to the reactor and stir for at least 30 minutes. The layers were allowed to settle for at least 15 minutes and then the aqueous layer was drained and transferred to a separate vessel (product was in aqueous layer). Approximately 1/3 of the 3N hydrochloric acid (133.3 L) was charged to the reactor and stirred for at least 30 minutes. The layers were allowed to settle for at least 15 minutes and then the aqueous layer was drained and transferred to a separate vessel (product was in aqueous layer). Aproximately 1/3 of the 3N hydrochloric acid (133.3 L) was charged to the reactor and stirred for at least 30 minutes. The layers were allowed to settle for at least 15 minutes and then the aqueous layer was drained and transferred to a separate vessel (product was in aqueous layer). The aqueous layers from previous steps were transferred into a clean reactor to which was charged activated carbon (1.0 kg) and then heated to 50 +/- °C and stirred for at least 30 minutes. The mixture was filtered through a Nutsche filter (prepared with Celite (5.0 kg) and USP purified water (12.5 L)) and the filter cake was washed with 3N hydrochloric acid (40.0 L) and the filtrate was added and washed into a clean reactor. The combined aqueous solutions were polish filtered through a 1 micron filter into a clean reactor and cooled to ≤ 10 °C. Ammonium hydroxide (115.0 L) was slowly charged to the reactor, adjusting the pH to between 8.5 and 9.0 (addition time 4.25 hours). The reaction temperature was adjusted to 25-30 °C and the mixture was allowed to stir for 30 minutes. Reaction mixture was then centrifuged and the product washed with USP purified water (300.0 L) and dried in a hot air dryer at 50 - 60 °C. Process yielded 15.0 kg (72%) of crude 2-(2-pyridyl)-4-nitrochlorobenzene.

Purification of 2-(2-pyridyl)-4-nitrochlorobenzene - The reactor was purged with nitrogen and kept under nitrogen throughout the synthesis. Dichloromethane (400.0 L) was charged to the reactor and stirring was begun. Crude 2-(2-pyridyl)-4-nitrochlorobenzene (40.0 kg) was charged to the reactor and stirred at 20 - 30 °C for at least 30 minutes and checked to see if all solids were dissolved. Silica gel (20.0 kg) was charged to the reactor and stirred for at least 2 hours. The mixture was filtered through a Nutsche filter (prepared with Celite (14.8 kg) and dichloromethane (14.8 L)) and the filter cake was washed with dichloromethane (80.0 L) and the filtrate was added and washed into a clean reactor. The reactor contents were heated to reflux under vacuum and 80-90% of the solvent was removed and the cooled to 20 - 30 °C and then n-hexane (240.0 L) was charged to the reactor which was stirred for at least 2 hours at 20 - 30 °C. The reaction mixture was filted and washed with n-hexane (80.0 L) and the product dried in a hot air dryer at 50 - 55 °C. Process yields 34.5 kg (86% recovery) of 2-(2-pyridyl)-4-nitrochlorobenzene as a beige solid.

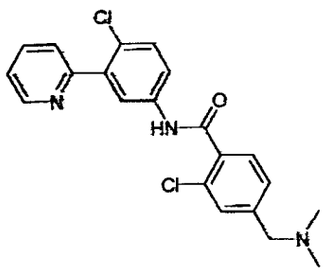
4-chloro-3-(pyridin-2-yl)aniline: 2-(2-pyridyl)-4-nitrochlorobenzene was charged to a suitably sized reactor under nitrogen. Platinum on carbon (5%, ~50% wet) (0.10 wt) was added with stirring, followed by tetrahydrofuran (9.68 wt). The reactor was pressurized with nitrogen to 40psi, then the pressure was released. This process was repeated two additional times. The reactor was then pressurized with hydrogen to 50psi while maintaining the internal temperature at 20-26°C. After the hydrogen uptake subsided (1-2 hours), the pressure was held at 50psi and the reactor was heated to 50°C for 2-3 hours. The reaction was checked by HPLC and once complete, cooled to 30°C. Next, the reactor was pressurized with nitrogen to 40psi, then the pressure was released. This process was repeated two additional times. To a separate tank, Celite (0.1 wt) and tetrahydrofuran (0.9 wt) were added. This slurry was then transferred to the reactor and stirred for a minimum of 30 minutes. The reaction mixture was filtered through a filter press and 0.2 micron filter, the cake was washed with tetrahydrofuran (2.2 wt) and all the organics were combined. Thiol silica gel (0.05 wt) was charged to the reactor and stirred for at least 30 minutes. This mixture was then filtered through a filter press into an adjacent, nitrogen purged, reactor. The filter cake was washed with tetrahyrdofuran (2.2 wt) and the wash was added back to the reactor. With stirring, heptanes (6.8 wt) were added to the reactor and the contents were heated to reflux under vacuum. Approximately two thirds of the solvent was removed by vacuum distillation. The reactor was cooled to 20-26°C and stirred for 2-3 hours. The reactor contents were centrifuged and washed with heptanes (1.0 wt) and dried in a vacuum oven at 20-25°C until a constant weight of 4-chloro-3-(pyridin-2-yl)aniline was obtained (typical yield ~80%).

N-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(ethylsulfonyl)benzamide - Tetrahydrofuran (10.24 wt) was charged to a suitably sized reactor under nitrogen. While stirring, 4-(2-hydroxy-2-methylpropylsulfonyl)-2-methylbenzoic acid (1.265 wt) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (0.815 wt) were added and stirred until dissolved. 4-methylmorpholine (0.564 wt) was slowly charged to the reactor while maintaining the internal temperature at ≤ 30°C. The mixture was allowed to stir at room temperature for at least 30 minutes then sampled by TLC. Once all of the 4-(2-hydroxy-2-methylpropylsulfonyl)-2-methylbenzoic acid was consumed, 4-chloro-3-(pyridin-2-yl)aniline (1.0 wt) was added. The reactor was heated to 50°C and stirred for at least 6 hours, at which time the reaction was sampled by HPLC. Once the reaction was complete by HPLC, a sodium bicarbonate solution (sodium bicarbonate (0.506 wt) and USP purified water (24.8 wt), stirred until all solids were dissolved) was added to the reaction. The reaction mixture wa heated to reflux (~70°C) and solvent (5.7 wt.) was distilled from the reactor. The reactor was cooled to ≤ 30°C and stirred for at least 20 hours. The reactor contents were centrifuged, washed with USP

purified water (3.47 wt) and dried in a vacuum oven at 45 °C until a constant weight of crude *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(ethylsulfonyl)benzamide was obtained (typical yield ~90%).

Methyl isobutyl ketone (20.0 wt) was charged to a suitably sized reactor under nitrogen. While stirring, crude *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(ethylsulfonyl)benzamide (1.0 wt) was added and the reactor was heated to 60 °C and stirred for at least one hour. The solution was polish filtered through a filter press into an adjacent, nitrogen purged, reactor and the cake was washed with methyl isobutyl ketone (2.56 wt.). The filtered solution was then heated to reflux (~115 °C) and distilled to remove ~2/3 of the solvent (~14.5 wt). The reactor was cooled to 100 °C and stirred for at least 15 minutes. The reactor was then cooled to 80 °C and the tip speed of the agitator was set to 2.0 m/s. A seed slurry was prepared by mixing *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(ethylsulfonyl)benzamide Form A (0.001 wt) and methyl isobutyl ketone (0.008 wt). This seed slurry was added to the reactor at 80 °C and stirred for at least 2.5 hours. The bath temperature was set to 70 °C and the contents were stirred until the internal temperature reached 70 °C. The bath temperature was set to 50 °C and the contents wee stirred until the internal temperature reached 50 °C. The bath temperature was set to 25 °C and the contents were stirred until the internal temperature reached 15-30 °C. Once this temperature was obtained, the mixture wa stirred for at least 12 hours. In a separate tank, a solution was prepared by charging methyl isobutyl ketone (3.0 wt) and heptanes (2.6 wt). The reactor contents were centrifuged, washed with the methyl isobutyl ketone/heptanes mixture (all) and dried in a vacuum oven at 60 °C until a constant weight of purified *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(ethylsulfonyl)benzamide was obtained. The solids were milled using a Fitzmill grinder utilizing an 18 mesh screen, hammers forward on low speed. (typical yield ~80%).

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

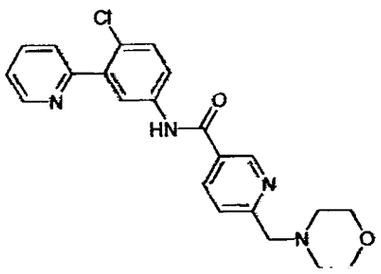


General procedure G was used to couple 4-(BOC-aminomethyl)-2-chloro-benzoic acid and 4-chloro-3-(pyridin-2-yl)aniline to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)-phenyl)-4-(BOC-

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

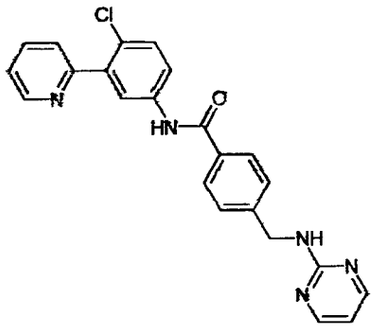


6-methylnicotinic acid (100 mg 0.14 mmol) was dissolved in 10% AcOH/benzene (1 mL) and treated with NBS (117 mg, 0.18 mmol) and benzoylperoxide (18 mg, 0.07 mmol). The reaction mixture was heated in a sealed microwave reactor at 120° C for 1 min. The reaction mixture was diluted with ethyl acetate, washed 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 $(M)^+$.

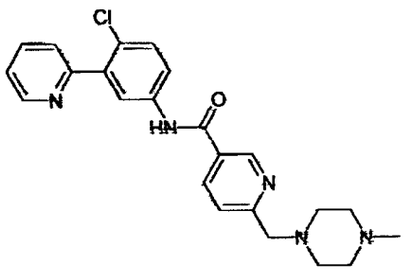
Example 23 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((pyrimidin-2-ylamino)methyl)benzamide



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.

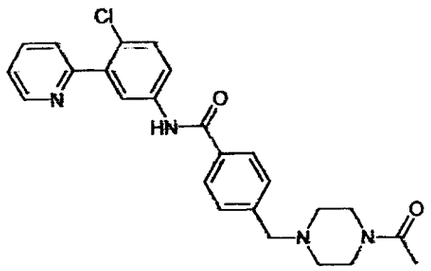
4-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide (85 mg) was dissolved in DMSO (0.5 mL) and treated with 2-aminopyridine (59 mg) at 150° C in a sealed microwave reactor for 5 min. The reaction mixture was concentrated, and the crude residue was purified by reverse phase HPLC to produce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



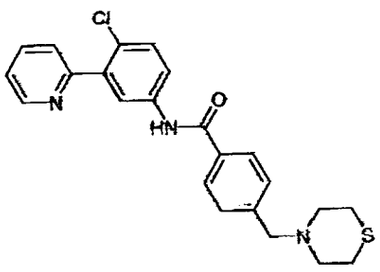
6-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)pyridine-3-carboxamide was dissolved in 1 mL of DMSO and stirred for 1 h with *N*-methylpiperazine. The reaction was concentrated, and the crude residue was purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-((4-methylpiperazin-1-yl)methyl)pyridine-3-carboxamide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



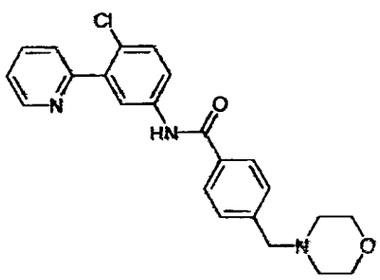
6-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)pyridine-3-carboxamide (85 mg) was dissolved in DMSO (1 mL) and stirred for 1 h with N-acetylpiperazine. The reaction mixture was concentrated, and the crude residue was purified by revered phase HPLC to yield 4-((4-acetylpiperazin-1-yl)methyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)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

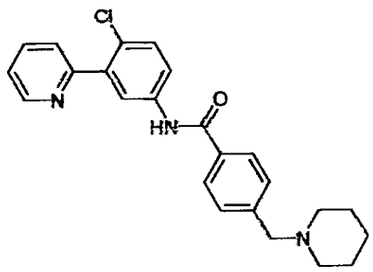
Example 27 *N*-(4-chloro-3-(pyridin-2-yl)phenyl) 4-(morpholinomethyl)benzamide



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

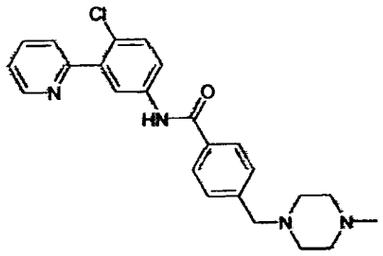
residue was purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(morpholinomethyl)benzamide. MS (Q1) 408.4 $(M)^+$.

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



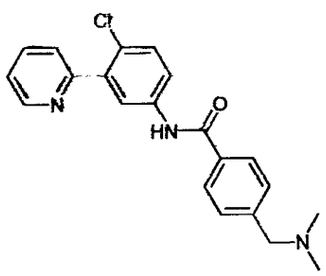
4-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide (85 mg) was dissolved in DMSO (1 mL) and stirred for 1 h with piperdine. The reaction mixture was concentrated, and the crude residue was purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((piperidin-1-yl)methyl)benzamide.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

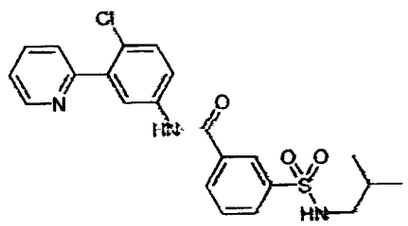
Example 30 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((dimethylamino)methyl)benzamide



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 $(M)^+$.

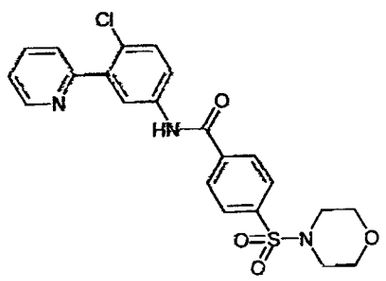
Example 31 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-[(2-methylpropyl)aminosulfonyl]-benzamide



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

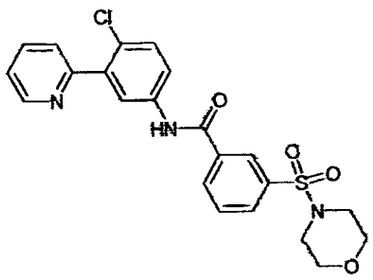


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Procedure H was performed to couple 4-(chlorosulfonyl)benzoic acid with morpholine to produce 4-(morpholinosulfamoyl)benzoic acid which was purified by reverse phase HPLC.

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 $(M)^+$.

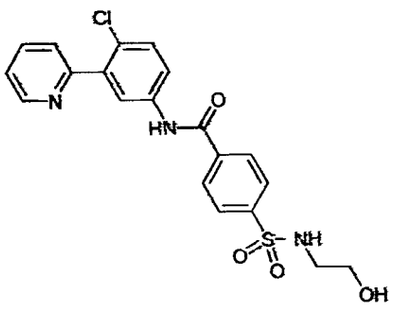
Example 33 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-(4-morpholinylsulfonyl)-benzamide



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.

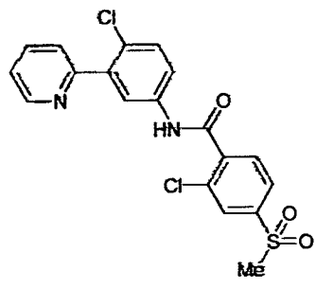
Procedure G was used to couple 3-(morpholinosulfamoyl)benzoic acid with 4-chloro-3-(pyridin-2-yl)aniline (25 mg) to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-(4-morpholinylsulfonyl)-benzamide. MS (Q1) 458.1 $(M)^+$.

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.

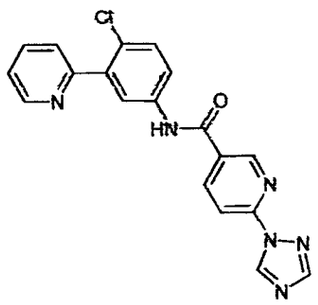
Example 37 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide



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.

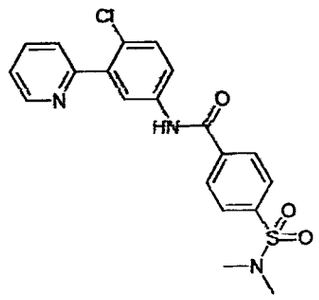
Procedure D may also be used to couple 4-chloro-3-(pyridin-2-yl)aniline and 2-chloro-4-(methylsulfonyl)benzoyl chloride to produce 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide which is collected by suction filtration and the HCl salt is washed with Et_2O (or alternatively 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



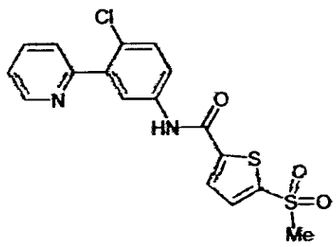
Procedure G was used to couple 4-chloro-3-(pyridin-2-yl)aniline (40 mg) and 6-(1*H*-1,2,4-triazol-1-yl)pyridine-3-carboxylic acid to produce *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(1*H*-1,2,4-triazol-1-yl)pyridine-3-carboxamide. MS (Q1) 377.0 $(M)^+$.

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



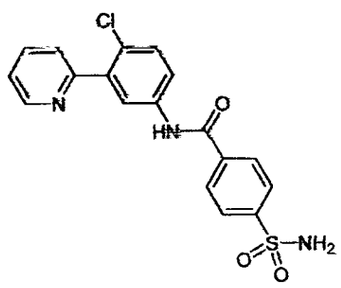
Procedure G was used to couple 4-chloro-3-(pyridin-2-yl)aniline (50 mg) and 4-[(dimethylamino)sulfonyl]benzoic acid to produce N-(4-chloro-3-(pyridin-2-yl)phenyl)-4-[(dimethylamino)sulfonyl]-benzamide. MS (Q1) 416.0 $(M)^+$.

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



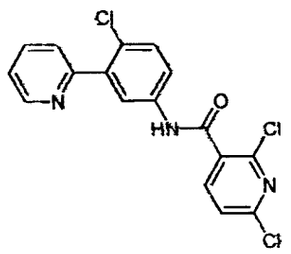
Procedure G was used to couple 4-chloro-3-(pyridin-2-yl)aniline (40 mg) and 5-(methylsulfonyl)thiophene-2-carboxylic acid to produce *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-5-(methylsulfonyl)thiophene-2-carboxamide. MS (Q1) 393.0 $(M)^+$.

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



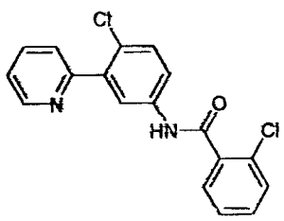
Procedure G was used to couple 4-chloro-3-(pyridin-2-yl)aniline (30 mg) and 4-carboxybenzenesulfonamide to produce *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(aminosulfonyl)-benzamide. MS (Q1) 388.0 $(M)^+$.

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



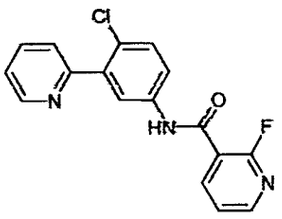
Procedure G was used to couple 4-chloro-3-(pyridin-2-yl)aniline (50 mg) and 2,6-dichloronicotinic acid to produce 2,6-dichloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)pyridine-3-carboxamide. MS (Q1) 378.1 $(M)^+$.

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



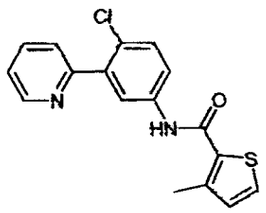
Procedure G was used to couple 4-chloro-3-(pyridin-2-yl)aniline (50 mg) and 2-chlorobenzoic acid to produce 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide. MS (Q1) 343.1 $(M)^+$.

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



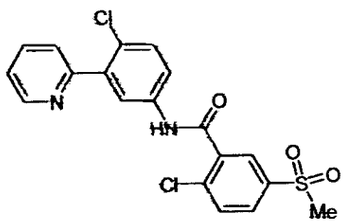
Procedure G was used to couple 4-chloro-3-(pyridin-2-yl)aniline (50 mg) and 2-fluoronicotinic acid to produce *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-fluoropyridine-3-carboxamide. MS (Q1) 328.1 $(M)^+$.

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



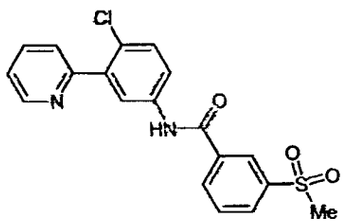
Procedure G was used to couple 4-chloro-3-(pyridin-2-yl)aniline (50 mg) and 3-methyl-2-thiophenecarboxylic acid to produce *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-methylthiophene-2-carboxamide. MS (Q1) 329.0 $(M)^+$.

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



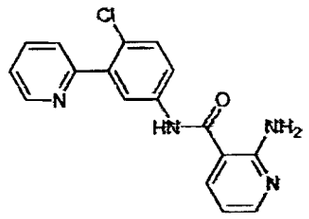
Procedure G was used to couple 4-chloro-3-(pyridin-2-yl)aniline and 2-chloro-5-(methanesulfonyl)benzoic acid to produce 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-5-(methylsulfonyl)benzamide. MS (Q1) 420.95 $(M)^+$.

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



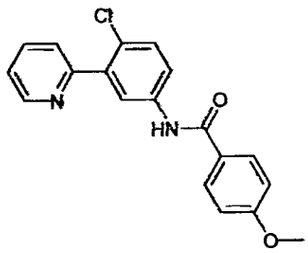
Procedure G was used to couple 4-chloro-3-(pyridin-2-yl)aniline and 3-(methanesulfonyl)benzoic acid to produce *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-(methylsulfonyl)benzamide. MS (Q1) 387.2 $(M)^+$.

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



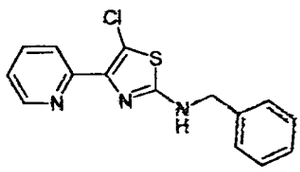
Procedure G was used to couple 4-chloro-3-(pyridin-2-yl)aniline (50 mg) and 2-aminonicotinic acid to produce 2-amino-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)pyridine-3-carboxamide. MS (Q1) 325.2 $(M)^+$.

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)phenyl)-4-methoxybenzamide. MS (Q1) 341.2 $(M)^+$.

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

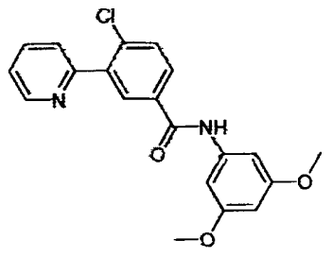


A solution of 2-(Bromoacetyl)pyridine hydrobromide (100 mg, 0.36 mmol) in ethanol (2 mL) was treated with 1-benzyl-2-thiourea (90 mg, 0.54 mmol). The resulting yellow solution was

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 $(M)^+$.

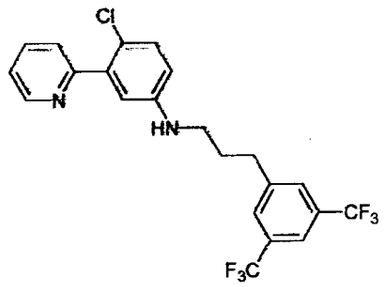
Example 51 4-chloro-*N*-(3,5-dimethoxyphenyl)-3-(pyridin-2-yl)benzamide



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



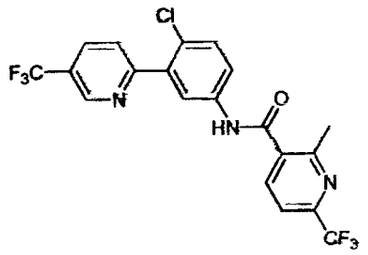
A solution of 3,5-bis(trifluoromethyl)hydrocinnamic acid (1.0 g, 3.5 mmol) and TEA (0.46 g, 4.5 mmol) in THF (16 mL) was cooled to –40°C (ethanol-water/dry ice bath). To this mixture was dropwise added isobutyl chloroformate (0.56 g, 4.1 mmol) and stirring was continued for another 1.5 hours while the 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.

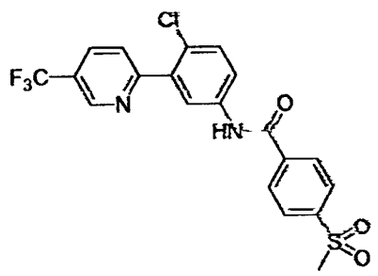
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Example 53 *N*-(4-chloro-3-(5-(trifluoromethyl)pyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide



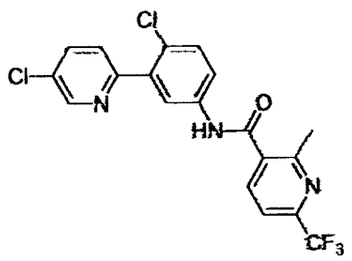
N-(4-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide (~ 0.5 mmol) was used in Procedure A with 5-trifluoromethyl-2-bromopyridine (113 mg, 0.5 mmol). Purified by silica gel chromatography (5-50% ethyl acetate/hexanes) to yield *N*-(4-chloro-3-(5-(trifluoromethyl)pyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)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



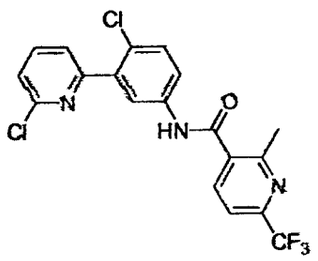
N-(4-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-(methylsulfonyl)benzamide (~ 1.0 mmol) was used in Procedure A with 5-trifluoromethyl-2-bromopyridine (226 mg, 1 mmol). Purified by silica gel chromatography (0-10% acetone/dichloromethane) to yield *N*-(4-chloro-3-(5-(trifluoromethyl)pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide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

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



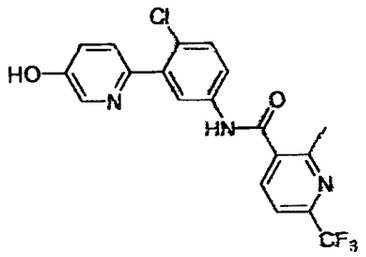
5-chloropyridin-2-yl trifluoromethanesulfonate (4.12 mmol) was used in Procedure I with trimethyltin chloride to yield 5-chloro-2-(trimethylstannyl)pyridine. The crude material (~4 mmol) was used in Procedure K with *N*-(4-chloro-3-iodophenyl)-2-methyl-6-(trifluoromethyl)nicotinamide (2 mmol). Purified 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



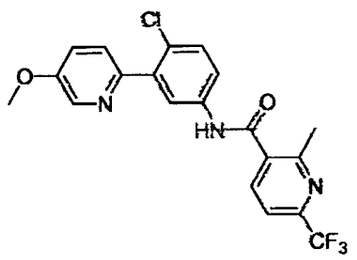
6-chloropyridin-2-yl trifluoromethanesulfonate (4.12 mmol) was used in Procedure I with trimethyltin chloride to yield 2-chloro-6-(trimethylstannyl)pyridine. The crude material (~4 mmol) was used in Procedure K with *N*-(4-chloro-3-iodophenyl)-2-methyl-6-(trifluoromethyl)nicotinamide (2 mmol). Purified 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



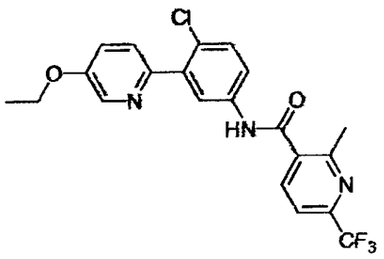
3-(triisopropylsilyloxy)pyridine (2.66 mmol) was used in Procedure J with hexamethyldistannane to yield 5-(triisopropylsilyloxy)-2-(trimethylstannyl)pyridine. The crude material (~0.55 mmol) was used in Procedure K with *N*-(4-chloro-3-iodophenyl)-2-methyl-6-(trifluoromethyl)nicotinamide (0.17 mmol). 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



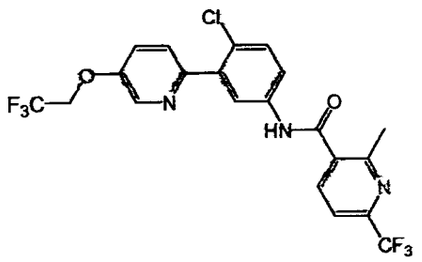
N-(4-chloro-3-(5-hydroxypyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide (0.12 mmol) was used in Procedure L with excess iodomethane. Purified by silica gel chromatography (0-100% ethyl acetate/hexane) to yield *N*-(4-chloro-3-(5-methoxypyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide 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



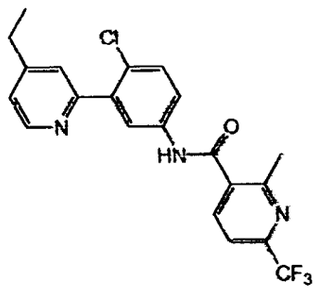
N-(4-chloro-3-(5-hydroxypyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide (0.05 mmol) was used in Procedure L with excess iodoethane. Purified by silica gel chromatography (0-100% ethyl acetate/hexane) to yield *N*-(4-chloro-3-(5-ethoxypyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide 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



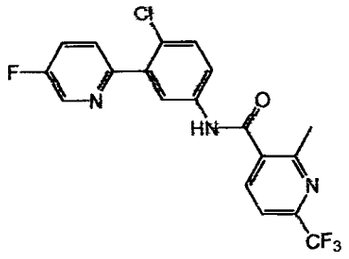
N-(4-chloro-3-(5-hydroxypyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide (0.12 mmol) was used in Procedure L with excess trifluoroethyl iodide. Purified by silica gel chromatography (0-40% ethyl acetate/hexane) to yield *N*-(4-chloro-3-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide 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



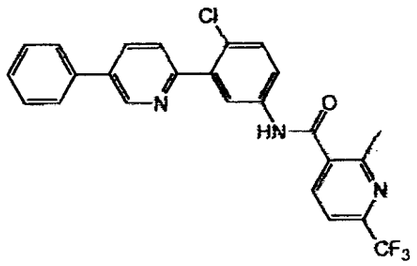
N-(4-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide (~ 1 mmol) was used in Procedure A with 4-ethyl-2-bromopyridine (1 mmol). Purified by silica gel chromatography (0-60% ethyl acetate/hexanes) to yield *N*-(4-chloro-3-(4-ethylpyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide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

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



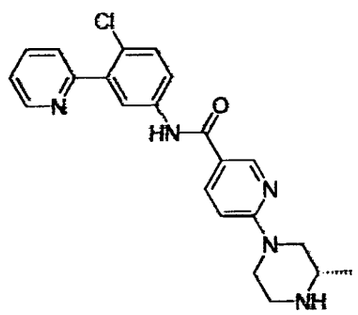
N-(4-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide (~ 1 mmol) was used in Procedure A with 5-fluoro-2-bromopyridine (1 mmol). Purified by silica gel chromatography (5-45% ethyl acetate/hexanes) to yield *N*-(4-chloro-3-(5-fluoropyridin-2-yl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide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

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



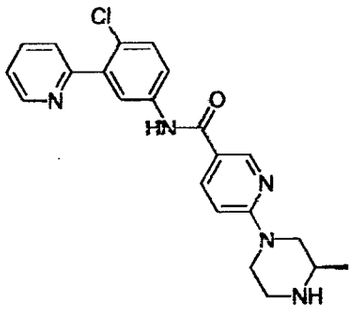
5-phenylpyridin-2-yl trifluoromethanesulfonate (1.5 mmol) was used in Procedure J with trimethyltin chloride to yield 5-phenyl-2-(trimethylstannyl)pyridine. The crude material (~1.25 mmol) was used in Procedure K with *N*-(4-chloro-3-iodophenyl)-2-methyl-6-(trifluoromethyl)nicotinamide (1 mmol). Purified 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



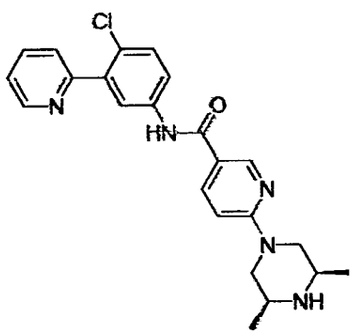
Procedure F was performed using N-(4-chloro-3-(pyridin-2-yl)phenyl)-6-chloro-3-carboxamide (50 mg) and 75 mg of (S)-2-methylpiperazine in 0.75 mL of butanol at 160°C for 60 min. Purification by reverse phase HPLC yielded (*S*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(3-methylpiperazin-1-yl)nicotinamide.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

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



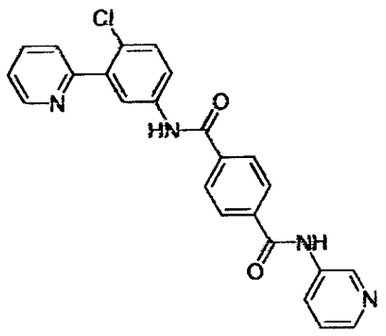
Procedure F was performed using N-(4-chloro-3-(pyridin-2-yl)phenyl)-6-chloro-3-carboxamide (50 mg) and 75 mg of (R)-2-methylpiperazine in 0.75 mL of butanol at 160°C for 60 min. Purification by reverse phase HPLC yielded (*R*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(3-methylpiperazin-1-yl)nicotinamide.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



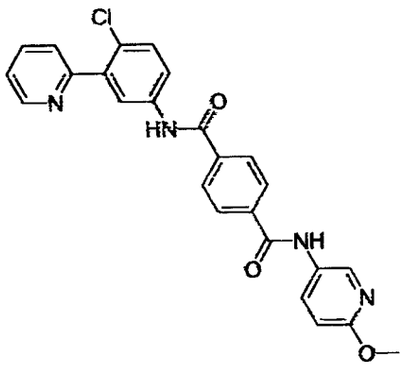
Procedure F was performed using N-(4-chloro-3-(pyridin-2-yl)phenyl)-6-chloro-3-carboxamide (75 mg) and 114 mg of 2,6-dimethylpiperazine in 1 mL of butanol at 160°C for 60 min. Purification by reverse phase HPLC yielded *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-((3*S*,5*R*)-3,5-dimethylpiperazin-1-yl)nicotinamide.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

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



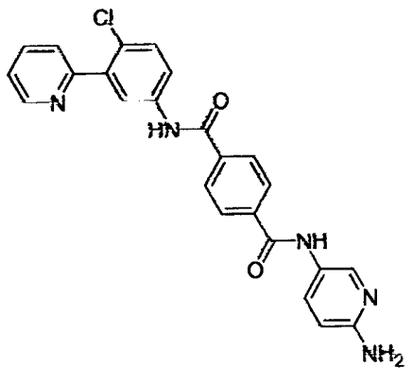
320 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 400 mg of 4-(methoxycarbonyl)benzoic acid via Procedure G to give methyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoate. 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoate was then hydrolyzed via Prodedure M to give 550 mg of 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic 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



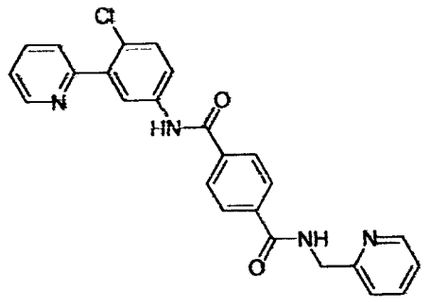
50 mg of 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 2-methoxy-5-aminopyridine via Procedure G. The product was purified on reverse phase HPLC to yield N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(6-methoxypyridin-3-yl)terephthalamide. MS (Q1) 459 $(M)^+$.

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



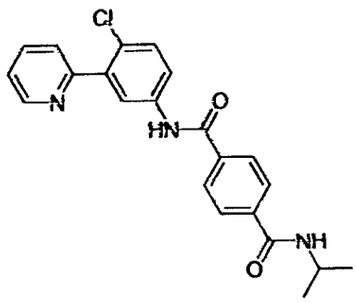
50 mg of 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 2,5-diaminopyridine via Procedure G. The product was purified on reverse phase HPLC to yield N^1-(6-aminopyridin-3-yl)-N^4-(4-chloro-3-(pyridin-2-yl)phenyl)terephthalamide. MS (Q1) 444 $(M)^+$.

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



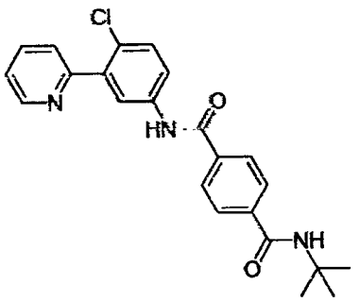
50 mg of 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 2-(aminomethyl)pyridine via Procedure G. The product was purified on reverse phase HPLC to yield N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(pyridin-2-ylmethyl)terephthalamide. MS (Q1) 443 $(M)^+$.

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



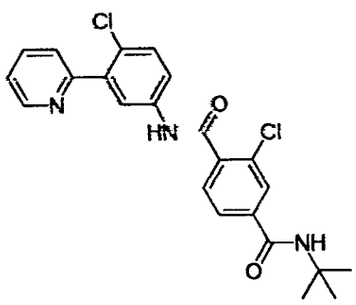
50 mg of 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to isopropylamine via Procedure G. The product was purified on reverse phase HPLC to yield N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-isopropylterephthalamide. MS (Q1) 394 $(M)^+$.

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



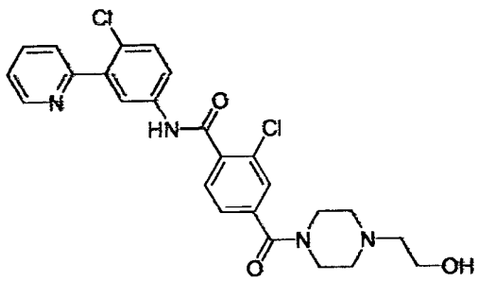
50 mg of 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to *tert*-butylamine via Procedure G. The product was purified on reverse phase HPLC to yield N^1-*tert*-butyl-N^4-(4-chloro-3-(pyridin-2-yl)phenyl)terephthalamide. MS (Q1) 408 $(M)^+$.

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



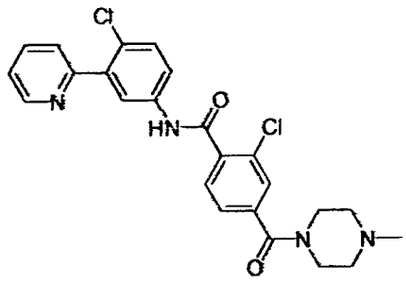
67 mL of 2-chloro-1,4-dimethylbenzene and 356 g of Potassium Permanganate were refluxed in 1.5 L of H_2O for several hours and monitored for disappearance of starting material by TLC. The Potassium Permanganate was filtered and the reaction mixture was acidified and filtered to yield 2-chloroterephthalic 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



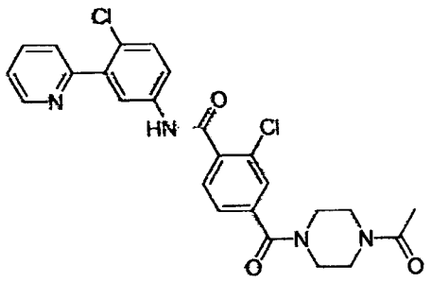
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to N-(2-hydroxyethyl)piperazine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(4-(2-hydroxyethyl)piperazine-1-carbonyl)benzamide. MS (Q1)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

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



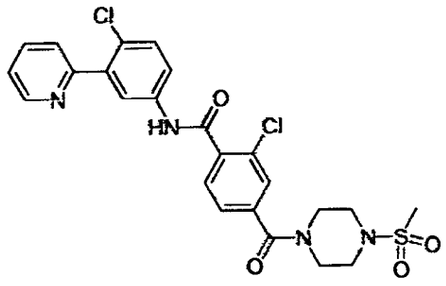
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 1-methylpiperazine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(4-methylpiperazine-1-carbonyl)benzamide. MS (Q1) 469 $(M)^+$.

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



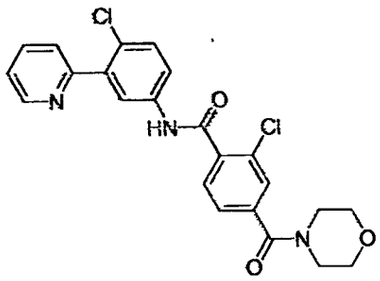
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 1-acetylpiperazine via Procedure G. The product was purified on reverse phase HPLC to yield 4-(4-acetylpiperazine-1-carbonyl)-2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide. MS (Q1) 497 $(M)^+$.

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



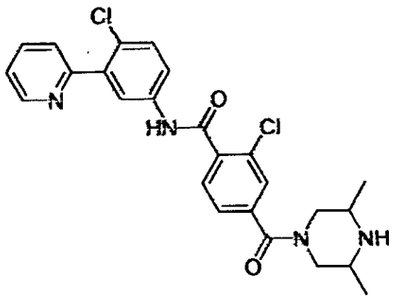
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 1-sulfonylpiperazine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(4-(methylsulfonyl)piperazine-1-carbonyl)benzamide. MS (Q1) 533 $(M)^+$.

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



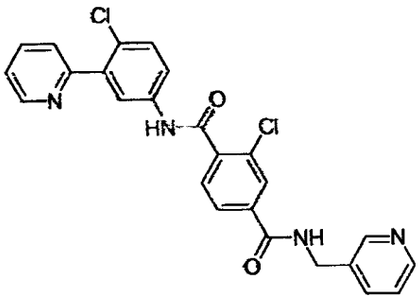
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to morpholine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(morpholine-4-carbonyl)benzamide. MS (Q1) 456 $(M)^+$.

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



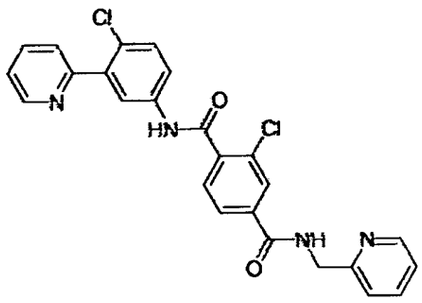
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 2,6-dimethylpiperazine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(3,5-dimethylpiperazine-1-carbonyl)benzamide. MS (Q1) 483 $(M)^+$.

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



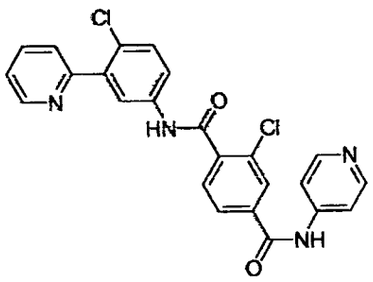
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 3-(aminomethyl)pyridine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(pyridin-3-ylmethyl)terephthalamide. MS (Q1) 477 $(M)^+$.

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



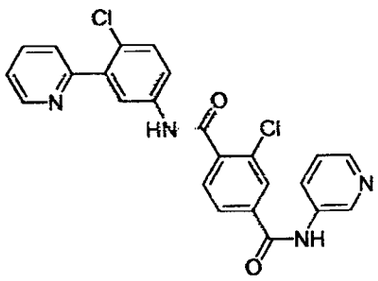
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 2-(aminomethyl)pyridine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(pyridin-2-ylmethyl)terephthalamide. MS (Q1) 477 $(M)^+$.

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



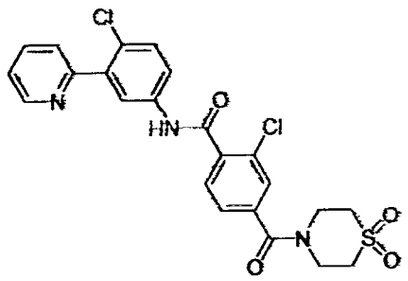
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 4-aminopyridine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(pyridin-4-yl)terephthalamide. MS (Q1) 463 $(M)^+$.

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



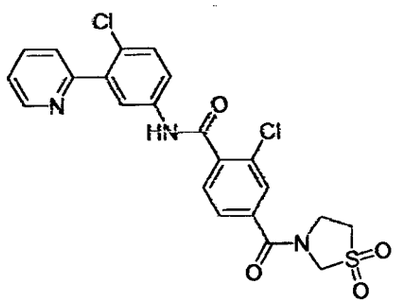
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 3-aminopyridine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(pyridin-3-yl)terephthalamide. MS (Q1) 463 $(M)^+$.

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



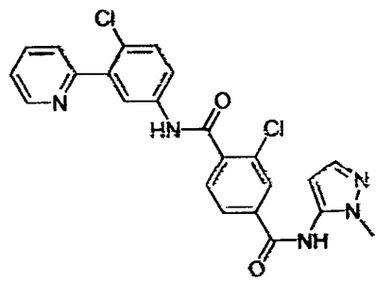
100 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to thiomorpholine via Procedure G. Crude 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(thiomorpholine-4-carbonyl)benzamide was reacted via Procedure R to oxidize the thiomorpholine sulfur and purified via reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(thiomorpholine-4-carbonyl)benzamide (in which the thiomorpholine 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)



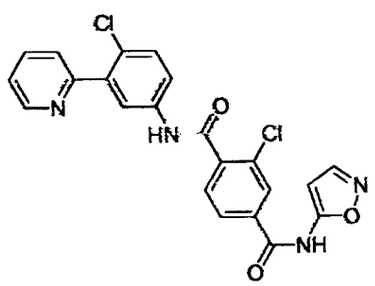
100 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to thiazolidine via Procedure G. Crude 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(thiazolidine-3-carbonyl)benzamide was reacted via Procedure R and purified via reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(thiazolidine-3-carbonyl)benzamide (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



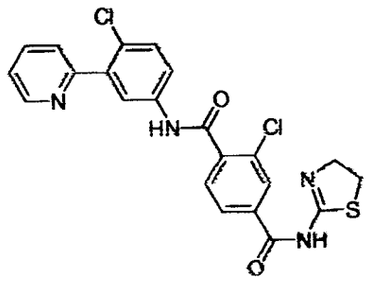
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 5-amino-1-methylpyrazole via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(1-methyl-1*H*-pyrazol-5-yl)terephthalamide. MS (Q1) 466 $(M)^+$.

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



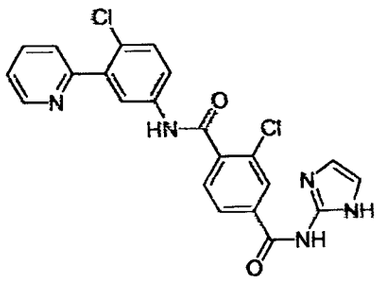
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 5-aminoisoxazole via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(isoxazol-5-yl)terephthalamide. MS (Q1) 463 $(M)^+$.

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



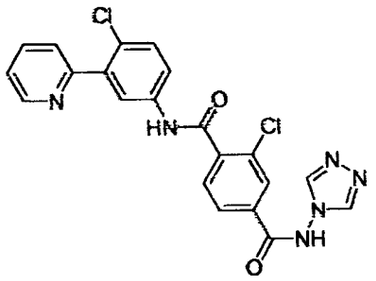
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 2-amino-4,5-dihydrothiazole via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(4,5-dihydrothiazol-2-yl)terephthalamide. MS (Q1) 471 $(M)^+$.

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



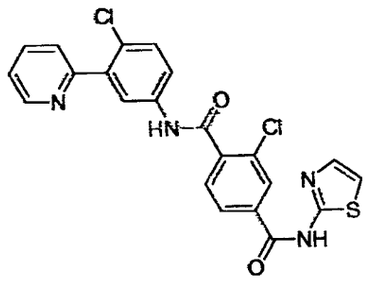
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 2-aminoimidazole via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(1*H*-imidazol-2-yl)terephthalamide. MS (Q1) 452 $(M)^+$.

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



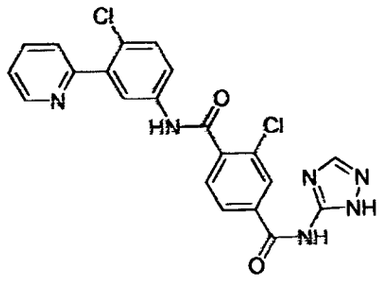
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 4-amino-1,2,4-triazole via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(4*H*-1,2,4-triazol-4-yl)terephthalamide. MS (Q1) 453 $(M)^+$.

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



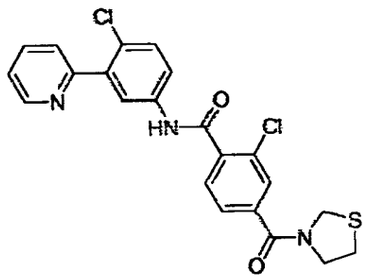
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 2-aminothiazole via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(thiazol-2-yl)terephthalamide. MS (Q1) 469 $(M)^+$.

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



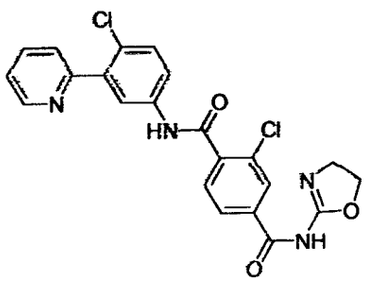
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 3-amino-1,2,4-triazole via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(1*H*-1,2,4-triazol-5-yl)terephthalamide. MS (Q1) 453 $(M)^+$.

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



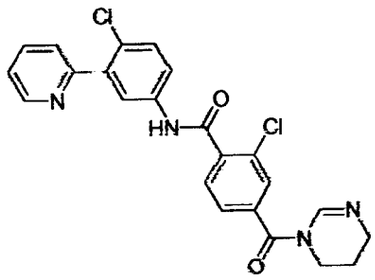
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to thiazoline via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(thiazolidine-3-carbonyl)benzamide. MS (Q1) 459 $(M)^+$.

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



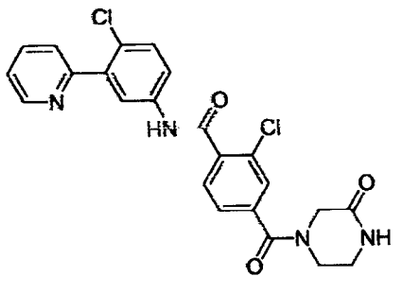
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 2-amino-4,5-dihydrooxazole via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(4,5-dihydrooxazol-2-yl)terephthalamide. MS (Q1) 456 $(M)^+$.

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 $(M)^+$.

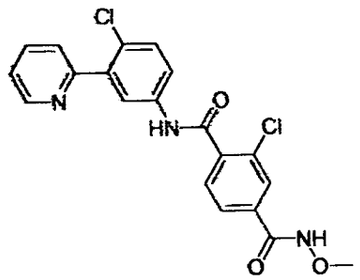
Example 96 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(3-oxopiperazine-1-carbonyl)benzamide



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-

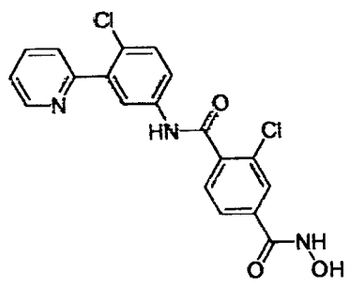
chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(3-oxopiperazine-1-carbonyl)benzamide. MS (Q1) 470 $(M)^+$.

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



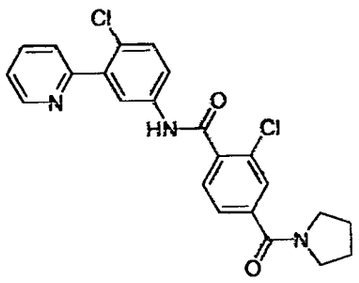
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to *N*-methylhydroxylamine hydrochloride via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-methoxyterephthalamide. MS (Q1) 417 $(M)^+$.

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



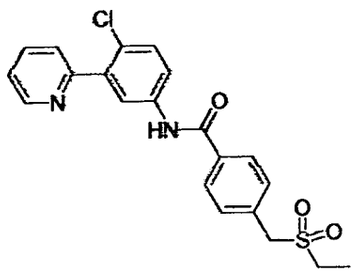
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to hydroxylamine hydrochloride via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-hydroxyterephthalamide. MS (Q1) 403 $(M)^+$.

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



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 $(M)^+$.

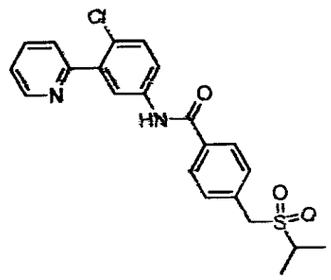
Example 100 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(ethylsulfonylmethyl)benzamide



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.

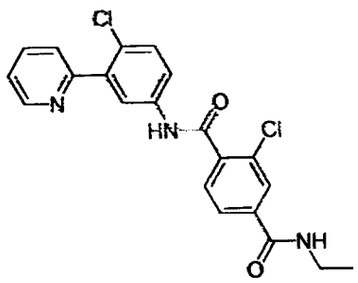
50 mg of 4-(ethylsulfonylmethyl)benzoic acid was coupled with 67mg of 4-chloro-3-(pyridin-2-yl)aniline via Procedure G. This product was recrystallized from methanol to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(ethylsulfonylmethyl)benzamide. MS (Q1) 415 $(M)^+$.

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



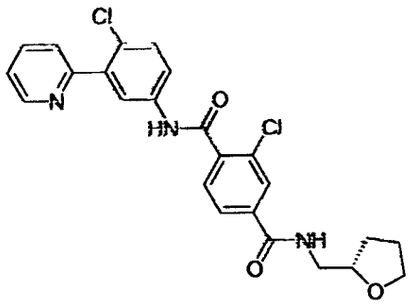
N-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(isopropylsulfonylmethyl)benzamide was prepared using the same procedure as *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(ethylsulfonylmethyl)benzamide except propane-2-sulfonyl chloride was substituted for ethanesulfonyl chloride. The product was purified on reverse 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



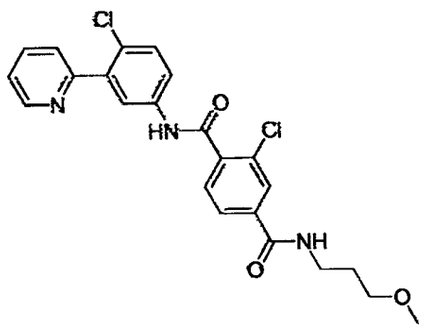
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to ethylamine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-ethylterephthalamide. MS (Q1) 415 $(M)^+$.

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



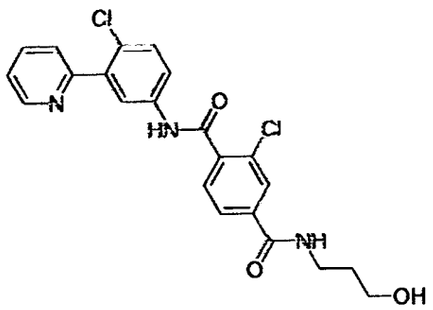
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to (S)-(+)-tetrahydrofurylamine via Procedure G. The product was purified on reverse phase HPLC to yield (*S*)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-((tetrahydrofuran-2-yl)methyl)terephthalamide. MS (Q1)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

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



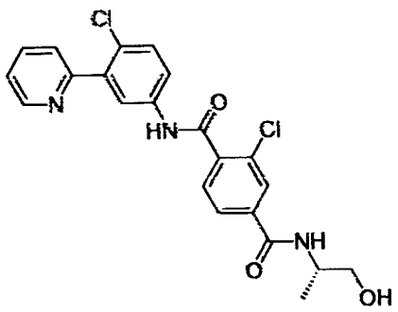
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 3-methoxypropylamine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(3-methoxypropyl)terephthalamide. MS (Q1) 459 $(M)^+$.

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



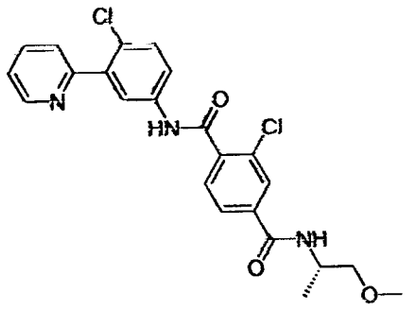
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 3-hydroxypropylamine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(3-hydroxypropyl)terephthalamide. MS (Q1) 445 $(M)^+$.

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



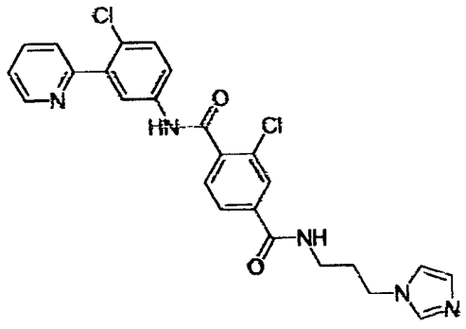
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to (S)-2-amino-1-propanol via Procedure G. The product was purified on reverse phase HPLC to yield (*S*)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(1-hydroxypropan-2-yl)terephthalamide. MS (Q1) 445 $(M)^+$.

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



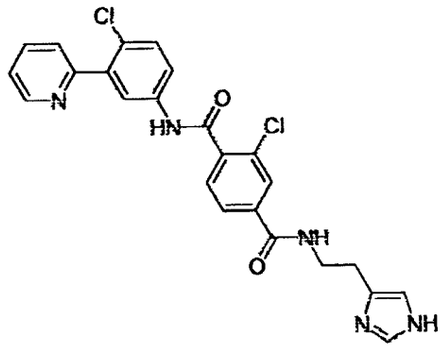
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to (S)-1-methoxy-2-propylamine via Procedure G. The product was purified on reverse phase HPLC to yield (*S*)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(1-methoxypropan-2-yl)terephthalamide. MS (Q1) 459 $(M)^+$.

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



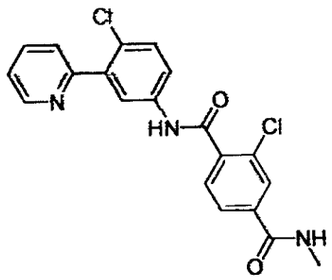
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 1-(3-aminopropyl)imidazole via Procedure G. The product was purified on reverse phase HPLC to yield N^4-(3-(1*H*-imidazol-1-yl)propyl)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)terephthalamide. MS (Q1) 495 $(M)^+$.

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



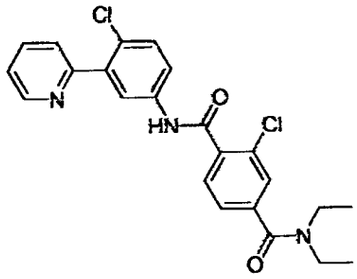
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to hystamine via Procedure G. The product was purified on reverse phase HPLC to yield N^4-(2-(1*H*-imidazol-4-yl)ethyl)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)terephthalamide. MS (Q1) 481 $(M)^+$.

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



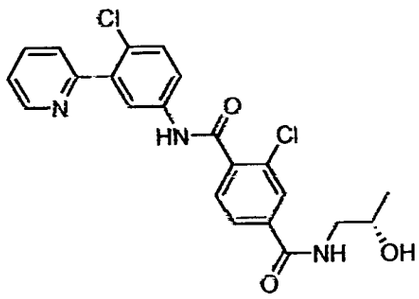
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to methylamine hydrochloride via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-methylterephthalamide. MS (Q1) 401 $(M)^+$.

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



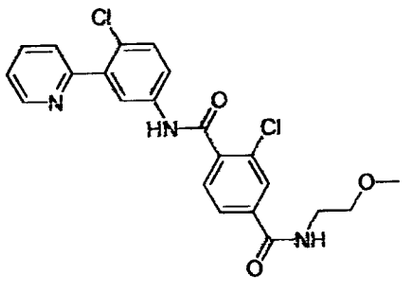
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to diethylamine hydrochloride via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4,N^4-diethylterephthalamide. MS (Q1) 443 $(M)^+$

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



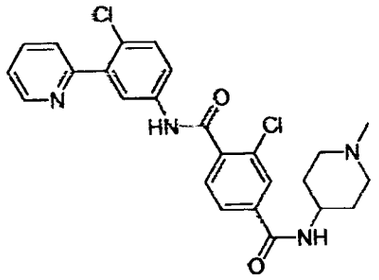
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to (S)-1-amino-2-propanol via Procedure G. The product was purified on reverse phase HPLC to yield (*S*)-2-chloro-*N*1-(4-chloro-3-(pyridin-2-yl)phenyl)-*N*4-(2-hydroxypropyl)terephthalamide. MS (Q1) 444 $(M)^+$.

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



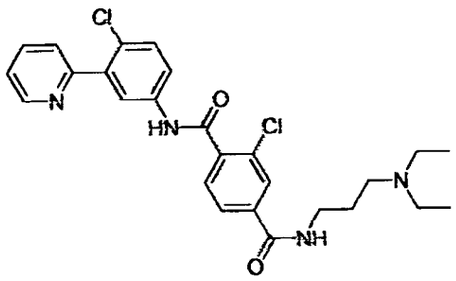
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 2-methoxyethanamine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-methoxyethyl)terephthalamide. MS (Q1) 444 $(M)^+$.

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



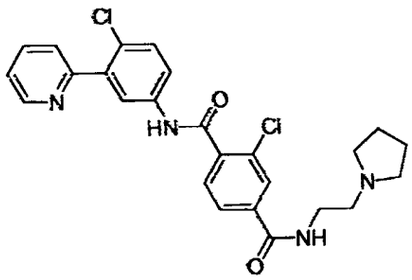
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 4-amino-1-methylpiperidine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(1-methylpiperidin-4-yl)terephthalamide. MS (Q1) 483 $(M)^+$.

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



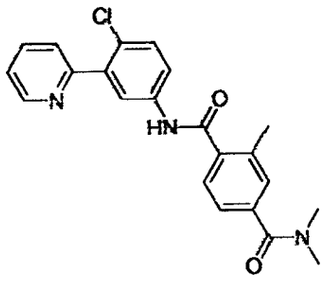
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to N,N-diethylpropylenediamine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(3-(diethylamino)propyl)terephthalamide. MS (Q1) 499 $(M)^+$.

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



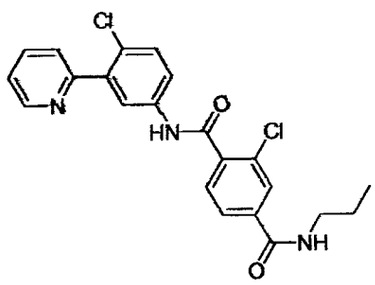
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to N-(2-aminoethyl)pyrrolidine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-(pyrrolidin-1-yl)ethyl)terephthalamide. MS (Q1) 483 $(M)^+$.

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



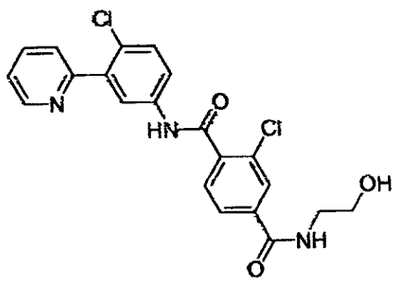
In a sealed tube, 1.94 g of dimethyl 2-bromoterephthalate was dissolved in 4 mL of HMPA and degassed with nitrogen prior to adding 1.1 mL of tetramethyl tin and 0.077 g of palladium tetrakistriphenylphosphene. After sealing the tube, the reaction was heated to 65° C for 16 h. The reaction was then partitioned 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



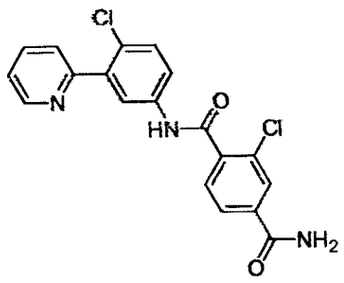
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to propylamine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-propylterephthalamide. MS (Q1) 430 $(M)^+$.

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



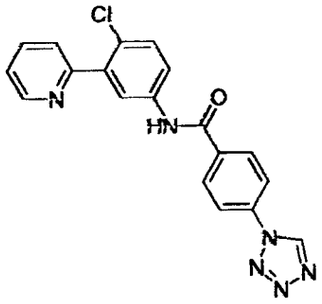
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to propanolamine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-hydroxyethyl)terephthalamide. MS (Q1) 428 $(M)^+$.

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



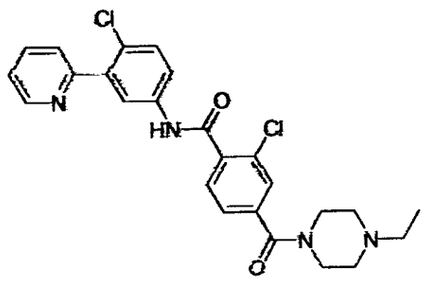
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to ammonium chloride via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)terephthalamide. MS (Q1) 386 $(M)^+$.

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



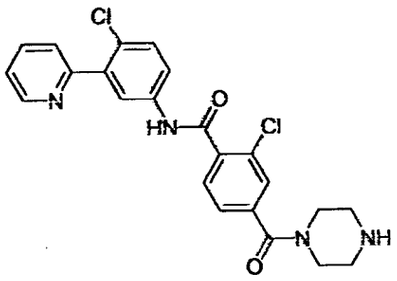
Procedure G was used to couple 4-chloro-3-(pyridin-2-yl)aniline (50 mg) and 4-(1*H*-tetrazol-1-yl)benzoic acid to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(1*H*-tetrazol-1-yl)benzamide. MS (Q1) 421.0 $(M)^+$.

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



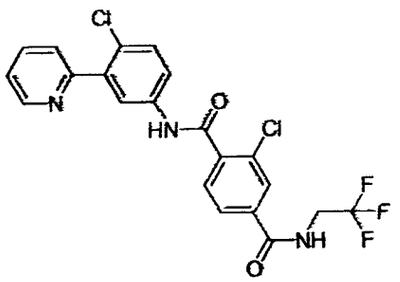
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 1-ethylpiperazine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(4-ethylpiperazine-1-carbonyl)benzamide. MS (Q1) 483 $(M)^+$.

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



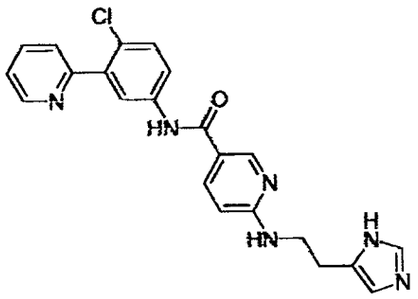
50 mg 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to Boc-piperazine via Procedure G. The organic layer was evaporated to dryness and treated with TFA. After 1 h the TFA was removed and the crude was purified on reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(piperazine-1-carbonyl)benzamide.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

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



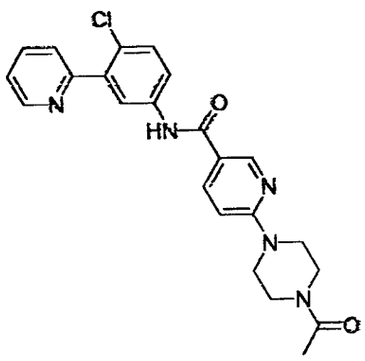
75 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 2,2,2-trifluoroethylamine via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2,2,2-trifluoroethyl)terephthalamide. MS (Q1) 469 $(M)^+$.

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



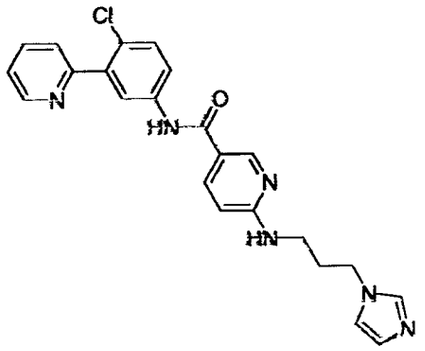
Procedure F was performed using *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-chloro-3-carboxamide (50 mg) and 100 mg of hystamine in butanol (0.5 mL). The crude reaction was purified by reverse phase HPLC to yield 6-(2-(1*H*-imidazol-5-yl)ethylamino)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide. MS (Q1)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

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



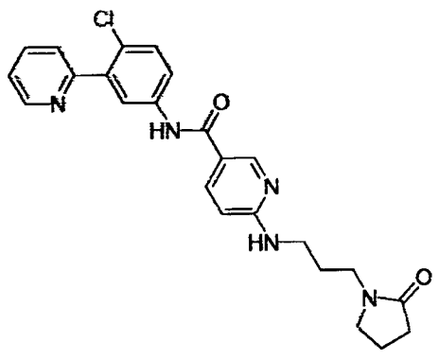
Procedure F was performed using *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-chloro-3-carboxamide (50 mg) and 0.12 mL of acetylpiperazine in butanol (0.5 mL). The crude reaction was purified by reverse phase HPLC to yield 6-(4-acetylpiperazin-1-yl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide. MS (Q1)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

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



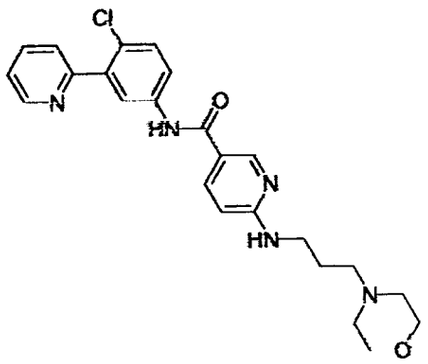
Procedure F was performed using *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-chloro-3-carboxamide (50 mg) and 125 mg of 1-(3-aminopropyl)imidazole in butanol (0.5 mL). The crude reaction was purified by reverse phase HPLC to yield 6-(3-(1*H*-imidazol-1-yl)propylamino)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide.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

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



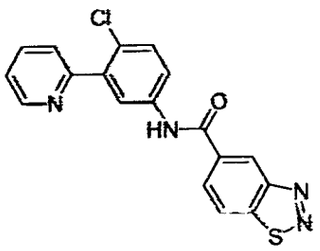
Procedure F was performed using *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-chloro-3-carboxamide (50 mg) and 0.42 mL of 1-(3-aminopropyl)-2-pyrrolidinone in butanol (0.5 mL). The crude reaction was purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(3-(2-oxopyrrolidin-1-yl)propylamino)nicotinamide.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

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



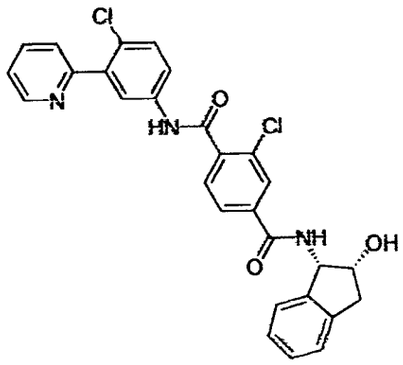
Procedure F was performed using *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-chloro-3-carboxamide (50 mg) and 0.14 mL of N-(3-aminopropyl)morpholine in butanol (0.5 mL). The crude reaction was purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(3-morpholinopropylamino)nicotinamide.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

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



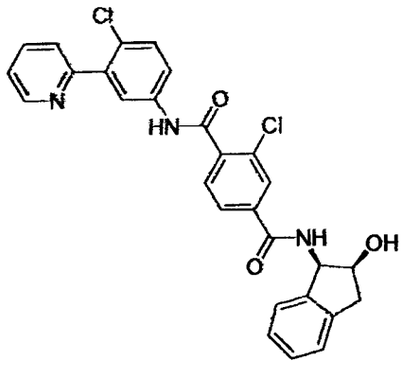
50 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to benzo-1,2,3-thiadiazole-5-carboxylic acid via Procedure G. The crude product was purified via reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzo[d][1,2,3]thiadiazole-5-carboxamide. MS (Q1) 367 $(M)^+$.

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



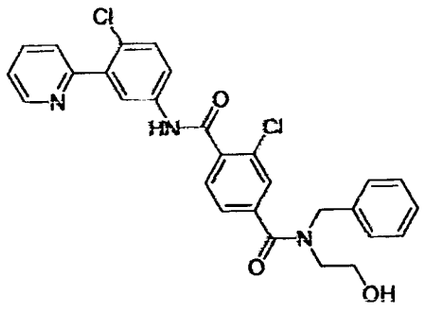
60 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to (1*S*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-ol via Procedure G. The crude product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)terephthalamide.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



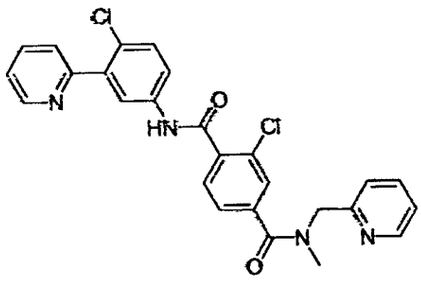
60 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol via Procedure G. The crude product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-((1*R*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)terephthalamide.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



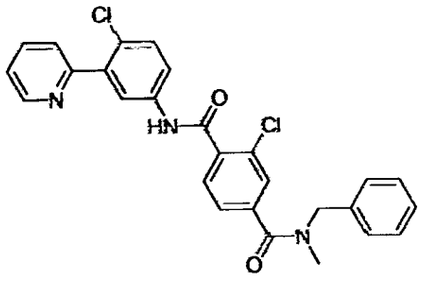
40 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 2-(benzylamino)ethanol via Procedure G. The crude product was purified on reverse phase HPLC to yield N^4-benzyl-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-hydroxyethyl)terephthalamide. MS (Q1) 520 $(M)^+$.

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



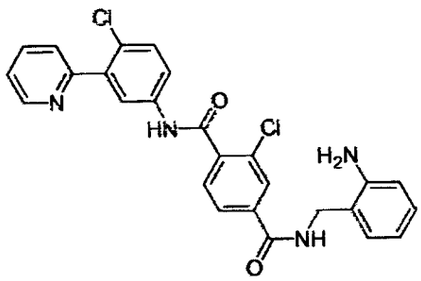
40 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to *N*-methyl-1-(pyridin-2-yl)methanamine via Procedure G. The crude product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-methyl-N^4-(pyridin-2-ylmethyl)terephthalamide.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

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



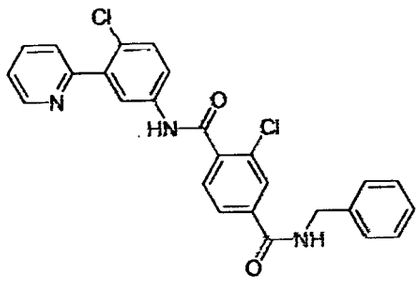
40 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to *N*-methyl-1-phenylmethanamine via Procedure G. The crude product was purified on reverse phase HPLC to yield N^4-benzyl-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-methylterephthalamide. MS (Q1) 490.1 $(M)^+$.

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



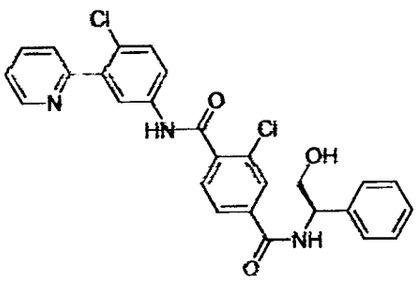
60 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to N^1-phenylethane-1,2-diamine via Procedure G. The crude product was purified on reverse phase HPLC to yield N^4-(2-aminobenzyl)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)terephthalamide. MS (Q1) 491 $(M)^+$.

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



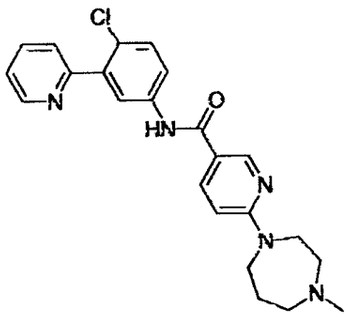
60 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to benzylamine via Procedure G. The crude product was purified on reverse phase HPLC to yield N^4-benzyl-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)terephthalamide. MS (Q1) 476 $(M)^+$.

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



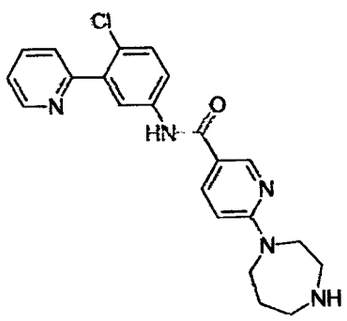
60 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to (*R*)-2-amino-2-phenylethanol via Procedure G. The crude product was purified on reverse phase HPLC to yield (*R*)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-hydroxy-1-phenylethyl)terephthalamide. MS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

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



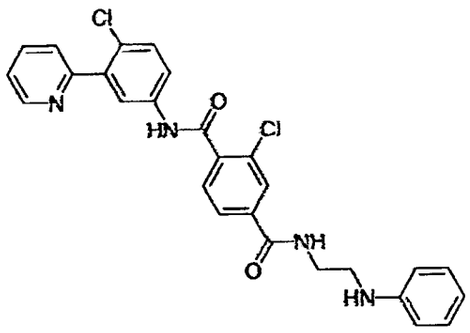
50 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide was reacted with 1-methyl-1,4-diazepane via Procedure F. The reaction was evaporated to dryness and purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(4-methyl-1,4-diazepan-1-yl)nicotinamide. MS (Q1) 422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

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



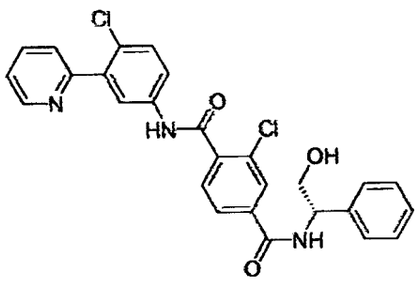
50 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide was reacted with 1,4-diazepane via Procedure F. The reaction was evaporated to dryness and purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(1,4-diazepan-1-yl)nicotinamide. MS (Q1) 408 $(M)^+$.

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



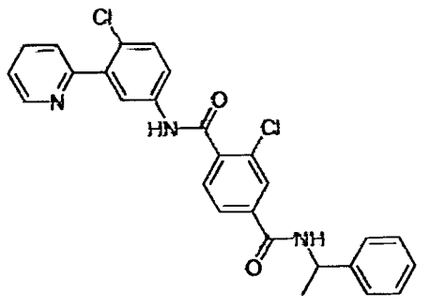
62 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to N^1-phenylethane-1,2-diamine via Procedure G. The crude product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-(phenylamino)ethyl)terephthalamide. MS (Q1) 505.1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

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



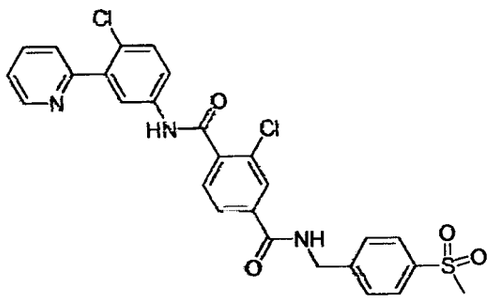
62 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to (*S*)-2-amino-2-phenylethanol via Procedure G. The crude product was purified on reverse phase HPLC to yield (*S*)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-hydroxy-1-phenylethyl)terephthalamide. MS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

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



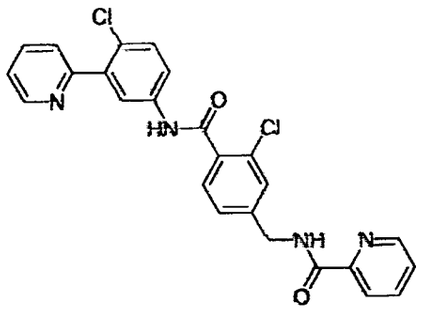
62 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 1-phenylethanamine via Procedure G. The crude product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(1-phenylethyl)terephthalamide. MS (Q1) 490.1 $(M)^+$.

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



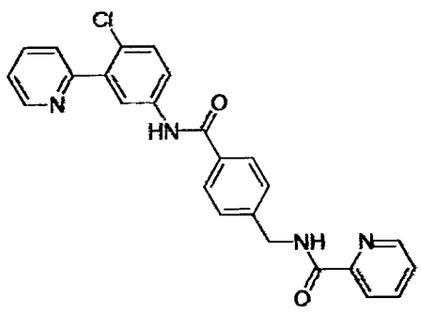
62 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to (4-(methylsulfonyl)phenyl)methanamine via Procedure G. The crude product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(4-(methylsulfonyl)benzyl)terephthalamide.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

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



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 $(M)^+$.

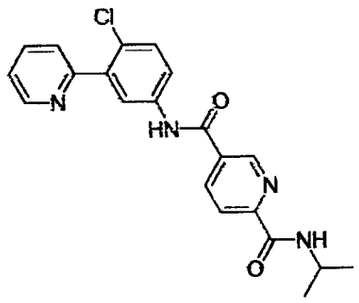
Example 146 *N*-(4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzyl)picolinamide



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

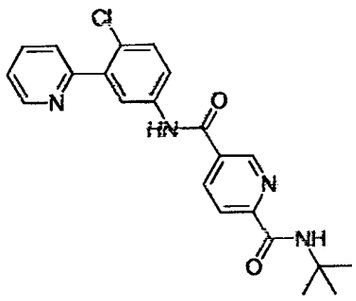
purified by reverse phase HPLC to yield *N*-(4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzyl)picolinamide. MS (Q1) 443.3 $(M)^+$.

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 $(M)^+$.

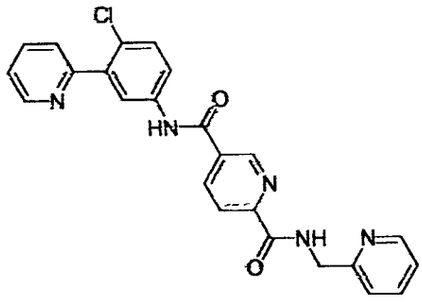
Example 148 N^2-*tert*-butyl-N^5-(4-chloro-3-(pyridin-2-yl)phenyl)pyridine-2,5-dicarboxamide



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

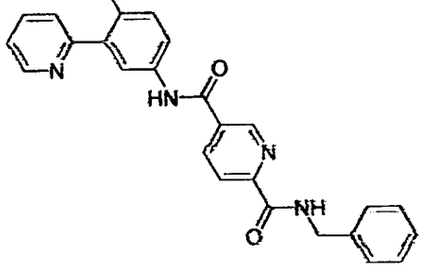
phase HPLC to yield N^2-*tert*-butyl-N^5-(4-chloro-3-(pyridin-2-yl)phenyl)pyridine-2,5-dicarboxamide. MS (Q1) 409 $(M)^+$.

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



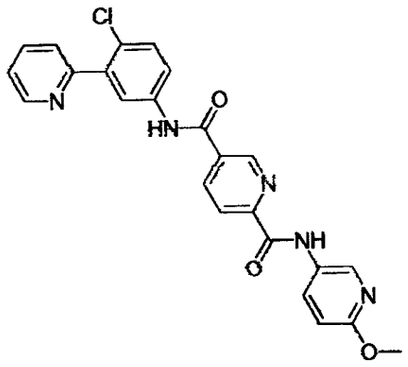
250 mg of 5-(methoxycarbonyl)picolinic acid was coupled to pyridin-2-ylmethanamine via Procedure G. Crude methyl 6-(pyridin-2-ylmethylcarbamoyl)nicotinate was hydrolyzed via Procedure M to yield 250 mg of 6-(pyridin-2-ylmethylcarbamoyl)nicotinic acid. 60 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled 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



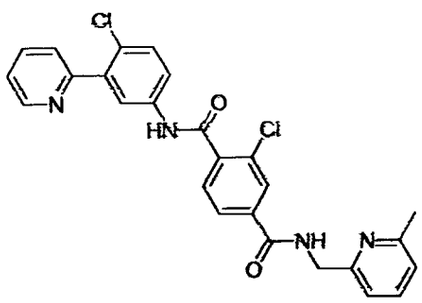
250 mg of 5-(methoxycarbonyl)picolinic acid was coupled to benzylamine via Procedure G. Crude methyl 6-(benzylcarbamoyl)nicotinate was hydrolyzed via Procedure M to yield 300 mg of 6-(benzylcarbamoyl)nicotinic acid. 60 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 6-(benzylcarbamoyl)nicotinic 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 $(M)^+$.

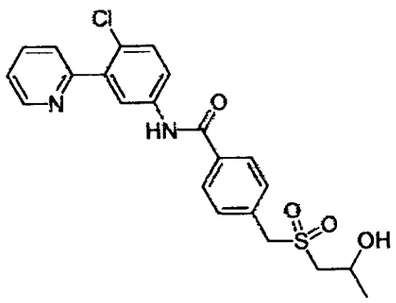
Example 152 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-((6-methylpyridin-2-yl)methyl)-terephthalamide



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

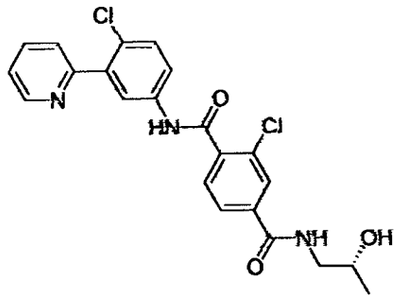
by TLC. Upon completion, the solvent was concentrated, the crude material was extracted in water and Chloroform 3 times and dried over Magnesium Sulfate. The crude was purified via ISCO Combi-Flash to yield 2-((6-methylpyridin-2-yl)methyl)isoindoline-1,3-dione. 350 mg of 2-((6-methylpyridin-2-yl)methyl)isoindoline-1,3-dione 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



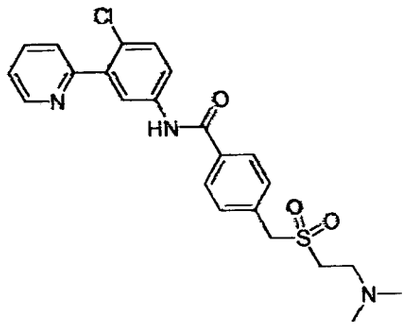
1 g of methyl 4-(bromomethyl)benzoate was reacted with 1-mercaptopropan-2-ol via Procedure Q. 1 g of methyl 4-((2-hydroxypropylthio)methyl)benzoate was oxidized with 2g of MCPBA in DCM at -78°C to form crude methyl 4-((2-hydroxypropylsulfonyl)methyl)benzoate. The reaction was evaporated and purified 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



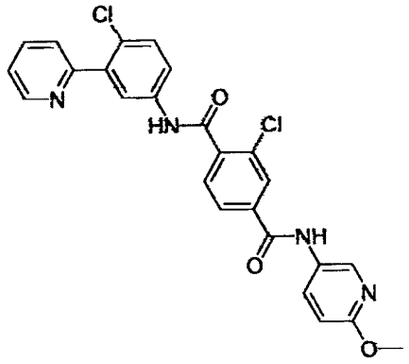
100 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to (*R*)-2-amino-2-phenylethanol via Procedure G. The crude product was purified on reverse phase HPLC to yield (*R*)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-hydroxypropyl)terephthalamide. MS (Q1) 444.3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

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



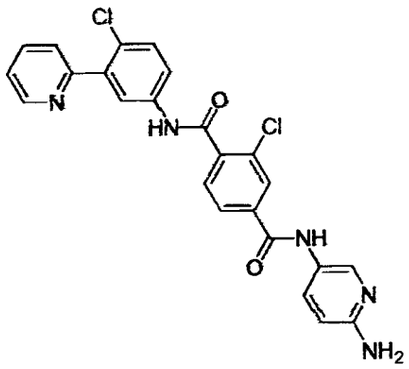
500 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-(bromomethyl)benzoic acid via Procedure E. 170 mg of 4-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide was reacted with 2-(dimethylamino)ethanethiol hydrochloride via Procedure Q. 140mg of crude *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((2-(dimethylamino)ethylthio)methyl)benzamide 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



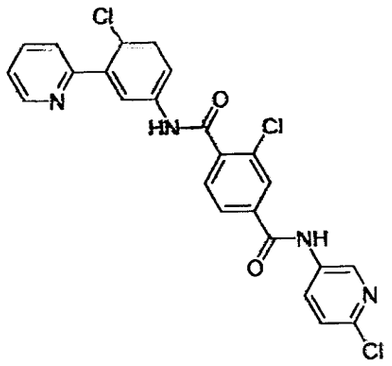
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 6-methoxypyridin-3-amine via Procedure G. The crude product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(6-methoxypyridin-3-yl)terephthalamide. MS (Q1) 493 $(M)^+$.

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



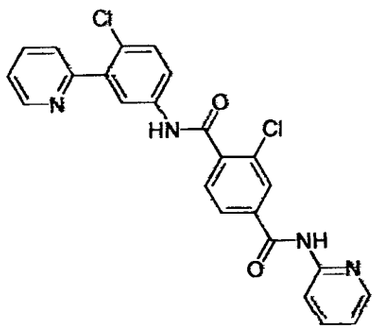
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to pyridine-2,5-diamine via Procedure G. The crude product was purified on reverse phase HPLC to yield N^4-(6-aminopyridin-3-yl)-2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)terephthalamide. MS (Q1) 478 $(M)^+$.

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



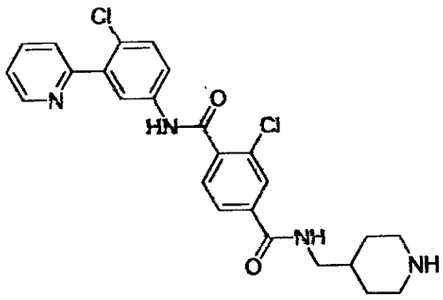
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 6-chloropyridin-3-amine via Procedure G. The crude product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(6-chloropyridin-3-yl)terephthalamide. MS (Q1) 497 $(M)^+$.

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



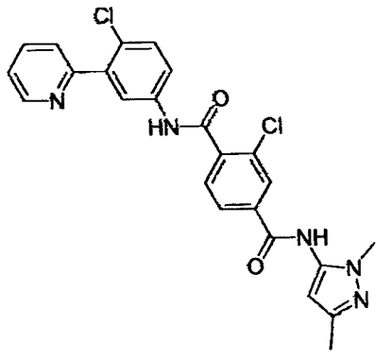
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to pyridin-2-amine via Procedure G. The crude product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(pyridin-2-yl)terephthalamide. MS (Q1) 463 $(M)^+$.

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



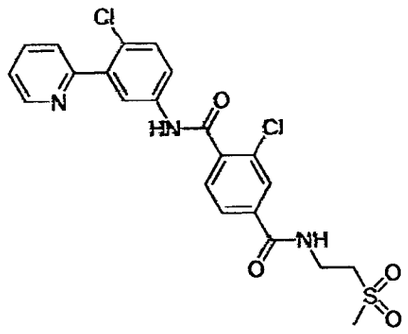
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to piperidin-4-ylmethanamine via Procedure G. The crude product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(piperidin-4-ylmethyl)terephthalamide. MS (Q1) 483 $(M)^+$.

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



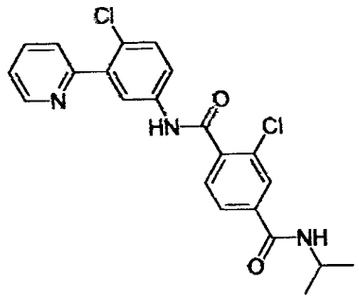
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 1,3-dimethyl-1*H*-pyrazol-5-amine via Procedure G. The crude product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(1,3-dimethyl-1*H*-pyrazol-5-yl)terephthalamide.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

Example 162 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-(methylsulfonyl)ethyl)-terephthalamide



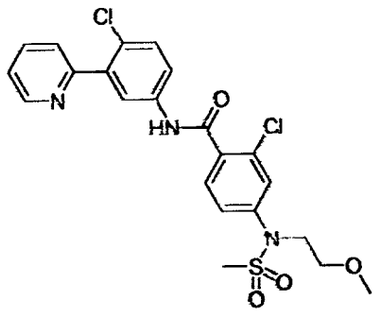
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to 2-(methylsulfonyl)ethanamine via Procedure G. The crude product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-(2-(methylsulfonyl)ethyl)terephthalamide. MS (Q1) 492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

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



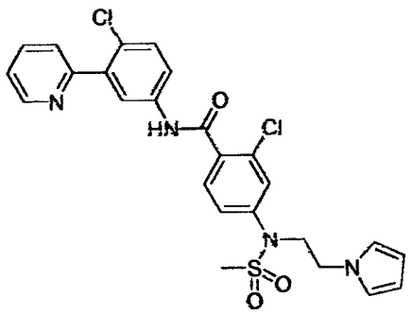
50 mg of 3-chloro-4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzoic acid was coupled to isopropylamine via Procedure G. The crude product was purified on reverse phase HPLC to yield 2-chloro-N^1-(4-chloro-3-(pyridin-2-yl)phenyl)-N^4-isopropylterephthalamide. MS (Q1) 428 $(M)^+$.

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 $(M)^+$.

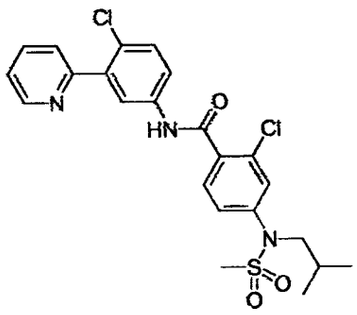
Example 165 4-(*N*-(2-(1*H*-pyrrol-1-yl)ethyl)methylsulfonamido)-2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide



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 $(M)^+$.

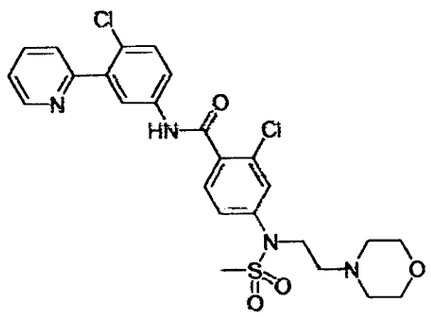
Example 166 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-isobutylmethylsulfonamido)-benzamide



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

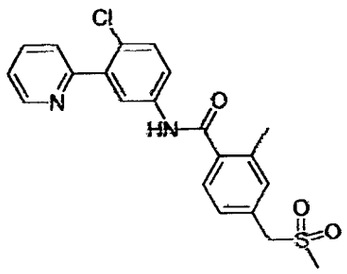
2-chloro-4-(*N*-isobutylmethylsulfonamido)benzoate. 120 mg of methyl 2-chloro-4-(*N*-isobutylmethylsulfonamido)benzoate was hydrolyzed via Procedure M to yield 110 mg of crude 2-chloro-4-(*N*-isobutylmethylsulfonamido)benzoic acid. 75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 2-chloro-4-(*N*-isobutylmethylsulfonamido)benzoic 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 $(M)^+$.

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



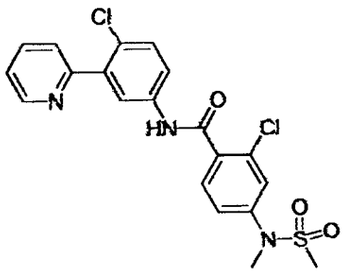
1.2 g of 4-(2-chloroethyl)morpholine and 2.5 g of Cesium Carbonate were added to 334 mg of methyl 2-chloro-4-(methylsulfonamido)benzoate in 7 mL of DMF and stirred in the microwave at 150°C for 30 minutes. The reaction mixture was extracted in Ethyl Acetate twice with water, dried over Magnesium Sulfate, 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



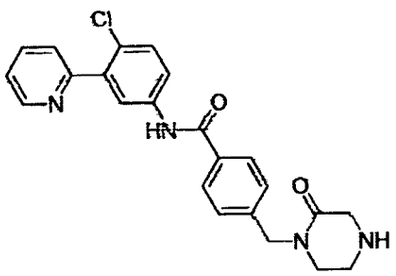
410 mg of dimethyl 2-methylterephthalate was hydrolyzed via Procedure M and purified by ISCO Combi-Flash to afford 4-(methoxycarbonyl)-3-methylbenzoic acid. 255 mg of 4-(methoxycarbonyl)-3-methylbenzoic acid was cooled to 0°C in 2 mL of THF before a solution of 2.6 mL of 1M BH_3-THF complex in THF was 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*-methylmethylsulfonamido)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

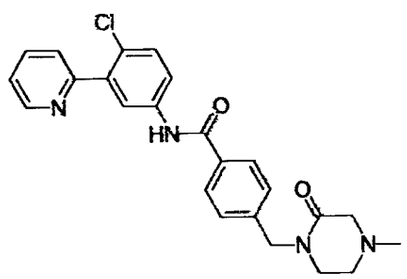


500 mg of methyl 4-(bromomethyl)benzoate was reacted with 480 mg of *tert*-butyl 3-oxopiperazine-1-carboxylate and 1 g of Cesium Carbonate in 9 mL of DMF at 45°C. Upon completion, the reaction was extracted in Ethyl Acetate 2 times saturated bicarbonate, dried over Magnesium Sulfate, filtered and concentrated 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

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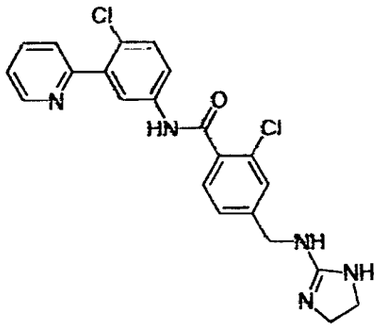
to 4-((4-(*tert*-butoxycarbonyl)-2-oxopiperazin-1-yl)methyl)benzoic acid via Procedure G. The crude product was extracted twice with saturated bicarbonate in Ethyl Acetate, dried over Magnesium Sulfate, filtered and concentrated to give crude *tert*-butyl 4-(4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzyl)-3-oxopiperazine-1-carboxylate. 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



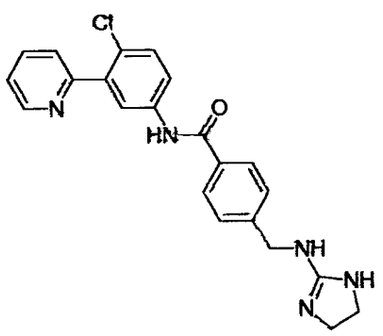
To 200 mg of the HCl salt of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((2-oxopiperazin-1-yl)methyl)benzamide was added 55 mg of Paraformaldehyde and 185 mg of Sodium Triacetoxyborohydride in 1 mL of 2% AcOH in DMF. After completion, the reaction is extracted once with bicarbonate and brine in Ethyl Acetate, 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



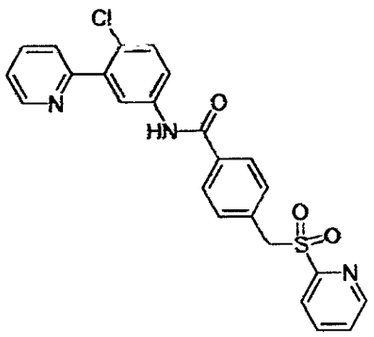
100 mg of the crude HCl salt of 4-(aminomethyl)-2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide was reacted with 72 mg of 1-(4,5-dihydro-1*H*-imidazol-2-yl)-3,5-dimethyl-1*H*-pyrazole and 100 µL of DIPEA in 500 µL of DMF in the microwave at 150°C for 5 minutes. The crude product was concentrated 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



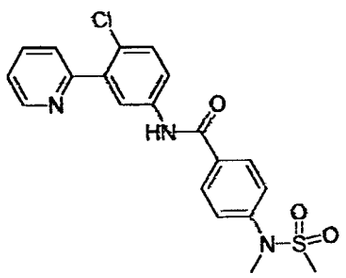
100 mg of the crude HCl salt of 4-(aminomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide was reacted with 80 mg of 1-(4,5-dihydro-1*H*-imidazol-2-yl)-3,5-dimethyl-1*H*-pyrazole and 110 µL of DIPEA in 1 mL of DMF in the microwave at 150°C for 5 minutes. The crude product was concentrated to dryness 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



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 $(M)^+$.

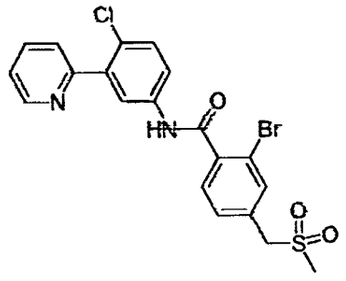
Example 175 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-methylmethylsulfonamido)benzamide



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

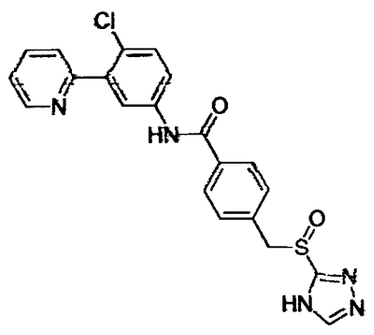
Procedure G. The crude product was purified by reverse phase HPLC to yield pure *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-methylmethylsulfonamido)benzamide. MS (Q1) 416.3 $(M)^+$.

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 $(M)^+$.

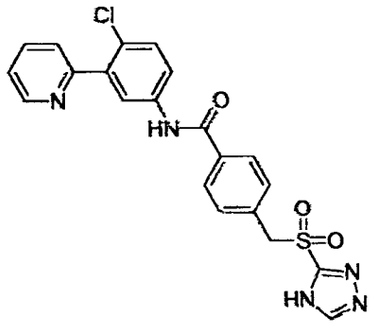
Example 177 4-((4*H*-1,2,4-triazol-3-ylsulfinyl)methyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide



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-

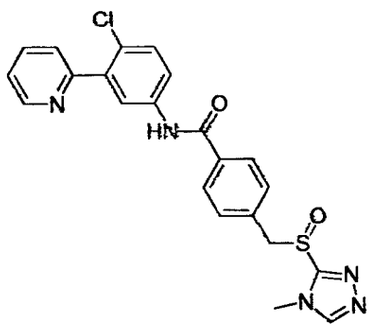
ylsulfinyl)methyl)benzoate and methyl 4-((4*H*-1,2,4-triazol-3-ylsulfonyl)methyl)benzoate. The mixture of 467 mg was hydrolyzed via Procedure M to give 4-((4*H*-1,2,4-triazol-3-ylsulfinyl)methyl)benzoic acid and 4-((4*H*-1,2,4-triazol-3-ylsulfonyl)methyl)benzoic acid. 107 mg of the mixture of 4-((4*H*-1,2,4-triazol-3-ylsulfinyl)methyl)benzoic 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 $(M)^+$.

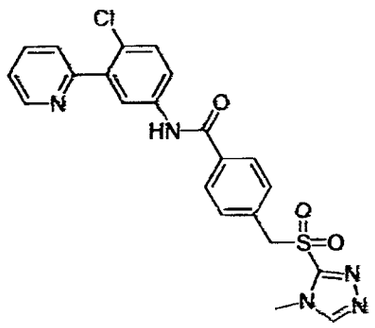
Example 179 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((4-methyl-4*H*-1,2,4-triazol-3-ylsulfinyl)-methyl)benzamide



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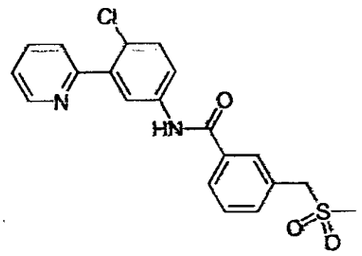
500 mg of methyl 4-(bromomethyl)benzoate was reacted with 4-methyl-4*H*-1,2,4-triazole-3-thiol via Procedure Q. 804 mg of methyl 4-((4-methyl-4*H*-1,2,4-triazol-3-ylthio)methyl)benzoate was subsequently reacted via Procedure R to give an approximate 1:9 mixture of methyl 4-((4-methyl-4*H*-1,2,4-triazol-3-ylsulfinyl)methyl)benzoate 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 $(M)^+$.

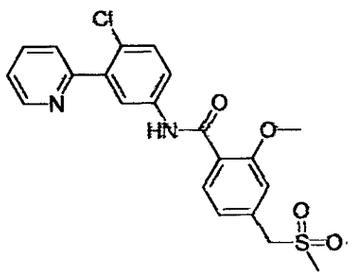
Example 181 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-(methylsulfonylmethyl)benzamide



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.

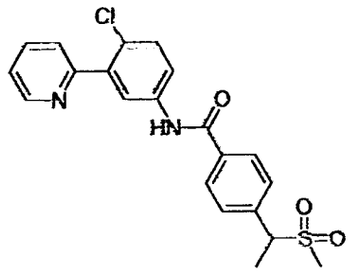
75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 3-(methylsulfonylmethyl)benzoic acid via Procedure G. The crude product was purified by reverse phase HPLC to yield pure *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-(methylsulfonylmethyl)benzamide. MS (Q1) 401 $(M)^+$.

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



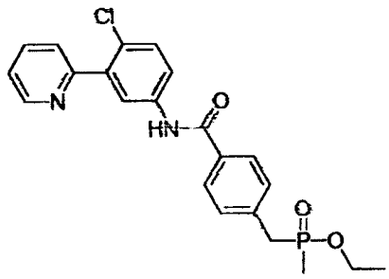
900 mg of 2-methoxy-4-methylbenzoic acid was brominated via Procedure N to afford 4-(bromomethyl)-2-methoxybenzoic acid. 100 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 132 mg of 4-(bromomethyl)-2-methoxybenzoic acid via Procedure E. 211 mg of 4-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methoxybenzamide 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



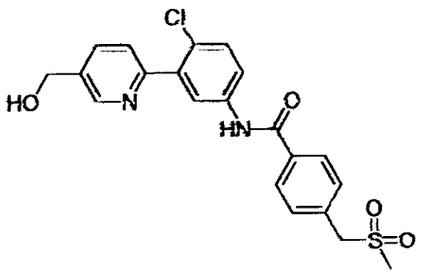
75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 93 mg of 4-(1-bromoethyl)benzoic acid via Procedure E. 153 mg of 4-(1-bromoethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide was reacted via Procedure O and purified by reverse phase HPLC to give pure *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(1-(methylsulfonyl)ethyl)benzamide.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

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



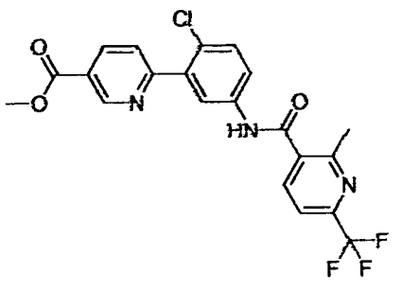
90 mg of 4-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide was reacted with 45 µL of diethyl methylphosphonite in the microwave at 120°C for 5 minutes. The reaction was evaporated to dryness and purified by reverse phase HPLC to give pure ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzyl(methyl)phosphinate.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

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



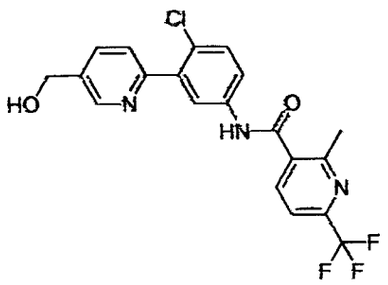
75 mL of (5-methylpyridin-2-yl)zinc(II) bromide was reacted with 4 g of 1-chloro-2-iodo-4-nitrobenzene via Procedure B. To 935 mg of 2-(2-chloro-5-nitrophenyl)-5-methylpyridine in 5 mL of Sulfuric Acid was slowly added 2.25 g of Chromium (III) Oxide and the reaction was stirred for several hours at room 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



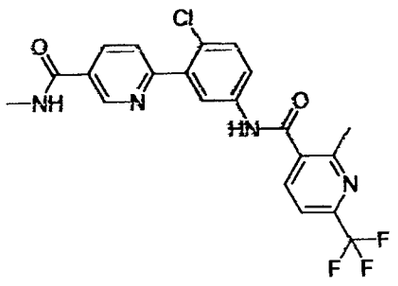
200 mg of methyl 6-(5-amino-2-chlorophenyl)nicotinate was treated with 255 μL of 2-methyl-6-(trifluoromethyl)nicotinoyl chloride via Procedure D and purified by reverse phase HPLC to give pure 6-(2-chloro-5-(2-methyl-6-(trifluoromethyl)nicotinamido)phenyl)nicotinate. MS (Q1) 450 $(M)^+$.

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



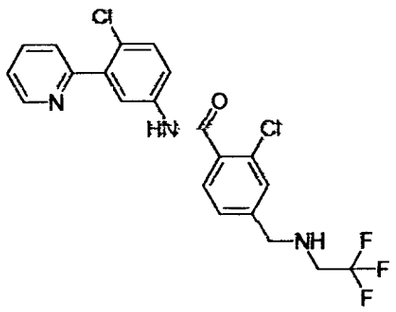
To 110 mg of methyl 6-(2-chloro-5-(2-methyl-6-(trifluoromethyl)nicotinamido)phenyl)nicotinate at 0°C in 5 mL of EtOH was slowly added 148 mg of Sodium Borohydride. The reaction was subsquently refluxed for 1 hour until complete, quenched with water and extracted with Ethyl Acetate. The organic layer 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



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 (QI) 449 $(M)^+$.

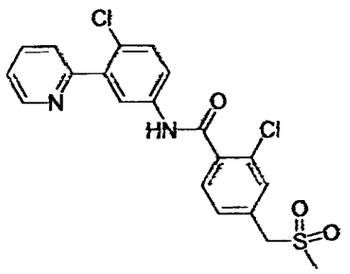
Example 189 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((2,2,2-trifluoroethylamino)methyl)benzamide.



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

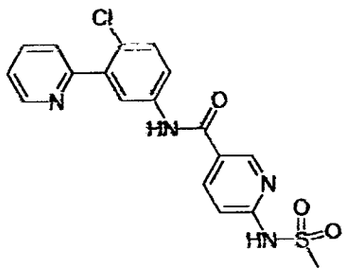
bath is removed. Upon completion, the reaction is re-cooled to 0°C and quenched with 3N HCl dropwise. The aqueous layer was extracted two times with Ethyl Acetate and the organic layer was then extracted once with bicarbonate solution and brine, dried over Magnesium Sulfate, filtered and concentrated 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



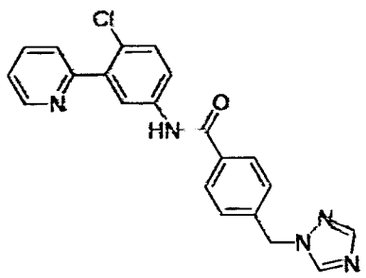
3.01 g of *tert*-butyl 4-(bromomethyl)-2-chlorobenzoate was reacted via Procedure O to give *tert*-butyl 2-chloro-4-(methylsulfonylmethyl)benzoate. 1.2 g of *tert*-butyl 2-chloro-4-(methylsulfonylmethyl)benzoate was treated with 10 mL of 4N HCl in Dioxane at 45°C and concentrated upon completion to give 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



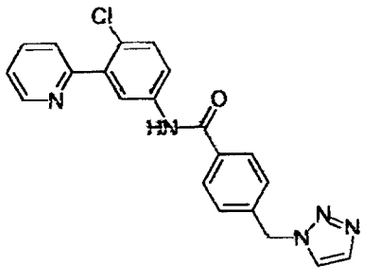
100 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide was reacted with methanesulfonamide and 108 µL of 2-*tert*-Butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine via Procedure F. The crude reaction was concentrated to dryness and purified by reverse phase HPLC to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



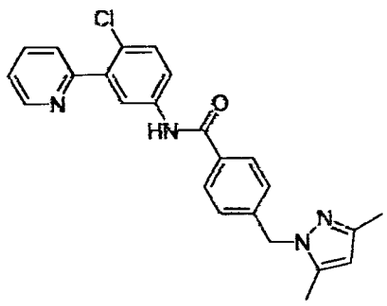
88 mg of 4-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide was coupled to 45 mg of 1*H*-1,2,4-triazole via Procedure P. The reaction was evaporated to dryness and purified by reverse phase HPLC to yield 4-((1*H*-1,2,4-triazol-1-yl)methyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide. MS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

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



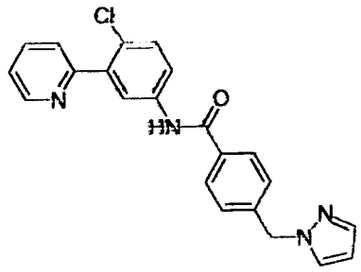
88 mg of 4-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide was coupled to 40 μL of 1*H*-1,2,3-triazole via Procedure P. The reaction was evaporated to dryness and purified by reverse phase HPLC to yield 4-((1*H*-1,2,3-triazol-1-yl)methyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide. MS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



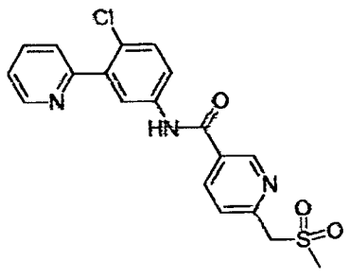
70 mg of 4-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide was coupled to 50 mg of 3,5-dimethyl-1*H*-pyrazole via Procedure P. The reaction was evaporated to dryness and purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((3,5-dimethyl-1*H*-pyrazol-1-yl)methyl)benzamide.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

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



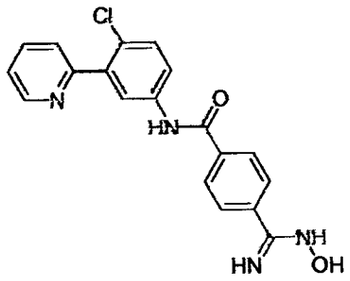
70 mg of 4-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide was coupled to 36 mg of 1*H*-pyrazole via Procedure P. The reaction was evaporated to dryness and purified by reverse phase HPLC to yield 4-((1*H*-pyrazol-1-yl)methyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide. MS (Q1) 389.3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

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



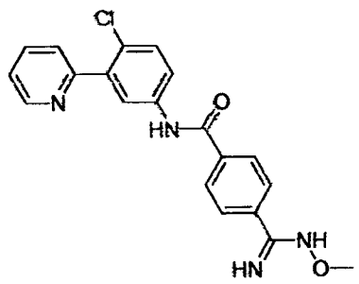
1.2 g of 6-methylnicotinic acid was brominated via Procedure N to give 6-(bromomethyl)nicotinic acid. 75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 87 mg of 6-(bromomethyl)nicotinic acid via Procedure E. 145 mg of 6-(bromomethyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide was reacted 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



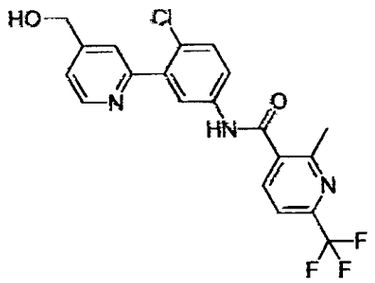
240 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 207 mg of 4-cyanobenzoic acid via Procedure G. To 445 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-cyanobenzamide and 2.5 mL of DIPEA in 10 mL of EtOH was added 793 mg Hydroxylamine Hydrochloride and heated to 60°C until reaction was complete. 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



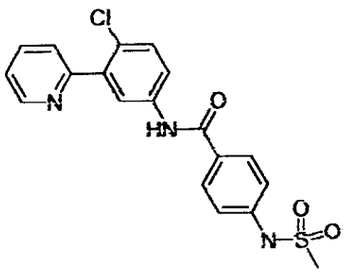
100 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-hydroxycarbamimidoyl)benzamide was cooled to 0°C in 1.5 mL of Dioxane. 5 mL of 2N NaOH was slowly added followed by dropwise addition of 33 µL of dimethylsulfate. The ice bath was removed and reaction was stirred at room temperature for 1 hour. The 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



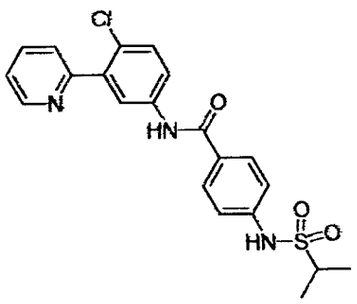
75 mL of (4-methylpyridin-2-yl)zinc(II) bromide was reacted with 4 g of 1-chloro-2-iodo-4-nitrobenzene via Procedure B. To 300 mg of 2-(2-chloro-5-nitrophenyl)-4-methylpyridine in 1.5 mL of Sulfuric Acid was slowly added 362 mg of Chromium (III) Oxide and the reaction was stirred for several hours at 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



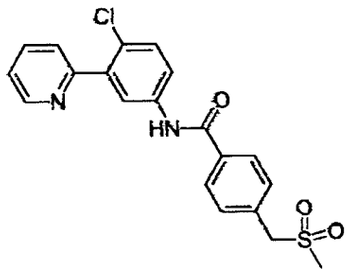
300 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 270 mg of 4-nitrobenzoic acid via Procedure G. To 520 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-nitrobenzamide in 2.5 mL of HCl in 10 mL of EtOH was added 1.3 g of Tin (II) Chloride and stirred at 55°C. Upon completion, the reaction was concentratd 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



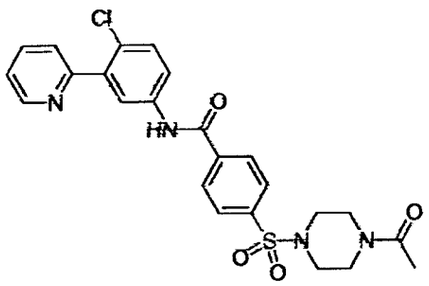
151 mg of 4-amino-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide was reacted with 105 µL of propane-2-sulfonyl chloride and 205 µL DIPEA in 500 µL DCM. The reaction mixture was evaporated, subjected to basic workup conditions and purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(1-methylethylsulfonamido)benzamide.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

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



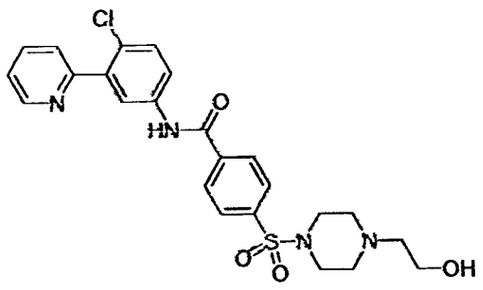
1 g of methyl 4-(bromomethyl)benzoate was reacted via Procedure O. 2.77 g of methyl 4-(methylsulfonylmethyl)benzoate was hydrolyzed via Procedure M. 1g of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 1.15 g of 4-(methylsulfonylmethyl)benzoic acid via Procedure G. The crude product was subjected to 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



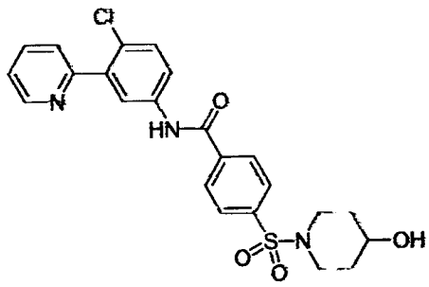
1 g of 4-(chlorosulfonyl)benzoic acid was reacted with 646 µL of 1-(piperazin-1-yl)ethanone via Procedure H. 75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 125 mg of 4-(4-acetylpiperazin-1-ylsulfonyl)benzoic acid via Procedure G and purified by reverse phase HPLC to yield 4-(4-acetylpiperazin-1-ylsulfonyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide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

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



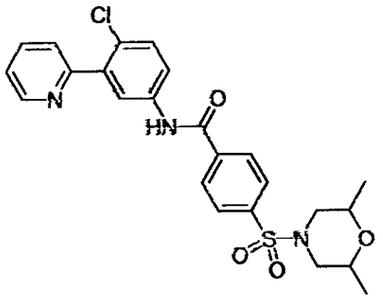
1 g of 4-(chlorosulfonyl)benzoic acid was reacted with 615 μL of 2-(piperazin-1-yl)ethanol via Procedure H. 75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 125 mg of 4-(4-(3-hydroxypropyl)piperazin-1-ylsulfonyl)benzoic acid by Procedure G and purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(4-(2-hydroxyethyl)piperazin-1-y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

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



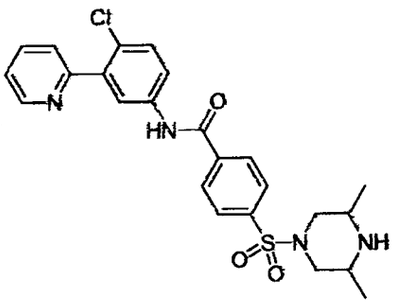
1 g of 4-(chlorosulfonyl)benzoic acid was reacted with 506 μL of piperidin-4-ol via Procedure H. 75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 114 mg of 4-(4-hydroxypiperidin-1-ylsulfonyl)benzoic acid via Procedure G and purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(4-hydroxypiperidin-1-ylsulfonyl)benzamide.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

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



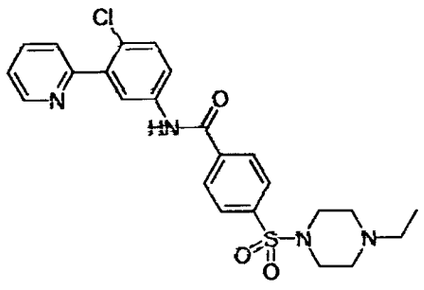
1 g of 4-(chlorosulfonyl)benzoic acid was reacted with 616 μL of 2,6-dimethylmorpholine via Procedure H. 75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 120 mg of 4-(2,6-dimethylmorpholinosulfonyl)benzoic acid via Procedure G and purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2,6-dimethylmorpholinosulfonyl)benzamide.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

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



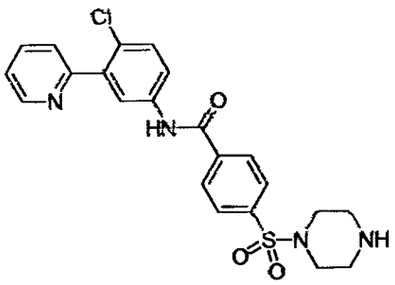
1 g of 4-(chlorosulfonyl)benzoic acid was reacted with 570 mg of 2,6-dimethylpiperazine via Procedure H. 75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 119 mg of 4-(3,5-dimethylpiperazin-1-ylsulfonyl)benzoic acid via Procedure G and purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(3,5-dimethylpiperazin-1-ylsulfonyl)benza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

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



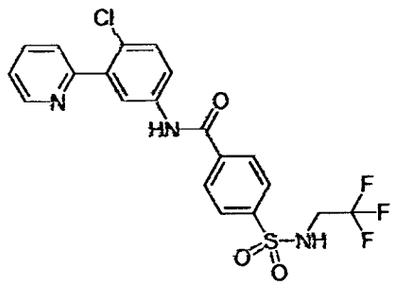
1 g of 4-(chlorosulfonyl)benzoic acid was reacted with 570 mg of 1-ethylpiperazine via Procedure H. 75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-(4-ethylpiperazin-1-ylsulfonyl)benzoic acid via Procedure G and purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(4-ethylpiperazin-1-ylsulfonyl).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

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



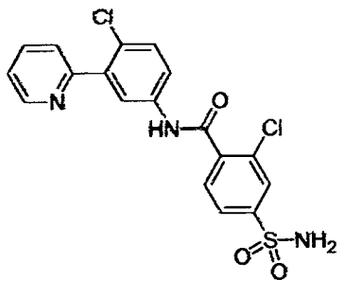
1 g of 4-(chlorosulfonyl)benzoic acid was reacted with 931 mg of *tert*-butyl piperazine-1-carboxylate via Procedure H. 75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 150 mg of 4-(4-(*tert*-butoxycarbonyl)piperazin-1-ylsulfonyl)benzoic acid via Procedure G. The crude product was subjected to 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



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 (QI) 470 $(M)^+$.

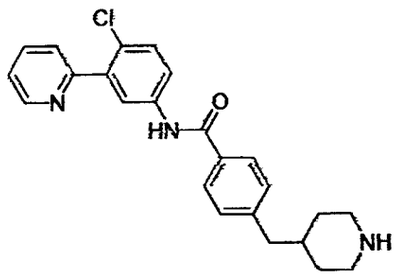
Example 211 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-sulfamoylbenzamide



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

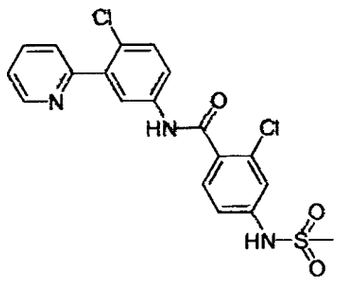
reaction was concentrated, extracted twice with saturated bicarbonate, dried with Magnesium Sulfate, filtered and concentrated to give methyl 2-chloro-4-sulfamoylbenzoate. 777 mg of methyl 2-chloro-4-sulfamoylbenzoate was hydrolyzed via Procedure M to yield crude 2-chloro-4-sulfamoylbenzoic acid. 75 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



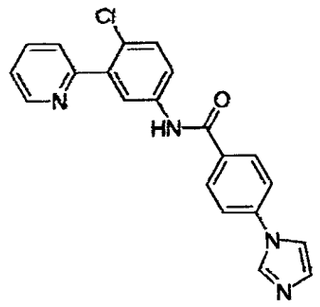
75 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 125 mg of 4-((1-(*tert*-butoxycarbonyl)piperidin-4-yl)methyl)benzoic acid via Procedure G. The crude product was treated with 4N HCl in Dioxane, evaporated and purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(piperidin-4-ylmethyl)benzamide.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

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



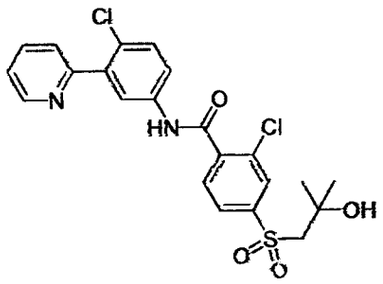
4.2 g of methyl 2-chloro-4-(methylsulfonamido)benzoate was hydrolyzed via Procedure M. 1 g of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 1.35 g of 2-chloro-4-(methylsulfonamido)benzoic acid via Procedure G. The crude product was purified by reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonamido)benzamide.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

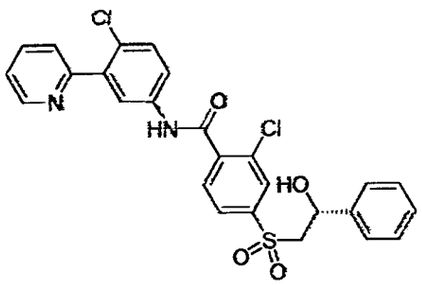
Example 215 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxy-2-methylpropylsulfonyl)-benzamide



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,

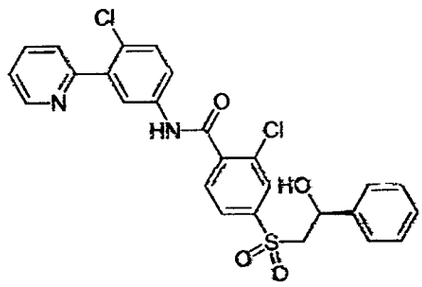
and then acidified to pH 3 by the addition of 10 N HCl. The solid was filtered and washed with H_2O to give 2-chloro-4-mercaptobenzonic acid. 3.8 g of 2-chloro-4-mercaptobenzonic acid in 40 mL of 5% sulfuric acid-methanol was refluxed under nitrogen atmosphere for 3h. After concentration of the reaction 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



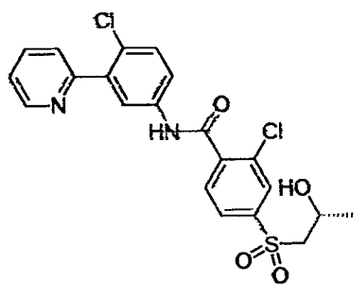
150 mg of (*R*)-styrene oxide was reacted with methyl 2-chloro-4-mercaptobenzoate via Procedure S to afford (*R*)-methyl 2-chloro-4-(2-hydroxy-2-phenylethylthio)benzoate. 190 mg of (*R*)-methyl-2-chloro-4-(2-hydroxy-2-phenylethylthio)benzoate was hydrolyzed via Procedure M to give (*R*)-2-chloro-4-(2-hydroxy-2-phenylethylthio)benzoic 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 $(M)^+$.

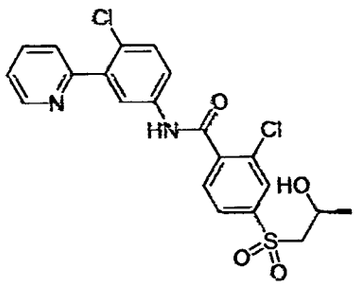
Example 218 (*R*)-2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxypropylsulfonyl)-benzamide



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-

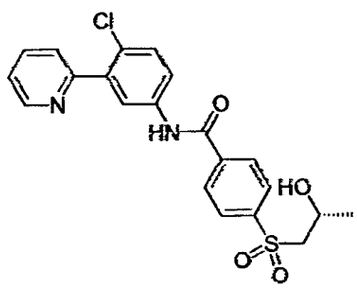
chloro-4-(2-hydroxypropylthio)benzoic acid. 403 mg of (*R*)-2-chloro-4-(2-hydroxypropylthio)benzoic acid was reacted via Procedure R to give (*R*)-2-chloro-4-(2-hydroxypropylsulfonyl)benzoic acid. 298 mg of 4-chloro-3-(pyridine-2-yl)aniline was coupled to (*R*)-2-chloro-4-(2-hydroxypropylsulfonyl)benzoic 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



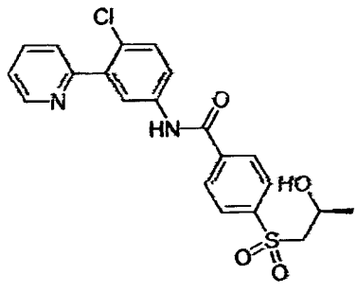
86 mg of (*S*)-propylene oxide was reacted with methyl 2-chloro-4-mercaptobenzoate via Procedure S to afford (*S*)-methyl 2-chloro-4-(2-hydroxypropylthio)benzoate. 275 mg of (*S*)-methyl-2-chloro-4-(2-hydroxypropylthio)benzoate was hydrolyzed via Procedure M to give (*S*)-2-chloro-4-(2-hydroxypropylthio)benzoic 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



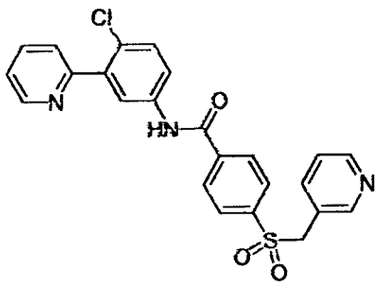
100 mg of (*R*)-propylene oxide was reacted with methyl 4-mercaptobenzoate via Procedure S to afford (*R*)-methyl 4-(2-hydroxypropylthio)benzoate. 169 mg of (*R*)-methyl 4-(2-hydroxypropylthio)benzoate was reacted via Procedure R to give (*R*)-methyl 4-(2-hydroxypropylsulfonyl)benzoate. 179 mg of (*R*)-methyl 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



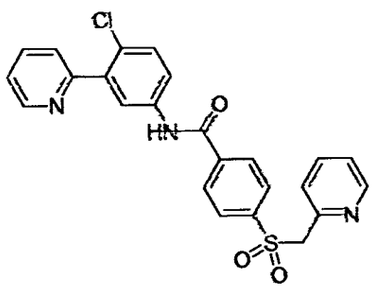
150 mg of (*S*)-propylene oxide was reacted with methyl 4-mercaptobenzoate via Procedure S to afford (*S*)-methyl 4-(2-hydroxypropylthio)benzoate. 650 mg of (*S*)-methyl 4-(2-hydroxypropylthio)benzoate was reacted via Procedure R to give (*S*)-methyl 4-(2-hydroxypropylsulfonyl)benzoate. 350 mg of (*S*)-methyl 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



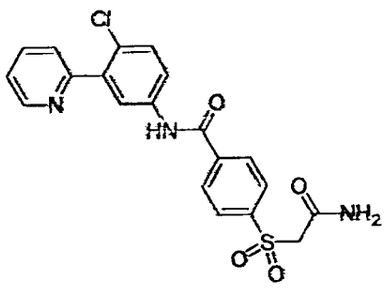
1g of 3-(bromomethyl)pyridine hydrobromide was reacted with methyl 4-mercaptobenzoate via Procedure Q to afford methyl 4-(pyridin-3-ylmethylthio)benzoate. 980 mg of methyl 4-(pyridin-3-ylmethylthio)benzoate was reacted via Procedure R to give methyl 4-(pyridin-3-ylmethylsulfonyl)benzoate. 760 mg of methyl 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



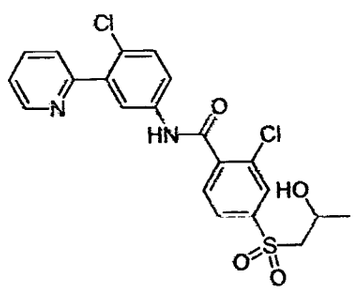
1g of 2-(bromomethyl)pyridine hydrobromide was reacted with methyl 4-mercaptobenzoate via Procedure Q to afford methyl 4-(pyridin-2-ylmethylthio)benzoate. 500 mg of methyl 4-(pyridin-2-ylmethylthio)benzoate was reacted via Procedure R to give methyl 4-(pyridin-2-ylmethylsulfonyl)benzoate. 470 mg of methyl 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



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 $(M)^+$.

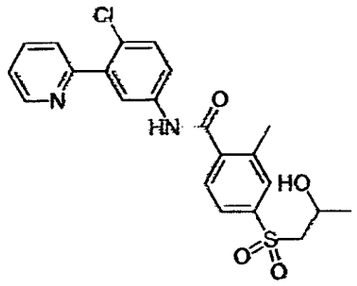
Example 225 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxypropylsulfonyl)benzamide



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-

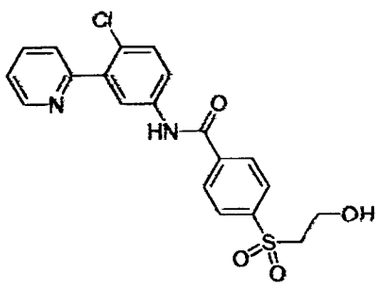
chloro-3-(pyridin-2-yl)aniline was coupled to 2-chloro-4-(2-hydroxypropylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxypropylsulfonyl)benzamide. MS (Q1) 465.2 $(M)^+$.

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 $(M)^+$.

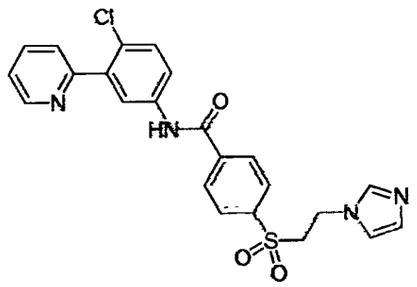
Example 227 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxyethylsulfonyl)benzamide



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

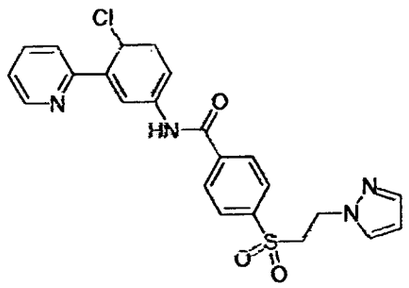
Procedure T to give 4-(2-hydroxyethylthio)benzoic acid. 1.0 g of 4-(2-hydroxyethylthio)benzoic acid was reacted via Procedure R to give 4-(2-hydroxyethylsulfonyl)benzoic acid. 80 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-(2-hydroxyethylsulfonyl)benzoic acid via Procedure G. The product 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



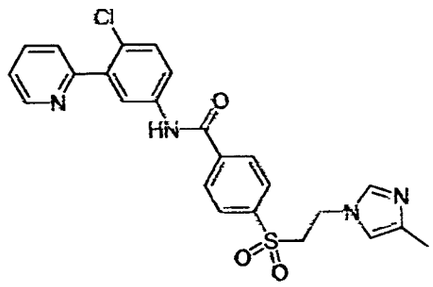
4 g of 4-(2-hydroxyethylthio)benzonitrile was reacted via Procedure R to yield 4-(2-hydroxyethylsulfonyl)benzonitrile. 3.0 g of triphenylphosphine was added to a solution of 2 g of 4-(2-hydroxyethylsulfonyl)benzonitrile and 4.7 g of carbon tetrabromide in dichloromethane at 0 °C. The reaction mixture 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 $(M)^+$.

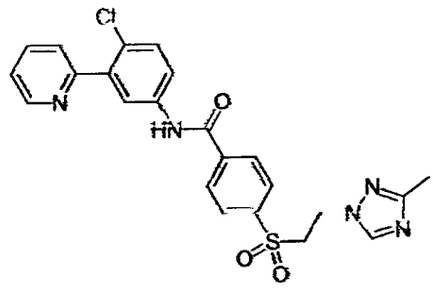
Example 230 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-(4-methyl-1*H*-imidazol-1-yl)ethylsulfonyl)benzamide



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 $(M)^+$.

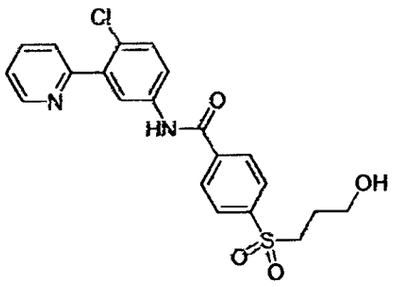
Example 231 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-(3-methyl-1*H*-1,2,4-triazol-1-yl)ethylsulfonyl)benzamide.



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.

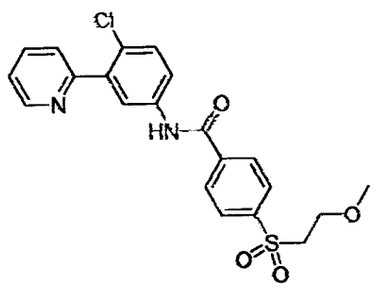
60 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-(2-(3-methyl-1*H*-1,2,4-triazole-1-yl)ethylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-(3-methyl-1*H*-1,2,4-triazol-1-yl)ethylsulfonyl)benzamide. MS (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 (Q1) 431.3 $(M)^+$.

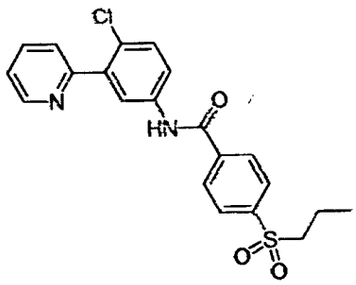
Example 233 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-methoxyethylsulfonyl)benzamide



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

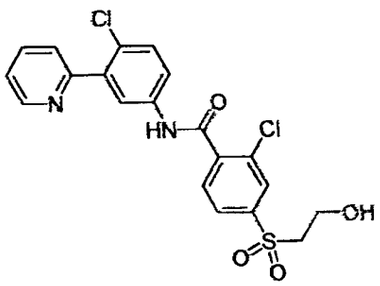
Procedure G. The product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-methoxyethylsulfonyl)benzamide. MS (Q1) 431.0 $(M)^+$.

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 $(M)^+$.

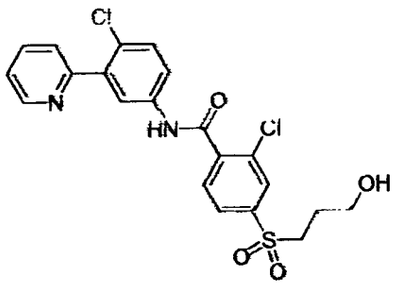
Example 235 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxyethylsulfonyl)benzamide



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-

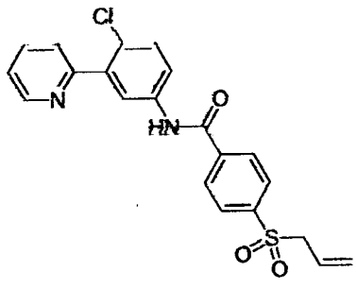
hydroxyethylsulfonyl)benzoic acid. 50 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 2-chloro-4-(2-hydroxyethylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-hydroxyethylsulfonyl)benzamide. MS (Q1)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

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



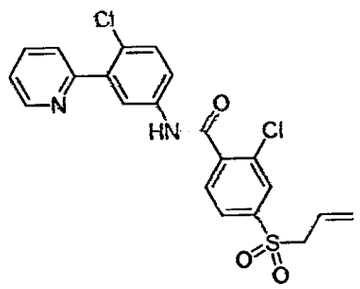
4 g of 2-chloro-4-fluorobenzonitrile was used in Procedure Q with 3-mercapto-1-propanol to afford 2-chloro-4-(3-hydroxypropylthio)benzonitrile. 1 g of 2-chloro-4-(3-hydroxypropylthio)benzonitrile was reacted via Procedure T to give 2-chloro-4-(3-hydroxypropylthio)benzoic acid. 1.2 g of 2-chloro-4-(3-hydroxypropylthio)benzoic 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



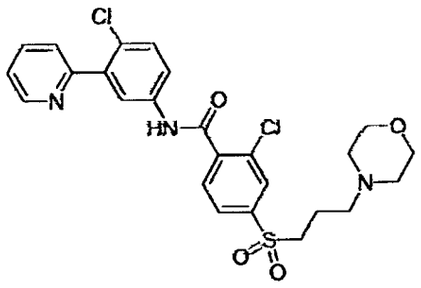
7.3 g of 4-(3-hydroxypropylthio)benzonitrile was reacted via Procedure R to yield 4-(3-hydroxypropylsulfonyl)benzonitrile. 1.9 g of NBS was added to a solution of 2 g of 4-(3-hydroxypropylsulfonyl)benzonitrile and 2.8 g of triphenylphosphine in 10 mL of dichloromethane at 0 °C. The reaction mixture was 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



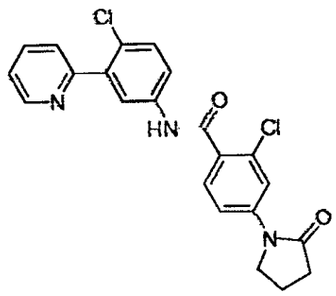
115 mg of NBS was added to a solution of 200 mg of 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(3-hydroxypropylsulfonyl)benzamide and 169 mg of triphenylphosphine in 3 mL of dichloromethane at 0 °C. The reaction mixture was stirred at 0 ~5 °C for 1h. The mixture was diluted with dichloromethane, 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



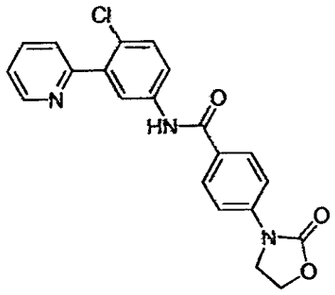
120 mg of 4 (3 bromopropylsulfonyl) 2 chloro *N* (4 chloro 3 (pyridin 2 yl)phenyl)benzamide was used in Procedure P with morpholine to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(3-morpholinopropylsulfonyl)benzamide. MS (Q1) 534.0 $(M)^+$.

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



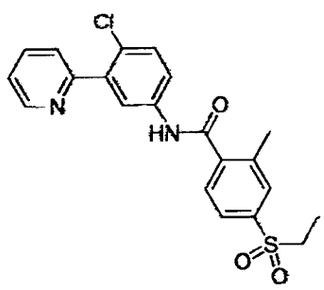
A mixture of 500 mg of 2 chloro 4 florobenzonitrile, 821 mg of 2 pyrrolidinone and 3 g of cesium carbonate in 5 mL of DMF was heated to 100 °C in a sealed microwave reactor for 15 min. The reaction mixture was diluted with ethyl acetate, washed with H_2O, dried ($MgSO_4$) and evaporated. Purified by 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



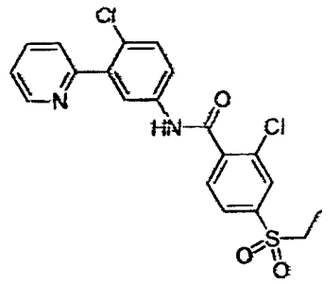
A mixture of 1 g of methyl 4 iodobenzoate, 399 mg of 2 oxozolidone, 1.1 g of potassium carbonate, 34 mg of N, N'-dimethylethylenediamine and 73 mg of copper iodide in 10 mL of toluene was heated to 150 °C in a sealed microwave reactor for 2h. The reaction mixture was diluted with ethyl acetate, washed 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



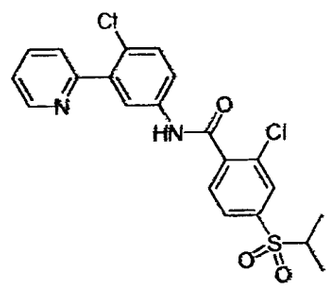
4 g of 4-bromo-2-methylbenzonitrile was used in Procedure Q with ethanethiol to afford 4-(ethylthio)-2-methylbenzonitrile. 2 g of 4-(ethylthio)-2-methylbenzonitrile was reacted via Procedure R to give 4-(ethylsulfonyl)-2-methylbenzonitrile. 2.5 g of 4-(ethylsulfonyl)-2-methylbenzonitrile was reacted 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 $(M)^+$.

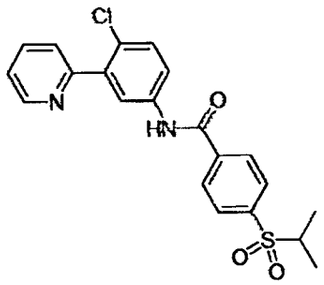
Example 244 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(isopropylsulfonyl)benzamide



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-(isopropylthio)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

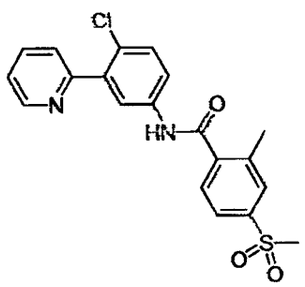
phase HPLC to yield 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(isopropylsulfonyl)benzamide. MS (Q1) 449.1 $(M)^+$.

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-(isopropylthio)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)

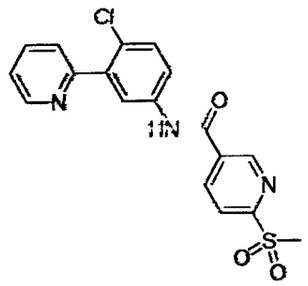
Example 246 *N* (4 chloro 3 (pyridin 2 yl)phenyl) 2 methyl 4 (methylsulfonyl)benzamide



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-

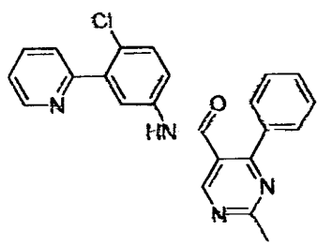
(methylthio)benzoic acid. 430 mg of 2-methyl-4-(methylthio)benzoic acid was reacted via Procedure R to yield 2-methyl-4-(methylsulfonyl)benzoic acid. 60 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 2-methyl-4-(methylsulfonyl)benzoic acid via Procedure G. The product was purified on reverse phase 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



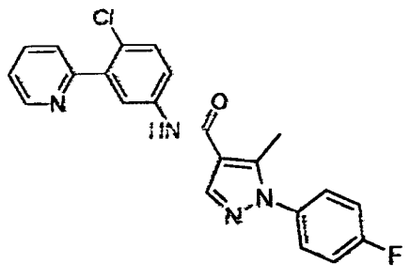
1 g of methyl 6 chloronicotinate was reacted via Procedure O to yield methyl 6-(methylsulfonyl)nicotinate. 1 g of methyl 6-(methylsulfonyl)nicotinate was hydrolyzed via Procedure M to give 6-(methylsulfonyl)nicotinic acid. 100 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 6-(methylsulfonyl)nicotinic 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



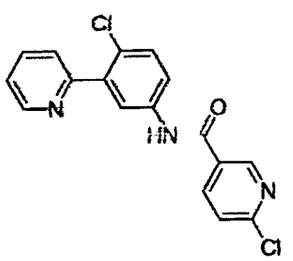
50 mg of 4 chloro 3 (pyridin 2 yl)aniline was coupled to 4 methyl 2 phenyl 5 pyrimidine carboxylic acid via Procedure G. The product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-4-phenylpyrimidine-5-carboxamide. MS (Q1) 401.1 $(M)^+$.

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



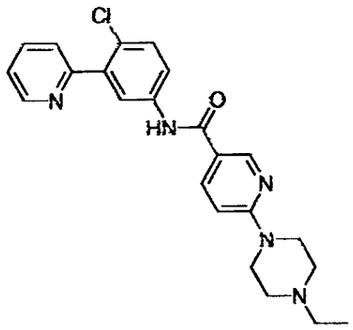
50 mg of 4 chloro 3 (pyridin 2 yl)aniline was coupled to 1 (4 fluorophenyl) 5 methyl 1*H*-pyrazole-4-carboxylic acid via Procedure G. The product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-1-(4-fluorophenyl)-5-methyl-1*H*-pyrazole-4-carboxamide. MS (Q1) 407.0 $(M)^+$.

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



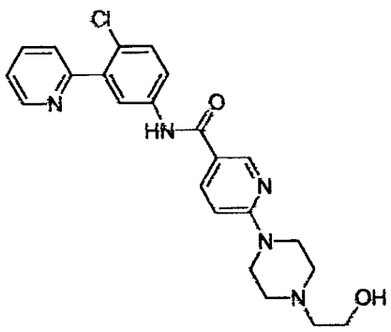
A mixture of 450 mg of 4 chloro 3 (pyridin 2 yl)aniline, 427 mg of 6 chloronicotinyl chloride and 1.9 g of PS-DIEA in 10 mL of dichloromethane was shook on the shaker for 3h. The reaction mixture was filtered and washed with dichloromethane. The filtrate was concentrated to yield 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide.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

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



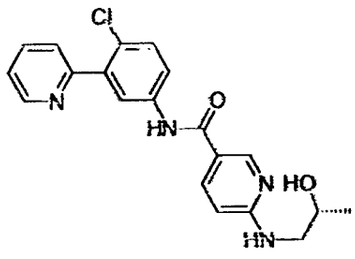
Procedure F was performed using 50 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide and 93 μL of 1-ethylpiperazine in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(4-ethylpiperazin-1-yl)nicotinamide. MS (Q1) 422.0 $(M)^+$.

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



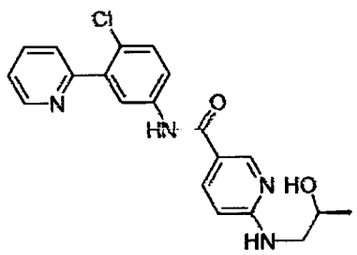
Procedure F was performed using 50 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide and 90 μL of 1-(2-hydroxyethyl)piperazine in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(4-(2-hydroxyethyl)piperazin-1-yl)nicotinamide. MS (Q1) 438.0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

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



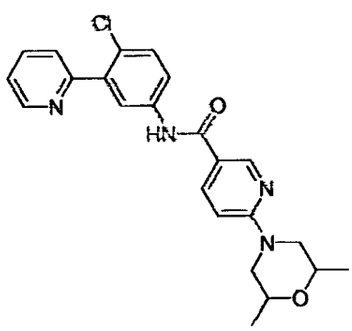
Procedure F was performed using 50 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide and 57 μL of R-1-Amino-2–propanol in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield (*R*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(2-hydroxypropylamino)nicotinamide. MS (Q1) 383.4 $(M)^+$.

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



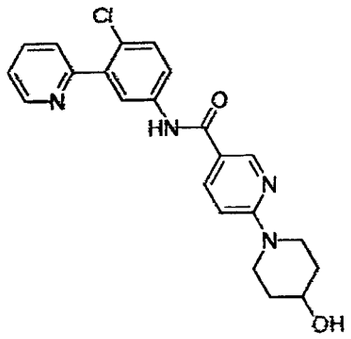
Procedure F was performed using 50 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide and 57 μL of S-1-Amino-2–propanol in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield (*S*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(2-hydroxypropylamino)nicotinamide. MS (Q1) 383.4 $(M)^+$.

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



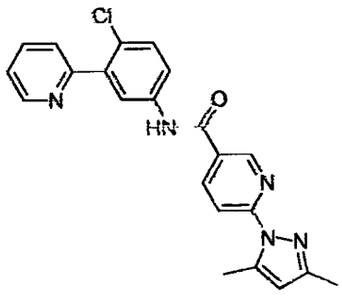
Procedure F was performed using 50 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)nicotinamide and 90 µL of 2,6-dimethylmorpholine in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(2,6-dimethylmorpholino)nicotinamide. MS (Q1) 423.4 $(M)^+$.

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 $(M)^+$.

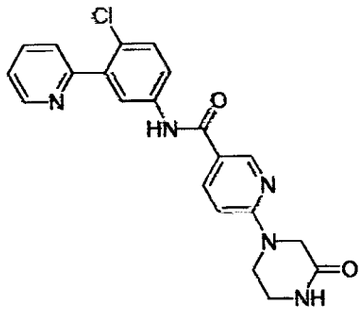
Example 257 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(3,5-dimethyl-1*H*-pyrazol-1-yl)nicotinamide



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

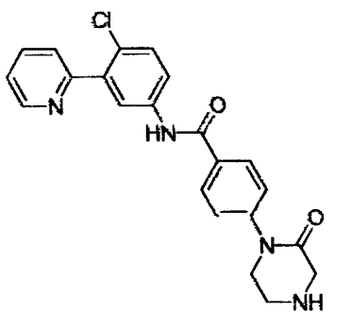
mixture was quenched with MeOH and evaporated. The product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(3,5-dimethyl-1*H*-pyrazol-1-yl)nicotinamide. MS (Q1) 404.3 $(M)^+$.

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 $(M)^+$.

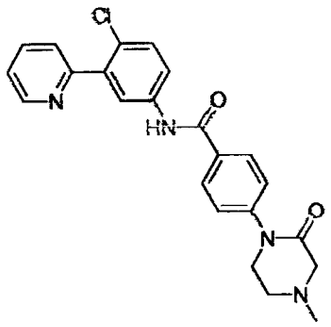
Example 259 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-oxopiperazin-1-yl)benzamide



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-

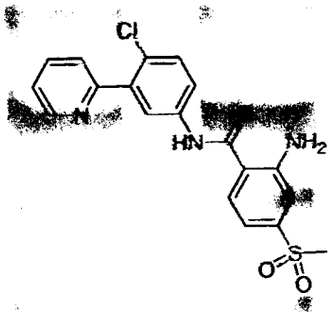
(methoxycarbonyl)phenyl)-3-oxopiperazine-1-carboxylate. 500 mg of tert-butyl 4-(4-(methoxycarbonyl)phenyl)-3-oxopiperazine-1-carboxylate was hydrolyzed via Procedure M to give 4-(4-(tert-buthoxycarbonyl)-2-oxopiperazin-1-yl)benzoic acid. 100 mg of 4-chloro-3-(pyridin-2-yl)aniline was coupled to 4-(4-(tert-buthoxycarbonyl)-2-oxopiperazin-1-yl)benzoic 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



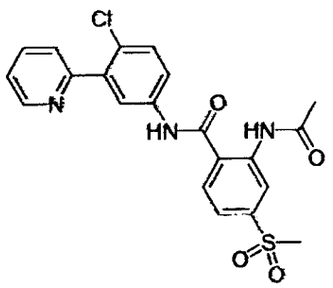
120 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(2-oxopiperazin-1-yl)benzamide was dissolved in 2 mL of DMF and then treated with 53 mg of paraformaldehyde, 187 mg of sodium triacetoxyborohydride and 0.2 mL of AcOH. After stirring 16 h, the reaction mixture was evaporated and the crude product was 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



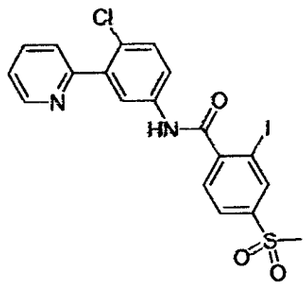
2.2 g of methyl 4-(methylsulfonyl)-2-nitrobenzoate was reacted via Procedure C to afford methyl 2-amino-4-(methylsulfonyl)benzoate. 500 mg of methyl 2-amino-4-(methylsulfonyl)benzoate was hydrolyzed via Procedure M to give 2-amino-4-(methylsulfonyl)benzoic acid. 100 mg of 4-chloro-3-(pyridin-2-yl)aniline 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



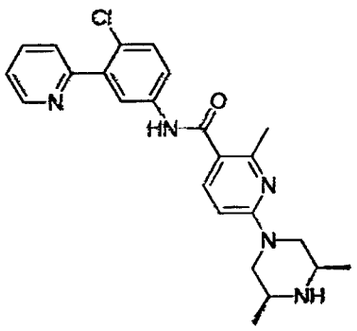
20 µL of acetyl chloride was added to a solution of 90 mg of 2-amino *N*-(4 chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide in 2 mL of pyridine at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2h. The reaction was quenched with MeOH and evaporated. The 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 $(M)^+$.

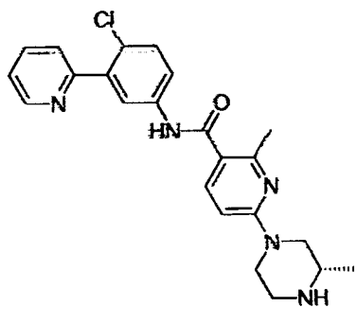
Example 264 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-((3*S*,5*R*)-3,5-dimethylpiperazin-1-yl)-2-methylnicotinamide



Stoichiometric amounts (0.04 mol) of methyl proplolate 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

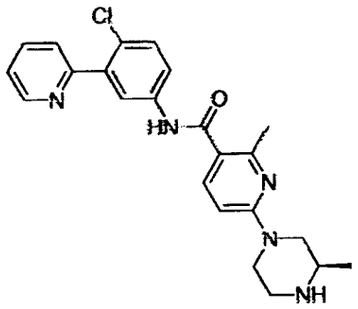
diluted with ethyl acetate, washed with H_2O, dried ($MgSO_4$) and evaporated to afford crude ethyl 6-hydroxy-2-methylnicotinate. A mixture of 800 mg of crude ethyl 6-hydroxy-2-methylnicotinate in 4 mL of phosphorus oxychloride was heated to 150 °C in a sealed microwave reactor for 15 min. The reaction 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



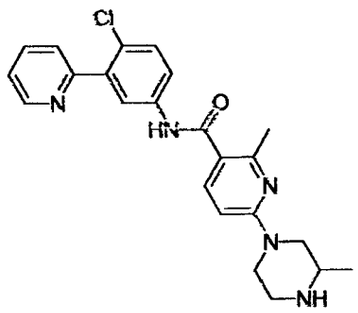
Procedure F was performed using 100 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 112 mg of S-(-)-2-methylpiperizine in 1 mL of BuOH. Purified by reverse phase HPLC to yield (*S*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(3-methylpiperazin-1-yl)nicotinamide. MS (Q1) 422.3 $(M)^+$.

Example 266 (*R*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(3-methylpiperazin-1-yl)nicotinamide.



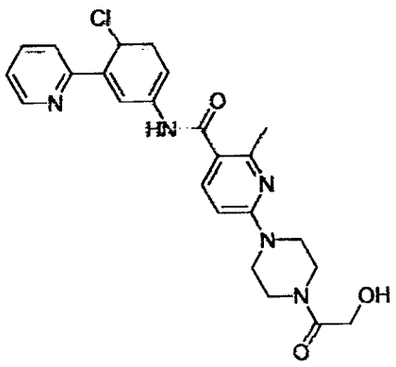
Procedure F was performed using 100 mg of 6 chloro *N* (4 chloro 3 (pyridin 2 yl)phenyl)-2-methylnicotinamide and 112 mg of R-(+)-2-methylpiperizine in 1 mL of BuOH. Purified by reverse phase HPLC to yield (*R*) *N* (4 chloro-3 (pyridin-2 yl)phenyl)-2 methyl-6-(3-methylpiperazin-1-yl)nicotinamide. MS (Q1) 422.3 $(M)^+$.

Example 267 *N* (4 chloro 3 (pyridin 2 yl)phenyl) 2 methyl 6 (3 methylpiperazin 1-yl)nicotinamide



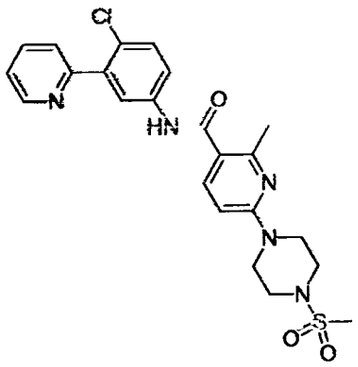
Procedure F was performed using 100 mg of 6 chloro *N* (4 chloro 3 (pyridin 2 yl)phenyl) 2-methylnicotinamide and 112 mg of 2-methylpiperizine in 1 mL of BuOH. Purified by reverse phase HPLC to yield *N* (4 chloro-3 (pyridin-2 yl)phenyl) 2 methyl 6-(3 methylpiperazin-1-yl)nicotinamide. MS (Q1) 422.3 $(M)^+$.

Example 268 *N* (4 chloro 3 (pyridin 2 yl)phenyl) 6 (4 (2 hydroxyacetyl)piperazin 1 yl) 2-methylnicotinamide



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 $(M)^+$.

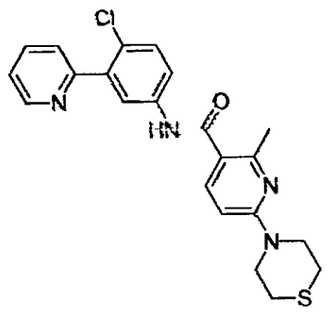
Example 269 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(4-(methylsulfonyl)piperazin-1-yl)nicotinamide



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

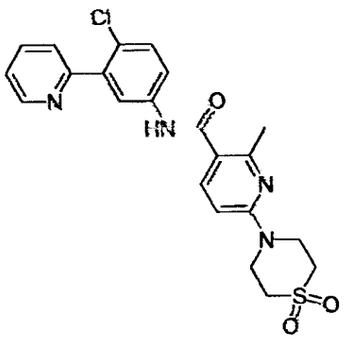
HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(4-(methylsulfonyl)piperazin-1-yl)nicotinamide. MS (Q1) 486.3 $(M)^+$.

Example 270 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-thiomorpholinonicotinamide



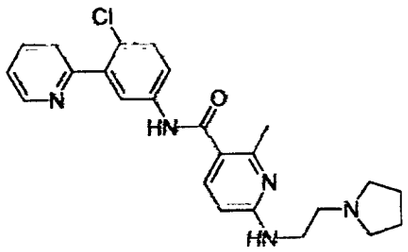
Procedure F was performed using 90 mg of 6-chloro *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 78 µL of thiomorpholine in 1 mL of BuOH. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-thiomorpholinonicotinamide. MS (Q1) 425.3 $(M)^+$.

Example 271 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-sulfonylmorpholinonicotinamide



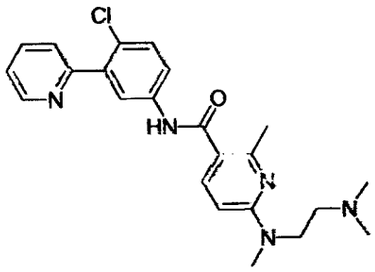
100 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-thiomorpholinonicotinamide was reacted via produce R. The product was purified on reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-sulfonylmorpholinonicotinamide. MS (Q1) 457.3 $(M)^+$.

Example 272 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(2-(pyrrolidin-1-yl)ethylamino)-nicotinamide



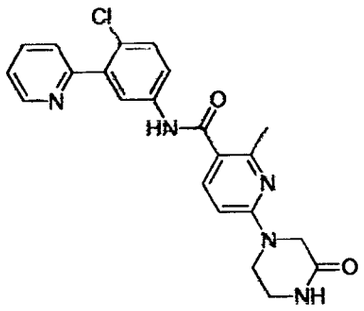
Procedure F was performed using 100 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 70 µL of 1-(2-aminoethyl)pyrrolidine in 1 mL of BuOH. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(2-(pyrrolidin-1-yl)ethylamino)nicotinamide. MS (Q1) 436.0 $(M)^+$.

Example 273 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-((2-(dimethylamino)ethyl)(methyl)amino)-2-methylnicotinamide



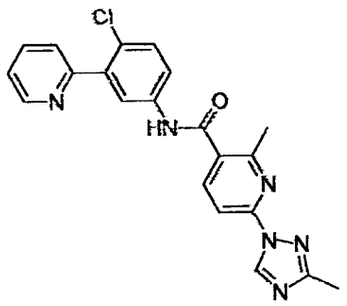
Procedure F was performed using 60 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 66 µL of N,N,N'-trimethylethylenediamine in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-((2-(dimethylamino)ethyl)(methyl)amino)-2-methylnicotinamide. MS (Q1) 424.0 $(M)^+$.

Example 274 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(3-oxopiperazin-1-yl)nicotinamide



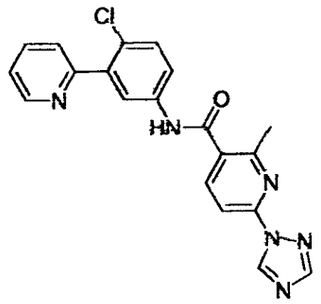
Procedure F was performed using 100 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 84 mg of piperazine-2-one in 1 mL of BuOH. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(3-oxopiperazin-1-yl)nicotinamide. MS (Q1) 422.3 $(M)^+$.

Example 275 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methyl-6-(3-methyl-1*H*-1,2,4-triazol-1-yl)nicotinamide



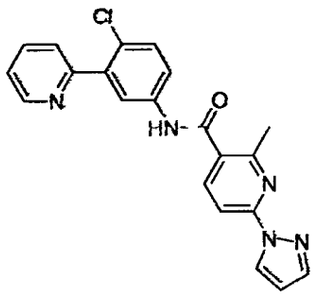
A mixture of 57 mg of 3-methyl 1,2,4 triazol and 16 mg of sodium hydride in 2 mL of DMF was stirred for 10 min. 80 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide was added. The reaction was heated to 140 °C for 16h. The reaction mixture was quenched with MeOH and evaporated. 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



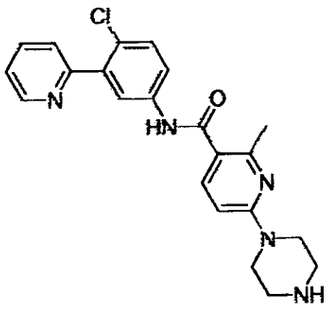
A mixture of 41 mg of 1,2,4-triazol and 14 mg of sodium hydride in 2 mL of DMF was stirred for 10 min. 70 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide was added. The reaction was heated to 140 °C for 6h. The reaction mixture was quenched with MeOH and evaporated. Purified 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



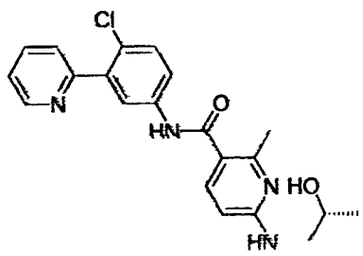
A mixture of 52 mg of pyrazole and 18 mg of sodium hydride in 2 mL of DMF were stirred for 10 min. 90 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide was added. The reaction was heated to 140 °C for 5h. The reaction mixture was quenched with MeOH and evaporated. Purified by 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



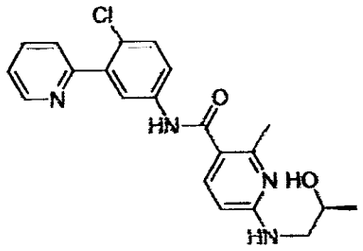
Procedure F was performed using 80 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 209 mg of 1-Boc-piperizine in 1 mL of BuOH. The reaction mixture was evaporated to afford tert-butyl 4-(5-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)-6-methylpyridin-2-yl)piperazine-1-carboxylate. 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



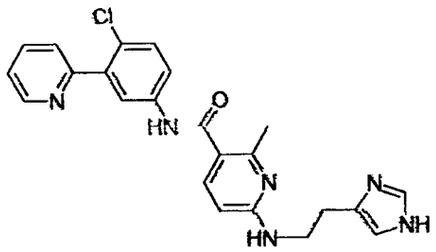
Procedure F was performed using 60 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 116 µL of R-(-)-1-amino-2-propanol in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield (*R*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(2-hydroxypropylamino)-2-methylnicotinamide. MS (Q1) 397.4 $(M)^+$.

Example 280 (*S*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(2-hydroxypropylamino)-2-methylnicotinamide



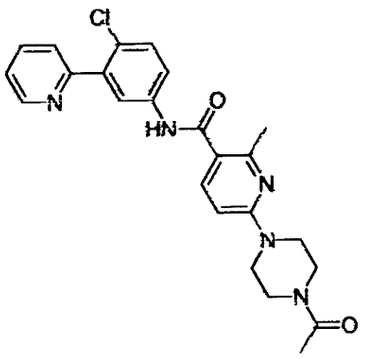
Procedure F was performed using 60 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 116 μL of S-(+)-1-amino-2-propanol in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield (*S*)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(2-hydroxypropylamino)-2-methylnicotinamide. MS (Q1) 397.4 $(M)^+$.

Example 281 6-(2-(1*H*-imidazol-4-yl)ethylamino) *N* (4 chloro 3-(pyridin-2-yl)phenyl)-2-methylnicotinamide



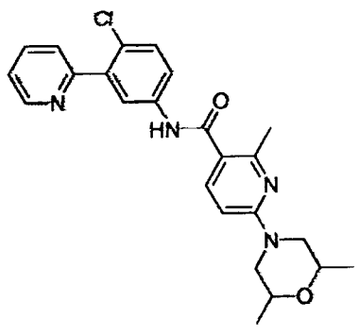
Procedure F was performed using 60 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 93 mg of histamine in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield 6-(2-(1*H*-imidazol-4-yl)ethylamino)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide. MS (Q1) 433.0 (M)

Example 282 6-(4-acetylpiperazin-1-yl) *N* (4 chloro 3 (pyridin 2-yl)phenyl)-2-methylnicotinamide



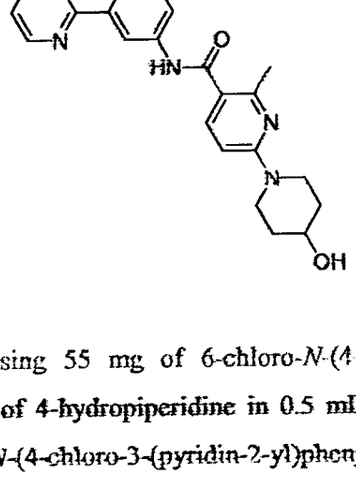
Procedure F was performed using 55 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 99 mg of 1-acetylpiperazine in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield 6-(4-acetylpiperazin-1-yl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide. MS (Q1) 450.4 $(M)^+$.

Example 283 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(2,6-dimethylmorpholino)-2-methylnicotinamide



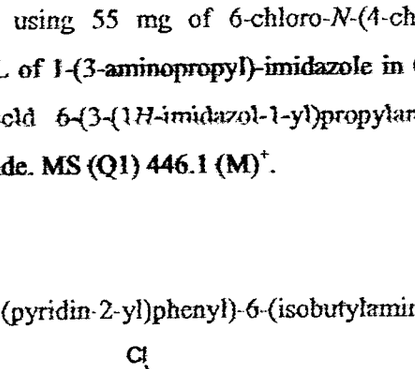
Procedure F was performed using 55 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 95 mg of 2,6-dimethylmorpholine in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(2,6-dimethylmorpholino)-2-methylnicotinamide. MS (Q1) 436.2 $(M)^+$.

Example 284 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(4-hydroxypiperidin-1-yl)-2-methylnicotinamide



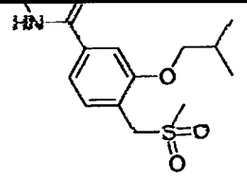
Procedure F was performed using 55 mg of 6-chloro-*N*-(4 chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 78 mg of 4-hydropiperidine in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(4-hydroxypiperidin-1-yl)-2-methylnicotinamide. MS (Q1) 422.1 $(M)^+$.

Example 285 6-(3-(1*H*-imidazol-1-yl)propylamino) *N*-(4 chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide



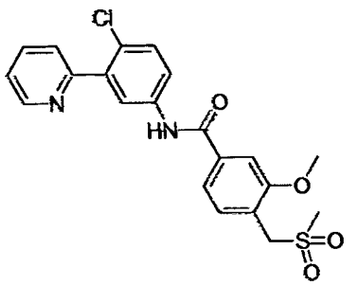
Procedure F was performed using 55 mg of 6-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide and 92 µL of 1-(3-aminopropyl)-imidazole in 0.5 mL of BuOH. Purified by reverse phase HPLC to yield 6-(3-(1*H*-imidazol-1-yl)propylamino)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-2-methylnicotinamide. MS (Q1) 446.1 $(M)^+$.

Example 286 *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-6-(isobutylamino)-2-methylnicotinamide



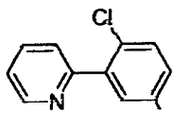
N-(4-chloro-3-(pyridin-2-yl)phenyl)-3-hydroxy-4-(methylsulfonylmethyl)benzamide (50 mg, 0.12 mmol) was treated with 1-bromo-2-methylpropane (26 µl, 0.24 mmol) via procedure U to yield 19 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-isobutoxy-4-(methylsulfonylmethyl)benzamide. MS (Q1) 473 $(M)^+$.

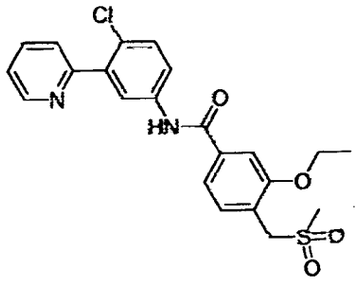
Example 291 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-3-methoxy-4-(methylsulfonylmethyl)benzamide



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 $(M)^+$.

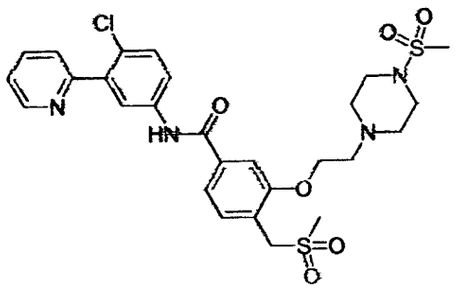
Example 292 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-3-ethoxy-4-(methylsulfonylmethyl)benzamide


Cl
N
O



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 $(M)^+$.

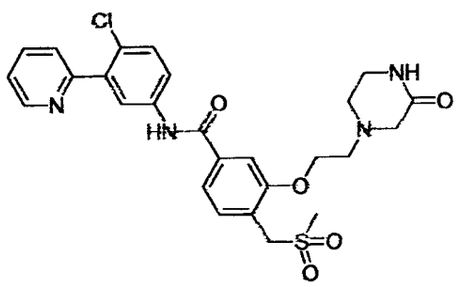
Example 293 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl) 3-(2-(4-(methylsulfonyl)piperazin-1-yl)ethoxy)-4-(methylsulfonylmethyl)benzamide



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

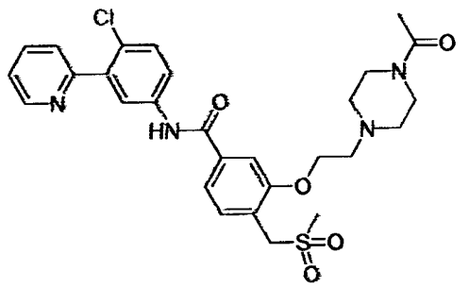
dichloromethane (1 ml) and treated with trifluoroacetic acid (3 ml) for 1 hour. The reaction was evaporated to dryness, and the crude solid was purified on reverse phase HPLC to yield 63 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)-3-(2-(piperazin-1-yl)ethoxy)benzamide as a white 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



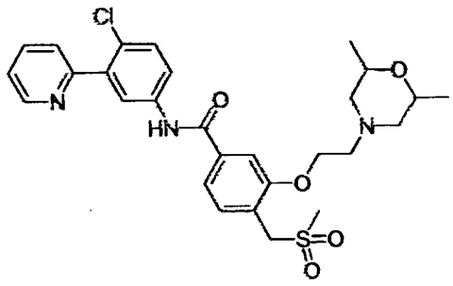
3-(2-Bromoethoxy)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide (50 mg, 0.095 mmol) was dissolved in DMF (1.0 ml) and treated with potassium carbonate (18 mg, 0.13 mmol) and piperazin-2-one (11 mg, 0.11 mmol) for 18 hours. The reaction was heated for 2.0 hours at 50°C, then 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 $(M)^+$.

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 $(M)^+$.

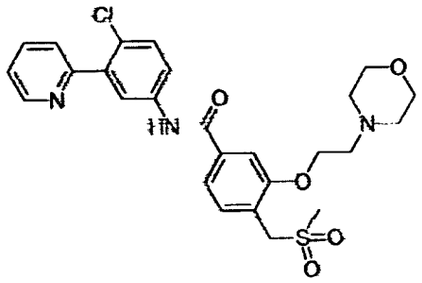
Example 296 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-3-(2-(2,6-dimethylmorpholino)ethoxy)-4-(methylsulfonylmethyl)benzamide



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

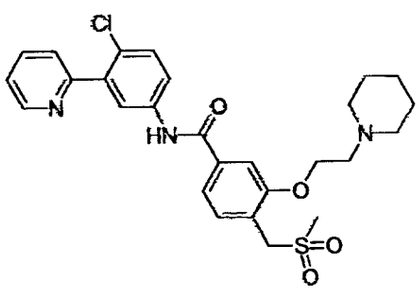
ethyl acetate extracts were washed with water once, brine once, dried with $MgSO_4$, and purified by reverse phase HPLC to yield 20 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-3-(2-(2,6-dimethylmorpholino)ethoxy)-4-(methylsulfonylmethyl)benzamide. MS (Q1) 571 $(M)^+$.

Example 297 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)-3-(2-morpholinoethoxy)benzamide



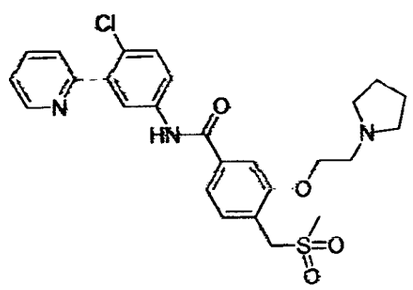
3-(2-Bromoethoxy)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide (50 mg, 0.095 mmol) was dissolved in acetonitrile (1.0 ml) and DMF (1.0 ml), treated with potassium carbonate (16 mg, 0.12 mmol) and morpholine (10 µl, 0.11 mmol), and stirred 18 hours at room temperature. The reaction 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



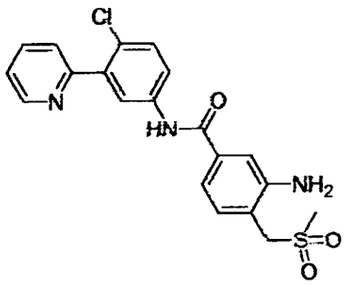
3-(2-Bromoethoxy)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide (50 mg, 0.095 mmol) was dissolved in dichloromethane (1.0 ml), treated with triethylamine (20 µl, 0.15 mmol) and piperidine (11 µl, 0.11 mmol), and stirred 2.0 hours at room temperature. Acetonitrile (0.25 ml) and *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



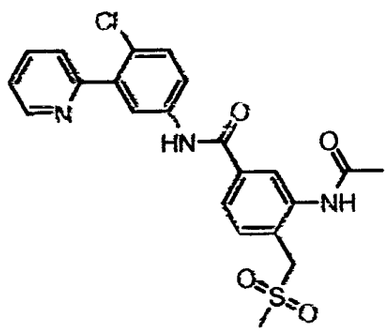
3-(2-Bromoethoxy)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide (40 mg, 0.076 mmol) was dissolved in acetonitrile (1.0 ml) and DMF (1.0 ml), treated with potassium carbonate (16 mg, 0.12 mmol) and pyrrolidine (7 µl, 0.084 mmol), and stirred 18 hours at room temperature. The 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



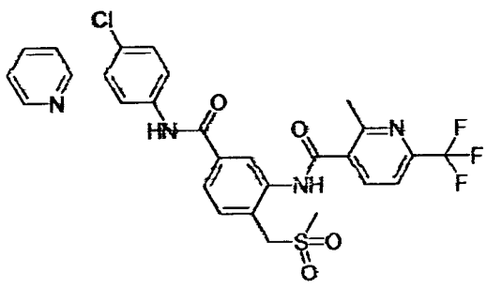
4-(Bromomethyl)-3-nitrobenzoic acid (2.00 g, 7.69 mmol) was dissolved in methanol (20 ml) and treated with 1 drop of concentrated sulfuric acid, then stirred 72 hours at room temperature. An additional 3 drops of concentrated sulfuric acid was added, and the reaction stirred at 50°C for 24 hours. The 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



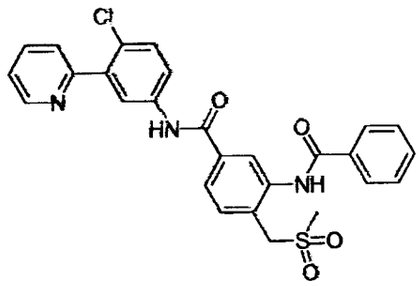
3-Amino-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide (30 mg, 0.072 mmol) was reacted with acetyl chloride (5.6 µl, 0.079 mol) via procedure V to afford 19 mg of 3-acetamido-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide as a white solid. MS (Q1) 458 $(M)^+$.

Example 302 *N*-(5-(4-Chloro-3-(pyridin-2-yl)phenylcarbamoyl)-2-(methylsulfonylmethyl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide



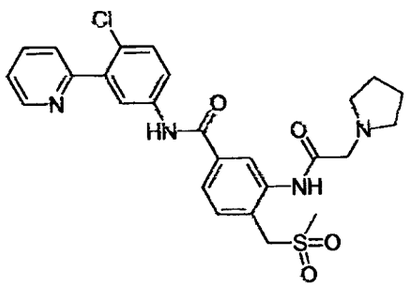
3-Amino-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)benzamide (30 mg, 0.072 mmol) was reacted with 2-methyl-6-(trifluoromethyl)nicotinoyl chloride (19 mg, 0.079 mmol) via procedure V to afford 16 mg of *N*-(5-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)-2-(methylsulfonylmethyl)phenyl)-2-methyl-6-(trifluoromethyl)nicotinamide as a white solid. MS (Q1) 603 $(M)^+$.

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) 570 $(M)^+$.

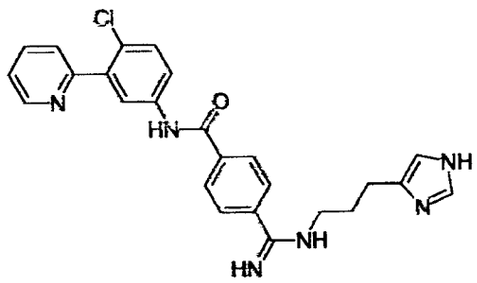
Example 304 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonylmethyl)-3-(2-(pyrrolidin-1-yl)acetamido)benzamide



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*-

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 $(M)^+$.

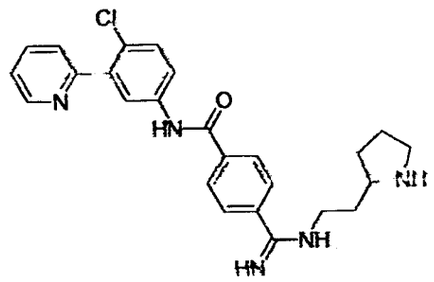
Example 305 4-(*N*-(3-(1*H*-Imidazol-4-yl)propyl)carbamimidoyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide



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.

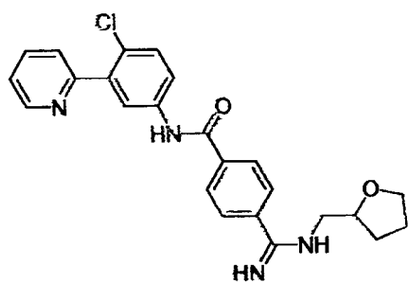
Ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzimidate (2.0 ml of a 0.075 M methanol solution, 0.15 mmol) was treated with 3-(1H-imidazol-4-yl)propan-1-amine (27 µl, 0.23 mmol) via procedure W to afford 83 mg of 4-(*N*-(3-(1*H*-imidazol-4-yl)propyl)carbamimidoyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide. 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 $(M)^+$.

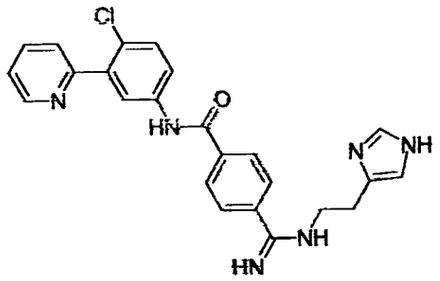
Example 307 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-((tetrahydrofuran-2-yl)methyl)carbamimidoyl)benzamide



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

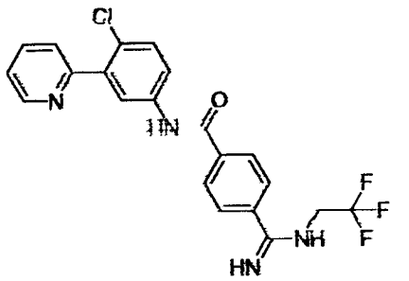
procedure W to afford 76 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-((tetrahydrofuran-2-yl)methyl)carbamimidoyl)benzamide. MS (Q1) 435 $(M)^+$.

Example 308 4-(*N*-(2-(1*H*-Imidazol-4-yl)ethyl)carbamimidoyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide



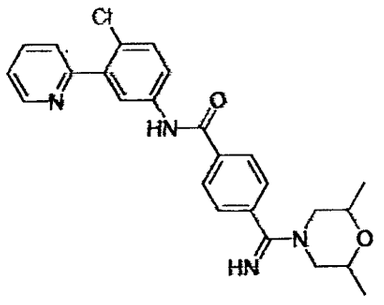
Ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzimidate (2.0 ml of a 0.075 M methanol solution, 0.15 mmol) was treated with 2-(1H-imidazol-4-yl)ethanamine (25 mg, 0.23 mmol) via procedure W to afford 90 mg of 4-(*N*-(2-(1*H*-imidazol-4-yl)ethyl)carbamimidoyl)-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)benzamide. MS (Q1) 445 $(M)^+$.

Example 309 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-(2,2,2-trifluoroethyl)carbamimidoyl)benzamide



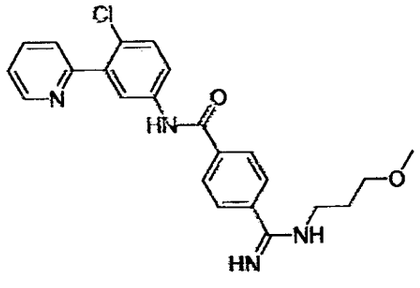
Ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzimidate (2.0 ml of a 0.075 M methanol solution, 0.15 mmol) was treated with 2,2,2-trifluoroethanamine (18 µl, 0.23 mmol) via procedure W to afford 56 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-(2,2,2-trifluoroethyl)carbamimidoyl)benzamide. MS (Q1) 433 $(M)^+$.

Example 310 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-((2,6-dimethylmorpholino)(imino)methyl)-benzamide



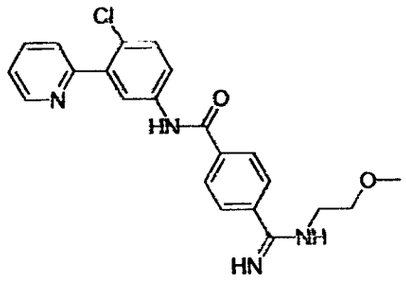
Ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzimidate (2.0 ml of a 0.075 M methanol solution, 0.15 mmol) was treated with 2,6-dimethylmorpholine (28 µl, 0.23 mmol) via procedure W to afford 74 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-((2,6-dimethylmorpholino)(imino)methyl)-benzamide. MS (Q1) 449 $(M)^+$.

Example 311 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-(3-methoxypropyl)carbamimidoyl)-benzamide



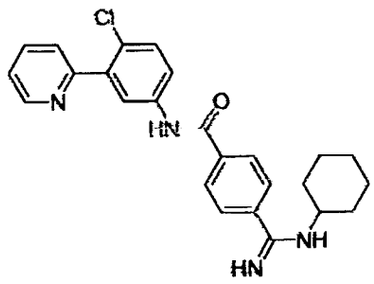
Ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzimidate (2.0 ml of a 0.075 M methanol solution, 0.15 mmol) was treated with 3-methoxypropan-1-amine (23 µl, 0.23 mmol) via procedure W to afford 68 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-(3-methoxypropyl)carbamimidoyl)-benzamide. MS (Q1) 423 $(M)^+$.

Example 312 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-(2-methoxyethyl)carbamimidoyl)benzamide



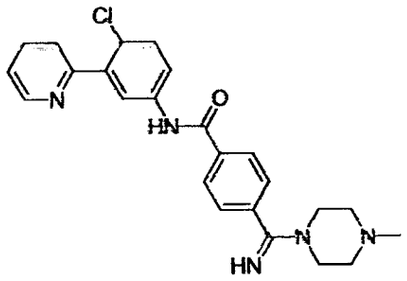
Ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzimidate (2.0 ml of a 0.075 M methanol solution, 0.15 mmol) was treated with 2-methoxyethanamine (19 µl, 0.23 mmol) via procedure W to afford 50 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-(2-methoxyethyl)carbamimidoyl)benzamide. MS (Q1) 409 $(M)^+$.

Example 313 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-cyclohexylcarbamimidoyl)benzamide



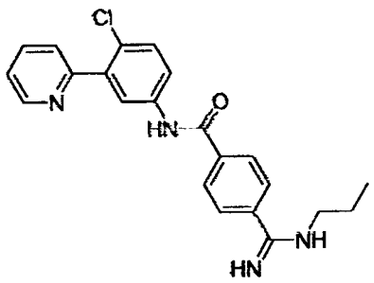
Ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzimidate (2.0 ml of a 0.075 M methanol solution, 0.15 mmol) was treated with cyclohexanamine (26 µl, 0.23 mmol) via procedure W to afford 30 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-cyclohexylcarbamimidoyl)benzamide. MS (Q1) 433 $(M)^+$.

Example 314 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(imino(4-methylpiperazin-1-yl)methyl)benzamide



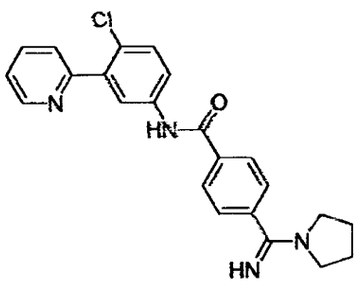
Ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzimidate (2.0 ml of a 0.075 M methanol solution, 0.15 mmol) was treated with 1-methylpiperazine (23 mg, 0.23 mmol) via procedure W to afford 35 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(imino(4-methylpiperazin-1-yl)methyl)benzamide. MS (Q1) 434 $(M)^+$.

Example 315 *N* (4-Chloro-3-(pyridin-2-yl)phenyl) 4 (*N* propylcarbanimidoyl)benzamide



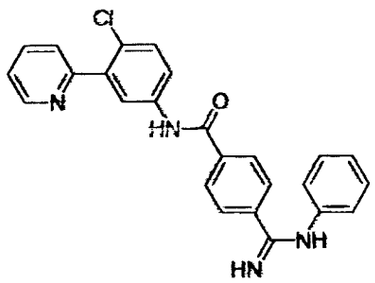
Ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzimidate (2.0 ml of a 0.075 M methanol solution, 0.15 mmol) was treated with propan-1-amine (18 µl, 0.23 mmol) via procedure W to afford 39 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(*N*-propylcarbamimidoyl)benzamide. MS (Q1) 393 $(M)^+$.

Example 316 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(imino(pyrrolidin-1-yl)methyl)benzamide



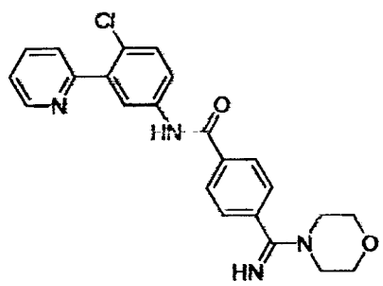
Ethyl 4-(4-chloro-3-(pyridin-2-yl)phenylcarbamoyl)benzimidate (2.0 ml of a 0.075 M methanol solution, 0.15 mmol) was treated with pyrrolidine (19 µl, 0.23 mmol) via procedure W to afford 25 mg of *N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(imino(pyrrolidin-1-yl)methyl)benzamide. MS (QI) 405 $(M)^+$.

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 (QI) 427 $(M)^+$.

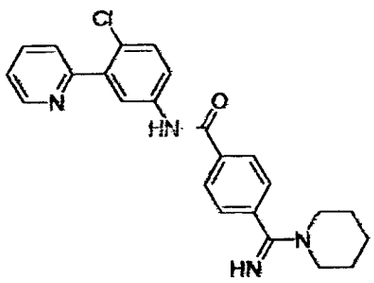
Example 318 *N*-(4-Chloro-3-(pyridin-2-yl)phenyl)-4-(imino(morpholino)methyl)benzamide



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 Serum (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.

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

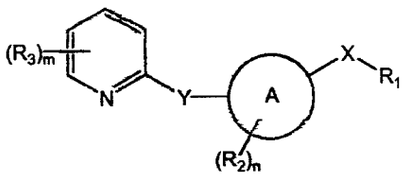
S12 and MZ24 cells genetically modified to contain a luciferase reporter gene driven by the hedgehog-reseponsive Gli promoter were maintained on tissue culture dishes in Growth Medium at 37°C and 5% CO_2. Cell cultures were passaged at sub-confluency at every 3-4 days. (1:20 to 1:40 for s12; 1:3 to 1:10 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.

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, 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;

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;

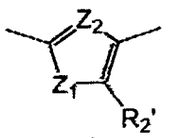
R_4 is H or alkyl;

m is 0-3;

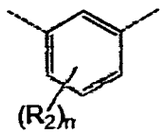
n is 0-3;

and salts and solvates thereof.

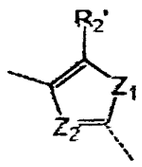
2. The compound of claim 1, wherein A is a ring selected from the group consisting of A^1, A^2, A^3, A^4 A^5, A^6 and A^7:



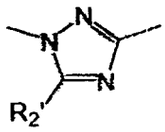
A^1



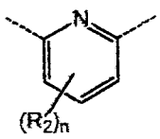
A^2



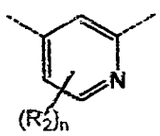
A^3



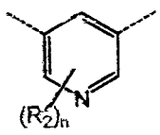
A^4



A^5



A^6



A^7

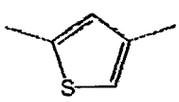
wherein Z_1 is O, S or NR_5 wherein R_5 is H or alkyl; Z_2 is CH, CR_2, or N; R_2 is halogen, hydroxyl, alkyl or alkoxy; R_2, is H, halogen, hydroxyl, alkyl or alkoxy; and n is 0-3.

3. The compound of claim 2, wherein A is ring A^1 wherein Z_1 is S and Z_2 is CH or N.

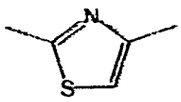
4. The compound of claim 2, wherein A is the ring A^2.

5. The compound of claim 2, wherein R_2 or R_2' is Cl.

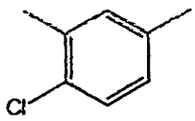
6. The compound of claim 1, wherein A is A^{1a}, A^{1b}, A^{2a}, A^{3a}, A^{3b}, A^{4a}, A^{5a}, A^{6a}, A^{7a},:



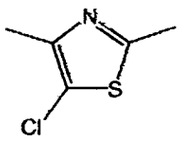
A^{1a}



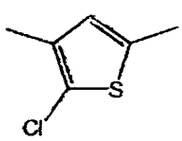
A^{1b}



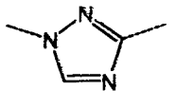
A^{2a}



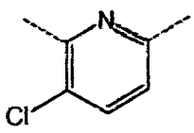
A^{3a}



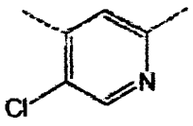
A^{3b}



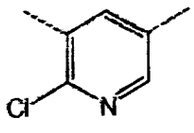
A^{4a}



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.

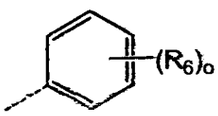
11. The compound of claim 1, wherein R_3 is Me or F.

12. The compound of claim 1, wherein R_3 is Me and m is 1 or 2.

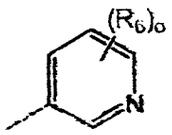
13. The compound of claim 1, wherein R_3 is F and m is 1 or 2.

14. The compound of claim 1, wherein m is 0.

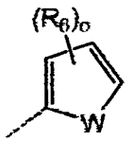
15. The compound claim 1, wherein R_1 is selected from the group consisting of formula IIa - IIo:



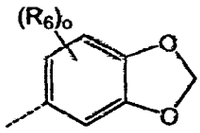
IIa



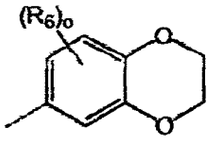
IIb



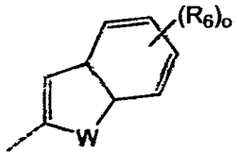
IIc



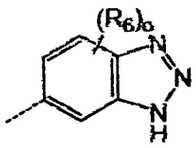
IId

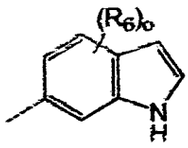


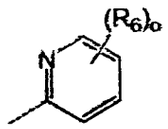
IIe

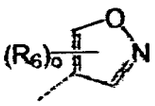


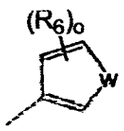
IIf

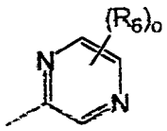

IIg

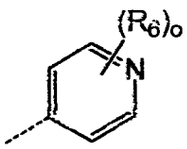

IIh

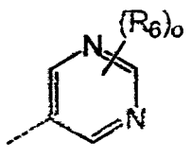

IIi

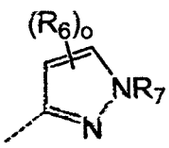

IIj


IIk


III


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;

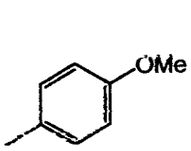
R_6 in each instance is independently hydroxyl, halogen, amino, carbonyl, nitro, cyano, acyl, alkyl, sulfonyl, alkylsulfonyl, alkylsulfinyl, alkoxy, alkylcarbamoyl, alkanoylamine, alkylsulfamoyl, alkylsulfonamide, a carbocycle or a heterocycle; wherein said amino, alkyl, carbonyl, acyl, sulfonyl, alkylsulfonyl, 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.

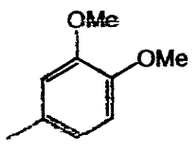
16. The compound of claim 15, wherein R_1 is the group of formula IIa.

17. The compound of claim 16, wherein R_6 is alkoxy and o is 1 or 2.

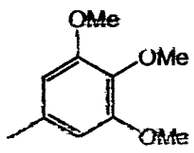
18. The compound of claim 16, wherein R_1 is selected from the group of formula IIa^1 - IIa^{28}:



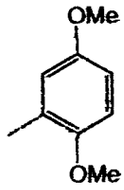
IIa[1]



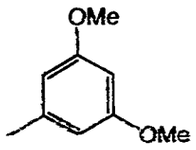
IIa[2]



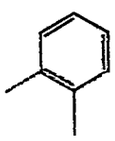
IIa[3]



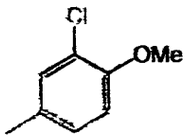
IIa[4]



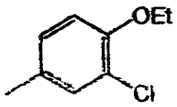
IIa[5]



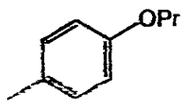
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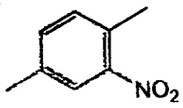
IIa[7]



IIa[8]

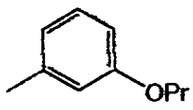


IIa[9]

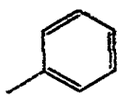


IIa[10]

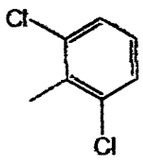
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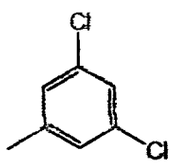
IIa[11]



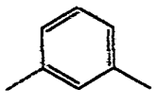
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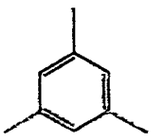
IIa[13]



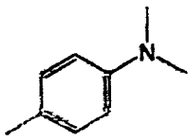
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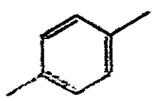
IIa[15]



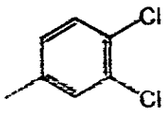
IIa[16]



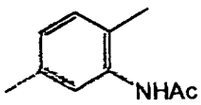
IIa[17]



IIa[18]

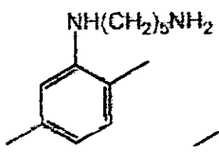


IIa[19]

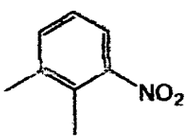


IIa[20]

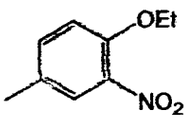
10



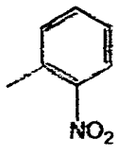
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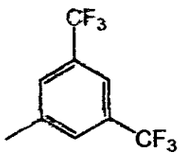
IIa[22]



IIa[23]

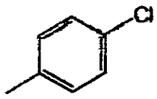


IIa[24]

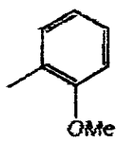


IIa[25]

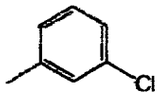
15



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.

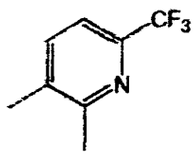
22. The compound of claim 3, wherein m is 0.

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.

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.

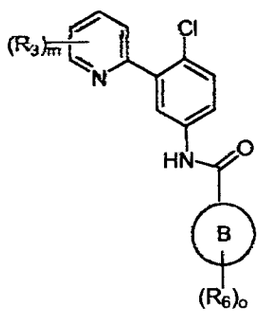
33. A method of treating cancer in a mammal, comprising administering to said mammal an effective amount of a compound of claim 1.

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''

whererin

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;

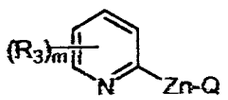
R_6 in each instance is independently hydroxyl, halogen, amino, carbonyl, nitro, cyano, acyl, alkyl, sulfonyl, alkylsulfonyl, alkylsulfinyl, alkoxy, alkylcarbamoyl, alkanoylamine, alkylsulfamoyl, alkylsulfonamide, a carbocycle or a heterocycle; wherein said amino, alkyl, carbonyl, acyl, sulfonyl, alkylsulfonyl, 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;

o is 0-3; and

m is 0-3;

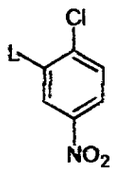
said process comprising

-reacting a compound of formula (a)



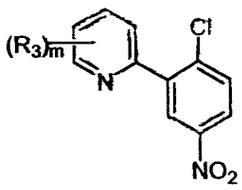
(a)

wherein Q is Cl, Br or I; with a compound of formula (b)



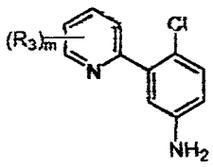
(b)

wherein L is Br, I or OTf; to yield a compound of formula (c);



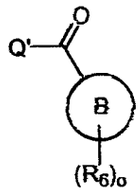
(c)

- 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''.

INHIBIDORES PIRIDILO DE SEÑALIZACIÓN DE HEDGEHOG

Reivindicación de prioridad

La presente solicitud reivindica prioridad de la solicitud de patente Estadounidense 61/044451 presentada en 11 de Abril de 2008.

Campo de la invención

La presente invención se refiere a compuestos orgánicos de utilidad para terapia y/o profilaxis en un mamífero, en particular a compuestos de piridilo que inhiben la vía de señalización de hedgehog y resultan útiles en el tratamiento de enfermedades hiperproliferativas y enfermedades mediadas por angiogénesis.

Antecedentes de la invención

La proteína hedgehog (Hh) fue identificada por primera vez en Drosophila melanogaster como un gen de polaridad de segmento involucrado en el modelado del embrión (Nusslein-Volhard et al., Roux. Arch. Dev. Biol. 193: 267-282 (1984)). Tres ortólogos de Drosophila hedgehog (Sónico, del Desierto e Indio) fueron posteriormente identificados en todos los vertebrados incluyendo peces, aves y mamíferos. El hedgehog del desierto (DHd) se expresa principalmente en los testículos, tanto en el desarrollo embriónico de ratones como en el roedor adulto y el ser humano; el hedgehog indio se expresa (IHh) participa en el desarrollo de los huesos durante la embriogénesis y en la formación de los huesos en el adulto; y, el hedgehog sónico (SHh) se expresa a altos niveles en la notocorda y piso de la placa de embriones de vertebrados en desarrollo. Los ensayos de explantos en vitro así como la expresión ectópica de SHh en animales transgénicos ha demostrado que SHs juega un papel clave en el modelado del tubo neuronal (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 además participa en el desarrollo de los miembros (Krauss et al., Cell 75: 1431-44 (1993); Laufer et al., Cell 79, 993-1003 (1994)), somitas (Fan y Tessier-Lavigne, Cell 79, 1175-86 (1994); Johnson et al., Cell 79: 1165-73 (1994)), lungs (Bellusci et al., Develop. 124: 53-63 (1997) y la piel (Oro et al., Science 276: 817-21 (1997)). Del mismo modo, IHh y DHh participan en el desarrollo de las células óseas, del intestino y germinales (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)).

SHh de origen humano se sintetiza como una proteína precursora de 45 kDa que ante el clivaje autocatalítico produce un fragmento N-terminal de 20 kDa responsable de la señalización de hedgehog normal, y un fragmento C-terminal de 25 kDa responsable de la actividad de auto procesamiento en la cual el fragmento N-terminal se conjuga con una porción de colesterol (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).

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El fragmento N-terminal comprende los residuos de aminoácidos 24-197 de la secuencia precursora de longitud completa que permanece asociada a la membrana mediante el colesterol en su término C (Porter, J.A., et al. (1996) Science 274, 255- 258; Porter, J.A., et al. (1995) Cell 86, 21-34). La conjugación con el colesterol es responsable de la localización del tejido de la señal de hedgehog.

En la superficie de la célula, se piensa que la señal Hh es transmitida por la proteína del dominio transmembrana Patched 12 (Ptc) (Hooper y Scott, Cell 59: 751-65 (1989); Nakano et al., Nature 341: 508-13 (1989)) y el receptor tipo acoplado a proteína G Smoothened (Smo) (Alcedo et al., Cell 86: 221-232 (1996); van den Heuvel y Ingham, Nature 382: 547-551 (1996)). Amba evidencia genética y bioquímica sopora un modelo de receptor donde Ptc y Smo son parte del complejo receptor multicomponente (Chen y Struhl, Cell 87: 553-63 (1996); Marigo et al., Nature 384: 176-9 (1996); Stone et al., Nature 384: 129-34 (1996)). Al unirse Hh a Ptc, se alivia el efecto inhibitorio nirmal de Ptc sobre Smo, permitiendo que Smo transduzca la señal Hh a través de la membrana plasmática. Sin embargo, el mecanismo exacto a través del cual Ptc controla la actividad de Smo aún no ha sido clarificado.

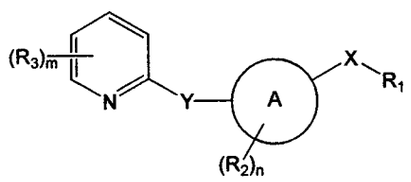
La cascada de señalización iniciada por Smo da como resultado la activación de los factores de transcripción Gli que se translocan en el núcleo donde controlan la transcripción de los genes blanco. Se ha demostrado que Gli influencia la transcripción de los inhibidores del camino de Hh como Ptc y Hip1 en un bucle de retroalimentación negativo indicando que es necesario un control estricto del camino de Hh para una adecuada diferenciación celular y formación de los órganos. La activación no controlada del camino de señalización Hh está asociada a ciertas malignidades en particular aquellas del cerebro, la piel los músculos, así como a la angiogénesis. Una explicación para ello radica en que se ha demostrado que el camino de Hh regula la proliferación celular en adultos mediante la activación de los genes involucrados en el avance del ciclo celular como ciclina D que participa en la transición G1-S. Además, SHh bloquea el arresto del ciclo celular mediado por p21, un inhibidor de quinasas dependientes de ciclina. La señalización de Hh además tiene participación en el cáncer induciendo componentes en la vía EGFR (EGF, Her2) que está relacionada con la proliferación así como en los componentes en los caminos PDGF (PDGFα) y VEGF involucrados en la angiogenesis. La pérdida de mutaciones funcionales en el gen Ptc ha sido identificada en pacientes con síndrome de nevo de células basales (BCNS), una enfermedad hereditaria caracterizada por múltiples carcinomas de células basales (BCCs). Las mutaciones del gen Ptc disfuncionales además se han asociado con un gran porcentaje de tumores de carcinomas de células basales esporádicos (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)). Se cree que la pérdida de la función de Ptc provoca una señalización de Smo descontrolada en el carcinoma de células basales. Asimismo, se han identificado mutaciones de Smo de activación en tumores BCC esporádicos (Xie et al., Nature 391: 90-2 (1998)), lo cual acentúa el rol de Smo como la sub-unidad de señalización en el complejo receptor para SHh.

Se han investigado varios inhibidores de la señalización de hedgehog como Ciclopamina, un alcaloide natural que ha demostrado arrestar el ciclo celular en G0-G1 e inducir la apoptosis en SCLC. Se cree que la Ciclopamina inhibe Smo uniéndose a su bundle heptahélico. Se ha demostrado que foscolina inhibe el camino de Hh caudal abajo desde Smo activando la proteína quinasa A (PKA) que mantiene los factores de transcripción Gli inactivos. A pesar de los avances con estos y otros compuestos, aún se necesitan inhibidores potentes del camino de señalización de hedgehog.

Resumen de la invención

En un aspecto de la presente invención se proveen nuevos inhibidores de hedgehog que poseen la fórmula general (I)



I

en la cual

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 es seleccionado del grupo integrado 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 un heterociclo; en tanto 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 de los cuales 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 heterociclo en tanto 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_4 es H o alquilo;

m es 0-3;

n es 0-3;

y sales y solvatos de los mismos.

En otro aspecto de la invención, se proveen composiciones que comprenden compuestos de la fórmula I y un portador, diluyente o excipiente.

En otro aspecto de la invención, se provee un método para tratar el cáncer que comprende administrar una cantidad efectiva de un compuesto de la fórmula I a un mamífero que lo necesita.

En otro aspecto de la invención, se provee un método para inhibir la señalización de hedgehog en una célula que comprende poner en contacto dicha célula con un compuesto de la fórmula I.

En otro aspecto de la invención, se provee un método para tratar una enfermedad o condición asociada con la señalización de hedgehog en un mamífero, que comprende administrar a dicho mamífero una cantidad efectiva de un compuesto de la fórmula I.

En otro aspecto de la invención, se proveen procesos para preparar los compuestos de la invención.

Descripción detallada de las realizaciones preferidas

"Acilo" hace referencia a un sustituyente que contiene carbonilo representado por la fórmula -C(O)-R en la cual R es H, alquilo, un carbociclo, un heterociclo, alquilo sustituido con carbociclo o alquilo sustituido con heterociclo en tanto el alquilo, alcoxi, carbociclo y heterociclo responden a la definición de la presente. Los grupos acilo incluyen alcanoilo (por ejemplo acetilo), aroilo (por ejemplo benzoilo), y heteroaroilo.

"Alquilo" hace referencia a un grupo hidrocarburo alifático saturado o insaturado (es decir, alquenilo, alquinilo) ramificado o sin ramificar, que posee hasta 12 átomos de carbono salvo indicación en contrario. Cuando se usa como parte de otro término, por ejemplo "alquilamino", la porción alquilo preferentemente es una cadena de hidrocarburos saturada, sin embargo además incluye cadenas de hidrocaburos insaturadas como "alquenilamino" y "alquinilamino. "Alquilfosfinato" hace referencia a un grupo alquilo –P(O)R en el cual R es H, alquilo, carbociclo-alquilo o heterociclo-alquilo. Los ejemplos de grupos alquilo preferidos 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" "C_1-C_4 alquilo" y "alquilo de 1 a 4 átomos de carbono" son sinónimos y se emplean indistintamente para hacer referencia a metilo, etilo, 1-propilo, isopropilo, ciclopropilo, 1-butilo, sec-butilo o t-butilo. Salvo indicación en contrario, los grupos alquilo sustituidos pueden contener uno (preferentemente), dos, tres o cuatro sustituyentes que pueden ser iguales o diferentes. Los ejemplos de los grupos alquilo sustituidos antes mencionados incluyen, entre otros; cianometilo, nitrometilo, hidroximetilo, tritiloximetilo, propioniloximetilo, aminometilo, carboximetilo, carboxietilo, carboxipropilo, alquilooxicarbonilmetilo, aliloxicarbonilaminometilo, carbamoiloximetilo, metoximetilo, etoximetilo, t-butoximetilo, acetoximetilo, clorometilo, bromometilo, yodometilo, trifluorometilo, 6-hidroxihexilo, 2,4-dicloro(n-butilo), 2-amino(iso-propilo), 2-carbamoiloxietilo y similares. El grupo alquilo puede además ser sustituido con un grupo carbociclo. Los ejemplos incluyen grupos ciclopropilmetilo, ciclobutilmetilo, ciclopentilmetilo, y ciclohexilmetil, así como los correspondientes grupos etilo, -propilo, -butilo, -pentilo, -hexilo, etc. Los alquilo sustituidos preferidos son metilos sustituidos por ejemplo un grupo metilo sustituido por los mismos sustituyentes que el grupo "C_n-C_m alquilo sustituido". Los ejemplos del grupo metilo sustituido incluyen grupos como hidroximetilo, hidroximetilo prptegido (por ejemplo tetrahidropiraniloximetilo), acetoximetilo, carbamoiloximetilo, trifluorometilo, clorometilo, carboximetilo, bromometilo y yodometilo.

"Amidina" o "amidino" hace referencia al grupo -C(NH)-NRR donde cada R es independientemente H, OH, alquilo, alcoxi, un carbociclo, un heterociclo, un alquilo sustituido con carbociclo o un alquilo sustituido con heterociclo; o ambos grupos R juntos forman un heterociclo. Una amidina prferida es el grupo -C(NH)-NH_2.

"Amino" denota aminas primarias (es decir –NH_2) , secondarias (es decir –NRH) y terciarias (es decir –NRR) donde R es independientemente alquilo, un carbociclo (por ejemplo arilo) , un heterociclo (por ejemplo heteroarilo), alquilo sustituido con carbociclo (por ejemplo bencilo) o un alquilo sustituido con heterociclo o alternativamente dos grupos R junto con el átomo de nitrógeno del cual dependen forman un heterociclo. Las

aminas secundarias y terciarias específicas son alquilamina, dialquilamina, arilamina, diarilamina, aralquilamina y diaralquilamina. Las aminas secundarias y terciarias específicas son metilamina, etilamina, propilamina, isopropilamina, fenilamina, bencilamina dimetilamina, dietilamina, dipropilamina y diisopropilamina.

Un "grupo de protección amino" de acuerdo a la presente hace referencia a un derivado de los grupos comúnmente empleados para bloquear o proteger un grupo amino mientras las reacciones se llevan a cabo sobre otros grupos funcionales en el compuesto. Los ejemplos de tales grupos de protección incluyen carbamatos, amidas, grupos alquilo y arilo, iminas, así como también muchos derivados de N-heteroátomos que pueden ser removidos para regenerar el grupo amino deseado. Los grupos de protección amino preferidos son Boc, Fmoc y Cbz. Otros ejemplos de estos grupos se encuentran en T. W. Greene y 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, y T.W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, NY, 1981. La expresión "amino protegido" hace referencia a un grupo amino sustituido con uno de los grupos de protección amino precedentes.

El término "arilo" solo o como parte de otro hace referencia a un grupo aromático carbocíclico fusionado o no con el número of átomos de carbono designado o en caso de no estar designado, de hasta 14 átomos de carbono. Los grupos arilo incluyen fenilo, naftilo, bifenilo, fenantrenilo, naftacenilo y similares (véase por ejemplo *Lang's Handbook of Chemistry* (Dean, J. A., ed) 13th ed. Table 7-2 [1985]). En una realización específica arilo puede ser fenilo. Fenilo sustituido o arilo sustituido denota un grupo fenilo o grupo arilo sustituido con uno, dos, tres, cuatro o cinco, como 1-2, 1-3 o 1-4 sustituyentes seleccionados, salvo indicación en contrario, entre halógeno (F, Cl, Br, I), hidroxi, hidroxi protegido, ciano, nitro, alquilo (por ejemplo C_1-C_6 alquilo), alcoxi (por ejemplo C_1-C_6 alcoxi), benciloxi, carboxi, carboxi protegido, carboximetilo, carboximetilo protegido, hidroximetilo, hidroximetilo protegido, aminometilo, aminometilo protegido, trifluorometilo, alquilsulfoniloamino, arilsulfonilamino, heterociclilsulfonilamino, heterociclilo, arilo, u otros grupos especificados. Uno o más sustituyentes metina (CH) y/o metileno (CH_2) en estos sustituyentes pueden a su vez ser sustituidos con un grupo similar a los antes descriptos. Los ejemplos de la expresión "fenilo sustituido" incluyen entre otros un grupo mono- o di(halo)fenilo 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 como 4-hidroxifenilo, 3-hidroxifenilo, 2,4-dihidroxifenilo, los derivados hidroxi protegidos de los mismos y similares; un grupo nitrofenilo como 3- o 4-nitrofenilo;

un grupo cianofenilo, por ejemplo, 4-cianofenilo; un grupo mono- o di(alquilo inferior)fenilo como 4-metilfenilo, 2,4-dimetilfenilo, 2-metilfenilo, 4-(iso-propilo)fenilo, 4-etilfenilo, 3-(n-propilo)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- o 4- trifluorometilfenilo; un grupo mono- o dicarboxifenilo o (carboxi protegido)fenilo como 4-carboxifenilo, ; mono- o di(hidroximetil)fenilo o (hidroxi protegidometil)fenilo como 3-(hidroxi protegidometil)fenil0 o 3,4-di(hidroximetil)fenilo; un mono- o di(aminometil)fenilo o (aminometil protegido)fenilo como 2-(aminometil)fenilo o 2,4-(aminometil protegido) fenilo; o un mono- o di(N-(metilsulfonilamino))fenilo como 3-(N-metilsulfonilamino)) fenilo. Además, la expresión "fenilo 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 también grupos fenilo trisustituidos donde los sustituyentes son diferentes, por ejemplo 3-metoxi-4-benciloxi-6-metil sulfonilamino, 3-metoxi-4-benciloxi-6-fenilo sulfonilamino, y grupos fenilo tetrasustituidos donde los sustituyentes son diferentes como 3-metoxi-4-benciloxi-5-metil-6-fenilo sulfonilamino. Los grupos fenilo sustituidos incluyen 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- metil sulfonil aminofenilo. Los anillos arilo fusionados pueden además estar sustituidos con cualquiera (por ejemplo 1, 2 o 3) de los sustituyentes especificados en la presente como los grupos alquilo sustituidos.

"Carbamoilo" hace referencia a un aminosustituyente que contiene carbonilo representado por la fórmula $-C(O)N(R)_2$ en la cual R es H, hidroxilo, alcoxi, alquilo, un carbociclo, un heterociclo, alquilo sustituido con carbociclo o alcoxi, o alquilo sustituido con heterociclo o alcoxi donde el alquilo, alcoxi, carbociclo y heterociclo responden a la definición de la presente. Los grupos carbamoilo incluyen alquilaminoecarbonilo (por ejemplo etilaminocarbonilo, Et-NH-CO-), arilaminocarbonilo (por ejemplo fenilaminocarbonilo), aralquilaminocarbonilo (por ejemplo benzoilaminocarbonilo) un heterocicloaminocarbonilo (por ejemplo piperizinilaminocarbonilo), y en particular un heteroarilaminocarbonilo (por ejemplo piridilaminocarbonilo).

"Carbociclilo", "carbocíclico", "carbociclo" y "carbociclo" solo y cuando se usan como una porción en un grupo complejo como un grupo carbocicloalquilo, hace referencia a un anillo alifático mono-, bi-, o tricíclico que posee de 3 a 14 átomos de carbono y preferentemente 3 a 7 átomos de carbono que pueden ser saturados o insaturados, aromáticos o no aromáticos. Los grupos carbocíclico saturados preferidos incluyen

grupos ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo y más aún ciclopropilo y ciclohexilo y más aún ciclohexilo. Los carbociclos insaturados preferidos son aromáticos por ejemplo grupos arilo de acuerdo a la definición anterior, más aún fenilo. Los términos "carbociclilo sustituido", y "carbociclo sustituido" salvo indicación en contrario hacen referencia a estos grupos sustituidos por los mismos sustituyentes que el grupo "alquilo sustituido".

"Grupo de protección carboxi" de acuerdo a la presente hace referencia a uno de los derivados éster del grupo ácido carboxílico comúnmente empleado para bloquear o proteger el grupo ácido carboxílico mientras las reacciones se llevan a cabo en otros grupos funcionales en el compuesto. Los ejemplos de tales grupos de protección de ácido carboxílico 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 como t-butilo o t-amilo, tritilo, 4-metoxitritilo, 4,4'-dimetoxitritilo, 4,4',4"-trimetoxitritilo, 2-fenilprop-2-ilo, trimetilsililo, t-butildimetilsililo, phenacilo, 2,2,2-tricloroetilo, beta-(trimetilsilil)etilo, beta-(di(n-butilo)metilsilil)etilo, p-toluenosulfoniletilo, 4-nitrobencilsulfoniletilo, alilo, cinamilo, 1-(trimetilsililmetil)prop-1-en-3-ilo, y porciones similares. La especie de grupo de protección carboxi empleada no es crítica en la medida en que el ácido carboxílico derivado sea estable a la condición de la o las reacciones subsecuentes sobre otras posiciones de la molécula y pueda ser removida en el momento adecuado sin alterar el resto de la molécula. En particular, es importante no someter una molécula carboxi protegida a bases nucleófílicas fuertes, como hidróxido de litio o NaOH, o condiciones reductivas que empleen hidruros metálicos altamente activados como $LiAlH_4$. (Tales condiciones de remoción rigurosas además pueden ser evitadas cuando se eliminan grupos de protección amino y grupos de protección hidroxi, según se expone seguidamente.) Los grupos de protección de ácido carboxílico preferidos son grupos alquilo (por ejemplo metilo, etilo, t-butilo), alilo, bencilo y p-nitrobencilo. Los grupos de protección carboxi similares usados en cefalosporina, penicilina y péptidos también pueden ser empleados en la protección de los sustituyentes de grupos carboxi. Otros ejemplos de estos grupos se encuentran en T. W. Greene y 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, y T.W. Greene, "Protective Groups in Organic Synthesis", John Wiley y Sons, New York, NY, 1981, Chapter 5. La expresión "carboxi protegido" hace referencia a un grupo carboxi sustituido con uno de los grupos de protección carboxi precedentes.

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"Guanidina" hace referencia al grupo -NH-C(NH)-NHR donde R es H, alquilo, un carbociclo, un heterociclo, un alquilo carbociclo-sustituido, o un alquilo sustituido con heterociclo. Un grupo guanidina específico es -NH-C(NH)-NH_2.

Las expresiones "grupo heterocíclico", "heterocíclico", "heterociclo", "heterociclilo", o "heterociclo" solas y cuando se usan como una porción en un grupo complejo como un grupo heterocicloalquilo, se emplean indistintamente y hacen referencia a cualquier anillo mono-, bi-, o tricíclico, saturado o insaturado, aromático (heteroarilo) o non-aromático que posee el número de átomos designado, en general entre 5 y aproximadamente 14 átomos de anillo, donde los átomos del anillo son carbono y por lo menos un heteroátomo (nitrógeno, azufre u oxígeno) y preferentemente 1 a 4 heteroátomos. "Heterociclosulfonilo" hace referencia a un grupo –SO_2-heterociclo; "heterociclosulfinilo" hace referencia a un grupo –SO-heterociclo. Típicamente, un anillo de 5 miembros posee de 0 a 2 doble enlaces y el anillo de 6- o 7-miembros posee 0 a 3 doble enlaces y los heteroátomos nitrógeno o azufre pueden opcionalmente oxidarse (por ejemplo SO, SO_2), y todo heteroátomo nitrógeno puede opcionalmente cuaternizarse. Los heterociclos no aromáticos preferidos incluyen morfolinilo (morfolino), pirrolidinilo, oxiranilo, oxetanilo, tetrahidrofuranilo, 2,3-dihidrofuranilo, 2H-piranilo, tetrahidropiranilo, tiiranilo, tietanilo, tetrahidrotietanilo, aziridinilo, azetidinilo, 1-metil-2-pirrolilo, piperazinil y piperidinilo. Un grupo "heterocicloalquilo" es un grupo heterociclo de acuerdo a la definición anterior covalentemente unido a un grupo alquilo de acuerdo a la definición anterior. Los heterociclos de 5 miembros preferidos que contienen un átomo de azufre u oxígeno y uno a tres átomos de nitrógeno incluyen tiazolilo, en particular tiazol-2-ilo y tiazol-2-ilo N-óxido, tiadiazolilo, en particular 1,3,4-tiadiazol-5-ilo y 1,2,4-tiadiazol-5-ilo, oxazolilo, preferentemente oxazol-2-ilo, y oxadiazolilo, como 1,3,4-oxadiazol-5-ilo, y 1,2,4-oxadiazol-5-ilo. Los anillo heterociclos de cinco miembros preferidos que contienen de 2 a 4 átomos de nitrógeno 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 heterociclos de 5 miembros benzo-fusionados preferidos son benzoxazol-2-ilo, benztiazol-2-ilo y benzimidazol-2-ilo. Los heterociclos de 6 miembros preferidos contienen uno a tres átomos de nitrógeno y opcionalmente un átomo de azufre u oxígeno, por ejemplo piridilo, 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 pirazinil. Se prefieren piridina N-óxidos y piridazina N-óxidos y los grupos piridilo, pirimid-2-ilo, pirimid-4-ilo, piridazinilo y 1,3,4-triazin-2-ilo. Los sustituyentes para heterociclos opcionalmente sustituidos, y otros ejemplos de sistemas de anillos de 5 y 6 miembros antes expuestos pueden encontrarse en W. Druckheimer *et al.*, Patente Estadounidense Número 4,278,793.

"Heteroarilo" solo y cuando se emplea como una porción en un grupo complejo como un grupo heteroaralquilo, hace referencia a cualquier sistema de anillos mono-, bi-, o tricíclico aromático que posee el número de átomos designado donde por lo menos un anillo es un anillo de 5-, 6- o 7-miembros que contiene entre uno y cuatro heteroátomos seleccionados del grupo integrado por nitrógeno, oxígeno, y azufre, y preferentemente por lo menos un heteroátomo es nitrógeno (*Lang's Handbook of Chemistry, supra*). Se incluyen en la definición los grupos bicíclicos donde cualquiera de los anillos heteroarilo precedentes se fusionan con un anillo de benceno. Se prefieren los heteroarilos en los cuales nitrógeno u oxígeno es el heteroátomo. Los siguientes sistemas de anillos son ejemplos de los grupos heteroarilo (sustituidos o insustituidos) indicados mediante la expresión "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]piridazinil y purinilo, así como también derivados benzo fusionados, por ejemplo benzoxazolilo, benzofurilo, benzotiazolilo, benzotiadiazolilo, benzotriazolilo, benzoimidazolilo e indolilo. Un grupo particularmente preferido de "heteroarilos" incluye; 1,3-tiazol-2-ilo, 4-(carboximetil)-5-metil-1,3-tiazol-2-ilo, sal de sodio 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 de sodio 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 de sodio de 1-(carboximetil)-1H-tetrazol-5-ilo, 1-(ácido metilsulfónico)-1H-tetrazol-5-ilo, sal de sodio 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, pirid-2-ilo N-óxido, 6-metoxi-2-(n-oxide)-piridaz-3-ilo, 6-hidroxipiridaz-3-ilo, 1-metilpirid-2-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 de sodio de 2,5-dihidro-5-oxo-6-hidroxi-as-triazin-3-ilo, sal de sodio 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 "heteroarilos" incluye; 4-(carboximetil)-5-metil-1,3-tiazol-2-ilo, sal de sodio 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-il)-1H-tetrazol-5-ilo, 1-(carboximetil)-1H-tetrazol-5-ilo, sal de sodio de 1-(carboximetil)-1H-tetrazol-5-ilo, 1-(ácido metilsulfónico)-1H-tetrazol-5-ilo, sal de sodio 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 de sodio 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 de protección hidroxi" de acuerdo a la presente hace referencia a un derivado del grupo hidroxi comúnmente empleado para bloquear o proteger el grupo hidroxi mientras las reacciones se llevan a cabo sobre otros grupos funcionales en el compuesto. Los ejemplos de tales grupos de protección incluyen los grupos tetrahidropiraniloxi, benzoilo, acetoxi, carbamoiloxi, bencilo, y sililéteres (por ejemplo TBS, TBDPS). Otros ejemplos de estos grupos se encuentran en 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, y T.W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, NY, 1981. la expresión "hidroxi protegido" hace referencia a un grupo hidroxi sustituido con uno de los grupos de protección hidroxi precedentes.

Las "sales farmacéuticamente aceptables" incluyen sales de adición ácidas y básicas. La "sal de adición ácida farmacéuticamente aceptable" hace referencia a aquellas sales que retienen la efectividad y propiedades biológicas de las bases libres y que no son biológica o de otro modo indeseables, constituidas por ácidos inorgánicos como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico, ácido carbónico, ácido fosfónico y similares, y los ácidos orgánicos pueden ser seleccionados entre ácidos orgánicos alifáticos, cicloalifáticos, aromáticos, aralifáticos, heterocíclicos, carboxílicos, y sulfónicos como ácido fórmico, ácido acético, ácido propiónico, ácido glicólico, ácido glucónico, ácido láctico, ácido pirúvico, ácido oxálico, ácido málico, ácido maleico, ácido maloneico, 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 salicíclico, y similares.

Las "sales de adición básicas farmacéuticamente aceptables" incluyen aquellas derivadas de bases inorgánicas como sales de sodio, potasio, litio, amonio, calcio, magnesio, hierro, zinc, cobre, manganeso, aluminio y similares. Particularmente se prefieren las sales de amonio, potasio, sodio, calcio y magnesio. Las sales derivadas de

bases no tóxicas orgánicas farmacéuticamente aceptables incluyen sales de aminas primarias, secundarias y terciarias, aminas sustituidas que incluyen aminas sustituidas naturales, aminas cíclicas, y resinas de intercambio iónico, como isopropilamina, trimetilamina, dietilamina, TEA, tripropilamina, etanolamina, 2-dietilaminoetanol, trimetamina, diciclohexilamina, lisina, arginina, histidina, cafeína, procaina, hidrabamina, colina, betaína, etilendiamina, glucosamina, metilglucamina, teobromo, purinas, piperizina, piperidina, N-etilpiperidina, poliamina y similares. Las bases no tóxicas orgánicas particularmente preferidas son isopropilamina, dietilamina, etanolamina, trimetamina, diciclohexilamina, colina, y cafeína.

"Fosfinato" hace referencia a –P(O)R-OR donde cada R es independientemente H, alquilo, carbociclo, heterociclo, carbocicloalquilo o heterocicloalquilo. Los grupos fosfinato específicos son alquilfosfinato (es decir –P(O)R-O-alquilo), por ejemplo –P(O)Me-OEt.

"Sulfamoilo" hace referencia a $–SO_2-N(R)_2$ donde cada R es independientemente H, alquilo, carbociclo, heterociclo, carbocicloalquilo o heterocicloalquilo. Los grupos sulfamoilo específicos son alquilsulfamoilo, por ejemplo metilsulfamoilo ($-SO_2-NHMe$); arilsulfamoilo, por ejemplo fenilsulfamoilo; aralquilsulfamoilo, por ejemplo bencilsulfamoilo.

"Sulfinilo" hace referencia a un grupo –SO-R donde R es alquilo, carbociclo, heterociclo, carbocicloalquilo o heterocicloalquilo. Los grupos sulfinilo específicos son alquilsulfinilo (es decir –SO-alquilo), por ejemplo metilsulfinilo; arilsulfinilo (es decir –SO-arilo) por ejemplo fenilsulfinilo; aralquilsulfinilo, por ejemplo bencilsulfinilo.

"Sulfonamida" hace referencia a $–NR-SO_2-R$ donde cada R es independientemente H, alquilo, carbociclo, heterociclo, carbocicloalquilo o heterocicloalquilo), un carbociclo o un heterociclo. Los grupos sulfonamida específicos 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.

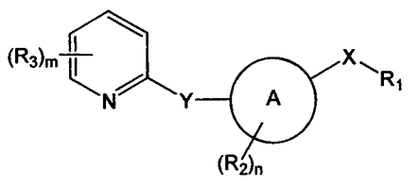
"Sulfonilo" hace referencia a un grupo $–SO_2-R$ donde R es alquilo, carbociclo, heterociclo, carbocicloalquilo o heterocicloalquilo. Los grupos sulfonilo específicos son alquilsulfonilo (es decir $–SO_2-$alquilo), por ejemplo metilsulfonilo; arilsulfonilo, por ejemplo fenilsulfonilo; aralquilsulfonilo, por ejemplo bencilsulfonilo.

La frase "y sales y solvatos de los mismos" de acuerdo a la presente hace referencia a que los compuestos de la invención pueden encontrarse en una o una mezcla de sales y

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solvatos. Por ejemplo, un compuesto de la invención puede ser estar sustancialmente puro en una sal o solvato o de lo contrario en una mezcla de dos o más sales o solvatos.

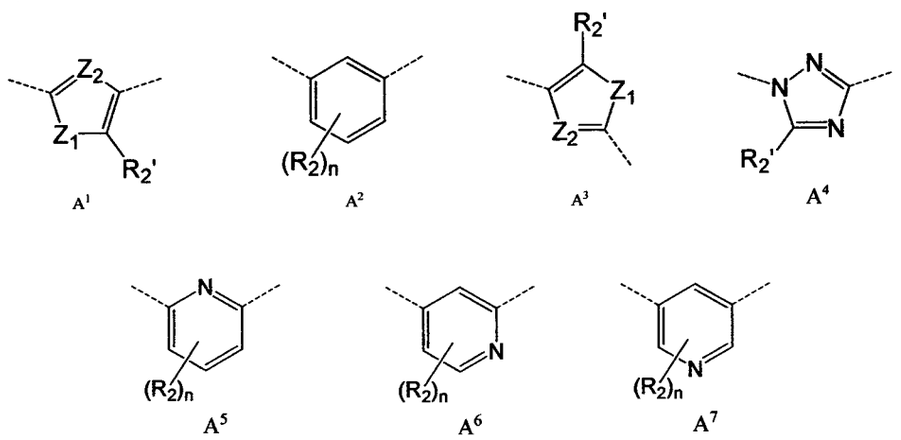
La presente invención provee nuevos compuestos que poseen la fórmula general I:



I

donde A, X, Y, R_1, R_2, y R_3 responden a la definición de la presente.

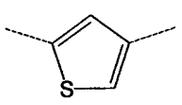
A es un anillo carbociclo o heterociclo sustituido con 0 a 3 (por ejemplo n es 0-3) grupos R_2 seleccionados del grupo integrado por halógeno, hidroxilo, alquilo, acilo o alcoxi cada uno de los cuales opcionalmente sustituido con hidroxilo, halógeno, amino, nitro, alquilo, acilo, alquilsulfonilo o alcoxi;. En una realización específica, A está opcionalmente sustituido con arilo o heteroarilo. En la realización específica A está opcionalmente sustituido con benceno, tiofeno, tiazol, imidazol, pirrol, N-alquil pirrol, piridina, pirazol o N-alquilo pirazol. En una realización específica A es un anillo seleccionado del grupo integrado por A^1, A^2, A^3, A^4 A^5, A^6 y A^7:



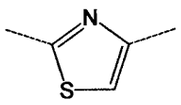
donde Z_1 es O, S o NR_5 en tanto R_5 es H o alquilo; Z_2 es CH, $CR_{2'}$ o N; R_2 es halógeno, hidroxilo, alquilo, acilo o alcoxi cada uno de los cuales opcionalmente sustituido con hidroxilo, halógeno, amino, nitro, alquilo, acilo, alquilsulfonilo o alcoxi; $R_{2'}$ es H, halógeno, hidroxilo, alquilo, acilo o alcoxi cada uno de los cuales opcionalmente sustituido con hidroxilo, halógeno, amino, nitro, alquilo, acilo, alquilsulfonilo o alcoxi; y n es 0-3. En una realización específica A es el anillo de la fórmula A^1. En una realización específica, A es el anillo de la fórmula A^1 donde Z_1 es S y Z_2 es CH o N. En otra realización, A es el anillo de la fórmula A^1 donde Z_1 es S y Z_2 es CH, es decir tiofeno. En otra realización, A es el anillo de la fórmula A^1 donde Z_1 es S y Z_2 es N, es decir tiazol. En otra realización, A es el

anillo de la fórmula A^1 donde $R_{2'}$ es H. En una realización, A es el anillo de la fórmula A^1 donde $R_{2'}$ es metilo. En otra realización, A es el anillo A^1 donde $R_{2'}$ es metilo. En una realización específica A es el anillo A^2. En otra realización, A es el anillo de la fórmula A^1 donde R_2 puede estar ausente, es decir n es 0. En otra realización, n es 1 y R_2 es Cl. En otra realización específica A es el anillo de la fórmula A^3. En una realización, A es un anillo de la fórmula A^3 donde Z_1 es S y Z_2 es N, es decir un tiazol. En otra realización, A es un anillo de la 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 la fórmula A^3 donde Z_1 es S, Z_2 es CH (es decir tiofeno) y R_2' es Cl.

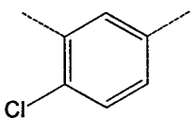
En una realización específica A es el anillo A^{1a}, A^{1b}, A^{2a}, A^{3a}, A^{3b}, A^{4a}, A^{5a}, A^{6a}, A^{7a},:



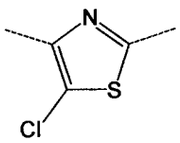
A^{1a}



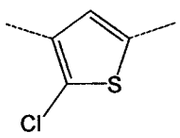
A^{1b}



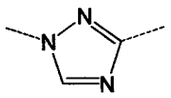
A^{2a}



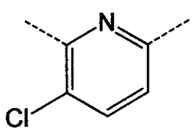
A^{3a}



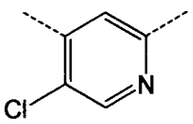
A^{3b}



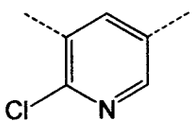
A^{4a}



A^{5a}



A^{6a}



A^{7a}

En una realización específica A es el anillo de la fórmula A^{1a}. En otra realización A es el anillo de la fórmula A^{1b}. En otra realización A es el anillo de la fórmula A^{2a}. En otra realización A es el anillo de la fórmula A^{3a}. En otra realización A es el anillo de la fórmula A^{3b}. En otra realización A es el anillo de la 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 específica X es $NR_4C(O)$ que forma un enlace amida entre el anillo A y R_1. En otra realización, X es $N_4C(S)$, que forma un enlace de tioamida entre el anillo A y R_1. En otra realización, X es $NR_4C(O)NH$ que forma un enlace urea entre el anillo A y R_1. En otra realización X es $NR_4C(S)NH$ con el cual NR_2 forma un enlace tiourea entre el anillo A

y R_1. En otra realización X es $N(C(O)R_1)C(O)$ es decir un nitrógeno con dos grupos -$C(O)R_1$ pendientes del mismo.

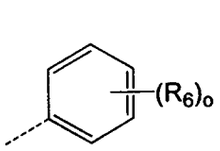
Y está ausente, CHR_4, O, S, SO, SO_2 o NR_4 donde R_4 mantienen la definición de la presente. En una realización específica Y es CHR_4. En una realización específica Y es NR_4. En una realización específica Y es O. En una realización específica Y es S. En una realización específica Y es SO. En una realización específica Y es SO_2. En otra realización Y está ausente es decir el anillo A está directamente unido al anillo piridilo en la posición 2.

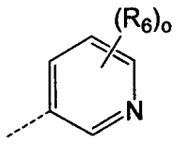
R_1 es seleccionado del grupo integrado por alquilo, un carbociclo o un heterociclo cada uno de los cuales está opcionalmente sustituido con hidroxilo, halógeno, amino, carboxilo amidino, guanidino, carbonilo (es decir =O), nitro, ciano, acilo, alquilo, haloalquilo, sulfonilo, sulfinilo, alcoxi, alquiltio, carbamoilo, acilamino, sulfamoilo, sulfonamida, un carbociclo o un heterociclo; en tanto dicho amino, amidino, alquilo, acilo, sulfonilo, sulfinilo, alcoxi, alquiltio, carbamoilo, acilamino, sulfamoilo, sulfonamida, carbociclo y heterociclo está opcionalmente sustituido 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 un heterociclo.

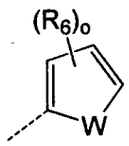
En otra realización R_1 es seleccionado del grupo integrado por alquilo, un carbociclo o un heterociclo cada uno de los cuales está opcionalmente sustituido con hidroxilo, halógeno, amino, carbonilo, nitro, ciano, acilo, alquilo, haloalquilo, alquilsulfonilo, alquilsulfinilo, alcoxi, alquilcarbamoilo (es decir -CONR-alquilo donde R es H o alquilo), alcanoilamina (es decir -NRCO-alquilo donde R es H o alquilo), alquilsulfamoilo (es decir -SO_2NR-alquilo donde R es H o alquilo), alquilsulfonamida (es decir -NR-SO_2-alquilo donde R es H o alquilo), un carbociclo o un heterociclo; en tanto 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 acil.

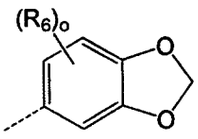
En una realización específica R_1 es un arilo o heteroarilo opcionalmente sustituido. En una realización específica R_1 es un grupo fenilo opcionalmente sustituido. En otra realización específica R_1 es un grupo piridina opcionalmente sustituido. En una

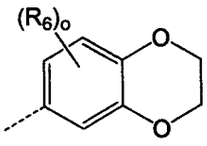
realización específica R_1 posee la fórmula IIa, IIb, IIc, IId, IIe, IIf, IIg, IIh, IIi, IIj, IIk, III, IIm, IEn o IIo:

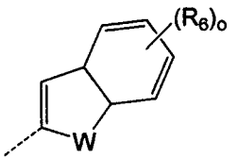

IIa

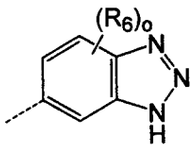

IIb

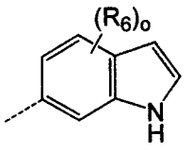

IIc

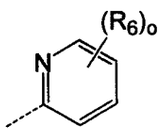

IId

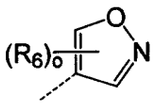

IIe

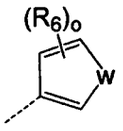

IIf

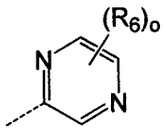

IIg

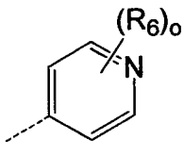

IIh

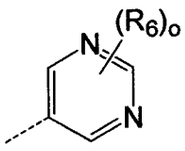

IIi

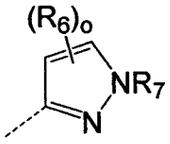

IIj


IIk


III


IIm


IIn


IIo

donde W es O, S o NR_7 donde R_7 es H, alquilo, acilo, un carbociclo o un heterociclo en tanto dicho alquilo, acilo, carbociclo y heterociclo está respectivamente opcionalmente sustituido con 1-3 aminos, halógenos, hidroxilos y haloalquilos; o es 0-3. En una realización específica W es S.

R_6 en cada caso es independientemente 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; en tanto dicho sustituyente amino, amidino, alquilo, acilo, sulfonilo, sulfinilo, alcoxi, alquiltio, carbamoilo, acilamino, sulfamoilo, sulfonamida, carbociclo y heterociclo está

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opcionalmente sustituido 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 un heterociclo.

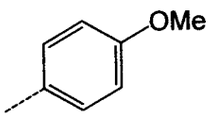
En una realización específica R_6 en cada caso es independientemente hidroxilo, halógeno, amino, carbonilo, nitro, ciano, acilo, alquilo, sulfonilo, alquilsulfonilo, alquilsulfinilo, alcoxi, alquilcarbamoilo, alcanoilamina, alquilsulfamoilo, alquilsulfonamida, un carbociclo o un heterociclo; en tanto 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 acil.

En una realización específica R_6 es independientemente en cada caso alquilo opcionalmente sustituido (por ejemplo metilo, trifluorometilo, dimetilaminometilo, piperidinilmetilo, morfolinometilo, tiomorfolinometil); halógeno (por ejemplo cloro); alcoxi (por ejemplo metoxi); carbonilo (por ejemplo morfolinocarbonilo, acetilo); un heterociclo (por ejemplo morfolino, N-metil-piperazin-4-ilo, N-acetil-piperazin-4-ilo, 1H-1,2,4-triazol); alquilamino (por ejemplo i-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, i-butilaminocarbonilo); alquilsulfamoilo (por ejemplo propilaminosulfonilo, i-butilaminosulfonilo, dimetilaminosulfonilo, dimetilaminoetilo hidroxietilamino sulfonilo, metoxietilamino sulfonilo, metoxipropilaminosulfonilo, metilsulfoniletilaminosulfonilo, propilaminosulfonilo sustituido con imidazol, hidroxipropilaminosulfonilo, 2-hidroxipropilaminosulfonilo); o sulfonilo (por ejemplo metilsulfonilo, etilsulfonilo, aminosulfonilo, dimetilaminopropilsulfonilo, N-metil-piperazin-4-il-sulfonilo, morfolino-4-il-sulfonilo, trifluorometilsulfonil).

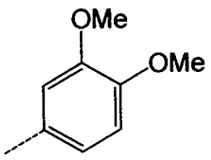
En una realización específica R_7 es H. En otra realización específica R_7 está opcionalmente sustituido con acilo. En otra realización específica R_7 está opcionalmente sustituido con alquilo (por ejemplo metilo). En otra realización específica R_7 está opcionalmente sustituido con acilo (por ejemplo acetilo, benzoilo). En otra realización específica R_7 es un grupo arilo opcionalmente sustituido (por ejemplo fenilo, bencilo).

En una realización específica R_1 es el grupo de la fórmula IIa. En tal realización R_6 puede ser alcoxi y o es 1, 2 o 3. Los grupos IIa específicos son IIa^1 - IIa^{28}:

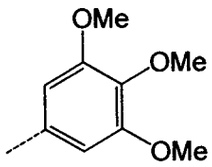
000293



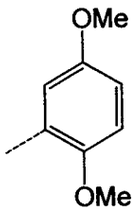
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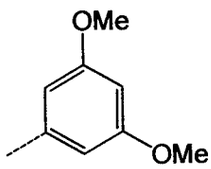
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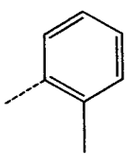
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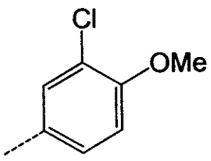
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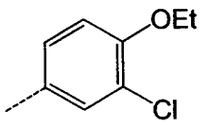
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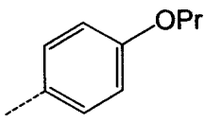
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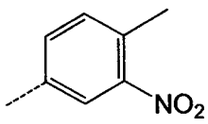
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IIa[8]

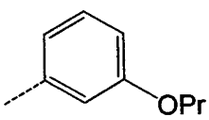


IIa[9]

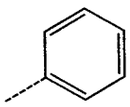


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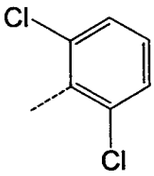
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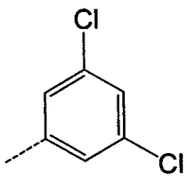
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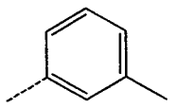
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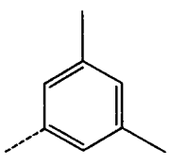
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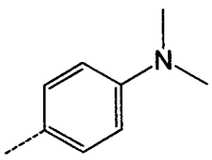
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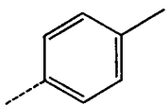
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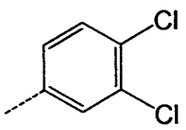
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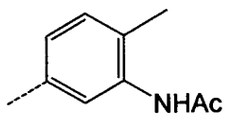
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IIa[18]

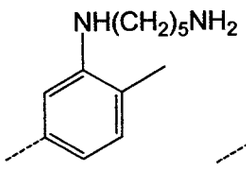


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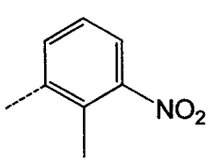


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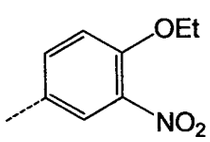
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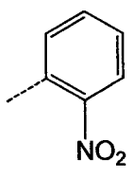
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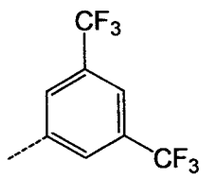
IIa[22]



IIa[23]

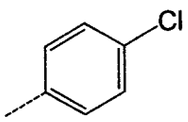


IIa[24]

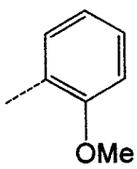


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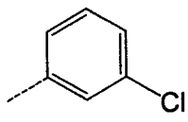
15



IIa^{26}

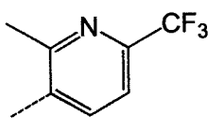


IIa^{27}

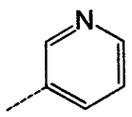


IIa^{28}

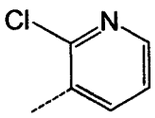
En otra realización específica R_1 es el grupo de la fórmula IIb. En tal realización R_6 puede ser alquilo o haloalquilo (por ejemplo CF_3). Los grupos IIb específicos son IIb^1 - IIb^3:



IIb^1



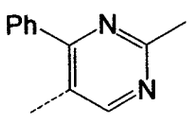
IIb^2



IIb^3

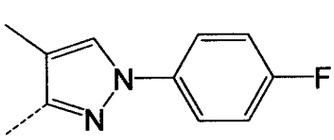
En una realización específica R_1 es el grupo de la fórmula IIc. En tal realización W puede ser S y o es 0. En otra realización específica R_1 es el grupo de la fórmula IId. En tal realización o puede ser 0. En otra realización específica R_1 es el grupo de la fórmula IIe. En tal realización o puede ser 0. En otra realización específica R_1 es el grupo de la fórmula IIf. En tal realización o puede ser 0.

En otra realización específica R_1 es el grupo de la fórmula IIn. En tal realización o puede ser 0 o 2 y R_6 puede ser alquilo o arilo. En una realización específica, el grupo IEn posee la fórmula IIn^1:



IIn^1

En otra realización específica R_1 es el grupo de la fórmula IIo. En tal realización o puede ser 0 o 2 y R_6 puede ser alquilo o arilo. En una realización específica, grupo IIo posee la fórmula IIo^1:



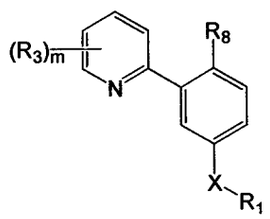
IIo^1

R_2 es halógeno, hidroxilo, alquilo, acilo o alcoxi cada uno de los cuales opcionalmente sustituido con hidroxilo, halógeno, amino, nitro, alquilo, acilo, alquilsulfonilo o alcoxi. n es 0-3, por ejemplo 0 o 1. En una realización específica R_2 es hidroxilo. En una realización

específica R_2 es alquilo o alquilo sustituido con halógeno, metilo o trifluorometilo. En una realización específica R_2 es acilo, por ejemplo alcanoilo por ejemplo acetilo. En una realización específica R_2 es halógeno, por ejemplo Cl o F. En otra realización específica R_2 es alcoxi, por ejemplo metoxi o etoxi.

R_3 es halógeno, hidroxilo, carboxilo alquilo, acilo, alcoxi, alcoxicarbonilo, carbamoilo, alquilsulfuro, sulfinilo, sulfonilo, un carbociclo o un heterociclo en tanto cada alquilo, acilo, alcoxi, alcoxicarbonilo, carbamoilo, alquilsulfuro, sulfinilo, sulfonilo, carbociclo y heterociclo está opcionalmente sustituido con hidroxilo, halógeno, amino, nitro, alquilo, acilo, sulfonil o alcoxi. En una realización específica R_3 es halógeno, hidroxilo, carboxilo alquilo, acilo, alcoxi, alcoxicarbonilo, carbamoilo, alquilsulfuro, alquilsulfinilo, alquilsulfonilo, un carbociclo o un heterociclo en tanto 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; en tanto m es 0 a 3. En una realización específica, R_3 es halógeno (por ejemplo F), carboxilo o alquilo opcionalmente sustituido (por ejemplo metilo, hidroximetilo, dimetilaminometilo), alcoxicarbonilo (por ejemplo metoxicarbonilo) o carbamoilo (por ejemplo dimetilaminocarbonilo). En una realización específica m es 0, es decir R_3 está ausente. En otra realización específica m es 1-3.

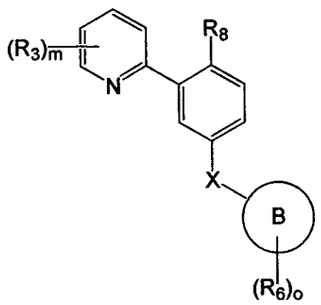
En una realización específica, los compuestos de la invención están representados por la fórmula general Ib:



Ib

donde X, R_1, R_3 y m responden a la definición de la presente y R_8 es halógeno. En una realización, los compuestos de la invención poseen la fórmula general Ib y X es NR_4CO. En una realización adicional, los compuestos poseen la fórmula Ib y R_3 es H o metilo.

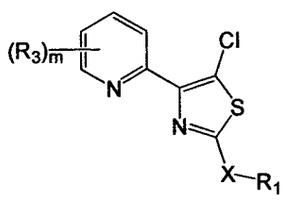
En otra realización específica, los compuestos de la invención están representados por la fórmula general Ib':



Ib'

donde X, R_3, R_6, m y o responden a la definición de la presente; R_8 es un halógeno; y el anillo B es un carbociclo o heterociclo. En una realización específica R_8 es Cl. En una realización específica el anillo B es fenilo o piridilo. En una realización específica X es $NR_4C(O)$ y R_4 mantienen la definición de la presente.

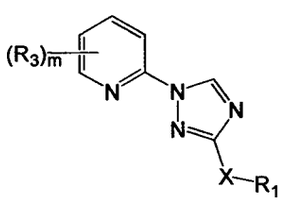
En otra realización específica, los compuestos de la invención poseen la fórmula general Ic:



Ic

donde X, R_1, R_3 y m responden a la definición de la presente. En una realización, los compuestos de la invención poseen la fórmula general Ib y X es NR_4CO. En una realización adicional, los compuestos poseen la fórmula Ic y R_3 es H o metilo y m es 0 o 1.

En otra realización específica, los compuestos de la invención poseen la fórmula general Id:



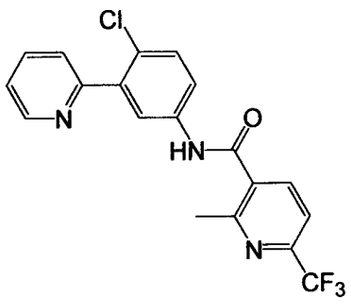
Id

donde X, R_1, R_3 y m responden a la definición de la presente. En una realización, los compuestos de la invención poseen la fórmula general Ib y X es NR_4CO. En una realización adicional, los compuestos poseen la fórmula Id y R_3 es H, Cl o trifluorometilo y m es 0 o 1.

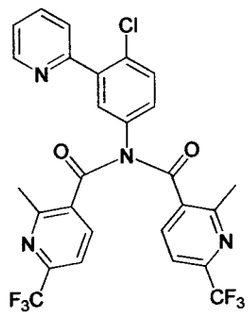
000302

Los compuestos específicos de la invención incluyen, entre otros los siguientes:

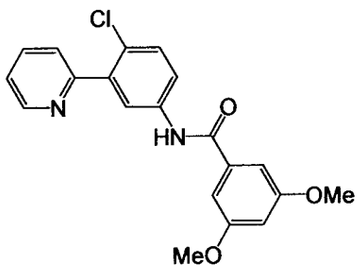
1



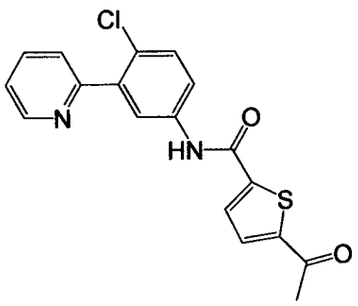
2



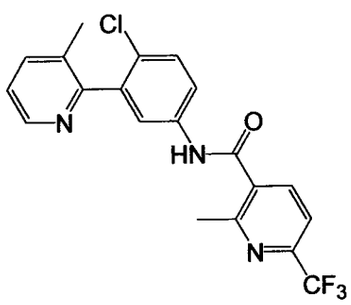
3



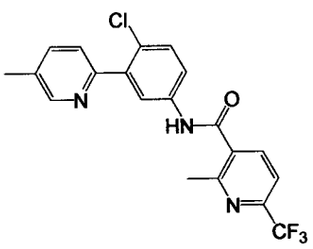
4



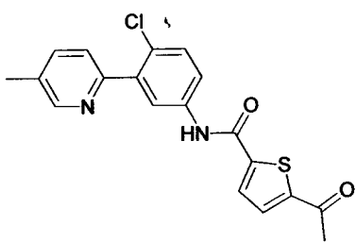
5



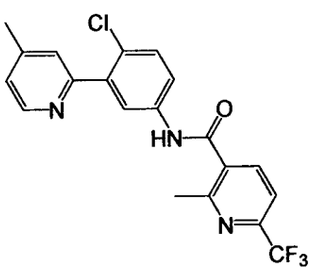
6



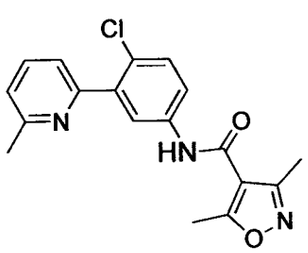
7



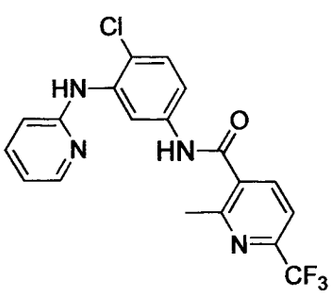
8



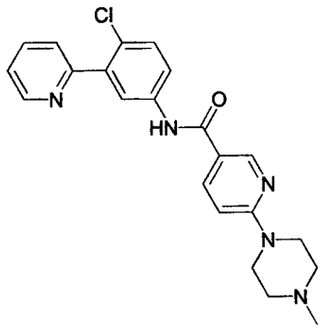
9



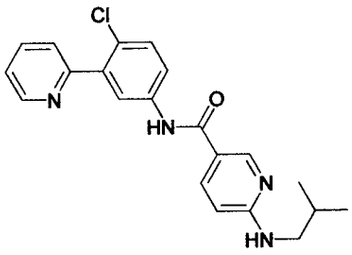
10



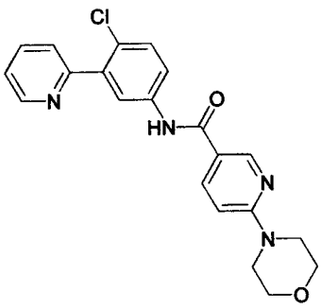
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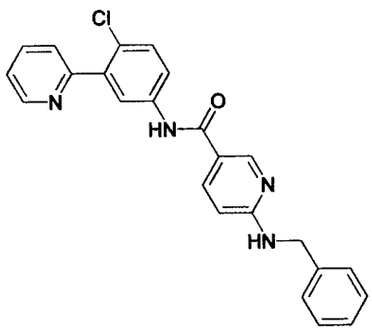
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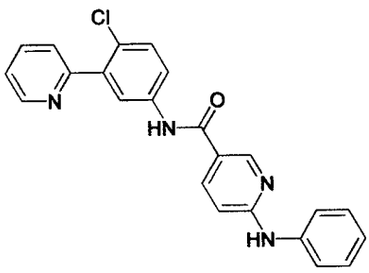
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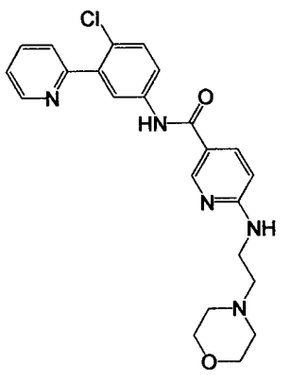
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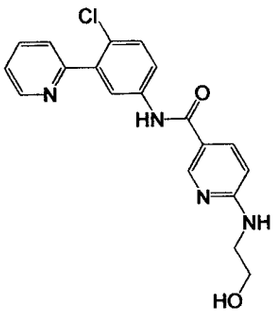
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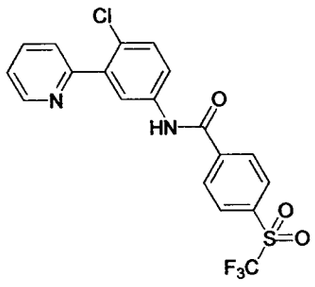
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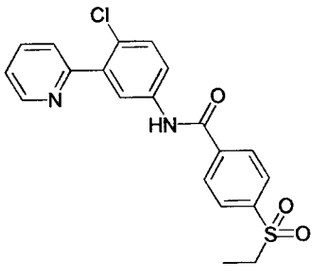
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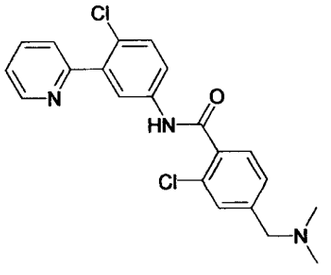
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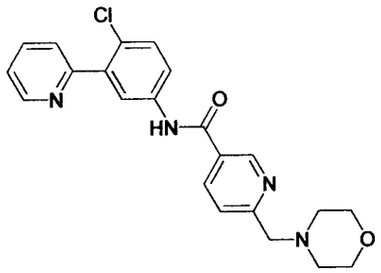
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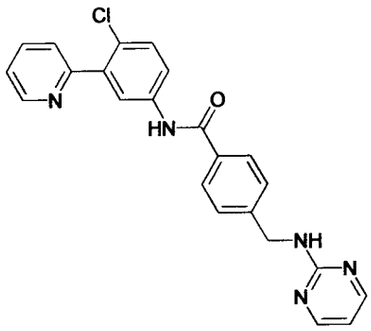
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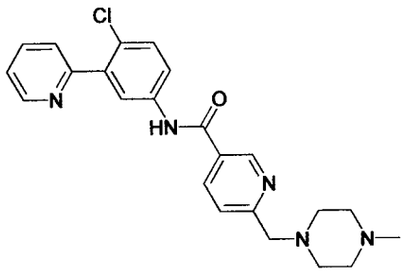
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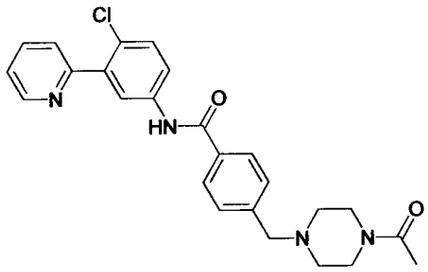
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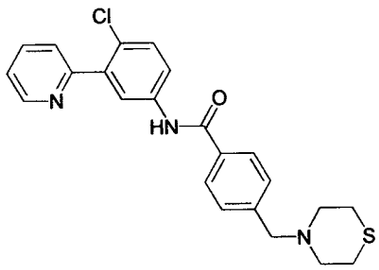
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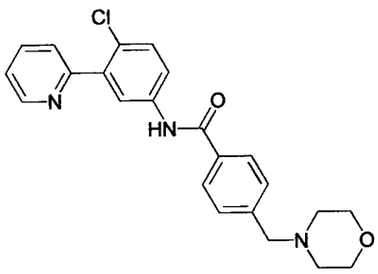
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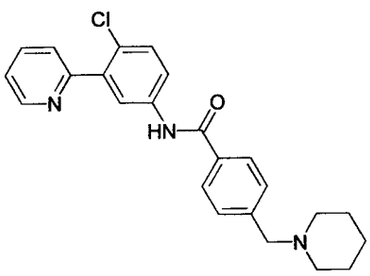
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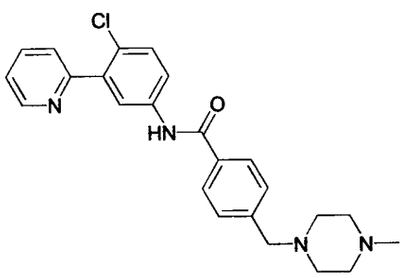
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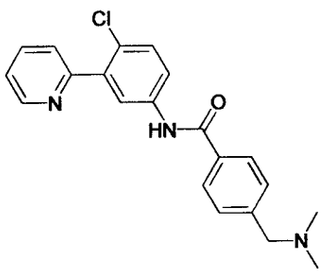
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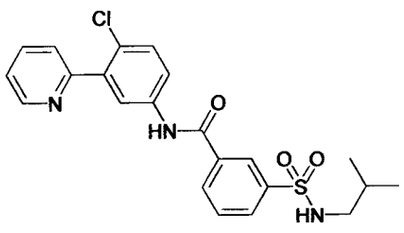
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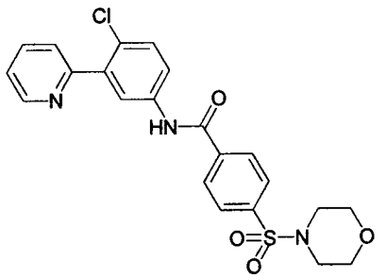
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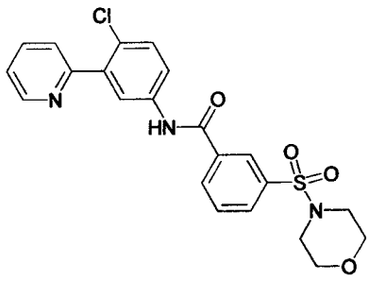
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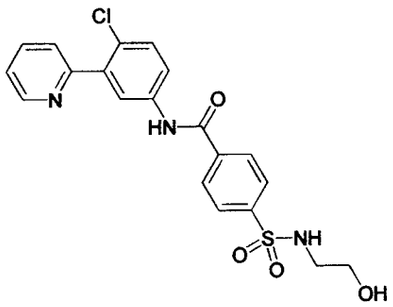
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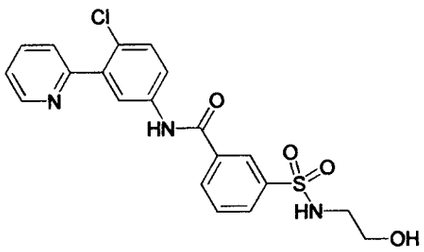
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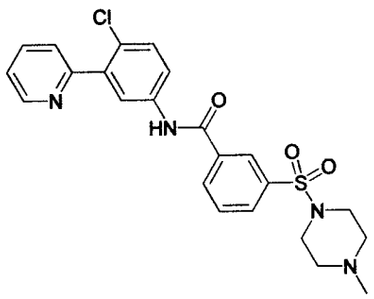
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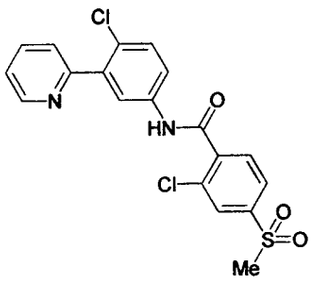
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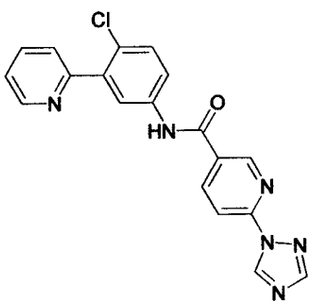
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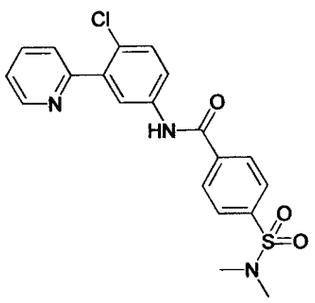
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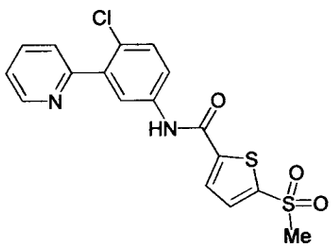
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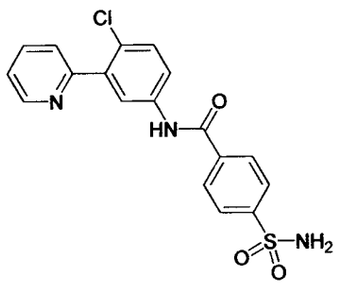
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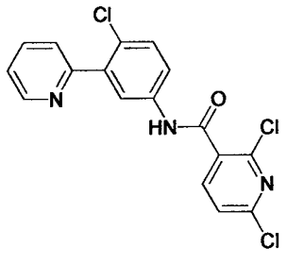
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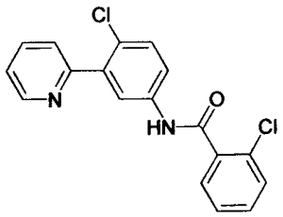
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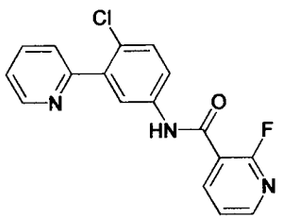
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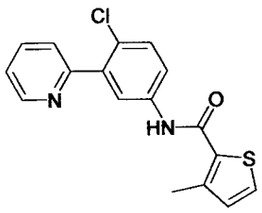
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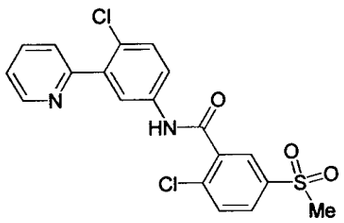
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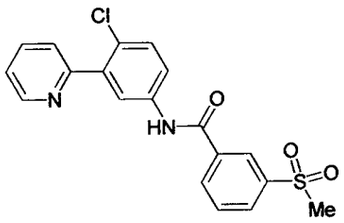
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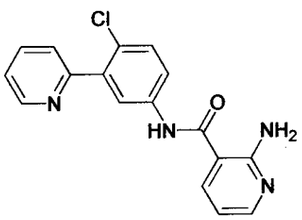
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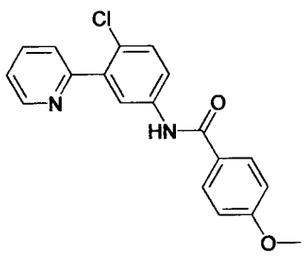
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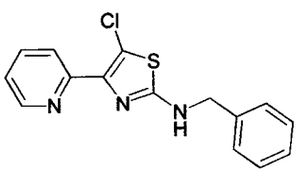
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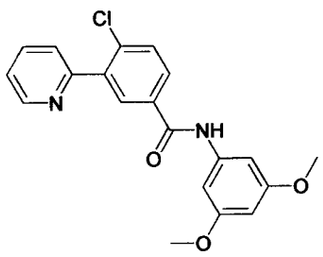
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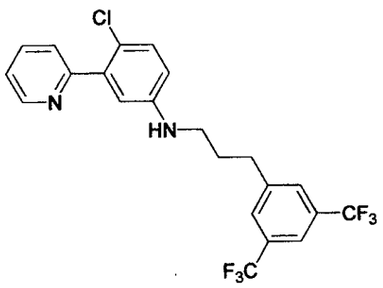
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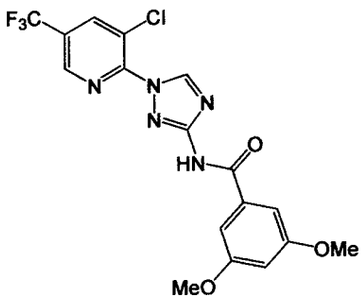
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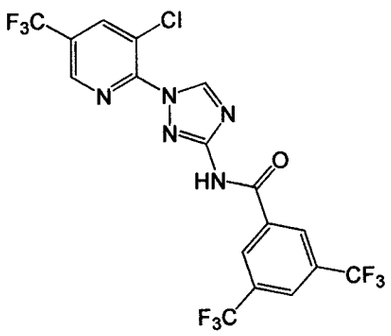
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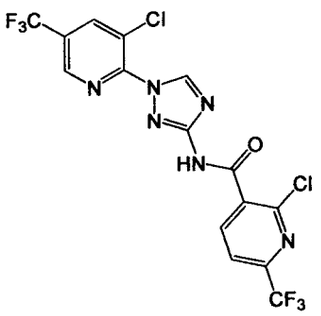
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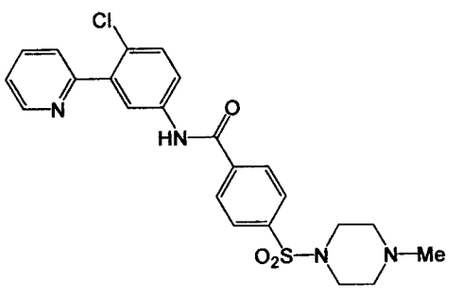
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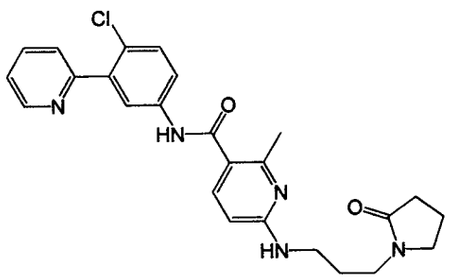
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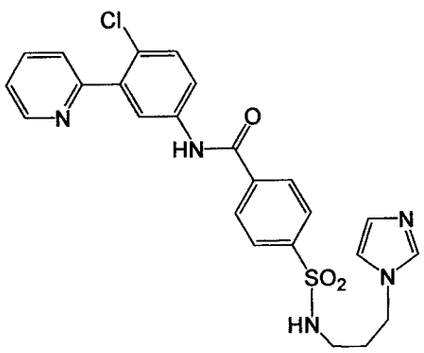
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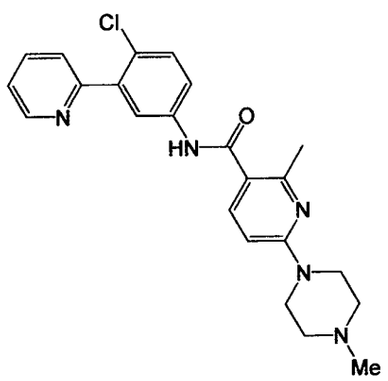
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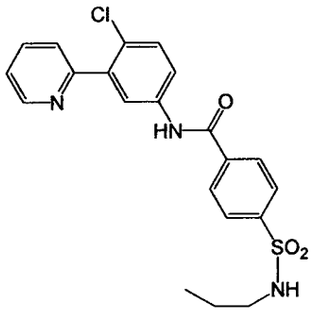
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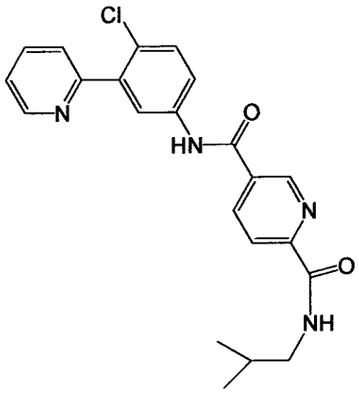
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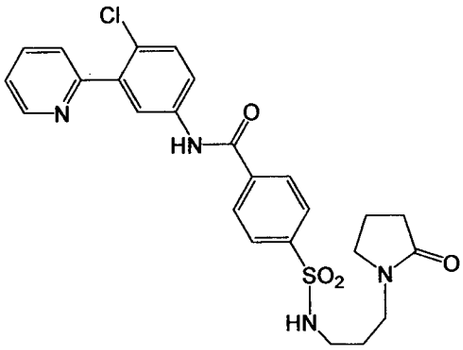
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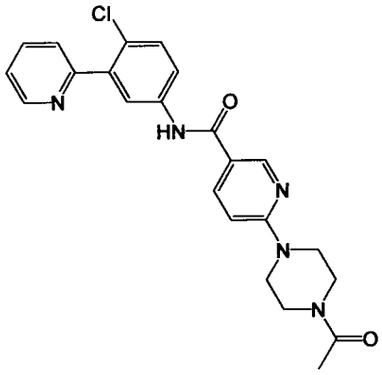
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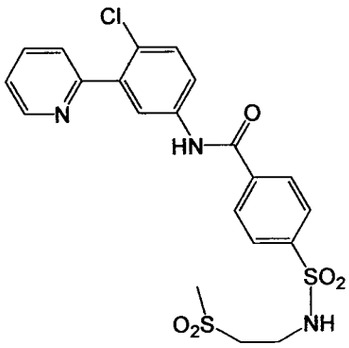
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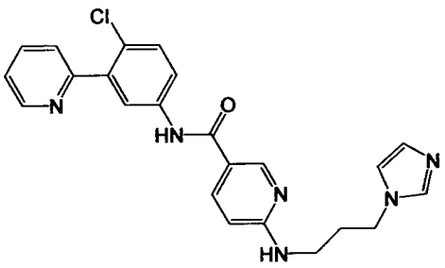
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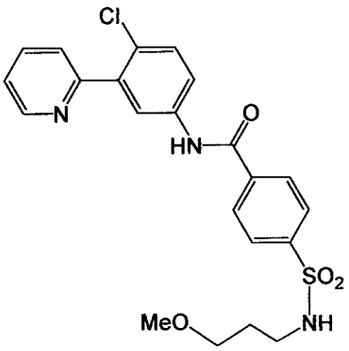
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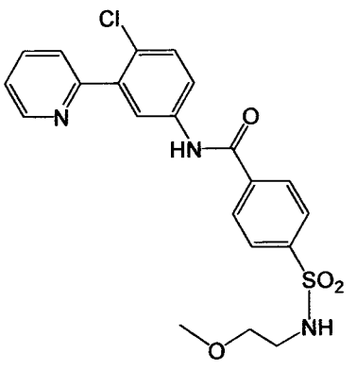
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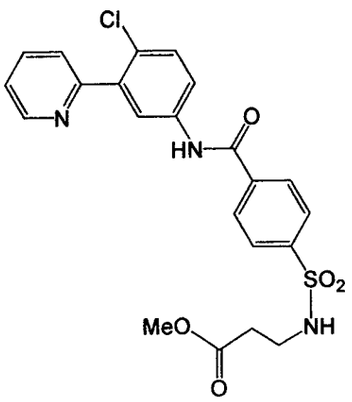
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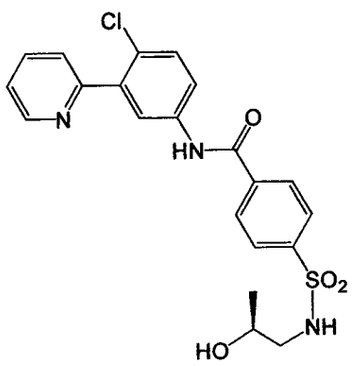
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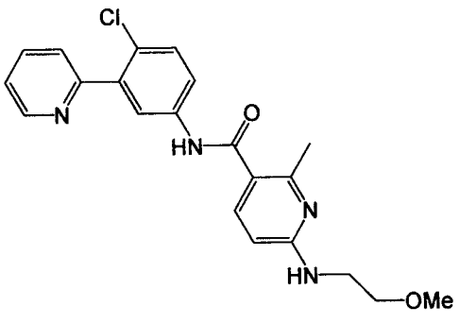
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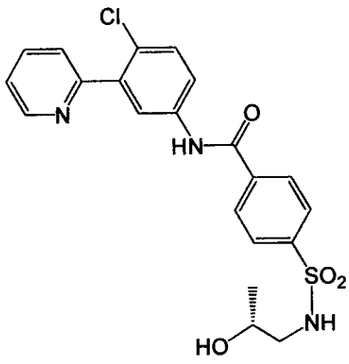
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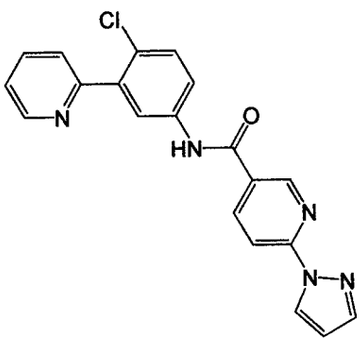
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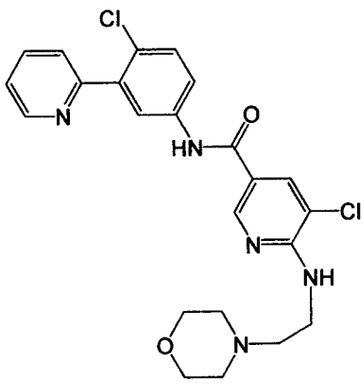
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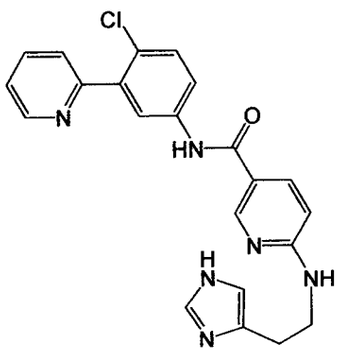
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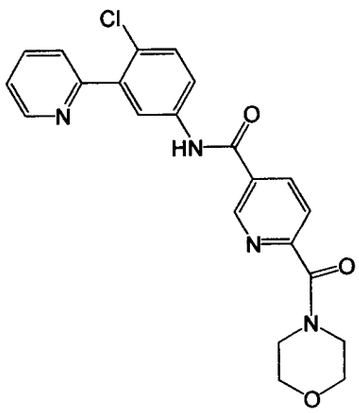
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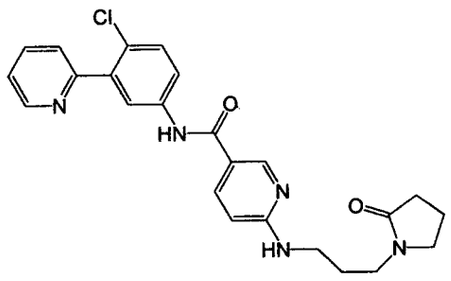


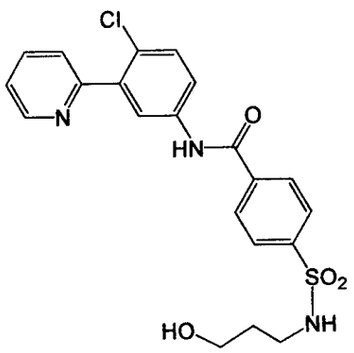
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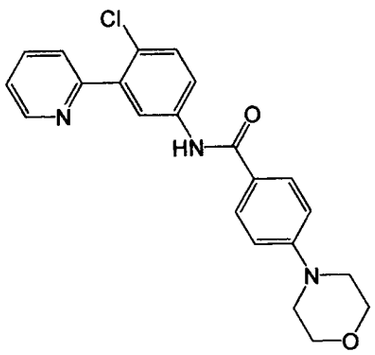


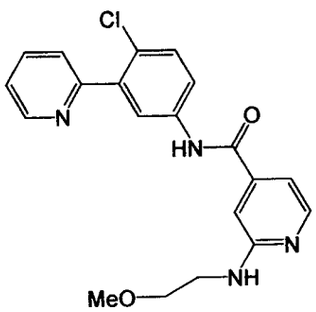
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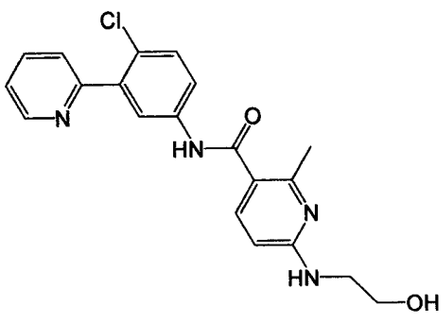


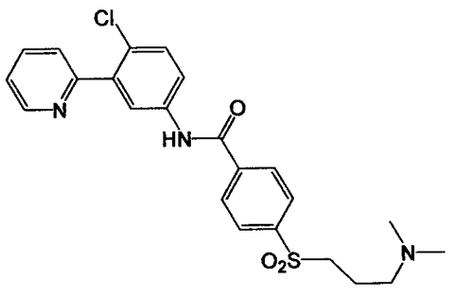
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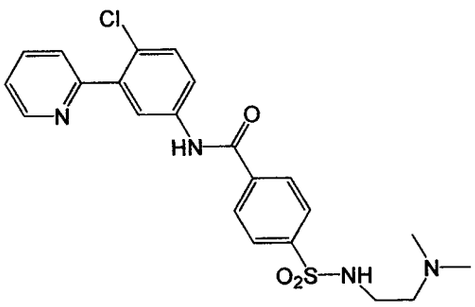
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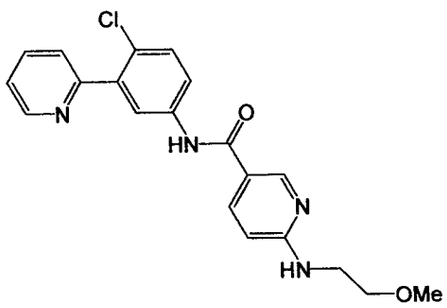
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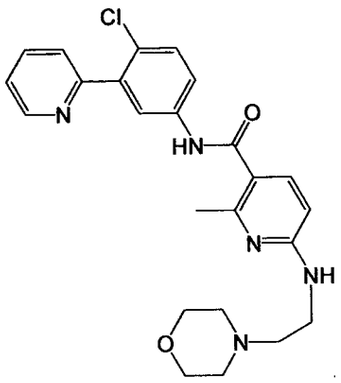
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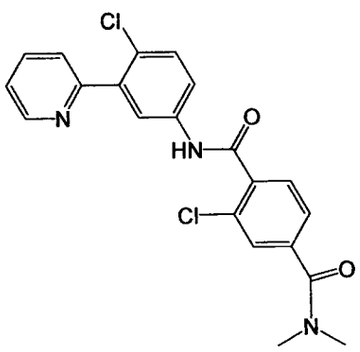
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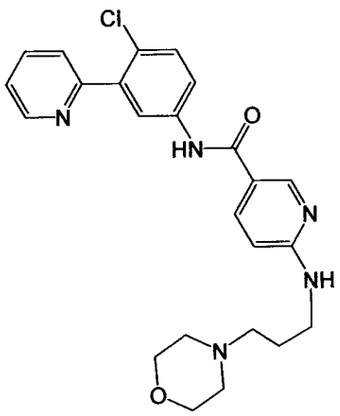
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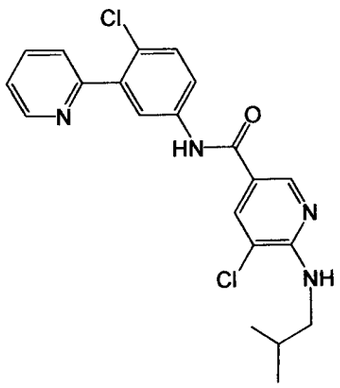
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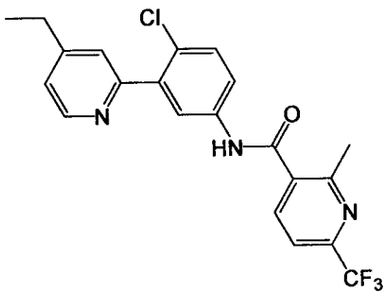
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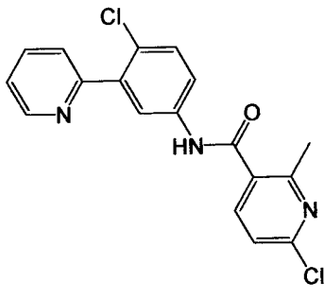
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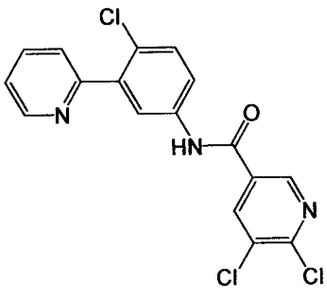
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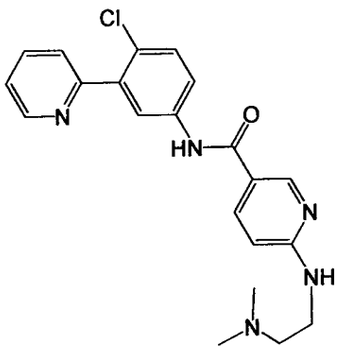
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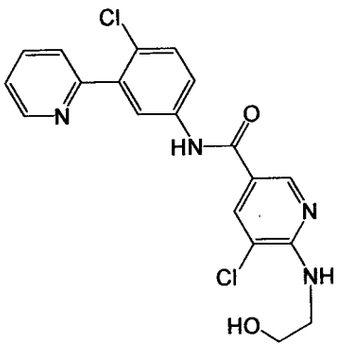
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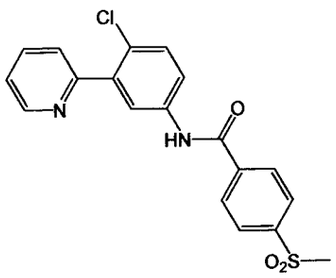
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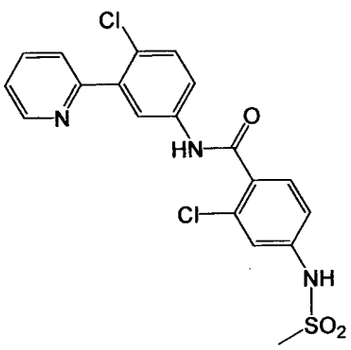
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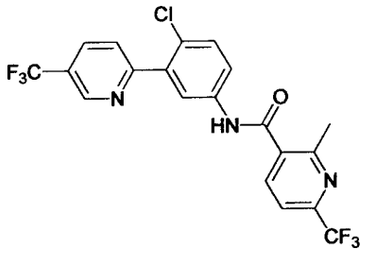
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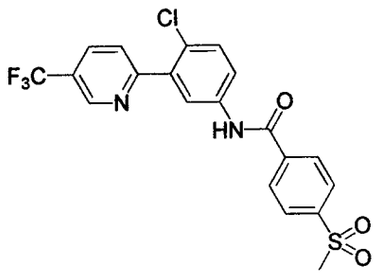


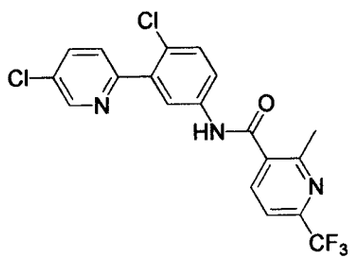
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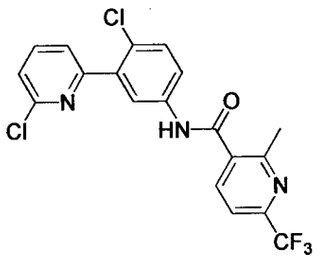
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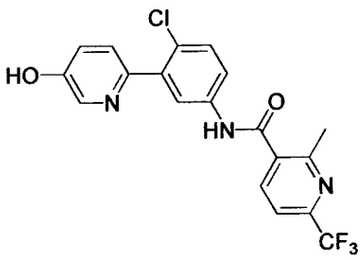
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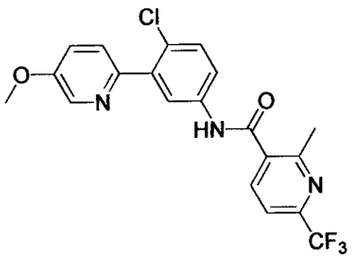
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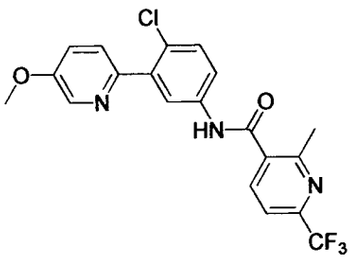
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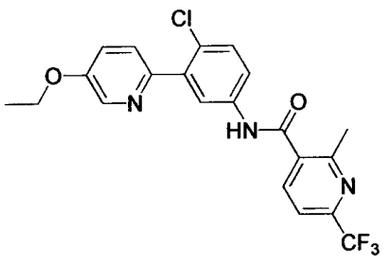
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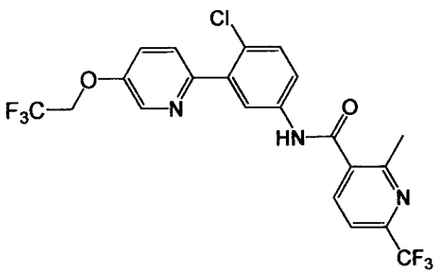
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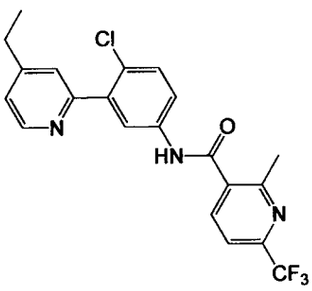
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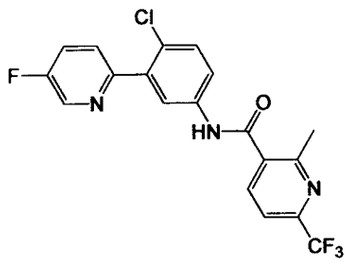
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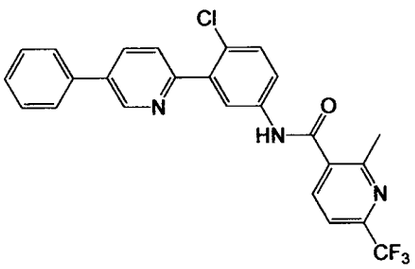
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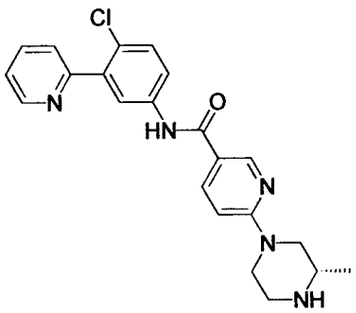
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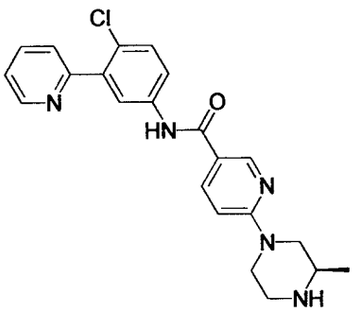
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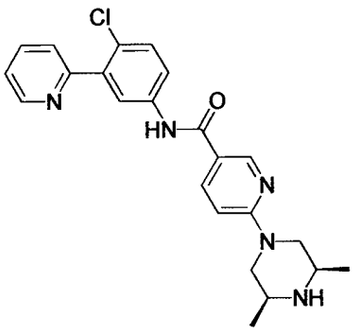
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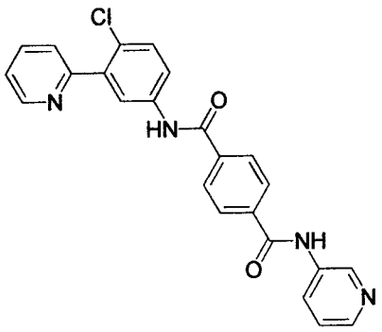


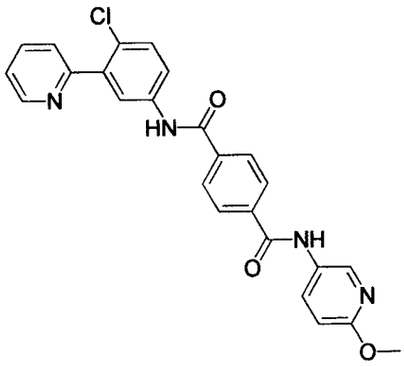
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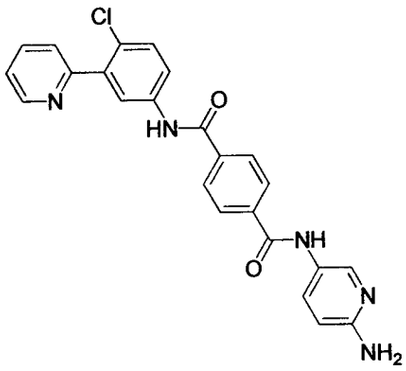


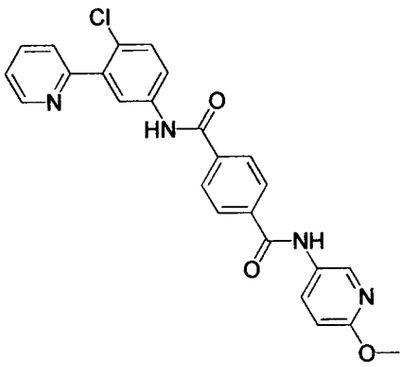
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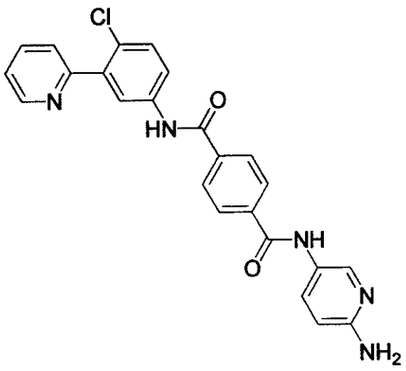


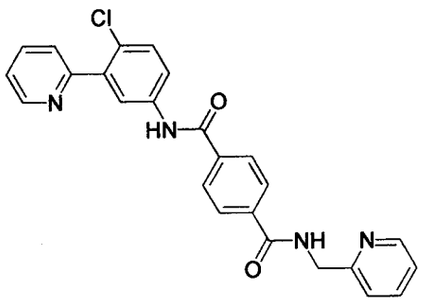
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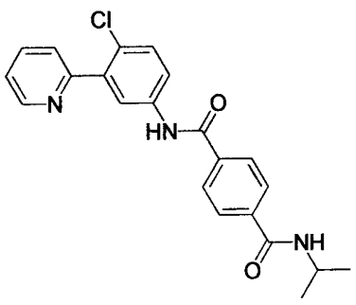
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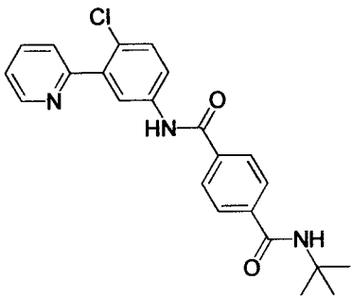
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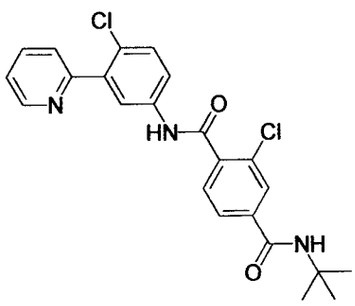
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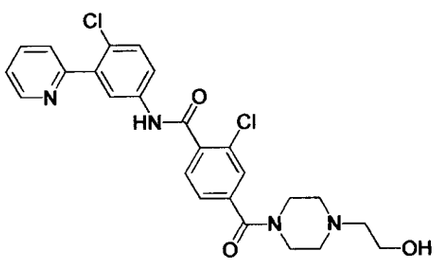
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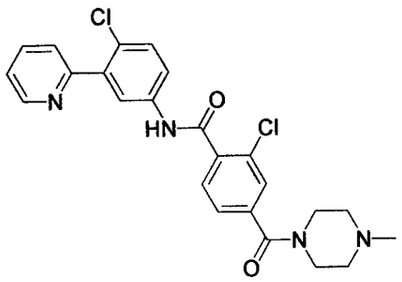
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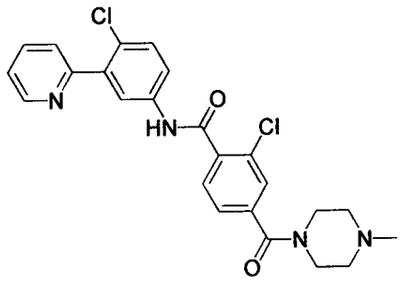
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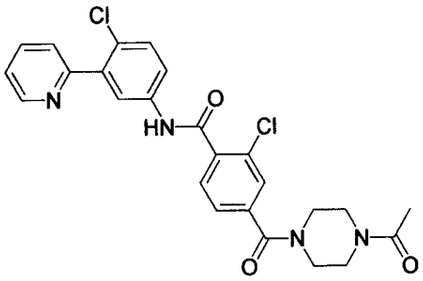
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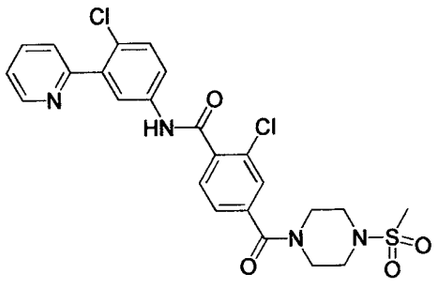
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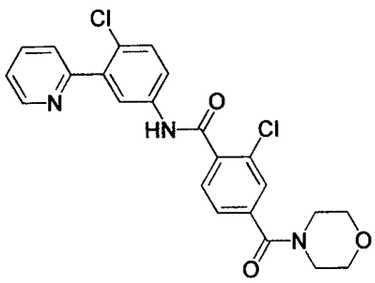
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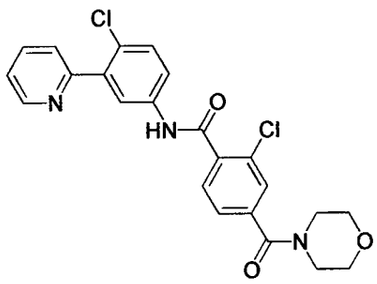
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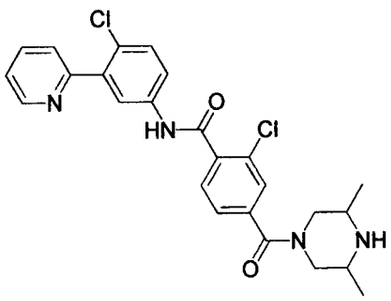
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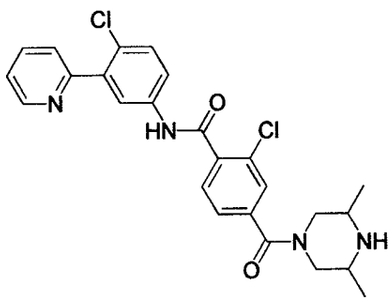
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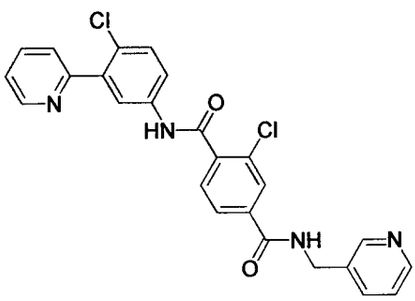
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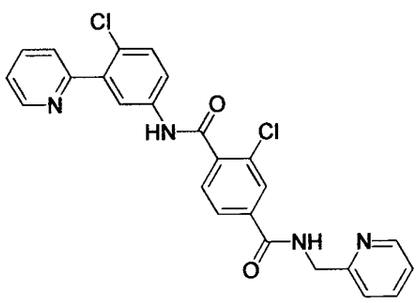
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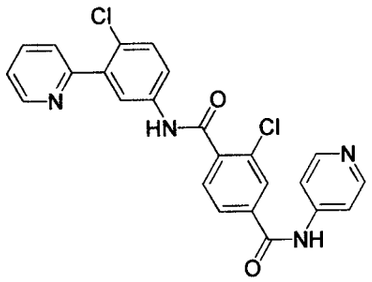
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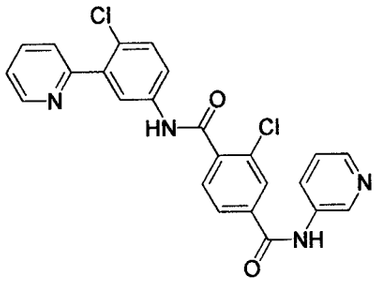
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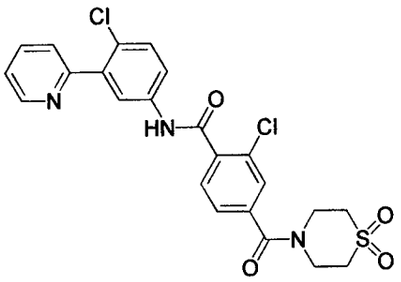
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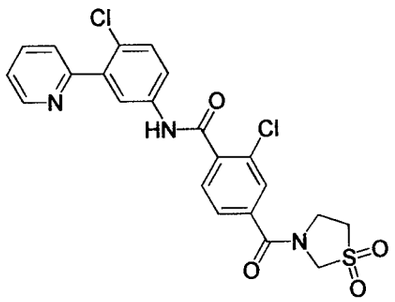
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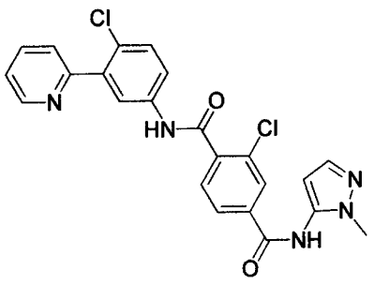
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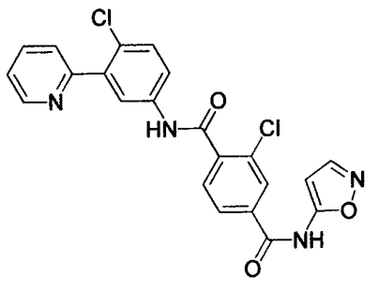
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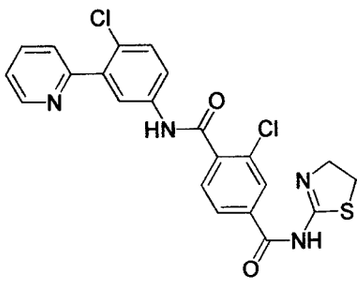
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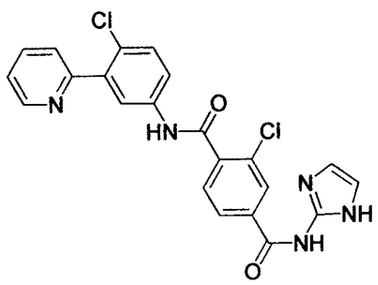
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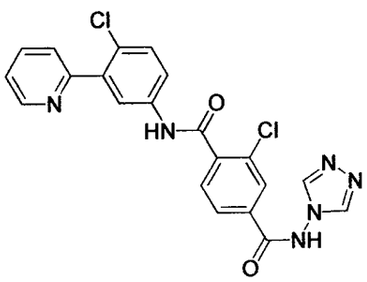
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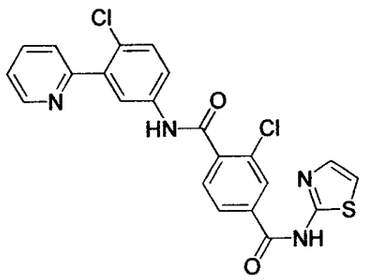
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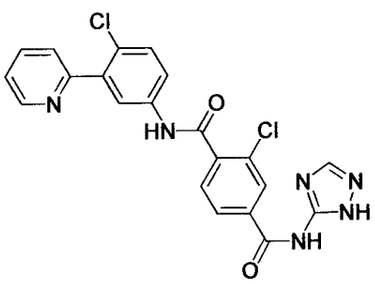
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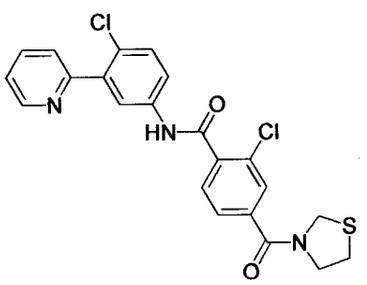
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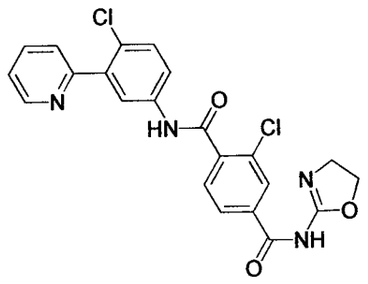
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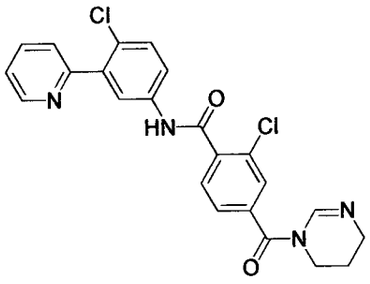
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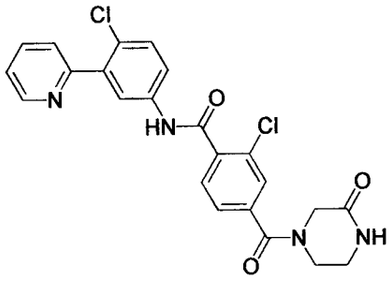
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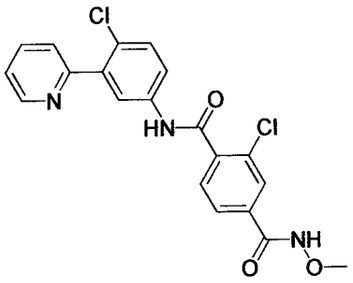
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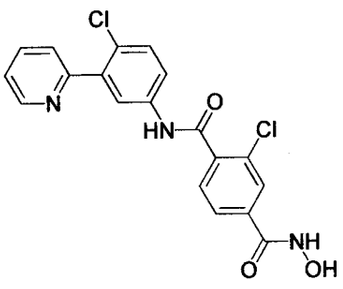
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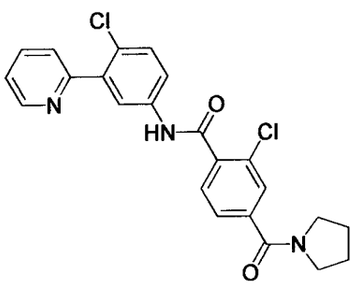
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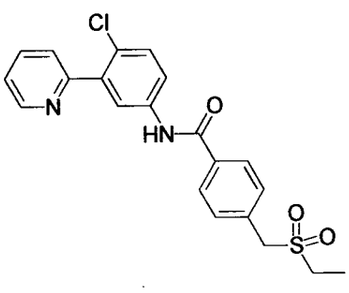
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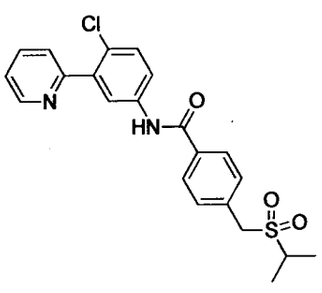
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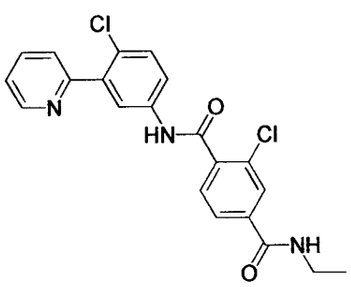
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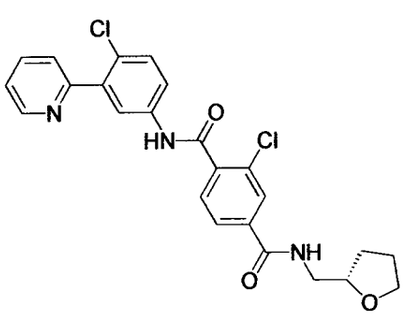
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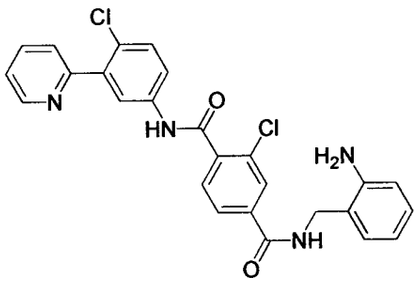
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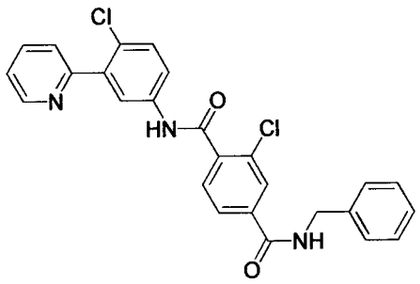
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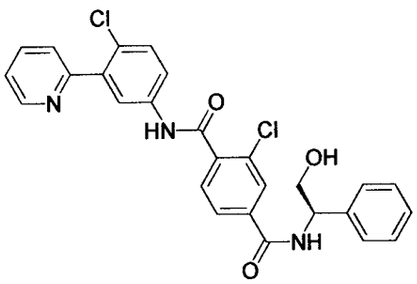
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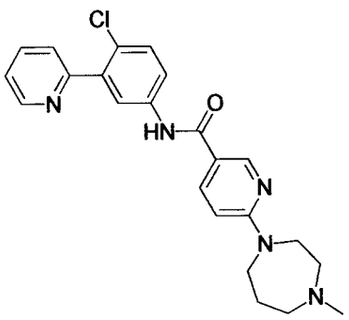
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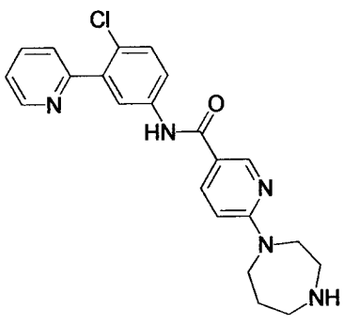
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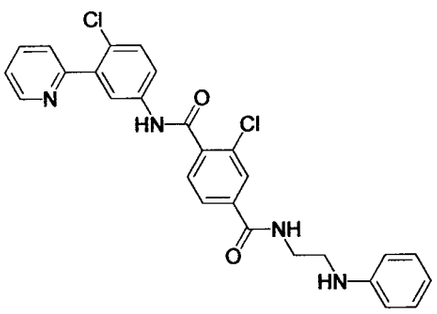
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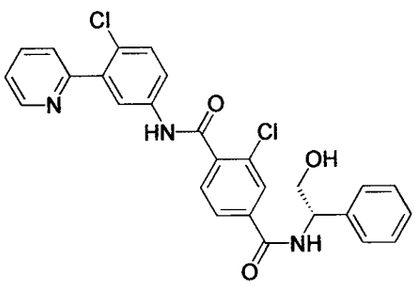
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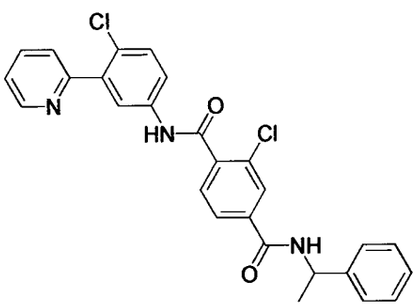
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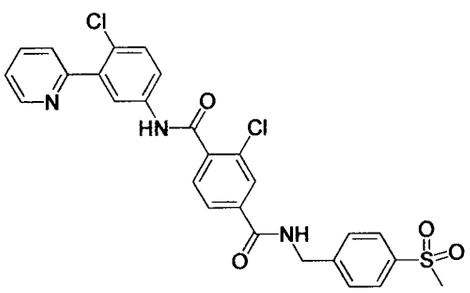
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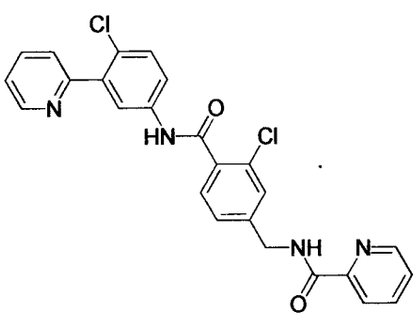
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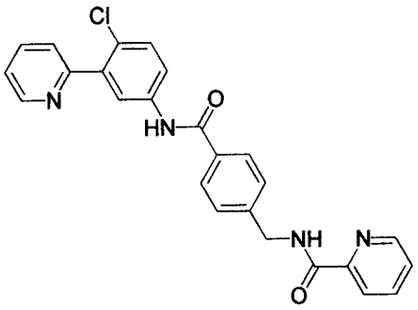


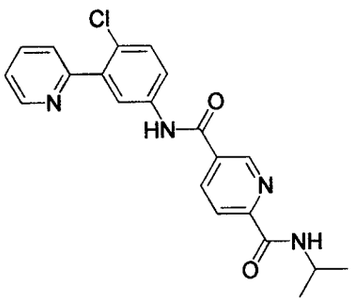
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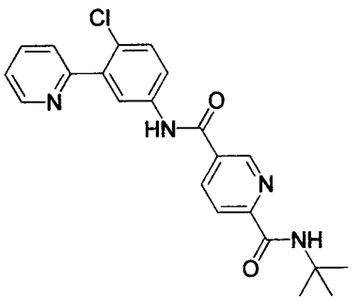


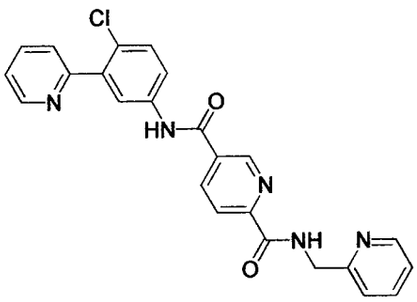
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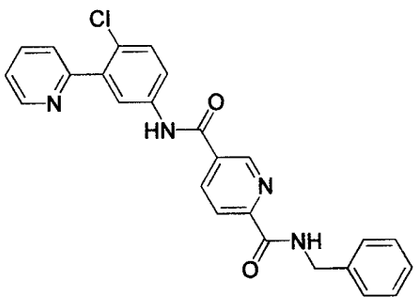


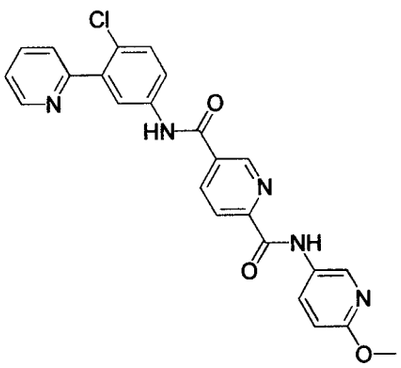
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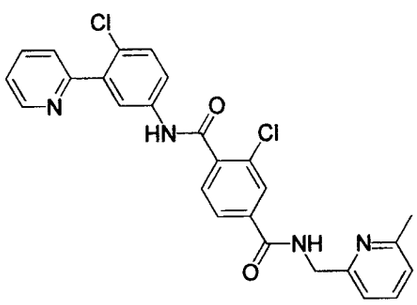
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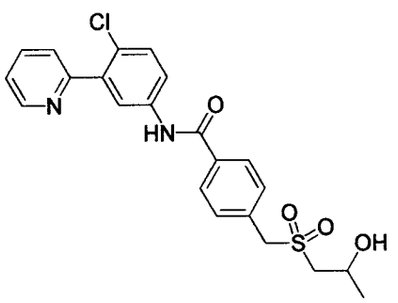
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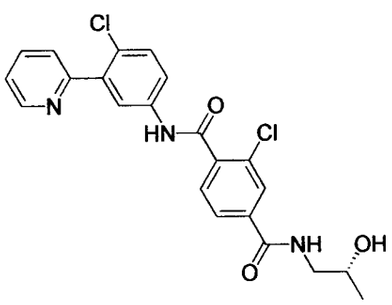
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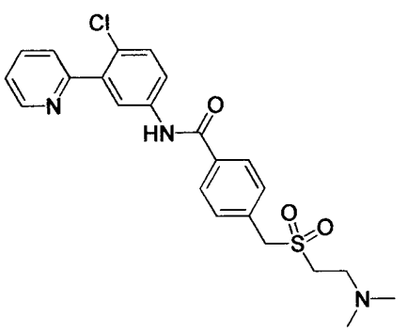
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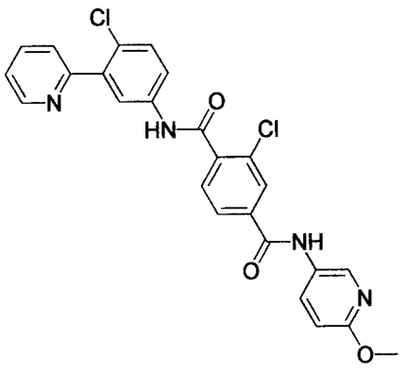
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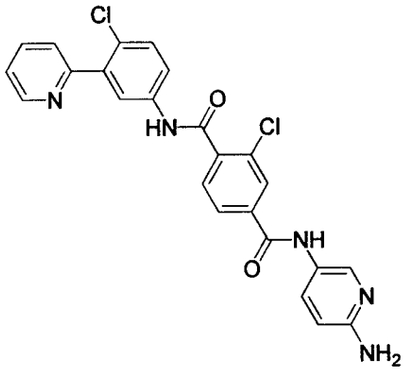
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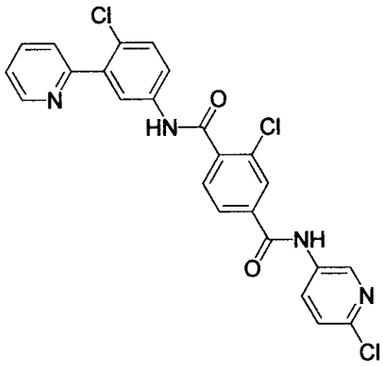
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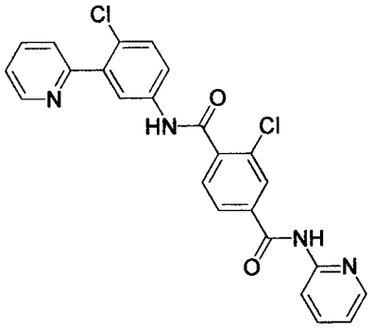
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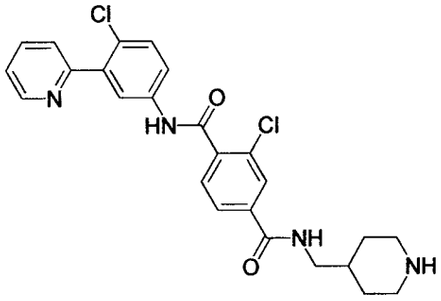
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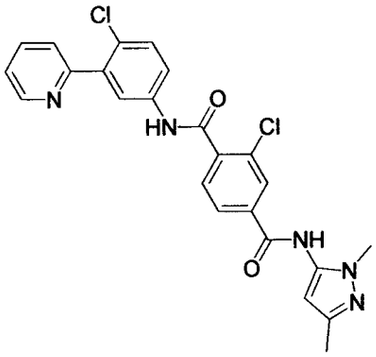
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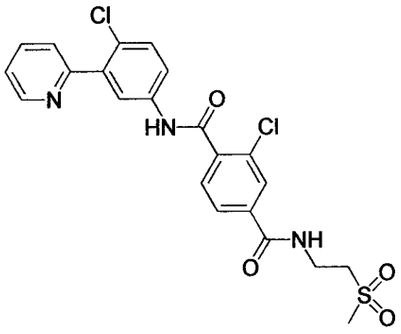
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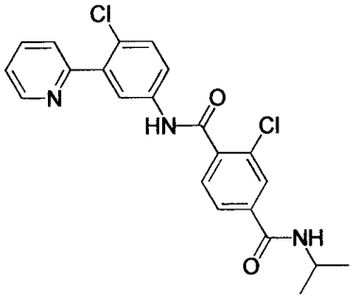
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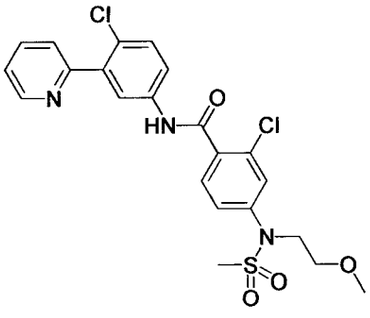
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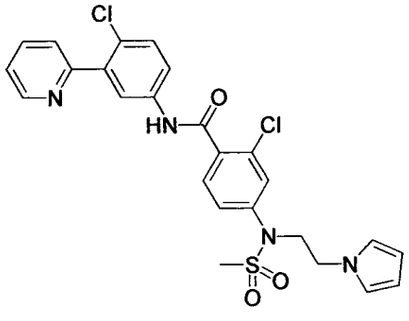
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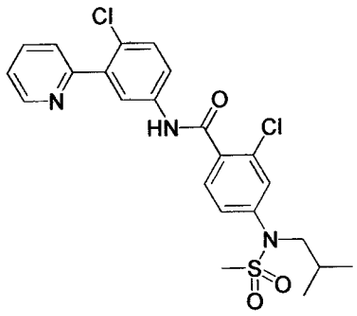
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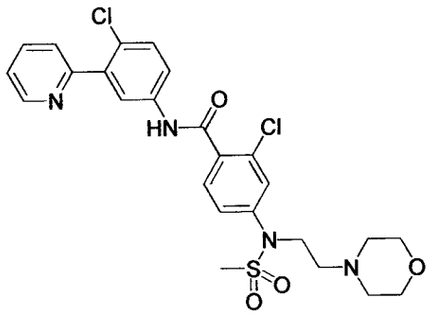


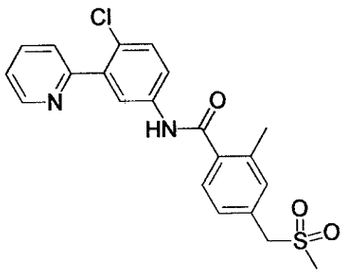
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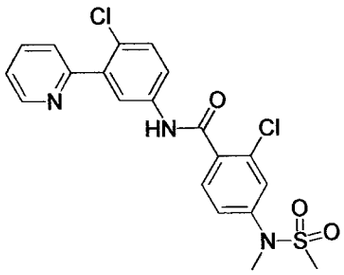


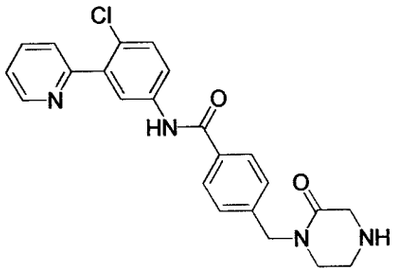
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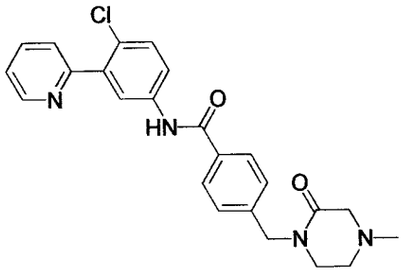
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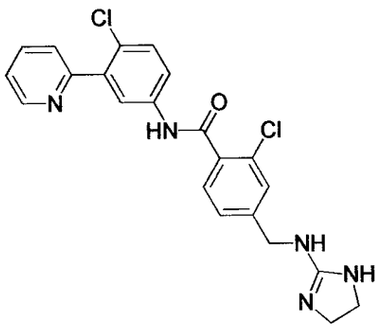
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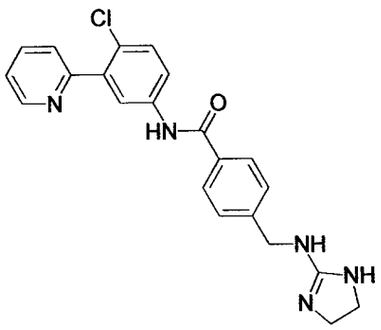
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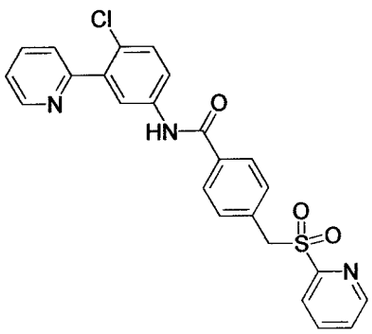
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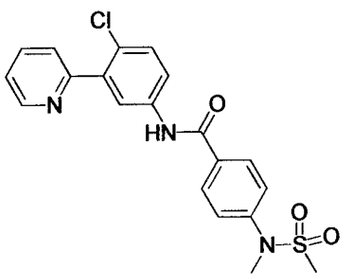
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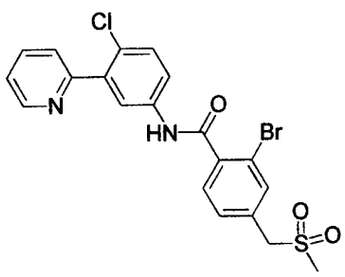
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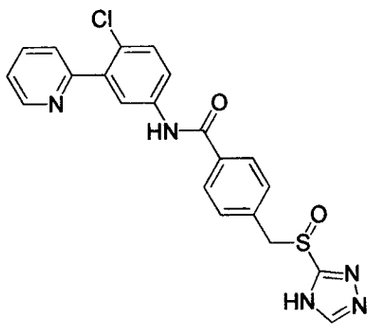
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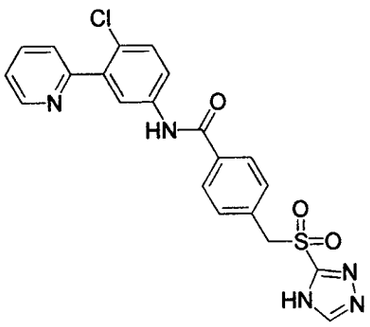
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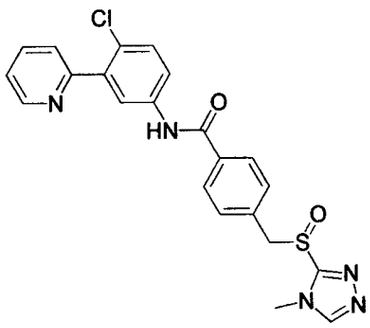
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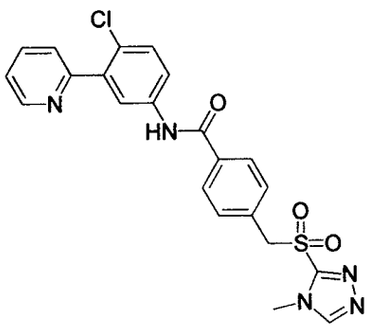
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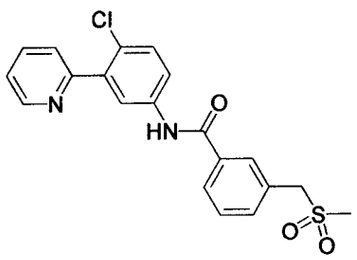
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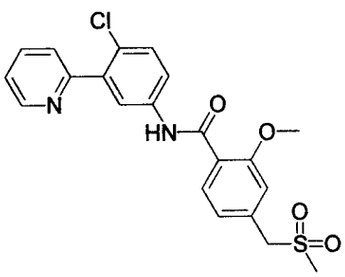
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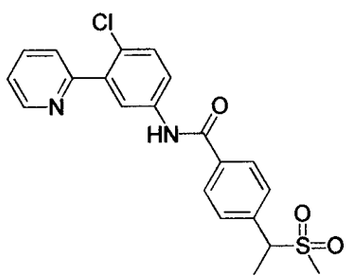
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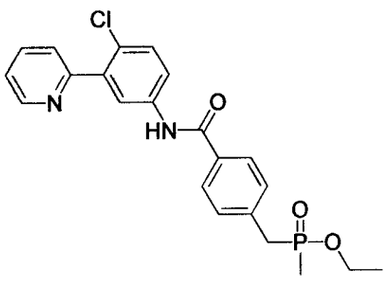
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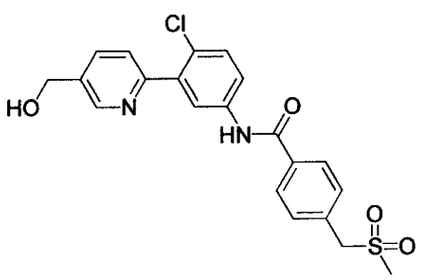
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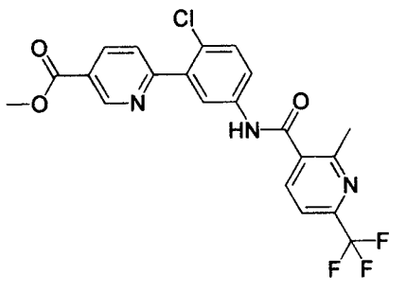
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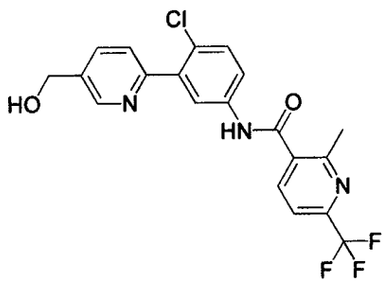
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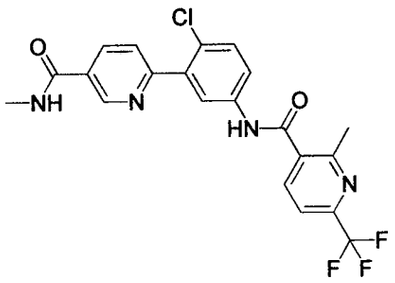
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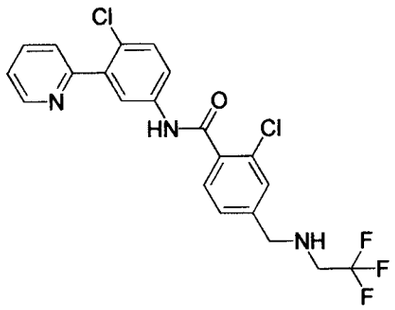
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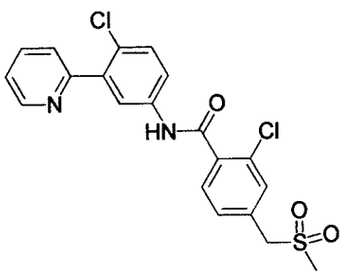
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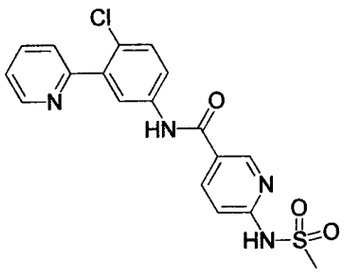
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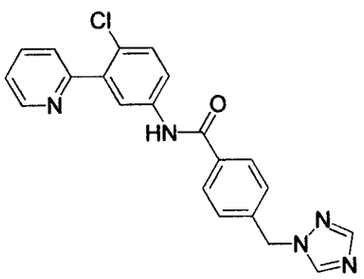
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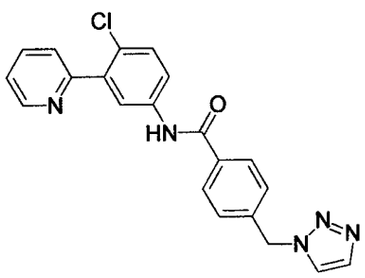
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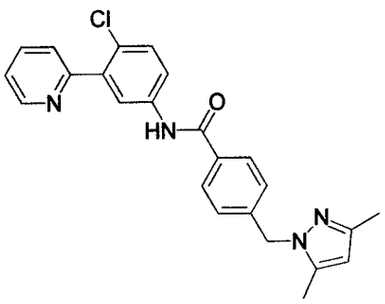
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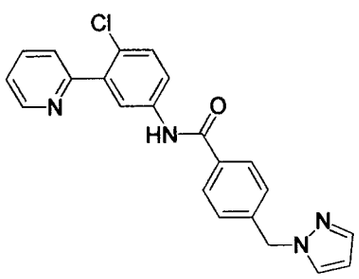
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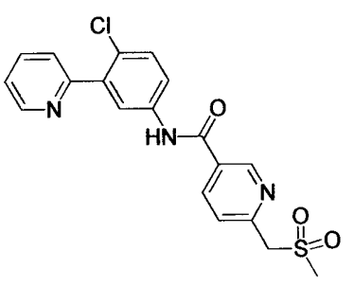
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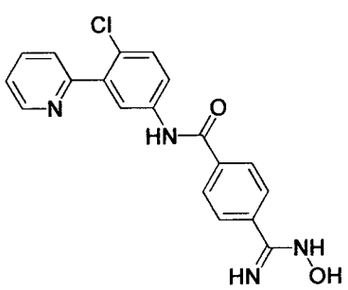
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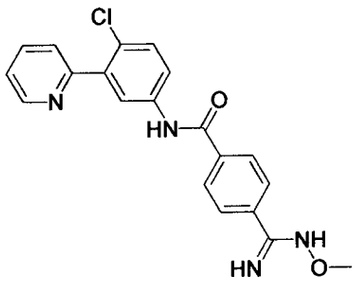
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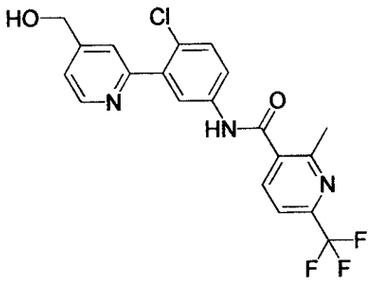
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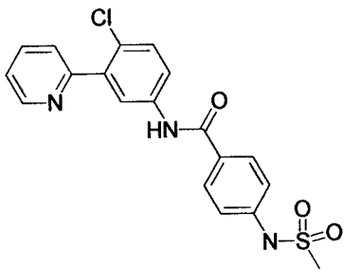
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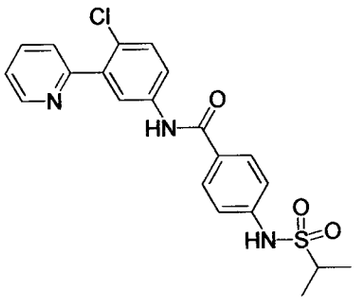
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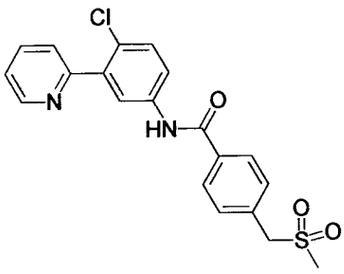
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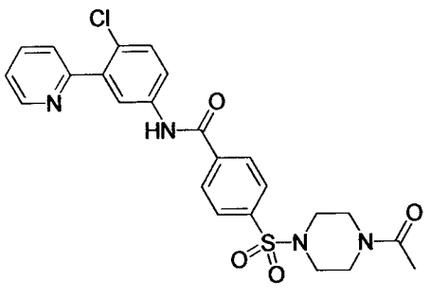
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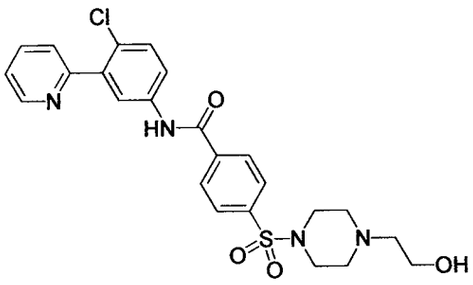
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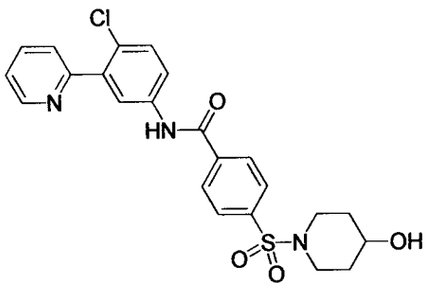
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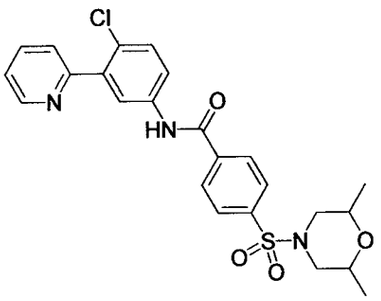
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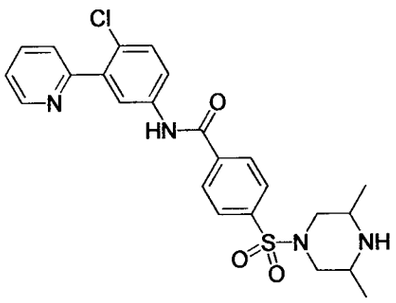
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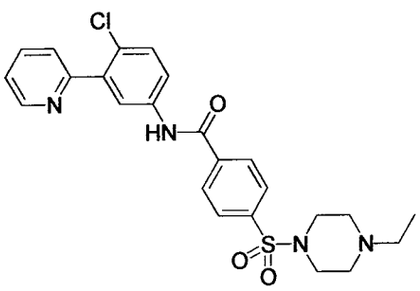
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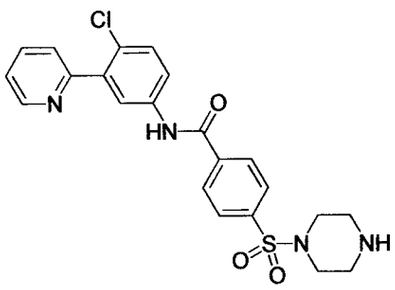
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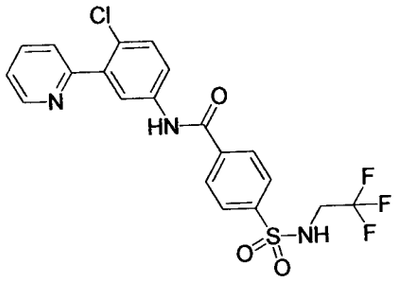
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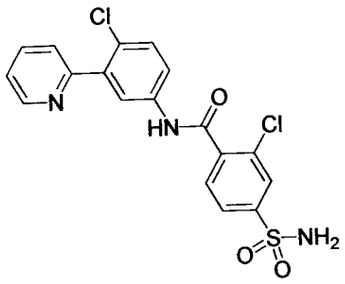
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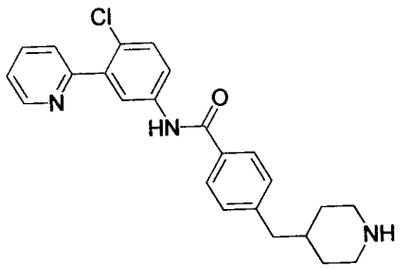
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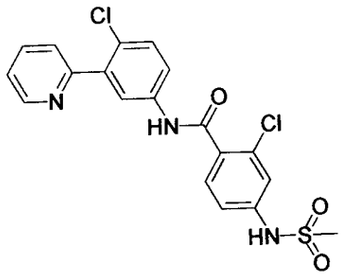
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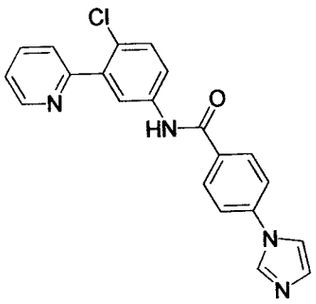
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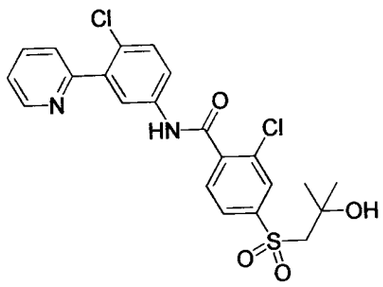
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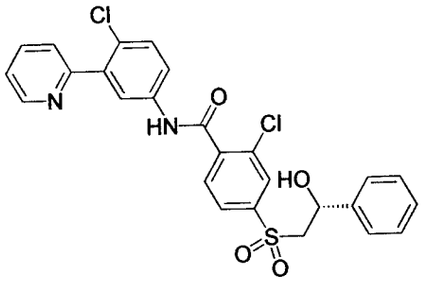
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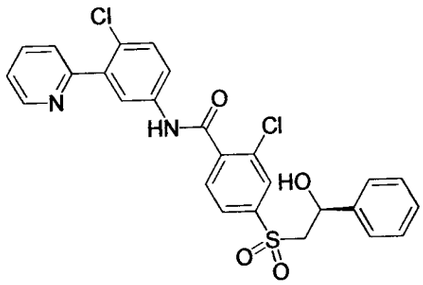
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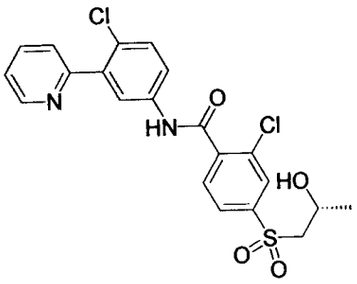
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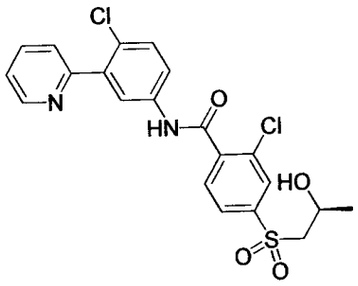
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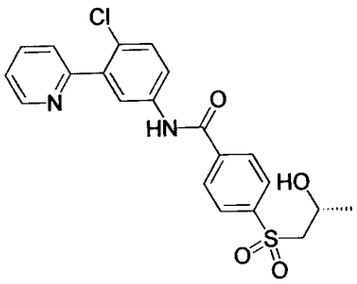
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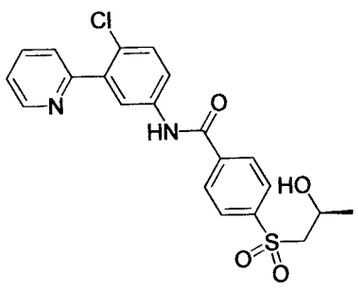
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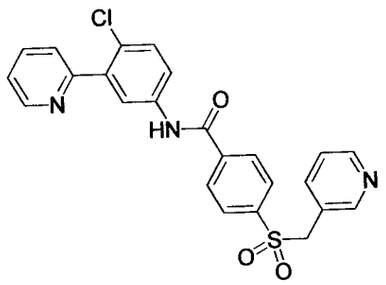
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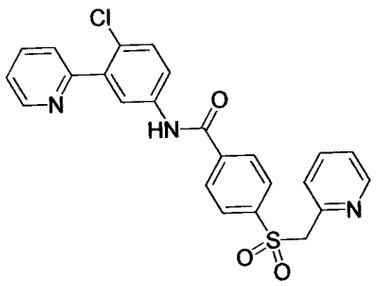
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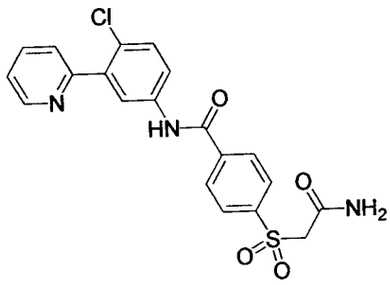
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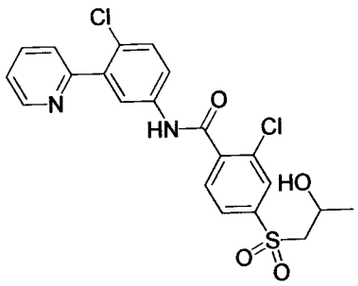
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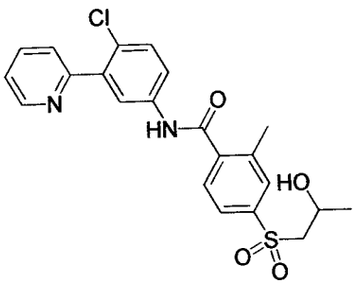
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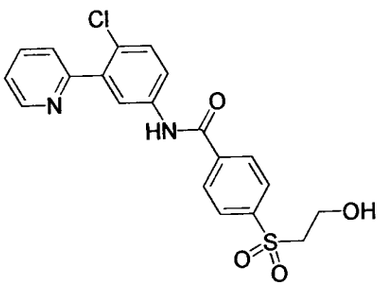
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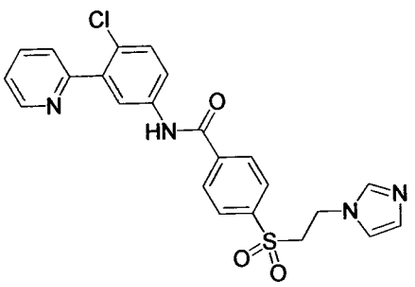
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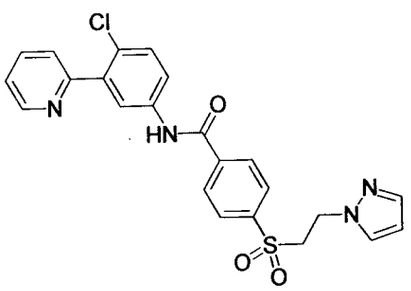
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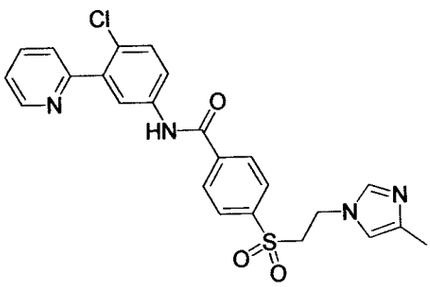
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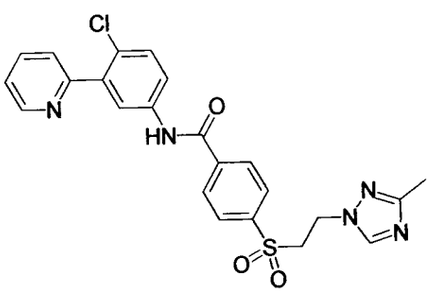
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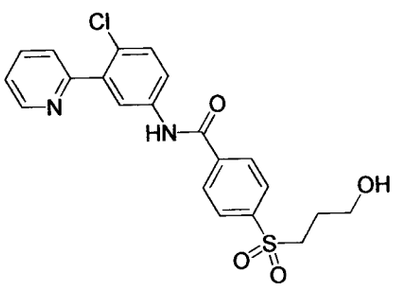
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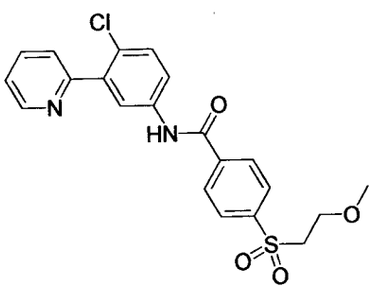
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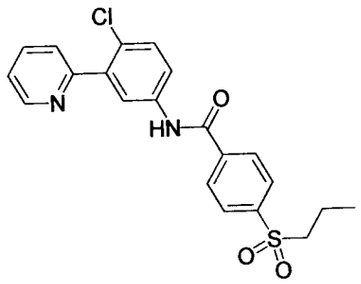
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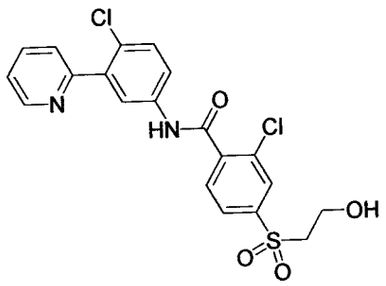
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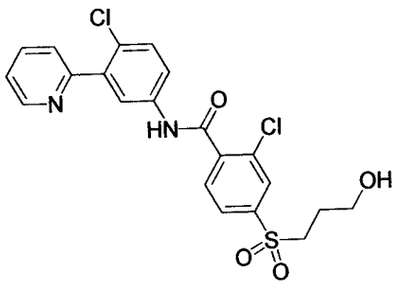
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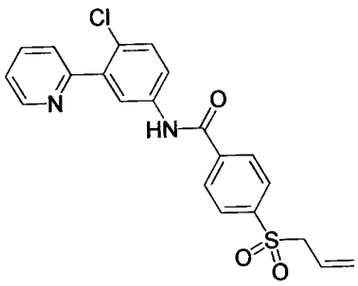
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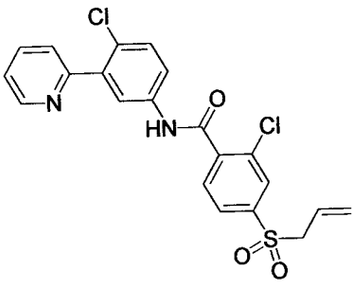
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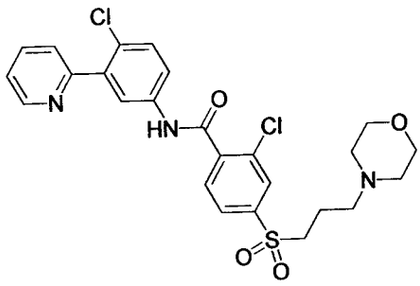
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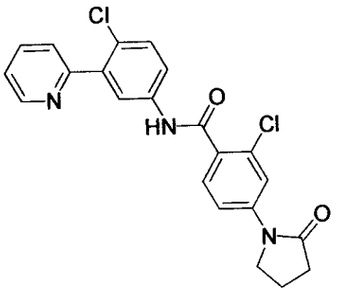
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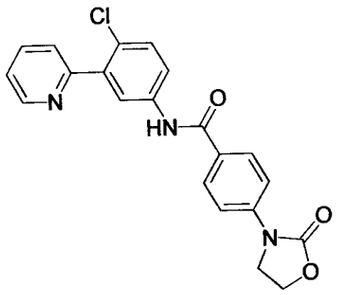
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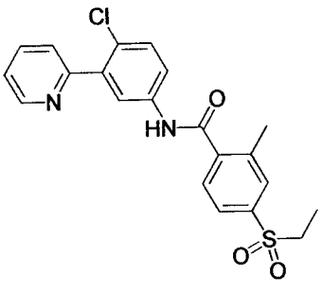
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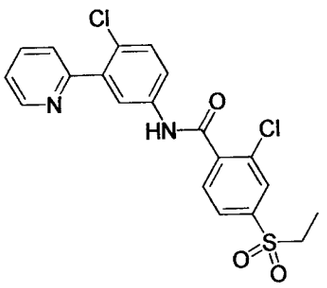
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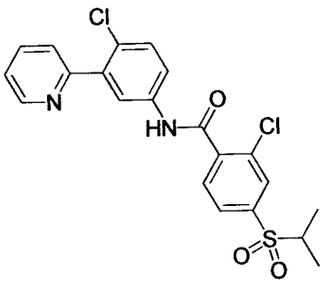
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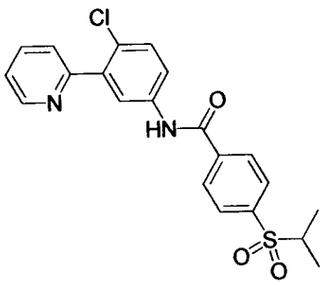
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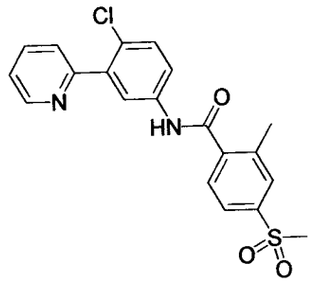
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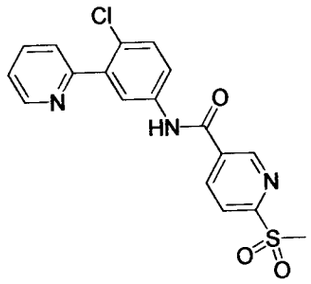
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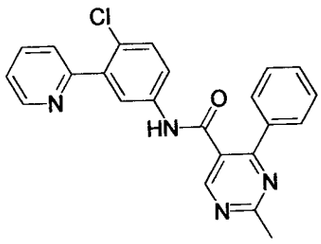
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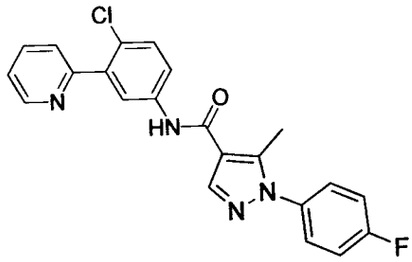
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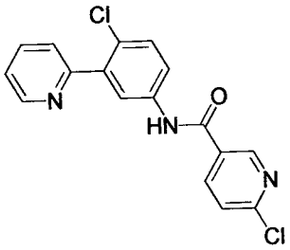
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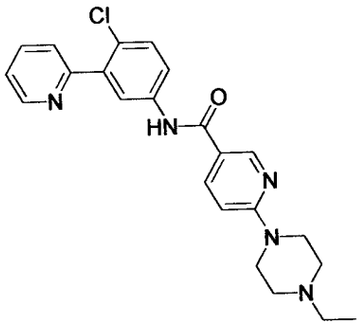
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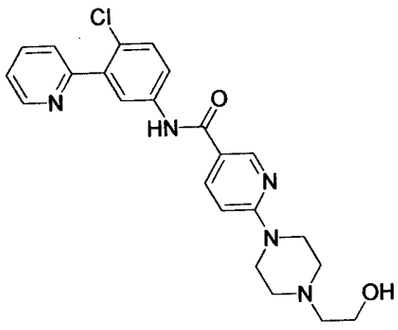
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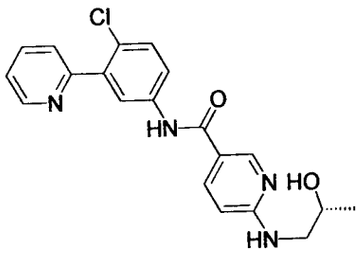
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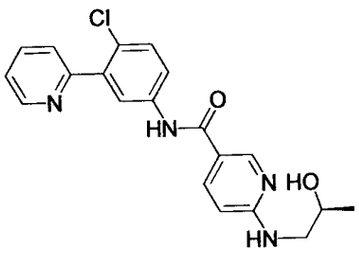
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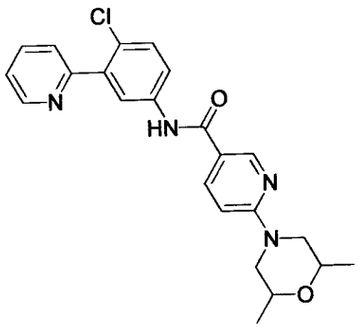
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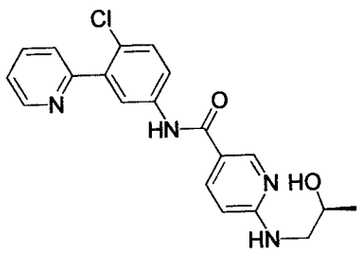
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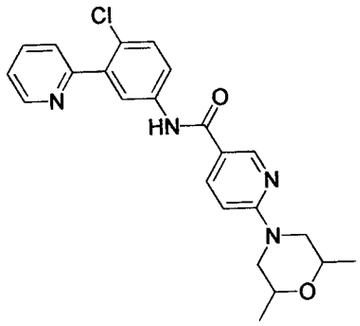
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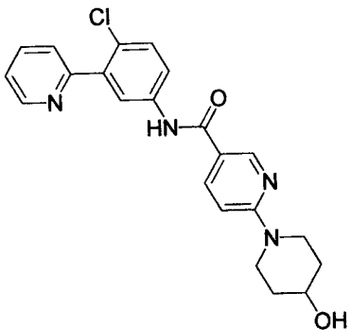
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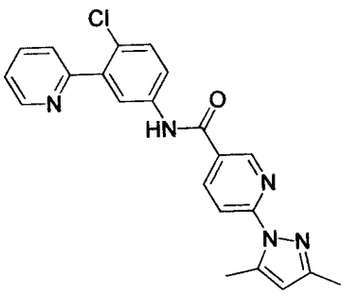
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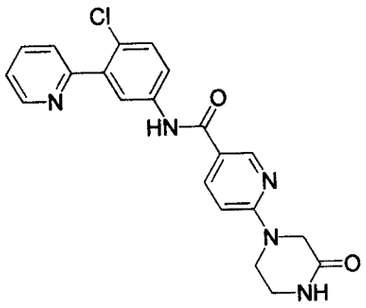
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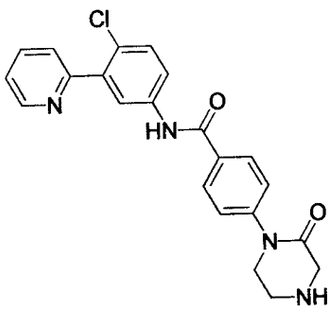
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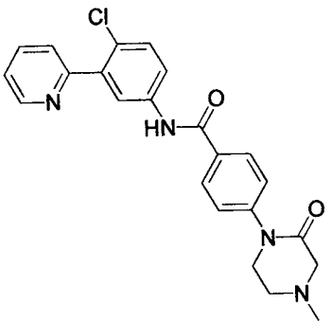
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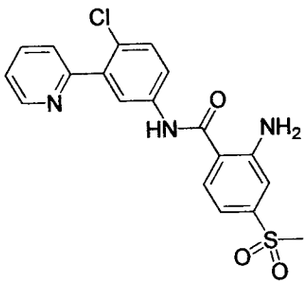
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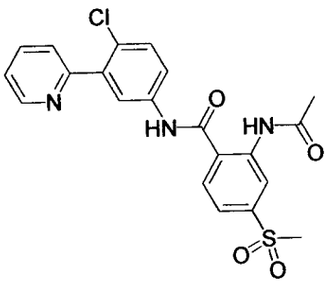
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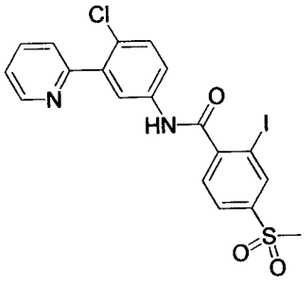
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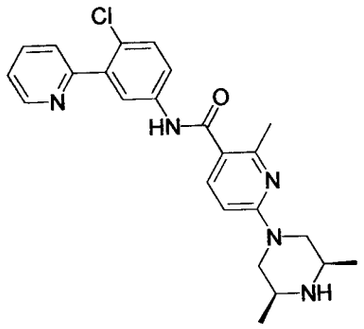
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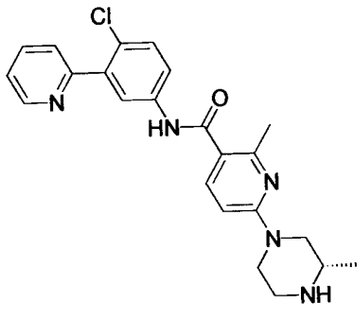
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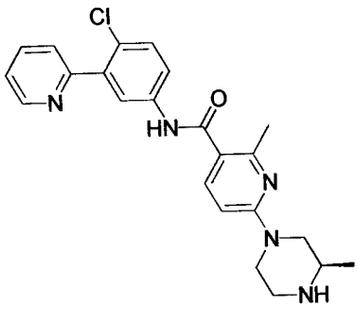
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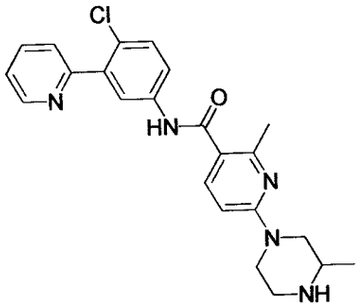
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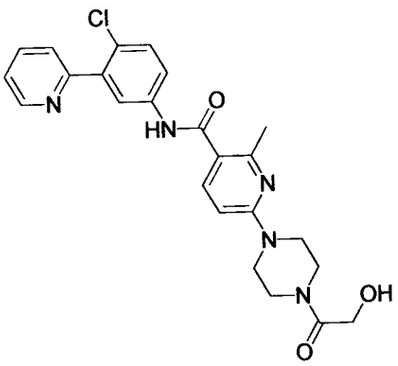
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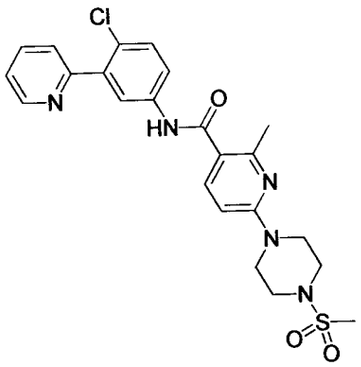
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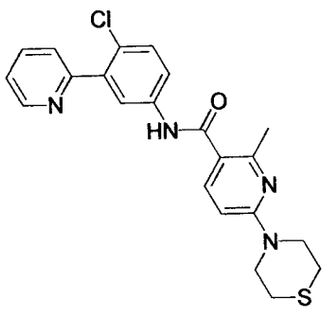
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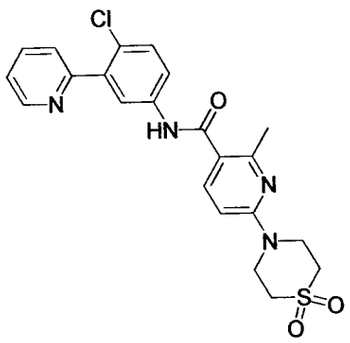
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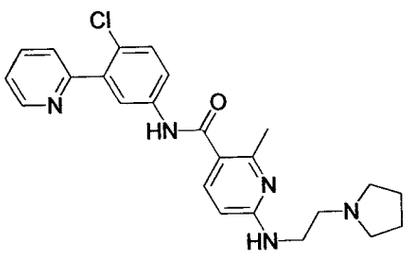
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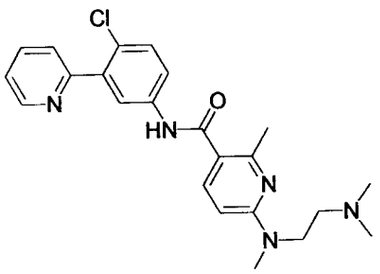
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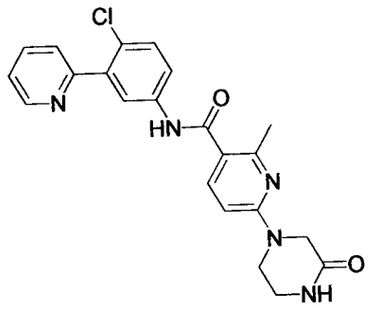


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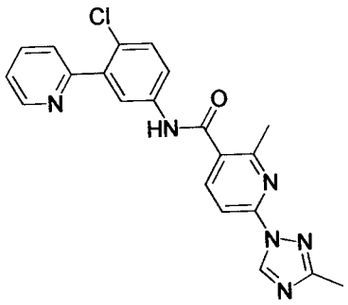


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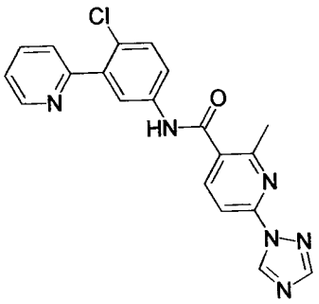
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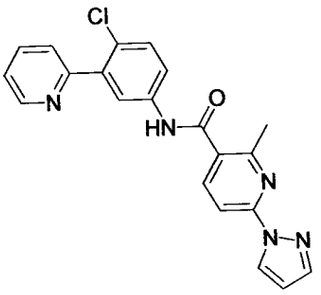
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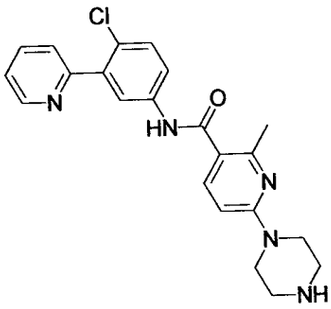
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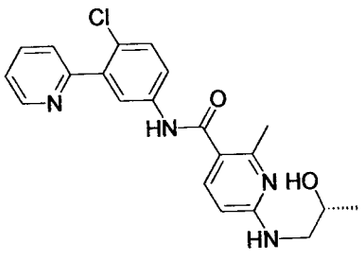
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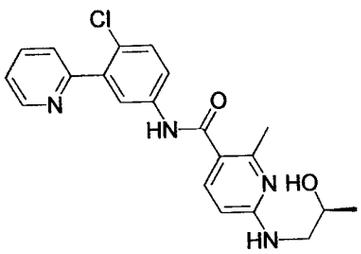
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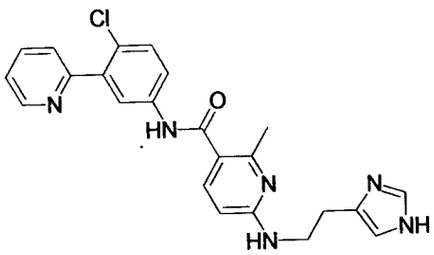
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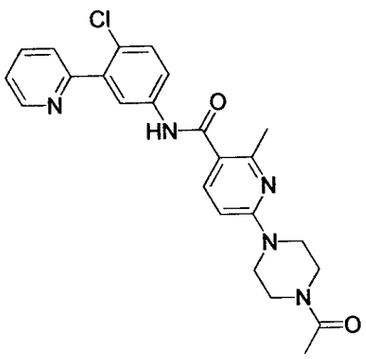
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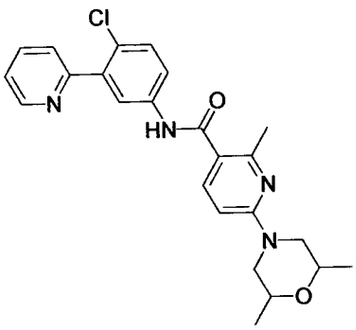
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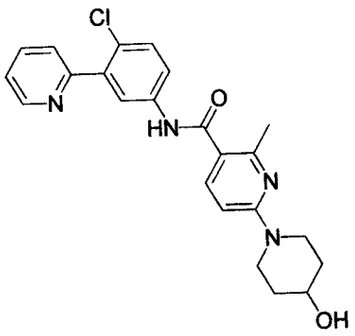


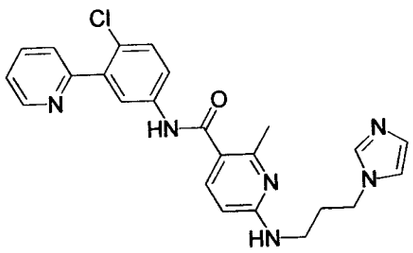
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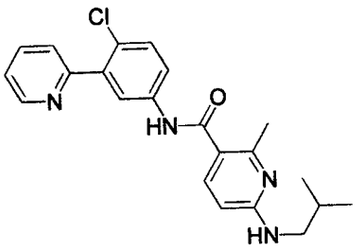


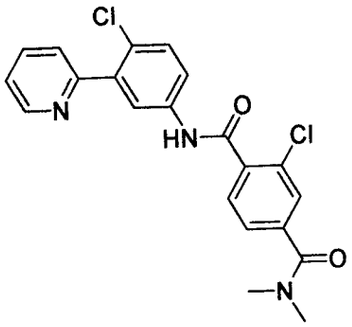
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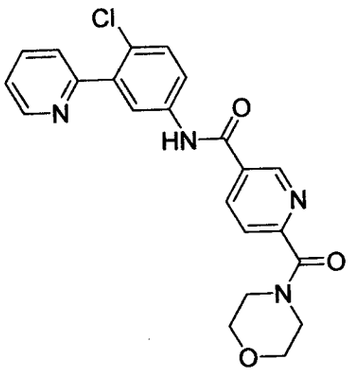


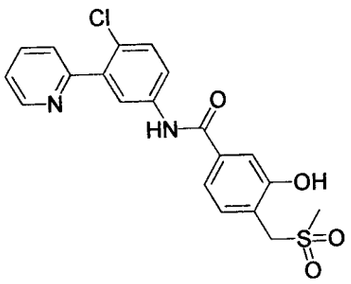
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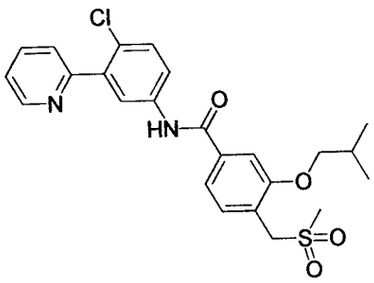
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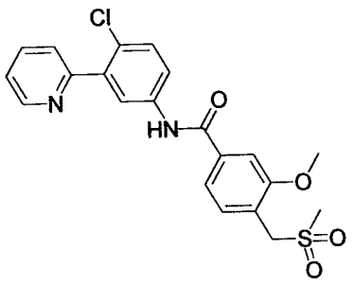
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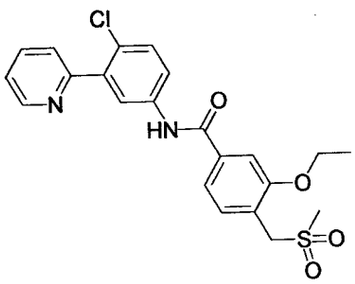
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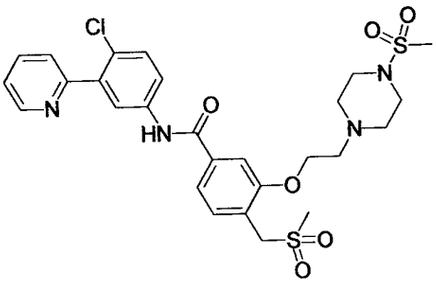
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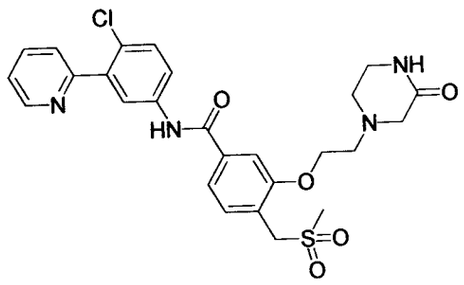
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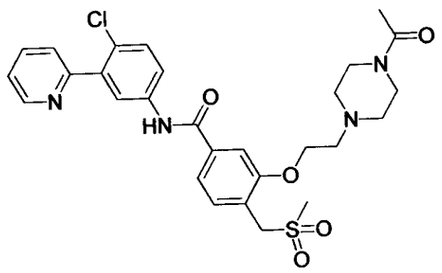
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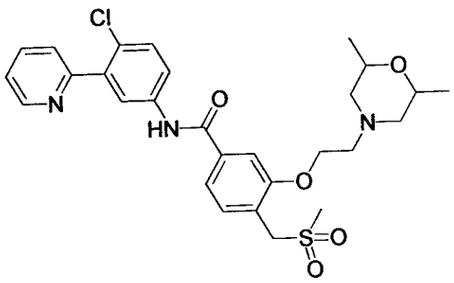
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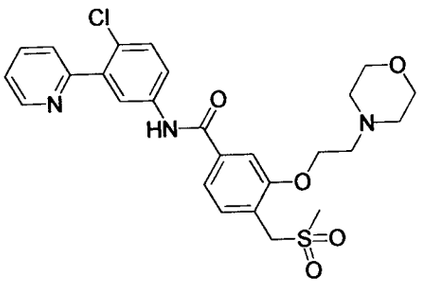
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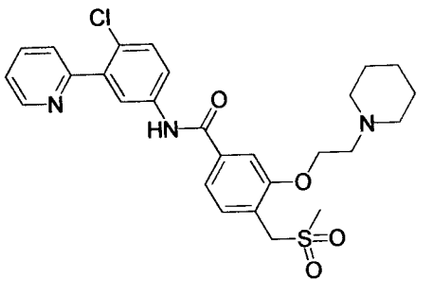
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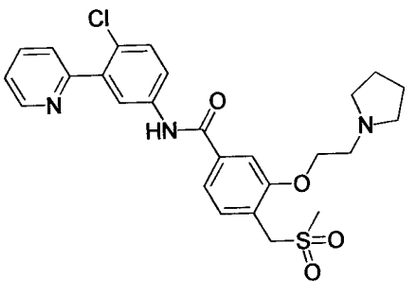
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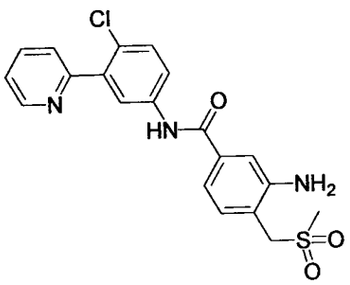
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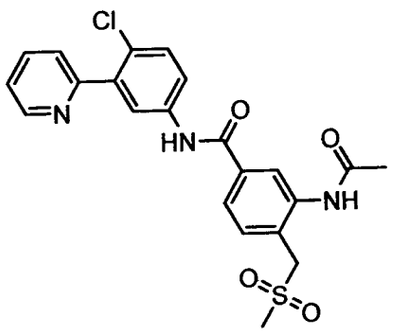
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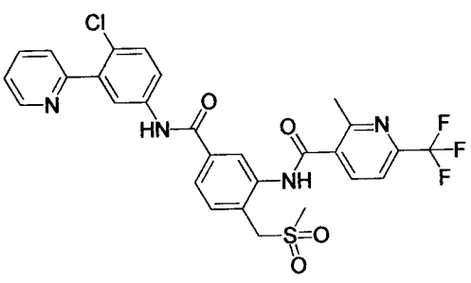
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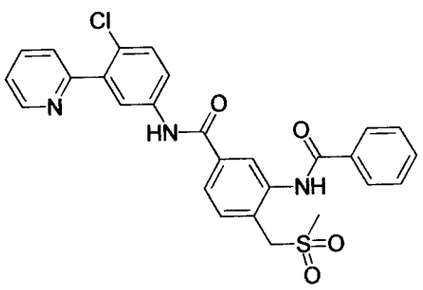
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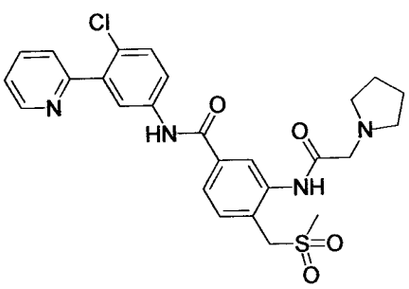
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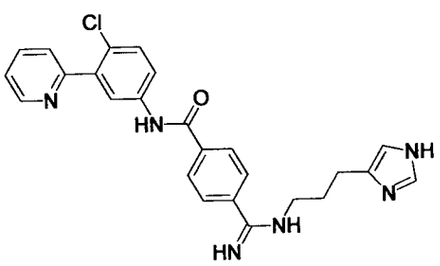
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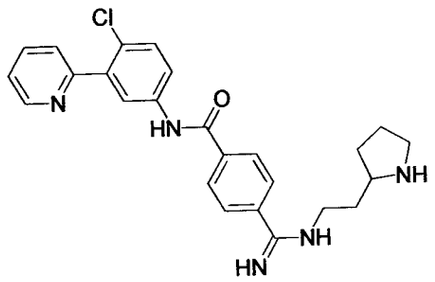
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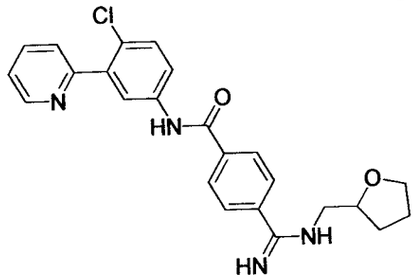
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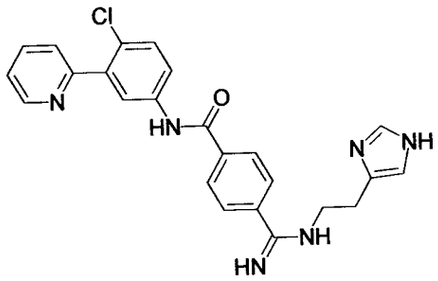
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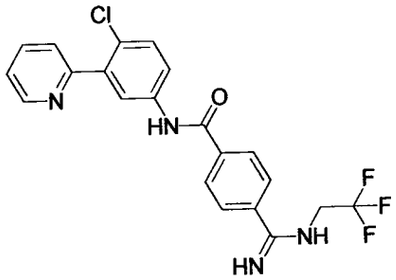
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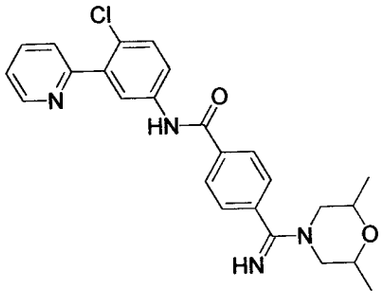
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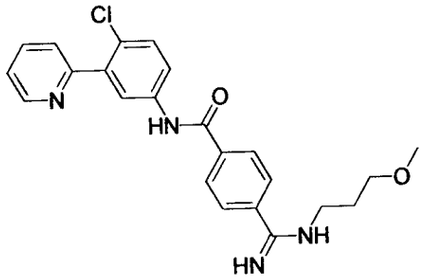
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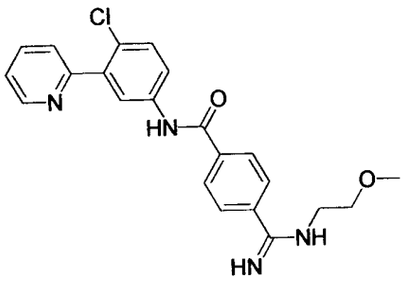
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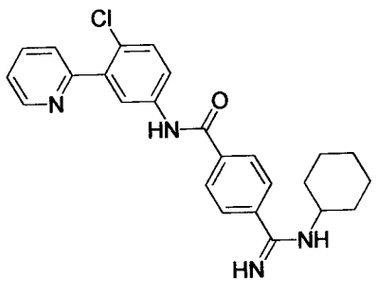
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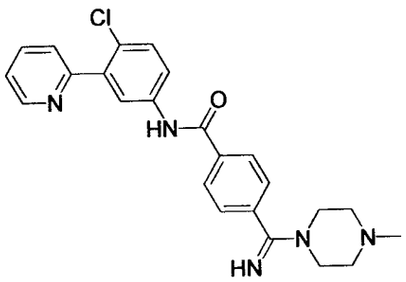
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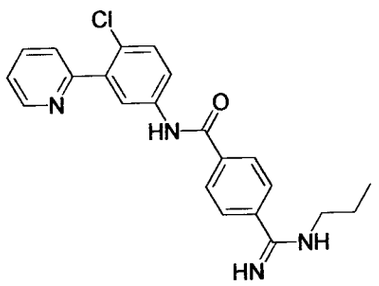
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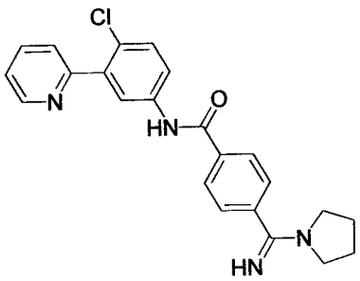
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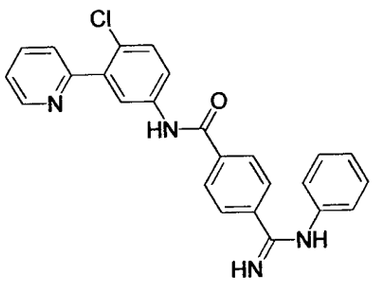
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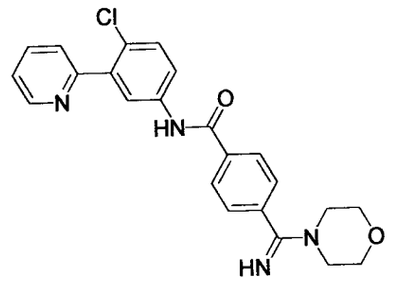
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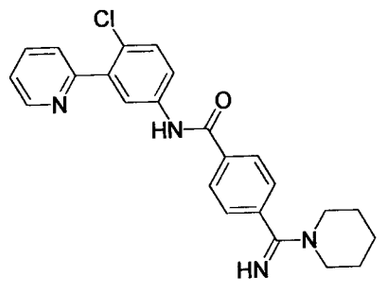
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Los compuestos de la invención pueden contener uno o más átomos de carbono asimétricos. En consecuencia, los compuestos pueden existir como diaestereómeros, enantiómeros o mezclas de los mismos. La síntesis de los compuestos puede emplear racematos, diastereómeros o enantiómeros como materiales iniciadores o intermedios. Los compuestos diaestereoméricos pueden ser separados por métodos cromatográficos o de cristalización. Asimismo, las mezclas enantioméricas pueden ser separadas usando las mismas u otras técnicas conocidas en el arte. Cada uno de los átomos de carbono asimétricos pueden tener la configuración R o S y ambas configuraciones caen dentro del alcance de la invención.

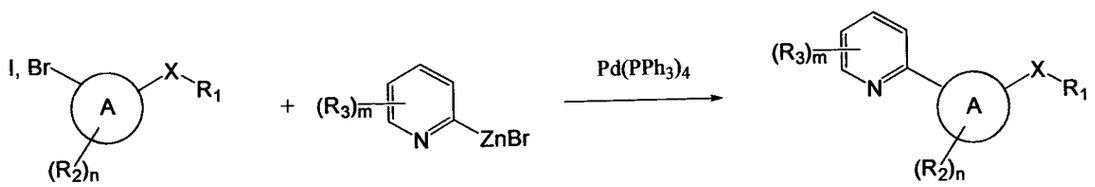
La invención además contempla profármacos de los compuestos antes descriptos. Los profármacos adecuados incluyen grupos de protección amino y carboxi conocidos que son liberados, por ejemplo hidrolizados, para obtener el compuesto madre bajo condiciones fisiológicas. Una clase específica de profármacos son los compuestos en los cuales un átomo de nitrógeno en un grupo amino, amidino, aminoalquilenoamino, iminoalquilenoamino o guanidino está sustituido con un grupo hidroxi (OH), un grupo alquilocarbonilo (-CO-R), un grupo alcoxicarbonilo (-CO-OR), un grupo aciloxialquilo-alcoxicarbonilo (-CO-O-R-O-CO-R) donde R es un grupo monovalente o divalente y de acuerdo a la definición anterior o un grupo que posee la fórmula -C(O)-O-CP1P2-haloalquilo, donde P1 y P2 son iguales o diferentes y son H, alquilo inferior, alcoxi inferior, ciano, halo alquilo inferior o arilo. Los compuestos profármacos pueden ser preparados sometiendo a una reacción los compuestos de la invención antes descriptos 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 activados adecuados contienen un grupo saliente bueno unido al carbono del carbonilo e incluyen sales de acil haluros, acil aminas, acil piridinio, acil alcóxidos, en particular acil fenóxidos como p-nitrofenoxi acilo, dinitrofenoxi acilo, fluorofenoxi acilo, y difluorofenoxi acilo. Las reacciones son en general exotérmicas y se llevan a cabo en solventes inertes a temperaturas reducidas como entre –78 y aproximadamente 50 °C. Las reacciones usualmente se ejecutan en presencia de una base inorgánica como carbonato de potasio o bicarbonato de sodio, o una base orgánica como una amina, incluyendo piridina, TEA,

etc. Una forma de preparación de profármacos ha sido descripta en USSN 08/843,369 presentada en Abril 15, 1997 (corresponde a la publicación por el PCT WO9846576) cuyos contenidos se incorporan por completo a la presente como referencia.

Síntesis

Los compuestos de la invención se preparan usando técnicas sintéticas orgánicas convencionales a partir de iniciadores y reactivos comercializados en el mercado. Se advertirá que los procedimientos sintéticos empleados en la preparación de los compuestos de la invención dependerán de los sustituyentes específicos presentes en un compuesto y que varios procedimientos de protección y desprotección pueden ser necesarios como es de rutina en lla síntesis orgánica. Los compuestos de la invención en los cuales Y está ausente pueden ser preparados mediante un procedimiento de acoplamiento de Negishi de acuerdo al siguiente esquema general 1:

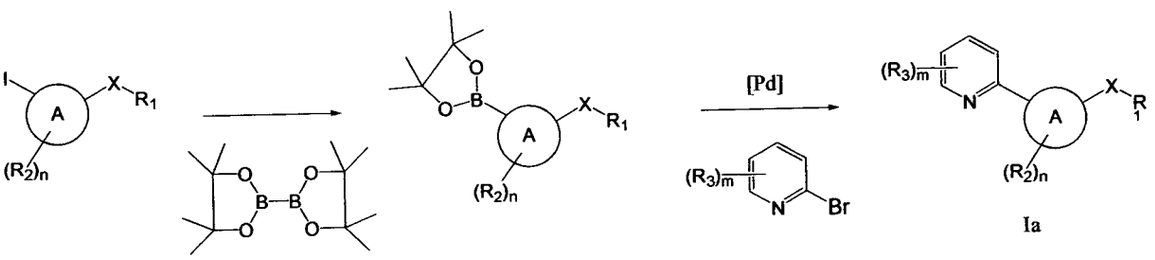
esquema 1



Ia

en el cual el bromuro de piridilo zinc (o alternativamente cloruro de piridilo zinc) se somete a una reacción con un anillo sustituido con yodo o bromo A para obtener el compuesto final Ia. Alternativamente, los compuestos Ia de la invención pueden ser preparados usando una reacción de acoplamiento de Suzuki de un anillo borilado A para proveer un enlace directo entre el piridilo adecuado y el anillo A de acuerdo al esquema 2.

esquema 2

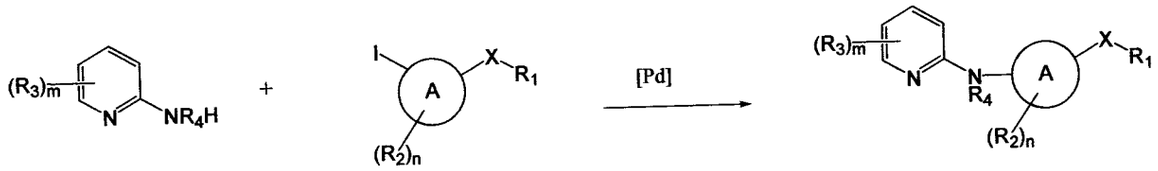


Ia

Un anillo sustituido con halógeno A se somete a una reacción con un éster de boro como pinacol diborano en presencia de catalizador paladio como $PdCl_2(dppf)$ y el éster boronado resultante es calentado con piridina sustituida con 2-halógeno y un catalizador paladio para obtener un compuesto final Ia de la invención.

Los compuestos de la invención en los cuales Y es NR_4 pueden ser preparados por aminación catalizada por paladio del anillo A sustituido con halógeno con la 2-aminopiridina deseada de acuerdo al esquema 3.

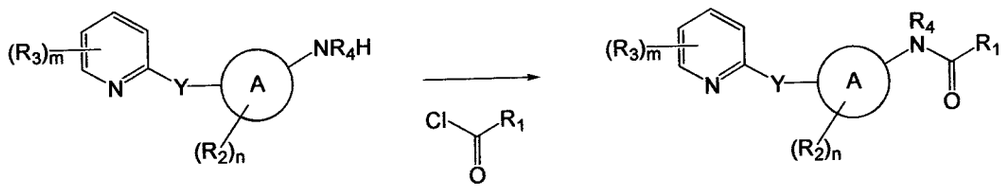
esquema 3



Ib

Los compuestos de la invención en los cuales X es NR_4CO pueden ser preparados mediante el esquema general 4 en el cual el anillo A sustituido con amina se somete a una reacción con el cloruro ácido deseado Cl-C(O)-R_1.

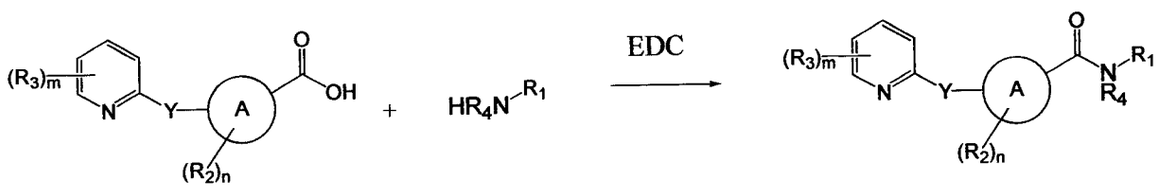
esquema 4



Alternativamente, tales compuestos pueden ser preparados mediante un acoplamiento catalizado por EDC de un anillo A sustituido con carboxi con un grupo R_1 sustituido con amina, es decir R_1-NR_4H. El mismo esquema puede ser usado para preparar los compuestos tioamida de la invención, es decir X es $NR_4C(S)$, empleando un cloruro tio ácido adecuado Cl-C(S)-R_1 en el paso de acilación.

Los compuestos de la invención en los cuales X es $C(O)NR_4$ también pueden ser preparados sometiendo a una reacción un anillo A sustituido con amina con un grupo R_1 sustituido con carboxi y catalizador EDC de acuerdo al esquema 5.

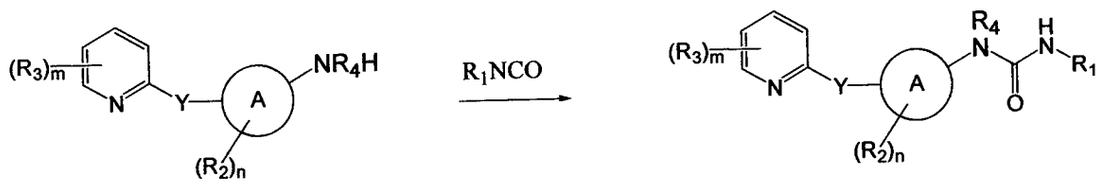
esquema 5



Un esquema similar puede ser usado para preparar los compuestos tioamida de la invención, es decir X es $C(S)NR_4$, empleando un anillo A sustituido con ácido tióico adecuado (por ejemplo -C(S)OH) o convirtiendo la amida con reactivo de Lawesson..

Los compuestos de la invención en los cuales X es $NR_4C(O)NH$ pueden ser preparados de acuerdo al esquema general 6 sometiendo a una reacción un anillo A sustituido con amina con el isocianato adecuado R_1-NCO.

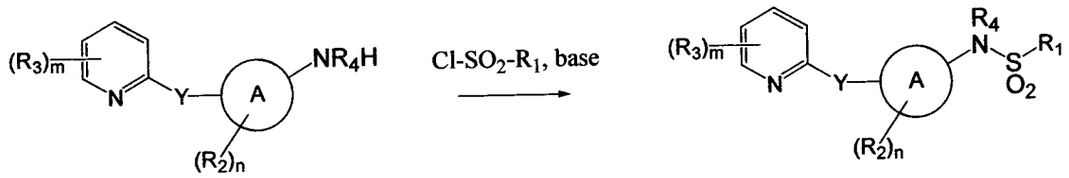
Esquema 6



El mismo esquema puede ser usado para preparar los compuestos tiourea de la invención, es decir X es $NR_4C(S)NH$, empleando un isotiocianate R_1-NCS adecuado en lugar del isocianate R_1-NCO.

Los compuestos de la invención en los cuales X es NR_4SO_2 pueden ser preparados de acuerdo al esquema general 7 sometiendo a una reacción un anillo A sustituido con amina con el sulfonil cloruro R_1-$S(O_2)Cl$ adecuado en presencia de una base no nucleofílica omo TEA o diisopropiletilamina para obtener la sulfonamida deseada.

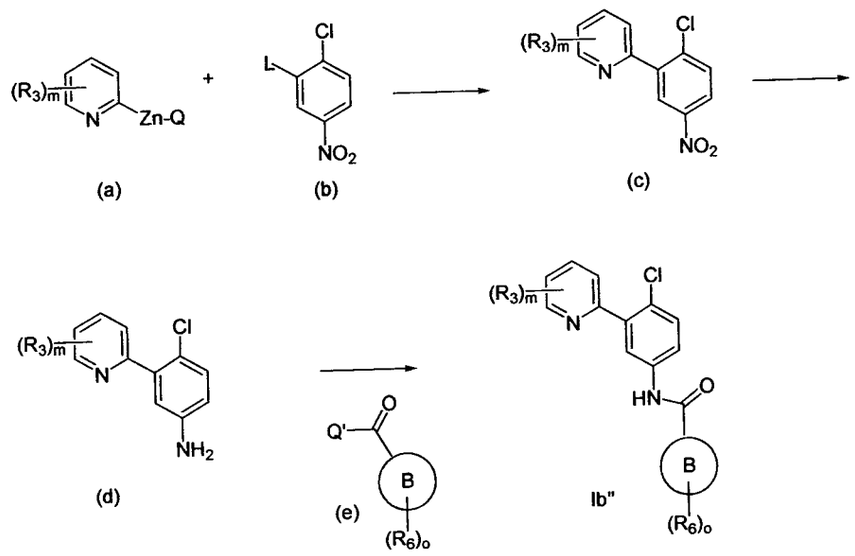
Esquema 7



Los compuestos de la invención en los cuales X es NR_4SO se preparan de manera similar usando el sulfinil cloruro R_1-SO-Cl adecuado en lugar del sulfonil cloruro R_1-$S(O_2)Cl$.

Los compuestos de la invención que poseen la estructura de la fórmula Ib' en la cual X es NHCO (es decir formula Ib") pueden ser preparados de acuerdo al esquema general 8 en el cual R_3, R_6, m y o responden a la definición de la presente y Q es Cl, Br o I; Q' es halógeno, OH, OR donde R es un grupo de activación; L es Br, I o OTf (por ejemplo O-SO2-CF_3):

Esquema 8



El reactivo haluro de zinc piridina (a) se somete a una reacción con reactivo 2-cloro-5-nitro-benceno (b) en una reacción de acoplamiento de Negishi en presencia de un catalizador adecuado como el complejo paladio tetrakis(trifenilfosfina) ($Pd(PPh_3)_4$). En una realización específica, el catalizador paladio tetrakis(trifenilfosfina) es estabilizado con trifenilfosfina (PPh_3). En una realización específica Q es Br. En una realización específica L es I. En una realización específica, la reacción de acoplamiento es ejecutada a una temperatura que oscila aproximadamente entr 50°C y aproximadamente 60°C.

El reactivo nitrobenceno (b) puede ser obtenido activando la correspondiente amina (es decir 2-cloro-5-nitroanilina) en una solución de ácido sulfúrico acuosa con nitrito de sodio y desplazando con un grupo L (por ejemplo con KI, KBr). En una realización específica, L es I. En una realización específica la reacción es conducida a menos de aproximadamente 15°C.

El producto intermedio resultante (c) es reducido, por ejemplo con Fe, Zn o $SnCl_2$ en presencia de ácido para producir el intermedio de amina (d). En una realización específica, el intermedio (c) es reducido con Fe, por ejemplo, en presencia de AcOH en EtOH. En una realización específica, el intermedio (c) es reducido con Zn, por ejemplo en presencia de AcOH en EtOH. En una realización especifca, el intermedio (c) es reducido con $SnCl_2$, por ejemplo en presencia de HCl en EtOH. En una realización específica la reacción de reducción es conducida a aproximadamente 60°C.

Finalmente, el intermedio (d) se somete a una reacción con un ácido activado (e) para producir el compuesto final Ib". En una realización específica, el ácido activado (e) es un

haluro ácido (por ejemplo Q' es cloruro) o éster activado (por ejemplo Q' es O-EDC). En una realización específica la reacción final es conducida a aproximadamente 0°C.

Los compuestos de la invención inhiben la señalización de hedgehog y resultan de utilidad para el tratamiento de cánceres asociados con una señalización de hedgehog aberrante, por ejemplo cuando Patched no puede, o inadecuadamente, reprime Smoothened (Ptc fenotipo de pérdida de función) y/o cuando Smoothened se activa independientemente de la represión Patched (fenotipo de ganancia de función Smo). Los ejemplos de tales tipos de cánceres incluyen carcinoma de células basales, tumores neuroectodérmicos como meduloblastoma, meningioma, hemangioma, glioblastoma, adenocarcinoma pancreáticco, carcinoma de pulmón escamoso, carcinoma de pulmón de células pequeñas, carcinoma de pulmón de células no pequeñas, condrosarcoma, carcinoma de mama, rabdomiosarcoma, cáncer oseofageal, cáncer de estómago, cáncer del tracto biliar, carcinoma renal, carcinoma tiroideo. Los compuestos de la invención pueden ser administrados antes, o concurrentemente, o luego de la administración de otros tratamientos contra el cáncer como terapia de radiación o quimioterapia. Los compuestos quimioterapéuticos citostáticos adecuados incluye, entre otros (i) antimetabolitos, como citarabina, fludarabina, 5-fluoro-2'-deoxiuiridina, gemcitabina, hidroxiurea o metotrexato; (ii) agentes de fragmentación de ADN, como bleomicina, (iii) agentes de entrecruzamiento de ADN, como chlorambucil, cisplatin, ciclophosphamida o mostaza de nitrógeno; (iv) agentes intercalantes como adriamicina (doxorubicina) o mitoxantrona; (v) inhibidores de la síntesis de proteínas, como L-asparaginasa, cicloheximida, puromicina o toxina de la difteria; (Vi) venenos de topoisomerasa I, como camptotecina o topotecan; (vii) venenos de topoisomerasa II, como etoposido (VP-16) o teniposido; (viii) agentes dirigidos a los microtúbulos, como colcemid, colquicina, paclitaxel, vinblastina o vincristina; (ix) inhibidores de quinasa como flavopiridol, staurosporin, STI571 (CPG 57148B) o UCN-01 (7-hidroxistaurosporina); (x) agentes experimentales varios como tioplatin, PS-341, fenilbutirato, ET-18- OCH_3, o inhibidores de farnesil transferasa (L-739749, L-744832); polifenoles como quercetin, resveratrol, piceatannol, epigalocatequina galato, teaflavinas, flavanoles, procianidinas, ácido betulínico y derivados de los mismos; (xi) hormonas como glucocorticoides o fenretinida; (xii) antagonistas de hormonas, como tamoxifen, finasteride o antagonistas de LHRH. En una realización específica, los compuestos de la presente invención son coadministrados con un compuesto citostático seleccionado del grupo integrado por cisplatin, doxorubicin, taxol, taxotere y mitomicina C.

Otra clase de compuestos activos que pueden ser utilizados en la presente invención son aquellos capaces de sensibilizar o inducir la apoptosis uniéndose a los receptores de la muerte ("agonistas de receptores de la muerte"). Tales agonistas de receptores de la

muerte incluyen ligandos de receptores de la muerte como el factor de necrosis tumoral (TNF-α), factor de necrosis tumoral ß (TNF-ß, linfotoxina-α) , LT-ß (linfotoxina-ß), TRAIL (Apo2L, ligando DR4), ligando CD95 (Fas, APO-1), ligando TRAMP (DR3, Apo-3), ligando DR6 así como también fragmentos y derivados de cualquiera de dichos ligandos. En una realización específica, el ligando de receptores de la muerte es TNF-α. En otra realización específica el ligando de receptores de la muerte es Apo2L/TRAIL. Además, los agonistas de receptores de la muerte comprenden anticuerpos antagonistas para receptores de la muerte como 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-Rl y anticuerpo anti-TRAMP (DR3) así como también fragmentos y derivados de cualquiera de dichos anticuerpos.

Con el fin de sensibilizar las células para la apoptosis, los compuestos de la presente invención también pueden ser utilizados en combinación con una terapia por radiación. La frase "terapia por radiación" hace referencia al uso de radiación electromagnética o particulada en el tratamiento de la neoplasia. La terapia por radiación se basa en el principio de que una alta dosis de radiación aplicada a un área específica dará como resultado la muerte de las células en reproducción en los tejidos tumoral y normal. El régimen de dosis de radiación en general se define en términos de la dosis absorbida de radiación (rad), tiempo y fraccionamiento, y debe ser cuidadosamente definido por el oncólogo. La cantidad de radiación que un paciente reciba dependerá de varias consideraciones incluyendo la localización del tumor con respecto a otros órganos del cuerpo, y el grado de expansión del tumor. Algunos ejemplos de agentes radioterapéuticos conocidos en el arte se encuentran en Hellman, Principles of Radiation Therapy, Cancer, in Principles I and Practice of Oncology, 24875 (Devita et al., 4th ed., vol 1, 1993). Avances recientes en la terapia de radiación incluyen la radiación de haces externos conformales tridimensionales, terapia de radiación de intensidad modulada (IMRT), radio-cirugía estereotáctica y branquiterapia (terapia de radiación intersticial), en el último caso se coloca la fuente de radiación directamente en el tumor como "semillas" implantadas. Estas modalidades de tratamiento más nuevas liberan mayores dosis de radiación al tumor, lo cual explica su mayor efectividad respecto la terapia por radiación de haces externos convencional.

La radiación por ionización con radionucleótidos emisores beta se considera la aplicación radioterapéutica de mayor utilidad dada la transferencia de energía lineal moderada (LET) de la partícula de ionización (electrón) y su alcance intermedio (típicamente varios milímetros en el tejido). Los rayos gamma liberan dosis a menores niveles sobre distancias mucho mayores. Las partículas alfa representan el otro extremo, entregan una dosis LET muy alta, pero poseen un alcance extremadamente limitado y deben, en consecuencia, estar en contacto íntimo con las células del tejido a tratar. Además, los emisores alfa en general son metales pesados, lo cual limita la química posible y genera

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peligros derivados de la fuga del radionucleótido del área a tratar. De acuerdo al tumor a ser tratado, todos los tipos de emisores caen dentro del alcance de la presente invención. Además, la presente invención contempla otros tipos de radiación no ionizante como por ejemplo radiación ultravioleta (UV), luz visible de alta energía, radiación por microondas (terapia por hipertermia), radiación infrarroja (IR) y láseres. En una realización específica de la presente invención se aplica radiación UV.

Los compuestos de la invención inhiben la angiogenesis y en consecuencia resultan de utilidad para el tratamiento de enfermedades o condiciones mediadas por la angiogenesis como tumores, en particular tumores sólidos como tumores de colon, pulmón, pancreático, ovárico, de mama y glioma. Además, los compuestos de la invención resultan de utilidad para tratar la degeneración macular por ejemplo la degeneración macular relacionada con la edad húmeda. Los compuestos de la invención además resultan de utilidad para el tratamiento de enfermedades inflamatorias/inmunológicas como mal de Crohn, enfermedad inflamatoria intestinal, síndrome de Sjogren, asma, rechazo a transplante de órganos, lupus eritematoso sistémico, artritis reumatoidea, artritis psoriásica y esclerosis múltiple. Los compuestos de la invención además resultan de utilidad como depilatorios.

La invención además incluye composiciones farmacéuticas o medicamentos que contienen los compuestos de la invención y un portador, diluyente o excipiente terapéuticamente inerte, así como también métodos de uso de los compuestos de la invención para preparar tales composiciones y medicamentos. Típicamente, los compuestos de la invención usados en los métodos de la invención son formulados mezclándolos a temperatura ambiente a un pH adecuado, y al grado deseado de pureza, con portadores fisiológicamente aceptables, es decir, portadores que no son tóxicos para los receptores a las dosis y concentraciones empleadas en una forma de administración galénica. El pH de la formulación depende fundamentalmente del uso particular y la concentración del compuesto, aunque puede oscilar aproximadamente entre 3 y aproximadamente 8. Una formulación específica es un buffer acetato a un pH de 5. Los compuestos a utilizar en la presente pueden estar en una formulación estéril. El compuesto puede ser almacenado como una composición sólida, a pesar que las formulaciones liofilizadas o soluciones acuosas son aceptables.

La composición de la invención será formulada, dosificada, y administrada en el marco de la buena práctica médica. Los factores a considerar en este contexto incluyen la enfermedad a tratar, el mamífero bajo tratamiento, la condición clínica del paciente, la causa de la enfermedad, el sitio de liberación del agente, el método de administración, el cronograma de administración, y demás factores conocidos por los médicos. La "cantidad efectiva" del compuesto a ser administrada dependerá de tales consideraciones, y es la cantidad mínima necesaria para reducir la señalización del

camino de hedgehog o de lo contrario es la cantidad mínima necesaria para provocar una reducción en el tamaño, volumen o masa del un tumor que responde a la señalización de hedgehog, o una reducción en el aumento de tamaño, volumen o masa de tal tumor con respecto al aumento en ausencia de la administración del compuesto de la invención. Alternativamente "cantidad efectiva" del compuesto hace referencia a la cantidad necesaria para reducir el número de células malignas o la velocidad de aumento del número de células malignas. Alternativamente, "cantidad efectiva" es la cantidad del compuesto de la invención necesaria para aumentar la sobrevida de pacientes afectados con un tumor sensible al camino anti-hedgehog. Esta cantidad puede ser inferior a la cantidad tóxica para las células normales, o para el mamífero en general. Con relación a las indicaciones fuera de las malignidades, "cantidad efectiva" hace referencia a la cantidad de compuesto de la invención necesaria para reducir la severidad de la indicación específica o sus síntomas.

En general, cantidad farmacéuticamente efectiva inicial del compuesto de la invención administrado por vía parenteral por dosis oscilará aproximadamente entre 0.01 y aproximadamente 100 mg/kg, por ejemplo aproximadamente entre 0.1 y aproximadamente 20 mg/kg de peso corporal del paciente por día, por ejemplo aproximadamente entre 0.3 y aproximadamente 15 mg/kg/día. Las formas de dosificación unitarias orales, como tabletas y cápsulas, pueden contener aproximadamente entre 25 y aproximadamente 1000 mg del compuesto de la invención.

El compuesto de la invención puede ser administrado mediante cualquier vía adecuada, incluyendo oral, tópica, transdérmica, parenteral, subcutánea, rectal, intraperitoneal, intrapulmonar, e intranasal, y, en caso de tratamiento local, en la lesión. Las infusiones parenterales incluyen administración por vía intramuscular, intravenosa, intraarterial, intraperitoneal, o subcutánea. Un ejemplo de una forma de dosificación adecuada es una tableta que contiene aproximadamente 25mg, 50mg, 100mg, 250mg, o 500mg del compuesto de la invención que comprende aproximadamente 90-30 mg lactosa anhidro, aproximadamente 5-40 mg de croscarmelosa sódica, aproximadamente 5-30mg de polivinilpirrolidona (PVP) K30, y aproximadamente 1-10 mg estearato de magnesio. Los ingredientes en polvo son mezclados en primer término entre si y luego con una solución de PVP. La composición resultante puede ser secada, granulada, mezclada con el estearato de magnesio y comprimida en una tableta usando equipo convencional. Una formulación en aerosol puede ser preparada disolviendo el compuesto, por ejemplo 5-400 mg, de la invención en una solución buffer adecuada, por ejemplo un buffer fosfato, agregando un tonificador, por ejemplo una sal con cloruro de sodio, si se desea. La solución por lo general es filtrada, por ejemplo usando un filtro de 0.2 micrones, con el fin de remover las impurezas y contaminantes. Las formulaciones tópicas incluyen pomadas,

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cremas, lociones, polvos, soluciones, pesarios, sprays, aerosoles y cápsulas. Las pomadas y cremas pueden ser formuladas con una base acuosa o aceitosa con la adición de agentes espesantes y/o gelificantes y/o solventes adecuados, Tales bases pueden incluir agua y/o un aceite como una parafina líquida o un aceite vegetal como aceite de araquis o aceite de ricino o un solvente como polietilen glicol. Los agentes espesantes que pueden utilizarse incluyen parafina blanda, estearato de aluminio, alcohol cetoestearílico, polietilen glicoles, cera microcristalina y cera de abejas. Las lociones pueden ser formuladas con una base acuosa o aceitosa y pueden contener uno o más agentes emulsionantes, agentes estabilizantes, agentes dispersantes, agentes de suspensión o agentes espesantes. Los polvos para aplicación externa pueden ser obtenidos con la ayuda de cualquier base para polvo adecuada, por ejemplo talco, lactosa o almidón. Las gotas pueden ser formuladas con una base acuosa o no acuosa, conteniendo además uno o más agentes dispersantes, agentes solubilizantes o agentes de suspensión.

EJEMPLOS

La invención será comprendida de una manera más completa con referencia a los siguientes ejemplos, Sin embargo, no debe considerarse que los mismos limitan el alcance de la invención. Las abreviaturas utilizadas en la presente son las siguientes:

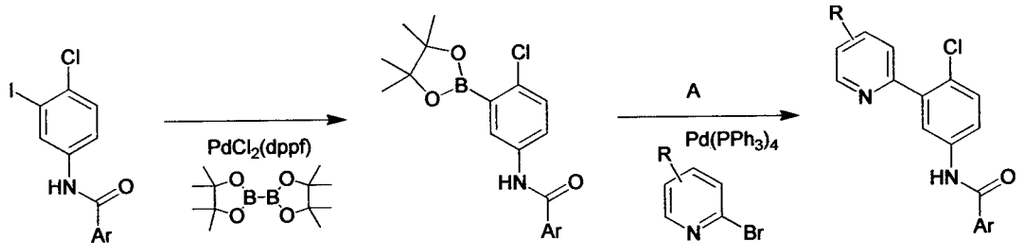
BuOH: butanol;
DIPEA: diisopropiletilamina;
DMA: NN-dimetilacetamida;
DMAP: 4- dimetilaminopiridina;
DME: 1,2-dimetoxietano;
DMF: dimetilformamida;
EDC: 1-etil-3-(3-dimetilaminopropilo)carbodiimida;
HATU: O-(7-Azobenzotriazol-1-il)-1,1,3,3-tetrametiluronio hexafluorofosfato;
HPLC: cromatografía de líquidos de alta presión
MPLC: cromatografía de líquidos de presión intermedia
NBS: N-Bromosuccinimida;
TEA: Trietilamina;
TASF: tris(dimetilamino)sulfonio difluorotrimetilsilicato;
THF: tetrahidrofurano;
EtOH: Etanol;
MeOH: Metanol;
□L: microlitro

Todos los reactivos fueron obtenidos en el mercado salvo indicación en contrario. Las reacciones fueron conducidas usando elementos de vidrio templado bajo una atmósfera de nitrógeno. Los líquidos y soluciones sensibles al aire y la humedad fueron transferidos mediante una jeringa o cánula de acero inoxidable. Las soluciones orgánicas fueron concentradas bajo presión reducida (ca. 15 mm Hg) por evaporación rotativa. Salvo indicación en contrario, todos los solventes usados fueron obtenidos en el mercado. La purificación cromatográfica de los productos fue realizada mediante el uso de un Isco CombiFlash Companion and media. Los tiempos de reacción se indican con fines ilustrativos solamente. El curso de las reacciones fue seguido por cromatografía en capa fina (TLC) y cromatografía de líquidos-espectromería de masa (LC-MS). La cromatografía en capa fina (TLC) fue ejecutada en placas de gel de sílice EM Science 60 F_{254} (250 μm). La visualización del cromatograma revelado se realizó por extinción de fluorescencia. Las LC-MS fueron adquiridas con un Shimadzu 10AD LC en una columna Phenomenex (50 x 4.6 mm, 5 μm) operando a 3 mL/minuto. Se usó un detector Shimadzu SPD-10A para monitorear 214 y 254 nm. Se ejecutó una espectrometría de masa cuadripolo simple en un espectrómetro de masa Applied Biosystems. Los espectros de resonancia magnética nuclear (NMR) fueron adquiridos en un espectrómetro Varian Inova operando a 400 MHz para ^1H y son referenciados internamente a tetrametilsilano (TMS) en partes por millión (ppm). Los datos de ^1H NMR son registrados de la siguiente forma: diferencia química (δ, ppm), multiplicidad (s, singlete; bs, singlete ancho; d, doblete; t, triplete; q, cuartero; quint, quinteto; sext, sexteto; hept, hepteto; m, multiplete; bm, multiplete ancho), e integración. La estructura y pureza de todos los productos finales fueron evaluadas mediante al menos una de las siguientes técnicas: LC-MS, NMR, TLC.

Ejemplo 1 Procedimientos Generales

Los compuestos de los ejemplos 2-51 fueron preparados de acuerdo a los siguientes procedimientos generales.

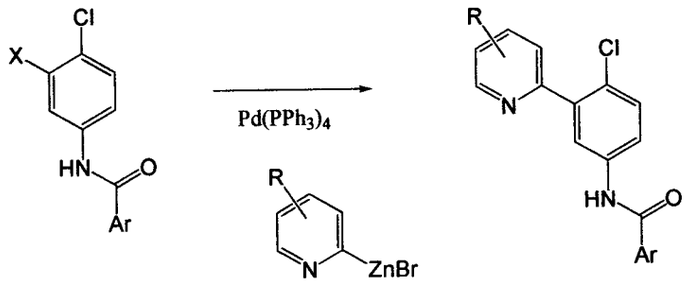
A: Procedimiento de Acoplamiento de Suzuki



Se agregaron 2 M aq. carbonato de potasio (5.0 eq) y una mezcla 4:1 de tolueno:etanol (2.5 mL) a un recipiente para microondas cargado con el éster boronato adecuado (2.6

eq), aril haluro (0.35 mmol, 1.0 eq), y $Pd(PPh_3)_4$ (0.04 eq). El recipiente fue sellado y calentado con agitación en el microondas a 160 °C por espacio de diez minutos. La solución fue vertida en 2 M aq. hidróxido de sodio (20 mL), extraída con acetato de etilo (2 x 20 mL), secada ($MgSO_4$), y concentrada. La purificación del producto crudo por cromatografía en gel de sílice (las condiciones se indican a continuación) dio como resultado el producto deseado.

B: Procedimiento de acoplamiento de Negishi

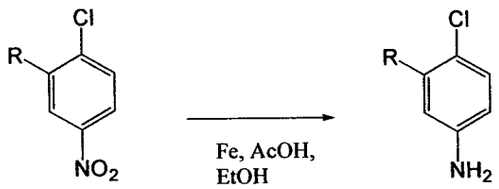


X = I o Br

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

Se agreró bromuro de arilo zinc (0.5 M en THF, 2.5 eq) a un recipiente para microondas templado cargado con el aril haluro adecuado (1.0 eq) y $Pd(PPh_3)_4$ (0.04 eq). El recipiente fue sellado y calentado con agitación en el microondas a 140 °C por espacio de 10 minutos. La mezcla de reacción cruda fue concentrada y purificada por cromatografía en gel de sílice (las condiciones se indican a continuación) para lograr el producto deseado.

C: Reducción con Hierro del Grupo Aril Nitro

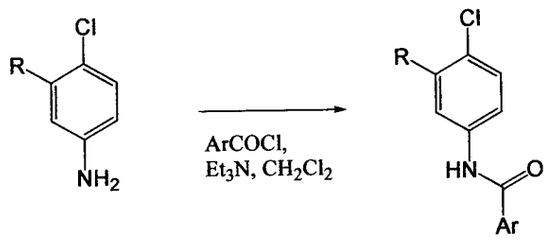


R = I o piridin-2-ilo

El nitro arilo adecuado (1 mmol, 1 eq) en AcOH/EtOH (1:1, 0.42 M) fue agregado lentamente a una solución de polvo de hierro (6.0 eq) en AcOH/EtOH (1:2, 2 M) a 60 °C. La solución fue agitada a 70 °C por espacio de 30-60 minutos. La mezcla de reacción fue enfriada a 23 °C, filtrada por celita, lavada con acetato de etilo, y concentrada. El residuo aceitoso fue disuelto en acetato de etilo (30 mL), lavado con NaHCO3 acuoso saturado (2

x 15 mL) y agua (2 x 10 mL), secado ($MgSO_4$), y concentrado. El residuo aceitoso se utilizó sin purificación adicional.

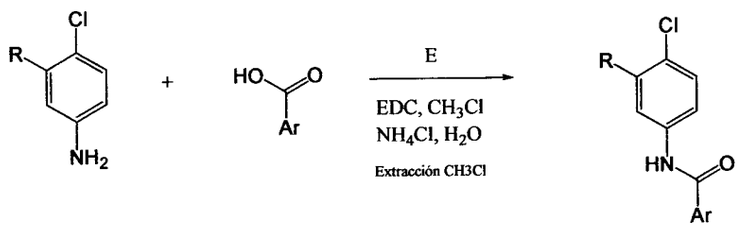
D: Formación de Enlace Amida



R = I o piridin-2-ilo

Se agregó cloruro ácido (1.05-1.1 eq) a una solución de anilina (1.0 eq) y TEA (1.1-1.5 eq) en cloruro de metileno a la temperatura indicada. La solución fue agitada durante 0.5-3 horas, vertida en $NaHCO_3$ saturado acuoso, extraída dos veces con cloruro de metileno, secada ($MgSO_4$), y concentrada. La purificación del producto crudo por cromatografía en gel de sílice (las condiciones se indican a continuación) dio como resultado el producto deseado.

E: EDC Formación de Enlace Amida

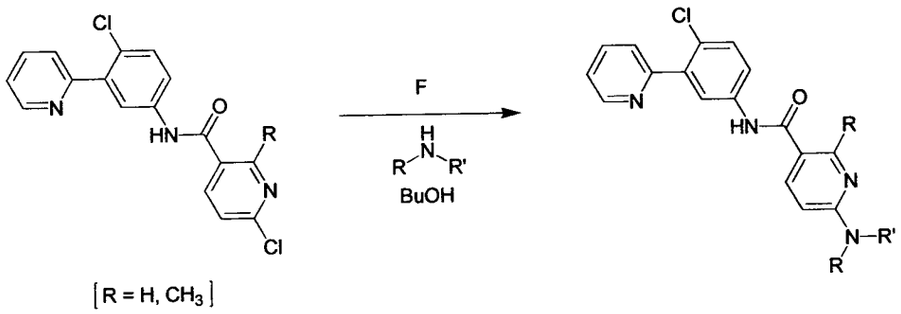


R = I o piridin-2-ilo

Se agregó ácido carboxílico (1.1 eq) a una solución de anilina (1.0 eq) y EDC (1.4 eq) en cloruro de metileno (0.7 M en anilina). La solución fue agitada a 23 °C por espacio de 2 horas, vertida en una mezcla 1:1 NH_4Cl acuosa saturada y agua, extraída dos veces con cloruro de metileno, secada ($MgSO_4$), y concentrada. La purificación del producto crudo por cromatografía en gel de sílice (las condiciones se indican a continuación) dio como resultado el producto deseado.

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F: adición de aminas a 2-cloropiridina

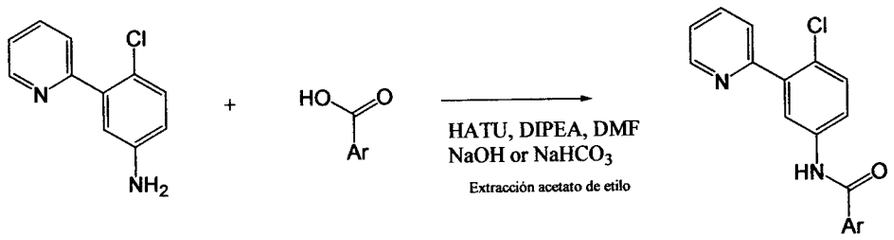


[R = H, CH_3]

NHRR' = etanolamina, analina, bencilamina, 2-metilpropilamina, N-metilpiperazina, morfolina, 2-morfolinoetilamina

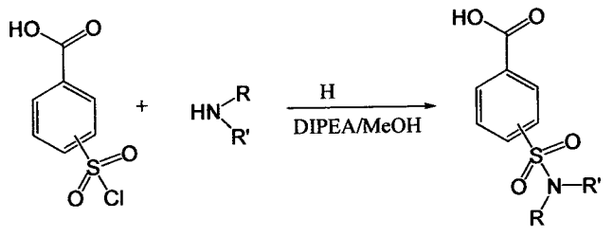
Se calentó amina primaria o secundaria (5 eq) en BuOH o una mezcla de BuOH/etilen glicol a 170 a 220 °C por espacio de 20 minutos en un tubo sellado. Se removió BuOH bajo presión reducida. En los casos en que se usó etilen glicol, la reacción fue diluida con agua, y el producto fue extraído en acetato de etilo, secado ($MgSO_4$), y concentrado. El residuo crudo fue purificado por HPLC de fase inversa para lograr el producto deseado.

G: Acoplamiento del enlace amida con HATU



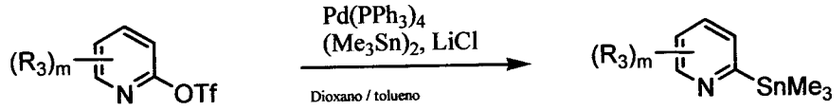
Se agregó anilina (1.0 eq) a una mezcla de ácido carboxílico (1.1 eq), HATU (1.1 eq) y DIPEA (2 eq) en DMF (0.1 - 0.2 M). Luego de agitar durante la noche, la mezcla de reacción fue diluida con 0.1 N hidróxido de sodio o $NaHCO_3$ saturada, extraída en acetato de etilo y las capas orgánicas combinadas fueron lavadas con solución salina. La capa orgánica fue secada ($MgSO_4$), concentrada y la mezcla cruda fue purificada por HPLC de fase inversa.

H: Preparación de ácidos benzoicos de sulfonamida



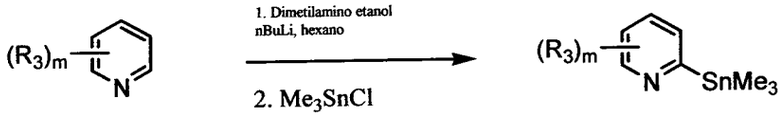
Se agregó ácido clorosulfonilbenzoico (1.0 eq) a una solución de amina (1.1 eq) en 10-20% DIPEA/metanol (1 M) a 4 °C. Luego de 1 h, la mezcla de reacción fue concentrada, y el residuo crudo fue purificado por HPLC de fase inversa.

I : Estanilación de 2-piridil triflatos



Se agregó una solución de tetrakis-trifenilfosfinapaladio (0.04 eq.) en tolueno (1 mL) a una solución de ariltriflato degasificada (1 eq), bis-trialquilotina (1.05 eq), y cloruro de litio (3 eq) en dioxano. Fue calentada a reflujo por espacio de 2 horas, enfriada a 23 °C, diluida con acetato de etilo, lavada con 10% $NH_4OH_{(aq)}$ y solución salina, secada ($MgSO_4$) y concentrada. El material crudo fue usado sin purificación adicional.

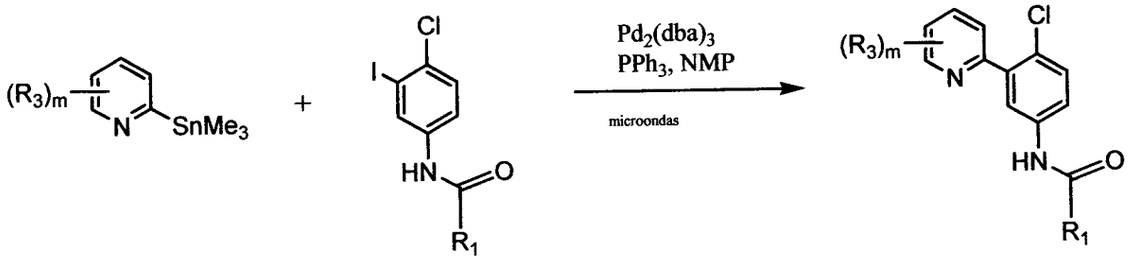
J: Estanilación de piridinas sustituidas



Se agregó n-butil litio (6 eq, 2.5 M en hexanos) por goteo a una solución de dimetilaminoetanol (3 eq) en hexano a 0 °C. La solución fue agitada a 0 °C por espacio de treinta minutos antes de agregar por goteo de la piridina sustituida (1 eq). La solución fue agitada a 0 °C durante una hora más, luego enfriada a –78 °C. Se agregó por goteo una solución de trialquilotin en hexano. La solución fue agitada a –78 °C por espacio de treinta minutos, calentada a 0 °C, extinguida con agua, extraída dos veces con éter, secada ($MgSO_4$), y concentrada.

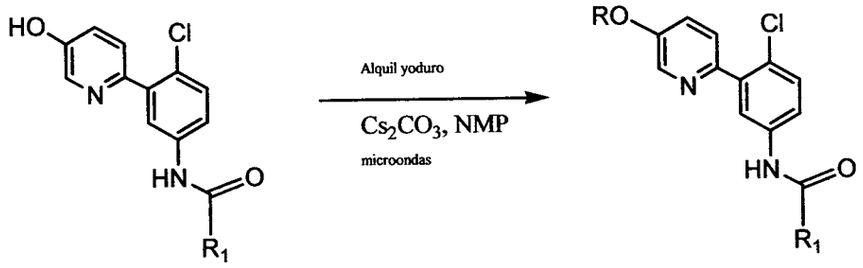
K: Acoplamiento de Stille

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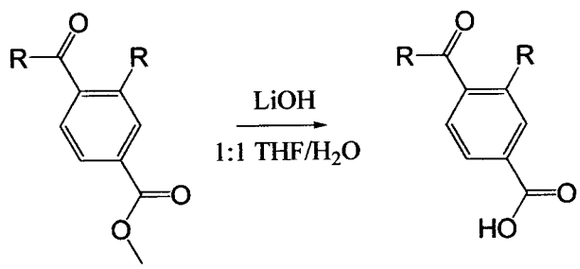
Se agregó catalizador paladio (0.02 eq) a una solución desgasificada de arilyoduro (1 eq), arilestanato (2 eq), y trifenilfosfina (0.16 eq) en NMP. Se calentó en microondas a 130 °C por espacio de 15 minutos. La mezcla de reacción fue diluida con acetato de etilo, lavada con 10% $NH_4OH_{(aq)}$ y solución salina, secada ($MgSO_4$), concentrada y purificada por cromatografía en gel de sílice.

L: Síntesis de alquiléteres



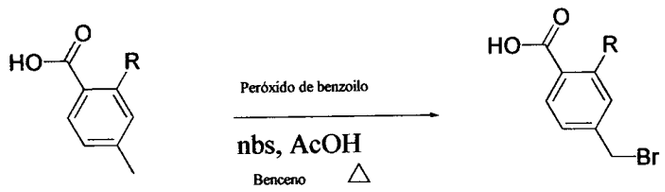
Una solución de hidroxipiridina (1 eq), alquilyoduro (exceso), y carbonato de cesio en NMP fue calentada en el microondas a 100 °C por espacio de diez minutos. La mezcla de reacción fue diluida con acetato de etilo, lavada con 10% $NH_4OH_{(aq)}$ y solución salina, secada ($MgSO_4$), concentrada y purificada por cromatografía en gel de sílice.

M: Saponificación de metil éster



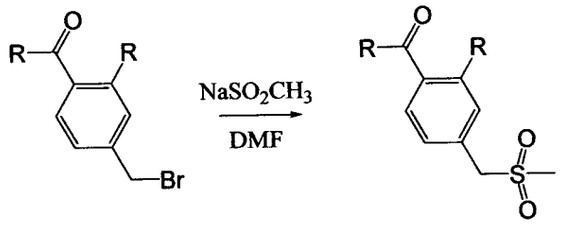
El metil ester (1eq) fue hidrolizado con LiOH (2eq) en una mezcla de 50/50 THF/agua. Finalizada la reacción el THF fue evaporado bajo presión reducida y la solución es acidificada con HCl a pH 2. El sólido resultante fue filtrado y secado para obtener el ácido puro.

N: Bromación en presencia de una funcionalidad de ácido libre



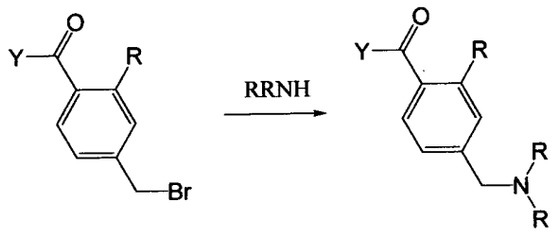
El ácido parametilbenzoico (1eq) fue combinado con Peróxido de Benzoilo (0.1eq) y N-Bromosuccinimida (0.9eq) en una solución de 5%AcOH en Benceno y calentado en el microondas a 120°C por espacio de 5-15minutos. El producto fue separado del material iniciador y el producto di-bromo via cromatografía instantánea ISCO con un sistema de solvente de acetato de etilo (con 1% AcOH) y hexanos.

O: Desplazamiento de bromo por metanosulfinato de sodio



Al material iniciador bromo (1eq) se agregó metanosulfinato de sodio (2eq) en DMF y se calentó a 120°C en el microondas durante 5 minutos. Alternativamente, la reacción fue calentada a 60°C en un baño de aceite durante varias horas hasta completarla. La mezcla de reacción fue concentrada bajo presión reducida y extraida en acetato de etilo y agua. La capa orgánica fue secada sobre sulfato de magnesio, filtrada y concentrada en vacío para obtener metilsulfona genérica.

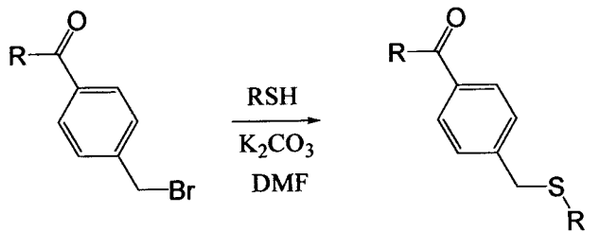
P: Desplazamiento de bromo con amina



Al material iniciador bromo (1eq) se agregó la amina adecuada (3eq) en DMSO o BuOH y se agitó a temperatura ambiente hasta completar. Para aminas o anilinas menos nucleofílicas, se forzó la conclusión de las reacciones usando condiciones de microondas que oscilan entre 150°-170°C por espacio de 15 minutos. Las reacciones crudas fueron concentradas hasta secarse y extraídas con acetato de etilo y bicarbonato saturado si se obtuvo un compuesto intermedio o purificadas por HPLC en caso de haberse obtenido un producto final.

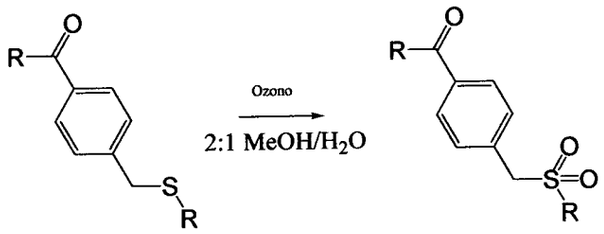
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Q: Desplazamiento de halógeno por tiol



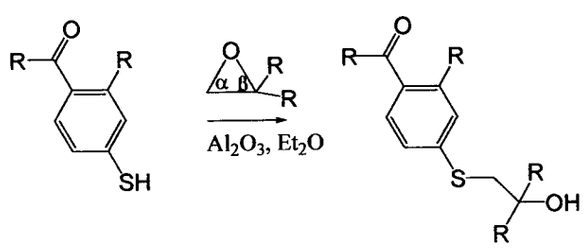
Se trató el parametilbromo benzoato (1eq) con carbonato de potasio (o cesio) (1.5eq) y el derivado de tiol adecuado (1,1eq) en DMF (o CH_3CN) y se agitó durante la noche a temperatura ambiente. La DMF se evaporó en vacío y la reacción fue extraída con acetato de etilo y agua. La capa orgánica fue secada sobre sulfato de magnesio, filtrada y concentrada para producir el tiol o compuesto de tiol derivado.

R: Oxidación con Ozono



El tiol derivado (1eq) fue disuelto en MeOH mientras se disolvió por separado Ozono (2eq) en la mitad de agua. Una vez disuelto todo del ozono, la solución fue agregada al tiol en solución de MeOH de una vez y agitada hasta completar. El MeOH se evaporó en vacío y el agua remanente fue extraída dos veces con acetato de etilo. La capa orgánica fue secada sobre sulfato de magnesio y concentrada para producir la sulfona.

S: Tiólisis de epóxidos en superficies de alúmina

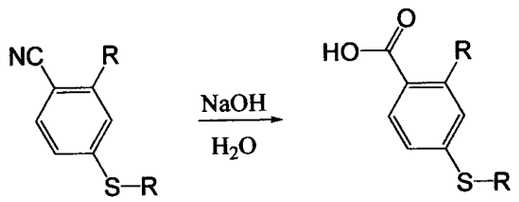


Una mezcla de epóxidos (1.0 eq), tiofenol (1.5 eq) y óxido de aluminio neutral (~70 eq) en dietil éter fue agitada durante 3 h a temperatura ambiente monitoreando por TLC. La mezcla de reacción fue filtrada por Celita, lavada con acetato de etilo y concentrada. Se

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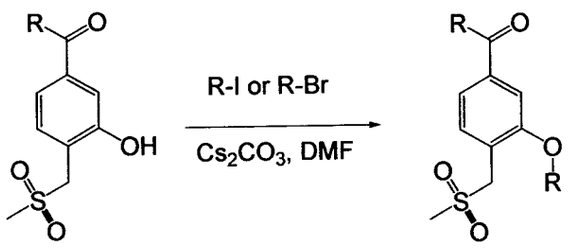
purificó por cromatografía en gel de sílice (0-40% acetato de etilo/hexano) para producir □ -producto hidrosulfuro.

T: Conversión del grupo nitrilo en ácido carboxílico



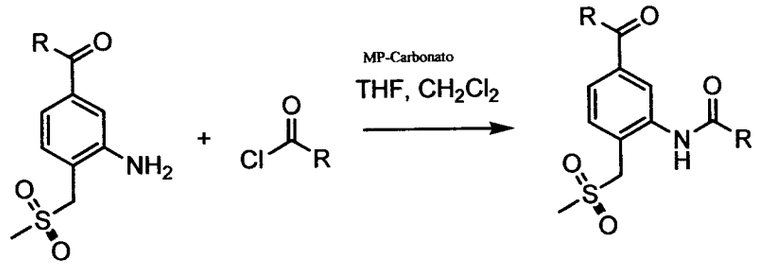
Una solución de benzonitrilo (1.0 eq) e hidróxido de sodio (2.0 eq) en H_2O fue calentada a 120 °C por espacio de 2h. La mezcla de reacción fue enfriada a temperatura ambiente y acidificada con HCl a pH 2. El sólido resultante fue filtrado para obtener el producto ácido puro.

U. Alquilación de fenoles



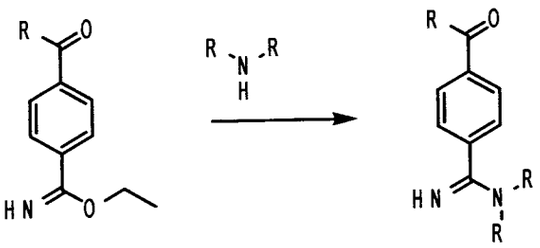
El fenol fue disuelto en DMF (1.0 ml). Se agregaron carbonato de cesio (1.0 eq.) y un alquil bromuro o alquilo yoduro (1.0 to 2.0 eq.), y la reacción fue agitada a temperatura ambiente durante 18 horas o 50°C por espacio de 1 a 24 horas. La reacción fue extinguida en agua, y extraída con acetato de etilo dos veces. Los extractos orgánicos fueron lavados con agua una vez, solución salina una vez, secada con $MgSO_4$, y evaporada a un aceite crudo que fue purificado en HPLC de fase inversa.

V. Formación de enlace amida con un cloruro ácido y una anilina



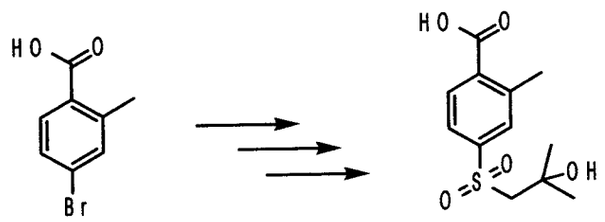
La anilina fue disuelta en THF (1.5 ml) y diclorometano (1.5 ml). Se agregaron MP-Carbonato (1.5 eq.) y un cloruro ácido (1.1 eq.), y la solución fue agitada a temperatura ambiente por espacio de 18 horas. La reacción fue diluida con metanol y diclorometano, y filtrada para remover el MP-Carbonato. Los licores madre fueron evaporados a un sólido y purificados por HPLC de fase inversa.

W. Formación de amidina a partir de un imidato



Una solución de imidato recién preparada en metanol fue tratada con una amina primaria o secundaria (1.5 eq.) a temperatura ambiente por espacio de 18 horas. El metanol fue removido en un evaporador rotativo y el residuo purificado por HPLC de fase inversa.

X. Acido 4-(2-hidroxi-2-metilpropilsulfonil)-2-metilbenzoico



Paso 1. Preparación de metil 4-bromo-2-metilbenzoato - Un frasco con cuello 3 de 1L con agitador mecánico, condensador de reflujo, sonda de temperatura interna y un burbujeador de nitrógeno fue cargado con ácido 4-bromo-2-metilbenzoico (50.35 g, 1eq., Hongda) y metanol (350 mL). y los contenidos del reactor fueron enfriados a 0 °C. Se agregó lentamente acetil cloruro (27.6g, 1eq.) a una velocidad que mantuvo una temperatura interna inferior a 30 °C. La mezcla de reacción fue calentada a reflujo por espacio de 16 horas, hasta que el material iniciador ya no fue detectado por LC. Finalizada la reacción, los contenidos del reactor fueron enfriados a temperatura ambiente y la mezcla de reacción fue concentrada en un aceite mediante un evaporador rotativo. El aceite fue diluido con diclorometano (100 mL) y lavado con solución de bicarbonato de sodio saturada (100 mL). La capa orgánica fue concentrada mediante un evaporador

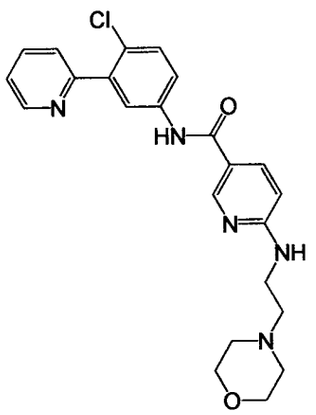
rotativo para obtener metil 4-bromo-2-metilbenzoato (51.22g, 95.5 %) como un aceite amarillo.

Paso 2. Acido 4-(2-hidroxi-2-metilpropiltio)-2-metilbenzoico - Un frasco de base redonda con cuello 3 de 12 L con agitador mecánico, condensador de reflujo, sonda de temperatura interna y un burbujeador de nitrógeno fue cargado con metil 4-bromo-2-metilbenzoato (500 g), tolueno (4,000 mL), 2-etilhexil 3-mercaptopropanoato (715 g), y diisopropiletilamina (564 g). Los contenidos del reactor fueron desgasificados repitiendo un ciclo de vacío/nitrógeno 3 veces. El reactor luego fue cargado con $Pd_2(dba)_3$ (59.97 g), y Xantphos (63.15 g) y desgasificado repitiendo un ciclo de vacío/nitrógeno 1 vez. Los contenidos del reactor luego fueron calentados a 95-100 °C por espacio de 16 horas, hasta que el material iniciador ya no fue detectado por LC. Una vez concluida la reacción, los contenidos del reactor fueron enfriados a 45 °C. El reactor luego fue cargado con Florisil (1000 g) y los contenidos del reactor fueron agitados a 50 °C por espacio de 2 horas, hasta que el material intermedio ya no fue detectado por LC. Finalizada la reacción, los contenidos del reactor fueron enfriados a temperatura ambiente y filtrados sobre un pad de celita. La torta filtrante fue lavada con acetato de etilo (4000 mL) y el filtrado fue concentrado en un aceite mediante un evaporador rotativo. El aceite luego fue transferido nuevamente al reactor con metanol (9000 mL) y el reactor fue cargado con metóxido de sodio (327 g). (adición exotérmica, ΔT~ 10 °C). Los contenidos del reactor luego fueron calentados a 50 °C por espacio de 1 hora, hasta que el material intermedio ya no fue detectado por LC. El reactor luego fue cargado con 2,2-dimetiloxirano (236 g), (adición exotérmica, ΔT~ 10 °C) y se prosiguió calentando a 50 °C por espacio de 1 hora, hasta que el material intermedio ya no fue detectado por LC. El reactor luego fue cargado con agua (500 mL) e hidróxido de litio monohidrato (91 g) y luego calentado a 60 °C por espacio de 12 horas, hasta que el material intermedio ya no fue detectado por LC. Finalizada la reacción, los contenidos del reactor fueron enfriados a temperatura ambiente y concentrados en un aceite mediante un evaporador rotativo a lo que siguió una dilución con agua (18 L), extracción con diclorometano (2 x 4 L), lavado de la fracción acuosa con heptano (2 x 4 L), acidificación de la fracción acuosa con HCl concentrado (manteniendo una temperatura inferior a 35 °C, y extracción con diclorometano (2 x 16 L). Cada fracción orgánica fue lavada con agua (1 x 8L) y concentrada hasta secarla para obtener ácido 4-(2-hidroxi-2-metilpropiltio)-2-metilbenzoico (472 g, 90 % producido) como un sólido amarillo.

Paso 3. Síntesis de ácido 4-(2-hidroxi-2-metilpropilsulfonil)-2-metilbenzoico – Un reactor de 2000 mL con agitador mecánico, sonda de temperatura interna y un burbujeador de

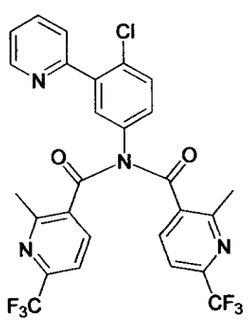
nitrógeno fue cargado con ácido 4-(2-hidroxi-2-metilpropiltio)-2-metilbenzoico (52 g), metanol (370 mL), agua (370 mL) y Oxone (146 g). (exoterma leve observada, ΔT ~15 °C) y agitado a temperatura ambiente por espacio de 18 horas, hasta que el material iniciador ya no fue detectadi por LC. El metanol fue removido mediante un evaporador rotativo y los contenidos del reactor fueron disueltos en 5% solución de bicarbonato de sodio (3L) y se agregó acetato de etilo (2L) a lo que siguió una acidificación con HCl concentrado a pH 1. Los orgánicos fueron concentrados hasta secarse mediante un evaporador rotativo para obtener ácido 4-(2-hidroxi-2-metilpropilsulfonil)-2-metilbenzoico (52 g, 88 % producido, 96.47 area % por LC) como un sólido blanco.

Ejemplo 2 6-(2-morfolinoetilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil)piridina-3-carboxamida



El procedimiento F fue ejecutado usando *N*-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (50 mg) y 2-morfolinoetilamina en butanol (0.5 mL). La reacción cruda fue purificada por HPLC de fase inversa para producir 6-(2-morfolinoetilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil)piridina-3-carboxamida como un sólido blanco. MS (Q1) 438.3 $(M)^+$.

Ejemplo 3 *N,N*-(4-Cloro-3-(piridin-2-il)fenil)-bis[6-(trifluorometil)-2-metilpiridina-3]-carboxamida

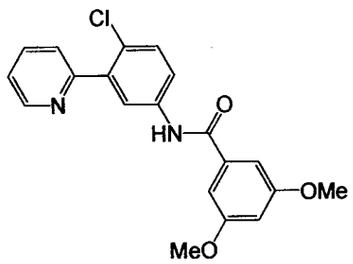


El procedimiento B fue ejecutado con 2-piridilzinc bromuro (4 mL, 2.0 mmol, 0.5 M en THF) y 3-bromo-4-cloro-nitrobenceno (236 mg, 1.0 mmol). Se purificó por cromatografía en gel de sílice (10% acetato de etilo/hexanos) para producir 2-(2-cloro-5-nitrofenil)piridina como un sólido amarillo claro.

El procedimiento C fue ejecutado con 2-(2-cloro-5-nitrofenil)piridina (122 mg, 0.52 mmol) para producir 4-cloro-3-(piridin-2-il)anilina como un sólido amarillo claro, que fue usado sin purificación adicional.

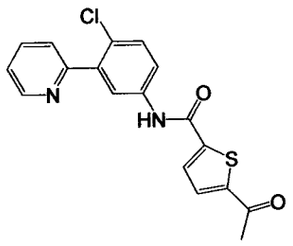
El procedimiento D fue ejecutado usando 4-cloro-3-(piridin-2-il)anilina (40 mg, 0.2 mmol). El residuo crudo fue purificado por cromatografía en gel de sílice (15-60% acetato de etilo/hexanos) para producir *N,N*-(4-Cloro-3-(piridin-2-il)fenil)-bis[6-(trifluorometil)-2-metilpiridina-3]-carboxamida como un residuo aceitoso: TLC R_f = 0.42 (35% acetato de etilo/hexanos); ^{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 $(M)^+$.

Ejemplo 4 *N*-(4-Cloro-3-(piridin-3-il)fenil)-3,5-dimetoxibenzamida



Se utilizó 4-cloro-3-(piridin-2-il)anilina (40 mg, 0.2 mmol) en el procedimiento D con 3,5-dimetoxibenzoil cloruro (43 mg, 0.216 mmol) a 23 °C por espacio de 2 horas. El residuo crudo fue purificado por cristalización (CH_2Cl_2/hexanos) para producir *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); ^{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 $(M)^+$.

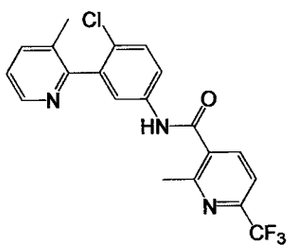
Ejemplo 5 5-Acetil-*N*-(4-cloro-3-(piridin-2-il)fenil)tiofeno-2-carboxamida



Se usó 4-Cloro-3-yodoanilina (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 por espacio de 2 horas. El material crudo fue purificado por cromatografía en gel de sílice (20-100% acetato de etilo/hexanos) para producir 5-Acetil-*N*-(4-cloro-3-yodofenil)tiofeno-2-carboxamida como un sólido amarillo.

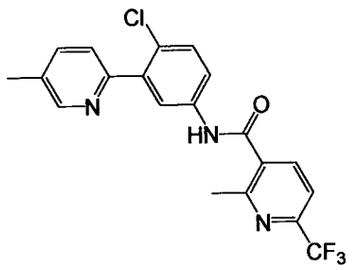
Se usó 5-Acetil-*N*-(4-cloro-3-yodofenil)tiofeno-2-carboxamida (202 mg, 0.5 mmol) en el procedimiento B con 2-piridilzincbromuro (2.5 mL, 1.25 mmol, 0.5 M en THF). Se purificó por cromatografía en gel de sílice (10-100% acetato de etilo/hexanos) para producir 5-acetil-*N*-(4-cloro-3-(piridin-2-il)fenil)tiofeno-2-carboxamida 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-metilpiridina-3-carboxamida



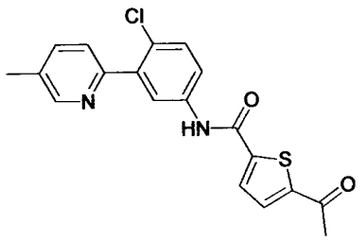
Se usó *N*-(4-Cloro-3-yodofenil)-6-(trifluorometil)-2-metilpiridina-3-carboxamida (142 mg, 0.32 mmol) en el procedimiento B con 6-metil-2-piridilzinc bromuro (1.75 mL, of a 0.5 M en THF). Se purificó por cromatografía en gel de sílice (5-100% Etil acetato/hexanos) para producir *N*-(4-cloro-3-(3-metilpiridin-2-il)fenil)-6-(trifluorometil)-2-metilpiridina-3-carboxamida 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-metilpiridina-3-carboxamida



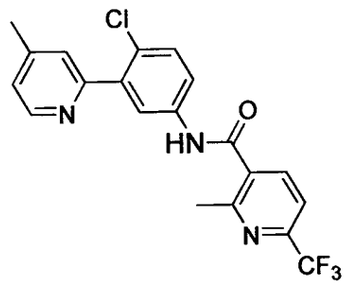
Se usó *N*-(4-Cloro-3-yodofenil)-6-(trifluorometil)-2-metilpiridina-3-carboxamida (150 mg, 0.34 mmol) en el procedimiento B con 4-metil-2-piridilzinc bromuro (1.7 mL de 0.5 M en THF). Se purificó por cromatografía en gel de sílice (5-75% Etil acetato/hexanos) para producir *N*-(4-cloro-3-(5-metilpiridin-2-il)fenil)-6-(trifluorometil)-2-metilpiridina-3-carboxamida 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



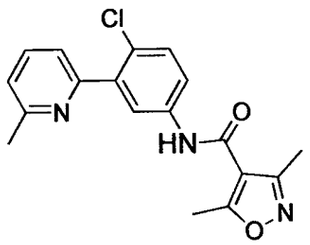
Se usó 5-acetil-*N*-(4-cloro-3-yodofenil)tiofeno-2-carboxamida (203 mg, 0.5 mmol), en el procedimiento B con 4-metil-2-piridilzinc bromuro (2.5 mL, 1.25 mmol, 0.5 M en THF). Se purificó por cromatografía en gel de sílice (30-100% acetato de etilo/hexanos) para producir 5-acetil-*N*-(4-cloro-3-(5-metilpiridin-2-il)fenil)tiofeno-2-carboxamida como un sólido 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), 7.60 (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 $(M)^+$.

Ejemplo 9 *N*-(4-Cloro-3-(4-metilpiridin-2-il)fenil)-6-(trifluorometil)-2-metilpiridina-3-carboxamida



El procedimiento B fue ejecutado con *N*-(4-Cloro-3-yodofenil)-6-(trifluorometil)-2-metilpiridina-3-carboxamida (440 mg, 1.0 mmol) y 4-metil-2-piridilzinc bromuro (5 mL de una solución 0.5 M en THF). El residuo crudo fue purificado por cromatografía en gel de sílice (5-100% Etil acetato/hexanos) para producir *N*-(4-cloro-3-(4-metilpiridin-2-il)fenil)-6-(trifluorometil)-2-metilpiridina-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 $(M)^+$.

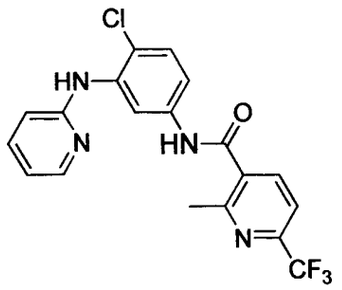
Ejemplo 10 *N*-(4-cloro-3-(6-metilpiridin-2-il)fenil)-3,5-dimetilisoxazol-4-carboxamida



Se usó 4-Cloro-3-yodoanilina (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 reacción cruda fue purificada por cromatografía en gel de sílice (0-15% acetato de etilo/CH_2Cl_2) para producir 3,5-dimetil-*N*-(4-cloro-3-yodofenil)isoxazol-4-carboxamida como un sólido blanco.

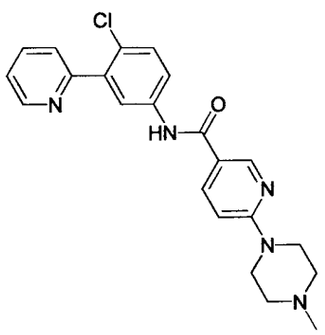
El procedimiento B fue ejecutado con 3,5-dimetil-*N*-(4-cloro-3-yodofenil)isoxazol-4-carboxamida (190 mg, 0.5 mmol) y 3-metil-2-piridilzinc bromuro (2.5 mL de una solución 0.5 M en THF). La reacción cruda fue purificada por cromatografía en gel de sílice (5-100% Etil acetato/hexanos) para producir *N*-(4-cloro-3-(6-metilpiridin-2-il)fenil)-3,5-dimetilisoxazol-4-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-metilpiridina-3-carboxamida



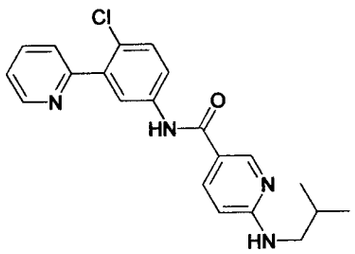
Se calentaron *N*-(4-Cloro-3-yodofenil)-6-(trifluorometil)-2-metil piridina-3-carboxamida (220 mg, 0.5 mmol), 2-aminopiridina (40 mg, 0.42 mmol), t-butóxido de potasio (66 mg, 0.59 mmol), $Pd_2(dba)_3$ (20 mg, 0.21 mmol), dppf (24 mg, 0.042 mmol) en tolueno (2.1 mL) a 100 °C por espacio de 1.5 días. La solución fue enfriada a 23 °C, diluida con éter, filtrada por celita, lavada con acetato de etilo, y concentrada. Se purificó por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-ilamino)fenil)-6-(trifluorometil)-2-metilpiridina-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)piridina-3-carboxamida



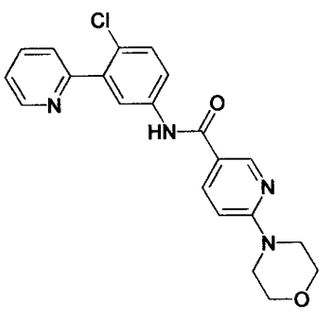
El procedimiento F fue ejecutado usando *N*-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (50 mg) y *N*-metilpiperazina en butanol (0.5 mL). La reacción cruda fue purificada por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(4-metilpiperazin-1-il)piridina-3-carboxamida como un sólido blanco. MS (Q1) 408.4 $(M)^+$.

Ejemplo 13 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(isobutilamino)piridina-3-carboxamida



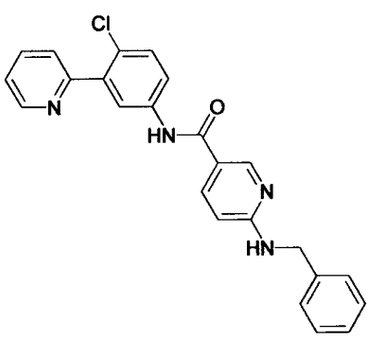
El procedimiento F fue ejecutado usando *N*-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (50 mg) y 2-metilpropilamina en butanol (0.5 mL). La reacción cruda fue purificada por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(isobutilamino)piridina-3-carboxamida como un sólido blanco. MS (Q1) 381.1 $(M)^+$.

Ejemplo 14 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-morfolinopiridina-3-carboxamida



El procedimiento F fue ejecutado usando *N*-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (50 mg) y morfolina en butanol (0.5 mL). La reacción cruda fue purificada por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-morfolinopiridina-3-carboxamida como un sólido blanco. MS (Q1) 401.3 $(M)^+$.

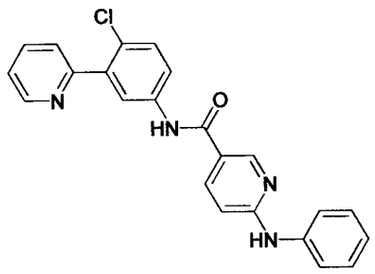
Ejemplo 15 6-(bencilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil)piridina-3-carboxamida



El procedimiento F fue ejecutado usando *N*-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (50 mg) y bencilamina en butanol (0.5 mL). La reacción cruda fue purificada

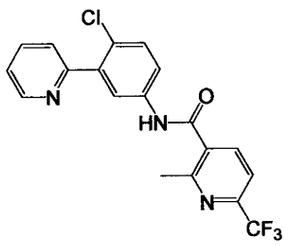
por HPLC de fase inversa para producir 6-(bencilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil)piridina-3-carboxamida como un sólido blanco. MS (Q1) 415.1 $(M)^+$.

Ejemplo 16 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(fenilamino)piridina-3-carboxamida



El procedimiento F fue ejecutado usando *N*-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (50 mg) y analina en butanol (0.5 mL). La reacción cruda fue purificada por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(fenilamino)piridina-3-carboxamida como un sólido blanco. MS (Q1) 401.0 $(M)^+$.

Ejemplo 17 *N*-(4-Cloro-3-(piridin-2-il)fenil)-6-(trifluorometil)-2-metilpiridina-3-carboxamida



El procedimiento C fue ejecutado con 1-cloro-2-yodo-4-nitrobenceno (283 mg, 1 mmol) para producir 4-cloro-3-yodoanilina que fue usado sin purificación adicional.

El procedimiento D fue ejecutado con 4-cloro-3-yodoanilina (225 mg, 0.889 mmol) y 6-(trifluorometil)-2-metilpiridina-3-carbonilo cloruro (237 mg, 0/93 mmol, 1.05 eq) a 0 °C por espacio de 30 minutos. El residuo crudo fue purificado por cromatografía en gel de sílice (2-50% acetato de etilo/hexanos) para producir *N*-(4-cloro-3-yodofenil)-6-(trifluorometil)-2-metilpiridina-3-carboxamida como un sólido blanco.

El procedimiento B fue ejecutado usando *N*-(4-Cloro-3-yodofenil)-6-(trifluorometil)-2-metilpiridina-3-carboxamida (88 mg, 0.2 mmol) con 2-piridilzinc bromuro (1 mL, 0.5 mmol, 0.5 M en THF). Se purificó por cromatografía en gel de sílice (10-80% acetato de etilo/hexanos) para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(trifluorometil)-2-metilpiridina-3-carboxamida como un sólido 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 $(M)^+$.

El siguiente es un procedimiento sintético alternativo. Se agregaron 75g (435 mmol) de 2-cloro-5-nitroanilina a una solución de agua (600 mL) y ácido sulfúrico concentrado (60 mL) en un frasco 3 de 3L equipado para agitación mecánica. La solución fue enfriada a 0 °C y una solución de nitrito de sodio (34.2 g, 496 mmol) en agua (130 mL) fue agregada lentamente. La mezcla fue agitada durante ½ hora y luego una solución de yoduro de potasio (130 g, 783 mmol) en agua (520 mL) fue agregada por goteo durante ½ hora manteniendo la temperatura por espacio de 15°C. La solución fue agitada durante 2 horas, luego extraída con EtOAc (3 x 500 mL). Los extractos orgánicos combinados fueron lavados con sat. $Na_2S_2O_3$ (2x 500 mL), secados (Na_2SO_4), y concentrados. El yoduro crudo fue disuelto en iPrOH caliente (500 mL) y se agregaron hexanos (200 mL). La reacción se dejó enfriar con agitación y el producto fue colectado por filtración por succión luego de agitar a 0°C por espacio de 2 horas obteniéndose 90g (318 mmol, 73%) de 2-cloro-5-nitro-yodobenceno como un sólido cristalino bronce claro.

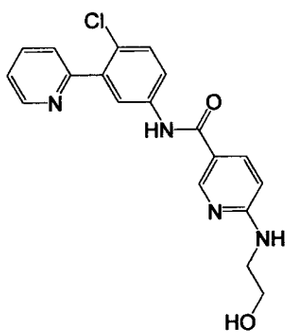
El 2-cloro-5-nitro-yodobenceno (5g, 17.6 mmol) fue disuelto en 5 mL DMA en un frasco templado y se agregó una solución 0.5M de 2-piridilzincbromuro (53 mL, 26.5 mmol, 0.5 M en THF). La solución fue desgasificada con N_2 por espacio de ½ hora, se agregaron PPh_3 (0.185g, 0.7 mmol) y $Pd(PPh_3)_4$ (0.825g, 0.7 mmol), se enjuagó con varios mLs de THF y la solución fue desgasificada durante 10 minutos más antes de calentar a 60°C bajo N_2. La reacción fue completada por TLC en ~8h, enfriada a TR, y vertida en una mezcla 1:1 de EtOAc/2.5N NaOH (500 mL). Esta solución fue agitada durante 10 minutos, pasada por un filtro de paso grueso que contiene celita para remover el sólido, y luego extraída. Los orgánicos fueron lavados con solución salina y concentrados en un sólido marrón. Las capas acuosas combinadas fueron retro-extraídas con Et_2O (1 x 200 mL). Esto se usó para suspender el producto crudo, que fue extraído con 1N HCl (1 x 200 mL, 3 x 100 mL). Los extractos acuosos combinados fueron enfriados a 0°C, diluidos con EtOAc (250 mL), y basificados con 10N NaOH (100 mL). Esta solución fue separada, la capa acuosa extraída con EtOAc, y los orgánicos combinados fueron secados sobre Na_2SO_4 y carbón con agitación. Esta solución was filtrada por celita y concentrada para producir 4-cloro-3-(piridin-2-il)nitrobenceno puro (2.47g, 10.5 mmol, 60% producido) que fue empleado en la siguiente reacción sin purificación adicional.

Se suspendió 4-cloro-3-(piridin-2-il)nitrobenceno (1.47g, 6.26 mmol) en EtOH (35 mL), y se agregaron $SnCl_2$ (3.87g; 20.4 mmol) y HCl concentrado (5 mL), se enjuagó con 5 ml más de EtOH. La solución fue colocada en un baño de aceite a 40°C y calentada a 60°C. La solución fue agitada a 60°C por espacio de 1 ½ hora , enfriada a TR y diluida con 1 N

HCl (100 mL). Esta solución fue vertida en una solución de Et_2O/1 N HCl (100 mL:150 mL) y extraída. La capa acuosa fue diluida con EtOAc (250 mL), enfriada a 0°C, y basificada con 10 N NaOH (50 mL). Esta solución fue extraída (EtOAc, 2x), y los orgánicos combinados fueron lavados con solución salina y secados sobre Na_2SO_4 y carbón. La filtración por succión produjo una solución incolora clara que fue concentrada para producir 4-cloro-3-(piridina-2-il)anilina (1.21g, 5.93 mmol, 94% producido) como un sólido cristalino color crema que fue empleado en la siguiente reacción sin purificación adicional.

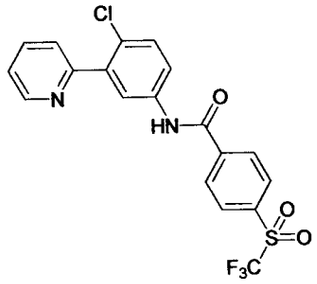
Se agregó 6-(trifluorometil)-2-metilpiridina-3-carbonilo cloruro (1.68g, 7.51 mmol) en 3 mL THF por goteo a una solución de 4-cloro-3-(piridina-2-il)anilina (1.21g, 5.93 mmol) en THF (15 mL) a 0°C. La solución fue agitada durante 10 minuto., vertida en EtOAc y lavada con NaHCO3 acuoso saturado(2x), y solución salina. Los orgánicos fueron secados (Na_2SO_4) y concentrados. El producto crudo fue suspendido en iPrOAc/Et_2O (10 mL, 1:1), agitado a 0°C por espacio de ½ hr, y colectado por filtración por succión para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(trifluorometil)-2-metilpiridina-3-carboxamida (2.04g, 5.21 mmol, 88% producido) como un sólido blanco: 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 $(M)^+$.

Ejemplo 18 6-(2-hidroxietilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil)piridina-3-carboxamida



El procedimiento F fue ejecutado usando *N*-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (50 mg) y etanolamina en butanol (0.5 mL). La reacción cruda fue purificada por HPLC de fase inversa para producir 6-(2-hidroxietilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil)piridina-3-carboxamida como un sólido blanco. MS (Q1) 369.0 $(M)^+$.

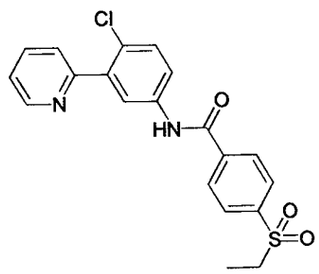
Ejemplo 19 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(trifluorometilsulfonil) benzamida



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 agitar durante 16 h, fue diluida con acetato de etilo y lavada con agua. La capa orgánica fue secada ($MgSO_4$) y concentrada para producir ácido 4-(trifluorometilsulfona) benzoico.

El procedimiento general G fue ejecutado usando ácido 4-(trifluorometilsulfona) benzoico y 4-cloro-3-(piridin-2-il)anilina. La mezcla de reacción cruda fue purificada por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(trifluorometilsulfonil) benzamida. MS (Q1) 440.95 $(M)^+$.

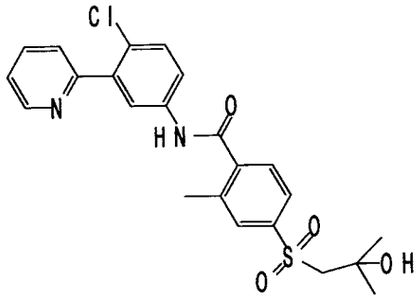
Ejemplo 20 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(etilsulfonil) benzamida



El procedimiento general G fue ejecutado usando ácido 4-(etiltio) benzoico y 4-cloro-3-(piridin-2-il)anilina para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(etiltio) benzamida.

Una solución de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(etiltio) benzamida (40 mg, 0.11 mmol) en MeOH (3 mL), enfriada a 0° C fue tratada con ozono (133 mg, 0.22 mmol), y se removió el baño de hielo. Luego de 1h de agitación, la mezcla de reacción fue concentrada, y el residuo fue disuelto en acetato de etilo. La solución orgánica fue lavada con agua, secada ($MgSO_4$) y concentrada. La mezcla de reacción cruda fue purificada por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(etilsulfonil) benzamida. MS (Q1) 401.0 $(M)^+$.

N-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxi-2-metilpropilsulfonil)-2-metilbenzamida



2-Cloro-5-nitroyodobenceno: El reactor usado fue purgado con nitrógeno y mantenido bajo nitrógeno durante toda la síntesis. El reactor fue cargado con agua purificada USP (400.0 L), agitado y cargado con 2-cloro-5-nitroanilina (50.0 kg) y luego los contenidos fueron enfriados a 0 - 5 °C. El agitación reactor fue cargado con ácido sulfúrico concentrado (40.0 L), manteniendo la temperatura a ≤10 °C (tiempo de adición ~3-4 hr) y los contenidos fueron agitados a 0 - 5 °C por espacio de por lo menos 15 minutos. En un recipiente separado se preparó una solución de nitrito de sodio (25.0 kg) y agua purificada USP (100.0L). La solución de nitrito de sodio fue lentamente cargada al reactor bajo agitación manteniendo la temperatura a ≤ 5 °C (exoterma y evolución de gas provocada, tiempo de adición ~2 horas) y luego los contenidos fueron agitados a ≤ 5 °C por espacio de por lo menos 1 hora. En un recipiente separado se preparó una solución de yoduro de potasio (60.0 kg) y agua purificada USP (240.0 L) y fue cargada lentamente al reactor bajo agitación manteniendo la temperatura a ≤5 °C (exoterma, evolución de gas provocada y generación de espuma, tiempo de adición ~7 hr). El enfriamiento fue gradualmente desactivado dejando que la reacción alcanzase la temperatura ambiente (~20 °C) y luego los contenidos fueron agitados durante por lo menos 18 horas a 15 – 25 °C, y luego sometidos a un muestreo por análisis HPLC (muestra disuelta en acetonitrilo), cuando permanecieron ≤ 5% de 2-cloro-5-nitroanilina se continuó a la siguiente etapa, sin embargo cuando el nivel de material iniciador fue de ≥ 5% se tomaron muestras a cada hora hasta finalizar la reacción. En un recipiente separado se preparó una solución de tiosulfato de sodio (30.0 kg) y agua purificada USP (600.0 L) y se cargó lentamente ~1/2 de la solución de tiosulfato de sodio al reactor bajo agitación, manteniendo la temperatura a 20 - 30 °C y a continuación de lo cual se agitó el contenido del reactor a 20 - 30 °C por espacio de por lo menos 20 minutos. Se cargó ciclohexano (300.0 L) al reactor y los contenidos fueron calentados a 55 - 60 °C y se agitó durante por lo menos 20 minutos a 55 - 60 °C. Se interrumpió la agitación para permitir que las capas reposaran durante por lo menos 10 minutos y luego fueron separadas (dejando de lado la capa orgánica) y incorporándose la capa acuosa nuevamente al reactor. Se cargó ciclohexano (200.0 L) al reactor y se agitó a 55 - 60 °C por espacio de por lo menos 20 minutos y luego la agitación fue interrumpida para permitir que las capas reposaran durante por lo menos 10 minutos y a continuación de lo cual se separaron las capas (se retiene la capa acuosa

para verificar el rendimiento) y se combinaron las capas orgánicas de las etapas previas en el reactor. El resto de la solución, ~1/2, de tiosulfato de sodio fue cargado al reactor bajo agitación, manteniendo la temperatura a 55 - 60 °C y agitada durante por lo menos 20 minutos a 55 - 60 °C. Se interrumpió la agitación para permitir que las capas reposaran durante por lo menos 10 minutos y la capa acuosa fue drenada del reactor. Luego se cargó agua purificada USP (300.0 L) al reactor y se agitó durante por lo menos 20 minutos a 55 - 60 °C y luego la agitación fue interrumpida para permitir que las capas reposaran durante por lo menos 10 minutos y la capa acuosa fue descartada. Los contenidos del reactor fueron calentados a ~45 °C y eliminado el ~65% del solvente por destilación al vacío. Los contenidos del reactor luego fueron enfriados a 0 - 5 °C y se agitó durante por lo menos 5 horas y luego los sólidos fueron filtrados y el producto lavado con ciclohexano frío (100.0 L). El producto fue colectado y secado en un secador de aire caliente 45 +/- 5 °C hasta que el LOD fue ≤ 1.0%. El proceso dio como resultado 50.0 kg (61 % producido) de 2-cloro-5-nitroyodobenceno como un sólido amarillo.

2-(2-piridil)-4-nitroclorobenceno crudo: El reactor fue purgado con nitrógeno y mantenido bajo nitrógeno durante toda la síntesis. Se cargó tolueno (375.0 L) al reactor y se inició la agitación, y se cargó cloruro de zinc (19.56 kg) al reactor. Usando destilación atmosférica los contenidos del reactor fueron separados a ~50% del volumen original y luego enfriados a ≤ 30 °C. Se cargó lentamente THF (100.0 L) al reactor (la adición fue exotérmica).

Preparación de reactivo de Grignard en reactor 2: El reactor fue purgado con nitrógeno y mantenido bajo nitrógeno durante toda la síntesis. Se inició la agitación y se cargó THF (50.0 L) al reactor.

Isopropil magnesio cloruro (89.0 kg, ajustado luego de la titulación) fue colocado en un tambor para mezclarlo, y luego se agregó lentamente, manteniendo la temperatura a ≤ 30 (exotérmica, tiempo de adición 30-40 min).

Se agregó lentamente 2-bromopiridina (22.3 kg) al reactor manteniendo la temperatura a ≤ 30 oC (exotérmica, tiempo de adición 50-60 min). Los contenidos del reactor luego fueron calentados a 50 +/- 5 °C y mantenidos durante por lo menos 1 hora. La solución de Grignard (del reactor 2) fue lentamente cargada al reactor (de la etapa previa) manteniendo la temperatura a ≤ 55 °C (la adición exotérmica generó espuma, tiempo de adición ~20 min). El reactor luego fue agitado a 50 +/- 5 °C por lo menos 1 hora manteniendo la temperatura. Se cargó diclorobistrifenilfosfina paladio (2.0 kg) al reactor y se agitó durante ~15 minutos. Se cargó trifenilfosfina (2.75 kg) al reactor y se agitó durante ~15 minutos. Se cargó lentamente 2-cloro-5-nitroyodobenceno (25.0 kg) al reactor bajo agitación (15 minutos tiempo de adición). Los contenidos del reactor fueron

calentados a 60 +/- 5 °C y se agitó durante por lo menos 14 horas a 60 +/- 5 °C, luego sometidos a un muestreo por análisis HPLC. Cuando la cantidad de material iniciador fue ≥ 4% se continuó calentando y se sometió a un muestreo nuevamente cada hora hasta que el nivel de material iniciador cayó por debajo del 4%. La mezcla de reacción fue enfriada a ~55 °C y luego los contenidos del reactor fueron calentados a reflujo bajo vacío y 75-90 L del solvente fueron removidos. Se cargó tolueno (120.0 L) al reactor con agitación. En un tanque separado, el cloruro de amonio (25.0 kg) fue disuelto en agua purificada USP (250.0 L) y la solución fue lentamente cargada en un reactor y se agitó durante por lo menos 30 minutos. La mezcla was filtrada mediante un filtro Nutsche (preparado con Celita (6.25 kg) y agua purificada USP (12.5 L)) y la torta filtrante fue lavada con tolueno (75.0 L) y el filtrado fue agregado y lavado en un reactor limpio. Las capas se dejaron reposar durante por lo menos 10 minutos y luego separadas (producto contenido en capa orgánica), deolviéndose la capa acuosa al reactor. Se cargó tolueno (75.0 L) al reactor y se agitó durante por lo menos 15 minutos y luego las capas se dejaron reposar durante por lo menos 10 minutos antes de la separación (producto contenido en capa orgánica). Las capas orgánicas de las etapas previas fueron cargadas a un reactor limpio. Se cargó agua purificada USP (125.0 L) al reactor y se agitó durante por lo menos 15 minutos y luego las capas se dejaron reposar durante por lo menos 10 minutos antes de drenar la capa acuosa, reteniéndose para el chequeo de rendimiento.

En un tanque separado, se preparó una solución de ácido clorhídrico 3N mezclando ácido clorhídrico concentrado (127.5 L) y agua purificada USP (272.5 L). Se cargaron aproximadamente 1/3 del ácido clorhídrico 3N (133.3 L) al reactor y se agitó durante por lo menos 30 minutos. Las capas se dejaron reposar durante por lo menos 15 minutos y luego la capa acuosa fue drenada y transferida a un recipiente separado (el producto estaba en la capa acuosa). Se cargó aproximadamente 1/3 del ácido clorhídrico 3N (133.3 L) al reactor y se agitó durante por lo menos 30 minutos. Las capas se dejaron reposar durante por lo menos 15 minutos y luego la capa acuosa fue drenada y transferida a un recipiente separado (el producto estaba en la capa acuosa). Se cargó aproximadamente 1/3 del ácido clorhídrico 3N (133.3 L) al reactor y se agitó durante por lo menos 30 minutos. Las capas se dejaron reposar durante por lo menos 15 minutos y luego la capa acuosa fue drenada y transferida a un recipiente separado (el producto estaba en la capa acuosa). Las capas acuosas de las etapas previas fueron transferidas a un reactor limpio al cual se cargó carbono activado (1.0 kg) y luego se calentó a 50 +/- °C y agitó durante por lo menos 30 minutos. La mezcla fue filtrada mediante un filtro de Nutsche (preparado con Celita (5.0 kg) y agua purificada USP (12.5 L)) y la torta filtrante fue lavada con ácido clorhídrico 3N (40.0 L) y el filtrado fue agregado y lavado en un reactor limpio. Las soluciones acuosas combinadas fueron filtradas con un filtro de 1 micrón a un reactor limpio y enfriadas to ≤ 10 °C. Se cargó lentamente hidróxido de

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amonio (115.0 L) al reactor, ajustándose el pH a un valor entre 8.5 y 9.0 (tiempo de adición 4.25 horas). La temperatura de reacción fue ajustada a 25-30 °C y la mezcla se dejó agitar durante 30 minutos. La mezcla de reacción luego fue centrifugada y el producto lavado con agua purificada USP (300.0 L) y secado en un secador de aire caliente a 50 - 60 °C. El proceso dio como resultado 15.0 kg (72%) de 2-(2-piridil)-4-nitroclorobenceno crudo.

Purificación de 2-(2-piridil)-4-nitroclorobenceno - El reactor fue purgado con nitrógeno y mantenido bajo nitrógeno durante toda la síntesis . Se cargó diclorometano (400.0 L) al reactor y se comenzó con la agitación. Se cargó 2-(2-piridil)-4-nitroclorobenceno crudo (40.0 kg) al reactor y se agitó a 20 - 30 °C por espacio de por lo menos 30 minutos, verificándose la disolución de todos los sólidos. Se cargó gel de sílice (20.0 kg) al reactor y se agitó durante por lo menos 2 horas. La mezcla fue filtrada por un filtro de Nutsche (preparada con Celita (14.8 kg) y diclorometano (14.8 L)) y la torta filtrante fue lavada con diclorometano (80.0 L) y el filtrado agregado y lavado en un reactor limpio. Los contenidos del reactor fueron calentados a reflujo bajo vacío y 80-90% del solvente fue removido y enfriado a 20 - 30 °C, a continuación de lo cual se cargó n-hexano (240.0 L) al reactor que fue agitado durante por lo menos 2 horas a 20 - 30 °C. La mezcla de reacción fue filtrada y lavada con n-hexano (80.0 L) y el producto secado en un secador de aire caliente a 50 - 55 °C. El proceso arroja 34.5 kg (86% recuperación) de 2-(2-piridil)-4-nitroclorobenceno como un sólido beige.

4-cloro-3-(piridin-2-il)anilina: Se cargó 2-(2-piridil)-4-nitroclorobenceno en un reactor de tamaño adecuado bajo nitrógeno. Se agregó platino en carbono (5%, ~50% húmedo) (0.10 en peso) bao agitación, y luego tetrahidrofurano (9.68 en peso). El reactor fue presurizado con nitrógeno a 40psi, luego la presión fue liberada. Este proceso fue repetido dos veces más. El reactor luego fue presurizado con hidrógeno a 50psi manteniendo la temperatura interna a 20-26°C. Luego de la absorción de hidrógeno (1-2 horas), la presión fue mantenida a 50psi y el reactor fue calentado a 50°C por espacio de 2-3 horas. La reacción fue chequeada por HPLC y una vez concluida, enfriada a 30°C. A continuación, el reactor fue presurizado con nitrógeno a 40psi, luego la presión fue liberada. Este proceso fue repetido dos veces más. A un tanque separado, se agregaron Celita (0.1 en peso) y tetrahidrofurano (0.9 en peso). Esta pasta acuosa luego fue transferida al reactor y agitada durante un mínimo de 30 minutos. La mezcla de reacción fue filtrada a través de una filtro prensa y un filtro de 0.2 micrones, la torta fue lavada con tetrahidrofurano (2.2 en peso) y todos los orgánicos fueron combinados. Se cargó gel de sílice (0.05 en peso) al reactor y se agitó durante por lo menos 30 minutos. Esta mezcla luego fue filtrada a través de una filtro prensa a un reactor adyacente, purgado con nitrógeno. La torta filtrante fue lavada con tetrahidrofurano (2.2 en peso) y el lavado fue

colocado nuevamente en el reactor. Con agitación, se agregaron los heptanos (6.8 en peso) al reactor y los contenidos fueron calentados a reflujo bajo vacío. Aproximadamente dos tercios del solvente fueron removidos por destilación al vacío. El reactor fue enfriado a 20-26ºC y agitado durante 2-3 horas. Los contenidos del reactor fueron centrifugados y lavados con heptanos (1.0 en peso) y secados en un horno al vacío a 20-25ºC hasta obtener un peso constante de 4-cloro-3-(piridin-2-il)anilina (rendimiento típico ~80%).

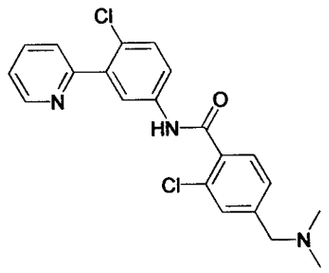
N-(4-cloro-3-(piridin-2-il)fenil)-4-(etilsulfonil) benzamida – Se cargó tetrahidrofurano (10.24 en peso) a un reactor del tamaño adecuado bajo nitrógeno. Bajo agitación, se agregaron ácido 4-(2-hidroxi-2-metilpropilsulfonil)-2-metilbenzoico (1.265 en peso) y 2-cloro-4,6-dimetoxi-1,3,5-triazina (0.815 en peso) y se agitó hasta disolver. Se cargó lentamente 4-metilmorfolina (0.564 en peso) al reactor manteniendo la temperatura interna a ≤ 30ºC. La mezcla se dejó agitar a temperatura ambiente durante por lo menos 30 minutos, luego se muestreó TLC. Una vez agitado el ácido 4-(2-hidroxi-2-metilpropilsulfonil)-2-metilbenzoico, se agregó 4-cloro-3-(piridin-2-il)anilina (1.0 en peso). El reactor fue calentado a 50ºC y agitado durante por lo menos 6 horas, momento en el cual la reacción fue muestreada por HPLC. Una vez concluida la reacción por HPLC, la solución de bicarbonato de sodio (bicarbonato de sodio (0.506 en peso) y agua purificada USP (24.8 en peso), agitados hasta disolver todos los sólidos) fue agregada a la reacción. La mezcla de reacción fue calentada a reflujo (~70ºC) y el solvente (5.7 en peso.) fue destilado del reactor. El reactor fue enfriado a □ 30ºC y agitado durante por lo menos 20 horas. Los contenidos del reactor fueron centrifugados, lavados con agua purificada USP (3.47 en peso) y secados en un horno al vacío a 45 ºC hasta obtener un peso constante de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(etilsulfonil) benzamida puro (rendimiento típico ~90%).

Se cargó metil isobutil cetona (20.0 en peso) a un reactor del tamaño adecuado bajo nitrógeno. Bajo agitación, se agregó *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(etilsulfonil) benzamida crudo (1.0 en peso) y el reactor fue calentado a 60 ºC y agitado durante por lo menos una hora. La solución fue filtrada a través de un filtro prensa en un reactor adyacente, purgado con nitrógeno, y la torta fue lavada con metil isobutil cetona (2.56 en peso.). La solución filtrada luego fue calentada a reflujo (~115 ºC) y destilada para remover ~2/3 del solvente (~14.5 en peso). El reactor fue enfriado a 100 ºC y agitado durante por lo menos 15 minutos. El reactor luego fue enfriado a 80 ºC y la velocidad de punta del agitator se fijó en 2.0 m/s. Se preparó una pasta mezclando *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(etilsulfonil) benzamida Forma A (0.001 en peso) y metil isobutil cetona (0.008 en peso). Esta pasta fue agregada al reactor a 80 ºC y agitada durante por lo menos 2.5 horas. La temperatura del baño se fijó en 70 ºC y los contenidos fueron agitados hasta que la temperatura interna alcanzó 70 ºC. La temperatura del baño se fijó

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en 50 °C y los contenidos fueron agitados hasta que la temperatura interna alcanzó 50 °C. La temperatura del baño se fijó en 25 °C y los contenidos fueron agitados hasta que la temperatura interna alcanzó 15-30 °C. Una vez obtenida esta temperatura, la mezcla fue agitada durante por lo menos 12 horas. En un tanque separado, se preparó una solución cargando metil isobutil cetona (3.0 en peso) y heptanos (2.6 en peso). Los contenidos del reactor fueron centrifugados, lavados con una mezcla de metil isobutil cetona/heptanos (all) y secada en un horno al vacío a 60 °C hasta obtener un peso constante de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(etilsulfonil) benzamida purificada. Los sólidos fueron molidos usando un molino Fitzmill utilizando una malla tamaño 18, martillos hacia adelante a baja velocidad. (rendimiento típico ~80%).

Ejemplo 21 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-((dimetilamino)metil) benzamida

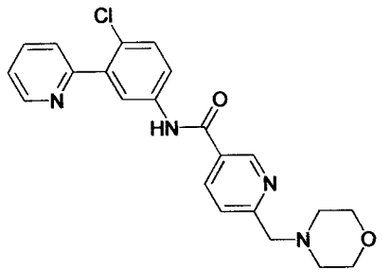


El procedimiento general G fue utilizado para acoplar ácido 4-(BOC-aminometil)-2-cloro-benzoico y 4-cloro-3-(piridin-2-il)anilina para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)-fenil)-4-(BOC-aminometil)-benzamida. La mezcla de reacción cruda fue tratada con TFA y vestigios de agua durante 1 h antes de concentrar hasta secar para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)-fenil)-4-(aminometil)-benzamida.

2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(aminometil) benzamida (80 mg, 0.20 mmol) fue disuelto en DMF (5 mL) y tratado con AcOH (10 uL), paraformaldehido (43 mg, 0.47 mmol), y sodio triacetoxiborohidruro (125 mg, 0.59 mmol). Luego de agitar durante 16 h, el solvente fue evaporado y el residuo fue disuelto en acetato de etilo. La capa orgánica fue lavada con 1 N hidróxido de sodio, secada ($MgSO_4$) y concentrada. El producto crudo fue purificado 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 $(M)^+$.

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Ejemplo 22 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(morfolinometil)piridina-3-carboxamida

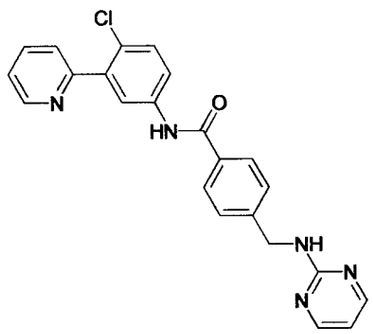


Se disolvió ácido 6-metilnicotínico (100 mg 0.14 mmol) en 10% AcOH/benceno (1 mL) y fue tratado con NBS (117 mg, 0.18 mmol) y benzoilperóxido (18 mg, 0.07 mmol). La mezcla de reacción fue calentada en un reactor a microondas sellado a 120° C por espacio de 1 minuto. La mezcla de reacción fue diluida con acetato de etilo, lavada con NaHCO3 saturado acuoso, secada ($MgSO_4$), concentrada y purificada por cromatografía en gel de sílice para producir ácido 6-(bromometil)piridina-3-carboxílico.

Se acopló ácido 6-(bromometil)piridina-3-carboxílico a 4-cloro-3-(piridin-2-il)anilina según lo descripto en el procedimiento general E para producir 6-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)piridina-3-carboxamida.

Se disolvió 6-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)piridina-3-carboxamida en DMSO (1 mL) tratado con morfolina (33 uL) durante 1 h. La reacción fue concentrada, y el residuo crudo fue purificado por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(morfolinometil)piridina-3-carboxamida. MS (Q1) 409.3 $(M)^+$.

Ejemplo 23 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((pirimidin-2-ilamino)metil) benzamida



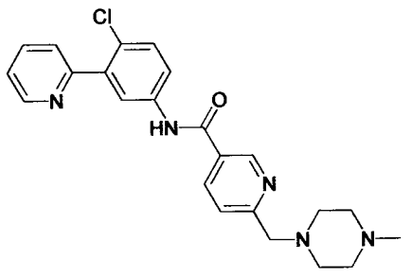
Se acopló ácido 4-(bromometil) benzoico a 4-cloro-3-(piridin-2-il)anilina según lo descripto en el procedimiento general E para producir 4-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida.

Se disolvió 4-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida (85 mg) en DMSO (0.5 mL) y fue tratado con 2-aminopiridina (59 mg) a 150° C en un reactor a microondas sellado por espacio de 5 minutos. La mezcla de reacción fue concentrada, y el residuo

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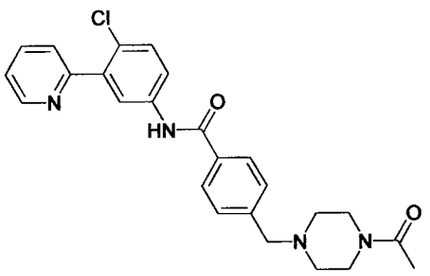
crudo fue purificado por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((pirimidin-2-ilamino)metil) benzamida pura. MS (Q1) 416.3 $(M)^+$.

Ejemplo 24 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-((4-metilpiperazin-1-il)metil)piridina-3-carboxamida



Se disolvió 6-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)piridina-3-carboxamida en 1 mL de DMSO y se agitó durante 1 h con *N*-metilpiperazina. La reacción fue concentrada, y el residuo crudo fue purificado por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-((4-metilpiperazin-1-il)metil)piridina-3-carboxamida como un producto crudo. MS (Q1) 422.3 $(M)^+$.

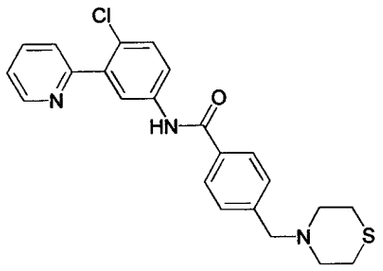
Ejemplo 25 4-((4-acetilpiperazin-1-il)metil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida



Se disolvió 6-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)piridina-3-carboxamida (85 mg) en DMSO (1 mL) y se agitó durante 1 h con N-acetilpiperazina. La mezcla de reacción fue concentrada, y el residuo crudo fue purificado por HPLC de fase inversa para producir 4-((4-acetilpiperazin-1-il)metil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida. MS (Q1) 449.1 $(M)^+$.

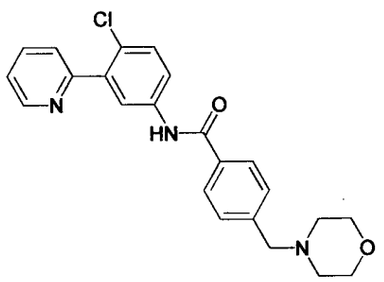
Ejemplo 26 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(tiomorfolinometil) benzamida

000379



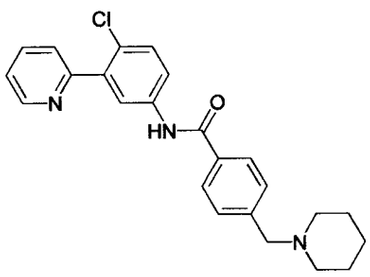
Se disolvió 4-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida (85 mg) en DMSO (1 mL) y se agitó durante 1 h con tiomorfolina. La mezcla de reacción fue concentrada, y el residuo crudo fue purificado por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(tiomorfolinometil) benzamida. MS (Q1) 424.0 $(M)^+$.

Ejemplo 27 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(morfolinometil) benzamida



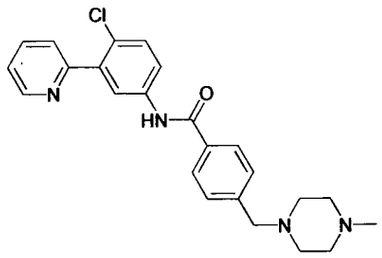
Se disolvió 4-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida (85 mg) en DMSO (1 mL) y se agitó durante 1 h con morfolina. La mezcla de reacción fue concentrada, y el residuo crudo fue purificado por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(morfolinometil) benzamida. MS (Q1) 408.4 $(M)^+$.

Ejemplo 28 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((piperidin-1-il)metil) benzamida



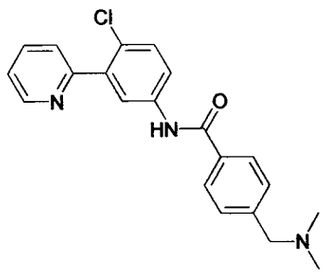
Se disolvió 4-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida (85 mg) en DMSO (1 mL) y se agitó durante 1 h con piperdina. La mezcla de reacción fue concentrada, y el residuo crudo fue purificado por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((piperidin-1-il)metil) benzamida. MS (Q1) 406.4 $(M)^+$.

Ejemplo 29 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((4-metilpiperazin-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 durante 1 h con metilpiperazina. La mezcla de reacción fue concentrada, y el residuo crudo fue purificado por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((4-metilpiperazin-1-il)metil) benzamida. MS (Q1) 421.3 $(M)^+$.

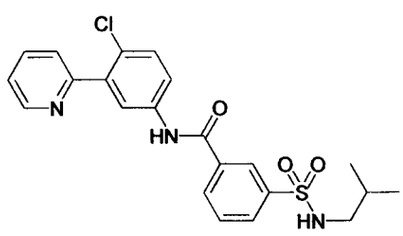
Ejemplo 30 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((dimetilamino)metil) benzamida



El procedimiento G fue utilizado para acoplar ácido BOC-4-(aminometil) benzoico (48 mg) con 4-cloro-3-(piridin-2-il)anilina (35 mg). La mezcla de reacción cruda fue tratada con TFA (1 mL) conteniendo vestigios de agua por espacio de 1 hora. La mezcla de reacción fue concentrada para producir 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 □L), paraformaldehido (48 mg), y sodio triacetoxiborohidruro (125 mg) por espacio de 16 h. La mezcla de reacción fue concentrada, y el residuo crudo fue disuelto en acetato de etilo y lavada con 1 N hidróxido de sodio, secado ($MgSO_4$) y concentrado. El producto crudo fue purificado por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((dimetilamino)metil) benzamida. MS (Q1) 365.0 $(M)^+$.

Ejemplo 31 *N*-(4-cloro-3-(piridin-2-il)fenil)-3-[(2-metilpropilo)aminosulfonil]-benzamida

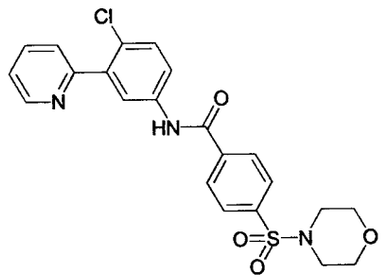


000381

El procedimiento H fue ejecutado para acoplar ácido 3-(clorosulfonil) benzoico con *sec*-butil amina para producir ácido 3-(sec-butilsulfamoil) benzoico que fue purificado por HPLC de fase inversa.

El procedimiento G fue utilizado para acoplar ácido 3-(sec-butilsulfamoil) benzoico con 4-cloro-3-(piridin-2-il)anilina (28 mg) para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-3-[(2-metilpropilo)aminosulfonil]-benzamida. MS (Q1) 444.0 $(M)^+$.

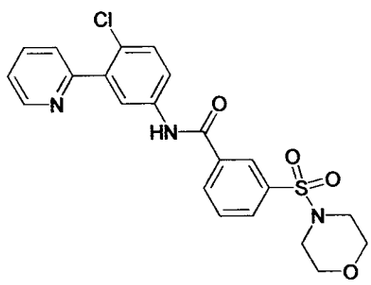
Ejemplo 32 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-morfolinilsulfonil)-benzamida



El procedimiento H fue ejecutado para acoplar ácido 4-(clorosulfonil) benzoico con morfolina para producir ácido 4-(morfolinosulfamoil) benzoico que fue purificado por HPLC de fase inversa.

El procedimiento G fue utilizado para acoplar ácido 4-(morfolinosulfamoil) benzoico con 4-cloro-3-(piridin-2-il)anilina (34 mg) para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-morfolinilsulfonil)-benzamida. MS (Q1) 458.1 $(M)^+$.

Ejemplo 33 *N*-(4-cloro-3-(piridin-2-il)fenil)-3-(4-morfolinilsulfonil)-benzamida

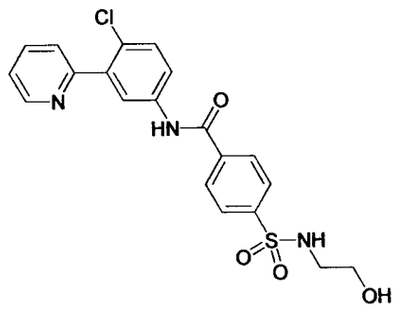


El procedimiento H fue ejecutado para acoplar ácido 3-(clorosulfonil) benzoico con morfolina para producir ácido 3-(morfolinosulfamoil) benzoico que fue purificado por HPLC de fase inversa.

000382

El procedimiento G fue utilizado para acoplar ácido 3-(morfolinosulfamoil) benzoico con 4-cloro-3-(piridin-2-il)anilina (25 mg) para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-3-(4-morfolinilsulfonil)-benzamida. MS (Q1) 458.1 $(M)^+$.

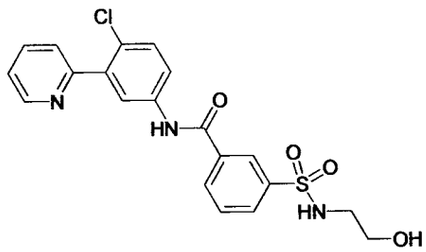
Ejemplo 34 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-[(2-hidroxietil)amino]sulfonil]-benzamida



El procedimiento H fue ejecutado para acoplar ácido 4-(clorosulfonil) benzoico con etanolamina para producir ácido 4-(2-hidroxietilsulfamoil) benzoico que fue purificado por HPLC de fase inversa.

El procedimiento G fue utilizado para acoplar ácido 4-(2-hidroxietilsulfamoil) benzoico con 4-cloro-3-(piridin-2-il)anilina (42 mg) para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-[(2-hidroxietil)amino]sulfonil]-benzamida. MS (Q1) 431.9 $(M)^+$.

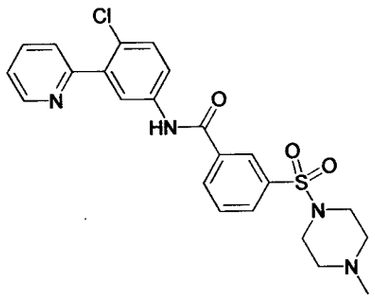
Ejemplo 35 *N*-(4-cloro-3-(piridin-2-il)fenil)-3-[(2-hidroxietil)amino]sulfonil]-benzamida



El procedimiento H fue ejecutado para acoplar ácido 3-(clorosulfonil) benzoico con etanolamina para producir ácido 3-(2-hidroxietilsulfamoil) benzoico que fue purificado por HPLC de fase inversa.

El procedimiento G fue utilizado para acoplar ácido 3-(2-hidroxietilsulfamoil) benzoico con 4-cloro-3-(piridin-2-il)anilina (42 mg) para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-3-[(2-hidroxietil)amino]sulfonil]-benzamida. MS (Q1) 432.0 $(M)^+$.

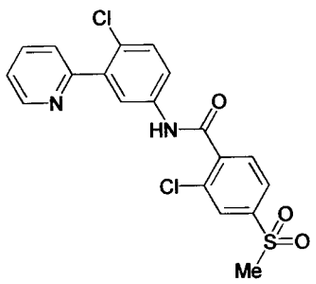
Ejemplo 36 *N*-(4-cloro-3-(piridin-2-il)fenil)-3-(4-morfolinilsulfonil)-benzamida



El procedimiento H fue ejecutado para acoplar ácido 3-(clorosulfonil) benzoico con piperazina para producir ácido 3-(N-metilpiperazinosulfamoil) benzoico que fue purificado por HPLC de fase inversa.

El procedimiento G fue utilizado para acoplar ácido 3-(N-metilpiperazinosulfamoil) benzoico con 4-cloro-3-(piridin-2-il)anilina (50 mg) para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-3-(4-morfolinilsulfonil)-benzamida. MS (Q1) 471.0 $(M)^+$.

Ejemplo 37 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonil) benzamida

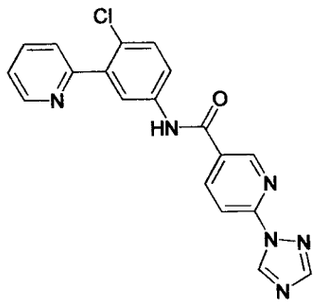


El procedimiento G fue utilizado para acoplar 4-cloro-3-(piridin-2-il)anilina (50 mg) y ácido 2-cloro-4-metilsulfonilbenzoico para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonil) benzamida. MS (Q1) 421.0 $(M)^+$. El producto luego fue disuelto en 1 N HCl solution a continuación de lo cual se procedió a un freebasing con 0.5 N solución de NaOH (pH to 11). El precipitado resultante fue filtrado y secado en vacío.

El procedimiento D también puede ser usado para acoplar 4-cloro-3-(piridin-2-il)anilina y 2-cloro-4-(metilsulfonil)benzoil cloruro para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonil) benzamida que es colectado por filtración por succión y la sal de HCl es lavada con Et_2O (o alternativamente con MTBE). Este material es sometido a un freebasing usando EtOAc/aq $NaHCO_3$ y los orgánicos son secados y concentrados. Este materiales cristalizado a partir de acetona:EtOAc (80:20, approx 10mL/g) finalmente es recristalizado a partir de una pasta caliente de iPrOAc. También puede disolverse la sal de HCl de 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonil) benzamida en agua

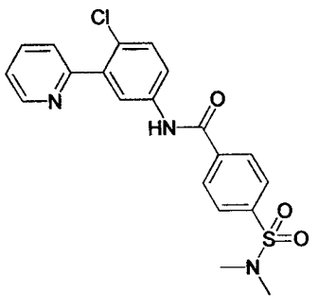
destilada a continuación de lo cual se procedió a un freebasing con 0.5 N solución de NaOH (pH to 11) y se filtró y secó al vacío el precipitado.

Ejemplo 38 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(1*H*-1,2,4-triazol-1-il)piridina-3-carboxamida



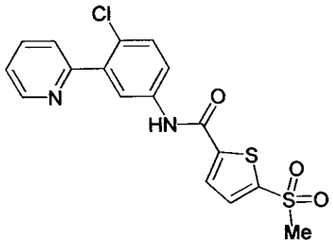
El procedimiento G fue utilizado para acoplar 4-cloro-3-(piridin-2-il)anilina (40 mg) y ácido 6-(1*H*-1,2,4-triazol-1-il)piridina-3-carboxílico para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(1*H*-1,2,4-triazol-1-il)piridina-3-carboxamida. MS (Q1) 377.0 $(M)^+$.

Ejemplo 39 N-(4-cloro-3-(piridin-2-il)fenil)-4-[(dimetilamino)sulfonil]-benzamida



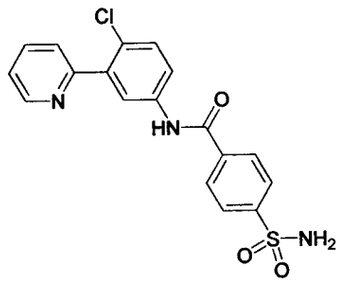
El procedimiento G fue utilizado para acoplar 4-cloro-3-(piridin-2-il)anilina (50 mg) y ácido 4-[(dimetilamino)sulfonil]benzoico para producir N-(4-cloro-3-(piridin-2-il)fenil)-4-[(dimetilamino)sulfonil]-benzamida. MS (Q1) 416.0 $(M)^+$.

Ejemplo 40 *N*-(4-cloro-3-(piridin-2-il)fenil)-5-(metilsulfonil)tiofeno-2-carboxamida



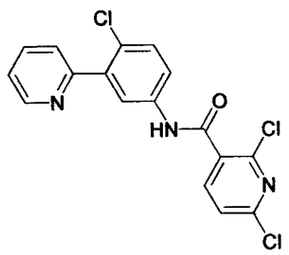
El procedimiento G fue utilizado para acoplar 4-cloro-3-(piridin-2-il)anilina (40 mg) y ácido 5-(metilsulfonil)tiofeno-2-carboxílico para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-5-(metilsulfonil)tiofeno-2-carboxamida. MS (Q1) 393.0 $(M)^+$.

Ejemplo 41 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(aminosulfonil)-benzamida



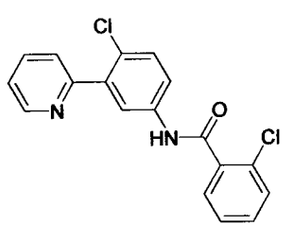
El procedimiento G fue utilizado para acoplar 4-cloro-3-(piridin-2-il)anilina (30 mg) y 4-carboxibencenosulfonamida para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(aminosulfonil)-benzamida. MS (Q1) 388.0 $(M)^+$.

Ejemplo 42 2,6-dicloro-*N*-(4-cloro-3-(piridin-2-il)fenil)piridina-3-carboxamida



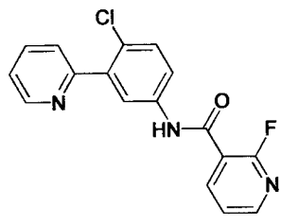
El procedimiento G fue utilizado para acoplar 4-cloro-3-(piridin-2-il)anilina (50 mg) y ácido 2,6-dicloronicotínico para producir 2,6-dicloro-*N*-(4-cloro-3-(piridin-2-il)fenil)piridina-3-carboxamida. MS (Q1) 378.1 $(M)^+$.

Ejemplo 43 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida



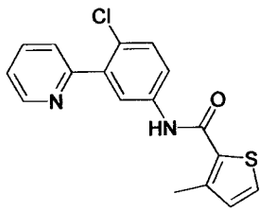
El procedimiento G fue utilizado para acoplar 4-cloro-3-(piridin-2-il)anilina (50 mg) y ácido 2-clorobenzoico para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida. MS (Q1) 343.1 $(M)^+$.

Ejemplo 44 *N*-(4-cloro-3-(piridin-2-il)fenil)-2-fluoropiridina-3-carboxamida



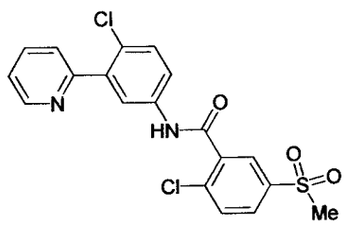
El procedimiento G fue utilizado para acoplar 4-cloro-3-(piridin-2-il)anilina (50 mg) y ácido 2-fluoronicotínico para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-2-fluoropiridina-3-carboxamida. MS (Q1) 328.1 $(M)^+$.

Ejemplo 45 *N*-(4-cloro-3-(piridin-2-il)fenil)-3-metiltiofeno-2-carboxamida



El procedimiento G fue utilizado para acoplar 4-cloro-3-(piridin-2-il)anilina (50 mg) y ácido 3-metil-2-tiofenocarboxílico para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-3-metiltiofeno-2-carboxamida. MS (Q1) 329.0 $(M)^+$.

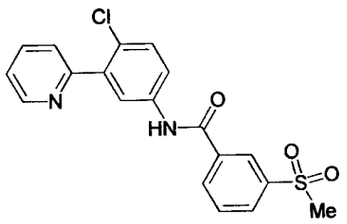
Ejemplo 46 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-5-(metilsulfonil) benzamida



El procedimiento G fue utilizado para acoplar 4-cloro-3-(piridin-2-il)anilina 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 $(M)^+$.

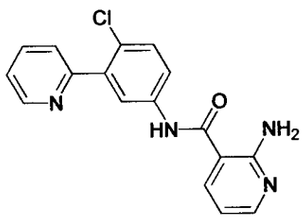
000387

Ejemplo 47 *N*-(4-cloro-3-(piridin-2-il)fenil)-3-(metilsulfonil) benzamida



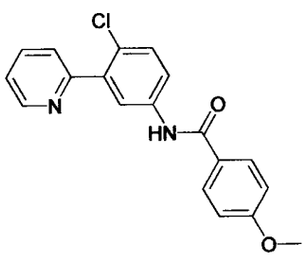
El procedimiento G fue utilizado para acoplar 4-cloro-3-(piridin-2-il)anilina y ácido 3-(metanosulfonil) benzoico para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-3-(metilsulfonil) benzamida. MS (Q1) 387.2 $(M)^+$.

Ejemplo 48 2-amino-*N*-(4-cloro-3-(piridin-2-il)fenil)piridina-3-carboxamida



El procedimiento G fue utilizado para acoplar 4-cloro-3-(piridin-2-il)anilina (50 mg) y ácido 2-aminonicotínico para producir 2-amino-*N*-(4-cloro-3-(piridin-2-il)fenil)piridina-3-carboxamida. MS (Q1) 325.2 $(M)^+$.

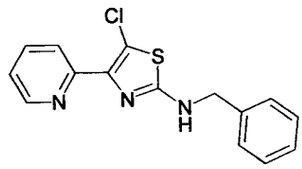
Ejemplo 49 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-metoxibenzamida



El procedimiento G fue utilizado para acoplar 4-cloro-3-(piridin-2-il)anilina y ácido 4-metoxilbenzoico para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-metoxibenzamida. MS (Q1) 341.2 $(M)^+$.

000383

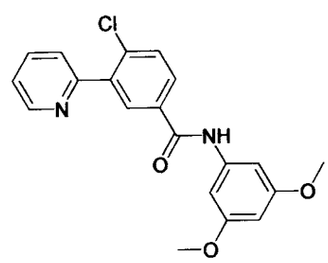
Ejemplo 50 *N*-bencil-5-cloro-4-(piridin-2-il)tiazol-2-amina



Una solución de 2-(Bromoacetil)piridina hidrobromuro (100 mg, 0.36 mmol) en etanol (2 mL) fue tratada con 1-bencil-2-tiourea (90 mg, 0.54 mmol). La solución amarilla resultante fue concentrada, y el residuo crudo fue purificado en HPLC de fase inversa para producir *N*-bencil-4-(piridin-2-il)tiazol-2-amina.

Una solución de *N*-bencil-4-(piridin-2-il)tiazol-2-amina (60 mg, 0.23 mmol) en DMF (2 mL) fue enfriada a 0 °C y tratada con *N*-clorosuccinimida (33 mg, 0.25 mmol), y la mezcla de reacción se dejó calentar a temperatura ambiente. El solvente fue evaporado, y el producto fue purificado en HPLC de fase inversa para producir *N*-bencil-5-cloro-4-(piridin-2-il)tiazol-2-amina. MS (Q1) 302.2 $(M)^+$.

Ejemplo 51 4-cloro-*N*-(3,5-dimetoxifenil)-3-(piridin-2-il) benzamida

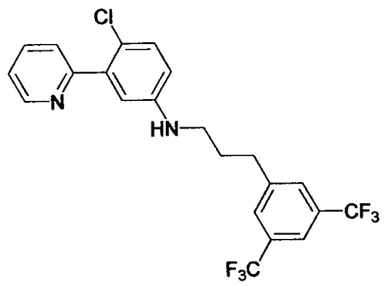


Una solución de ácido 3-bromo-4-clorobenzoico (250 mg, 1.1 mmol) en DMF (2 mL) fue tratada con PyBop (550 mg, 1.1 mmol) y DIPEA (370 uL, 2.1 mmol). Luego se agitó la mezcla de reacción por espacio de 5 minutos. Se agregó 3,5-dimetoxi analina (105 mg, 0.69 mmol) y la reacción fue agitada durante 16 h. La mezcla de reacción fue diluida con acetato de etilo y lavada con 0.1 N HCl, 0.1 N hidróxido de sodio y solución salina, sucesivamente. La capa orgánica fue secada ($MgSO_4$) y concentrada, y se usó 3-bromo-4-cloro-*N*-(3,5-dimetoxifenil) benzamida crudo sin purificación adicional.

Se disolvió 3-bromo-4-cloro-*N*-(3,5-dimetoxifenil) benzamida en 0.5 M 2-piridilzincbromuro (2.5 mL) y se trató con $Pd(PPh_3)_4$ (20 mg, 0.02 mmol). La mezcla de reacción fue calentada a 155° C en un tubo sellado por espacio de 20 minutos en un reactor a microondas. La solución resultante fue diluida con Etil acetato y lavada con 0.1 N hidróxido de sodio y luego solución salina. La capa orgánica fue secada ($MgSO_4$) y

concentrada, y el residuo crudo fue parcialmente purificado por cromatografía en gel de sílice. Se obtuvo 4-cloro-*N*-(3,5-dimetoxifenil)-3-(piridin-2-il) benzamida pura mediante una segunda purificación en HPLC de fase inversa. MS (Q1) 369.1 $(M)^+$.

Ejemplo 52 *N*-(3-(3,5-bis(trifluorometil)fenil)propilo)-4-cloro-3-(piridin-2-il)benzenamina



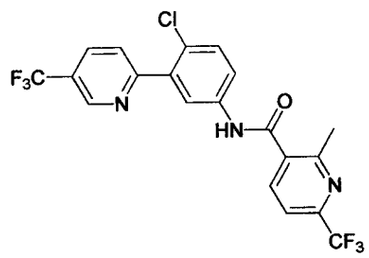
Una solución de ácido 3,5-bis(trifluorometil)hidrocinámico (1.0 g, 3.5 mmol) y TEA (0.46 g, 4.5 mmol) en THF (16 mL) fue enfriada a –40°C (baño de etanol-agua/hielo seco). A esta mezcla se agregó por goteo isobutilo cloroformato (0.56 g, 4.1 mmol) y la agitación continuó durante 1.5 horas mientras la temperatura del baño de enfriamiento se mantuvo entre –40 °C y –20 °C. Se agregó $NaBH_4$ sólido (0.53 g, 14 mmol), luego H_2O (1.3 mL). La mezcla turbia fue agitada durante la noche mientras se calentó a temperatura ambiente. Luego de concentrar en vacío, el residuo fue particionado entre acetato de etilo y agua. La capa acuosa fue acidificada a pH 1 con 37% HCl y extraída con acetato de etilo. Las capas orgánicas combinadas fueron lavadas sucesivamente con $NaHCO_3$ saturado, y solución salina, luego secada ($MgSO_4$) y concentrada. El aceite resultante fue purificado por cromatografía instantánea en gel de sílice (6:4 etilo éter-hexano) para producir 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 fue agitada a 0 °C por espacio de 10 minutos, luego diluida con pentano (30 mL) y $NaHCO_3$ saturado (30 mL). La capa acuosa fue separada y lavada con etil éter, y las capas orgánicas combinadas fueron secadas ($MgSO_4$) y concentradas. El residuo fue purificado por cromatografía instantánea en gel de sílice (99:1 etilo éter-hexano) para producir 0.8 g, (74%) del 3-[3',5'-bis(trifluorometil)fenil]-1-bromopropano.

Se agitaron 4-cloro-3-(2'-piridil)anilina (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 fue acidificada con 1N HCl (aq.) y extraída con acetato de etilo. Las capas orgánicas combinadas fueron lavadas con solución salina,

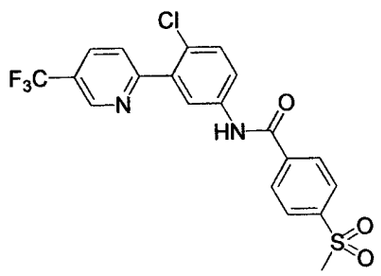
secadas ($MgSO_4$) y concentradas. El crudo fue purificado por HPLC preparatoria para producir *N*-(3-(3,5-bis(trifluorometil)fenil)propilo)-4-cloro-3-(piridin-2-il)benzenamina.

Ejemplo 53 *N*-(4-cloro-3-(5-(trifluorometil)piridin-2-il)fenil)-2-metil-6-(trifluorometil) nicotinamida



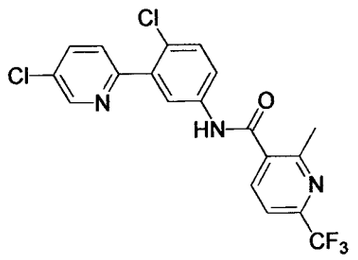
Se usó *N*-(4-cloro-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-2-metil-6-(trifluorometil) nicotinamida (~ 0.5 mmol) en el procedimiento A con 5-trifluorometil-2-bromopiridina (113 mg, 0.5 mmol). Se purificó por cromatografía en gel de sílice (5-50% acetato de etilo/hexanos) para producir *N*-(4-cloro-3-(5-(trifluorometil)piridin-2-il)fenil)-2-metil-6-(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 por cromatografía en gel de sílice (0-10% acetona/diclorometano) para producir *N*-(4-cloro-3-(5-(trifluorometil)piridin-2-il)fenil)-4-(metilsulfonil) benzamida como un sólido blanco: MS (Q1) 455 $(M)^+$.

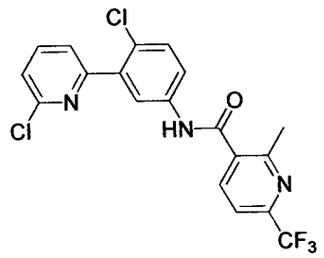
Ejemplo 55 *N*-(4-cloro-3-(5-cloropiridin-2-il)fenil)-2-metil-6-(trifluorometil) nicotinamida



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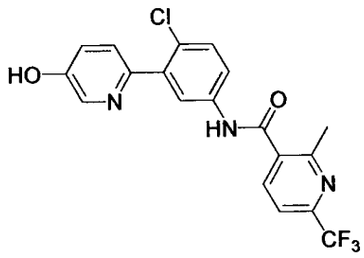
Se usó 5-cloropiridin-2-il trifluoro metanosulfonato (4.12 mmol) en el procedimiento I con trimetil estaño cloruro para producir 5-cloro-2-(trimetilestanil) piridina. El material crudo (~4 mmol) fue usado en el procedimiento K con *N*-(4-cloro-3-yodofenil)-2-metil-6-(trifluorometil) nicotinamida (2 mmol). Se purificó por cromatografía en gel de sílice (0-50% acetato de etilo/hexano) para producir *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 6-cloropiridin-2-il trifluorometano sulfonato (4.12 mmol) en el procedimiento I con trimetiltin cloruro para producir 2-cloro-6-(trimetilestanil)piridina. El material crudo (~4 mmol) fue usado en el procedimiento K con *N*-(4-cloro-3-yodofenil)-2-metil-6-(trifluorometil) nicotinamida (2 mmol). Se purificó por cromatografía en gel de sílice (5-45% acetato de etilo/hexano) para producir *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

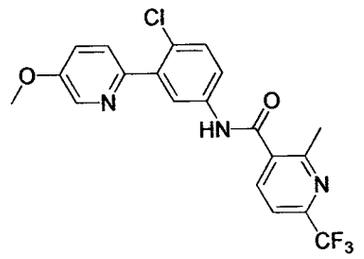


Se usó 3-(triisopropilsililoxi) piridina (2.66 mmol) en el procedimiento J con hexametil diestanato para producir 5-(triisopropilsililoxi)-2-(trimetilestanil)piridina. El material crudo (~0.55 mmol) fue usado en el procedimiento K con *N*-(4-cloro-3-yodofenil)-2-metil-6-(trifluorometil) nicotinamida (0.17 mmol). Se purificó por cromatografía en gel de sílice (0-40% acetato de etilo/hexano) para producir *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) fue tratado con TBAF (2 mL, 1 M en THF) en THF (1 mL) a 23 °C por espacio de treinta

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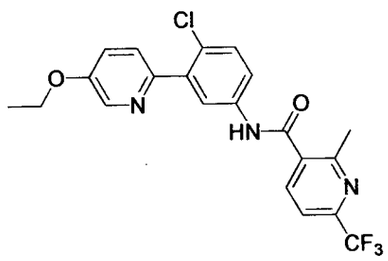
minutos, concentrado, rediluido en acetato de etilo, lavado con solución salina, secado ($MgSO_4$), y concentrado. El sólido crudo fue purificado por cromatografía en gel de sílice (0-10 % isopropanol/diclorometano) para producir *N*-(4-cloro-3-(5-hidroxipiridin-2-il)fenil)-2-metil-6-(trifluorometil) 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



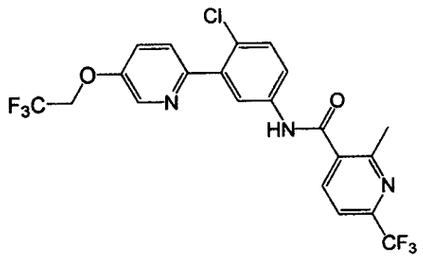
N-(4-cloro-3-(5-hidroxipiridin-2-il)fenil)-2-metil-6-(trifluorometil) nicotinamida (0.12 mmol) fue usado en el procedimiento L con exceso de yodometano. Se purificó por cromatografía en gel de sílice (0-100% acetato de etilo/hexano) para producir *N*-(4-cloro-3-(5-metoxipiridin-2-il)fenil)-2-metil-6-(trifluorometil) 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



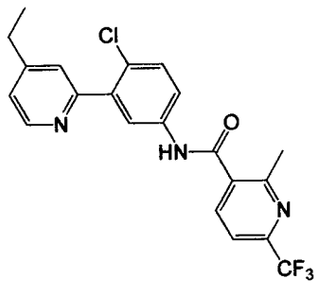
N-(4-cloro-3-(5-hidroxipiridin-2-il)fenil)-2-metil-6-(trifluorometil) nicotinamida (0.05 mmol) fue usado en el procedimiento L con exceso de yodoetano. Se purificó por cromatografía en gel de sílice (0-100% acetato de etilo/hexano) para producir *N*-(4-cloro-3-(5-etoxipiridin-2-il)fenil)-2-metil-6-(trifluorometil) 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



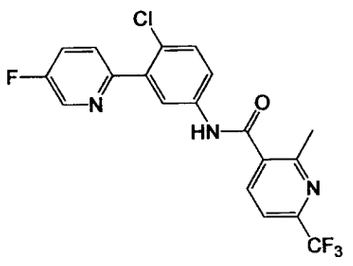
N-(4-cloro-3-(5-hidroxipiridin-2-il)fenil)-2-metil-6-(trifluorometil) nicotinamida (0.12 mmol) fue usado en el procedimiento L con exceso de trifluoroetilo yoduro. Se purificó por cromatografía en gel de sílice (0-40% acetato de etilo/hexano) para producir *N*-(4-cloro-3-(5-(2,2,2-trifluoroetoxi)piridin-2-il)fenil)-2-metil-6-(trifluorometil) 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



N-(4-cloro-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-2-metil-6-(trifluorometil) nicotinamida (~ 1 mmol) fue usado en el procedimiento A con 4-etil-2-bromopiridina (1 mmol). Se purificó por cromatografía en gel de sílice (0-60% acetato de etilo/hexanos) para producir *N*-(4-cloro-3-(4-etilpiridin-2-il)fenil)-2-metil-6-(trifluorometil) nicotinamida como un sólido tostado: MS (Q1) 419 $(M)^+$.

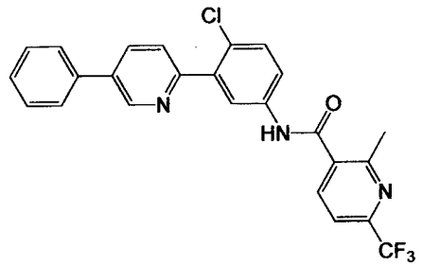
Ejemplo 62 *N*-(4-cloro-3-(5-fluoropiridin-2-il)fenil)-2-metil-6-(trifluorometil) nicotinamida



N-(4-cloro-3-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)-2-metil-6-(trifluorometil) nicotinamida (~ 1 mmol) fue usado en el procedimiento A con 5-fluoro-2-bromopiridina (1 mmol). Se purificó por cromatografía en gel de sílice (5-45% acetato de etilo/hexanos) para producir *N*-(4-cloro-3-(5-fluoropiridin-2-il)fenil)-2-metil-6-(trifluorometil) nicotinamida como un sólido tostado: MS (Q1) 409 $(M)^+$.

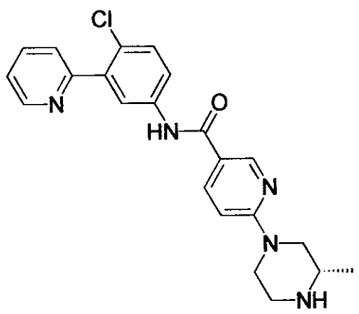
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Ejemplo 63 *N*-(4-cloro-3-(5-fenilpiridin-2-il)fenil)-2-metil-6-(trifluorometil)-nicotinamida



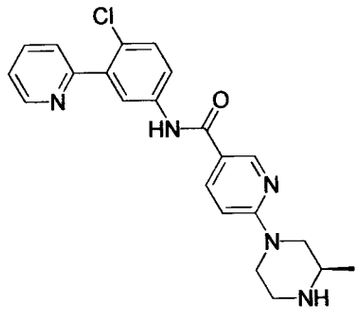
5-fenilpiridin-2-ilo trifluorometano sulfonato (1.5 mmol) fue usado en el procedimiento J con trimetil estaño cloruro para producir 5-fenil-2-(trimetilestanil) piridina. El material crudo (~1.25 mmol) fue usado en el procedimiento K con *N*-(4-cloro-3-yodofenil)-2-metil-6-(trifluorometil) nicotinamida (1 mmol). Se purificó por cromatografía en gel de sílice (1% acetona/cloruro de metileno) para producir *N*-(4-cloro-3-(5-fenilpiridin-2-il)fenil)-2-metil-6-(trifluorometil) nicotinamida como un sólido 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



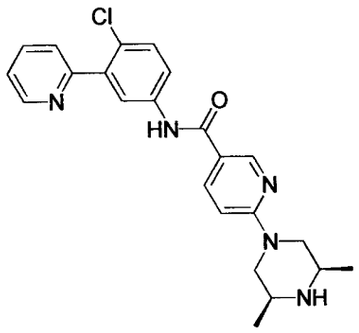
El procedimiento F fue ejecutado usando N-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (50 mg) y 75 mg de (S)-2-metilpiperazina en 0.75 mL de butanol a 160°C por espacio de 60 minutos. La purificación por HPLC de fase inversa produjo (*S*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-6-(3-metilpiperazin-1-il) nicotinamida. MS (Q1) 408 $(M)^+$.

Ejemplo 65 (*R*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-6-(3-metilpiperazin-1-il) nicotinamida



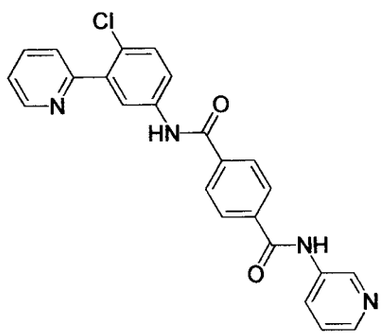
El procedimiento F fue ejecutado usando N-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (50 mg) y 75 mg de (R)-2-metilpiperazina en 0.75 mL de butanol a 160°C por espacio de 60 minutos. La purificación por HPLC de fase inversa produjo (*R*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-6-(3-metilpiperazin-1-il) 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



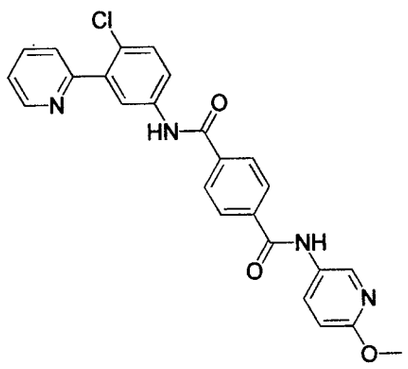
El procedimiento F fue ejecutado usando N-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (75 mg) y 114 mg de 2,6-dimetilpiperazina en 1 mL de butanol a 160°C por espacio de 60 minutos. La purificación por HPLC de fase inversa produjo *N*-(4-cloro-3-(piridin-2-il)fenil)-6-((3*S*,5*R*)-3,5-dimetilpiperazin-1-il) nicotinamida. MS (Q1) 422.1 $(M)^+$.

Ejemplo 67 N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(piridin-3-il) tereftalamida



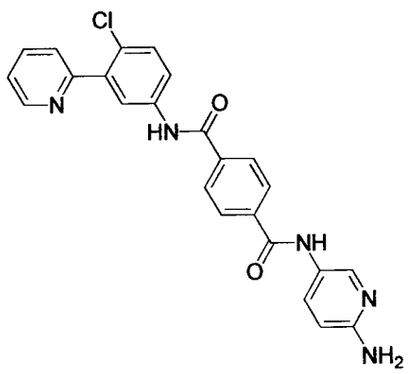
320 mg de 4-cloro-3-(piridin-2-il)anilina fueron acoplados a 400 mg de ácido 4-(metoxicarbonil) benzoico mediante el procedimiento G para producir metil 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoato. Luego se hidrolizó 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoato mediante el Procedimiento M para producir 550 mg de ácido 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico. Se acoplaron 50 mg de ácido 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 3-aminopiridina mediante el procedimiento G. La capa orgánica fue evaporada hasta secarse y purificada en HPLC de fase inversa para producir 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 acoplaron 50 mg de ácido 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 2-metoxi-5-aminopiridina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(6-metoxipiridin-3-il) tereftalamida. MS (Q1) 459 $(M)^+$.

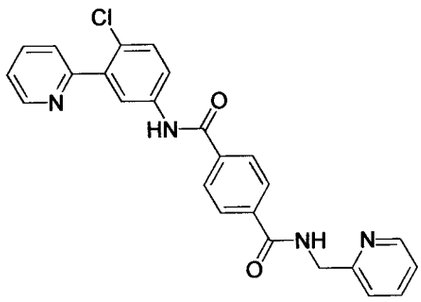
Ejemplo 69 N^1-(6-aminopiridin-3-il)-N^4-(4-cloro-3-(piridin-2-il)fenil) tereftalamida



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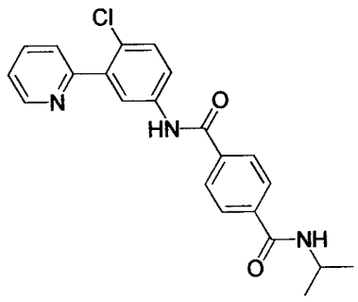
Se acoplaron 50 mg de ácido 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 2,5-diaminopiridina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir N^1-(6-aminopiridin-3-il)-N^4-(4-cloro-3-(piridin-2-il)fenil) tereftalamida. MS (Q1) 444 $(M)^+$.

Ejemplo 70 N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(piridin-2-ilmetil) tereftalamida



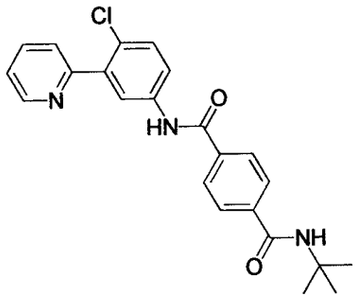
Se acoplaron 50 mg de ácido 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 2-(aminometil)piridina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(piridin-2-ilmetil) tereftalamida. MS (Q1) 443 $(M)^+$.

Ejemplo 71 N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-isopropiltereftalamida



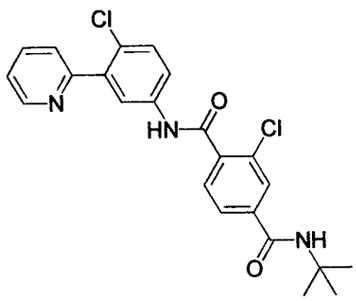
Se acoplaron 50 mg de ácido 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a isopropilamina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-isopropiltereftalamida. MS (Q1) 394 $(M)^+$.

Ejemplo 72 N^1-*tert*-butil-N^4-(4-cloro-3-(piridin-2-il)fenil) tereftalamida



Se acoplaron 50 mg de ácido 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a *tert*-butilamina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir N^1-*tert*-butil-N^4-(4-cloro-3-(piridin-2-il)fenil) tereftalamida. MS (Q1) 408 $(M)^+$.

Ejemplo 73 N^4-*tert*-butil-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil) tereftalamida

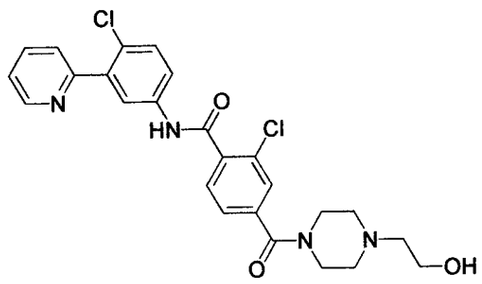


Se sometieron a reflujo 67 mL de 2-cloro-1,4-dimetilbenceno y 356 g de permanganato de potasio en 1.5 L de H_2O durante varias horas y se monitoreó la desaparición del material iniciador por TLC. El permanganato de potasio fue filtrado y la mezcla de reacción fue acidificada y filtrada para producir ácido 2-cloroterefálico. Se trataron 46.8 g de ácido 2-cloroterefálico con una solución gaseosa de HCl saturado en MeOH durante la noche a temperatura ambiente. La mezcla de reacción fue concentrada, sometida a un tratamiento básico y secada para producir el dimetil 2-cloroterefalato. Se enfriaron 20 g de dimetil 2-cloroterefalato a 0°C en DCM y 87 mL de a 1M en solución DCM de BBr_3 fueron agregados por goteo durante varias horas. La mezcla de reacción fue subsecuentemente calentada a temperatura ambiente y agitada hasta completar. Luego del tratamiento básico, se purificó ácido 2-cloro-4-(metoxicarbonil) benzoico or ISCO Combi-Flash. Se acoplaron 959 mg de ácido 2-cloro-4-(metoxicarbonil) benzoico a 750 mg de 4-cloro-3-(piridin-2-il)anilina mediante el procedimiento G. Se hidrolizaron 1 g de metil 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoato mediante el procedimiento M para producir ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico. Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a *tert*-

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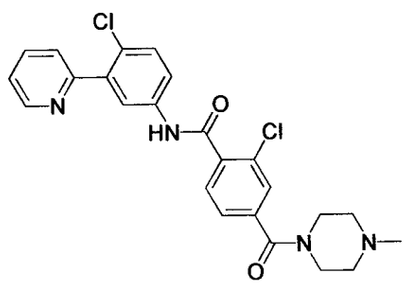
butilamina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir N^4-*tert*-butil-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil) tereftalamida. MS (Q1) 443.2 $(M)^+$.

Ejemplo 74 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-(2-hidroxietil)piperazina-1-carbonil) benzamida



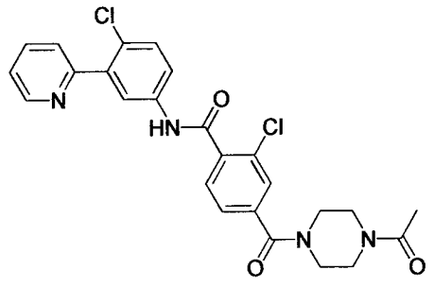
Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a N-(2-hidroxietil)piperazina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-(2-hidroxietil)piperazina-1-carbonil) benzamida. MS (Q1) 499 $(M)^+$.

Ejemplo 75 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-metilpiperazina-1-carbonil) benzamida



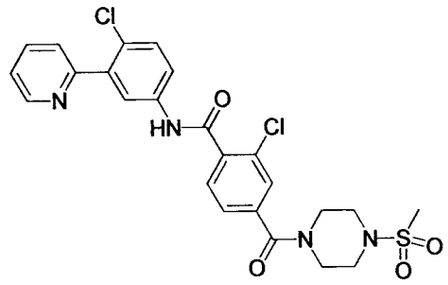
Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 1-metilpiperazina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-metilpiperazina-1-carbonil) benzamida. MS (Q1) 469 $(M)^+$.

Ejemplo 76 4-(4-acetilpiperazina-1-carbonil)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida



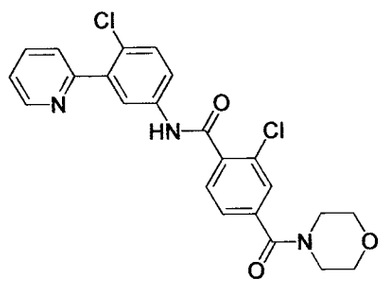
Se acoplaron Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 1-acetilpiperazina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 4-(4-acetilpiperazina-1-carbonil)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida. MS (Q1) 497 $(M)^+$.

Ejemplo 77 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-(metilsulfonil)piperazina-1-carbonil) benzamida



Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico en 1-sulfonilpiperazina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 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-(morfolina-4-carbonil) benzamida

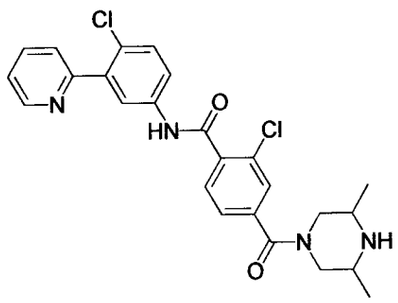


Se acoplaron Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a morfolina mediante el procedimiento G. El producto fue purificado en HPLC

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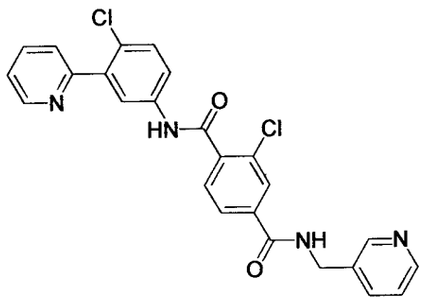
de fase inversa para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(morfolina-4-carbonil) benzamida. MS (Q1) 456 $(M)^+$.

Ejemplo 79 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(3,5-dimetilpiperazina-1-carbonil) benzamida



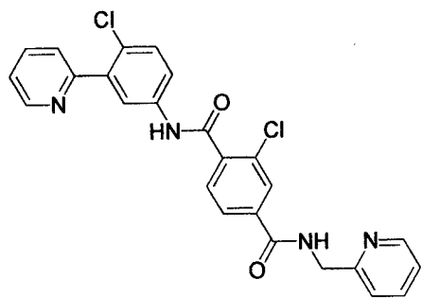
Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 2,6-dimetilpiperazina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(3,5-dimetilpiperazina-1-carbonil) benzamida. MS (Q1) 483 $(M)^+$.

Ejemplo 80 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(piridin-3-ilmetil) tereftalamida



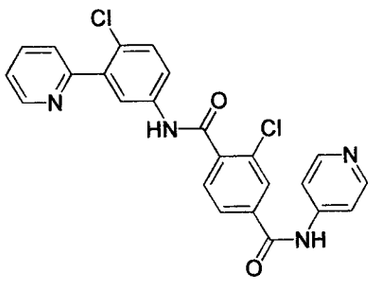
Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 3-(aminometil) piridina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(piridin-3-ilmetil) tereftalamida. MS (Q1) 477 $(M)^+$.

Ejemplo 81 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(piridin-2-ilmetil) tereftalamida



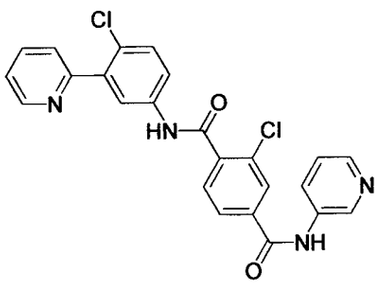
Se acoplaronb Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 2-(aminometil) piridina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(piridin-2-ilmetil) tereftalamida. MS (Q1) 477 $(M)^+$.

Ejemplo 82 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(piridin-4-il) tereftalamida



Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 4-aminopiridina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(piridin-4-il) tereftalamida. MS (Q1) 463 $(M)^+$.

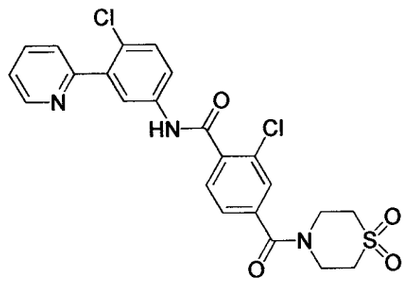
Ejemplo 83 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(piridin-3-il) tereftalamida



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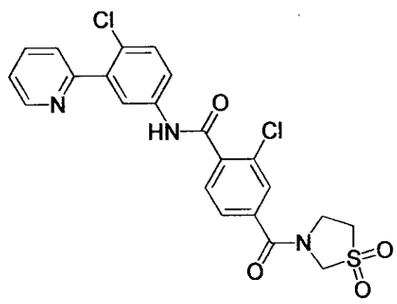
Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 3-aminopiridina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(piridin-3-il) tereftalamida. MS (Q1) 463 $(M)^+$.

Ejemplo 84 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(tiomorfolina-4-carbonil) benzamida (tiomorfolina S oxidada)



Se acoplaron 100 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a tiomorfolina mediante el procedimiento G. Se sometió a una reacción 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(tiomorfolina-4-carbonil) benzamida cruda mediante el procedimiento R para oxidar tiomorfolina azufre y se purificó mediante HPLC de fase inversa para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(tiomorfolina-4-carbonil) benzamida (en el cual tiomorfollina azufre se oxida en SO_2). MS (Q1) 504 $(M)^+$.

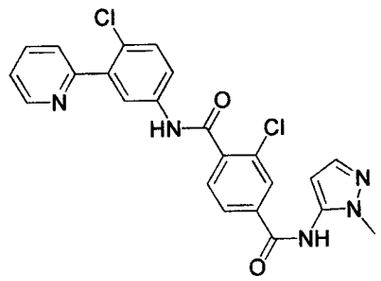
Ejemplo 85 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(tiazolidina-3-carbonil) benzamida (tiazolidina S oxidada)



Se acoplaron 100 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) a tiazolidina mediante el procedimiento G. Se sometió a una reacción 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(tiazolidina-3-carbonil) benzamida cruda mediante el procedimiento R y se purificó por HPLC de fase inversa para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-

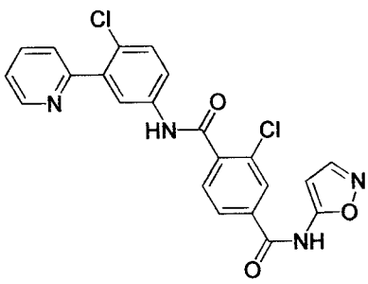
(tiazolidina-3-carbonil) benzamida (en el cual se oxida tiazolidina azufre en SO_2). MS (Q1) 490 $(M)^+$.

Ejemplo 86 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(1-metil-1*H*-pirazol-5-il) tereftalamida



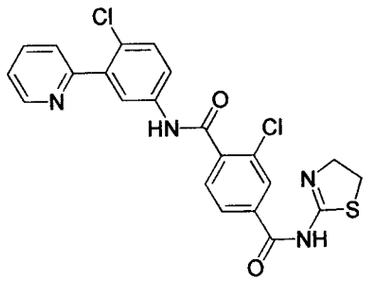
Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 5-amino-1-metilpirazol mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(1-metil-1*H*-pirazol-5-il) tereftalamida. MS (Q1) 466 $(M)^+$.

Ejemplo 87 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(isoxazol-5-il) tereftalamida



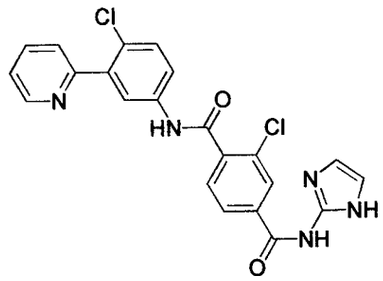
Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 5-aminoisoxazol mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(isoxazol-5-il) tereftalamida. MS (Q1) 463 $(M)^+$.

Ejemplo 88 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(4,5-dihidrotiazol-2-il) tereftalamida



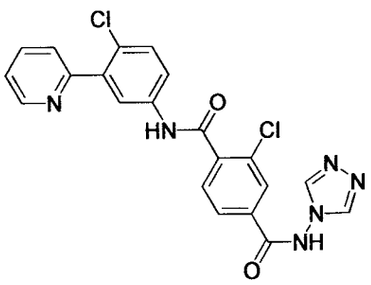
Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 2-amino-4,5-dihidrotiazol mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(4,5-dihidrotiazol-2-il) tereftalamida. MS (Q1) 471 $(M)^+$.

Ejemplo 89 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(1*H*-imidazol-2-il) tereftalamida



Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 2-aminoimidazol mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(1*H*-imidazol-2-il) tereftalamida. MS (Q1) 452 $(M)^+$.

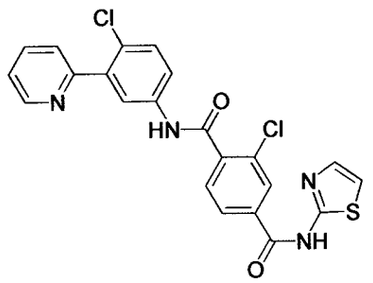
Ejemplo 90 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(4*H*-1,2,4-triazol-4-il) tereftalamida



000406

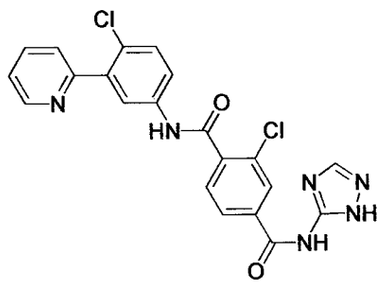
Se acoplaron Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 4-amino-1,2,4-triazol mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(4*H*-1,2,4-triazol-4-il) tereftalamida. MS (Q1) 453 $(M)^+$.

Ejemplo 91 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(tiazol-2-il) tereftalamida



Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 2-aminotiazol mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(tiazol-2-il) tereftalamida. MS (Q1) 469 $(M)^+$.

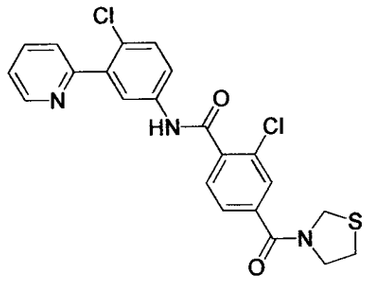
Ejemplo 92 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(1*H*-1,2,4-triazol-5-il) tereftalamida



Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 3-amino-1,2,4-triazol mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 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 $(M)^+$.

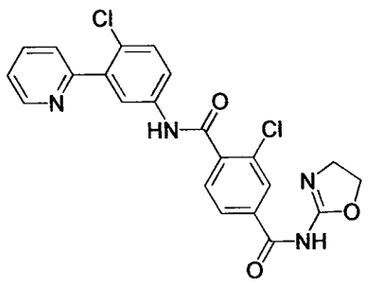
Ejemplo 93 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(tiazolidina-3-carbonil) benzamida

000107



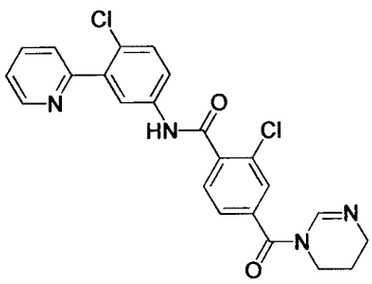
Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a tiazolina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(tiazolidina-3-carbonil) benzamida. MS (Q1) 459 $(M)^+$.

Ejemplo 94 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(4,5-dihidrooxazol-2-il) tereftalamida



Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 2-amino-4,5-dihidrooxazol mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(4,5-dihidrooxazol-2-il) tereftalamida. MS (Q1) 456 $(M)^+$.

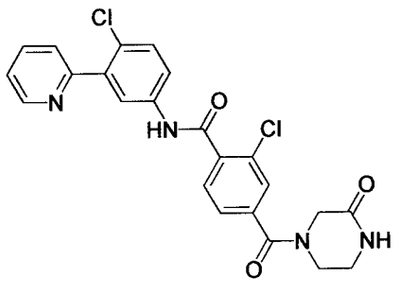
Ejemplo 95 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(1,4,5,6-tetrahidropirimidina-1-carbonil) benzamida



000408

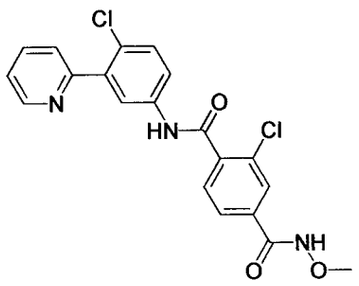
Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 1,4,5,6-tetrahidropirimidina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(1,4,5,6-tetrahidropirimidina-1-carbonil) benzamida. MS (Q1) 454 $(M)^+$.

Ejemplo 96 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(3-oxopiperazina-1-carbonil) benzamida



Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 3-oxopiperazina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(3-oxopiperazina-1-carbonil) benzamida. MS (Q1) 470 $(M)^+$.

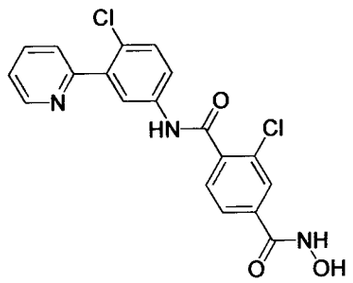
Ejemplo 97 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-metoxitereftalamida



Se acoplaron 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a *N*-metilhidroxilamina clorhidrato mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-metoxitereftalamida. MS (Q1) 417 $(M)^+$.

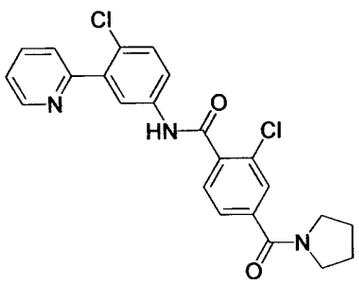
Ejemplo 98 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-hidroxitereftalamida

000109



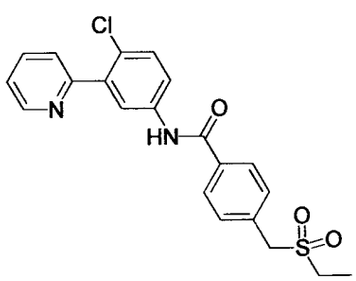
Se acoplaron 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a hidroxilamina clorhidrato mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-hidroxitereftalamida. MS (Q1) 403 $(M)^+$.

Ejemplo 99 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(pirrolidina-1-carbonil) benzamida



Se acoplaron 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a pirolidina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(pirrolidina-1-carbonil) benzamida. MS (Q1) 441 $(M)^+$.

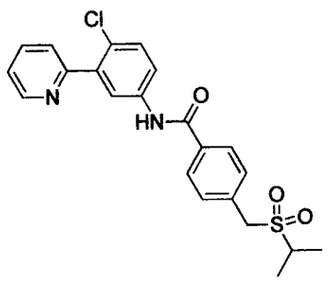
Ejemplo 100 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(etilsulfonilmetil) benzamida



Se redujo etanosulfonil cloruro en etanosulfinato de sodio de acuerdo al procedimiento en J. Med. Chem. 1989, vol. 32, no. 11, p2436. Brevemente, se agregaron 2.5 ml de etanosulfonil cloruro 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. Luego de finalizada la reacción el agua fue evaporada y los sólidos fueron suspendidos en etanol y calentados a 80° C por espacio de 1 h antes del filtrado. El filtrado luego fue evaporado para producir 2.5 gramos del etanosulfinato de sodio. 293 mg del etano sulfinato de sodio fueron combinados con 230 mg de metil (4-bromoetil) benzoato en 2 mL de DMF y calentados a 120 C por espacio de 5 minutos en un reactor a microondas. La reacción luego fue extraída con acetato de etilo y solución salina para producir 250 mg de metil 4-(etilsulfonilmetil) benzoato luego de evaporar la capa orgánica. Se hidrolizaron 200 mg de metil 4-(etilsulfonilmetil) benzoato mediante el procedimiento M para producir 119 mg de ácido 4-(etilsulfonilmetil) benzoico.

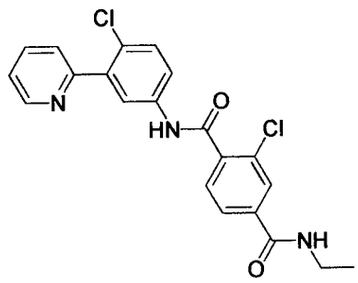
Se acoplaron 50 mg de ácido 4-(etilsulfonilmetil) benzoico a 67mg de 4-cloro-3-(piridin-2-il)anilina mediante el procedimiento G. Este producto fue recristalizado a partir de metanol para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(etilsulfonilmetil) benzamida. MS (Q1) 415 $(M)^+$.

Ejemplo 101 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(isopropilsulfonilmetil) benzamida



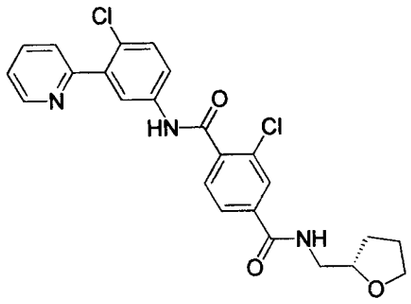
Se preparó *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(isopropilsulfonilmetil) benzamida usando el mismo procedimiento que para *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(etilsulfonilmetil) benzamida con la diferencia que se sustituyó propano-2-sulfonil cloruro por etanosulfonil cloruro. El producto fue purificado en HPLC de fase inversa para producir *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



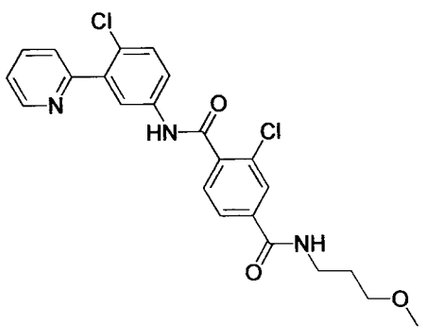
Se acoplaron 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a etilamina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-etiltereftalamida. MS (Q1) 415 $(M)^+$.

Ejemplo 103 (*S*)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-((tetrahidrofuran-2-il)metil) tereftalamida



Se acoplaron 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a (S)-(+)-tetrahidrofurilamina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir (*S*)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-((tetrahidrofuran-2-il)metil) tereftalamida. MS (Q1) 471 $(M)^+$.

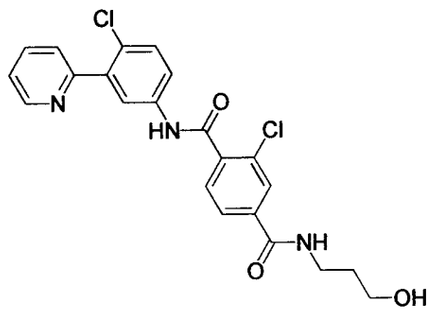
Ejemplo 104 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(3-metoxipropilo) tereftalamida



000412

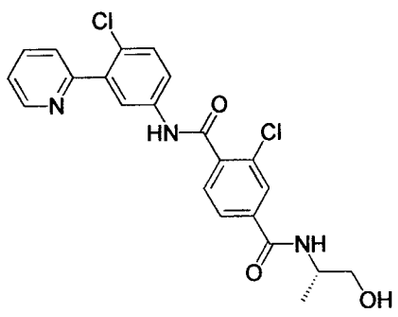
Se acoplaron 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 3-metoxipropilamina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(3-metoxipropilo) tereftalamida. MS (Q1) 459 $(M)^+$.

Ejemplo 105 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(3-hidroxipropilo) tereftalamida



Se acoplaron 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 3-hidroxipropilamina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(3-hidroxipropilo) tereftalamida. MS (Q1) 445 $(M)^+$.

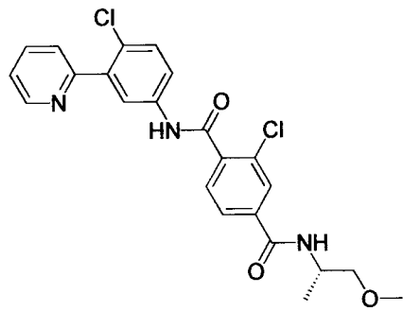
Ejemplo 106 (*S*)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(1-hidroxipropan-2-il) tereftalamida



Se acoplaron 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a (S)-2-amino-1-propanol mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir (*S*)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(1-hidroxipropan-2-il) tereftalamida. MS (Q1) 445 $(M)^+$.

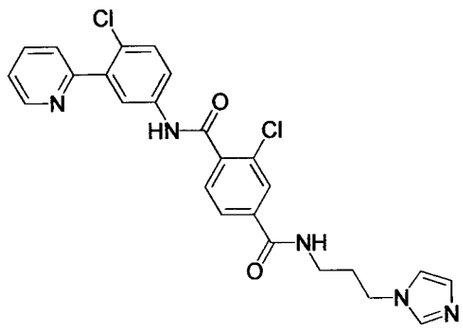
000113

Ejemplo 107 (*S*)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(1-metoxipropan-2-il) tereftalamida



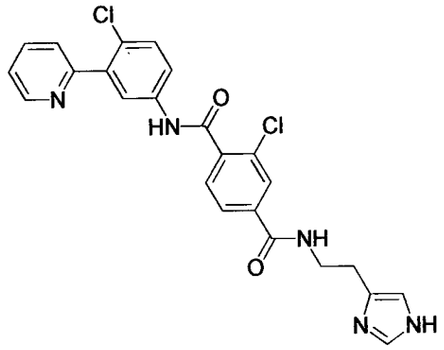
Se acoplaron 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a (S)-1-metoxi-2-propilamina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir (*S*)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(1-metoxipropan-2-il) tereftalamida. MS (Q1) 459 $(M)^+$.

Ejemplo 108 N^4-(3-(1*H*-imidazol-1-il)propilo)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil) tereftalamida



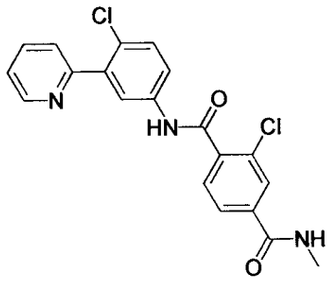
Se acoplaron 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 1-(3-aminopropilo)imidazol mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir N^4-(3-(1*H*-imidazol-1-il)propilo)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil) tereftalamida. MS (Q1) 495 $(M)^+$.

Ejemplo 109 N^4-(2-(1*H*-imidazol-4-il)etil)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil) tereftalamida



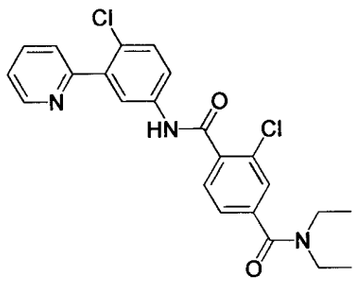
Se acoplaron 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a histamina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir N^4-(2-(1*H*-imidazol-4-il)etil)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil) tereftalamida. MS (Q1) 481 $(M)^+$.

Ejemplo 110 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-metiltereftalamida



Se acoplaron 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a metilamina clorhidrato mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-metiltereftalamida. MS (Q1) 401 $(M)^+$.

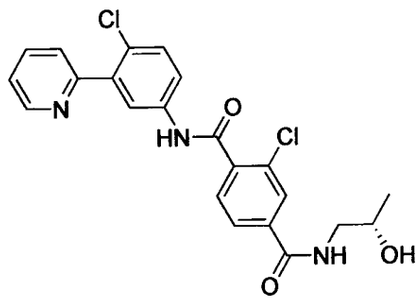
Ejemplo 111 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4,N^4-dietiltereftalamida



000415

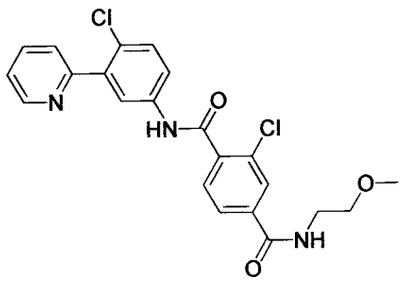
Se acoplaron 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a dietilamina clorhidrato mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4,N^4-dietiltereftalamida. MS (Q1) 443 $(M)^+$

Ejemplo 112 (*S*)-2-cloro-*N*1-(4-cloro-3-(piridin-2-il)fenil)-*N*4-(2-hidroxipropilo)-tereftalamida



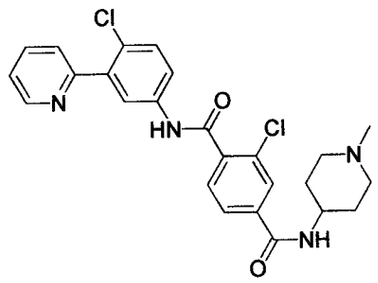
Se acoplaron 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a (S)-1-amino-2-propanol mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir (*S*)-2-cloro-*N*1-(4-cloro-3-(piridin-2-il)fenil)-*N*4-(2-hidroxipropilo) tereftalamida. MS (Q1) 444 $(M)^+$.

Ejemplo 113 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-metoxietil) tereftalamida



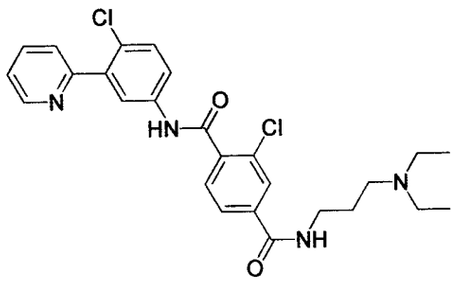
Se acoplaron 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 2-metoxietanamina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-metoxietil) tereftalamida. MS (Q1) 444 $(M)^+$.

Ejemplo 114 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(1-metilpiperidin-4-il) tereftalamida



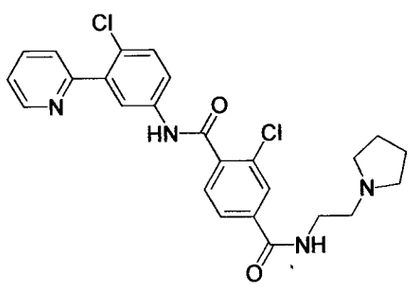
Se acoplaron 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 4-amino-1-metilpiperidina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(1-metilpiperidin-4-il) tereftalamida. MS (Q1) 483 $(M)^+$.

Ejemplo 115 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(3-(dietilamino)propilo) tereftalamida



Se acoplaron 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a N,N-dietilpropilenediamina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(3-(dietilamino)propilo) tereftalamida. MS (Q1) 499 $(M)^+$.

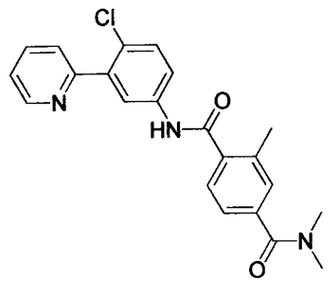
Ejemplo 116 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-(pirrolidin-1-il)etil) tereftalamida



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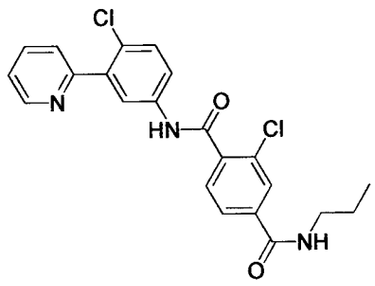
Se acoplaron 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a N-(2-aminoetil)pirrolidina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-(pirrolidin-1-il)etil) tereftalamida. MS (Q1) 483 $(M)^+$.

Ejemplo 117 N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4,N^4,2-trimetiltereftalamida



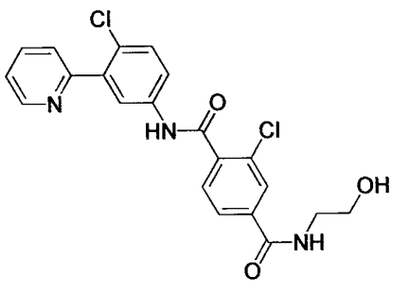
En un tubo sellado, se disolvieron 1.94 g de dimetil 2-bromotereftalato en 4 mL de HMPA y se desgasificó con nitrógeno antes de agregar 1.1 mL de tetrametil estaño y 0.077 g de paladio tetrakistrifenilfosfeno. Luego de sellar el tubo, la reacción fue calentada a 65° C por espacio de 16 h. La reacción luego fue particionada en éter etílico y agua y extraída. Las capas orgánicas fueron lavadas con 5% hidróxido de amonio, 1N HCl, nuevamente con 5% hidróxido de amonio, y finalmente con agua. La filtración del solvente por sulfato de sodio y la evaporación dieron como resultado 1.44 g de dimetil 2-metiltereftalato crudo. 210 mg de dimetil 2-metiltereftalato fueron hidrolizados mediante el procedimiento M para producir ácidop 4-(metoxicarbonil)-3-metilbenzoico. Se realizó una cromatografía en gel de sílice (0% a 70% EtOAc gradiente en hexanos) para producir 115 mg de ácido 4-(metoxicarbonil)-3-metilbenzoico acid. Luego se acopló el ácido 4-(metoxicarbonil)-3-metilbenzoico a dimetilamina clorhidrato mediante el procedimiento G. El metil 4-(dimetilcarbamoil)-2-metilbenzoato crudo luego fue hidrolizado mediante el procedimiento M para producir 110 mg de ácido 4-(dimetilcarbamoil)-2-metilbenzoico. Se acopló 4-cloro-3-(piridin-2-il)anilina a 110 mg de ácido 4-(dimetilcarbamoil)-2-metilbenzoico mediante el procedimiento G para producir 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



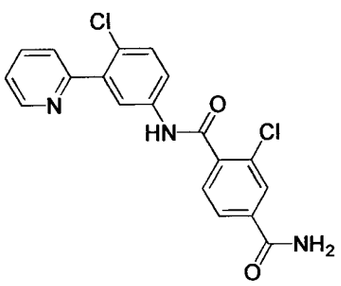
Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a propilamina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-propiltereftalamida. MS (Q1) 430 $(M)^+$.

Ejemplo 119 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-hidroxietil) tereftalamida



Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a propanolamina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-hidroxietil) tereftalamida. MS (Q1) 428 $(M)^+$.

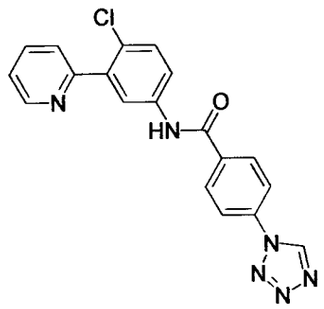
Ejemplo 120 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil) tereftalamida



Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a cloruro de amonio mediante el procedimiento G. El producto fue purificado en HPLC de

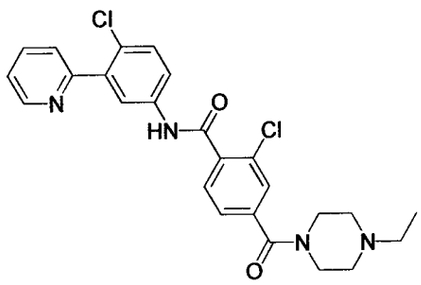
fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil) tereftalamida. MS (Q1) 386 $(M)^+$.

Ejemplo 121 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(1*H*-tetrazol-1-il) benzamida



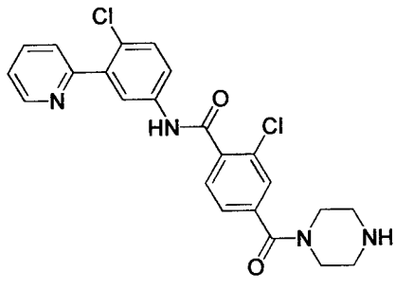
El procedimiento G fue utilizado para acoplar 4-cloro-3-(piridin-2-il)anilina (50 mg) y ácido 4-(1*H*-tetrazol-1-il) benzoico para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(1*H*-tetrazol-1-il) benzamida. MS (Q1) 421.0 $(M)^+$.

Ejemplo 122 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-etilpiperazina-1-carbonil) benzamida



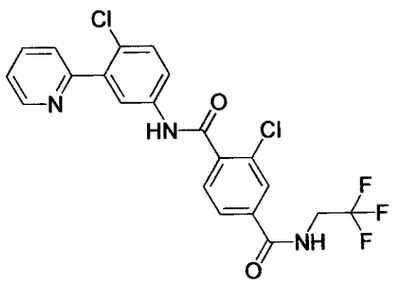
Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 1-etilpiperazina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-etilpiperazina-1-carbonil) benzamida. MS (Q1) 483 $(M)^+$.

Ejemplo 123 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(piperazina-1-carbonil) benzamida



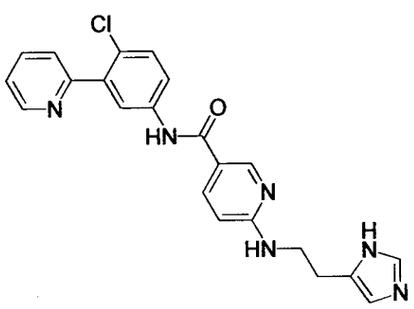
Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a Boc-piperazina mediante el procedimiento G. La capa orgánica fue evaporada hasta secarse y tratada con TFA. Luego de 1 h el TFA fue removido y el crudo fue purificado en HPLC de fase inversa para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(piperazina-1-carbonil) 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



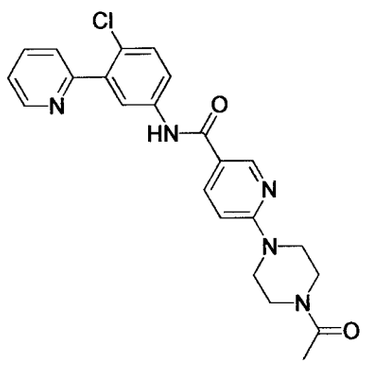
Se acoplaron 75 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 2,2,2-trifluoroetilamina mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2,2,2-trifluoroetil) tereftalamida. MS (Q1) 469 $(M)^+$.

Ejemplo 125 6-(2-(1*H*-imidazol-5-il)etilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil) nicotinamida



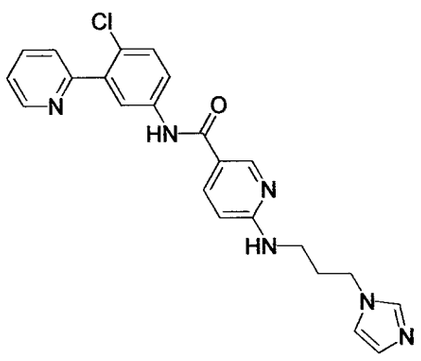
El procedimiento F fue ejecutado usando *N*-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (50 mg) y 100 mg de histamina en butanol (0.5 mL). La reacción cruda fue purificada por HPLC de fase inversa para producir 6-(2-(1*H*-imidazol-5-il)etilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil) nicotinamida. MS (Q1) 419 $(M)^+$.

Ejemplo 126 6-(4-acetilpiperazin-1-il)-*N*-(4-cloro-3-(piridin-2-il)fenil) nicotinamida



El procedimiento F fue ejecutado 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 reacción cruda fue purificada por HPLC de fase inversa para producir 6-(4-acetilpiperazin-1-il)-*N*-(4-cloro-3-(piridin-2-il)fenil) nicotinamida. MS (Q1) 436 $(M)^+$.

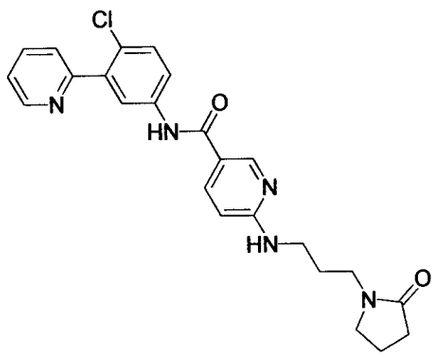
Ejemplo 127 6-(3-(1*H*-imidazol-1-il)propilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil) nicotinamida



El procedimiento F fue ejecutado usando *N*-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (50 mg) y 125 mg de 1-(3-aminopropilo)imidazol en butanol (0.5 mL). La reacción cruda fue purificada por HPLC de fase inversa para producir 6-(3-(1*H*-imidazol-1-il)propilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil) nicotinamida. MS (Q1) 433 $(M)^+$.

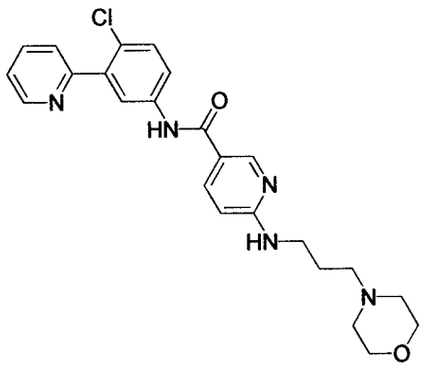
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Ejemplo 128 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(3-(2-oxopirrolidin-1-il)propilamino) nicotinamida



El procedimiento F fue ejecutado usando *N*-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (50 mg) y 0.42 mL de 1-(3-aminopropilo)-2-pirrolidinona en butanol (0.5 mL). La reacción cruda fue purificada por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(3-(2-oxopirrolidin-1-il)propilamino) nicotinamida. MS (Q1) 450 $(M)^+$.

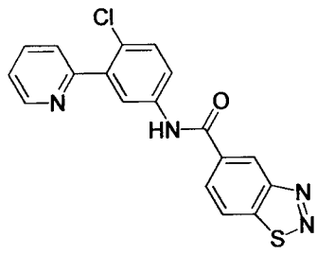
Ejemplo 129 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(3-morfolinopropilamino) nicotinamida



El procedimiento F fue ejecutado usando *N*-(4-cloro-3-(piridin-2-il)fenil)-6-cloro-3-carboxamida (50 mg) y 0.14 mL de N-(3-aminopropilo) morfolina en butanol (0.5 mL). La reacción cruda fue purificada por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(3-morfolinopropilamino) nicotinamida. MS (Q1) 452 $(M)^+$.

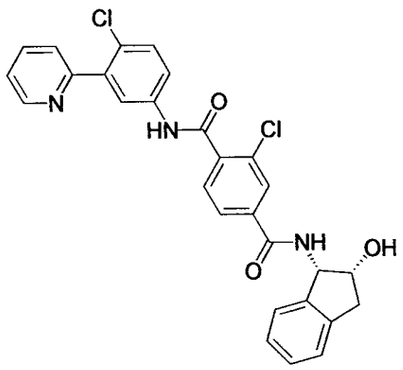
Ejemplo 130 *N*-(4-cloro-3-(piridin-2-il)fenil)benzo[d][1,2,3]tiadiazol-5-carboxamida

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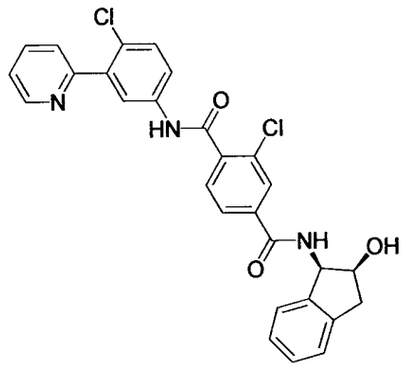
Se acoplaron 50 mg de 4-cloro-3-(piridin-2-il)anilina a ácido benzo-1,2,3-tiadiazol-5-carboxílico mediante el procedimiento G. El producto crudo se purificó por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)benzo[d][1,2,3]tiadiazol-5-carboxamida. MS (Q1) 367 $(M)^+$.

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



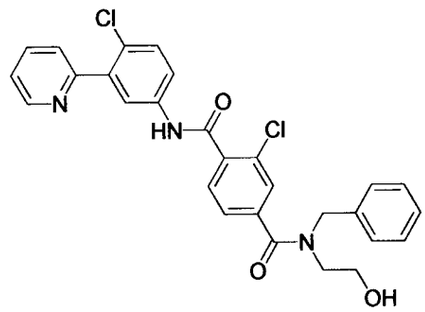
60 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico fueron acoplados a (1*S*,2*R*)-1-amino-2,3-dihidro-1*H*-inden-2-ol mediante el procedimiento G. El producto crudo fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-((1*S*,2*R*)-2-hidroxi-2,3-dihidro-1*H*-inden-1-il) 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 acoplaron 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 mediante el procedimiento G. El producto crudo fue purificado en HPLC de fase inversa para producir 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 $(M)^+$.

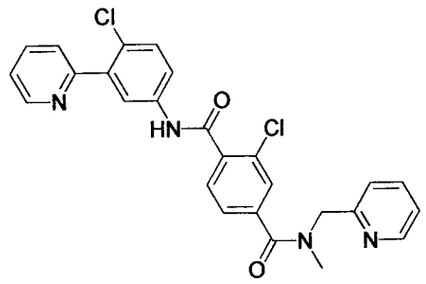
Ejemplo 133 N^4-bencil-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-hidroxietil)-tereftalamida



Se acoplaron 40 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 2-(bencilamino)etanol mediante el procedimiento G. El producto crudo fue purificado en HPLC de fase inversa para producir N^4-bencil-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-hidroxietil) tereftalamida. MS (Q1) 520 $(M)^+$.

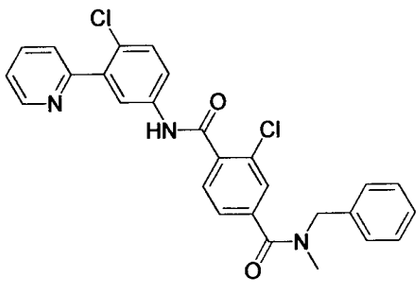
Ejemplo 134 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-metil-N^4-(piridin-2-ilmetil) tereftalamida

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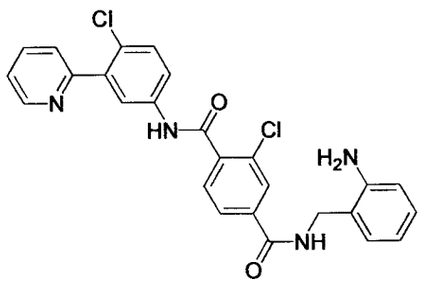
Se acoplaron 40 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a *N*-metil-1-(piridin-2-il)metanamina mediante el procedimiento G. El producto crudo fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-metil-N^4-(piridin-2-ilmetil) 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 acoplaron 40 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a *N*-metil-1-fenilmetanamina mediante el procedimiento G. El producto crudo fue purificado en HPLC de fase inversa para producir N^4-bencil-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-metiltereftalamida. MS (Q1) 490.1 $(M)^+$.

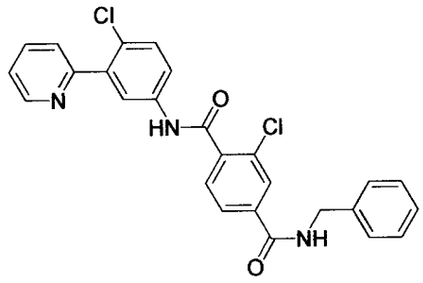
Ejemplo 136 N^4-(2-aminobencil)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil) tereftalamida



Se acoplaron 60 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a N^1-feniletano-1,2-diamina mediante el procedimiento G. El producto crudo fue purificado

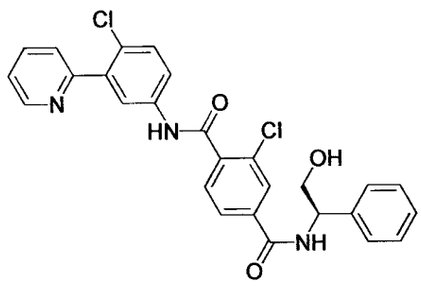
en HPLC de fase inversa para producir N^4-(2-aminobencil)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil) tereftalamida. MS (Q1) 491 $(M)^+$.

Ejemplo 137 N^4-bencil-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil) tereftalamida



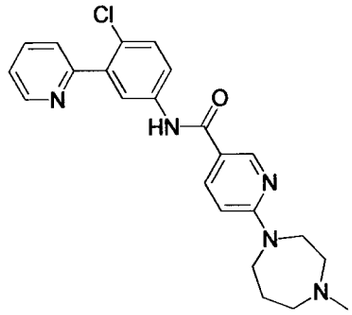
Se acoplaron 60 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a bencilamina mediante el procedimiento G. El producto crudo fue purificado en HPLC de fase inversa para producir N^4-bencil-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil) tereftalamida. MS (Q1) 476 $(M)^+$.

Ejemplo 138 (*R*)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-hidroxi-1-feniletil) tereftalamida



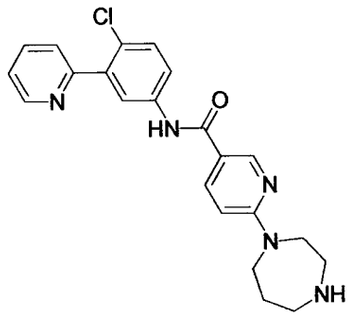
Se acoplaron 60 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a (*R*)-2-amino-2-feniletanol mediante el procedimiento G. El producto crudo fue purificado en HPLC de fase inversa para producir (*R*)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-hidroxi-1-feniletil) tereftalamida. MS (Q1) 506 $(M)^+$.

Ejemplo 139 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(4-metil-1,4-diazepan-1-il) nicotinamida



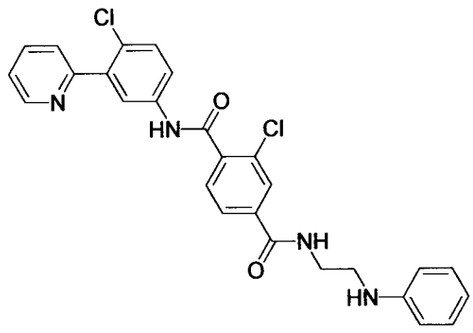
Se sometieron a una reacción 50 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil) nicotinamida con 1-metil-1,4-diazepan mediante el procedimiento F. La reacción fue evaporada hasta secarse y purificada en HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(4-metil-1,4-diazepan-1-il) nicotinamida. MS (Q1) 422 $(M)^+$.

Ejemplo 140 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(1,4-diazepan-1-il) nicotinamida



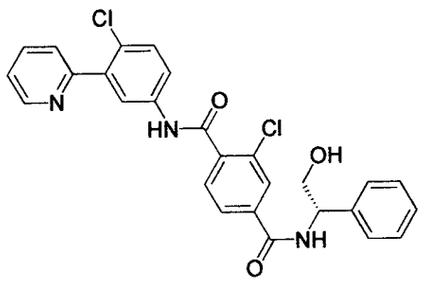
Se sometieron a una reacción 50 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil) nicotinamida con 1,4-diazepan mediante el procedimiento F. La reacción fue evaporada hasta secarse y purificada en HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(1,4-diazepan-1-il) nicotinamida. MS (Q1) 408 $(M)^+$.

Ejemplo 141 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-(fenilamino)etil) tereftalamida



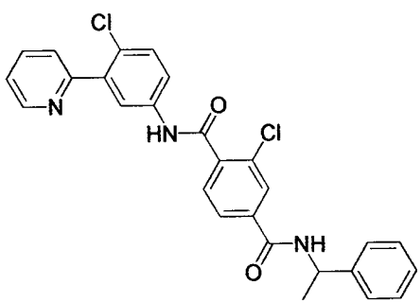
Se acoplaron 62 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a N^1-feniletano-1,2-diamina mediante el procedimiento G. El producto crudo fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-(fenilamino)etil) tereftalamida. 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



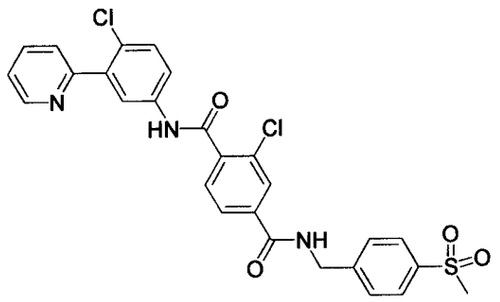
Se acoplaron 62 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a (*S*)-2-amino-2-feniletanol mediante el procedimiento G. El producto crudo fue purificado en HPLC de fase inversa para producir (*S*)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-hidroxi-1-feniletil) tereftalamida. MS (Q1) 506 $(M)^+$.

Ejemplo 143 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(1-feniletil) tereftalamida



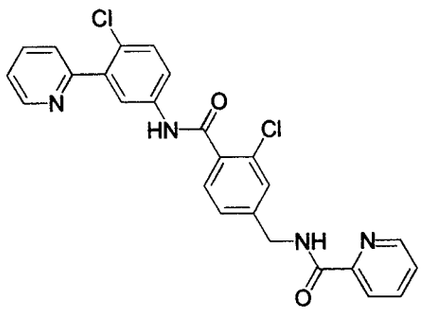
Se acoplaron 62 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 1-feniletanamina mediante el procedimiento G. El producto crudo fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(1-feniletil) tereftalamida. MS (Q1) 490.1 $(M)^+$.

Ejemplo 144 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(4-(metilsulfonil)bencil)-tereftalamida



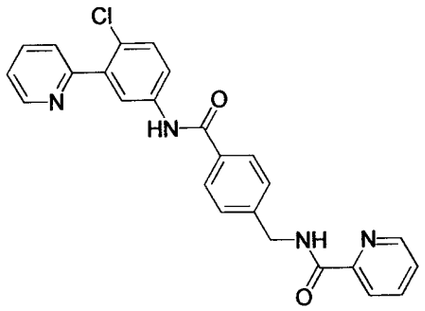
Se acoplaron 62 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a (4-(metilsulfonil)fenil)metanamina mediante el procedimiento G. El producto crudo fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(4-(metilsulfonil)bencil) tereftalamida. MS (Q1) 554 $(M)^+$.

Ejemplo 145 *N*-(3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencil) picolinamida



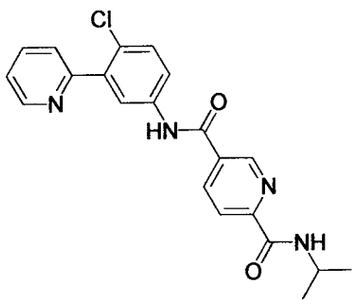
Se acoplaron 75 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 4-((*tert*-butoxicarbonilamino)metil)-2-clorobenzoico mediante el procedimiento G para producir *tert*-butil 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) bencilcarbamato. Luego se trató *tert*-butil 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) bencilcarbamato con 4N HCl en Dioxano para remover el grupo de protección Boc y formar la sal HCl de 4-(aminometil)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida. Se acoplaron 54 mg de la sal HCl cruda de 4-(aminometil)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida a ácido picolínico mediante el procedimiento G. El producto crudo fue purificado por HPLC de fase inversa para producir *N*-(3-cloro-4-(4-cloro-3-(piridin-2-il) fenilcarbamoil) bencil) picolinamida. MS (Q1) 477.3 $(M)^+$.

Ejemplo 146 *N*-(4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencil) picolinamida



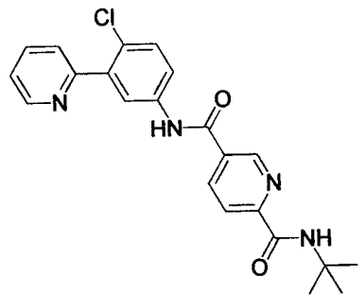
Se acoplaron 75 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 4-((*tert*-butoxicarbonilamino)metil) benzoico mediante el procedimiento G para producir *tert*-butil 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) bencilcarbamato. Luego se trató *tert*-butil 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) bencilcarbamato con 4N HCl en Dioxano para remover el grupo de protección Boc y formar la sal HCl de 4-(aminometil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida. Se acoplaron 50 mg de la sal HCl cruda de 4-(aminometil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida a ácido picolínico mediante el procedimiento G. El producto crudo fue purificado por HPLC de fase inversa para producir *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-isopropilpiridina-2,5-dicarboxamida



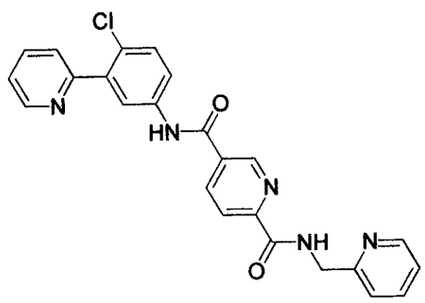
Se acoplaron 250 mg de ácido 5-(metoxicarbonil) picolínico a isopropilamina mediante el procedimiento G. El metil 6-(isopropilcarbamoil) nicotinato crudo fue hidrolizado mediante el procedimiento M para producir 227 mg de ácido 6-(isopropilcarbamoil) nicotínico. Se acoplaron 60 mg de 4-cloro-3-(piridin-2-il) anilina a ácido 6-(isopropilcarbamoil) nicotínico mediante el procedimiento G. El producto crudo fue purificado por HPLC de fase inversa para producir N^5-(4-cloro-3-(piridin-2-il)fenil)-N^2-isopropilpiridina-2,5-dicarboxamida. MS (Q1) 395.1 $(M)^+$.

Ejemplo 148 N^2-*tert*-butil-N^5-(4-cloro-3-(piridin-2-il)fenil)piridina-2,5-dicarboxamida



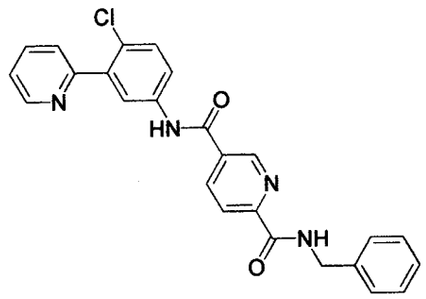
Se acoplaton 250 mg de ácido 5-(metoxicarbonil) picolínico a *tert*-butilamina mediante el procedimiento G. El metil 6-(tert-butilcarbamoil) nicotinato crudo fue hidrolizado mediante el procedimiento M para producir 250 mg de ácido 6-(*tert*-butilcarbamoil) nicotínico. Se acoplaron 60 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 6-(*tert*-butilcarbamoil) nicotínico mediante el procedimiento G. El producto crudo fue purificado por HPLC de fase inversa para producir N^2-*tert*-butil-N^5-(4-cloro-3-(piridin-2-il)fenil)piridina-2,5-dicarboxamida. MS (Q1) 409 $(M)^+$.

Ejemplo 149 N^5-(4-cloro-3-(piridin-2-il)fenil)-N^2-(piridin-2-ilmetil)piridina-2,5-dicarboxamida



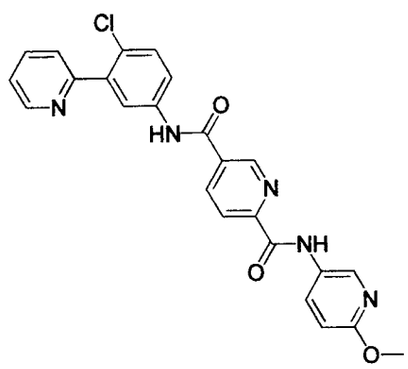
Se acoplaron 250 mg de 5-(metoxicarbonil) picolínico a piridin-2-ilmetanamina mediante el procedimiento G. El metil 6-(piridin-2-ilmetilcarbamoil) nicotinato crudo fue hidrolizado mediante el procedimiento M para producir 250 mg de ácido 6-(piridin-2-ilmetilcarbamoil) nicotínico. Se acoplaron 60 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 6-(piridin-2-ilmetilcarbamoil) nicotínico mediante el procedimiento G. El producto crudo fue purificado por HPLC de fase inversa para producir N^5-(4-cloro-3-(piridin-2-il)fenil)-N^2-(piridin-2-ilmetil)piridina-2,5-dicarboxamida. MS (Q1) 444.1 $(M)^+$.

Ejemplo 150 N^2-bencil-N^5-(4-cloro-3-(piridin-2-il)fenil)piridina-2,5-dicarboxamida



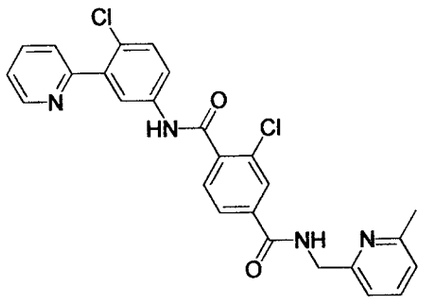
Se acoplaron 250 mg de ácido 5-(metoxicarbonil) picolínico a bencilamina mediante el procedimiento G. El metil 6-(bencilcarbamoil) nicotinato crudo fue hidrolizado mediante el procedimiento M para producir 300 mg de ácido 6-(bencilcarbamoil) nicotínico. Se acoplaron 60 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 6-(bencilcarbamoil) nicotínico mediante el procedimiento G. El producto crudo fue purificado por HPLC de fase inversa para producir N^2-bencil-N^5-(4-cloro-3-(piridin-2-il)fenil)piridina-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)piridina-2,5-dicarboxamida



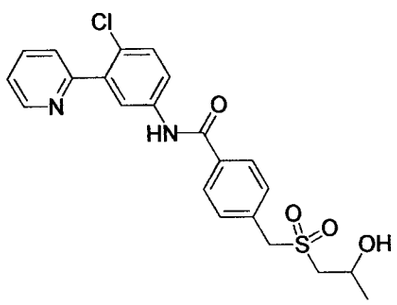
Se acoplaron 250 mg de ácido 5-(metoxicarbonil) picolínico a 6-metoxipiridin-3-amina mediante el procedimiento G. El metil 6-(6-metoxipiridin-3-ilcarbamoil) nicotinato crudo fue hidrolizado mediante el procedimiento M para producir 196 mg de ácido 6-(6-metoxipiridin-3-ilcarbamoil) nicotínico. Se acoplaron 60 mg de 4-cloro-3-(piridin-2-il) anilina a ácido 6-(6-metoxipiridin-3-ilcarbamoil) nicotínico mediante el procedimiento G. El producto crudo fue recristalizado para producir N^5-(4-cloro-3-(piridin-2-il)fenil)-N^2-(6-metoxipiridin-3-il)piridina-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 agregaron por goteo 2.5 mL de diisopropilazodicarboxilato en 1.5mL de THF a una solución de 250 mg de (6-metilpiridin-2-il)metanol, 2.8g de trifenilfosfina y 1.6 g de isoindolina-1,3-diona en THF anhidro a temperatura ambiente. La reacción fue agitada durante 2 horas y monitoreada por TLC. Finalizada, el solvente fue concentrado, el material crudo fue extraido en agua y cloroformo 3 veces y secado sobre sulfato de magnesio. El crudo fue purificado por ISCO Combi-Flash para producir 2-((6-metilpiridin-2-il)metil)isoindolina-1,3-diona. Se trataron 350 mg de 2-((6-metilpiridin-2-il)metil)isoindolina-1,3-diona con 440 µL de hidrazina monohidrato en EtOH y se sometió a reflujo durante varias horas para producir (6-metilpiridin-2-il)metanamina. El crudo (6-metilpiridin-2-il)metanamina fue evaporado y directamente acoplado a 50mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico mediante el procedimiento G. El producto crudo fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-((6-metilpiridin-2-il)metil) tereftalamida. MS (Q1) 491.1 $(M)^+$.

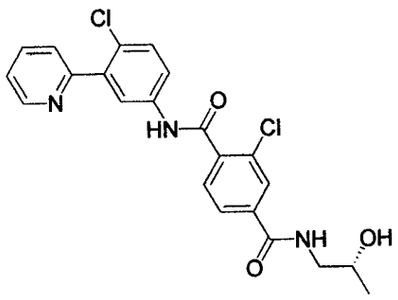
Ejemplo 153 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((2-hidroxipropilsulfonil)metil) benzamida



Se sometió a una reacción 1 g de metil 4-(bromometil) benzoato con 1-mercaptopropan-2-ol mediante el procedimiento Q. 1 g de metil 4-((2-hidroxipropiltio)metil) benzoato fue oxidado con 2g de MCPBA en DCM a –78°C para formar metil 4-((2-hidroxipropilsulfonil)metil) benzoato crudo. La reacción fue evaporada y purificada por ISCO Combi-Flash para producir 567 mg de metil 4-((2-hidroxipropilsulfonil)metil) benzoato puro que luego fue hidrolizado mediante el procedimiento M para producir 328 mg de ácido 4-((2-hidroxipropilsulfonil)metil) benzoico. Se acoplaron 50 mg de 4-cloro-3-

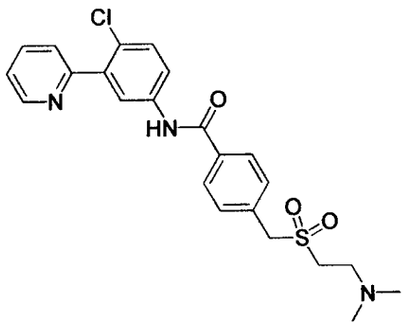
(piridin-2-il)anilina a ácido 4-((2-hidroxipropilsulfonil)metil) benzoico mediante el procedimiento G. El producto crudo fue purificado en HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((2-hidroxipropilsulfonil)metil) benzamida. MS (Q1) 445.3 $(M)^+$.

Ejemplo 154 (*R*)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-hidroxipropilo) tereftalamida



Se acoplaron 100 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a (*R*)-2-amino-2-feniletanol mediante el procedimiento G. El producto crudo fue purificado en HPLC de fase inversa para producir (*R*)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-hidroxipropilo) tereftalamida. MS (Q1) 444.3 $(M)^+$.

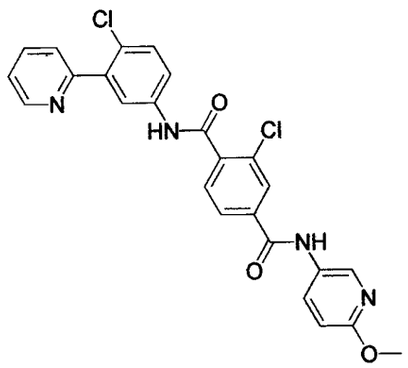
Ejemplo 155 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((2-(dimetilamino)etilsulfonil)metil)-benzamida



Se acoplaron 500 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 4-(bromometil) benzoico mediante el procedimiento E. Se sometieron a una reacción 170 mg de 4-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida con 2-(dimetilamino)etanotiol clorhidrato mediante el procedimiento Q. Se sometieron a una reacción 140mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((2-(dimetilamino)etiltio)metil) benzamida cruda con ozono mediante el procedimiento R. El producto crudo fue purificado por HPLC de fase inversa para

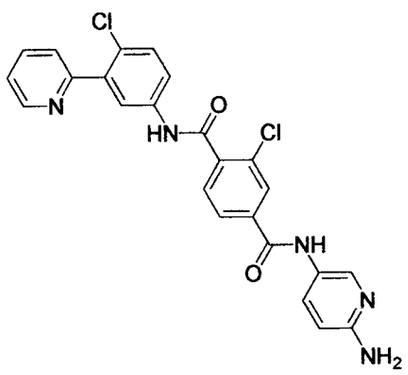
producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((2-(dimetilamino)etilsulfonil)metil) benzamida. MS (Q1) 458.3 $(M)^+$.

Ejemplo 156 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(6-metoxipiridin-3-il) tereftalamida



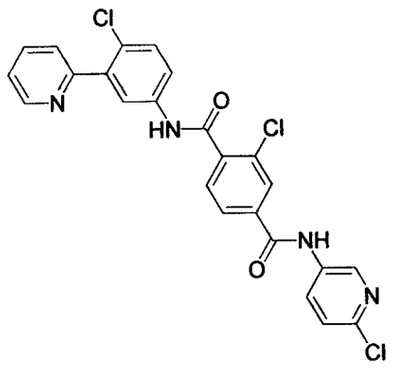
Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 6-metoxipiridin-3-amina mediante el procedimiento G. El producto crudo fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(6-metoxipiridin-3-il) tereftalamida. MS (Q1) 493 $(M)^+$.

Ejemplo 157 N^4-(6-aminopiridin-3-il)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-tereftalamida



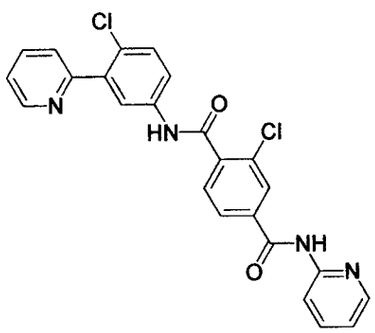
Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a piridina-2,5-diamina mediante el procedimiento G. El producto crudo fue purificado en HPLC de fase inversa para producir N^4-(6-aminopiridin-3-il)-2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil) tereftalamida. MS (Q1) 478 $(M)^+$.

Ejemplo 158 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(6-cloropiridin-3-il) tereftalamida



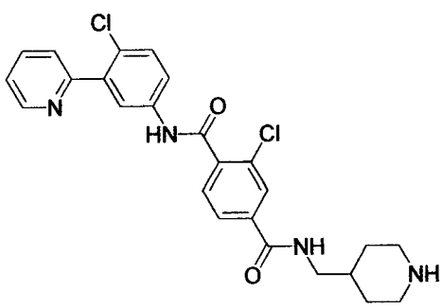
Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 6-cloropiridin-3-amina mediante el procedimiento G. El producto crudo fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(6-cloropiridin-3-il) tereftalamida. MS (Q1) 497 $(M)^+$.

Ejemplo 159 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(piridin-2-il) tereftalamida



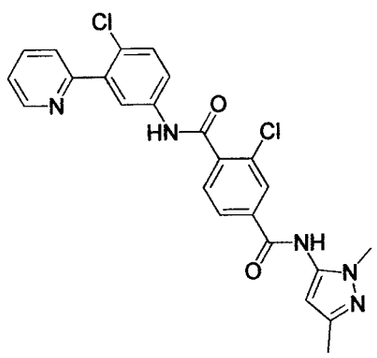
Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a piridin-2-amina mediante el procedimiento G. El producto crudo fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(piridin-2-il) tereftalamida. MS (Q1) 463 $(M)^+$.

Ejemplo 160 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(piperidin-4-ilmetil) tereftalamida



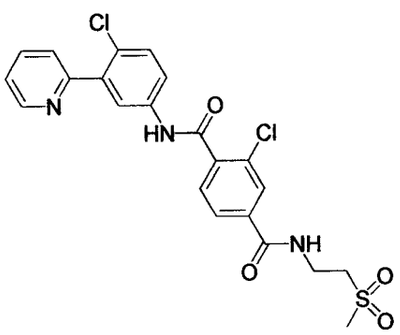
Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a piperidin-4-ilmetanamina mediante el procedimiento G. El producto crudo fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(piperidin-4-ilmetil) tereftalamida. MS (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 acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 1,3-dimetil-1*H*-pirazol-5-amina mediante el procedimiento G. El producto crudo fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(1,3-dimetil-1*H*-pirazol-5-il) tereftalamida. MS (Q1) 480 $(M)^+$.

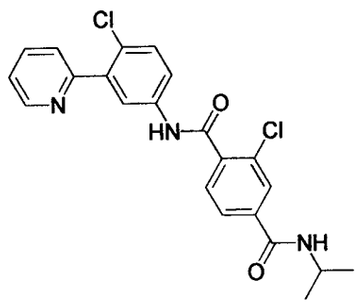
Ejemplo 162 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-(metilsulfonil)etil)-tereftalamida



Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a 2-(metilsulfonil) etanamina mediante el procedimiento G. El producto crudo fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-(2-(metilsulfonil)etil) tereftalamida. MS (Q1) 492 $(M)^+$.

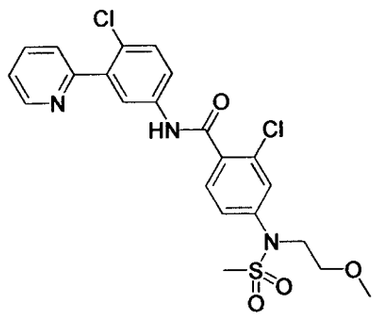
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Ejemplo 163 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-isopropiltereftalamida



Se acoplaron 50 mg de ácido 3-cloro-4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzoico a isopropilamina mediante el procedimiento G. El producto crudo fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4-isopropiltereftalamida. MS (Q1) 428 $(M)^+$.

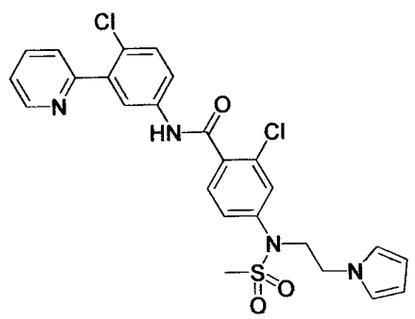
Ejemplo 164 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-(2-metoxietil)metil-sulfonamido) benzamida



A 5 g de metil 2-cloro-4-nitrobenzoato en 100 mL de EtOH se agregaron 20 g de cloruro de estaño (II) en porciones. La reacción fue calentada a 55°C y monitoreada por TLC hasta completar. El solvente fue concentrado y la extracción fue ejecutada en acetato de etilo y agua con TEA para reducir las emulsiones. La capa orgánica fue secada sobre sulfato de magnesio, filtrada y concentrada para producir 3.9 g de metil 4-amino-2-clorobenzoato. 1 g de metil 4-amino-2-clorobenzoato fue enfriado a 0°C en DCM con 485 µL de piridina antes de agregar por goteo metanosulfonil cloruro. La reacción se dejó calentar a temperatura ambiente y fue agitada durante la noche. El solvente fue concentrado y el material crudo fue disuelto en acetato de etilo y extraído con una solución de bicarbonato saturada y luego solución salina. El material crudo fue secado sobre sulfato de magnesio, filtrado y concentrado para producir 1.54 g de metil 2-cloro-4-(metilsulfonamido) benzoato. Se agregaron 107 µL de 1-bromo-2-metoxietano y 556 mg de carbonato de cesio a 150 mg de metil 2-cloro-4-(metilsulfonamido) benzoato en DMF y se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción fue extraida en

acetato de etilo dos veces con bicarbonato saturado y una vez con solución salina, secada sobre sulfato de magnesio, filtrada y concentrada para producir metil 2-cloro-4-(*N*-(2-metoxietil)metilsulfonamido) benzoato. 182 mg de metil 2-cloro-4-(*N*-(2-metoxietil)metilsulfonamido) benzoato fueron hidrolizados mediante el procedimiento M para producir 169 mg de ácido 2-cloro-4-(*N*-(2-metoxietil)metilsulfonamido) benzoico crudo. Se acoplaron 65 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 2-cloro-4-(*N*-(2-metoxietil)metilsulfonamido) benzoico mediante el procedimiento G. El producto crudo fue purificado por HPLC de fase inversa para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-(2-metoxietil)metilsulfonamido) benzamida. MS (Q1) 494 $(M)^+$.

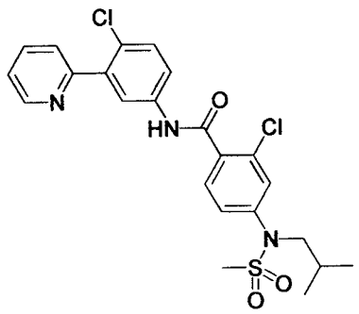
Ejemplo 165 4-(*N*-(2-(1*H*-pirrol-1-il)etil)metilsulfonamido)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida



Se agregaron 200 µL de 1-(2-bromoetil)-1*H*-pirrol y 556 mg de carbonato de cesio a 150 mg de metil 2-cloro-4-(metilsulfonamido) benzoato en DMF y se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción fue extraida en acetato de etilo dos veces con bicarbonato saturado y una vez con solución salina, secada sobre sulfato de magnesio, filtrada y concentrada para producir metil 4-(*N*-(2-(1*H*-pirrol-1-il)etil)metilsulfonamido)-2-clorobenzoato. 230 mg de metil 4-(*N*-(2-(1*H*-pirrol-1-il)etil)metilsulfonamido)-2-clorobenzoato fueron hidrolizados mediante el procedimiento M para producir 221 mg de ácido 4-(*N*-(2-(1*H*-pirrol-1-il)etil)metilsulfonamido)-2-clorobenzoico crudo.

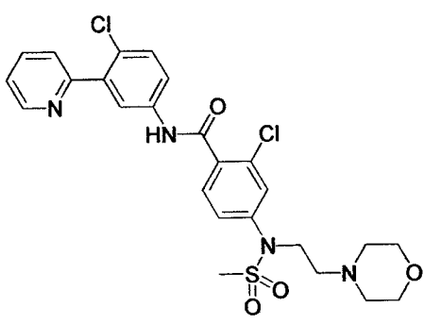
Se acoplaron 64 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 4-(*N*-(2-(1*H*-pirrol-1-il)etil)metilsulfonamido)-2-clorobenzoico mediante el procedimiento G. El producto crudo fue purificado por HPLC de fase inversa para producir 4-(*N*-(2-(1*H*-pirrol-1-il)etil)metilsulfonamido)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil) 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 metil 2-cloro-4-(metilsulfonamido) benzoato en 2 mL de DMF y se agitó en el microondas a 140°C por espacio de 30 minutos. La mezcla de reacción fue extraida en acetato de etilo dos veces con agua, secada sobre sulfato de magnesio, filtrada, concentrada y purificada en ISCO Combi-Flash para producir metil 2-cloro-4-(*N*-isobutilmetilsulfonamido) benzoato. 120 mg de metil 2-cloro-4-(*N*-isobutilmetilsulfonamido) benzoato fueron hidrolizados mediante el procedimiento M para producir 110 mg de ácido 2-cloro-4-(*N*-isobutilmetilsulfonamido) benzoico crudo. Se acoplaron 75 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 2-cloro-4-(*N*-isobutilmetilsulfonamido) benzoico mediante el procedimiento G. El producto crudo fue purificado por HPLC de fase inversa para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-isobutilmetilsulfonamido) benzamida. MS (Q1) 492 $(M)^+$.

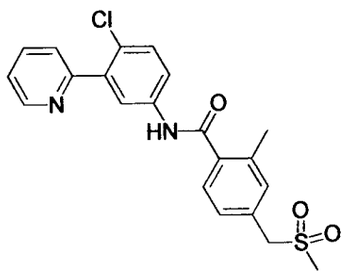
Ejemplo 167 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-(2-morfolinoetil)metil-sulfonamido) benzamida



Se agregaron 1.2 g de 4-(2-cloroetil) morfolina y 2.5 g de carbonato de cesio a 334 mg de metil 2-cloro-4-(metilsulfonamido) benzoato en 7 mL de DMF y se agitó en el microondas a 150°C por espacio de 30 minutos. La mezcla de reacción fue extraida en acetato de etilo dos veces con agua, secada sobre sulfato de magnesio, filtrada, concentrada para

producir metil 2-cloro-4-(*N*-(2-morfolinoetil)metilsulfonamido) benzoato crudo. 476 mg de metil 2-cloro-4-(*N*-(2-morfolinoetil)metilsulfonamido) benzoato fueron hidrolizados mediante el procedimiento M y purificados por HPLC de fase inversa para producir 460 mg de ácido 2-cloro-4-(*N*-(2-morfolinoetil)metilsulfonamido) benzoico crudo. Se acoplaron 100 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 2-cloro-4-(*N*-(2-morfolinoetil)metilsulfonamido) benzoico mediante el procedimiento G. El producto crudo fue purificado por HPLC de fase inversa para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-(2-morfolinoetil)metilsulfonamido) benzamida. MS (Q1) 549 $(M)^+$.

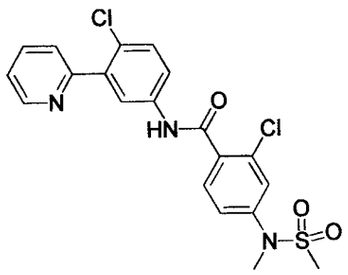
Ejemplo 168 *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-4-(metilsulfonilmetil) benzamida



410 mg de dimetil 2-metiltereftalato fueron hidrolizados mediante el procedimiento M y purificados por ISCO Combi-Flash para obtener ácido 4-(metoxicarbonil)-3-metilbenzoico. Se enfriaron 255 mg de ácido 4-(metoxicarbonil)-3-metilbenzoico a O°C en 2 mL de THF antes de agregar por goteo una solución de 2.6 mL de 1M complejo BH_3-THF en THF. El baño de hielo fue subsecuentemente removido y la reacción fue agitada a temperatura ambiente hasta alcanzar ~50% por TLC. La reacción was re-enfriada a 0°C y otros 2.6 mL de BH_3-THF fueron agregados por goteo antes de remover el baño de hielo. Ante la finalización, la reacción fue re-enfriada a 0°C y apagada con 3N HCl por goteo. La capa acuosa fue extraída 2 veces con acetato de etilo y la capa orgánica luego fue extraida una vez con solución de bicarbonato y solución salina, secada sobre sulfato de magnesio, filtrada y concentrada para producir metil 4-(hidroximetil)-2-metilbenzoato. Se enfriaron 220 mg de metil 4-(hidroximetil)-2-metilbenzoato a 0°C en 5 mL de DCM antes de agregar 260 mg de trifenilfosfina y 395 mg de NBS. La reacción fue concentrada y purificada directamente mediante ISCO Combi-Flash para producir metil 4-(bromometil)-2-metilbenzoato puro. Se sometieron a una reacción 255 mg de metil 4-(bromometil)-2-metilbenzoato mediante el procedimiento O para producir metil 2-metil-4-(metilsulfonilmetil) benzoato. Luego se hidrolizaron 250 mg de metil 2-metil-4-(metilsulfonilmetil) benzoato calentando a 45°C por espacio de 1 hora mediante el procedimiento M para producir ácido 2-metil-4-(metilsulfonilmetil) benzoico. Se acoplaron 202 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 2-metil-4-(metilsulfonilmetil) benzoico

mediante el procedimiento G. El producto crudo fue purificado por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-4-(metilsulfonilmetil) benzamida. MS (Q1) 415 $(M)^+$.

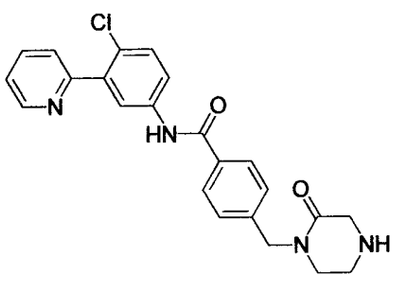
Ejemplo 169 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-metilmetil-sulfonamido) benzamida



Se agregaron 78 µL de yodometano y 447 mg de carbonato de cesio a 300 mg de metil 2-cloro-4-(metilsulfonamido) benzoato en 3 mL de DMF y se agitó a temperatura ambiente por espacio de 16 horas. La mezcla de reacción fue extraida en acetato de etilo dos veces con bicarbonato saturado y una vez con solución salina, secada sobre sulfato de magnesio, filtrada y concentrada para producir metil 2-cloro-4-(*N*-metilmetilsulfonamido) benzoato crudo. 295 mg de metil 2-cloro-4-(*N*-metilmetilsulfonamido) benzoato fueron hidrolizados mediante el procedimiento M para producir 249 mg de ácido 2-cloro-4-(*N*-metilmetilsulfonamido) benzoico.

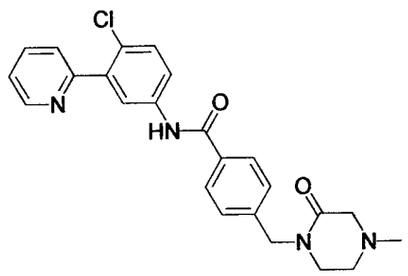
Se acoplaron 100 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 2-cloro-4-(*N*-metilmetilsulfonamido) benzoico mediante el procedimiento G. El producto crudo fue purificado por HPLC de fase inversa para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-metilmetilsulfonamido) benzamida. MS (Q1) 450 $(M)^+$.

Ejemplo 170 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((2-oxopiperazin-1-il)metil) benzamida



Se sometieron a una reacción 500 mg de metil 4-(bromometil) benzoato con 480 mg de *tert*-butil 3-oxopiperazina-1-carboxilato y 1 g de carbonato de cesio en 9 mL de DMF a 45°C. Ante la finalización, la reacción fue extraida en acetato de etilo, 2 veces en bicarbonato saturado, secada sobre sulfato de magnesio, filtrada y concentrada para producir *tert*-butilo 4-(4-(metoxicarbonil)bencil)-3-oxopiperazina-1-carboxilato. 613 mg de *tert*-butilo 4-(4-(metoxicarbonil)bencil)-3-oxopiperazina-1-carboxilato fueron hidrolizados mediante el procedimiento M para producir ácido 4-((4-(*tert*-butoxicarbonil)-2-oxopiperazin-1-il)metil) benzoico. Se acoplaron 200 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 4-((4-(*tert*-butoxicarbonil)-2-oxopiperazin-1-il)metil) benzoico mediante el procedimiento G. El producto crudo fue extraído dos veces con bicarbonato saturado en acetato de etilo, secado sobre sulfato de magnesio, filtrado y concentrado para producir *tert*-butil 4-(4-(4-cloro-3-(piridin-2-il) fenilcarbamoil) bencil)-3-oxopiperazina-1-carboxilato crudo. Luego se agregó 4N HCl al *tert*-butil 4-(4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencil)-3-oxopiperazina-1-carboxilato crudo y se concentró para producir the sal HCl de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((2-oxopiperazin-1-il)metil) benzamida. La reacción fue purificada por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((2-oxopiperazin-1-il)metil) benzamida pura. MS (Q1) 421.3 $(M)^+$.

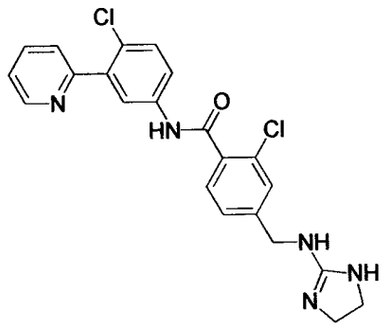
Ejemplo 171 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((4-metil-2-oxopiperazin-1-il)metil) benzamida



A 200 mg de la sal HCl de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((2-oxopiperazin-1-il)metil) benzamida se agregaron 55 mg de paraformaldehído y 185 mg de triacetoxi borohidruro de sodio en 1 mL de 2% AcOH en DMF. Luego de la finalización, la reacción es extraída una vez con bicarbonato y solución salina en acetato de etilo, secada sobre sulfato de magnesio, concentrada y purificada por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((4-metil-2-oxopiperazin-1-il)metil) benzamida pura. MS (Q1) 435.3 $(M)^+$.

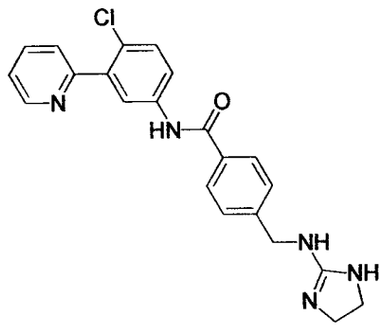
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Ejemplo 172 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-((4,5-dihidro-1*H*-imidazol-2-ilamino)metil) benzamida



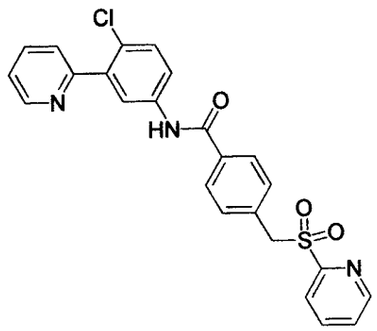
Se sometieron a una reacción 100 mg de la sal HCl cruda de 4-(aminometil)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida con 72 mg de 1-(4,5-dihidro-1*H*-imidazol-2-il)-3,5-dimetil-1*H*-pirazol y 100 µL de DIPEA en 500 µL de DMF en el microondas a 150°C por espacio de 5 minutos. El producto crudo fue concentrado hasta secarse y purificado por HPLC de fase inversa para producir 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



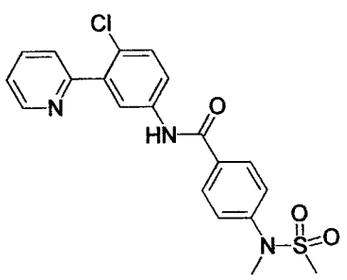
Se sometieron a una reacción 100 mg de la sal HCl cruda de 4-(aminometil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida con 80 mg de 1-(4,5-dihidro-1*H*-imidazol-2-il)-3,5-dimetil-1*H*-pirazol y 110 µL de DIPEA en 1 mL de DMF en el microondas a 150°C por espacio de 5 minutos. El producto crudo fue concentrado hasta secarse y purificado por HPLC de fase inversa para producir *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 sometieron a una reacción 500 mg de metil 4-(bromometil) benzoato con piridina-2-tiol mediante el procedimiento Q. 260 mg de metil 4-((piridin-2-iltio)metil) benzoato fueron reaccionados mediante el procedimiento R para producir metil 4-((piridin-2-ilsulfonil)metil) benzoato. 275 mg de metil 4-((piridin-2-ilsulfonil)metil) benzoato fueron hidrolizados mediante el procedimiento M para producir ácido 4-((piridin-2-ilsulfonil)metil) benzoico. Se acoplaron 75 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 4-((piridin-2-ilsulfonil)metil) benzoico mediante el procedimiento G. El producto crudo fue purificado por HPLC de fase inversa para producir *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

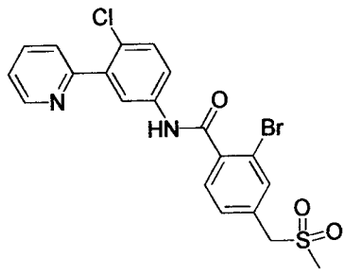


Se enfriaron 500 mg de metil 4-(metilamino) benzoato a 0°C en DCM con 270 µL de piridina antes de agregar por goteo 260 µL metanosulfonil cloruro. La reacción se dejó calentar a temperatura ambiente y fue agitada durante la noche. El solvente fue concentrado y el material crudo fue disuelto en acetato de etilo y extraído con 0.1N solución de NaOH dos veces. El material crudo fue secado sobre sulfato de magnesio, filtrado y concentrado para producir metil 4-(*N*-metilmetilsulfonamido) benzoato. 698 mg de metil 4-(*N*-metilmetilsulfonamido) benzoato fueron hidrolizados mediante el procedimiento M para producir ácido 4-(*N*-metilmetilsulfonamido) benzoico. Se acoplaron 100 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 4-(*N*-metilmetilsulfonamido) benzoico mediante el procedimiento G. El producto crudo fue purificado por HPLC de fase inversa

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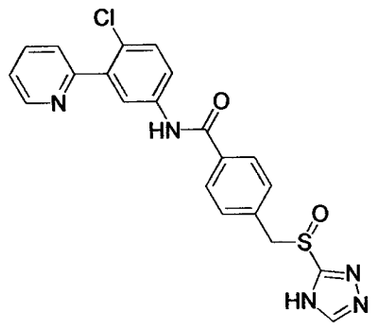
para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-metilmetilsulfonamido) benzamida pura. MS (Q1) 416.3 $(M)^+$.

Ejemplo 176 2-bromo-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil) benzamida



Se bromaron 1.2 g de ácido 2-bromo-4-metilbenzoico mediante el procedimiento N. Se acoplaron 100 mg de 4-cloro-3-(piridin-2-il)anilina a 160 mg de ácido 2-bromo-4-(bromometil) benzoico mediante el procedimiento E. Se sometieron a una reacción 213 mg de 2-bromo-4-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida mediante el procedimiento O para producir 2-bromo-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil) benzamida que fue purificada por HPLC de fase inversa para obtener 2-bromo-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil) benzamida pura. MS (Q1) 481.2 $(M)^+$.

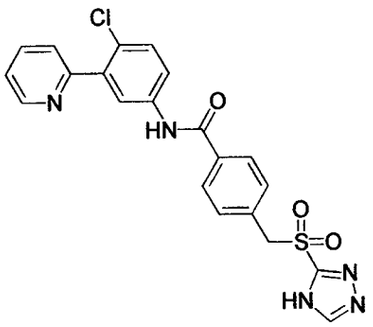
Ejemplo 177 4-((4*H*-1,2,4-triazol-3-ilsulfinilo)metil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida



Se sometieron a una reacción 500 mg de metil 4-(bromometil) benzoato con 4*H*-1,2,4-triazol-3-tiol mediante el procedimiento Q. Luego se sometieron a una reacción 542 mg de metil 4-((4*H*-1,2,4-triazol-3-iltio)metil) benzoato mediante el procedimiento R para producir una mezcla aproximadamente a 1:9 de metil 4-((4*H*-1,2,4-triazol-3-ilsulfinilo)metil) benzoato y metil 4-((4*H*-1,2,4-triazol-3-ilsulfonil)metil) benzoato. La mezcla de 467 mg fue hidrolizada mediante el procedimiento M para producir ácido 4-((4*H*-1,2,4-triazol-3-

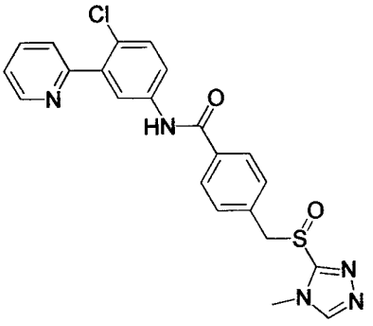
ilsulfinilo)metil) benzoico y ácido 4-((4*H*-1,2,4-triazol-3-ilsulfonil)metil) benzoico. Se acoplaron 107 mg de la mezcla de ácido 4-((4*H*-1,2,4-triazol-3-ilsulfinilo)metil) benzoico y ácido 4-((4*H*-1,2,4-triazol-3-ilsulfonil)metil) benzoico a 75 mg de 4-cloro-3-(piridin-2-il)anilina mediante el procedimiento G. La mezcla fue separada en HPLC de fase inversa para producir 4-((4*H*-1,2,4-triazol-3-ilsulfinilo)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 acoplaron 107 mg de una mezcla de ácido 4-((4*H*-1,2,4-triazol-3-ilsulfinilo)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)anilina mediante el procedimiento G. La mezcla fue separada en HPLC de fase inversa para producir 4-((4*H*-1,2,4-triazol-3-ilsulfonil)metil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida. MS (Q1) 454.3 $(M)^+$.

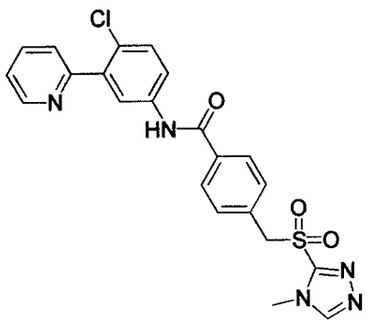
Ejemplo 179 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((4-metil-4*H*-1,2,4-triazol-3-ilsulfinilo)-metil) benzamida



Se sometieron a una reacción 500 mg de metil 4-(bromometil) benzoato con 4-metil-4*H*-1,2,4-triazol-3-tiol mediante el procedimiento Q. Luego se sometieron a una reacción 804

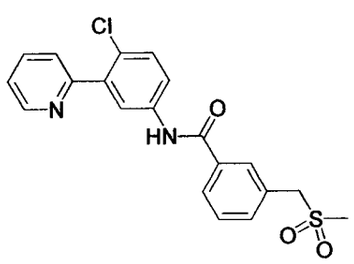
mg de metil 4-((4-metil-4*H*-1,2,4-triazol-3-iltio)metil) benzoato mediante el procedimiento R para producir una mezcla aproximadamente a 1:9 de metil 4-((4-metil-4*H*-1,2,4-triazol-3-ilsulfinilo)metil) benzoato y metil 4-((4-metil-4*H*-1,2,4-triazol-3-ilsulfonil)metil) benzoato. La mezcla de 740 mg fue hidrolizada mediante el procedimiento M para producir ácido 4-((4-metil-4*H*-1,2,4-triazol-3-ilsulfinilo)metil) benzoico y ácido 4-((4-metil-4*H*-1,2,4-triazol-3-ilsulfonil)metil) benzoico. Se acoplaron 114 mg de la mezcla de ácido 4-((4-metil-4*H*-1,2,4-triazol-3-ilsulfinilo)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)anilina mediante el procedimiento G. La mezcla fue separada en HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((4-metil-4*H*-1,2,4-triazol-3-ilsulfinilo)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 acoplaron 114 mg de la mezcla de ácido 4-((4-metil-4*H*-1,2,4-triazol-3-ilsulfinilo)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)anilina mediante el procedimiento G. La mezcla fue separada en HPLC de fase inversa para producir *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 $(M)^+$.

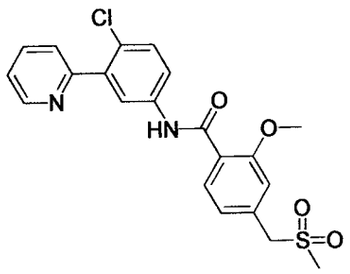
Ejemplo 181 *N*-(4-cloro-3-(piridin-2-il)fenil)-3-(metilsulfonilmetil) benzamida



Se sometieron a una reacción 300 mg de metil 3-(bromometil) benzoato mediante el procedimiento O para producir metil 3-(metilsulfonilmetil) benzoato. Se sometieron a una reacción 230 mg de metil 3-(metilsulfonilmetil) benzoato mediante el procedimiento M para producir ácido 3-(metilsulfonilmetil) benzoico.

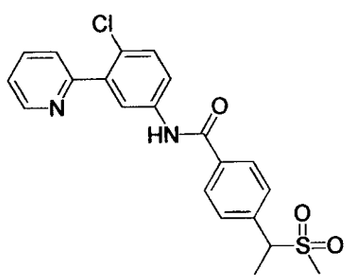
Se acoplaron 75 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 3-(metilsulfonilmetil) benzoico mediante el procedimiento G. El producto crudo fue purificado por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-3-(metilsulfonilmetil) benzamida pura. MS (Q1) 401 $(M)^+$.

Ejemplo 182 *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metoxi-4-(metilsulfonilmetil) benzamida



Se bromaron 900 mg de ácido 2-metoxi-4-metilbenzoico mediante el procedimiento N para obtener ácido 4-(bromometil)-2-metoxibenzoico. Se acoplaron 100 mg de 4-cloro-3-(piridin-2-il)anilina a 132 mg de ácido 4-(bromometil)-2-metoxibenzoico mediante el procedimiento E. Se sometieron a una reacción 211 mg de 4-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metoxibenzamida mediante el procedimiento O y se purificó por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metoxi-4-(metilsulfonilmetil) benzamida pura. MS (Q1) 431 $(M)^+$.

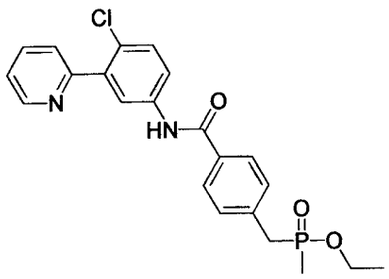
Ejemplo 183 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(1-(metilsulfonil)etil) benzamida



Se acoplaron 75 mg de 4-cloro-3-(piridin-2-il)anilina a 93 mg de ácido 4-(1-bromoetil) benzoico mediante el procedimiento E. Se sometieron a una reacción 153 mg de 4-(1-

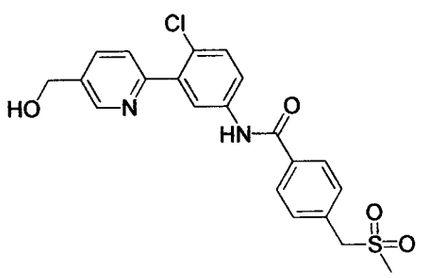
bromoetil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida mediante el procedimiento O y se purificó por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(1-(metilsulfonil)etil) benzamida pura. MS (Q1) 415.3 $(M)^+$.

Ejemplo 184 etilo 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencil(metil)fosfinato



Se sometieron a una reacción 90 mg de 4-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida con 45 µL de dietil metilfosfonita en el microondas a 120°C por espacio de 5 minutos. La reacción fue evaporada hasta secarse y purificada por HPLC de fase inversa para producir etil 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)bencil(metil)fosfinato puro. MS (Q1) 429 $(M)^+$.

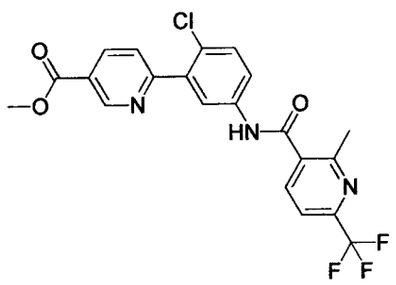
Ejemplo 185 *N*-(4-cloro-3-(5-(hidroximetil)piridin-2-il)fenil)-4-(metilsulfonil-metil) benzamida



Se sometieron a una reacción 75 mL de (5-metilpiridin-2-il)zinc(II) bromuro con 4 g de 1-cloro-2-yodo-4-nitrobenceno mediante el procedimiento B. A 935 mg de 2-(2-cloro-5-nitrofenil)-5-metilpiridina en 5 mL de ácido sulfúrico se agregaron lentamente 2.25 g de óxido de cromo (III) y la reacción fue agitada durante varias horas a temperatura ambiente hasta completar. Se agregó agua helada para diluir la reacción y la capa acuosa fue extraída 3 veces con acetato de etilo. Las capas orgánicas fueron combinadas, secadas sobre sulfato de magnesio, filtradas y concentradas para producir ácido 6-(2-cloro-5-nitrofenil) nicotínico. 704 mg de ácido 6-(2-cloro-5-nitrofenil) nicotínico

fueron esterificados con 3.1 mL de 4N HCl en dioxano en 20 mL de MeOH. La reacción fue concentrada y sometida a un tratamiento básico, secada sobre sulfato de magnesio, filtrada y concentrada para producir metil 6-(2-cloro-5-nitrofenil) nicotinato. 681 mg de metil 6-(2-cloro-5-nitrofenil) nicotinato fueron tratados con 2.1 g de cloruro de estaño (II) y 1 mL de HCl en 25 mL de EtOH. Ante la finalización, el EtOH fue concentrado y la reacción fue extraída con acetato de etilo y agua con TEA para reducir las emulsiones. La capa orgánica fue secada sobre sulfato de magnesio, filtrada y concentrada para producir metil 6-(5-amino-2-clorofenil) nicotinato crudo. Se acoplaron 296 mg de metil 6-(5-amino-2-clorofenil) nicotinato a 266 mg de ácido 4-(metilsulfonilmetil) benzoico mediante el procedimiento G. A 518 mg de metil 6-(2-cloro-5-(4-(metilsulfonilmetil)benzamido)fenil) nicotinato a 0°C en 20 mL de EtOH se agregaron lentamente 640 mg de borohidruro de sodio. La reacción fue subsecuentemente sometida a reflujo 1 hora hasta completar, extinguida con agua y extraída con acetato de etilo. La capa orgánica fue secada sobre sulfato de magnesio, filtrada, concentrada y purificada por HPLC de fase inversa para producir *N*-(4-cloro-3-(5-(hidroximetil)piridin-2-il)fenil)-4-(metilsulfonilmetil) benzamida pura. MS (Q1) 431.1 $(M)^+$.

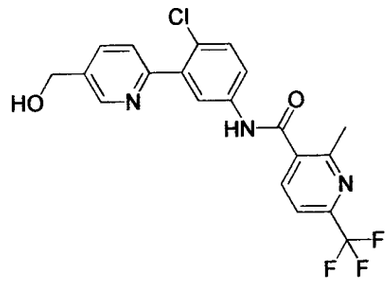
Ejemplo 186 6-(2-cloro-5-(2-metil-6-(trifluorometil)nicotinamido)fenil) nicotinato



200 mg de metil 6-(5-amino-2-clorofenil) nicotinato fueron tratados con 255 µL de 2-metil-6-(trifluorometil)nicotinoil cloruro mediante el procedimiento D y purificados por HPLC de fase inversa para producir 6-(2-cloro-5-(2-metil-6-(trifluorometil)nicotinamido)fenil) nicotinato puro. MS (Q1) 450 $(M)^+$.

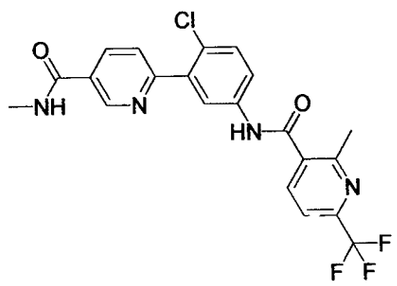
Ejemplo 187 *N*-(4-cloro-3-(5-(hidroximetil)piridin-2-il)fenil)-2-metil-6-(trifluorometil) nicotinamida

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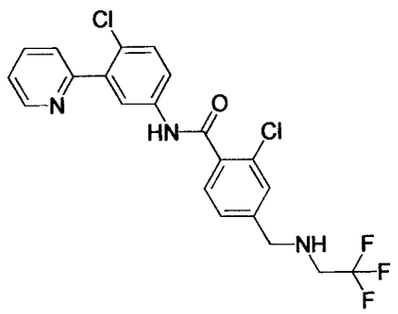
A 110 mg de metil 6-(2-cloro-5-(2-metil-6-(trifluorometil)nicotinamido)fenil) nicotinato a 0°C en 5 mL de EtOH se agregaron lentamente 148 mg de borohidruro de sodio. La reacción fue subsecuentemente sometida a reflujo 1 hora hasta completar, extinguida con agua y extraída con acetato de etilo. La capa orgánica fue secada sobre sulfato de magnesio, filtrada, concentrada y purificada por HPLC de fase inversa para producir *N*-(4-cloro-3-(5-(hidroximetil)piridin-2-il)fenil)-2-metil-6-(trifluorometil) nicotinamida pura. MS (Q1) 422.1 $(M)^+$.

Ejemplo 188 *N*-(4-cloro-3-(5-(metilcarbamoil)piridin-2-il)fenil)-2-metil-6-(trifluorometil) nicotinamida



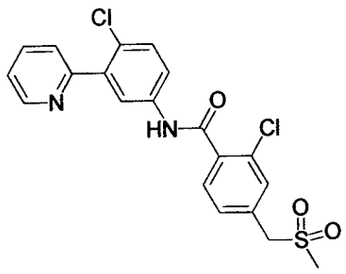
Se hidrolizaron 120 mg de 6-(2-cloro-5-(2-metil-6-(trifluorometil)nicotinamido)fenil) nicotinato mediante el procedimiento M. Se acoplaron 112 mg de ácido 6-(2-cloro-5-(2-metil-6-(trifluorometil)nicotinamido)fenil) nicotínico a metilamina clorhidrato mediante el procedimiento G y se purificó por HPLC de fase inversa para producir *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.



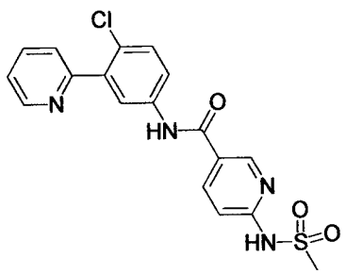
A 24.9 g de ácido 2-cloro-4-(metoxicarbonil) benzoico y 2 mL de ácido sulfúrico en 350 mL de DCM se agregó gas de isobutileno a –78°C hasta saturar el solvente y se destapó con cuidado. Se dejaron transcurrir varios días a temperatura ambiente y se reenfrió –78°C antes de retirar la tapa. Se concentra el solvente, extrae con acetato de etilo y bicarbonato, se seca con sulfato de magnesio, se filtra y concentra para producir 31.4 g de 1-*tert*-butil 4-metil 2-cloroterefталato. 3.35 g de 1-*tert*-butilo 4-metil 2-cloroterefталato fueron hidrolizados mediante el procedimiento M. 2.5 g de ácido 4-(*tert*-butoxicarbonil)-3-clorobenzoico fueron enfriados a O°C en 25 mL de THF antes de agregar una solución de 19.5 mL de complejo 1M BH_3-THF en THF por goteo. El baño de hielo fue subsecuentemente removido y la reacción fue agitada a temperatura ambiente hasta completarla en ~50% por TLC. La reacción es re-enfriada a 0°C y se agregan otros 19.5 mL de BH_3-THF por goteo antes de remover el baño de hielo. Ante la finalización, la reacción es re-enfriada a 0°C y extinguida con 3N HCl por goteo. La capa acuosa fue extraída dos veces con acetato de etilo y la capa orgánica luego fue extraida una vez con solución de bicarbonato y solución salina, secada sobre sulfato de magnesio, filtrada y concentrada para producir *tert*-butil 2-cloro-4-(hidroximetil) benzoato. 564 mg de *tert*-butil 2-cloro-4-(hidroximetil) benzoato fueron enfriados a 0°C en 5 mL de DCM antes de agregar 665 mg de trifenilfosfina y 417 mg de NBS. La reacción fue concentrada y purificada directamente mediante ISCO Combi-Flash para producir *tert*-butil 2-cloro-4-(hidroximetil) benzoato puro. Se sometieron a una reacción 147 mg de *tert*-butil 4-(bromometil)-2-clorobenzoato con 2,2,2-trifluoroetanamina en DMSO mediante el procedimiento P. Se trataron 141 mg de tert-butil 2-cloro-4-((2,2,2-trifluoroetilamino)metil) benzoato con 4N HCl en Dioxano a 45°C y concentrados para producir ácido 2-cloro-4-((2,2,2-trifluoroetilamino)metil) benzoico. Se acoplaron 50 mg de 4-cloro-3-(piridin-2-il)anilina a 75 mg de ácido 2-cloro-4-((2,2,2-trifluoroetilamino)metil) benzoico mediante el procedimiento G . El producto crudo fue purificado por HPLC de fase inversa para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-((2,2,2-trifluoroetilamino)metil) benzamida pura. MS (Q1) 454.6 $(M)^+$.

Ejemplo 190 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil) benzamida



Se sometieron a una reacción 3.01 g de *tert*-butilo 4-(bromometil)-2-clorobenzoato mediante el procedimiento O para producir tert-butil 2-cloro-4-(metilsulfonilmetil) benzoato. 1.2 g de tert-butil 2-cloro-4-(metilsulfonilmetil) benzoato fueron tratados con 10 mL de 4N HCl en Dioxano a 45°C y concentrados a la finalización para producir ácido 2-cloro-4-(metilsulfonilmetil) benzoico crudo. Se acoplaron 775 mg de 4-cloro-3-(piridin-2-il)anilina a 1 g de ácido 2-cloro-4-(metilsulfonilmetil) benzoico mediante el procedimiento G. El producto crudo fue purificado por HPLC de fase inversa para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil) benzamida pura. MS (Q1) 435 $(M)^+$.

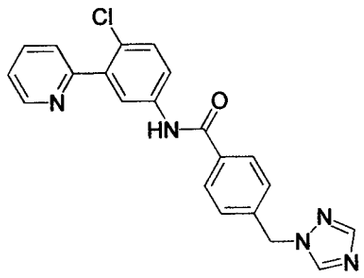
Ejemplo 191 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(metilsulfonamido) nicotinamida



Se sometieron a una reacción 100 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil) nicotinamida con metanosulfonamida y 108 µL de 2-*tert*-butilimino-2-dietilamino-1,3-dimetil-perhidro-1,3,2-diazafosforina mediante el procedimiento F. La reacción cruda fue concentrada hasta secarse y purificada por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(metilsulfonamido) nicotinamida pura. MS (Q1) 403 $(M)^+$.

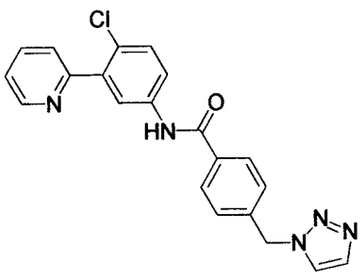
Ejemplo 192 4-((1*H*-1,2,4-triazol-1-il)metil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida

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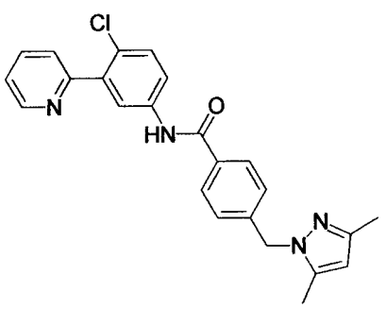
Se acoplaron 88 mg de 4-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida a 45 mg de 1*H*-1,2,4-triazol mediante el procedimiento P. La reacción fue evaporada hasta secarse y purificada por HPLC de fase inversa para producir 4-((1*H*-1,2,4-triazol-1-il)metil)-*N*-(4-cloro-3-(piridin-2-il)fenil) 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



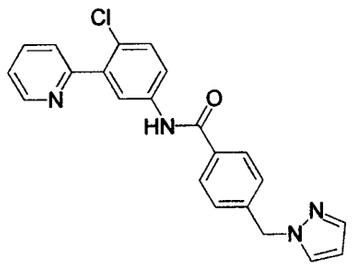
Se acoplaron 88 mg de 4-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida a 40 µL de 1*H*-1,2,3-triazol mediante el procedimiento P. La reacción fue evaporada hasta secarse y purificada por HPLC de fase inversa para producir 4-((1*H*-1,2,3-triazol-1-il)metil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida. 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



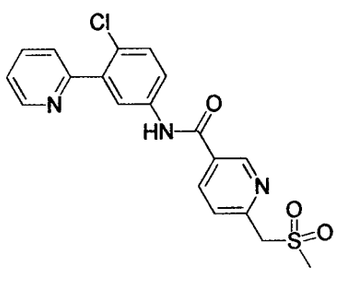
Se acoplaron 70 mg de 4-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida a 50 mg de 3,5-dimetil-1*H*-pirazol mediante el procedimiento P. La reacción fue evaporada hasta secarse y purificada por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((3,5-dimetil-1*H*-pirazol-1-il)metil) 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 acoplaron 70 mg de 4-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida 36 mg de 1*H*-pirazol mediante el procedimiento P. La reacción fue evaporada hasta secarse y purificada por HPLC de fase inversa para producir 4-((1*H*-pirazol-1-il)metil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida. MS (Q1) 389.3 $(M)^+$.

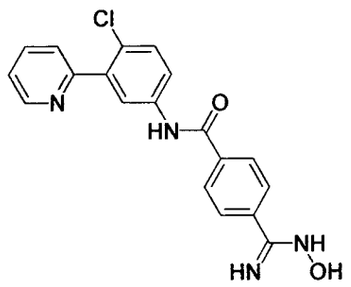
Ejemplo 196 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(metilsulfonilmetil) nicotinamida



Se bromaron 1.2 g de ácido 6-metilnicotínico mediante el procedimiento N para producir ácido 6-(bromometil) nicotínico. Se acoplaron 75 mg de 4-cloro-3-(piridin-2-il)anilina a 87 mg de ácido 6-(bromometil) nicotínico mediante el procedimiento E. 145 mg de 6-(bromometil)-*N*-(4-cloro-3-(piridin-2-il)fenil) nicotinamida fueron sometidos a una reacción mediante el procedimiento O y purificados por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(metilsulfonilmetil) nicotinamida pura. MS (Q1) 402 $(M)^+$.

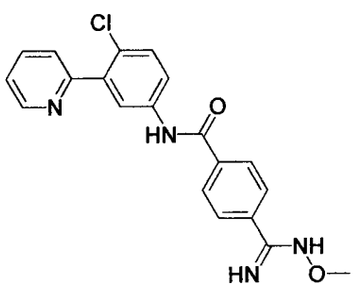
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Ejemplo 197 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-hidroxicarbamimidoil) benzamida



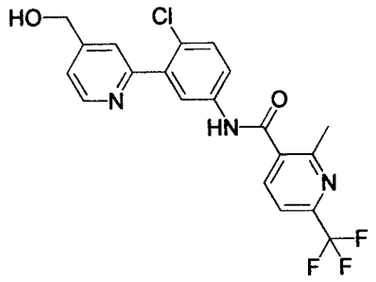
Se acoplaron 240 mg de 4-cloro-3-(piridin-2-il)anilina a 207 mg de ácido 4-cianobenzoico mediante el procedimiento G. A 445 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-cianobenzamida y 2.5 mL de DIPEA en 10 mL de EtOH se agregaron 793 mg de hidroxilamina clorhidrato y se calentó a 60°C hasta finalizar la reacción. Luego el solvente fue evaporado, se extrajo dos veces con agua en acetato de etilo, se secó con sulfato de magnesio, filtró y concentró. El producto crudo fue purificado por HPLC de fase inversa para producir *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



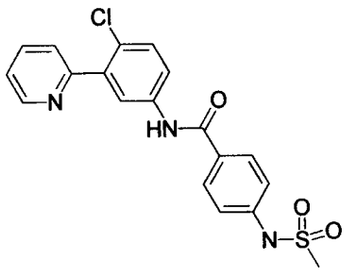
Se enfriaron 100 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-hidroxicarbamimidoil) benzamida a 0°C en 1.5 mL de Dioxano. Se agregaron lentamente 5 mL de 2N NaOH luego de lo cual se agregaron por goteo 33 µL de dimetilsulfato. El baño de hielo fue retirado y la reacción fue agitada a temperatura ambiente por espacio de 1 hora. La reacción fue subsecuentemente evaporada y extraída con agua dos veces en acetato de etilo, secada con sulfato de magnesio, filtrada y concentrada para producir *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



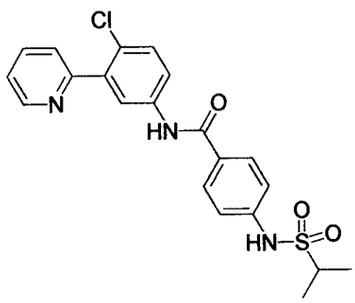
Se sometieron a una reacción 75 mL de (4-metilpiridin-2-il)zinc(II) bromuro con 4 g de 1-cloro-2-yodo-4-nitrobenceno mediante el procedimiento B. A 300 mg de 2-(2-cloro-5-nitrofenil)-4-metilpiridina en 1.5 mL de ácido sulfúrico se agregaron lentamente 362 mg de óxido de cromo (III) y la reacción fue agitada durante varias horas a temperatura ambiente hasta completar. Se agregó agua helada para diluir la reacción y la capa acuosa fue extraída 3 veces con acetato de etilo. Las capas orgánicas fueron combinadas, secadas sobre sulfato de magnesio, filtradas y concentradas para producir ácido 2-(2-cloro-5-nitrofenil)isonicotínico. Se esterificaron 300 mg de ácido 2-(2-cloro-5-nitrofenil)isonicotínico con 750 µL de 4N HCl en Dioxano en 10 mL de MeOH a 55°C por espacio de 16 horas. La reacción fue concentrada y sometida a un tratamiento básico, secada sobre sulfato de magnesio, filtrada y concentrada para producir metil 2-(2-cloro-5-nitrofenil) isonicotinato. 259 mg de metil 2-(2-cloro-5-nitrofenil)iso nicotinato fueron tratados con 200 mg de cloruro de estaño (II) y 500 µL de HCl en 10 mL de EtOH. Ante la finalización, EtOH fue concentrado y la reacción fue extraída con acetato de etilo y agua con TEA para reducir las emulsiones. La capa orgánica fue secada sobre sulfato de magnesio, filtrada y concentrada para producir metil 2-(5-amino-2-clorofenil)isonicotinato crudo. 240 mg de metil metil 2-(5-amino-2-clorofenil)iso nicotinato fueron tratados con 204 µL de 2-metil-6-(trifluorometil)nicotinoil cloruro mediante el procedimiento D. A 100 mg de metil 2-(2-cloro-5-(2-metil-6-(trifluorometil)nicotinamido)fenil)iso nicotinato a 0°C en 5 mL de EtOH se agregaron lentamente 135 mg de borohidruro de sodio. La reacción fue subsecuentemente sometida a reflujo 1 hora hasta completar, extinguida con agua y extraída con acetato de etilo. La capa orgánica fue secada sobre sulfato de magnesio, filtrada, concentrada y purificada por HPLC de fase inversa para producir *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



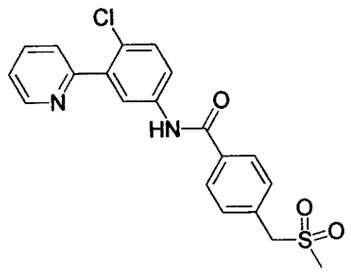
Se acoplaron 300 mg de 4-cloro-3-(piridin-2-il)anilina a 270 mg de ácido 4-nitrobenzoico mediante el procedimiento G. A 520 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-nitrobenzamida en 2.5 mL de HCl en 10 mL de EtOH se agregaron 1.3 g de cloruro de estaño (II) y se agitó a 55°C. Ante la finalización, la reacción fue concentrada y extraída con acetato de etilo en agua con TEA para reducir las emulsiones. La capa orgánica fue secada sobre sulfato de magnesio, filtrada y concentrada para producir 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 fueron sometidos a una reacción con 30 µL de metanosulfonil cloruro y 90 µL DIPEA en 500 µL DCM. La mezcla de reacción fue evaporada, sometida a un tratamiento básico y purificada por HPLC de fase inversa para producir *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



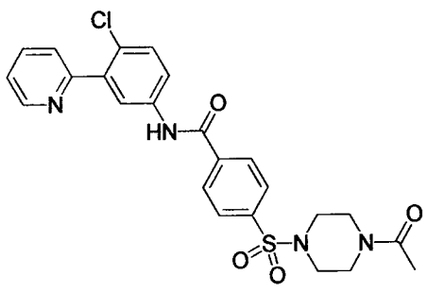
Se sometieron a una reacción 151 mg de 4-amino-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida con 105 µL de propano-2-sulfonil cloruro y 205 µL DIPEA en 500 µL DCM. La mezcla de reacción fue evaporada, sometida a condiciones de tratamiento básicas y purificada por HPLC de fase inversa para obtener *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(1-metiletilsulfonamido) benzamida. MS (Q1) 430 $(M)^+$.

Ejemplo 202 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil) benzamida



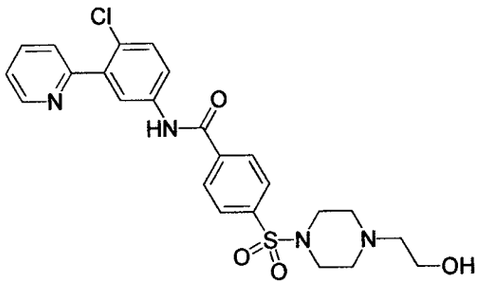
Se sometieron a una reacción 1 g de metil 4-(bromometil) benzoato mediante el procedimiento O. 2.77 g de metil 4-(metilsulfonilmetil) benzoato fueron hidrolizados mediante el procedimiento M. 1g de 4-cloro-3-(piridin-2-il)anilina fue acoplado a 1.15 g de ácido 4-(metilsulfonilmetil) benzoico mediante el procedimiento G. El producto crudo fue sometido a un tratamiento básico y recristalizado con 1:1 isopropilacetato y éter para producir *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



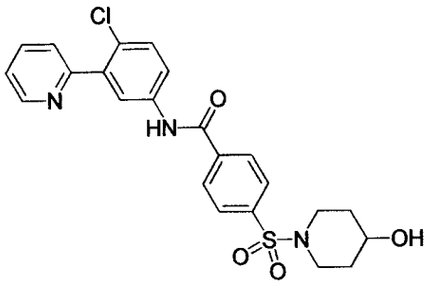
Se sometió a una reacción 1 g de ácido 4-(clorosulfonil) benzoico con 646 µL de 1-(piperazin-1-il)etanona mediante el procedimiento H. Se acoplaron 75 mg de 4-cloro-3-(piridin-2-il)anilina a 125 mg de ácido 4-(4-acetilpiperazin-1-ilsulfonil) benzoico mediante el procedimiento G y se purificó por HPLC de fase inversa para producir 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



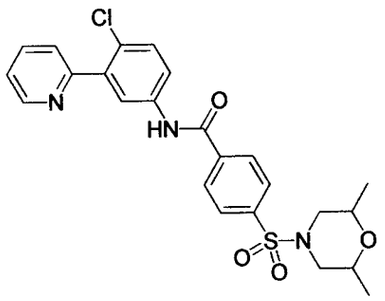
Se sometieron a una reacción 1 g de ácido 4-(clorosulfonil) benzoico con 615 µL de 2-(piperazin-1-il)etanol mediante el procedimiento H. Se acoplaron 75 mg de 4-cloro-3-(piridin-2-il)anilina a 125 mg de ácido 4-(4-(3-hidroxipropilo)piperazin-1-ilsulfonil) benzoico mediante el procedimiento G y se purificó por HPLC de fase inversa para producir *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-hidroxipiperidin-1-ilsulfonil) benzamida



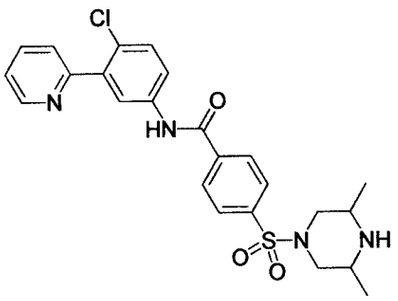
Se sometió a una reacción 1 g de ácido 4-(clorosulfonil) benzoico con 506 µL de piperidin-4-ol mediante el procedimiento H. 75 mg de 4-cloro-3-(piridin-2-il)anilina fueron acoplados a 114 mg de ácido 4-(4-hidroxipiperidin-1-ilsulfonil) benzoico mediante el procedimiento G y se purificó por HPLC de fase inversa para producir *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



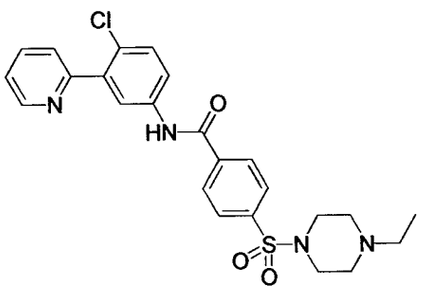
Se sometieron a una reacción 1 g de ácido 4-(clorosulfonil) benzoico con 616 µL de 2,6-dimetilmorfolina mediante el procedimiento H. Se acoplaron 75 mg de 4-cloro-3-(piridin-2-il)anilina a 120 mg de ácido 4-(2,6-dimetilmorfolinosulfonil) benzoico mediante el procedimiento G y se purificó por HPLC de fase inversa para producir *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 sometió a una reacción 1 g de ácido 4-(clorosulfonil) benzoico con 570 mg de 2,6-dimetilpiperazina mediante el procedimiento H. Se acoplaron 75 mg de 4-cloro-3-(piridin-2-il)anilina a 119 mg de ácido 4-(3,5-dimetilpiperazin-1-ilsulfonil) benzoico mediante el procedimiento G y se purificó por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(3,5-dimetilpiperazin-1-ilsulfonil) benzamida. MS (Q1) 485.4 $(M)^+$.

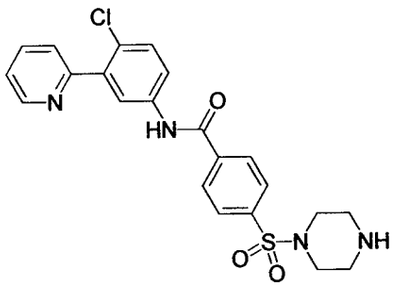
Ejemplo 208 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-etilpiperazin-1-ilsulfonil) benzamida



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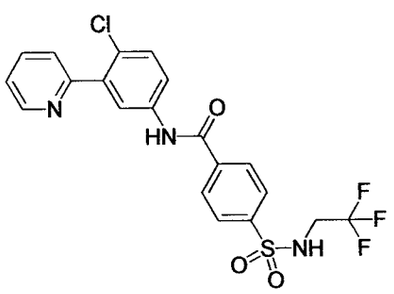
Se sometió a una reacción 1 g de ácido 4-(clorosulfonil) benzoico con 570 mg de 1-etilpiperazina mediante el procedimiento H. Se acoplaron 75 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 4-(4-etilpiperazin-1-ilsulfonil) benzoico mediante el procedimiento G y se purificó por HPLC de fase inversa para producir *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



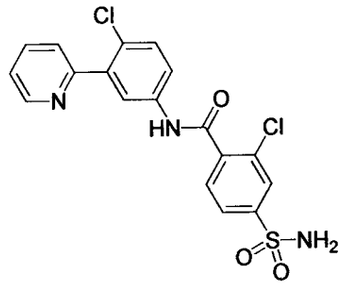
Se sometió a una reacción 1 g de ácido 4-(clorosulfonil) benzoico con 931 mg de *tert*-butil piperazina-1-carboxilato mediante el procedimiento H. Se acoplaron 75 mg de 4-cloro-3-(piridin-2-il)anilina a 150 mg de ácido 4-(4-(*tert*-butoxicarbonil)piperazin-1-ilsulfonil) benzoico mediante el procedimiento G. El producto crudo fue sometido a condiciones de tratamiento básicas, tratado con TFA para remover el grupo Boc y purificado por HPLC de fase inversa para producir *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



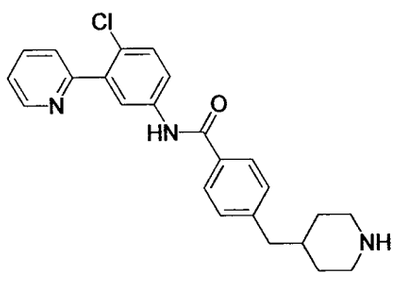
Se sometió a una reacción 1 g de ácido 4-(clorosulfonil) benzoico con 500 µL de 2,2,2-trifluoroetanamina mediante el procedimiento H. Se acoplaron 60 mg de 4-cloro-3-(piridin-2-il)anilina a 92 mg de ácido 4-(*N*-(2,2,2-trifluoroetil)sulfamoil) benzoico mediante el procedimiento G y se purificó por HPLC de fase inversa para producir *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



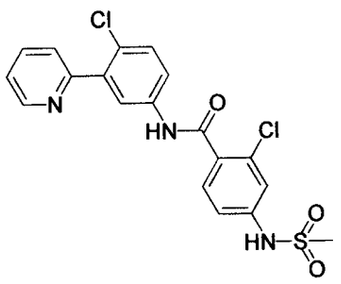
Una solución de 818 mg de nitrito de sodio en 13 mL de agua se agregó por goteo a una solución de 2g de metil 4-amino-2-clorobenzoato en 5 mL de HCl y 15 mL de AcOH a 0°C. La reacción fue removida del baño de hielo y agitado a temperatura ambiente por espacio de 15 minutos. Simultáneamente una solución de 460 mg de cloruro de cobre II dihidrato en 1 mL de agua se agregó a una solución de gas dióxido de azufre saturada en 10 mL de AcOH a 0°C. La solución enfriada conteniendo cloruro de cobre II y gas dióxido de azufre fue lentamente agregada a la solución inicial re-enfriada que contiene nitrito de sodio. La reacción fue calentada a temperatura ambiente y agitada hasta que el gas ya no evolucionó. La reacción fue filtrada por celita y vertida en un vaso de agua helada bajo agitación hasta lograr un sólido amarillo-anaranjado. La solución de agua helada fue filtrada a través de un embudo Buchner para colectar el precipitado de metil 2-cloro-4-(clorosulfonil) benzoato y se procedió a secar durante 24 horas bajo vacío. Se agregó 1g de metil 2-cloro-4-(clorosulfonil) benzoato a una solución de 2 mL de solución de Ammonia 2M en MeOH y 970 µL DIPEA en 5 mL MeOH. Ante la finalización, la reacción fue concentrada, extraída dos veces con bicarbonato saturado, secada con sulfato de magnesio, filtrada y concentrada para producir metil 2-cloro-4-sulfamoilbenzoato. Se hidrolizaron 777 mg de metil 2-cloro-4-sulfamoilbenzoato mediante el procedimiento M para producir ácido 2-cloro-4-sulfamoilbenzoico crudo. Se acoplaron 75 mg de 4-cloro-3-(piridin-2-il)anilina a 91 mg de ácido 2-cloro-4-sulfamoilbenzoico crudo mediante el procedimiento G. El producto crudo fue purificado por HPLC de fase inversa para producir 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



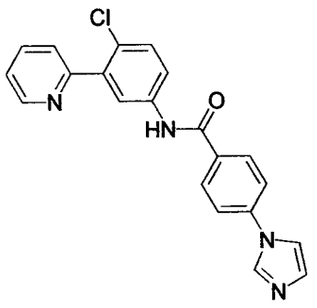
Se acoplaron 75 mg de 4-cloro-3-(piridin-2-il)anilina a 125 mg de ácido 4-((1-(*tert*-butoxicarbonil)piperidin-4-il)metil) benzoico mediante el procedimiento G. El producto crudo fue tratado con 4N HCl en Dioxano, evaporado y purificado por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(piperidin-4-ilmetil) benzamida. MS (Q1) 406.1 $(M)^+$.

Ejemplo 213 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonamido) benzamida



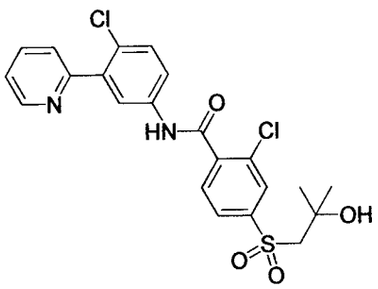
Se hidrolizaron 4.2 g de metil 2-cloro-4-(metilsulfonamido) benzoato mediante el procedimiento M. Se acopló 1 g de 4-cloro-3-(piridin-2-il)anilina a 1.35 g de ácido 2-cloro-4-(metilsulfonamido) benzoico mediante el procedimiento G. El producto crudo fue purificado por HPLC de fase inversa para producir 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 acoplaron 75 mg de 4-cloro-3-(piridin-2-il)anilina a 78 mg de ácido 4-(1*H*-imidazol-1-il) benzoico mediante el procedimiento G . El producto crudo fue purificado por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(1*H*-imidazol-1-il) benzamida. MS (Q1) 375.3 $(M)^+$.

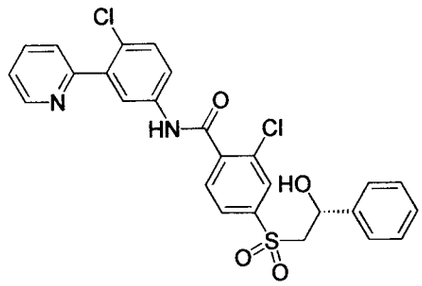
Ejemplo 215 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxi-2-metilpropilsulfonil)-benzamida



Se disolvieron 8 g de metil 4-amino-2-clorobenzoato en 16 mL de MeOH, 8 mL de H_2O y 8 mL de ácido clorhídrico concentrado y luego se enfrió a 0 °C. Una solución de 3.9 g de nitrito de sodio en 15 mL de H_2O fue agregada por goteo durante 30 minutos. La reacción fue agitada a 0 °C por espacio de una hora más. La mezcla de diazonación fría fue agregada a una solución de 13.8 g de etil xantato de potasio en 10 mL de H_2O a 50~60 °C. La reacción fue calentada a 65 °C por espacio de 2h y monitoreada por TLC hasta completar. La mezcla fue enfriada a 25 °C y extraída con acetato de etilo. Los extractos orgánicos combinados fueron lavados con solución salina, secados ($MgSO_4$), y concentrados. Se purificó por cromatografía en gel de sílice (0-10% acetato de etilo/hexano) para obtener metil 2-cloro-4-(etoxicarbonotioyltio) benzoato. Una solución de 2.6 g de hidróxido de sodio en 20 mL de H_2O se agregaron a 5.9 g de metil 2-cloro-4-(etoxicarbonotioiltio) benzoato en 40 mL de EtOH La mezcla de reacción fue calentada a 70 °C por espacio de 1h. Ante la finalización, la mezcla fue enfriada a 25 °C, y luego acidificada a pH 3 mediante la adición de 10 N HCl. El sólido fue filtrado y lavado con H_2O para producir ácido 2-cloro-4-mercaptobenzonico. Se sometieron a reflujo 3.8 g de ácido 2-cloro-4-mercaptobenzonico en 40 mL de 5% ácido sulfúrico-metanol bajo una atmósfera de nitrógeno durante 3h. Luego de la concentración de la mezcla de reacción, se agregaron 10 mL de H_2O y la mezcla resultante fue alcalinizada con hidrógeno carbonato de sodio, y extraída con acetato de etilo. La capa orgánica fue lavada con solución salina, secada ($MgSO_4$), y evaporada para producir metil 2-cloro-4-mercaptobenzoato. Se sometieron a una reacción 80 mg de óxido de isobutileno con metil 2-cloro-4-mercaptobenzoato mediante el procedimiento S para obtener metil 2-cloro-4-(2-hidroxi-2-metilpropiltio) benzoato. 190 mg de metil 2-cloro-4-(2-hidroxi-2-metilpropiltio) benzoato fueron hidrolizados mediante el procedimiento M para producir ácido 2-cloro-4-(2-hidroxi-2-metilpropiltio) benzoico. Se sometieron a una reacción 160 mg de ácido 2-cloro-4-(2-hidroxi-2-metilpropiltio) benzoico mediante el procedimiento R para producir ácido 2-cloro-4-(2-hidroxi-2-metilpropilsulfonil) benzoico. Se acoplaron 60 mg de 4-cloro-3-(piridina-2-il)anilina a ácido 2-cloro-4- (2-hidroxi-2-metilpropilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase

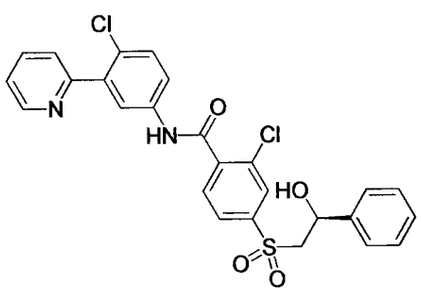
inversa para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxi-2-metilpropilsulfonil) benzamida. MS (Q1) 479.1 $(M)^+$.

Ejemplo 216 (*R*)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxi-2-feniletilsulfonil) benzamida



Se sometieron a una reacción 150 mg de (*R*)-óxido de estireno con metil 2-cloro-4-mercaptobenzoato mediante el procedimiento S para obtener (*R*)-metil 2-cloro-4-(2-hidroxi-2-feniletiltio) benzoato. Se hidrolizaron 190 mg de (*R*)-metil-2-cloro-4-(2-hidroxi-2-feniletiltio) benzoato mediante el procedimiento M para producir ácido (*R*)-2-cloro-4-(2-hidroxi-2-feniletiltio) benzoico. Se sometieron a una reacción 170 mg de ácido (*R*)-2-cloro-4-(2-hidroxi-2-feniletiltio) benzoico mediante el procedimiento R para producir ácido (*R*)-2-cloro-4-(2-hidroxi-2-feniletilsulfonil) benzoico. Se acoplaron 60 mg de 4-cloro-3-(piridina-2-il)anilina a ácido (*R*)-2-cloro-4-(2-hidroxi-2-feniletilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir (*R*)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxi-2-feniletilsulfonil) benzamida. MS (Q1) 527.2 $(M)^+$.

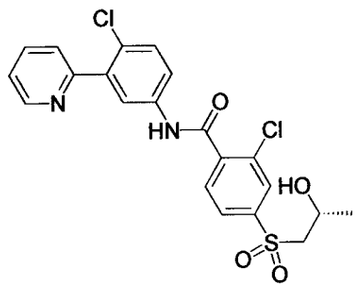
Ejemplo 217 (*S*)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxi-2-feniletil-sulfonil) benzamida



Se sometieron a una reacción 119 mg de (*S*)-óxido de estireno con metil 2-cloro-4-mercaptobenzoato mediante el procedimiento S para obtener (*S*)-metil 2-cloro-4-(2-hidroxi-2-feniletiltio) benzoato. 230 mg de (*S*)-metil-2-cloro-4-(2-hidroxi-2-feniletiltio)

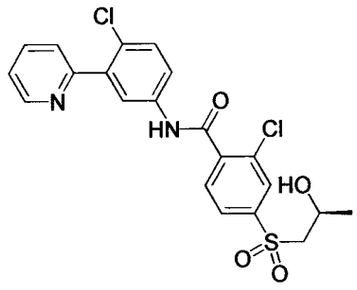
benzoato fueron hidrolizados mediante el procedimiento M para producir ácido (*S*)-2-cloro-4-(2-hidroxi-2-feniletiltio) benzoico. Se sometieron a una reacción 180 mg de ácido (*S*)-2-cloro-4-(2-hidroxi-2-feniletiltio) benzoico mediante el procedimiento R para producir ácido (*S*)-2-cloro-4-(2-hidroxi-2-feniletilsulfonil) benzoico. Se acoplaron 60 mg de 4-cloro-3-(piridina-2-il)anilina a ácido (*S*)-2-cloro-4-(2-hidroxi-2-feniletilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir (*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-hidroxipropilsulfonil)-benzamida



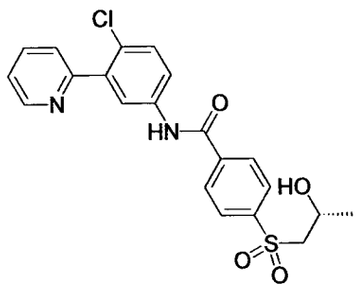
Se sometieron a una reacción 140 mg de (*R*)-óxido de propileno con metil 2-cloro-4-mercaptobenzoato mediante el procedimiento S para obtener (*R*)-metil 2-cloro-4-(2-hidroxipropiltio) benzoato. 435 mg de (*R*)-metil-2-cloro-4-(2-hidroxipropiltio) benzoato fueron hidrolizados mediante el procedimiento M para producir ácido (*R*)-2-cloro-4-(2-hidroxipropiltio) benzoico. 403 mg de ácido (*R*)-2-cloro-4-(2-hidroxipropiltio) benzoico fueron sometidos a una reacción mediante el procedimiento R para producir ácido (*R*)-2-cloro-4-(2-hidroxipropilsulfonil) benzoico. Se acoplaron 298 mg de 4-cloro-3-(piridina-2-il)anilina a ácido (*R*)-2-cloro-4-(2-hidroxipropilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir (*R*)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxipropilsulfonil) benzamida. MS (Q1) 465.1 $(M)^+$.

Ejemplo 219 (*S*)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxipropilsulfonil)-benzamida



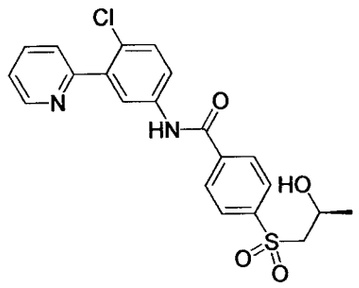
Se sometieron a una reacción 86 mg de (*S*)-óxido de propileno con metil 2-cloro-4-mercaptobenzoato mediante el procedimiento S para obtener (*S*)-metil 2-cloro-4-(2-hidroxipropiltio) benzoato. 275 mg de (*S*)-metil-2-cloro-4-(2-hidroxipropiltio) benzoato fueron hidrolizados mediante el procedimiento M para producir ácido (*S*)-2-cloro-4-(2-hidroxipropiltio) benzoico. Se sometieron a una reacción 220 mg de ácido (*S*)-2-cloro-4-(2-hidroxipropiltio) benzoico mediante el procedimiento R para producir ácido (*S*)-2-cloro-4-(2-hidroxipropilsulfonil) benzoico. Se acoplaron 70 mg de 4-cloro-3-(piridina-2-il)anilina a ácido (*S*)-2-cloro-4-(2-hidroxipropilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir (*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



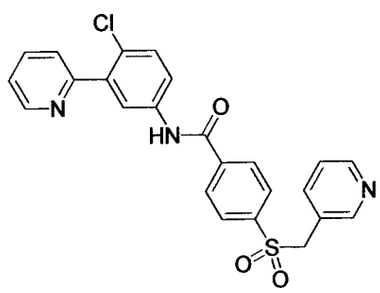
Se sometieron a una reacción 100 mg de (*R*)-óxido de propileno con metil 4-mercaptobenzoato mediante el procedimiento S para obtener (*R*)-metil 4-(2-hidroxipropiltio) benzoato. Se sometieron a una reacción 169 mg de (*R*)-metil 4-(2-hidroxipropiltio) benzoato mediante el procedimiento R para producir (*R*)-metil 4-(2-hidroxipropilsulfonil) benzoato. 179 mg de (*R*)-metil 4-(2-hidroxipropilsulfonil) benzoato fueron hidrolizados mediante el procedimiento M para producir ácido (*R*)-4-(2-hidroxipropilsulfonil) benzoico. Se acoplaron 45 mg de 4-cloro-3-(piridina-2-il)anilina a ácido (*R*)-4-(2-hidroxipropilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir (*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 sometieron a una reacción 150 mg de (*S*)-óxido de propileno con metil 4-mercaptobenzoato mediante el procedimiento S para obtener (*S*)-metil 4-(2-hidroxipropiltio) benzoato. Se sometieron a una reacción 650 mg de (*S*)-metil 4-(2-hidroxipropiltio) benzoato mediante el procedimiento R para producir (*S*)-metil 4-(2-hidroxipropilsulfonil) benzoato. 350 mg de (*S*)-metil 4-(2-hidroxipropilsulfonil) benzoato fueron hidrolizados mediante el procedimiento M para producir ácido (*S*)-4-(2-hidroxipropilsulfonil) benzoico. Se acoplaron 45 mg de 4-cloro-3-(piridina-2-il)anilina a ácido (*S*)-4-(2-hidroxipropilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir (*S*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxipropilsulfonil) benzamida. MS (Q1) 431.3 $(M)^+$.

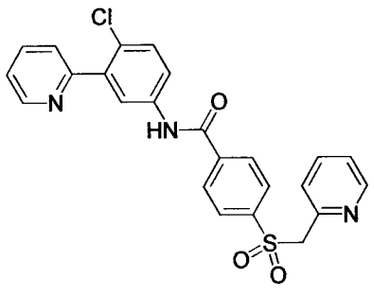
Ejemplo 222 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(piridin-3-ilmetilsulfonil) benzamida



Se sometieron a una reacción 1g de 3-(bromometil)piridina hidrobromuro con metil 4-mercaptobenzoato mediante el procedimiento Q para obtener metil 4-(piridin-3-ilmetiltio) benzoato. Se sometieron a una reacción 980 mg de metil 4-(piridin-3-ilmetiltio) benzoato mediante el procedimiento R para producir metil 4-(piridin-3-ilmetilsulfonil) benzoato. 760 mg de metil 4-(piridin-3-ilmetilsulfonil) benzoato fueron hidrolizados mediante el procedimiento M para producir ácido 4-(piridin-3-ilmetilsulfonil) benzoico. Se acoplaron 60 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 4-(piridin-3-ilmetilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(piridin-3-ilmetilsulfonil) benzamida. MS (Q1) 464.1 $(M)^+$.

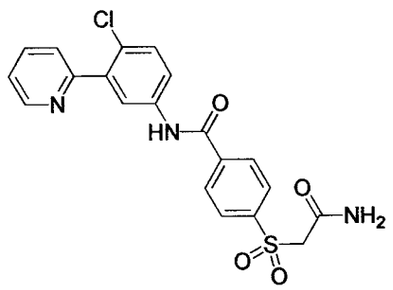
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Ejemplo 223 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(piridin-2-ilmetilsulfonil) benzamida



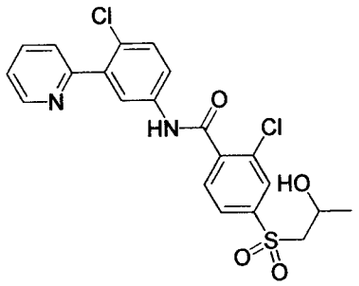
Se sometió a una reacción 1g de 2-(bromometil)piridina hidrobromuro con metil 4-mercaptobenzoato mediante el procedimiento Q para obtener metil 4-(piridin-2-ilmetiltio) benzoato. Se sometieron a una reacción 500 mg de metil 4-(piridin-2-ilmetiltio) benzoato mediante el procedimiento R para producir metil 4-(piridin-2-ilmetilsulfonil) benzoato. 470 mg de metil 4-(piridin-2-ilmetilsulfonil) benzoato fueron hidrolizados mediante el procedimiento M para producir ácido 4-(piridin-2-ilmetilsulfonil) benzoico. Se acoplaron 70 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 4-(piridin-2-ilmetilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir *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



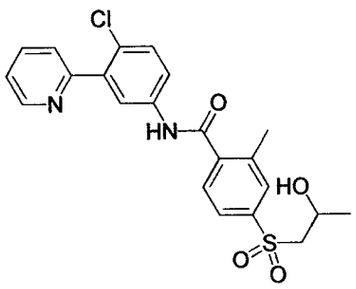
Se sometieron a una reacción 2.5 g de 2-bromoacetamida con metil 4-mercaptobenzoato mediante el procedimiento Q para obtener metil 4-(2-amino-2-oxoetiltio) benzoato. Se sometieron a una reacción 2.6 g de metil 4-(2-amino-2-oxoetiltio) benzoato mediante el procedimiento R para producir metil 4-(2-amino-2-oxoetilsulfonil) benzoato. 1 g de metil 4-(2-amino-2-oxoetilsulfonil) benzoato fue hidrolizado mediante el procedimiento M para producir ácido 4-(2-amino-2-oxoetilsulfonil) benzoico. Se acoplaron 150 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 4-(2-amino-2-oxoetilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 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 sometieron a una reacción 2 g de 2-cloro-4-fluorobenzonitrilo con 1-mercapto-2-propanol mediante el procedimiento Q para obtener 2-cloro-4-(2-hidroxipropiltio)benzonitrilo. Se sometieron a una reacción 2.5 g de 2-cloro-4-(2-hidroxipropiltio)benzonitrilo mediante el procedimiento T para producir ácido 2-cloro-4-(2-hidroxipropiltio) benzoico. Se sometieron a una reacción 2.1 g de ácido 2-cloro-4-(2-hidroxipropiltio) benzoico mediante el procedimiento R para producir ácido 2-cloro-4-(2-hidroxipropilsulfonil) benzoico. Se acoplaron 70 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 2-cloro-4-(2-hidroxipropilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxipropilsulfonil) benzamida. MS (Q1) 465.2 $(M)^+$.

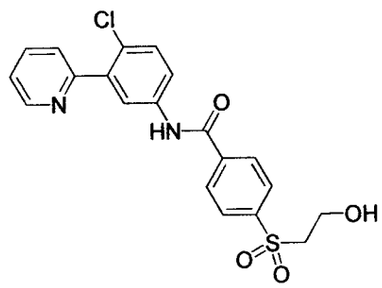
Ejemplo 226 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxipropilsulfonil)-2-metilbenzamida



Se sometieron a una reacción 2 g de 4-bromo-2-metilbenzonitrilo con 1-mercapto-2-propanol mediante el procedimiento Q para obtener 4-(2-hidroxipropiltio)-2-metilbenzonitrilo. Se sometieron a una reacción 950 mg de 4-(2-hidroxipropiltio)-2-metilbenzonitrilo mediante el procedimiento T para producir ácido 4-(2-hidroxipropiltio)-2-metilbenzoico. Se sometió a una reacción 1.0 g de ácido 4-(2-hidroxipropiltio)-2-metilbenzoico mediante el procedimiento R para producir ácido 4-(2-hidroxipropilsulfonil)-2-metilbenzoico. Se acoplaron 100 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 4-(2-hidroxipropilsulfonil)-2-metilbenzoico mediante el procedimiento G. El producto fue

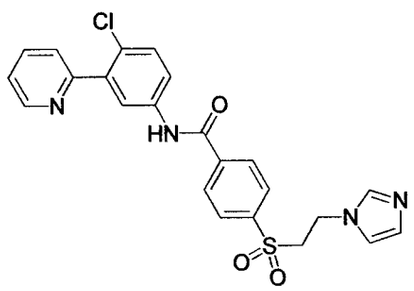
purificado en HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxipropilsulfonil)-2-metilbenzamida. MS (Q1) 445.3 $(M)^+$.

Ejemplo 227 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxietilsulfonil) benzamida



5 g de 4-fluorobenzonitrilo fueron usados en el procedimiento Q con 2-mercaptoetanol para obtener 4-(2-hidroxietiltio)benzonitrilo. Se sometieron a una reacción 900 mg de 4-(2-hidroxietiltio)benzonitrilo mediante el procedimiento T para producir ácido 4-(2-hidroxietiltio) benzoico. Se sometió a una reacción 1.0 g de ácido 4-(2-hidroxietiltio) benzoico mediante el procedimiento R para producir ácido 4-(2-hidroxietilsulfonil) benzoico. Se acoplaron 80 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 4-(2-hidroxietilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir *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

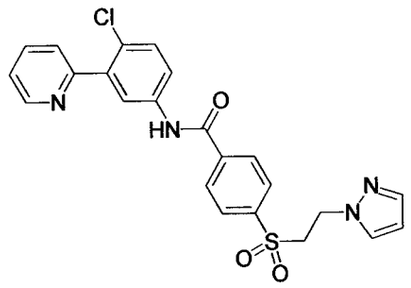


Se sometieron a una reacción 4 g de 4-(2-hidroxietiltio)benzonitrilo mediante el procedimiento R para producir 4-(2-hidroxietilsulfonil)benzonitrilo. Se agregaron 3.0 g de trifenilfosfina a una solución de 2 g de 4-(2-hidroxietilsulfonil)benzonitrilo y 4.7 g de tetrabromuro de carbono en diclorometano a 0 °C. La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante 1h. La mezcla fue diluida con diclorometano, lavada con H_2O, secada ($MgSO_4$) y evaporada. Se purificó por

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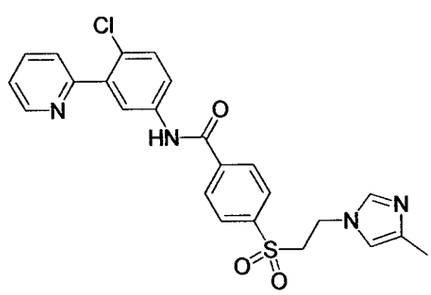
cromatografía en gel de sílice (0-70% acetato de etilo/hexano) para obtener 4-(2-bromoetilsulfonil)benzonitrilo. 250 mg de 4-(2-bromoetilsulfonil)benzonitrilo fueron usados en el procedimiento P con imidazol para producir 4-(2-(1*H*-imidazol-1-il)etilsulfonil)benzonitrilo. 300 mg de 4-(2-(1*H*-imidazol-1-il)etilsulfonil)benzonitrilo fueron sometidos a una reacción mediante el procedimiento T para producir ácido 4-(2-(1H-imidazol-1-il)etilsulfonil) benzoico. Se acoplaron 60 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 4-(2-(1H-imidazol-1-il)etilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 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 usaron 250 mg de 4-(2-bromoetilsulfonil)benzonitrilo en el procedimiento P con pirazol para producir 4-(2-(1*H*-pirazol-1-il)etilsulfonil)benzonitrilo. 300 mg de 4-(2-(1*H*-pirazol-1-il)etilsulfonil)benzonitrilo fueron sometidos a una reacción mediante el procedimiento T para producir ácido 4-(2-(1H-pirazol-1-il)etilsulfonil) benzoico. Se acoplaron 75 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 4-(2-(1H-pirazol-1-il)etilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 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

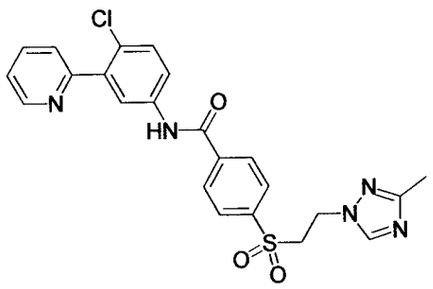


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Se usaron 270 mg de 4-(2-bromoetilsulfonil)benzonitrilo en el procedimiento P con 4-metilimidazol para producir 4-(2-(4-metil-1*H*-imidazol-1-il)etilsulfonil)benzonitrilo. 320 mg de 4-(2-(4-metil-1*H*-imidazol-1-il)etilsulfonil)benzonitrilo fueron sometidos a una reacción mediante el procedimiento T para producir ácido 4-(2-(4-metil-1H-imidazol-1-il)etilsulfonil) benzoico.

Se acoplaron 70 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 4-(2-(4-metil-1H-imidazol-1-il)etilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-(4-metil-1*H*-imidazol-1-il)etilsulfonil) benzamida. MS (Q1) 481.0 $(M)^+$.

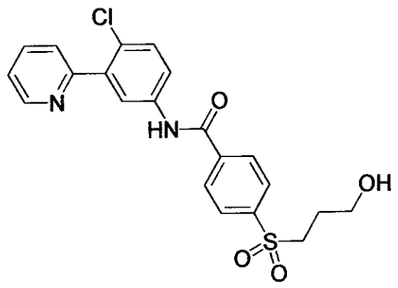
Ejemplo 231 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-(3-metil-1*H*-1,2,4-triazol-1-il)etilsulfonil) benzamida.



A una suspensión bajo agitación de 10 g de tiosemicarbazida en 100 mL de piridina se agregaron lentamente 7.8 ml de acetil cloruro a 0 °C. La temperatura fue mantenida durante toda la adición (0 °C - 4 °C). La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante 16 h. La evaporación dio como resultado 1-acetil tiosemicarbazida. El crudo 1-acetil tiosemicarbazida fue disuelto en 70 mL de MeOH y 12 g de metóxido de sodio, y sometido a reflujo por espacio de 10 h. El solvente fue removido y el residuo fue disuelto en H_2O, luego acidificado a pH 2 mediante la adición de 1N HCl. El sólido resultante fue filtrado y lavado con H_2O para producir 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 fue agitada durante 1h a 0 °C, y basificada con carbonato de sodio saturado y concentrada. El residuo fue disuelto con MeOH y filtrado. El filtrado fue evaporado para producir 3-metil-1,2,4-triazol. 230 mg de 4-(2-bromoetilsulfonil)benzonitrilo fueron usados en el procedimiento P con 3-metil-1,2,4-triazol para producir 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 fueron sometidos a una reacción mediante el procedimiento T para producir ácido 4-(2-(3-metil-1H-1,2,4-triazol-1-il)etilsulfonil) benzoico.

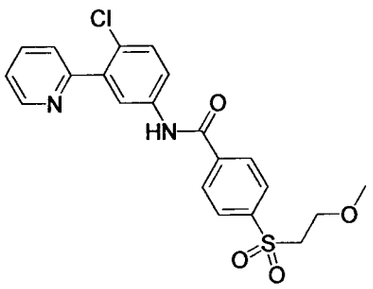
Se acoplaron 60 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 4-(2-(3-metil-1H-1,2,4-triazol-1-il)etilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-(3-metil-1*H*-1,2,4-triazol-1-il)etilsulfonil) benzamida. MS (Q1) 482.1 $(M)^+$.

Ejemplo 232 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(3-hidroxipropilsulfonil) benzamida

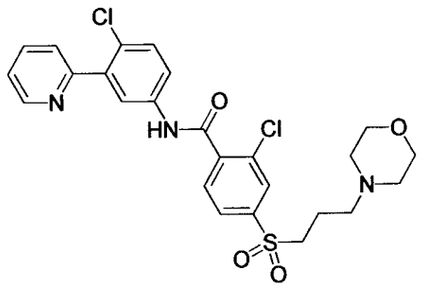


Se usaron 5 g de 4-fluorobenzonitrilo en el procedimiento Q con 3-mercapto-1-propanol para obtener 4-(3-hidroxipropiltio)benzonitrilo. 1.8 g de 4-(3-hidroxipropiltio)benzonitrilo fueron sometidos a una reacción mediante el procedimiento T para producir ácido 4-(3-hidroxipropiltio) benzoico. 1.2 g de ácido 4-(3-hidroxipropiltio) benzoico fueron sometidos a una reacción mediante el procedimiento R para producir ácido 4-(3-hidroxipropilsulfonil) benzoico. Se acoplaron 50 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 4-(3-hidroxipropilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir *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

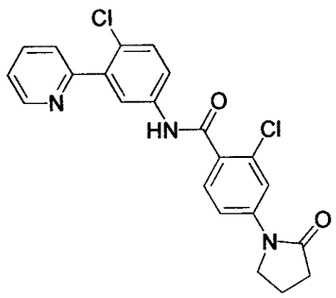


Una mezcla de 500 mg de metil 4-mercaptobenzoato, 1.6 g de carbonato de potasio, 1.2 g de 2-bromoetiléter etílico y 329 mg de tetrabutilamonio yoduro en 10 mL de acetona fueron sometidos a reflujo por espacio de 16 h. La mezcla de reacción fue diluida con acetato de etilo, lavada con H_2O y concentrada. Se purificó por cromatografía en gel de sílice (0-50% acetato de etilo/ hexano) para producir 4-(2-metoxietiltio) benzoato. 240 mg



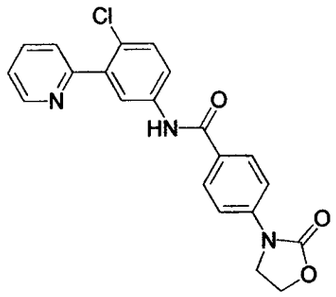
120 mg de 4-(3-bromopropilsulfonil)-2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida fueron usados en el procedimiento P con morfolina para producir 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(3-morfolinopropilsulfonil) benzamida. MS (Q1) 534.0 $(M)^+$.

Ejemplo 240 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-oxopirrolidin-1-il) benzamida



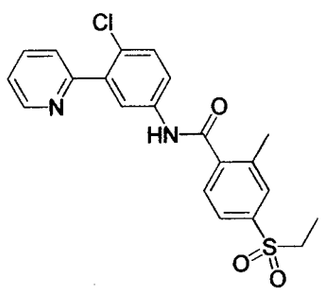
Una mezcla de 500 mg de 2-cloro-4-florobenzonitrilo, 821 mg de 2-pirrolidinona y 3 g de carbonato de cesio en 5 mL de DMF fue calentada a 100 °C en un reactor a microondas sellado por espacio de 15 minutos. La mezcla de reacción fue diluida con acetato de etilo, lavada con H_2O, secada ($MgSO_4$) y evaporada. Se purificó por cromatografía en gel de sílice (20-80% acetato de etilo/hexano) para obtener 2-cloro-4-(2-oxopirrolidin-1-il)benzonitrilo. 890 mg de 2-cloro-4-(2-oxopirrolidin-1-il)benzonitrilo fueron sometidos a una reacción mediante el procedimiento T para producir ácido 2-cloro-4-(2-oxopirrolidin-1-il) benzoico. 80 mg de 4-cloro-3-(piridin-2-il)anilina se acoplaron al ácido 2-cloro-4-(2-oxopirrolidin-1-il) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 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



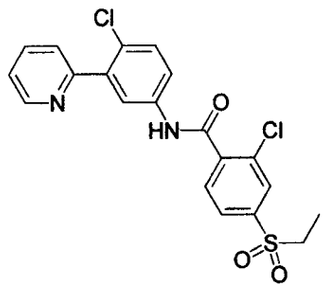
Una mezcla de 1 g de metil 4-yodobenzoato, 399 mg de 2-oxozolidona, 1.1 g de carbonato de potasio, 34 mg de N, N'-dimetiletilenediamina y 73 mg de yoduro de cobre en 10 mL de tolueno fue calentada a 150 °C en un reactor a microondas sellado por espacio de 2h. La mezcla de reacción fue diluida con acetato de etilo, lavada con H_2O, secada ($MgSO_4$) y evaporada. Se purificó por cromatografía en gel de sílice (20-70% acetato de etilo/hexano) para obtener metil 4-(2-oxooxazolidin-3-il) benzoato. 530 mg de metil 4-(2-oxooxazolidin-3-il) benzoato fueron hidrolizados mediante el procedimiento M para producir ácido 4-(2-oxooxazolidin-3-il) benzoico. Se acoplaron 70 mg de 4-cloro-3-(piridin-2-il)anilina al ácido 4-(2-oxooxazolidin-3-il) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir *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



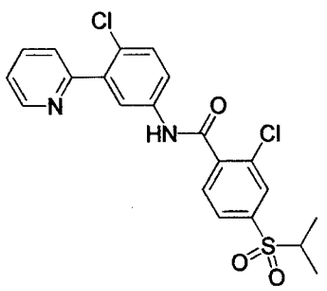
4 g de 4-bromo-2-metilbenzonitrilo fueron usados en el procedimiento Q con etanotiol para obtener 4-(etiltio)-2-metilbenzonitrilo. 2 g de 4-(etiltio)-2-metilbenzonitrilo fueron sometidos a una reacción mediante el procedimiento R para producir 4-(etilsulfonil)-2-metilbenzonitrilo. 2.5 g de 4-(etilsulfonil)-2-metilbenzonitrilo fueron sometidos a una reacción mediante el procedimiento T para producir ácido 4-(etilsulfonil)-2-metilbenzoico. Se acoplaron 75 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 4-(etilsulfonil)-2-metilbenzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir *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



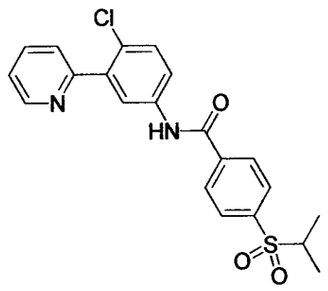
4 g de 2-cloro-4-fluorobenzonitrilo fueron usados en el procedimiento Q con etanotiol para obtener 2-cloro-4-(etiltio)benzonitrilo. 2 g de 2-cloro-4-(etiltio)benzonitrilo fueron sometidos a una reacción mediante el procedimiento T para producir ácido 2-cloro 4-(etiltio) benzoico. 1.5 g de ácido 2-cloro 4-(etiltio) benzoico fueron sometidos a una reacción mediante el procedimiento R para producir ácido 2-cloro-4-(etilsulfonil) benzoico. Se acoplaron 75 mg de 4-cloro-3-(piridin-2-il)anilina al ácido 2-cloro-4-(etilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 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



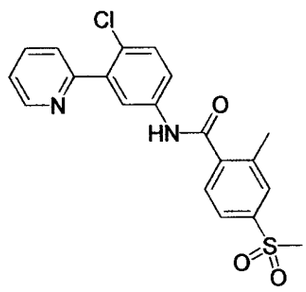
2 g de 2-cloro-4-fluorobenzonitrilo fueron usados en el procedimiento Q con 2-propanotiol para obtener 2-cloro-4-(isopropiltio)benzonitrilo. 1.6 g de 2-cloro-4-(isopropiltio)benzonitrilo fueron sometidos a una reacción mediante el procedimiento T para producir ácido 2-cloro-4-(isopropiltio) benzoico. 1 g de ácido 2-cloro-4-(isopropiltio) benzoico fue sometido a una reacción mediante el procedimiento R para producir ácido 2-cloro-4-(isopropilsulfonil) benzoico. Se acoplaron 75 mg de 4-cloro-3-(piridin-2-il)anilina al ácido 2-cloro-4-(isopropilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 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



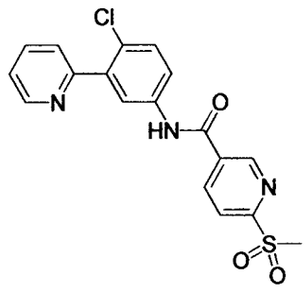
2 g de 4-fluorobenzonitrilo fueron usados en el procedimiento Q con 2-propanotiol para obtener 4-(isopropiltio)benzonitrilo. 900 mg de 4-(isopropiltio)benzonitrilo fueron sometidos a una reacción mediante el procedimiento T para producir ácido 4-(isopropiltio) benzoico. 730 mg de ácido 4-(isopropiltio) benzoico fueron sometidos a una reacción mediante el procedimiento R para producir 4-ácido (isopropilsulfonil) benzoico. Se acoplaron 75 mg de 4-cloro-3-(piridin-2-il)anilina al 4-ácido (isopropilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir *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



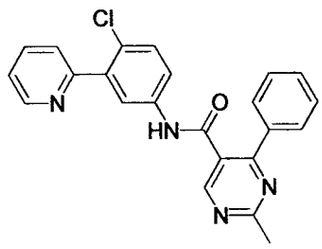
Una solución de 500 mg de 4-bromo-2-metilbenzonitrilo y 268 mg de sodio tiometóxido en 3 mL de DMF fue agitada durante 1h. La mezcla de reacción fue diluida con acetato de etilo, lavada con H_2O, secada ($MgSO_4$) y evaporada para obtener 2-metil-4-(metiltio)benzonitrilo. 400 mg de 2-metil-4-(metiltio)benzonitrilo fueron sometidos a una reacción mediante el procedimiento T para producir ácido 2-metil-4-(metiltio) benzoico. 430 mg de ácido 2-metil-4-(metiltio) benzoico fueron sometidos a una reacción mediante el procedimiento R para producir ácido 2-metil-4-(metilsulfonil) benzoico. 60 mg de 4-cloro-3-(piridin-2-il)anilina fueron acoplados al ácido 2-metil-4-(metilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir *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



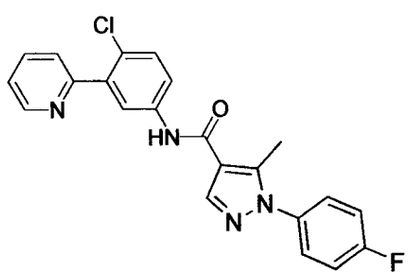
1 g de metil 6-cloro nicotinato fue sometido a una reacción mediante el procedimiento O para producir metil 6-(metilsulfonil) nicotinato. 1 g de metil 6-(metilsulfonil) nicotinato fue hidrolizado mediante el procedimiento M para producir ácido 6-(metilsulfonil) nicotínico. Se acoplaron 100 mg de 4-cloro-3-(piridin-2-il)anilina al ácido 6-(metilsulfonil) nicotínico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir *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-fenilpirimidina-5-carboxamida



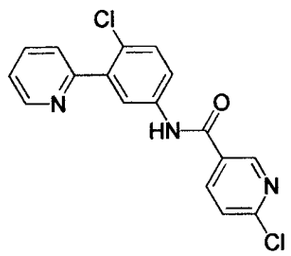
Se acoplaron 50 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 4-metil-2-fenil-5-pirimidina carboxílico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-4-fenilpirimidina-5-carboxamida. MS (Q1) 401.1 $(M)^+$.

Ejemplo 249 *N*-(4-cloro-3-(piridin-2-il)fenil)-1-(4-fluorofenil)-5-metil-1*H*-pirazol-4-carboxamida



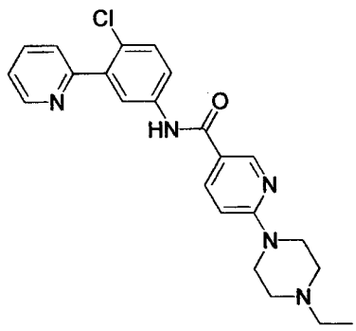
Se acoplaron 50 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 1-(4-fluorofenil)-5-metil-1*H*-pirazol-4-carboxílico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-1-(4-fluorofenil)-5-metil-1*H*-pirazol-4-carboxamida. MS (Q1) 407.0 $(M)^+$.

Ejemplo 250 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil) nicotinamida



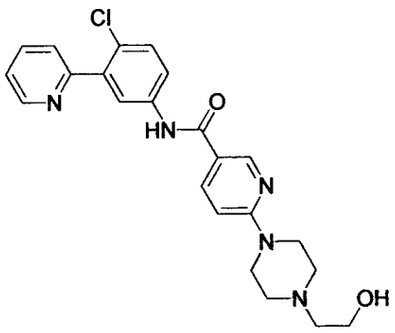
Una mezcla de 450 mg de 4-cloro-3-(piridin-2-il)anilina, 427 mg de 6-cloronicotinil cloruro y 1.9 g de PS-DIEA en 10 mL de diclorometano fue agitada en el agitador por espacio de 3h. La mezcla de reacción fue filtrada y lavada con diclorometano. El filtrado fue concentrado para producir 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil) nicotinamida. MS (Q1) 344.2 $(M)^+$.

Ejemplo 251 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(4-etilpiperazin-1-il) nicotinamida



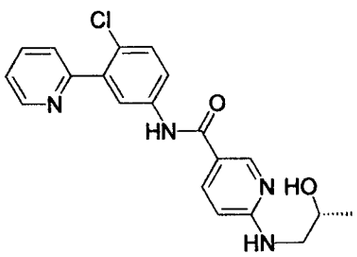
El procedimiento F fue ejecutado usando 50 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil) nicotinamida y 93 µL de 1-etilpiperazina en 0.5 mL de BuOH. Se purificó por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(4-etilpiperazin-1-il) nicotinamida. MS (Q1) 422.0 $(M)^+$.

Ejemplo 252 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(4-(2-hidroxietil)piperazin-1-il) nicotinamida



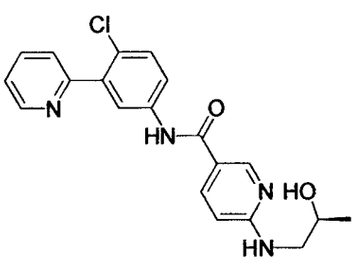
El procedimiento F fue ejecutado usando 50 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil) nicotinamida y 90 µL de 1-(2-hidroxietil)piperazina en 0.5 mL de BuOH. Se purificó por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(4-(2-hidroxietil)piperazin-1-il) nicotinamida. MS (Q1) 438.0 $(M)^+$.

Ejemplo 253 (*R*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-6-(2-hidroxipropilamino) nicotinamida.



El procedimiento F fue ejecutado 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 producir (*R*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-6-(2-hidroxipropilamino) nicotinamida. MS (Q1) 383.4 $(M)^+$.

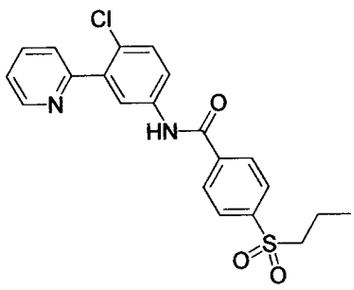
Ejemplo 254 (*S*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-6-(2-hidroxipropilamino) nicotinamida



El procedimiento F fue ejecutado 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

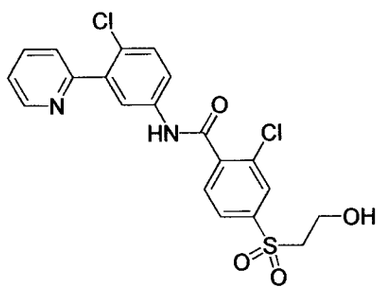
de 4-(2-metoxietiltio) benzoato fueron sometidos a una reacción mediante el procedimiento R para producir 4-(2-metoxietilsulfonil) benzoato. 120 mg de 4-(2-metoxietilsulfonil) benzoato fueron hidrolizados mediante el procedimiento M para producir ácido 4-(2-metoxietilsulfonil) benzoico. Se acoplaron 50 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 4-(2-metoxietilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir *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



1 g de 4-fluorobenzonitrilo fue usado en el procedimiento Q con 1-propanotiol para obtener 4-(propiltio)benzonitrilo. 860 mg de 4-(propiltio)benzonitrilo fueron sometidos a una reacción mediante el procedimiento T para producir ácido 4-(propiltio) benzoico. 700 mg de ácido 4-(propiltio) benzoico fueron sometidos a una reacción mediante el procedimiento R para producir ácido 4-(propilsulfonil) benzoico. Se acoplaron 60 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 4-(propilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(propilsulfonil) benzamida. MS (Q1) 415.0 $(M)^+$.

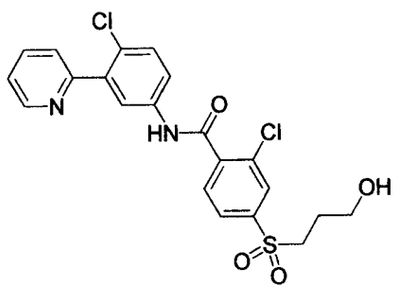
Ejemplo 235 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-hidroxietilsulfonil) benzamida



Se usaron 4 g de 2-cloro-4-fluorobenzonitrilo en el procedimiento Q con 2-mercaptoetanol para obtener 2-cloro-4-(2-hidroxietiltio)benzonitrilo. 1 g de 2-cloro-4-(2-

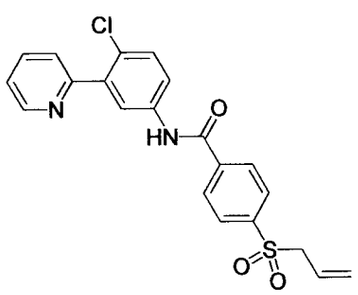
hidroxietiltio)benzonitrilo fueron sometidos a una reacción mediante el procedimiento T para producir ácido 2-cloro- 4-(2-hidroxietiltio) benzoico. 1 g de ácido 2-cloro- 4-(2-hidroxietiltio) benzoico fueron sometidos a una reacción mediante el procedimiento R para producir ácido 2-cloro 4-(2-hidroxietilsulfonil) benzoico. Se acoplaton 50 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 2-cloro 4-(2-hidroxietilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 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



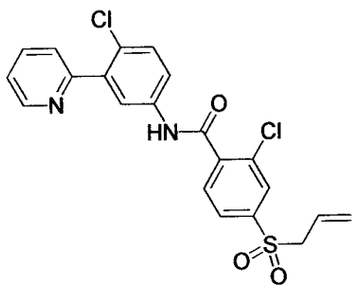
Se usaron 4 g de 2-cloro-4-fluorobenzonitrilo en el procedimiento Q con 3-mercapto-1-propanol para obtener 2-cloro-4-(3-hidroxipropiltio)benzonitrilo. 1 g de 2-cloro-4-(3-hidroxipropiltio)benzonitrilo fue sometido a una reacción mediante el procedimiento T para producir ácido 2-cloro 4-(3-hidroxipropiltio) benzoico. 1.2 g de ácido 2-cloro 4-(3-hidroxipropiltio) benzoico fueron sometidos a una reacción mediante el procedimiento R para producir ácido 2-cloro-4-(2-hidroxipropilsulfonil) benzoico. Se acoplaron 75 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 2-cloro-4-(2-hidroxipropilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 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



7.3 g de 4-(3-hidroxipropiltio)benzonitrilo fueron sometidos a una reacción mediante el procedimiento R para producir 4-(3-hidroxipropilsulfonil)benzonitrilo. 1.9 g de NBS se agregaron 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 fue agitada a 0 ~5 °C por espacio de 1h. La mezcla fue diluida con diclorometano, lavada con H_2O, secada ($MgSO_4$) y evaporada. Se purificó por cromatografía en gel de sílice (10-70% acetato de etilo/hexano) para obtener 4-(3-bromopropilsulfonil)benzonitrilo. 300 mg de 4-(3-bromopropilsulfonil)benzonitrilo fueron sometidos a una reacción mediante el procedimiento T para producir ácido 4-(alilsulfonil) benzoico. Se acoplaron 40 mg de 4-cloro-3-(piridin-2-il)anilina a ácido 4-(alilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 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-il)fenil) benzamida

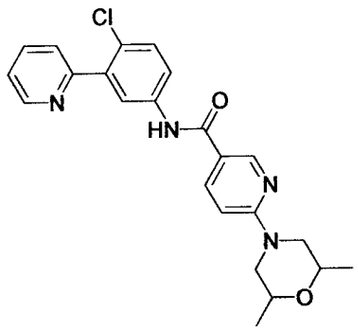


115 mg de NBS se agregaron a una solución de 200 mg de 2-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(3-hidroxipropilsulfonil) benzamida y 169 mg de trifenilfosfina en 3 mL de diclorometano a 0 °C. La mezcla de reacción fue agitada a 0 ~5 °C por espacio de 1h. La mezcla fue diluida con diclorometano, lavada con H_2O, secada ($MgSO_4$) y evaporada. Se purificó por TLC preparatoria (60% acetato de etilo/hexano) para obtener 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 fueron calentados a 100 °C en un reactor a microondas sellado durante 20 minutos. La mezcla de reacción fue evaporada, y el producto fue purificado en HPLC de fase inversa para producir 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

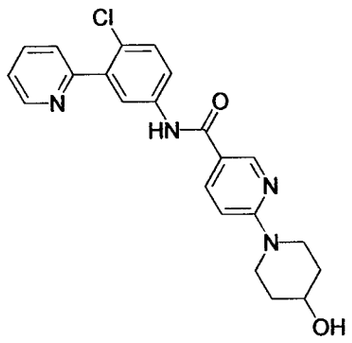
HPLC de fase inversa para producir (*S*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-6-(2-hidroxipropilamino) nicotinamida. MS (Q1) 383.4 $(M)^+$.

Ejemplo 255 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(2,6-dimetilmorfolino) nicotinamida



El procedimiento F fue ejecutado 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 producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(2,6-dimetilmorfolino) nicotinamida. MS (Q1) 423.4 $(M)^+$.

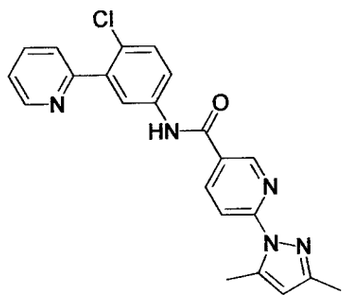
Ejemplo 256 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(4-hidroxipiperidin-1-il) nicotinamida



El procedimiento F fue ejecutado 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 producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(4-hidroxipiperidin-1-il) nicotinamida. MS (Q1) 409.3 $(M)^+$.

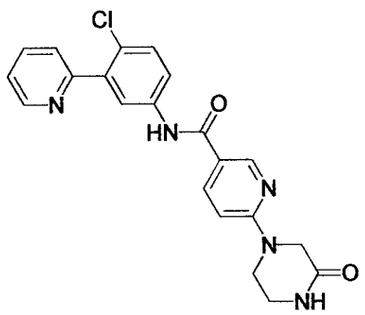
Ejemplo 257 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(3,5-dimetil-1*H*-pirazol-1-il) nicotinamida

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21 mg de hidruro de sodio se agregaron a una solución de 84 mg de 3,5-dimetilpirazol en 2 mL de DMF. La mezcla de reacción fue agitada durante 10 min, y luego se agregaron 100 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil) nicotinamida. La reacción fue calentada a 140 °C por espacio de 16h. La mezcla fue extinguida con MeOH y evaporada. El producto fue purificado en HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(3,5-dimetil-1*H*-pirazol-1-il) nicotinamida. MS (Q1) 404.3 $(M)^+$.

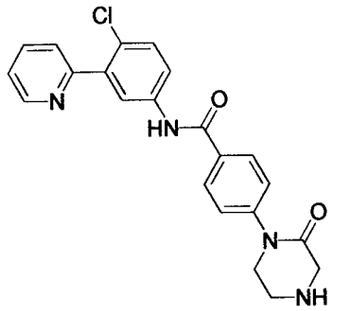
Ejemplo 258 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(3-oxopiperidin-1-il) nicotinamida



El procedimiento F fue ejecutado 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 producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(3-oxopiperidin-1-il) nicotinamida. MS (Q1) 408.3 $(M)^+$.

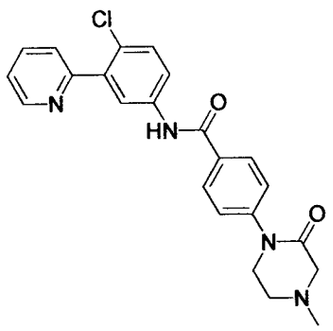
Ejemplo 259 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-oxopiperazin-1-il) benzamida

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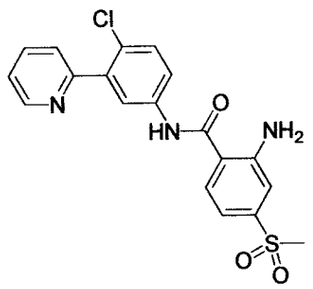
Una mezcla de 1 g de metil 4-yodobenzoato, 920 mg de 4-Boc-piperazinona, 1.1 g de carbonato de potasio, 32 mg de N, N'-dimetiletilenediamina y 70 mg de yoduro de cobre en 10 mL de tolueno fue calentada a 150 °C en un reactor a microondas sellado por espacio de 3h. La mezcla de reacción fue diluida con acetato de etilo, lavada con H_2O, secada ($MgSO_4$) y evaporada. Se purificó por cromatografía en gel de sílice (20-80% acetato de etilo/hexano) para obtener tert-butil 4-(4-(metoxicarbonil)fenil)-3-oxopiperazina-1-carboxilato. 500 mg de tert-butil 4-(4-(metoxicarbonil)fenil)-3-oxopiperazina-1-carboxilato fueron hidrolizados mediante el procedimiento M para producir ácido 4-(4-(tert-buthoxicarbonil)-2-oxopiperazin-1-il) benzoico. 100 mg de 4-cloro-3-(piridin-2-il)anilina fueron acoplados al ácido 4-(4-(tert-buthoxicarbonil)-2-oxopiperazin-1-il) benzoico mediante el procedimiento G. La mezcla de reacción fue diluida con acetato de etilo, lavada con 0.1 N hidróxido de sodio y solución salina, secada ($MgSO_4$) y evaporada para obtener tert-butil 4-(4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)fenil)-3-oxopiperazina-1-carboxilato. 300 mg de tert-butil 4-(4-(4-cloro-3-(piridin-2-il)fenilcarbamoil)fenil)-3-oxopiperazina-1-carboxilato crudo fueron tratados con TFA (2 mL) que contiene vestgios de H_2O por espacio de 1h. La mezcla de reacción fue evaporada y el producto crudo fue purificado por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-oxopiperazin-1-il) benzamida. MS (Q1) 407.3 $(M)^+$.

Ejemplo 260 *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(4-metil-2-oxopiperazin-1-il) benzamida



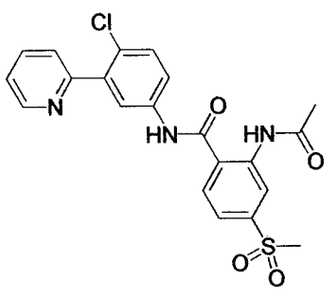
120 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(2-oxopiperazin-1-il) benzamida fueron disueltos en 2 mL de DMF y luego tratados con 53 mg de paraformaldehido, 187 mg de sodio triacetoxiborohidruro y 0.2 mL de AcOH. Luego de agitación 16 h, la mezcla de reacción fue evaporada y el producto crudo fue purificado por HPLC de fase inversa para producir *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



2.2 g de metil 4-(metilsulfonil)-2-nitrobenzoato fueron sometidos a una reacción mediante el procedimiento C para obtener metil 2-amino-4-(metilsulfonil) benzoato. 500 mg de metil 2-amino-4-(metilsulfonil) benzoato fueron hidrolizados mediante el procedimiento M para producir ácido 2-amino-4-(metilsulfonil) benzoico. Se acoplaron 100 mg de 4-cloro-3-(piridin-2-il)anilina al ácido 2-amino-4-(metilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-amino-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonil) benzamida. MS (Q1) 402.0 $(M)^+$.

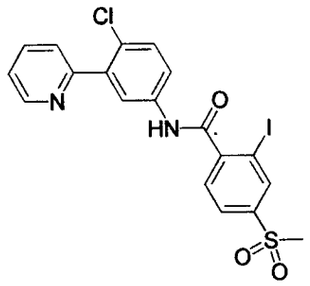
Ejemplo 262 2-acetamido-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonil) benzamida



20 µL de acetil cloruro se agregaron 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 calentar a temperatura ambiente y se agitó durante 2h. La reacción fue extinguida con MeOH y evaporada. El producto fue purificado en HPLC de fase inversa

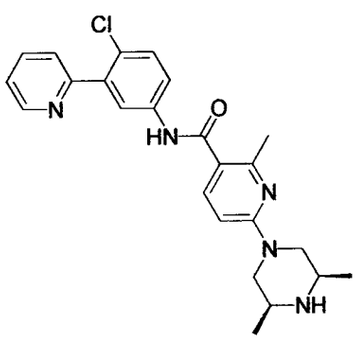
para producir 2-acetamido-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonil) benzamida. MS (Q1) 444.0 $(M)^+$.

Ejemplo 263 *N*-(4-cloro-3-(piridin-2-il)fenil)-2-yodo-4-(metilsulfonil) benzamida



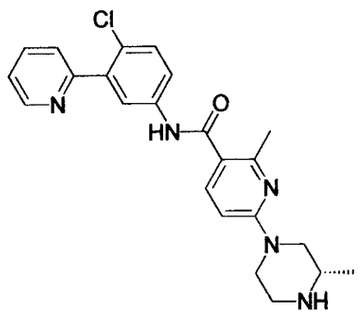
600 mg de metil 2-amino-4-(metilsulfonil) benzoato se agregaron a una solución de 4 mL of H_2O y 1 mL de ácido sulfúrico concentrado. La solución fue enfriada a 0 °C y una solución de 206 mg de nitrito de sodio en 1 mL de H_2O fue agregada lentamente. La mezcla de reacción fue agitada durante 2 h y luego 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 calentar a temperatura ambiente y se agitó durante 5 h. La mezcla fue extraída con acetato de etilo. Los extractos orgánicos combinados fueron lavados con $Na_2S_2O_3$ saturada, secada ($MgSO_4$) y evaporada. Se purificó por cromatografía en gel de sílice (5-50% acetato de etilo/hexano) para obtener metil 2-yodo-4-(metilsulfonil) benzoato. 160 mg de metil 2-yodo-4-(metilsulfonil) benzoato fueron hidrolizados mediante el procedimiento M para producir ácido 2-yodo-4-(metilsulfonil) benzoico. Se acoplaron 60 mg de 4-cloro-3-(piridin-2-il)anilina al ácido 2-yodo-4-(metilsulfonil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-2-yodo-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-metil nicotinamida



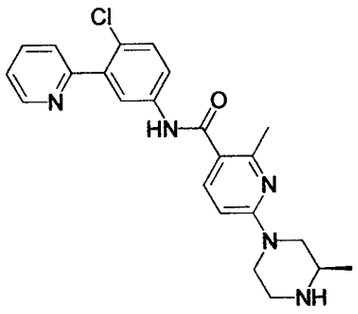
Cantidades estequiométricas (0.04 mol) de metil proplolato y etilo 3-aminocrotonato fueron calentadas a 140 °C por espacio de 1h. 1 g del (2E,4Z)-metil-4-(1-aminoetilideno)-5-oxooct-2-enoato crudo en 4 mL de DMF fue calentado a 230 °C en un reactor a microondas sellado durante 40 minutos. La mezcla de reacción fue diluida con acetato de etilo, lavada con H_2O, secada ($MgSO_4$) y evaporada para obtener etilo 6-hidroxi-2-metilnicotinato crudo. Una mezcla de 800 mg de etilo 6-hidroxi-2-metil nicotinato crudo en 4 mL de oxicloruro de fósforo fue calentada a 150 °C en un reactor a microondas sellado por espacio de 15 minutos. La mezcla de reacción fue vertida en hielo/agua, extraída con éter dietílico. Las capas orgánicas combinadas fueron secadas ($MgSO_4$) y evaporadas. Se purificó por cromatografía en gel de sílice (0-20% acetato de etilo/hexano) para producir etilo 6-cloro-2-metilnicotinato. 400 mg de etilo 6-cloro-2-metil nicotinato fueron hidrolizados mediante el procedimiento M para producir ácido 6-cloro-2-metilnicotínico. 300 mg de 4-cloro-3-(piridin-2-il)anilina fueron acoplados al ácido 6-cloro-2-metilnicotínico mediante el procedimiento G. La mezcla de reacción fue diluida con acetato de etilo, lavada con 0.1 N hidróxido de sodio y solución salina, secada ($MgSO_4$) y evaporada para obtener 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida. El procedimiento F fue ejecutado usando 100 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida y 128 mg de 2,6-dimetilpiperazina en 1 mL de BuOH. Se purificó por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-((3*S*,5*R*)-3,5-dimetilpiperazin-1-il)-2-metil nicotinamida. MS (Q1) 436.3 $(M)^+$.

Ejemplo 265 (*S*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(3-metilpiperazin-1-il) nicotinamida



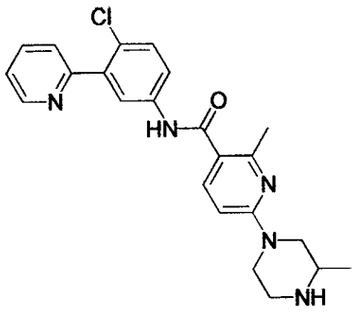
El procedimiento F fue ejecutado usando 100 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida y 112 mg de S-(-)-2-metilpiperizina en 1 mL de BuOH. Se purificó por HPLC de fase inversa para producir (*S*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(3-metilpiperazin-1-il) nicotinamida. MS (Q1) 422.3 $(M)^+$.

Ejemplo 266 (*R*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(3-metilpiperazin-1-il) nicotinamida.



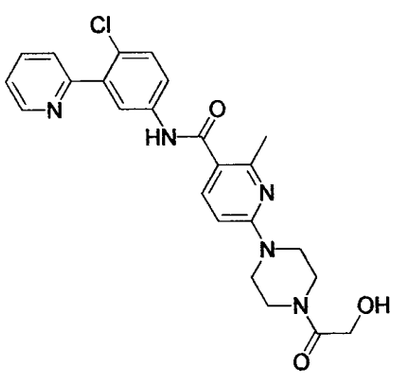
El procedimiento F fue ejecutado usando 100 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida y 112 mg de R-(+)-2-metilpiperizina en 1 mL de BuOH. Se purificó por HPLC de fase inversa para producir (*R*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(3-metilpiperazin-1-il) nicotinamida. MS (Q1) 422.3 $(M)^+$.

Ejemplo 267 *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(3-metilpiperazin-1-il) nicotinamida



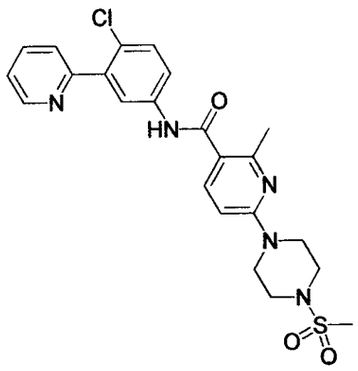
El procedimiento F fue ejecutado usando 100 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida y 112 mg de 2-metilpiperizina en 1 mL de BuOH. Se purificó por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(3-metilpiperazin-1-il) nicotinamida. MS (Q1) 422.3 $(M)^+$.

Ejemplo 268 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(4-(2-hidroxiacetil)piperazin-1-il)-2-metil nicotinamida



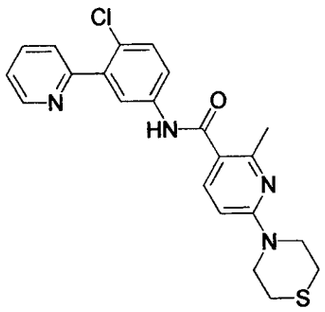
Se acoplaron 100 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(piperazin-1-il) nicotinamida a ácido glicólico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(4-(2-hidroxiacetil)piperazin-1-il)-2-metil nicotinamida. MS (Q1) 466.3 $(M)^+$.

Ejemplo 269 *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(4-(metilsulfonil)piperazin-1-il) nicotinamida



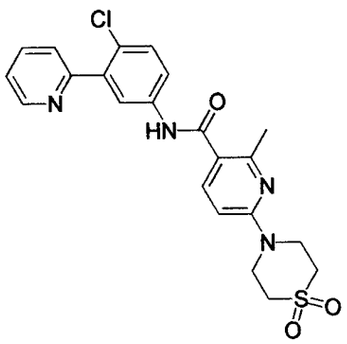
Se agregaron lentamente 1.3 mL de metanosulfonil cloruro a una solución de 2 g de 1-Boc–piperazina y 1.3 mL de piridina en 6 mL de diclorometano a 0 ° C. La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante 2h mientras era monitoreada por TLC. Ante la finalización, la mezcla fue diluida con diclorometano, lavada con H_2O, secada ($MgSO_4$) y evaporada. Se purificó por cromatografía en gel de sílice (20-100% acetato de etilo/hexano) para obtener tert-butil-4-(metilsulfonil)piperazina-1-carboxilato. 930 mg de tert-butil-4-(metilsulfonil)piperazina-1-carboxilato fueron tratados con 4N HCl en dioxano por espacio de 2h. La mezcla de reacción fue evaporada para producir la sal HCl de 1-(metilsulfonil)piperazina. El procedimiento F fue ejecutado usando 50 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida, 69 mg de 1-(metilsulfonil)piperazina y DIEPA(1 eq) en 0.5 mL de BuOH. Se purificó por HPLC de fase inversa para producir *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



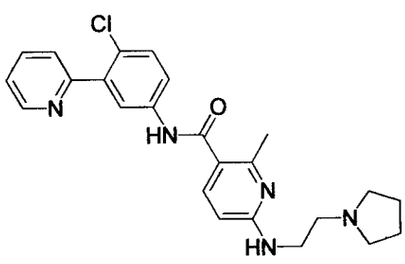
El procedimiento F fue ejecutado usando 90 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida y 78 µL de tiomorfolina en 1 mL de BuOH. Se purificó por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-tiomorfolinonicotinamida. MS (Q1) 425.3 $(M)^+$.

Ejemplo 271 *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-sulfonilmorfolinonicotinamida



100 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-tiomorfolinonicotinamida fueron sometidos a una reacción via procedimiento R. El producto fue purificado en HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-sulfonilmorfolinonicotinamida. MS (Q1) 457.3 $(M)^+$.

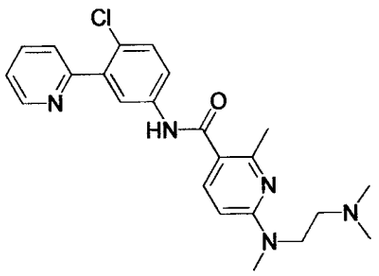
Ejemplo 272 *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(2-(pirrolidin-1-il)etilamino)-nicotinamida



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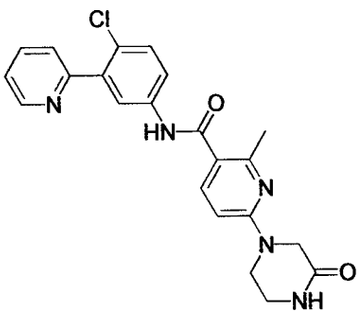
El procedimiento F fue ejecutado usando 100 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida y 70 µL de 1-(2-aminoetil)pirrolidina en 1 mL de BuOH. Se purificó por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(2-(pirrolidin-1-il)etilamino) nicotinamida. MS (Q1) 436.0 $(M)^+$.

Ejemplo 273 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-((2-(dimetilamino)etil)(metil)amino)-2-metil nicotinamida



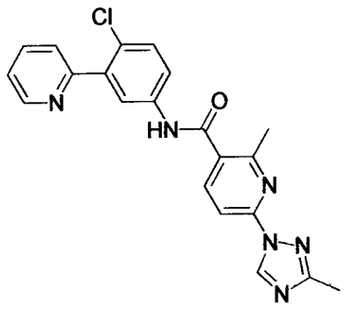
El procedimiento F fue ejecutado usando 60 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida y 66 µL de N,N,N'-trimetiletilenediamina en 0.5 mL de BuOH. Se purificó por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-((2-(dimetilamino)etil)(metil)amino)-2-metil nicotinamida. MS (Q1) 424.0 $(M)^+$.

Ejemplo 274 *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(3-oxopiperazin-1-il) nicotinamida



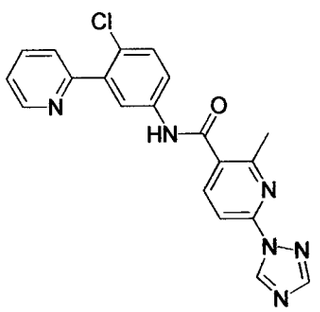
El procedimiento F fue ejecutado usando 100 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida y 84 mg de piperazina-2-ona en 1 mL de BuOH. Se purificó por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(3-oxopiperazin-1-il) nicotinamida. MS (Q1) 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



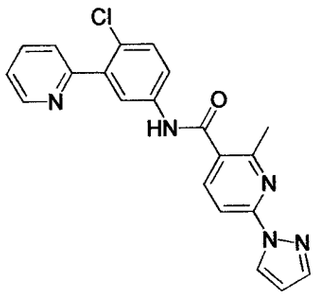
Una mezcla de 57 mg de 3-metil-1,2,4-triazol y 16 mg de hidruro de sodio en 2 mL de DMF fue agitada durante 10 minutos. Se agregaron 80 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida. La reacción fue calentada a 140 °C por espacio de 16h. La mezcla de reacción fue extinguida con MeOH y evaporada. Se purificó por HPLC de fase inversa para producir *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 $(M)^+$.

Ejemplo 276 *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(1*H*-1,2,4-triazol-1-il) nicotinamida



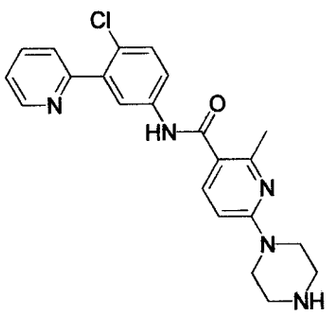
Una mezcla de 41 mg de 1,2,4-triazol y 14 mg de hidruro de sodio en 2 mL de DMF fue agitada durante 10 minuto. Se agregaron 70 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida. La reacción fue calentada a 140 °C por espacio de 6h. La mezcla de reacción fue extinguida con MeOH y evaporada. Se purificó por HPLC de fase inversa para producir *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 fue agitada durante 10 minutos. Se agregaron 90 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida. La reacción fue calentada a 140 °C por espacio de 5h. La mezcla de reacción fue extinguida con MeOH y evaporada. Se purificó por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(1*H*-pirazol-1-il) nicotinamida. MS (Q1) 390.0 $(M)^+$.

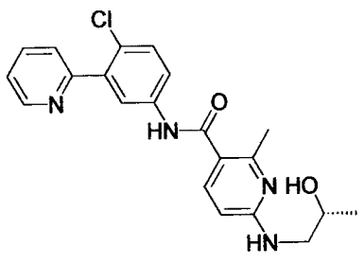
Ejemplo 278 *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(piperazin-1-il) nicotinamida



El procedimiento F fue ejecutado usando 80 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida y 209 mg de 1-Boc-piperizina en 1 mL of BuOH. La mezcla de reacción fue evaporada para obtener tert-butilo 4-(5-(4-cloro-3-(piridin-2-il)fenilcarbamoil)-6-metilpiridin-2-il)piperazina-1-carboxilato. 150 mg de tert-butil 4-(5-(4-cloro-3-(piridin-2-il)fenilcarbamoil)-6-metilpiridin-2-il)piperazina-1-carboxilato fueron tratados con TFA (1 mL) que contiene vestgios de H_2O por espacio de 2 h. La mezcla de reacción fue diluida con acetato de etilo, lavada con 0.1N hidróxido de sodio y solución salina, secada ($MgSO_4$) y evaporada. Se purificó por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil-6-(piperazin-1-il) nicotinamida. MS (Q1) 408.3 $(M)^+$.

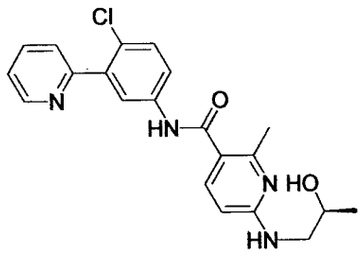
Ejemplo 279 (*R*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-6-(2-hidroxipropilamino)-2-metil nicotinamida

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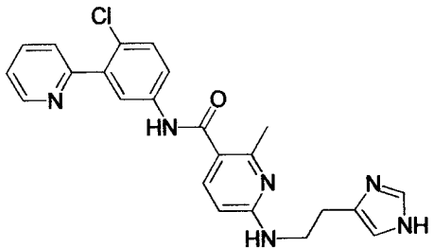
El procedimiento F fue ejecutado usando 60 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida y 116 µL de R-(-)-1-amino-2-propanol en 0.5 mL de BuOH. Se purificó por HPLC de fase inversa para producir (*R*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-6-(2-hidroxipropilamino)-2-metil nicotinamida. MS (Q1) 397.4 $(M)^+$.

Ejemplo 280 (*S*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-6-(2-hidroxipropilamino)-2-metil nicotinamida



El procedimiento F fue ejecutado usando 60 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida y 116 µL de S-(+)-1-amino-2-propanol en 0.5 mL de BuOH. Se purificó por HPLC de fase inversa para producir (*S*)-*N*-(4-cloro-3-(piridin-2-il)fenil)-6-(2-hidroxipropilamino)-2-metil nicotinamida. MS (Q1) 397.4 $(M)^+$.

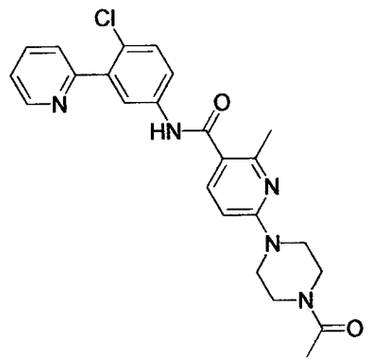
Ejemplo 281 6-(2-(1*H*-imidazol-4-il)etilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida



El procedimiento F fue ejecutado usando 60 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida y 93 mg de histamina en 0.5 mL de BuOH. Se purificó por HPLC de fase inversa para producir 6-(2-(1*H*-imidazol-4-il)etilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida. MS (Q1) 433.0 (M)

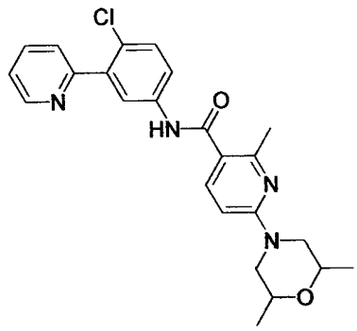
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Ejemplo 282 6-(4-acetilpiperazin-1-il)-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida



El procedimiento F fue ejecutado usando 55 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida y 99 mg de 1-acetilpiperazina en 0.5 mL de BuOH. Se purificó por HPLC de fase inversa para producir 6-(4-acetilpiperazin-1-il)-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida. MS (Q1) 450.4 $(M)^+$.

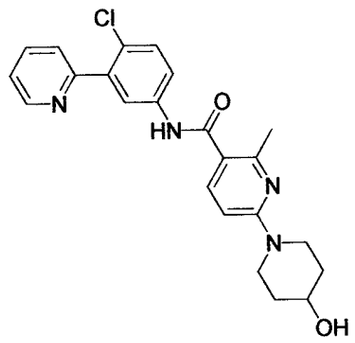
Ejemplo 283 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(2,6-dimetilmorfolino)-2-metil nicotinamida



El procedimiento F fue ejecutado usando 55 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida y 95 mg de 2,6-dimetilmorfolina en 0.5 mL de BuOH. Se purificó por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(2,6-dimetilmorfolino)-2-metil nicotinamida. MS (Q1) 436.2 $(M)^+$.

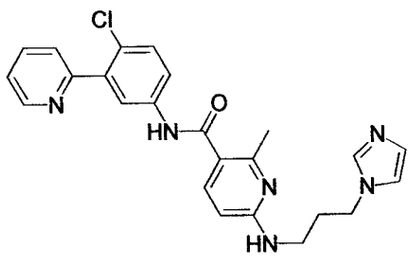
Ejemplo 284 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(4-hidroxipiperidin-1-il)-2-metil nicotinamida

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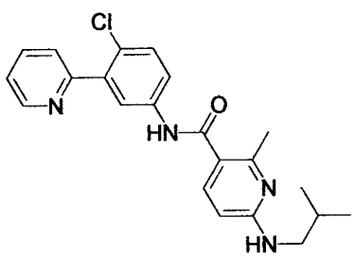
El procedimiento F fue ejecutado usando 55 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida y 78 mg de 4-hidropiperidina en 0.5 mL de BuOH. Se purificó por HPLC de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(4-hidroxipiperidin-1-il)-2-metil nicotinamida. MS (Q1) 422.1 $(M)^+$.

Ejemplo 285 6-(3-(1*H*-imidazol-1-il)propilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida



El procedimiento F fue ejecutado usando 55 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida y 92 µL de 1-(3-aminopropilo)-imidazol en 0.5 mL de BuOH. Se purificó por HPLC de fase inversa para producir 6-(3-(1*H*-imidazol-1-il)propilamino)-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida. MS (Q1) 446.1 $(M)^+$.

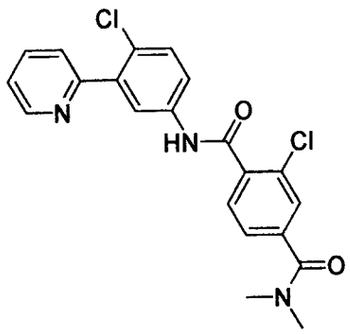
Ejemplo 286 *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(isobutilamino)-2-metil nicotinamida



El procedimiento F fue ejecutado usando 50 mg de 6-cloro-*N*-(4-cloro-3-(piridin-2-il)fenil)-2-metil nicotinamida y 70 µL de isobutilamina en 0.5 mL de BuOH. Se purificó por HPLC

de fase inversa para producir *N*-(4-cloro-3-(piridin-2-il)fenil)-6-(isobutilamino)-2-metil nicotinamida. MS (Q1) 395.4 $(M)^+$.

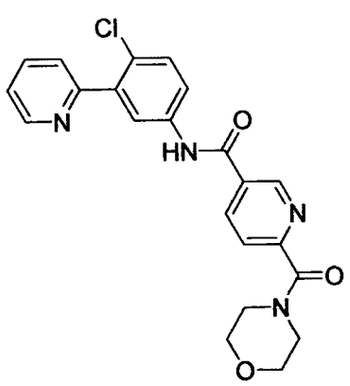
Ejemplo 287 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4,N^4-dimetiltereftalamida



Se acoplaron 290 mg de dimetilamina clorhidrato a 1 g de ácido 4-(tert-butoxicarbonil)-3-clorobenzoico mediante el procedimiento G. La mezcla de reacción fue diluida con acetato de etilo, lavada con 0.1 N HCl, 0.1 N NaOH y solución salina, secada ($MgSO_4$) y evaporada para obtener tert-butil 2-cloro-4-(dimetilcarbamoil) benzoato. 1.1g de tert-butil 2-cloro-4-(dimetilcarbamoil) benzoato fueron tratados con TFA (4 mL) que contienen vestgios de H_2O por espacio de 2 h. La mezcla de reacción fue evaporada, y luego se agregó 0.1 N HCl. El sólido resultante fue filtrado y lavado con H_2O para producir ácido 2-cloro-4-(dimetilcarbamoil) benzoico. Se acoplaron 100 mg de 4-cloro-3-(piridina-2-il)anilina a ácido 2-cloro-4-(dimetilcarbamoil) benzoico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro-N^1-(4-cloro-3-(piridin-2-il)fenil)-N^4,N^4-dimetiltereftalamida.

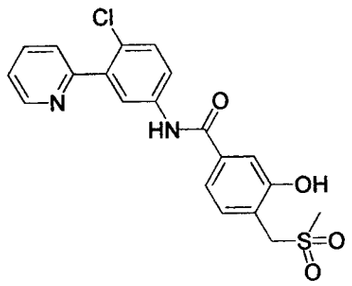
MS (Q1) 414.1 $(M)^+$.

Ejemplo 288 N-(4-cloro-3-(piridin-2-il)fenil)-6-(morfolina-4-carbonil) nicotinamida



Se acoplaron 63 mg de morfolina a 120 mg de ácido 5-(metoxicarbonil)piridina-2-carboxílico mediante el procedimiento G. La mezcla de reacción fue diluida con acetato de etilo, lavada con bicarbonato de sodio saturado y solución salina, secada ($MgSO_4$) y evaporada para obtener metil 6-(morfolina-4-carbonil) nicotinato. 180 mg de metil 6-(morfolina-4-carbonil) nicotinato fueron hidrolizados mediante el procedimiento M para producir ácido 6-(morfolina-4-carbonil) nicotínico. Se acoplaron 100 mg de 4-cloro-3-(piridina-2-il)anilina al ácido 6-(morfolina-4-carbonil) nicotínico mediante el procedimiento G. El producto fue purificado en HPLC de fase inversa para producir 2-cloro- N-(4-cloro-3-(piridin-2-il)fenil)-6-(morfolina-4-carbonil) nicotinamida. MS (Q1) 423.4 $(M)^+$.

Ejemplo 289 *N*-(4-Cloro-3-(piridin-2-il)fenil)-3-hidroxi-4-(metilsulfonilmetil) benzamida

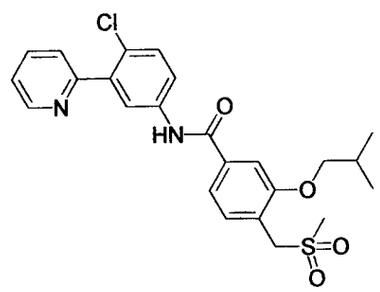


Se disolvió ácido 3-hidroxi-4-metilbenzoico (6.86 g, 45.1 mmol) en metanol (200 ml). Se agregó 4N HCl en 1,4-dioxano (34 ml, 0.135 mmol HCl) y la solución fue calentada a 55°C por espacio de 18 horas. El solvente fue concentrado en un evaporador rotativo, y luego dividido entre agua y acetato de etilo. La porción acuosa fue extraída con acetato de etilo una vez, y los extractos de acetato de etilo fueron combinados y lavados con agua una vez, solución salina una vez, secados con $MgSO_4$, y evaporados en metil 3-hidroxi-4-metilbenzoato como un sólido bronce crudo (6.66 g) que fue usado sin purificación. Se disolvió metil 3-hidroxi-4-metilbenzoato (6.66 g, 40.1 mmol) en diclorometano (200 ml), se trató con piridina (4.3 ml, 60.2 mmol), y se enfrió en un baño de agua helada. Se agregó acetil cloruro (3.6 ml, 50.1 mmol) por goteo. La solución se dejó calentar a temperatura ambiente, con agitación, durante 18 horas. La solución fue lavada con 1 N HCl acuoso dos veces, agua una vez, solución salina una vez, secada con $MgSO_4$, y evaporada en metil 3-acetoxi-4-metilbenzoato como un aceite bronce crudo (6.93 g) que fue usado sin purificación. Se disolvió metil 3-acetoxi-4-metilbenzoato (6.38 g, 30.6 mmol) en tetracloruro de carbono (130 ml) y fue tratado con peroxi anhídrido benzoico (200 mg, 0.83 mmol) y NBS (5.45 g, 30.6 mmol), luego se calentó a 85°C por espacio de 3 horas. Luego de enfriar a temperatura ambiente, la solución fue filtrada por Celita 545 y evaporada en un sólido amarillo crudo que fue purificado por cromatografía instantánea en gel de sílice (5% diclorometano/hexanos aumentando hasta 35%

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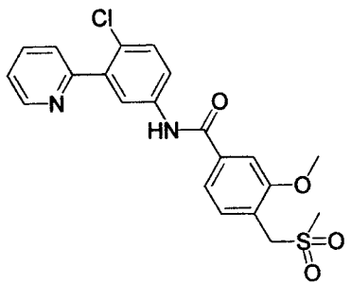
diclorometano/hexanos) para producir metil 3-acetoxi-4-(bromometil) benzoato como un sólido blanquecino (4.18 g). Se usó metil 3-acetoxi-4-(bromometil) benzoato (2.00 g, 6.97 mmol) en el procedimiento O para obtener metil 3-acetoxi-4-(metilsulfonilmetil) benzoato como un sólido blanco (1.67 g) que fue usado sin purificación. Se saponificó metil 3-acetoxi-4-(metilsulfonilmetil) benzoato (1.67 g, 5.83 mmol) mediante el procedimiento M para obtener ácido 3-hidroxi-4-(metilsulfonilmetil) benzoico como un sólido blanco (1.05 g) que fue usado sin purificación. El ácido 3-hidroxi-4-(metilsulfonilmetil) benzoico (860 mg, 3.74 mmol) fue disuelto en 1,4-dioxano (25 ml) y tratado con tionil cloruro (8 ml) y DMF (5 gotas), luego fue calentado a 50°C por espacio de 2 horas. La reacción fue enfriada y evaporada en un aceite. El residuo de aceite fue disuelto en diclorometano (40 ml), enfriado en un baño de agua helada, y tratado por goteo con una solución de 4-cloro-3-(piridin-2-il)anilina (767 mg, 3.74 mmol) en diclorometano (30 ml). La reacción fue agitada 18 horas, dejando calentar a temperatura ambiente. La reacción fue diluida con diclorometano (40 ml) y agitada vigorosamente con agua (50 ml) mientras se acidificói a pH 6 con 1 M ácido cítrico. La porción de diclorometano fue separada, y se agregó suficiente metanol para disolver los sólidos precipitados. La solución fue lavada con agua una vez, solución salina una vez, secada con $MgSO_4$, y evaporada en un sólido que fue triturado con diclorometano, filtrado, y secado al aire para producir 909 mg de producto crudo. Una porción (20 mg) fue purificada en HPLC de fase inversa para producir 16 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-3-hidroxi-4-(metilsulfonilmetil) benzamida purificada como un sólido blanco. MS (Q1) 417 $(M)^+$.

Ejemplo 290 *N*-(4-Cloro-3-(piridin-2-il)fenil)-3-isobutoxi-4-(metilsulfonilmetil) benzamida



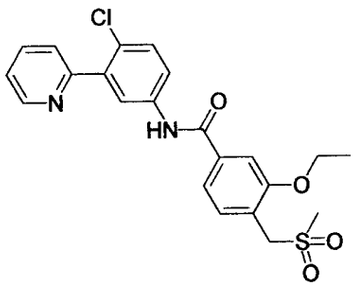
Se trató *N*-(4-cloro-3-(piridin-2-il)fenil)-3-hidroxi-4-(metilsulfonilmetil) benzamida (50 mg, 0.12 mmol) con 1-bromo-2-metilpropano (26 µl, 0.24 mmol) mediante el procedimiento U para producir 19 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-3-isobutoxi-4-(metilsulfonilmetil) benzamida. MS (Q1) 473 $(M)^+$.

Ejemplo 291 *N*-(4-Cloro-3-(piridin-2-il)fenil)-3-metoxi-4-(metilsulfonilmetil) benzamida



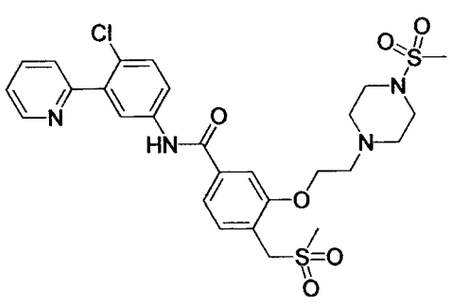
Se trató *N*-(4-Cloro-3-(piridin-2-il)fenil)-3-hidroxi-4-(metilsulfonilmetil) benzamida (50 mg, 0.12 mmol) con yodometano (7.5 µl, 0.12 mmol) mediante el procedimiento U para producir 12 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-3-metoxi-4-(metilsulfonilmetil) benzamida. MS (Q1) 431 $(M)^+$.

Ejemplo 292 *N*-(4-Cloro-3-(piridin-2-il)fenil)-3-etoxi-4-(metilsulfonilmetil) benzamida



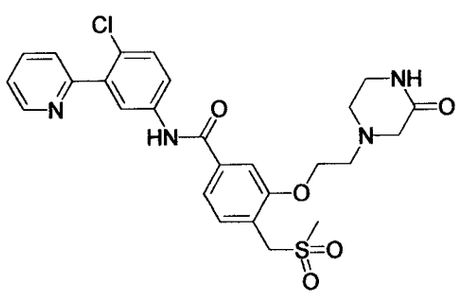
N-(4-Cloro-3-(piridin-2-il)fenil)-3-hidroxi-4-(metilsulfonilmetil) benzamida (50 mg, 0.12 mmol) fue tratada con yodoetano (10 µl, 0.12 mmol) mediante el procedimiento U para producir 22 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-3-etoxi-4-(metilsulfonilmetil) benzamida. MS (Q1) 445 $(M)^+$.

Ejemplo 293 *N*-(4-Cloro-3-(piridin-2-il)fenil)-3-(2-(4-(metilsulfonil)piperazin-1-il)etoxi)-4-(metilsulfonilmetil) benzamida



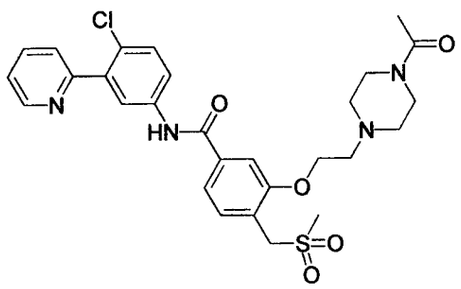
N-(4-Cloro-3-(piridin-2-il)fenil)-3-hidroxi-4-(metilsulfonilmetil) benzamida (1.00 g, 2.40 mmol) fue disuelta en DMF (20 ml). Se agregaron carbonato de cesio (1.56 g, 4.8 mmol) y 1,2-dibromoetano (0.83 ml, 9.6 mmol), y la reacción fue agitada a 50°C por espacio de 18 horas. La reacción fue extinguida con agua, basificada con 10% NaOH acuoso, y extraída con acetato de etilo dos veces. Los extractos de etilo fueron lavados con agua una vez, solución salina una vez, secados con $MgSO_4$, y evaporados a un aceite crudo que purificado por cromatografía (25% hexanos en acetato de etilo) para producir 490 mg de 3-(2-bromoetoxi)-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil) benzamida como un sólido amarillo. 3-(2-Bromoetoxi)-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil) benzamida (100 mg, 0.19 mmol) fue disuelta en DMF (2.0 ml), y se agregó carbonato de potasio (32 mg, 0.23 mmol) y tert-butilo piperazina-1-carboxilato (38 mg, 0.21 mmol). La reacción fue agitada durante 18 horas a temperatura ambiente, extinguida en agua, y extraída con acetato de etilo dos veces. Los extractos de acetato de etilo fueron lavados con agua una vez, solución salina una vez, secados con $MgSO_4$, y evaporados a un aceite crudo. El aceite fue disuelto en diclorometano (1 ml) y tratado con trifluoroácido acético (3 ml) por espacio de 1 hora. La reacción fue evaporada hasta secarse, y el sólido crudo fue purificado en HPLC de fase inversa para producir 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) fue disuelta en diclorometano (1.5 ml) y THF (1.0 ml). Se agregaron *N*-etil-*N*-isopropilpropan-2-amina (18 µl, 0.10 mmol) y metanosulfonil cloruro (4 µl, 0.051 mmol), y la reacción fue agitada a temperatura ambiente por espacio de 72 horas. Se agregó más *N*-etil-*N*-isopropilpropan-2-amina (9 µl, 0.051 mmol) y metanosulfonil cloruro (4 µl, 0.051 mmol) y la reacción fue agitada durante 2 horas. Luego de una adición adicional de metanosulfonil cloruro (4 µl, 0.051 mmol), la reacción fue agitada durante 2 horas y evaporada en un sólido crudo que fue purificado en HPLC de fase inversa para producir 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



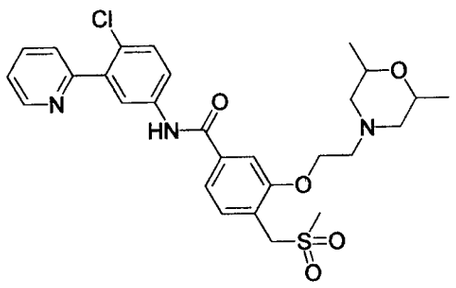
3-(2-Bromoetoxi)-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil) benzamida (50 mg, 0.095 mmol) fue disuelta en DMF (1.0 ml) y tratada con carbonato de potasio (18 mg, 0.13 mmol) y piperazin-2-ona (11 mg, 0.11 mmol) por espacio de 18 horas. La reacción fue calentada por espacio de 2.0 horas a 50°C, luego se agregó más carbonato de potasio (18 mg, 0.13 mmol) y piperazin-2-ona (11 mg, 0.11 mmol). Luego de 2 horas, la reacción fue extinguida en 5% NaOH y extraída con acetato de etilo dos veces. Los extractos de acetato de etilo fueron lavados con agua una vez, solución salina una vez, secados con $MgSO_4$, y purificados por HPLC de fase inversa para producir 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



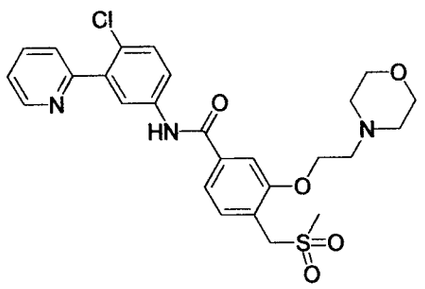
3-(2-Bromoetoxi)-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil) benzamida (50 mg, 0.095 mmol) fue disuelta en DMF (1.0 ml) y tratada con carbonato de potasio (18 mg, 0.13 mmol) y 1-(piperazin-1-il)etanona (15 mg, 0.11 mmol) por espacio de 18 horas. La reacción fue calentada por espacio de 2.0 horas a 50°C, luego se agregó más carbonato de potasio (18 mg, 0.13 mmol) y 1-(piperazin-1-il)etanona (15 mg, 0.11 mmol). Luego de 2 horas, la reacción fue extinguida en 5% NaOH y extraída con acetato de etilo dos veces. Los extractos de acetato de etilo fueron lavados con agua una vez, solución salina una vez, secados con $MgSO_4$, y purificados por HPLC de fase inversa para producir 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



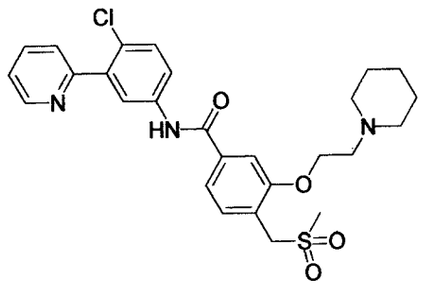
3-(2-Bromoetoxi)-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil) benzamida (50 mg, 0.095 mmol) fue disuelta en DMF (1.0 ml) y tratada con carbonato de potasio (18 mg, 0.13 mmol) y 2,6-dimetilmorfolina (14 µl, 0.11 mmol), y agitada a temperatura ambiente por espacio de 18 horas. La reacción fue extinguida en 5% NaOH y extraída con acetato de etilo dos veces. Los extractos de acetato de etilo fueron lavados con agua una vez, solución salina una vez, secados con $MgSO_4$, y purificados por HPLC de fase inversa para producir 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



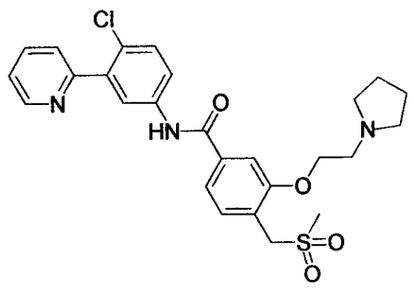
3-(2-Bromoetoxi)-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil) benzamida (50 mg, 0.095 mmol) fue disuelta en acetonitrilo (1.0 ml) y DMF (1.0 ml), tratada con carbonato de potasio (16 mg, 0.12 mmol) y morfolina (10 µl, 0.11 mmol), y agitada 18 horas a temperatura ambiente. La reacción fue calentada a 50°C por espacio de 8 horas, y luego se agitó 18 horas a temperatura ambiente. La reacción fue extinguida en agua y extraída con acetato de etilo dos veces. Los extractos de acetato de etilo fueron lavados con agua una vez, solución salina una vez, secados con $MgSO_4$, y evaporados en un aceite que fue purificado por HPLC de fase inversa para producir 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



3-(2-Bromoetoxi)-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil) benzamida (50 mg, 0.095 mmol) fue disuelta en diclorometano (1.0 ml), tratada con trietilamina (20 µl, 0.15 mmol) y piperidina (11 µl, 0.11 mmol), y agitada durante 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 fue agitada durante 45 horas adicionales. La reacción fue extinguida en agua y extraída con diclorometano dos veces. Los extractos de diclorometano fueron lavados con agua una vez, solución salina una vez, secados con $MgSO_4$, y evaporados en un sólido que fue purificado por HPLC de fase inversa para producir 17 mg *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)-3-(2-(piperidin-1-il)etoxi) benzamida. MS (Q1) 528 $(M)^+$.

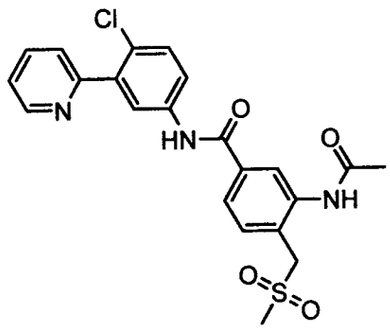
Ejemplo 299 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)-3-(2-(pirrolidin-1-il)etoxi) benzamida



3-(2-Bromoetoxi)-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil) benzamida (40 mg, 0.076 mmol) fue disuelta en acetonitrilo (1.0 ml) y DMF (1.0 ml), tratada con carbonato de potasio (16 mg, 0.12 mmol) y pirrolidina (7 µl, 0.084 mmol), y agitada 18 horas a temperatura ambiente. La reacción fue extinguida en agua y extraída con acetato de etilo dos veces. Los extractos de acetato de etilo fueron lavados con agua una vez, solución salina una vez, secados con $MgSO_4$, y evaporados en un aceite que fue purificado por

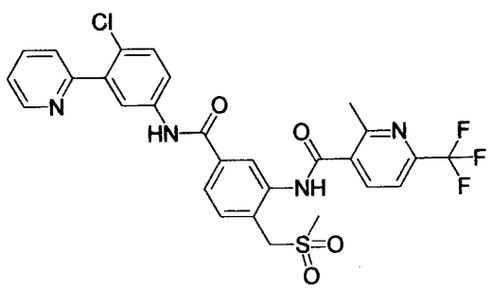
y se agregó trietilamina (10 ml) para basificar la solución. La reacción fue evaporada en un sólido amarillo que fue licuado en acetato de etilo. La pasta fue filtrada por Celita 545, y los licores madres fueron lavados con agua dos veces, solución salina una vez, secados con $MgSO_4$, y evaporados en 552 mg como un sólido amarillo crudo, 20 mg del cual fueron purificados por HPLC de fase inversa para obtener 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



3-Amino-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil) benzamida (30 mg, 0.072 mmol) fue sometida a una reacción con acetil cloruro (5.6 µl, 0.079 mol) mediante el procedimiento V para obtener 19 mg de 3-acetamido-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil) benzamida como un sólido blanco. MS (Q1) 458 $(M)^+$.

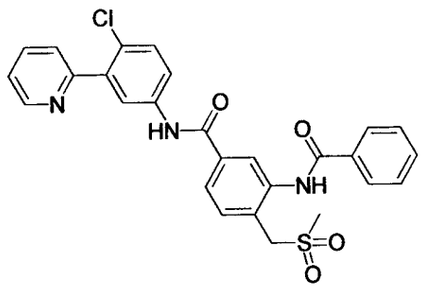
Ejemplo 302 *N*-(5-(4-Cloro-3-(piridin-2-il)fenilcarbamoil)-2-(metilsulfonilmetil)fenil)-2-metil-6-(trifluorometil) nicotinamida



3-Amino-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil) benzamida (30 mg, 0.072 mmol) fue sometida a una reacción con 2-metil-6-(trifluorometil)nicotinoil cloruro (19 mg, 0.079 mmol) mediante el procedimiento V para obtener 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 $(M)^+$.

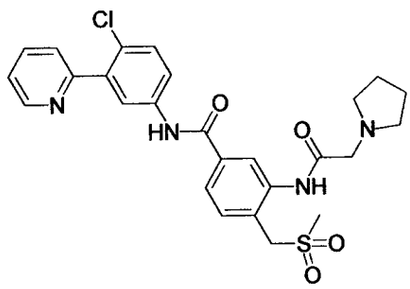
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Ejemplo 303 3-Benzamido-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil) benzamida



3-Amino-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil) benzamida (30 mg, 0.072 mmol) fue sometida a una reacción con benzoil cloruro (9 µl, 0.079 mmol) mediante el procedimiento V para obtener 17 mg de 3-benzamido-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil) benzamida como un sólido blanco. MS (Q1) 520 $(M)^+$.

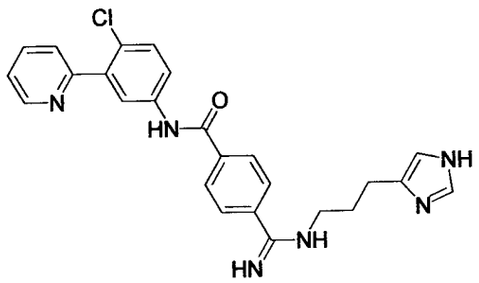
Ejemplo 304 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil)-3-(2-(pirrolidin-1-il)acetamido) benzamida



3-Amino-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil) benzamida (100 mg, 0.24 mmol) fue disuelta en 1,4-dioxano (5.0 ml), tratada con trietilamina (274 µl, 1.97 mmol) y 2-bromoacetil bromuro (121 µl, 1.39 mmol). La reacción fue calentada a reflujo for 10 minutos, y agitada a temperatura ambiente por espacio de 18 horas. La reacción fue extinguida con agua, y extraída dos veces con acetato de etilo. Los extractos de acetato de etilo fueron filtrados, lavados con agua una vez, solución salina una vez, secados con $MgSO_4$, evaporados en 158 mg de un aceite marrón crudo, 3-(2-bromoacetamido)-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonilmetil) benzamida, que fue usado sin purificación adicional. Se disolvió 3-(2-bromoacetamido)-*N*-(4-cloro-3-(piridin-2-il)fenil)-4-(metilsulfonil-metil) benzamida cruda (158 mg) en DMF, y fue tratada con *N*-etil-*N*-isopropilpropan-2-amina (61 µl, 0.35 mmol) y pirrolidina (27 µl, 0.32 mmol), y agitada a temperatura ambiente por espacio de 18 horas. La reacción fue extinguida con agua y extraída con acetato de etilo dos veces. Los extractos de acetato de etilo fueron lavados con agua una vez, solución salina una vez, secados con $MgSO_4$, evaporados en un sólido bronce que

fue purificado por HPLC de fase inversa para obtener 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)propilo)carbamimidoil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida

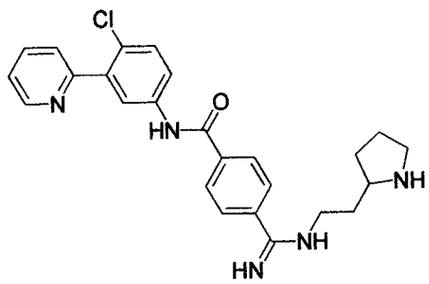


4-Cloro-3-(piridin-2-il)anilina (687 mg, 3.36 mmol) fue disuelta en diclorometano (8.0 ml) y THF (8.0 ml), tratada con piridina (0.33 ml, 4.0 mmol), y enfriada a 0°C. Se agregó 4-cianobenzoil cloruro (612 mg, 3.7 mmol) y la reacción fue agitada durante 1.0 hora. La reacción fue diluida con diclorometano y se agregó metanol para disolver todos los sólidos. La solución fue lavada con agua una vez, solución salina una vez, secada con $MgSO_4$, y evaporada en un sólido anaranjado que fue purificado por cromatografía en columna instantánea de gel de sílice (50% acetato de etilo/50% hexanos) para obtener 908 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-cianobenzamida como un sólido amarillo. Se licuaron *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-cianobenzamida (500 mg, 1.5 mmol) en etanol (75 ml) y se calentó hasta disolver. La solución fue enfriada en un baño de hielo, y saturada con gas HCl. La solución fue calentada brevemente a 70°C para disolver los sólidos precipitados, enfriada en un baño de hielo, y resaturada con gas HCl. La solución luego fue almacenada a 0°C por espacio de 18 horas. La solución fue saturada nuevamente con gas HCl, calentada a 70°C hasta que todos los sólidos se disolvieron, enfriada a 0°C, resaturada con gas HCl, y almacenada a 0°C por espacio de 18 horas. Finalmente, se burbujeó nitrógeno a través de la solución por espacio de 1.0 hora, y la solución fue evaporada hasta secarse. El residuo fue disuelto en metanol, tratado con MP-carbonato (2.57 g) y agitado durante 30 minutos. La solución fue filtrada para obtener una solución metanólica neutral etil 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzimidato, que fue diluida con suficiente metanol para obtener una solución 0.075 M.

Etil 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzimidato (2.0 ml de una solución de metanol 0.075 M, 0.15 mmol) fue tratado con 3-(1H-imidazol-4-il)propan-1-amina (27 µl,

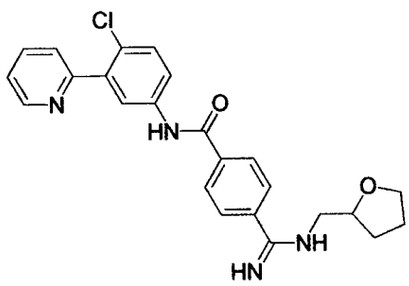
0.23 mmol) mediante el procedimiento W para obtener 83 mg de 4-(*N*-(3-(1*H*-imidazol-4-il)propilo)carbamimidoil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida. MS (Q1) 459 $(M)^+$.

Ejemplo 306 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(*N*-(2-(pirrolidin-2-il)etil) carbamimidoil) benzamida



Una solución de etil 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzimidato (2.0 ml de una solución de metanol 0.075 M, 0.15 mmol) fue tratada con 2-(pirrolidin-2-il) etanamina (28 µl, 0.23 mmol) mediante el procedimiento W para obtener 90 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-(2-(pirrolidin-2-il)etil) carbamimidoil) benzamida. MS (Q1) 448 $(M)^+$.

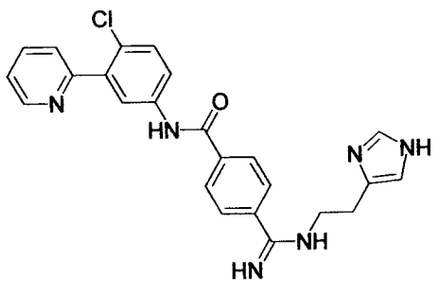
Ejemplo 307 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(*N*-((tetrahidrofuran-2-il)metil) carbamimidoil) benzamida



Una solución de etil 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzimidato (2.0 ml de una solución de metanol 0.075 M, 0.15 mmol) fue tratado con (tetrahidrofuran-2-il) metanamina (23 µl, 0.23 mmol) mediante el procedimiento W para obtener 76 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-((tetrahidrofuran-2-il)metil)carbamimidoil) benzamida. MS (Q1) 435 $(M)^+$.

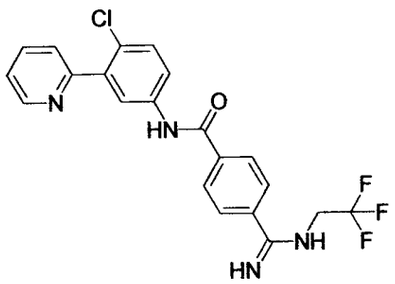
Ejemplo 308 4-(*N*-(2-(1*H*-Imidazol-4-il)etil)carbamimidoil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida

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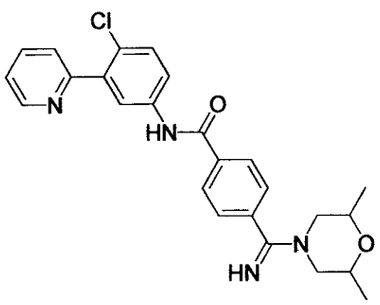
Etil 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzimidato (2.0 ml de una solución de metanol 0.075 M, 0.15 mmol) fue tratado con 2-(1H-imidazol-4-il)etanamina (25 mg, 0.23 mmol) mediante el procedimiento W para obtener 90 mg de 4-(*N*-(2-(1*H*-imidazol-4-il)etil)carbamimidoil)-*N*-(4-cloro-3-(piridin-2-il)fenil) benzamida. MS (Q1) 445 $(M)^+$.

Ejemplo 309 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(*N*-(2,2,2-trifluoroetil)carbamimidoil) benzamida



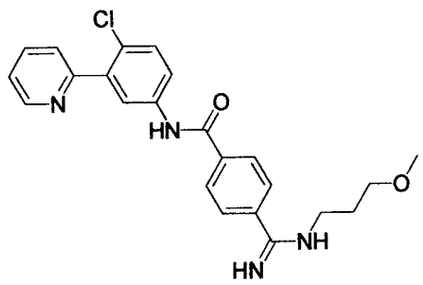
Etil 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzimidato (2.0 ml de una solución de metanol 0.075 M, 0.15 mmol) fue tratado con 2,2,2-trifluoroetanamina (18 µl, 0.23 mmol) mediante el procedimiento W para obtener 56 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-(2,2,2-trifluoroetil)carbamimidoil) benzamida. MS (Q1) 433 $(M)^+$.

Ejemplo 310 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-((2,6-dimetilmorfolino)(imino)metil)-benzamida



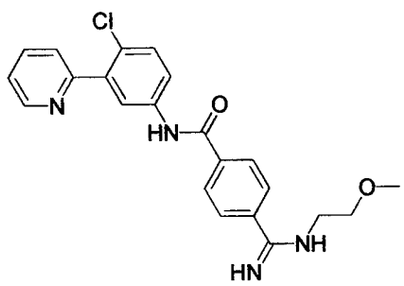
Etil 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzimidato (2.0 ml de una solución de metanol 0.075 M, 0.15 mmol) fue tratado con 2,6-dimetilmorfolina (28 µl, 0.23 mmol) mediante el procedimiento W para obtener 74 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-((2,6-dimetilmorfolino)(imino)metil)-benzamida. MS (Q1) 449 $(M)^+$.

Ejemplo 311 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(*N*-(3-metoxipropilo)carbamimidoil)-benzamida



Etil 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzimidato (2.0 ml de una solución de metanol 0.075 M, 0.15 mmol) fue tratado con 3-metoxipropan-1-amina (23 µl, 0.23 mmol) mediante el procedimiento W para obtener 68 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-(3-metoxipropilo)carbamimidoil)-benzamida. MS (Q1) 423 $(M)^+$.

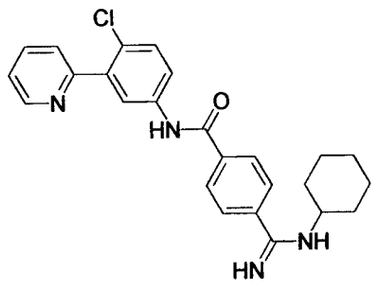
Ejemplo 312 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(*N*-(2-metoxietil)carbamimidoil) benzamida



Etil 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzimidato (2.0 ml de una solución de metanol 0.075 M, 0.15 mmol) fue tratado con 2-metoxietanamina (19 µl, 0.23 mmol) mediante el procedimiento W para obtener 50 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-(2-metoxietil)carbamimidoil) benzamida. MS (Q1) 409 $(M)^+$.

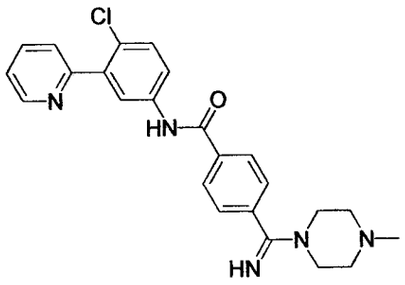
Ejemplo 313 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(*N*-ciclohexilcarbamimidoil) benzamida

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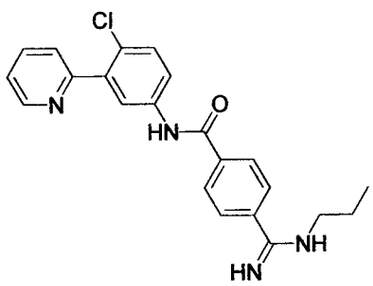
Etil 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzimidato (2.0 ml de una solución de metanol 0.075 M, 0.15 mmol) fue tratado con ciclohexanamina (26 µl, 0.23 mmol) mediante el procedimiento W para obtener 30 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-ciclohexilcarbamimidoil) benzamida. MS (Q1) 433 $(M)^+$.

Ejemplo 314 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(imino(4-metilpiperazin-1-il)metil) benzamida



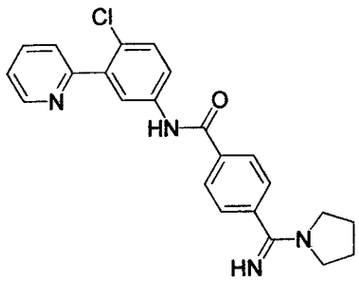
Etil 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzimidato (2.0 ml de una solución de metanol 0.075 M, 0.15 mmol) fue tratado con 1-metilpiperazina (23 mg, 0.23 mmol) mediante el procedimiento W para obtener 35 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(imino(4-metilpiperazin-1-il)metil) benzamida. MS (Q1) 434 $(M)^+$.

Ejemplo 315 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(*N*-propilcarbamimidoil) benzamida



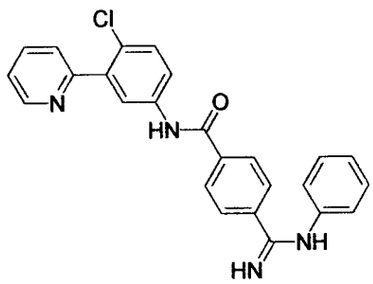
Etil 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzimidato (2.0 ml de una solución de metanol 0.075 M, 0.15 mmol) fue tratado con propan-1-amina (18 µl, 0.23 mmol) mediante el procedimiento W para obtener 39 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-propilcarbamimidoil) benzamida. MS (Q1) 393 $(M)^+$.

Ejemplo 316 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(imino(pirrolidin-1-il)metil) benzamida



Etil 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzimidato (2.0 ml de una solución de metanol 0.075 M, 0.15 mmol) fue tratado con pirrolidina (19 µl, 0.23 mmol) mediante el procedimiento W para obtener 25 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(imino(pirrolidin-1-il)metil) benzamida. MS (Q1) 405 $(M)^+$.

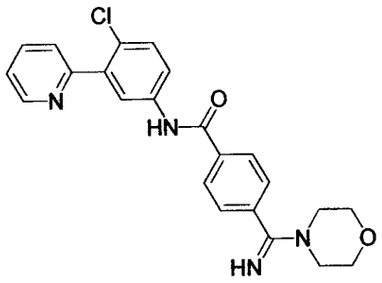
Ejemplo 317 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(*N*-fenilcarbamimidoil) benzamida



Etil 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzimidato (2.0 ml de una solución de metanol 0.075 M, 0.15 mmol) fue tratado con anilina (21 µl, 0.23 mmol) mediante el procedimiento W para obtener 7 mg de *N*-(4-cloro-3-(piridin-2-il)fenil)-4-(*N*-fenilcarbamimidoil) benzamida. MS (Q1) 427 $(M)^+$.

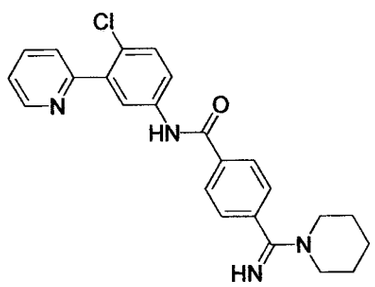
Ejemplo 318 *N*-(4-Cloro-3-(piridin-2-il)fenil)-4-(imino(morfolino)metil) benzamida

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N-(4-cloro-3-(piridin-2-il)fenil)-4-cianobenzamida (300 mg, 0.899 mmol) fue licuada en 45 ml etanol y tratada con 10 ml de etanol saturado con HCl. La reacción fue almacenada a 0°C por espacio de 3 días, luego calentada a 75°C por espacio de 3.0 horas, y enfriada a temperatura ambiente por espacio de 18 horas. La reacción fue enfriada en un baño de hielo, y saturada con gas HCl. Luego de almacenar a 0°C por espacio de 3 días más, se burbujeó gas N_2 a través de la solución por espacio de 1.0 hora, y la solución fue diluida con suficiente etanol para obtener una solución 0.0155 M de etil 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzimidato. Se trató etil 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzimidato (17.5 ml de una solución de etanol 0.0155M, 0.27 mmol) con morfolina (1.0 ml, 11.4 mmol) por espacio de 3 días. El etanol fue evaporado, y el residuo purificado por HPLC de fase inversa para obtener 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



Etil 4-(4-cloro-3-(piridin-2-il)fenilcarbamoil) benzimidato (17.5 ml de una solución 0.0155 M, 0.27 mmol) fue tratado con piperidina (1.0 ml, 10.0 mmol) por espacio de 3 días. El etanol fue evaporado, y el residuo purificado por HPLC de fase inversa para obtener 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 de células reporteras de ratón – Células 10T1/2-GliLuc [S12] (derivadas de la línea de células C3H10T1/2 ATCC #CCL-226) ; Fibroblastos Embriónicos de Ratón); Medio Groen pesoh: Medio de Eagles modificado de Dulbecco (DMEM) suplementado con 10% de Suero Fetal Bovino (FBS), 10 unidades/mL penicilina, 100 ug/mL estreptomicina, 2mM glutamina, y 10mM HEPES.

Líneas de células reporteras humanas – Células HEPM-GliLuc [MZ24] - (derivadas de HEPM, Mesénquima Palatal Embriónico Humano ATCC #CRL-1486); Medio Groen pesoh: Medio Esencial Mínimo (MEM; con sales de Earle) suplementado con 10-20% Suero Bovino Fetal (FBS), 10 unidades/mL penicilina, 100ug/mL estreptomicina, 2mM glutamina, y 10mM HEPES pH 7.2.

Hedgehog sónico - conjugado recombinante humano SHh N-terminal octilado

Placas de Microtitulación (MTPs) – Para el ensayo de Luciferasa las células son colocadas en placas de 96 cavidades (MTP) (White, Flat-bottom, Clear-View).

Luciferasa - Medio de Ensayo - DMEM suplementado con 0.5% FBS, 10 unidades/mL penicilina, 100ug/mL estreptomicina, 2mM glutamina, y 10mM HEPES pH 7.2.

Mezcla PBS/Ca/Mg – Solución Salina de Buffer Fosfato (PBS) suplementada con 0.5mM $CaCl_2$ y 1mM $MgCl_2$.

Procedimiento del ensayo

Células S12 y MZ24 genéticamente modificadas para contener un gen reportador de luciferasa accionadas por el promotor Gli que responde a hedgehog fueorn mantenidas en placas de cultivo de tejido en Medio Groen pesoh Medium a 37°C y 5% CO_2. Los cultivos de células fueron pasadas a sub-confluencia cada 3-4 días. (1:20 a 1:40 para s12; 1:3 a 1:10 parar MZ24). Las células fueron colectadas y diluidas en Medio Groen pesoh de modo que pudiesen ser colocadas en una placa de microtitulación a razón de 10,000-20,000 células (s12), o 20,000-30,000 células (MZ24), por 100ul, por cavidad. Las células fueron además incubadas durante ~24-48 horas a 37°C y 5% CO_2.

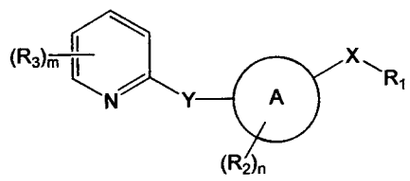
Luego de ~24-48 horas de incubación el medio Groen pesoh en las placas de microtitulación fue reemplazado por Medio de Ensayo de Luciferasa (100 ul por cavidad), con y sin conjugado hedgehog-octilo sónico, 0.1-0.3 ug/ml (S12) o 0.5-1.0 ug/ml (MZ24), y los compuestos de prueba. Las células luego fueron incubadas durante 24 horas más.

Las placas de microtitulación luego fueron sometidas al kit de ensayo de gen reportador de luciferasa (LucLite™), con modificaciones al procedimiento del fabricante de acuerdo a las cuales el medio fue removido y el substrato reconstituido con 1:1 PBS/Ca/Mg : buffer de lisis en lugar de buffer de lisis solo. Brevemente, se mezcló PBS/Ca/Mg 1:1 con buffer de lisis y se agregaron 10mL a cada recipiente (del kit de ensayo 1000). Luego el medio de ensayo de la placa de microtitulación fue descartado, y se agregaron 100 ul de esta mezcla de substrato a cada cavidad. Las placas fueron incubadas a temperatura ambiente por espacio de 20-30 minutos y luego se determinaron las Unidades de Luz Relativa (RLUS) que representan el nivel de expresión relativa del gen reportador de luciferasa con un lector Topcount (Packard) o un lector Analyst (Molecular Devices). Los compuestos de la invención testeados en los ensayos demostraron una menor expresión de Gli en las líneas de células reportadoras indicando la inhibición de la señalización del camino de hedgehog.

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REIVINDICACIONES

1. Un compuesto de la fórmula I:



I

caracterizado porque

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 es seleccionado del grupo integrado 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 un heterociclo; en tanto dicho sustituyente amino, amidino, alquilo, acilo, sulfonilo, sulfinilo, alcoxi, alquiltio, carbamoilo, acilamino, sulfamoilo, sulfonamida, carbociclo y heterociclo está opcionalmente sustituido 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 un heterociclo;

R_2 es halógeno, hidroxilo, alquilo, acilo o alcoxi, en tanto 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 en tanto cada alquilo, acilo, alcoxi, alcoxicarbonilo, carbamoilo, alquilsulfuro, sulfinilo, sulfonilo, carbociclo y heterociclo está opcionalmente sustituido con hidroxilo, halógeno, amino, nitro, alquilo, acilo, sulfonil o alcoxi;

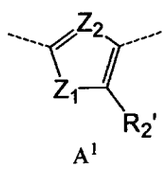
R_4 es H o alquilo;

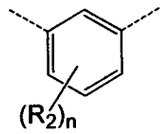
m es 0-3;

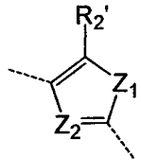
n es 0-3;

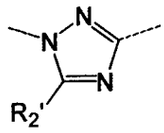
y sales y solvatos del mismo.

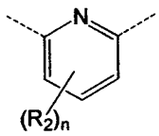
2. El compuesto de la Reivindicación 1, caracterizado porque A es un anillo seleccionado del grupo integrado por A^1, A^2, A^3, A^4 A^5, A^6 y A^7:

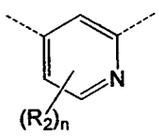

A^1

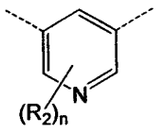

A^2


A^3


A^4


A^5


A^6


A^7

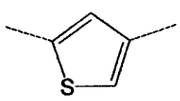
donde Z_1 es O, S o NR_5 donde R_5 es H o alquilo; Z_2 es CH, $CR_{2'}$ o N; R_2 es halógeno, hidroxilo, alquilo o alcoxi; $R_{2'}$ es H, halógeno, hidroxilo, alquilo o alcoxi; y n es 0-3.

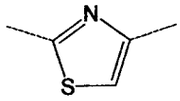
3. El compuesto de la Reivindicación 2, caracterizado porque A es el anillo A^1 donde Z_1 es S y Z_2 es CH o N.

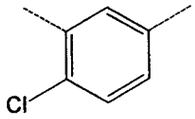
4. El compuesto de la Reivindicación 2, caracterizado porque A es el anillo A^2.

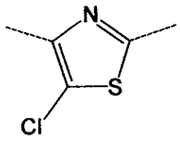
5. El compuesto de la Reivindicación 2, caracterizado porque R_2 o R_2' es Cl.

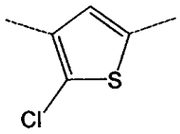
6. El compuesto de la Reivindicación 1, caracterizado porque A es A^{1a}, A^{1b}, A^{2a}, A^{3a}, A^{3b}, A^{4a}, A^{5a}, A^{6a}, A^{7a},:

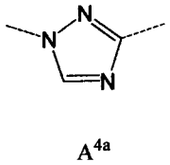

A^{1a}

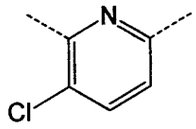

A^{1b}


A^{2a}

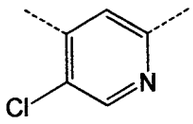

A^{3a}


A^{3b}

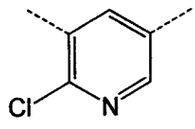

A^{4a}



A^{5a}



A^{6a}



A^{7a}

7. El compuesto de la Reivindicación 1, caracterizado porque X es $NR_4C(O)$.

8. El compuesto de la Reivindicación 1, caracterizado porque X es NR_4SO_2.

9. El compuesto de la Reivindicación 7, caracterizado porque R_4 es H o Me.

10. El compuesto de la Reivindicación 9, caracterizado porque R_4 es H.

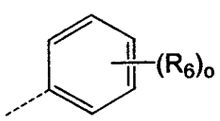
11. El compuesto de la Reivindicación 1, caracterizado porque R_3 es Me o F.

12. El compuesto de la Reivindicación 1, caracterizado porque R_3 es Me y m es 1 o 2.

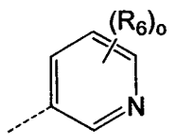
13. El compuesto de la Reivindicación 1, caracterizado porque R_3 es F y m es 1 o 2.

14. El compuesto de la Reivindicación 1, caracterizado porque m es 0.

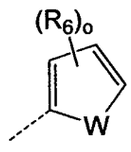
15. El compuesto de la Reivindicación 1, caracterizado porque R_1 es seleccionado del grupo integrado por la formula IIa - IIo:



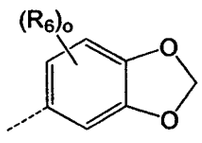
IIa



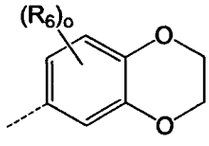
IIb



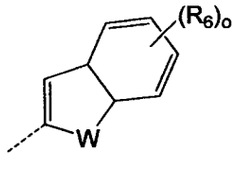
IIc



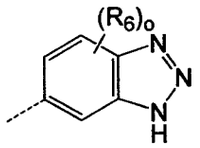
IId

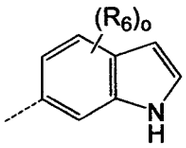


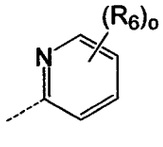
IIe



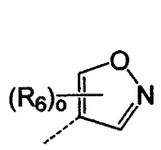
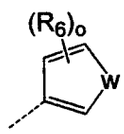
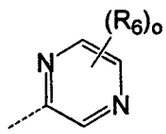
IIf



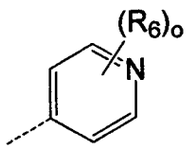
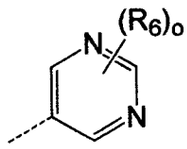
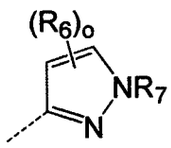




IIg IIh IIi

IIj IIk III

IIm IIn IIo

en tanto

W es O, S o NR_7 donde R_7 es H, alquilo, acilo, un carbociclo o un heterociclo en tanto dicho alquilo carbociclo y heterociclo está respectivamente opcionalmente sustituido con 1-3 amino, halógeno, hidroxilo y haloalquilo;

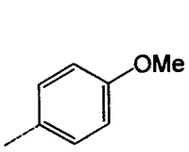
R_6 en cada caso es independientemente hidroxilo, halógeno, amino, carbonilo, nitro, ciano, acilo, alquilo, sulfonilo, alquilsulfonilo, alquilsulfinilo, alcoxi, alquilcarbamoilo, alcanoilamina, alquilsulfamoilo, alquilsulfonamida, un carbociclo o un heterociclo; en tanto dicho sustituyente amino, alquilo, 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; y

o es 0-3.

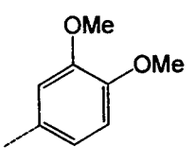
16. El compuesto de la Reivindicación 15, caracterizado porque R_1 es el grupo de la fórmula IIa.

17. El compuesto de la Reivindicación 16, caracterizado porque R_6 es alcoxi y o es 1 o 2.

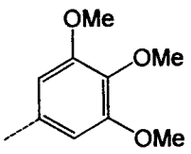
18. El compuesto de la Reivindicación 16, caracterizado porque R_1 es seleccionado del grupo de la fórmula IIa^1 - IIa^{28}:



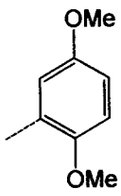
IIa[1]



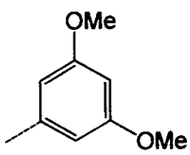
IIa[2]



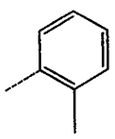
IIa[3]



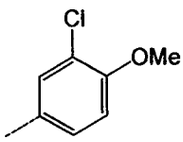
IIa[4]



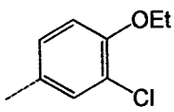
IIa[5]



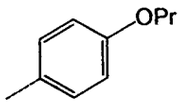
IIa[6]



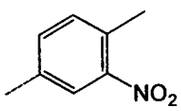
IIa[7]



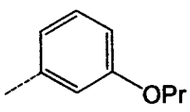
IIa[8]



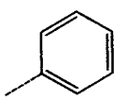
IIa[9]



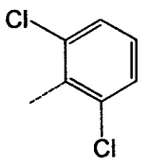
IIa[10]



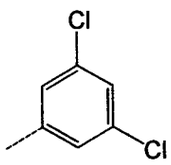
IIa[11]



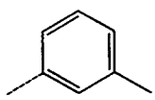
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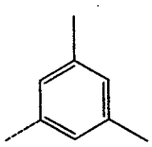
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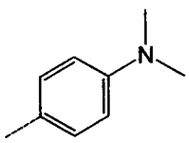
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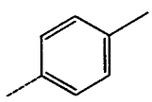
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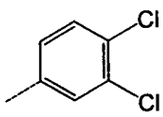
IIa[16]



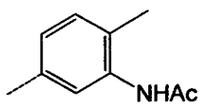
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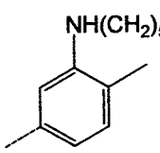
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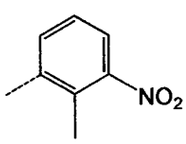
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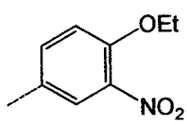
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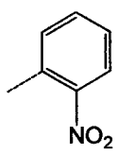
IIa[21]



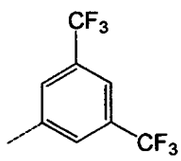
IIa[22]



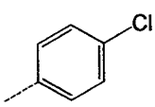
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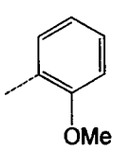
IIa[24]



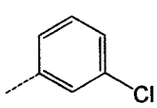
IIa[25]



IIa[26]



IIa[27]



IIa[28]

000527

19. El compuesto de la Reivindicación 16, caracterizado porque A es el anillo A^1 o A^2.

20. El compuesto de la Reivindicación 16, caracterizado porque A es el anillo A^{2a}.

21. El compuesto de la Reivindicación 16, caracterizado porque R_3 es Me o F.

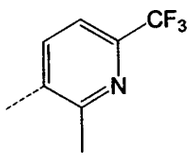
22. El compuesto de la Reivindicación 3, caracterizado porque m es 0.

23. El compuesto de la Reivindicación 3, caracterizado porque X es $NR_4C(O)$.

24. El compuesto de la Reivindicación 15, caracterizado porque R_1 es el grupo de la fórmula IIb.

25. El compuesto de la Reivindicación 24, caracterizado porque R_6 es alquilo o haloalquilo.

26. El compuesto de la Reivindicación 24, caracterizado porque R_1 es el grupo de la fórmula IIb^1



IIb^1

27. El compuesto de la Reivindicación 24, caracterizado porque A es el anillo A^1 o A^2.

28. El compuesto de la Reivindicación 24, caracterizado porque A es el anillo $A^{2'}$.

29. El compuesto de la Reivindicación 24, caracterizado porque R_3 es H, Me o F.

30. El compuesto de la Reivindicación 24, caracterizado porque R_3 es H.

31. El compuesto de la Reivindicación 24, caracterizado porque X es $NR_4C(O)$.

32. Una composición caracterizada porque comprende un compuesto de la Reivindicación 1 y un portador farmacéuticamente aceptable.

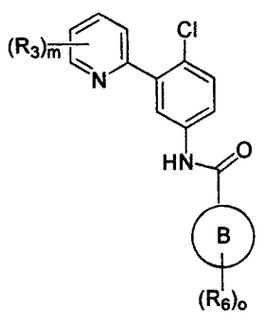
33. Un método para tratar el cáncer en un mamífero, caracterizado porque comprende administrar a dicho mamífero una cantidad efectiva de un compuesto de la Reivindicación 1.

34. El método de la Reivindicación 33, caracterizado porque dicho cáncer es carcinoma de células basales, meduloblastoma, adenocarcinoma pancreático, carcinoma de pulmón de células pequeñas, carcinoma de mama, rabdomiosarcoma, cáncer oesofageal, cáncer de estómago, cáncer del tracto biliar.

35. Un método para inhibir la angiogénesis en un mamífero, caracterizado porque comprende administrar a dicho mamífero una cantidad efectiva de un compuesto de la Reivindicación 1.

36. Un método para inhibir la señalización del camino de hedgehog en una célula, caracterizado porque comprende poner en contacto dicha célula con una cantidad efectiva de un compuesto de la Reivindicación 1.

37. Un proceso de preparación de un compuesto de la 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 en tanto 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 caso es independientemente hidroxilo, halógeno, amino, carbonilo, nitro, ciano, acilo, alquilo, sulfonilo, alquilsulfonilo, alquilsulfinilo, alcoxi, alquilcarbamoilo, alcanoilamina, alquilsulfamoilo, alquilsulfonamida, un carbociclo o un heterociclo; en tanto dicho sustituyente amino, alquilo,

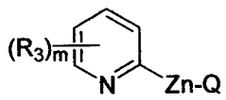
carbonilo, acilo, sulfonilo, alquilsulfonilo, alquilsulfinilo, alcoxi, alquilcarbamoilo, alcanoilamina, alquilsulfamoilo, alquilsulfonamida, carbociclo y heterociclo está opcionalmente sustituido con amino, halógeno, hidroxilo, carbonilo, o un carbociclo o heterociclo que está opcionalmente sustituido con hidroxilo, amino, halógeno, haloalquilo, alquilo, alcoxi o acilo;

o es 0-3; y

m es 0-3;

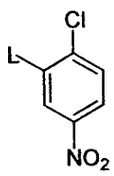
caracterizado porque comprende

-someter a una reacción un compuesto de la fórmula (a)



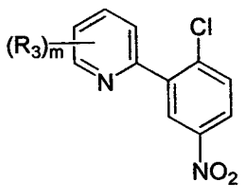
(a)

donde Q es Cl, Br o I; con un compuesto de la fórmula (b)



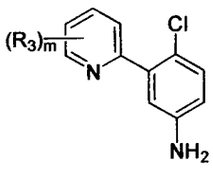
(b)

donde L es Br, I o OTf; para producir un compuesto de la fórmula (c);



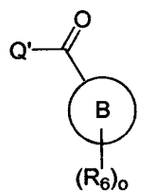
(c)

- reducir dicho compuesto de la fórmula (c) para producir un compuesto de la fórmula (d)



(d)

- y someter a una reacción dicho compuesto de la fórmula (d) con un compuesto de la fórmula (e)



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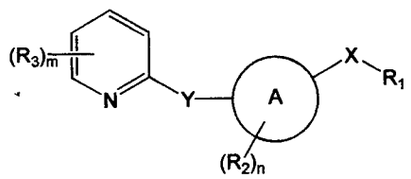
(e)

donde Q' es halógeno, OH, OR donde R es un grupo de activación; para producir dicho compuesto de la fórmula Ib".

5

RESUMEN DE LA INVENCIÓN

La invención provee nuevos inhibidores de la señalización de hedgehog que resultan de utilidad como agentes terapéuticos para tratar malignidades, los compuestos poseen la fórmula general I:



I

donde A, X, Y R_1, R_2, R_3, R_4, m y n responden a la descripción precedente..

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO PROPIETARIOS

PATENTE DE INVENCION ____ PCT __X__ MODELO DE UTILIDAD ____ DISEÑO INDUSTRIAL ___

(21) Nº de solicitud: (22) Fecha de solicitud:
(51) Clasificación Internacional :

(71)Solicitante(s) **GENENTECH, INC., CURIS INC.**

(72) Inventor(es) **JANET L. GUNZNER, DANIEL P. SUTHERLIN, MARK S. STANLEY, LIANG BAO, GEORGETTE CASTANEDO, REBECCA L. LALONDE, SHUMEI WANG, MARK E. REYNOLDS, SCOTT J. SAVAGE, KIMBERLY MALESKY, MICHAEL S. DINA**

(74) Apoderado: **DRA. MARGARITA CASTELLANOS ABONDANO**

(30) Prioridad	(31)	**No. Prioridad**	32)	**Fecha**	(33)	**País**
		61/044.451		**11/04/2008**		**US**

(85) Fecha inicio fase nacional:
(86) Datos relativos a la presentación de la solicitud PCT
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Nº publicación: **WO 2009/126863 A2**

(54) Titulo: **INHIBIDORES PIRIDILO DE SEÑALIZACION DE HEDGEHOG**

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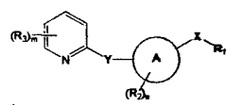
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) N° de solicitud:	(51) Int. Cl.:
22) Fecha de solicitud:	(71)Solicitante(s) **GENENTECH, INC.** **CURIS INC.**
(30) Prioridad (31) N° Prioridad **61/044.451** 32) Fecha **11/04/2008** (33) País **US**	(72) Inventor(es) **JANET L. GUNZNER** **DANIEL P. SUTHERLIN** **MARK S. STANLEY** **Y OTROS**
	(74) Apoderado: **MARGARITA CASTELLANOS ABONDANO**
(85) Fecha limite inicio fase nacional: (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud: **10/04/2009** N° de solicitud **PCT/US2009/040165**	(87) Publicación internacional Fecha: **15/10/2009** N° publicación: **WO 2009/126863 A2**

(54) Titulo: **INHIBIDORES PERIFERICOS DE SEÑALIZACION DE HEDGEHOG**

Reivindicación(es):

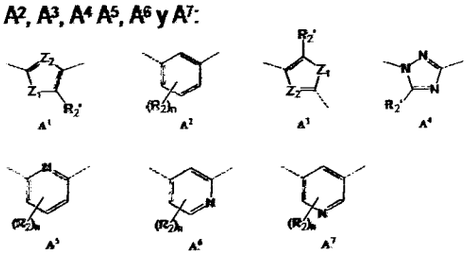
1. Un compuesto de la fórmula I:



I

caracterizado porque
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 es seleccionado del grupo integrado 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 un heterociclo; en tanto dicho sustituyente amino, amidino, alquilo, acilo, sulfonilo, sulfinilo, alcoxi, alquiltio, carbamoilo, acilamino, sulfamoilo, sulfonamida, carbociclo y heterociclo está opcionalmente sustituido 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 un heterociclo;
R_2 es halógeno, hidroxilo, alquilo, acilo o alcoxi, en tanto 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 en tanto cada alquilo, acilo, alcoxi, alcoxicarbonilo, carbamoilo, alquilsulfuro, sulfinilo, sulfonilo, carbociclo y heterociclo está opcionalmente sustituido con hidroxilo, halógeno, amino, nitro, alquilo, acilo, sulfonil o alcoxi;
R_4 es H o alquilo;
m es 0-3;
n es 0-3;
y sales y solvatos del mismo.

2. El compuesto de la Reivindicación 1, caracterizado porque A es un anillo seleccionado del grupo integrado por A^1, A^2, A^3, A^4 A^5, A^6 y A^7:



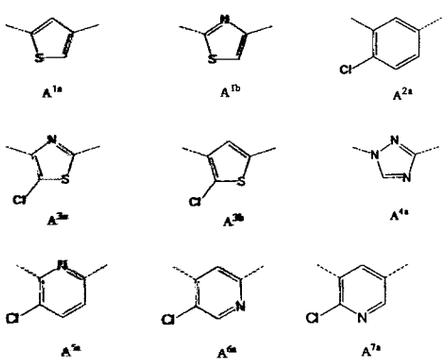
donde Z_1 es O, S o NR_5 donde R_5 es H o alquilo; Z_2 es CH, CR_2 o N; R_2 es halógeno, hidroxilo, alquilo o alcoxi; R_2' es H, halógeno, hidroxilo, alquilo o alcoxi; y n es 0-3.

3. El compuesto de la Reivindicación 2, caracterizado porque 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, caracterizado porque A es el anillo A^2.

5. El compuesto de la Reivindicación 2, caracterizado porque R_2 o R_2' es Cl.

6. El compuesto de la Reivindicación 1, caracterizado porque A es 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, caracterizado porque X es $NR_4C(O)$.

8. El compuesto de la Reivindicación 1, caracterizado porque X es NR_4SO_2.

9. El compuesto de la Reivindicación 7, caracterizado porque R_4 es H o Me.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900174099-2

RECIBO OFICIAL DE CAJA : 10 - 94,704
FECHA : NOVIEMBRE 8 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-140789- -00000-0000
Fecha: 2010-11-10 13:53:59 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 535

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ALVARO CASTELLANOS	CONSIGNACION	BANCO DE BOGOTA	062754387	387632416	08/11/2010	13,764,000.00

**** 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	554,000.00
		TOTAL : $	554,000.00

SON: QUINIENTOS CINCUENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

535

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900112036-7

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-140789- -00000-0000
Fecha: 2010-11-10 13:53:59 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 535

RECIBO OFICIAL DE CAJA : 10 - 95,573
FECHA : NOVIEMBRE 10 DE 2010

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

DEPOSITANTE	TIPO PAGO	BANCO	CHEQUE	No PAGO	FECHA PAG	Vr. PAGO
ALVARO CASTELLANOS	CONSIGNACION	BANCO DE BOGOTA	062754797	387632412	10/11/2010	3,572,000.00

***** C O N C E P T O *****

CANT. DE TRAMITE	CONCEPTO	TOTAL CONCEPTO
02	90005-01-01 SOLICITUDES	*** REVISION CONTRARIA ORDINARIA 702,000.00
		TOTAL : $ 702,000.00

SON: SETECIENTOS DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____