08 44683

Industria y Comercio

SUPERINTENDENCIA

Organizacion y Digitalizacion CSA Ltda

CSA047452

"SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO" INVENTARIO

Delegatura de Propiedad Industrial

División de Nuevas Creciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

1. **EXPEDIENTE No.** 08-44683

1. **TÍTULO** INHIBIDORES DE MEK Y METODOS PARA SU USO

CLASIFICACIÓN INTERNACIONAL C07D 205/04; 205/56, 401/ A61K 31/397; A61P 35/00

SOLICITANTE EXELIXIS, Inc.

DOMICILIO SOUTH SAN FRANCISCO, CALIFORNIA, USA.

APODERADO CARLOS ORLANDO MAYA RODRIGUEZ

BOGOTÁ, D. C., 30 de ABRIL /2008

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-044683- -00000-0000
Fecha: 2008-05-02 11:14:48 Dep: 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 908

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1. SOLICITUD DE:

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

[X] Capitulo I [ ] Capitulo II

SOLICITANTE (71)	Nombre: **Exelixis, Inc.** Dirección: 210 East Grand Avenue, P.O. Box 511 South San Francisco. California Domicilio: South San Francisco, California 94083-0511, US Lugar de Constitución: **DELAWARE** Teléfono: Fax E-mail:	**IDENTIFICACION** C.C. [ ] NIT [ ] C.E. [ ] Otro [ ] Cual Número:
3. REPRESENTANTE O APODERADO	Nombre: **CARLOS ORLANDO MAYA RODRIGUEZ** Dirección: **Cr. 13 A No 28-38, Mz 2 Bufete 245. Parque Central Bavaria** Teléfono: **3419841** Fax **3368592** E-mail: **patent@tmtamayo.net**	**IDENTIFICACION** C.C. [X] NIT [ ] C.E. [ ] Otro [ ] Cual Número: **17.117.818** TP: **17.402**
4. INVENTOR(ES) (72)	Nombres: **1.- AAY, Naing** **2.- ANAND, Neel Kumar** Dirección: 1.- 112 North Rochester Street, San Mateo, CA 94401 EE.UU. 2.- 977 El Camino Real, #303, Burlingame, CA 94010 EE.UU.. Nacionalidad o Domicilio: 1.- CIUDADANO DE: EE.UU 2.- CIUDADANO DE: EE.UU **OTROS INVENTORES EN HOJA ANEXA**	

5. PCT (86)
Solicitud internacional No. **PCT/US2006/039126** Fecha: **Octubre 05/2006**
Publicación internacional No. **WO 2007/044515 A1** Fecha: **abril 19 de 2007**

6. Título (54) INHIBIDORES DE MEK Y MÉTODOS PARA SU USO

7. Clasificación Internacional (51) C07D 205/04, 205/06, 401/06; A61K 31/397, A61P 35/00.

8. Prioridad Si [X] No [ ]

(33) País de Origen	(32) Fecha	(31) Número deSolicidud
EE.UU.	07-Oct-05	60/724,578
EE.UU.	23-May-06	60/802,840

9. Comprobante de pago No. **08-34,741 y 08-34,742** Fecha **Abril 30 de 2008**

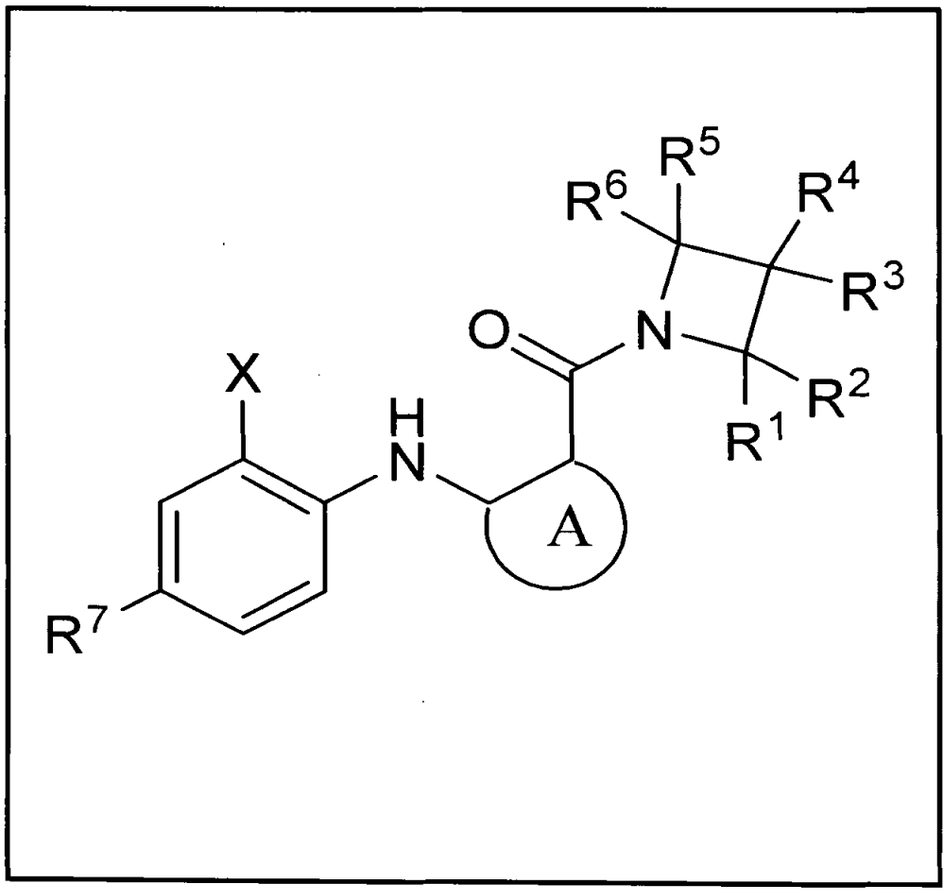
HOJA ANEXA INVENTORES

4.	Nombres:	3.- **BOWLES, Owen Joseph** 4.- **BUSSENIUS, Joerg** 5.- **COSTANZO, Simona** 6.- **CURTIS, Jeffry Kimo** 7.- **DUBENKO, Larisa** 8.- **JOSHI, Anagha Abhijit** 9.- **KENNEDY, Abigail R.** 10.- **KIM, Angie Inyoung** 11.- **KOLTUN, Elena** 12.- **MANALO, Jean-Claire Limun** 13.- **PETO, Csaba J.** 14.- **RICE, Kenneth D.** 15.- **TSANG, Tsze H.** 16.- **DeFina, Steven Charles** 17.- **BLAZEY, Charles M**
INVENTOR(ES) **(72)**	Dirección:	3.- 268 Manor Drive, Apt. D3, Pacifica, CA 94044 EE.UU.. 4.- 223 Bonita Lane, Foster City, CA 94404 EE.UU.. 5.- 215 North El Monte Avenue, Los Altos, CA 94022 EE.UU.. 6.- 310 Redwood Road, San Anselmo, CA 94960 EE.UU.. 7.- 584 46th Avenue, San Francisco, CA 94121 EE.UU.. 8.- 36340 Easterday Way, Fremont, CA 94536 EE.UU.. 9.- 2417 East 28th Street, Oakland, CA 94601 EE.UU.. 10.- 928 Shoal Drive, San Mateo, CA 94404 EE.UU.. 11.- 1075 Grebe Street, Foster City, CA 94404 EE.UU.. 12.- 4159 Callan Boulevard, Daly City, CA 94015 EE.UU.. 13.- 9 Christensen Court, Alameda, CA 94903 EE.UU.. 14.- 444 Montecillo Road, San Rafael, CA 94903 EE.UU.. 15.- 8367 Kent Drive, El Cerrito, CA 94530 EE.UU.. 16.- 1232 Floribunda Ave., 6, Burlingame, CA 94010 EE.UU.. 17.- 171 Randall Street, San Francisco, CA 94131 EE.UU..
	Nacionalidad o Domicilio:	3.- Ciudadano de Canada 4.- Ciudadano de Alemania 5.- Ciudadano de Italia 6.- Ciudadano de EE.UU 7.- Ciudadano de EE.UU 8.- Ciudadano de India 9.- Ciudadano de EE.UU 10.- Ciudadano de EE.UU 11.- Ciudadano de Rusia 12.- Ciudadano de EE.UU 13.- Ciudadano de EE.UU 14.- Ciudadano de EE.UU 15.- Ciudadano de EE.UU 16.- Ciudadano de EE.UU 17.- . Ciudadano de EE.UU

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 (VER Exp: 07-18563 ORIGINAL)
- [X] Poderes, si fuere el caso
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [X] Copia de la solicitud Internacional (Resumen, descripción, reivindicaciones, dibujos)
- [X] Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA)
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico
- [X] Arte final 12 x 12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extrajero 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 ANEXO CD PARA PUBLICACIÓN**

11. FIGURA CARACTERISTICA



12. Solicito la concesión de la patente,

NOMBRE: **CARLOS ORLANDO MAYA RODRIGUEZ**

FIRMA:

C.C **17.117.818** TP **17.402**

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-044683- -00000-0000

Fecha: 2008-05-02 11:14:48 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 908

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 34,741
FECHA : ABRIL 30 DE 2008

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CARLOS TAMAYO Y ASOCIADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	2273714	30/04/2008	2,097,000.00

***** 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	501,000.00
			TOTAL : $	501,000.00

SON: QUINIENTOS UN MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

5

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-044683- -00000-0000
Fecha: 2008-05-02 11:14:48 Dep: 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 34.742
FECHA : ABRIL 30 DE 2008

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CARLOS TAMAYO Y ASOCIADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	2273714	30/04/2008	2.097.000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1590	50005-01-01 SOLICITUDES	117 PALABRA ADICIONAL (DE MAS DE 150)	795.000.00
		TOTAL : $	795.000.00

SON: SETECIENTOS NOVENTA Y CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

COLEGIO DE ESCRIBANOS · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL · REPUBLICA ARGENTINA

ACTUACION NOTARIAL
LEY 404

N 007410568

LEGALIZACION
UEUBH - LEY404 GCBA
$20.00 14:42:24 19/02/2007
07021903350 6

APOSTILLA
UEUBH - LEY404 GCBA
$30.00 14:42:29 19/02/2007
07021905388 3

FOLIO 336.- PRIMERA COPIA.- ESCRITURA NUMERO CIENTO SESENTA Y OCHO.- En la Ciudad de Buenos Aires, Capital de la República Argentina, a nueve de febrero de dos mil siete, ante mi, Escribano Autorizante, COMPARECE don **Daniel GOYTIA**, argentino, mayor de edad, casado, Libreta de Enrolamiento número 4.526.965, domiciliado en Bartolomé Mitre 226, 4° piso, de esta Ciudad.- El compareciente es persona de mi conocimiento, doy fe, así como que DICE: I.- Que por escritura del dia de la fecha pasada ante mi, al folio 327 del Protocolo de este mismo Registro, se protocolizó un **Poder** otorgado por **EXELIXIS, INC.**, con domicilio en 170 Harbor Way P.O. Box 511, South San Francisco, California 94083, USA, a su favor.- II.- Que viene por la presente a **SUSTITUIR** el citado mandato, reservándose para si las facultades, a favor de **"CARLOS TAMAYO & ASOCIADOS" y/o Carlos Orlando Maya Rodriguez y/o Gustavo Calderon Rosero y/o Carmen Graciela Florez y/o Clara Cortes Charry y/o Mayerling Rocio Castelblanco S.**, con domicilio en Carrera 13A N° 28-38, Buffette 245, Manzana 02, Parque Central Bavaria, Bogotá, **COLOMBIA**, para actuar en [illegible] con las siguientes facultades: "... poder amplio y suficiente para ante [illegible] de las autoridades nacionales que corresponda, sean estas administrativas y/o judiciales, la obtención de **"PATENTES, MARCAS, MODELOS, DISEÑOS Y SUS RENOVACIONES"**, y realizar todos los trámites conducentes para proteger los derechos de la mandante, a cuyo efecto, los faculta para efectuar ante dichas autoridades nacionales, administrativas y/o judiciales todos los trámites necesarios a los objetos indicados; presentar solicitudes, alegatos, oposiciones, protestas, apelaciones y demandas; desistir, arreglar y transigir; aceptar cesiones y transferencias; solicitar testimonios; recibir documentos y

Como Notaria Dieciocho de este Círculo hago constar que la [illegible] que he tenido a la vista
30 ENE 2008
NOTARIA DIECIOCHO BOGOTA D.C.

N 007410568

otros valores; justificar explotaciones; cobrar y percibir; firmar instrumentos públicos, privados y escrituras públicas; para renunciar o no a las gestiones judiciales; y hacer cuanto fuere necesario ante las autoridades nacionales, judiciales y/o administrativas, sea como demandante o como demandado, para proteger los intereses del mandante, con facultad de substituir este instrumento y revocar tal substitución. Se deja constancia que las facultades enumeradas en este mandato, son meramente ejemplificativas y no limitativas de otras facultades implicitas, por cuyo motivo, los mandatarios quedan autorizados para ejercer sin restricción alguna todos los derechos que acuerde la ley que se relacionen y/o emerjan y/o que sean consecuencia del objeto del presente poder y ya sea ello en razón de la legislación vigente y/o de la legislación que en el futuro se promulgue. Este documento tiene validez a partir del 01 de diciembre de 2006...".- LO TRANSCRIPTO ES COPIA FIEL, doy fe, de las partes pertinentes del mandato relacionado.- LEIDA y ratificada, así lo expresó, otorgó, aceptó y firmó, por ante mi, doy fe.- "SIGUE UNA FIRMA".- Esta mi sello.- Ante mi: ALEJANDRO M. LIPORACE.- CONCUERDA con su escritura matriz que pasó ante mi, al folio 336 del Protocolo del Registro 1331, a mi cargo. PARA LOS APODERADOS expido esta **PRIMERA COPIA** en UNA FOJA de Actuación Notarial número N 007410568 que sello y firmo en el mismo lugar y fecha de su otorgamiento, doy fe.-

Como Notaria Décimocha... del Círculo hago constar que esta FOTOCOPIA coincide con su original que he tenido a la vista
20 FEB. 2008
Victoria Bernal Trujillo
NOTARIA DIECIOCHO
BOGOTA

ALEJANDRO M. LIPORACE
Matricula 3837
ESCRIBANO PUBLICO

7

COLEGIO DE ESCRIBANOS · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL - REPUBLICA ARGENTINA

LEGALIZACION

LEY 404

L 007464707

EL COLEGIO DE ESCRIBANOS de la Ciudad de Buenos Aires, Capital Federal de la República Argentina, en virtud de las facultades que le confiere la ley vigente, LEGALIZA la firma y sello del escribano ALEJANDRO MARIA LIPORACE **obrantes en el documento anexo, presentado en el día de la fecha bajo el Nº** 070219083506/6 **La presente legalización no juzga sobre el contenido y forma del documento.**

Buenos Aires, Lunes 19 de Febrero de 2007

COLEGIO DE ESCRIBANOS · LEGALIZACION · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL - REPUBLICA ARGENTINA

ESC. EDDA ENRIQUETA SINELLI
COLEGIO DE ESCRIBANOS
CONSEJERA

Como Notaria Dieciocho de este Círculo hago constar que esta FOTOCOPIA coincide con su original que he tenido a la vista

30 ABR. 2008

Victoria Bernal Trujillo
NOTARIA DIECIOCHO
BOGOTA D.C.

Power of Attorney

The undersigned (1)

EXELIXIS, INC.

Residing at (2)
170 Harbor Way P.O. Box 511. South San Francisco, California 94083. USA.

hereby grants to DANIEL GOYTIA

residing in Buenos Aires, Argentina
full and ample power of attorney to represent him (it) and to apply to the proper national authorities, either administrative or judiciary for

Patents, Trademarks, Models, Designs and their Renewals

and to carry out all the necessary steps to protect our rights, to which effect they are empowered to take all necessary steps before the said national authorities, either administrative and/or judicial, for the aforementioned purposes, including to file petitions, arguments oppositions, protests, appeals and claims, to waive, settle and compromise; to accept assignments and transfers; to apply for certified copy; to receive documents and other valuable things; to prove workings; to collect monies; to sign public and private instruments and deeds; to either waive or not at their discretion the right of resorting to court proceedings; to do all and whatever shall be necessary before any national judicial and/or administrative authorities to protect the constituent's interests, either as plaintiff or defendant, with power to substitute this instrument and to revoke such substitution. It being understood that the above powers enumerated in this mandate are merely exemplifying and not limitative of other powers and therefore the attorneys-in-fact are authorized to exercise without any restriction whatsoever, all the rights granted by Law or emerging from it or which, may be a consequence of the objects of this mandate and whether this be under legislation at present in force or legislation which may be promulgated in the future.

Dated (3)
Day 24 Of January 2007

Poder

52465

El abajo firmante (1)

EXELIXIS, INC.

Domiciliado en (2)
170 Harbor Way P.O. Box 511. South San Francisco, California 94083. USA

por el presente otorga a DANIEL GOYTIA

domiciliado en Buenos Aires, Argentina
poder amplio y suficiente para recabar de las autoridades nacionales que corresponda, sean éstas administrativas y/o judiciales, la obtención de

Patentes, Marcas, Modelos, Diseños y sus renovaciones

y realizar todos los tramites conducentes para proteger los derechos de la mandante, a cuyo efecto, los faculta para efectuar ante dichas autoridades nacionales, administrativas y/o judiciales, todos los tramites necesarios a los objetos indicados; presentar solicitudes, alegatos, oposiciones, protestas, apelaciones y demandas; desistir, arreglar y transigir; aceptar cesiones y transferencias, solicitar testimonios, recibir documentos y otros valores; justificar explotaciones, cobrar y percibir; firmar instrumentos públicos, privados y escrituras publicas; para renunciar o no a las gestiones judiciales; y hacer cuanto fuere necesario ante las autoridades nacionales, judiciales y/o administrativas, sea como demandante o como demandado, para proteger los intereses del mandante, con facultad de substituir este instrumento y revocar tal substitución. Se deja constancia que las facultades enumeradas en este mandato, son meramente ejemplificativas y no limitativas de otras facultades implícitas, por cuyo motivo, los mandatarios quedan autorizados para ejercer sin restricción alguna todos los derechos que acuerde la ley que se relacionen y/o emerjan y/o que sean consecuencia del objeto del presente poder y ya sea ello en razón de la legislación vigente y/o de la legislación que en el futuro se promulgue.

(3) Fechado el
de de 2007

(4) .....
Pamela A. Simonton, Senior Vice President, Patents & Licensing
(1) Applicant's name – (2) Applicant's address – (3) Date – (4) Applicant's Signature

*****This document is effective as of December 01, 2006*****

Como Notaria Dieciocho de este Circulo hago constar que esta FOTOCOPIA coincide con su original que he tenido a la vista
30 ABR. 2008
Victoria Bernal Trujillo
NOTARIA DIECIOCHO
BOGOTA D.C.

ALEJANDRO M. LIPORACE
Matricula 3837
ESCRIBANO PUBLICO

de 200 ___ ante mí, Notario Público o Funcionario Autorizado de

compareció(eron) personalmente

a quien(es) doy fe de conocer y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede, y quien(es) tiene(n) capacidad legal para otorgarlo

200 ___ before me, a Notary Public or Attesting Official of

personally appeared

to me known, and known to me to be the person(s) who executed that foregoing document, and who has(have) legal capacity to execute it.

--- NOTARIO PÚBLICO O FUNCIONARIO AUTORIZADO --- NOTARY PUBLIC OR ATTESTING OFICIAL ---

CERTIFICACIÓN NOTARIAL (SOCIEDAD)

A los _____ días del mes de _____

de 200 _____ compareció(eron) ante mí,

Quien(es) conozco personalmente y que firma(n) este documento en representación de la Sociedad/compañía denominada

Certifico:

1. Que he visto los siguientes documentos:*

2. Que dichos documentos prueban lo siguiente:

2.1. Que es una Sociedad/Compañía legalmente constituida y existente de acuerdo con las leyes del Estado de

2.2. Que el domicilio de dicha Sociedad/Compañía es

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

2.4. Que el(los) Sr.(Sres.) _____

está(n) autorizado(s) para otorgar el presente Poder.

Ciudad _____

Estado _____

Hoy _____ de 200 __

--- NOTARIO PÚBLICO O FUNCIONARIO AUTORIZA

NOTARIAL CERTIFICATION (CORPORATION)

On this _____ day of _____

200 ____ appeared before me

who(m) I know personally and who(m) signed this document as representative(s) of the Corporation/Company named

I certify:

1. That I have seen the following documents:*
   Articles of Incorporation;
   Statement of Information from the Secretary of State of the State of California;
   Certificate of Good Standing from the Secretary of State of the State of Delaware;

2. That the above documents duly prove the following:
2.1. That is a Corporation/Company legally constituted and in existence in accordance with the laws of the State of Delaware

2.2 That the domicile of said Corporation/Company is California

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

2.4. That Mr.(Messrs.) Pamela A. Simonton

is(are) authorized to grant the present Power of Attorney

City: South San Francisco
State: California, United States of America
This 29th day of January, 2007

ATTESTING OFFICIAL
Christoph Pereira
Vice President, Legal Affairs and Secretary

Notaría Dieciocho del Círculo hago constar que ésta FOTOCOPIA coincide con su original que he tenido a la vista
APR 2008
Victoria Bernal Pulido
NOTARIA DIECIOCHO
BOGOTA, D.C.

ALEJANDRO M. LIPORACE
Matrícula 3837
ESCRIBANO PUBLICO

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 J. COHEN*
3. *acting in the capacity of Notary Public, State of California*
4. *bears the seal/stamp of J. COHEN, Notary Public, State of California*

CERTIFIED

5. *At Sacramento, California*
6. *the 6th day of February 2007*
7. *by Deputy Secretary of State, State of California*
8. *No. 351842*
9. *Seal/Stamp:*

10. *Signature*

Secretary of State

NP-24 A (REV. 1-07)

BY

OSP 06 99602

Como Notaria Dieciocho de este Circulo hago constar que la copia coincide con su original que he tenido a la vista

30 APR 2008

NOTARIA DIECIOCHO BOGOTA, D.C.

EL GRAN SELLO DEL ESTADO DE CALIFORNIA

ALEJANDRO M. LIPORACE
Matrícula 3837
ESCRIBANO PUBLICO

CALIFORNIA ALL-PURPOSE ACKNOWLEDGMENT

State of California

County of San Mateo

On 24 January 2007 (Date) before me, J. Cohen, Notary Public (Name and Title of Officer (e.g., "Jane Doe, Notary Public")),

personally appeared Pamela A. Simonton & Christoph Pereira (Name(s) of Signer(s))

☑ personally known to me

☐ (or 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.

WITNESS my hand and official seal.

J. COHEN
Commission # 1417900
Notary Public - California
San Mateo County
My Comm. Expires Jun 11, 2007

Place Notary Seal Above

Signature of Notary Public

OPTIONAL

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

Description of Attached Document

Title or Type of Document: Power of Attorney

Document Date: _____ Number of Pages: 1 page + certs.

Signer(s) Other Than Named Above: _____

Capacity(ies) Claimed by Signer(s)

Signer's Name: Pamela A Simonton	Signer's Name: Christoph Pereira
☐ Individual	☐ Individual
☑ Corporate Officer — Title(s): Senior Vice President	☑ Corporate Officer — Title(s): Secretary
☐ Partner — ☐ Limited ☐ General	☐ Partner — ☐ Limited ☐ General
☐ Attorney in Fact	☐ Attorney in Fact
☐ Trustee	☐ Trustee
☐ Guardian or Conservator	☐ Guardian or Conservator
☐ Other: _____	☐ Other: _____
Signer Is Representing: Exelixis, Inc	Signer Is Representing: Exelixis
RIGHT THUMBPRINT OF SIGNER — Top of thumb here	RIGHT THUMBPRINT OF SIGNER — Top of thumb here

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EL GRAN SELLO DEL ESTADO DE CALIFORNIA

Como Notaria Dieciocho de este Circulo hago constar que esta FOTOCOPIA coincide con su original que he tenido a la vista
30 ABR 2008
Victoria Bernal Trujillo
NOTARIA DIECIOCHO
BOGOTA D.C.

ALEJANDRO M. LIPORACE
Matricula 3837
ESCRIBANO PUBLICO

TRADUCCIÓN PÚBLICA ----------

[Página 1] ----------

DANIEL GOYTÍA - PATENTES Y MARCAS ----------

[Luego de un PODER, redactado en idiomas inglés y español aparece lo siguiente:] ----------

(3) Fechado a los 24 días de enero de 2007 ----------

(4) [Aparece una firma ilegible debajo de la cual se lee:] Pamela A. Simonton, Vicepresidente Senior, Patentes y Licencias

(1) Nombre del Solicitante, (2) Domicilio del Solicitante, (3) Fecha, (4) Firma del Solicitante ----------

*****Este documento tiene validez a partir del 01 de diciembre de 2006***** ----------

---

[Página 2] ----------

[Siguen dos Certificados Notariales en idiomas español e inglés. Luego del segundo Certificado Notarial aparece lo siguiente:] ----------

Ciudad: San Francisco. ----------

Estado: California, Estados Unidos de Norteamérica. ----------

A los 24 días de enero de 2007. ----------

[Aparece una firma ilegible debajo de la cual se lee:] FUNCIONARIO CERTIFICANTE. Christoph Pereira, Vicepresidente, Asuntos Legales y Secretario. ----------

---

[Página 3] ----------

ESTADO DE CALIFORNIA ----------

EL GRAN SELLO DEL ESTADO DE CALIFORNIA ----------

Como Notaria Dieciocho de este Círculo hago constar que esta FOTOCOPIA coincide con su original que he tenido a la vista

30 ABR 2008

Victoria Bernal Trujillo
NOTARIA DIECIOCHO
BOGOTA D.C.

ALEJANDRO M. LIPORACE
Matricula 3837
ESCRIBANO PUBLICO

SECRETARIO DE ESTADO ----------

APOSTILLA ----------

[Aparece una frase en otro idioma] ----------

1. País: Estados Unidos de Norteamérica ----------

Este documento público ----------

2. ha sido firmado por J. COHEN ----------

3. actuando en carácter de Escribano Público, Estado de California ----------

4. lleva el sello/timbre de J. COHEN, Escribano Público, Estado de California ----------

CERTIFICADO ----------

5. en Sacramento, California ----------

6. el 06 de febrero de 2007 ----------

7. por el Subsecretario de Estado, Estado de California -------

8. No. 351842 ----------

9. Sello/Timbre: El Gran Sello del Estado de California ------

10. Firma: [Aparece una firma ilegible debajo de la cual se lee:] Secretario de Estado. ----------

Por: [Aparece una firma ilegible] ----------

[Sigue un sello circular que reza:] OFICINA DEL SECRETARIO DE ESTADO, EL GRAN SELLO DEL ESTADO DE CALIFORNIA ----------

---

[Página 4] ----------

CERTIFICACIÓN PARA TODOS LOS PROPÓSITOS DE CALIFORNIA----------

Estado de California. Condado de San Mateo.----------

A los (FECHA) 24 días del mes de enero del año 2007, por ante mí, (NOMBRE Y CARGO DEL FUNCIONARIO (E.J., "JANE DOE, ESCRIBANO

Como Notaria Dieciocho de este Círculo hago constar que esta FOTOCOPIA coincide con su original que he tenido a la vista
30 ABR. 2008
Victoria Bernal Trujillo
NOTARIA DIECIOCHO
BOGOTA, D.C.

PÚBLICO)) J. Cohen, Escribano Público, compareció personalmente (NOMBRE DE LA PERSONA(S) FIRMANTE(S)) Pamela A. Simonton & Christoph Pereira, [X] a quienes conozco personalmente---------

[ ] (o demostraron ante mí con pruebas suficientes)----------

que son las personas cuyos nombres suscriben el instrumento adjunto y certificaron ante mí que lo otorgaron en su carácter de autorizados, y que con sus firmas en el instrumento las personas o la persona de existencia ideal en nombre de la cual actuaron las personas, otorgaron el instrumento.----------

CERTIFICO con mi firma y sello oficial.----------

[Aparece una firma ilegible debajo de la cual se lee:] Firma del Escribano Público----------

Colocar el sello notarial más arriba [Aparece un sello que reza:] El Gran Sello del Estado de California. J. COHEN. MANDATO NO. 1417900. ESCRIBANO PÚBLICO - CALIFORNIA. CONDADO DE SAN MATEO. Mi mandato vence el 11 de junio de 2007----------

INFORMACIÓN OPTATIVA----------

La información que aparece a continuación no ese exigida por ley. Sin embargo, podría ser valiosa para las personas que confían en el documento e impediría que la presente certificación se adjunte en forma fraudulenta a otro documento.----------

Descripción del Documento Adjunto.----------

Título o Tipo de Documento: **Poder**----------

Fecha del Documento: [en blanco] ----------

Número de Páginas: 1 página más cer[illegible]---------

Persona(s) Firmante(s) distinta de l[illegible]anteriormente:

Como Notaria Dieciocho de Bogotá Circulo hago constar que esta FOTOCOPIA concuerda con su original que he tenido a la vista
30 ABR. 2008
Victoria Bernal Trujillo
NOTARIA DIECIOCHO
BOGOTA D.C.

ALEJANDRO M. LIPORACE
Matrícula 3837
ESCRIBANO PUBLICO

16

[en blanco].----------

CARÁCTER INDICADO POR EL FIRMANTE----------

Nombre de la Persona Firmante: Pamela A. Simonton----------

[ ] Persona Física----------

[X] Funcionario de Sociedad Anónima. Cargo(s): Vicepresidente Senior----------

[ ] Socio(s) - [ ] Limitado [ ] General----------

[ ] Apoderado----------

[ ] Síndico----------

[ ] Tutor o Curador----------

[ ] Otro: [en blanco]----------

El firmante representa a: **Exelixis, Inc.**----------

Huella digital del pulgar derecho del firmante----------

[Aparece un casillero en blanco con una leyenda que reza:] Coloque aquí la parte superior de la huella digital del pulgar derecho.----------

Nombre de la Persona Firmante: Christoph Pereira.----------

[ ] Persona Física----------

[X] Funcionario de Sociedad Anónima. Cargo(s): Secretario.-----

[ ] Socio(s) - [ ] Limitado [ ] General----------

[ ] Apoderado----------

[ ] Síndico----------

[ ] Tutor o Curador----------

[ ] Otro: [Aparece una línea en blanco]----------

El firmante representa a: Exelixis----------

Huella digital del pulgar derecho del firmante----------

Como Notaria Dieciocho de éste Círculo hago constar que ésta FOTOCOPIA coincide con su original que he tenido a la vista
30 ABR. 2008
Victoria Bernal Trujillo
NOTARIA DIECIOCHO
18 BOGOTA D.C.

[Aparece un casillero en blanco con una leyenda que reza:] Coloque aquí la parte superior de la huella digital del pulgar derecho.----------

2006 Asociación Nacional de Escribanos. 9350 De Soto Ave., P.O. Box 2402, Chatsworth, CA 91313-2402, Ítem No. 5907, Nuevo Pedido: Llamar a la línea gratuita 1-800-876-6827. ----------

---

CERTIFICO POR LA PRESENTE QUE LO QUE ANTECEDE ES TRADUCCIÓN FIEL Y COMPLETA AL ESPAÑOL DE LAS PARTES PERTINENTES EN IDIOMA INGLÉS DEL DOCUMENTO ORIGINAL QUE TUVE ANTE MÍ Y AL CUAL ME REMITO. EN LA CIUDAD DE BUENOS AIRES, A LOS 09 DÍAS DEL MES DE FEBRERO DE DOS MIL SIETE. ----------

COLEGIO DE TRADUCTORES PUBLICOS
DE LA CIUDAD DE BUENOS AIRES
Corresponde a la Legalización
Nº 74- 2424/07
ESTEBAN SANTIAGO ALLEGRETTI

DANIEL GOYTIA
AGENTE Nº 464

ALEJANDRO M. LIPORACE
Matricula 3837

Como Notaria Dieciocho de éste Círculo hago constar que ésta FOTOCOPIA coincide con su original que he tenido a la vista
30 ABR 2008
Victoria Bernal Trujillo
NOTARIA DIECIOCHO
BOGOTA, D.C.

COLEGIO DE TRADUCTORES PÚBLICOS
DE LA CIUDAD DE BUENOS AIRES

REPÚBLICA ARGENTINA
LEY 20.305

LEGALIZACIÓN

ır la presente, el COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES,

virtud de la facultad que le confiere el artículo 10, inc. d) de la Ley 20.305, certifica únicamente que la

ma y el sello que aparecen en la traducción adjunta, concuerdan con los correspondientes

Traductor Público **FIORI UGARTE, VALERIA**

ıe obran en los registros de esta institución en el folio tomo

INGLES	233	13

ıenos Aires, **Legalización Número: 3424 / 2007 / T4**

Fecha: 09/02/07

MARCELO F. SIGALOFF
Encargado Dto. de Legalizaciones
Colegio de Traductores Públicos
de la Ciudad de Buenos Aires

ESTA LEGALIZACIÓN NO SE CONSIDERARÁ VÁLIDA SIN EL CORRESPONDIENTE TIMBRADO EN LA ÚLTIMA HOJA DE LA TRADUCCIÓN ADJUNTA

Como Notaria(o) encargada(o) de disposiciones relativas a Archivo, hago constar que esta FOTOCOPIA coincide con su original que he tenido a la vista
30 ABR. 2008
Victoria Bernal Trujillo
NOTARIA DIECIOCHO
BOGOTA

COLEGIO DE ESCRIBANOS · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL · REPUBLICA ARGENTINA

CERTIFICACION DE REPRODUCCIONES
LEY 404

T 005904431

A. LIPORACE
3837
PUBLICO

Buenos Aires, 14 de Febrero.- de 2007.-

En mi carácter de Escribano Titular del Registro 1331 de Capital Federal.-

CERTIFICO que la reproducción anexa, extendida en Diez.-

foja/s, que sello y firmo, es COPIA FIEL de su original, que tengo a la vista, doy fe.

El Autorizante deja constancia que el documento cuyas fotocopias se certifican consiste en un PODER redactado en idioma extranjero con su correspondiente traducción al español.-

ALEJANDRO M. LIPORACE
Matricula 3837
ESCRIBANO PUBLICO

Como Notaria Duclocho de éste Circulo hago constar que ésta FOTOCOPIA coincide con su original que he tenido a la vista

30 ABR 2008

Victoria Bernal Trujillo
NOTARIA DUCLOCHO
BOGOTA D.C.

CECBA - LEY404 GCBA

APOSTILLA

070219053886

$39.00

9/02/2007 14:42:29

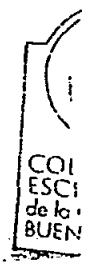
CECBA - LEY404 GCBA

LEGALIZACION

070219083510

$20.00

19/02/2007 14:42:24



Como Notaria Dieciocho de este Circulo hago constar que esta FOTOCOPIA coincide con su original que he tenido a la vista

30 ABR. 2008

Victoria Bernal Trujillo

NOTARIA DIECIOCHO BOGOTA, D.C.

COLEGIO DE ESCRIBANOS · CIUDAD DE BUENOS AIRES · CAPITAL FEDERAL · REPUBLICA ARGENTINA

LEGALIZACION
LEY 404

L 007464710

EL COLEGIO DE ESCRIBANOS de la Ciudad de Buenos Aires, Capital Federal de la República Argentina, en virtud de las facultades que le confiere la ley vigente, LEGALIZA la firma y sello del escribano ALEJANDRO MARIA LIPORACE **obrantes en el documento anexo, presentado en el día de la fecha bajo el N°** 070219083510/8 **La presente legalización no juzga sobre el contenido y forma del documento.**

Buenos Aires, Lunes 19 de Febrero de 2007

ESC. EDDA ENRIQUETA SINELLI
COLEGIO DE ESCRIBANOS
CONSEJERA

Como Notaria Dieciocho de este Circulo hago constar que esta FOTOCOPIA coincide con su original que he tenido a la vista
20 FEB. 2008
Victoria Bernal Trujillo
NOTARIA DIECIOCHO
BOGOTA D.C.

APOSTILLE

REPUBLICA ARGENTINA

(Convention de La Haye du 5 octobre 1961)

A 00104499

1. PAÍS: REPUBLICA ARGENTINA

El presente documento público

2. Ha sido firmado por EDDA ENRIQUETA SINELLI

3. Quien actúa en calidad de CONSEJERA

4. Lleva el sello / timbre de COLEGIO DE ESCRIBANOS DE LA CIUDAD DE BUENOS AIRES

5. En LA CIUDAD DE BUENOS AIRES 6. El día 19/02/2007

7. Por EL COLEGIO DE ESCRIBANOS DE LA CIUDAD DE BUENOS AIRES

MINISTERIO DE RELACIONES EXTERIORES, COMERCIO INTERNACIONAL Y CULTO

(Convenio 02/09/2003)

8. Bajo el número: 070219053886

9. Sello / Timbre

COLEGIO DE ESCRIBANOS APOSTILLA

10. Firma

ESC. HUGO L. R. CHIOCCI
COLEGIO DE ESCRIBANOS
LEGALIZADOR

Apostille

(Convention de La Haye du 5 Octobre 1961)

1. *Country: United States of America*

This public document:

2. *has been signed by Harriet Smith Windsor*

3. *acting in the capacity of Secretary of State of Delaware*

4. *bears the seal/stamp of Office of Secretary of State*

Certified

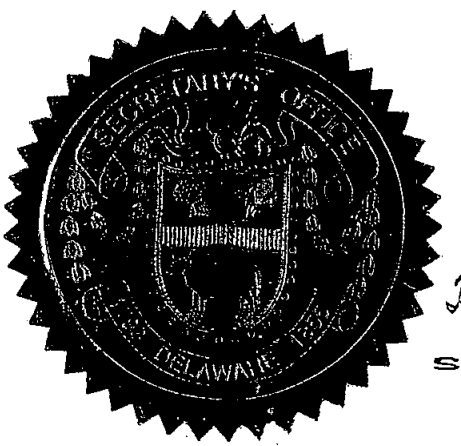
5. *at Dover, Delaware*

6. *the sixteenth day of February, A.D. 2007*

7. *by Secretary of State, Delaware Department of State*

8. *No. 0307885*

9. *Seal/Stamp:*



10. *Signature:*

Harriet Smith Windsor

Secretary of State

Delaware

The First State

I, HARRIET SMITH WINDSOR, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE RESTATED CERTIFICATE OF "EXELIXIS, INC.", FILED IN THIS OFFICE ON THE FOURTEENTH DAY OF APRIL, A.D. 2000, AT 10 O'CLOCK A.M.



Harriet Smith Windsor

Harriet Smith Windsor, Secretary of State

2452819 810C

AUTHENTICATION: 5438027

070176006

DATE: 02-16-07

84

AMENDED AND RESTATED CERTIFICATE OF INCORPORATION OF EXELIXIS, INC.

GEORGE SCANGOS and GLEN SATO hereby certify that:

1. The original name of this corporation is Exelixis Pharmaceuticals, Inc. and the date of filing the original Certificate of Incorporation of this corporation with the Secretary of State of the State of Delaware is November 15, 1994.

2. They are the duly elected and acting President and Chief Executive Officer and Secretary, respectively, of Exelixis, Inc., a Delaware Corporation.

3. The Certificate of Incorporation of this corporation is hereby amended and restated to read as follows:

I.

The name of the Corporation is Exelixis, Inc. (the "Corporation").

II.

The address of the registered office of the Corporation in the State of Delaware is:

Corporation Trust Center
1209 Orange Street
Wilmington, Delaware 19805
County of New Castle

The name of the registered agent of the Corporation at such address is The Corporation Trust Company.

III.

The purpose of the Corporation is to engage in any lawful act or activity for which corporations may be organized under the General Corporation Law of the State of Delaware.

IV.

This Corporation is authorized to issue two classes of stock to be designated, respectively, "Common Stock" and "Preferred Stock." The total number of shares which the corporation is authorized to issue is one hundred and ten million (110,000,000) shares. One hundred million (100,000,000) shares shall be Common Stock, each having a par value of one-tenth of one cent ($0.001). Ten million (10,000,000) shares shall be Preferred Stock, each having a par value of one-tenth of one cent ($0.001).

STATE OF DELAWARE
SECRETARY OF STATE
DIVISION OF CORPORATIONS
FILED 10:00 AM 04/14/2000
001191686 - 2452819

25

Preferred Stock. The Preferred Stock may be issued from time to time in one or more series. The board of Directors is hereby authorized, by filing a certificate (a "Preferred Stock Designation") pursuant to the Delaware General corporation Law ("DGCL"), to fix or alter from time to time the designation, powers, preferences, and rights of the shares of each such series and the qualifications, limitations or restrictions of any wholly unissued series of Preferred Stock, and to establish from time to time the number of shares constituting any such series or any of them; and to increase or decrease the number of shares of any series subsequent to the issuance of shares of that series, but not below the number of shares of such series then outstanding. In case the number of shares of any series shall be decreased in accordance with the foregoing sentence, the shares constituting such decrease shall resume the status that they had prior to adoption of the resolution originally fixing the number of shares of such series.

V.

A. **Board of Directors.** For the management of the business and the conduct of the affairs of the Corporation, and in further definition, limitation and regulation of the powers of the Corporation, of its directors and of its stockholders or any class thereof, as the case may be, it is further provided that:

1. **Powers.** The management of the business and the conduct of the affairs of the Corporation shall be vested in its Board of Directors.

2. **Number of Directors.** The number of directors which shall constitute the whole Board of Directors shall be fixed exclusively by one or more resolutions adopted by the Board of Directors.

3. **Election of Directors.** Subject to the rights of the holders of any series of Preferred Stock to elect additional directors under specified circumstances, following the closing of the initial public offering pursuant to an effective registration statement under the Securities Act of 1933, as amended (the "1933 Act"), covering the offer and sale of Common Stock to the public (the "Initial Public Offering"), the directors shall be divided into three classes designated as Class I, Class II and Class III, respectively. Directors shall be assigned to each class in accordance with a resolution or resolutions adopted by the Board of Directors. At the first annual meeting of stockholders following the closing of the Initial Public Offering, the term of office of the Class I directors shall expire and Class I directors shall be elected for a full term of three years. At the second annual meeting of stockholders following the closing of the Initial Public Offering, the term of office of the Class II directors shall expire and Class II directors shall be elected for a full term of three years. At the third annual meeting of stockholders following the closing of the Initial Public Offering, the term of office of the Class III directors shall expire and Class III directors shall be elected for a full term of three years. At each succeeding annual meeting of stockholders, directors shall be elected for a full term of three years to succeed the directors of the class whose terms expire at such annual meeting.

Notwithstanding the foregoing provisions of this section, each director shall serve until his successor is duly elected and qualified or until his death, resignation or removal. No decrease in the number of directors constituting the Board of Directors shall shorten the term of any incumbent director.

4. **Removal of Directors.**

a. Neither the Board of Directors nor any individual director may be removed without cause.

b. Subject to any limitation imposed by law, any individual director or directors may be removed with cause by the holders of a majority of the voting power of the corporation entitled to vote at an election of directors.

5. **Vacancies.**

a. Subject to the rights of the holders of any series of Preferred Stock, any vacancies on the Board of Directors resulting form death, resignation, disqualification, removal or other causes and any newly created directorships resulting from any increase in the number of directors, shall, unless the Board of Directors determines by resolution that any such vacancies or newly created directorships shall be filled by the stockholders, except as otherwise provided by law, be filled only by the affirmative vote of a majority of the directors then in office, even though less than a quorum of the Board of Directors, and not by the stockholders. Any director elected in accordance with the preceding sentence shall hold office for the remainder of the full term of the director for which the vacancy was created or occurred and until such director's successor shall have been elected and qualified.

b. If at the time of filling any vacancy or any newly created directorship, the directors then in office shall constitute less than a majority of the whole board (as constituted immediately prior to any such increase), the Delaware Court of Chancery may, upon application of any stockholder or stockholders holding at least ten percent (10%) of the total number of the shares at the time outstanding having the right to vote for such directors, summarily order an election to be held to fill any such vacancies or newly created directorships, or to replace the directors chosen by the directors then in offices as aforesaid, which election shall be governed by Section 211 of the DGCL.

B.

1. **Bylaw Amendments.** Subject to paragraph (h) of Section 43 of the Bylaws, the Bylaws may be altered or amended or new Bylaws adopted by the affirmative vote of at least sixty-six and two-thirds percent (66-2/3%) of the voting power of all of the then-outstanding shares of the voting stock of the corporation entitled to vote. The Board of Directors shall also have the power to adopt, amend, or repeal Bylaws.

2. **Election of Directors by Written Ballot.** The directors of the corporation need not be elected by written ballot unless the Bylaws so provide.

3. **Action by Written Consent of the Stockholders.** No action shall be taken by the stockholders of the corporation except at an annual or special meeting of stockholders called in accordance with the Bylaws or by written consent of stockholders in accordance with the Bylaws prior to the closing of the Initial Public Offering and following the closing of the Initial Public Offering no action shall be taken by the stockholders by written consent.

4. **Notice of Meetings.** Advance notice of stockholder nominations for the election of directors and of business to be brought by stockholders before any meeting of the stockholders of the corporation shall be given in the manner provided in the Bylaws of the corporation.

VI.

A. **Indemnification.** A director of the Corporation shall not be personally liable to the Corporation or its stockholders for monetary damages for any breach of fiduciary duty as a director, except for liability (i) for any breach of the director's duty of loyalty to the Corporation or its stockholders, (ii) for acts or omissions not in good faith or which involve intentional misconduct or a knowing violation of law, (iii) under Section 174 of the Delaware General Corporation Law, or (iv) for any transaction from which the director derived an improper personal benefit. If the Delaware General Corporation Law is amended after approval by the stockholders of this Article to authorize corporate action further eliminating or limiting the personal liability of directors, then the liability of a director shall be eliminated or limited to the fullest extent permitted by the Delaware General Corporation Law, as so amended.

B. **Amendments to Articles VII of the Certificate of Incorporation.** Any repeal or modification of this Article VI shall be prospective and shall not affect the rights under this Article VI in effect at the time of the alleged occurrence of any act or omission to act giving rise to liability or indemnification.

VII.

A. **Amendments to Certificate of Incorporation.** The Corporation reserves the right to amend, alter, change or repeal any provision contained in this Certificate of Incorporation, in the manner now or hereafter prescribed by statute, except as provided in paragraph B. of this Article VIII, and all rights conferred upon the stockholders herein are granted subject to this reservation.

B. **Amendments to Articles V, VI, and VII of the Certificate of Incorporation.** Notwithstanding any other provisions of this Certificate of Incorporation or any provision of law which might otherwise permit a lesser vote or no vote, but in addition to any affirmative vote of the holders of any particular class or series of the voting stock required by law, this Certificate of Incorporation or any Preferred Stock Designation, the affirmative vote of the holders of at least sixty-six and two-thirds percent (66-2/3%) of the voting power of all of the then-outstanding shares of the voting stock, voting together as a single class, shall be required to alter, amend or repeal Articles V, VI, VII and VIII.

***

4. This Amended an Restated Certificate of Incorporation has been duly approved by the Board of Directors of this Corporation.

5. This Amended and Restated Certificate of Incorporation has been duly adopted in accordance with the provisions of Sections 228, 242 and 245 of the General Corporation Law of the State of Delaware by the Board of Directors and the stockholders of the Corporation. The

total number of outstanding shares entitled to vote or act by written consent was 10,672,686 shares of Common stock, 5,328,571 shares of Series A Preferred stock, 12,300,000 shares of Series B Preferred Stock, 7,875,000 shares of Series C Preferred Stock and 5,000,000 shares of Series D Preferred Stock. The number of shares voting in favor of the amendment and restatement equaled or exceed the vote required. The percentage vote required was a majority of the outstanding shares of Common Stock, Series A Convertible Preferred Stock, Series B Convertible Preferred Stock, Series C Convertible Preferred Stock and Series D Convertible Preferred Stock of the Corporation, voting together as a single class, holders of a majority of the outstanding shares of Common Stock of the Corporation, voting as a separate class, holders of at least 60% of the outstanding shares of Series A Convertible Preferred Stock of the Corporation, voting as a separate class, holders of a at least 71% of the outstanding shares of Series B Convertible Preferred Stock of the Corporation, voting as a separate class, holders of at least 66 2/3% of the outstanding shares of Series C Convertible Preferred Stock of the Corporation, voting as a separate class, and holders of at least 66 2/3% of the outstanding shares of Series D Convertible Preferred Stock of the Corporation, voting as a separate class. Such vote approved this Amended and Restated Certificate of Incorporation by written consent in accordance with Section 228 of the General Corporation Law of the State of Delaware and written notice of such was given by the Corporation in accordance with said Section 228.

IN WITNESS WHEREOF, Exelixis, Inc. has entered this Amended and Restated Certificate of Incorporation to be signed by its President and Chief Executive Officer and the Secretary in South San Francisco, California, this 14th day of April, 2000.

EXELIXIS, INC.

George A. Scangos
President and Chief Executive Officer

ATTEST:

Glen Y. Sato
Secretary

TRADUCCIÓN PÚBLICA----------

APOSTILLA----------

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

1. País: Estados Unidos de América----------

Este documento público----------

2. ha sido firmado por Harriet Smith Windsor----------

3. actuando en su carácter de Secretaria de Estado de Delaware----------

4. lleva el sello/timbre de la Oficina del Secretario de Estado----------

CERTIFICADO----------

5. en Dover, Delaware----------

6. a los dieciséis días del mes de febrero del Año del Señor 2007----------

7. por el Secretario de Estado, Departamento de Estado de Delaware----------

8. 0307885----------

9. Sello/Timbre: [Aparece un sello que reza:] Oficina del Secretario - 1793 Delaware 1855----------

10. Firma: [Aparece una firma ilegible y debajo reza:] Secretario de Estado----------

Delaware. El Primer Estado. Página 1----------

Yo, HARRIET SMITH WINDSOR, Secretaria de Estado del Estado de Delaware, por la presente certifico que la adjunta es copia fiel del Acta Constitutiva Declarada Nuevamente de "Exelixis,

Inc.", presentado ante esta Oficina a los catorce días del mes de abril del Año del Señor 2000, a las 10:00.----------

[Aparece una firma ilegible y una aclaración de firma que reza:] Harriet Smith Windsor, Secretaria de Estado----------

[Aparece un sello con una leyenda que reza:] Oficina del Secretario. 1793 Delaware 1855----------

2452819 8100----------

070176006----------

AUTENTICACIÓN: 5438027. FECHA: 16-02-07----------

Estado de Delaware. Secretaría de Estado. Sección de Sociedades Anónimas. Presentado el 14/04/2000 a las 10:00. 001191686 - 2452819----------

ACTA CONSTITUTIVA REFORMADA Y DECLARADA NUEVAMENTE DE EXELIXIS, INC.----------

George Scangos y Glen Sato por la presente certifican que:----

1. La denominación original de esta sociedad anónima es Exelixis Pharmaceuticals, Inc. y la fecha de presentación del Acta Constitutiva original de esta sociedad anónima ante la Secretaría de Estado del Estado de Delaware es el 15 de noviembre de 1994.----------

2. Son el Presidente y Director Ejecutivo y el Secretario debidamente elegidos y en ejercicio de sus cargos, respectivamente, de Exelixis, Inc., una Sociedad Anónima de Delaware.----------

3. El Acta Constitutiva de esta sociedad anónima por la presente se reforma y se declara nuevamente y reza lo siguiente:----------

I. La denominación de la Sociedad Anónima es Exelixis, Inc. (la "Sociedad Anónima").----------

II. El domicilio de la sede de la Sociedad Anónima en el Estado de Delaware es: Coporation Trust Center. 1209 Orange Street, Wilmington, Delaware 19805, Condado de New Castle-----

El nombre del agente inscripto de la Sociedad Anónima en ese domicilio es The Corporation Trust Company----------

III. El objeto de la Sociedad Anónima es realizar todos los actos o las actividades lícitas para las cuales se pueden constituir sociedades anónimas conforme a la Ley General de Sociedades Anónimas del Estado de Delaware.----------

IV. La Sociedad Anónima está facultada para emitir dos clases de acciones que se denominarán, respectivamente, "Acciones Ordinarias" y "Acciones Preferidas". El número total de acciones que la sociedad anónima está autorizada a emitir es de ciento diez millones (110.000.000) de acciones. Cien millones (100.000.000) de acciones serán Acciones Ordinarias, cada una de las cuales tiene una valor nominal de una décima de centavo de dólar estadounidense ($0,001). Diez millones (10.000.000) de acciones serán Acciones Preferidas, cada una de las cuales tiene un valor nominal una décima de centavo de dólar estadounidense ($0,001).----------

Acciones Preferidas. Las Acciones Preferidas pueden emitirse periódicamente en una o más series. Por la presente se autoriza al Directorio, mediante la presentación de un certificado (una "Denominación de Acciones Preferidas") conforme a la Ley General de Sociedades Anónimas de Delaware ("DGCL"), a fijar o modificar periódicamente la denominación, las facultades, preferencias y derechos de las acciones de cada una de las series y las habilitaciones, limitaciones o restricciones de todas las series no emitidas en forma completa de Acciones Preferidas, y a establecer periódicamente el número de acciones que constituyen alguna de las series o alguna de ellas; y a aumentar o disminuir el número de acciones de cualquier serie con posterioridad a la emisión de acciones de esa serie, pero no por debajo del número de acciones de esa serie que están en circulación a esa fecha. En el caso de que el número de acciones de alguna serie se disminuya de acuerdo con la oración precedente, las acciones que constituyen es disminución reanudarán el estatus que tenían con anterioridad a la aprobación de la resolución que originalmente fijó el número de acciones de esa serie.--------

V. A. Directorio. Para la administración del giro societario y la dirección de las operaciones de la Sociedad Anónima, y como una mayor definición, limitación y regulación de las facultades de la Sociedad Anónima, de sus directores y de sus

accionistas o cualquier clase de ellos, según sea el caso, se establece que:----------

1. Facultades. La administración del giro societario y la dirección de las operaciones de la Sociedad Anónima será ejercida por su Directorio.----------

2. Número de Directores. El número de directores que constituirán el Directorio completo se fijará exclusivamente por una o más resoluciones aprobadas por el Directorio.-------

3. Elección de Directores. De acuerdo con los derechos de los tenedores de cualquier serie de Acciones Preferidas de elegir directores en las circunstancias especificadas, con posterioridad al cierre de la oferta pública inicial conforme a una declaración de inscripción efectiva conforme a la Ley de Títulos Valores de 1933, y sus modificaciones (la "Ley de 1933"), que cubre la oferta y la venta de Acciones Ordinarias al público (la "Oferta Pública Inicial"), los directores se dividirán en tres clases denominadas Clase I, Clase II y Clase III, respectivamente. Se asignará a los Directores a cada clase de acuerdo con una resolución o resoluciones aprobadas por el Directorio. En la primera asamblea ordinaria de accionistas posterior al cierre de la Oferta Pública Inicial, el período de ejercicio del cargo de los directores de la Clase I vencerá y se elegirá a directores de la Clase I para un período completo de tres años. En la segunda asamblea ordinaria de accionistas posterior al cierre de la Oferta

Pública Inicial, el período de ejercicio de los directores de la Clase II vencerá y se elegirá a directores de la Clase II para un período completo de tres años. En la tercera asamblea ordinaria de accionistas posterior a la Oferta Pública Inicial, el período de ejercicio de los directores de la Clase III vencerá y se elegirá a directores de la Clase III para un período completo de tres años. En cada asamblea ordinaria de accionistas sucesiva, se elegirá a directores para un período completo de tres años para que sucedan a los directores de la clase cuyos períodos de ejercicio venzan en esa asamblea ordinaria.----------

Sin perjuicio de las disposiciones precedentes de esta cláusula, cada director se desempeñará en el cargo hasta que su sucesor sea debidamente elegido y habilitado o hasta su fallecimiento, renuncia o remoción. Ninguna disminución en el número de directores que constituyen el Directorio acortará el período de ejercicio de ningún director con incumbencia.------

4. Remoción de Directores----------

a. Ni el Directorio ni ningún director individual podrá ser removido sin causa.----------

b. Sujeto a todas las limitaciones impuestas por ley, cualquier director o directores individuales podrá ser removido con causa por los tenedores de la mayoría del derecho a voto de la sociedad anónima con derecho a votar en la elección de los directores.----------

5. Vacantes----------

a. Sujeto a los derechos de cualquier serie de Acciones Preferidas, todas las vacantes en el Directorio que sean el resultado del fallecimiento, de la renuncia, de la inhabilitación, de la remoción o por otros motivos y todos los nuevos cargos de director creados como resultado de un aumento en el número de directores, serán, a menos que el Directorio determine por una resolución que todas esas vacantes o cargos de director creados nuevos sean cubiertos por los accionistas, excepto que por ley se disponga de otro modo, cubiertos solamente por el voto afirmativo de la mayoría de los directores que estén en ejercicio de sus cargos a esa fecha, aún cuando haya un número menor que el quórum del Directorio, y no por los accionistas. Todos los directores elegidos de acuerdo con la oración precedente ejercerán el cargo durante el resto del período completo del director para quien se creó u ocurrió la vacante y hasta que el sucesor de ese director haya sido elegido y habilitado.----------

b. Si en el momento de cubrirse una vacante o un cargo de director creado nuevo, los directores que entonces están desempeñando sus cargos constituyen una cantidad inferior a la mayoría del directorio completo (como estaba constituido con anterioridad inmediata ese aumento), el Tribunal del "Chancery" de Delaware podrá a pedido de un accionista o accionistas que sean tenedores de por lo menos el diez por

ciento (10%) del número total de las acciones en circulación a esa fecha que tienen derecho de votar por esos directores, ordenar en forma sumaria que se realice una elección para cubrir todas las vacantes o cargos de director creados nuevos, o para reemplazar a los directores elegidos por los directores que estaban desempeñando sus cargos en esa fecha como se dijo anteriormente, cuya elección estará regida por el Articulo 211 de la DGCL.----------

B. 1. Reformas del Estatuto. Conforme al párrafo (b) del Artículo 43 del Estatuto, el Estatuto podrá modificarse o reformarse o se podrá aprobar un nuevo Estatuto por el voto afirmativo de por lo menos el sesenta y seis y dos tercios por ciento (66-2/3%) de la facultad de voto de la totalidad de las acciones len circulación a esa fecha de las acciones votantes de la sociedad anónima que tienen derecho a voto. El Directorio también tendrá la facultad de aprobar, reformar o impugnar el Estatuto.----------

2. Elección de Directores mediante Boleta por Escrito. Los directores de la sociedad anónima no necesitan ser elegidos mediante boleta por escrito a menos que el Estatuto así lo establezca.----------

3. Medidas tomadas con el Consentimiento por Escrito de los Accionistas. Los accionistas de la sociedad anónima no tomarán ninguna medida excepto en una asamblea ordinaria o extraordinaria convocada de acuerdo con el Estatuto o por el

consentimiento dado por escrito de los accionistas de acuerdo con el Estatuto con anterioridad al cierre de la Oferta Pública Inicial y con posterioridad al cierre de la Oferta Pública Inicial los accionistas no tomarán ninguna medida por el consentimiento por escrito.----------

4. Notificación de Asambleas. La notificación con anticipación de las candidaturas de accionistas para la elección de directores y de los asuntos que presentarán los accionistas ante una asamblea de los accionistas de la sociedad anónima se efectuará en la forma establecida en el Estatuto de la sociedad anónima.----------

VI. A. Indemnización. Un director de la Sociedad anónima no será personalmente responsable ante la Sociedad Anónima o sus accionistas por daños y perjuicios monetarios por ninguna violación de un deber fiduciario como director, excepto por la responsabilidad (i) por una violación del deber de lealtad del director hacia la Sociedad Anónima o sus accionistas, (ii) por acciones u omisiones no realizados de buena fe o que implican inconducta deliberada o una violación deliberada de la ley, (iii) conforme al Artículo 174 de la Ley General de Sociedades Anónimas, o (iv) por una transacción de la cual el director obtuvo un beneficio personal impropio. Si la Ley General de Sociedades Anónimas se reforma con posterioridad a la aprobación por los accionistas de esta Cláusula para autorizar una medida de la sociedad que elimine o limite adicionalmente

la responsabilidad personal de los directores, entonces la responsabilidad del director se eliminará o limitará en la medida máxima permitida por la Ley General de Sociedades Anónimas de Delaware, así reformada.----------

B. Reformas a las Cláusulas VII del Acta Constitutiva. Todas las impugnaciones o reformas de la presente Cláusula VI serán hacia el futuro y no afectarán los derechos otorgados conforme a la presente Cláusula VI que estén vigentes en la fecha en que supuestamente ocurra alguna acción u omisión de acción que dé origen a la responsabilidad o indemnización.----------

VII. A. Reformas del Acta Constitutiva. La Sociedad Anónima se reserva el derecho de reformar, modificar, cambiar o impugnar cualquier cláusula contenida en la presente Acta Constitutiva, en la forma establecida hoy o en adelante por ley, excepto por lo establecido en el párrafo B de la Cláusula VIII, y todos los derechos otorgados a los accionistas en la presente se otorgan conforme a esta reserva.----------

B. Reformas de las Cláusulas V, VI y VII del Acta Constitutiva. Sin perjuicio de otras cláusulas de la presente Acta Constitutiva o de toda disposición legal que de otro modo permitiría un voto menor o ningún voto, pero adicionalmente al voto afirmativo de los tenedores de cualquier clase o serie particular de las acciones votantes establecido por ley, la presente Acta Constitutiva o cualquier denominación de Acciones Preferidas, se necesitará el voto afirmativo de los

tenedores de por lo menos el sesenta y seis y dos tercios po: ciento (66-2/3%) del derecho a voto de la totalidad de la: acciones en circulación a esa fecha de las acciones votantes votando juntas como una sola clase, para modificar, reformar impugnar las Cláusulas V, VI, VII y VIII.----------

4. La presente Acta Constitutiva Reformada y Declarad: Nuevamente ha sido debidamente aprobada por el Directorio d esta Sociedad Anónima.----------

5. La presente Acta Constitutiva Reformada y Declarad: Nuevamente ha sido debidamente aprobada de acuerdo con la: disposiciones de los Artículos 228, 242 y 245 de la Le: General de Sociedades Anónimas del Estado de Delaware por e: Directorio y los accionistas de la Sociedad Anónima. El númer total de acciones en circulación que tienen derecho de votar actuar por el consentimiento por escrito fue de 10.672.68 Acciones Ordinarias, 5.328.571 Acciones Preferidas de la Serie A, 12.300.000 Acciones Preferidas de la Serie B, 7.875.00 Acciones Preferidas de la Serie C y 5.000.000 Acciones Preferidas de la Serie D. El número de acciones que votaron a favor de la reforma y declaración nueva equivalió o superó e: voto exigido. El porcentaje de votos necesarios fue la mayoría de las Acciones Ordinarias en circulación, Acciones Preferidas Convertibles de la Serie A, Acciones Preferidas Convertibles de la Serie B, Acciones Preferidas Convertibles de la Serie y Acciones Preferidas Convertibles de la Serie D, votand

juntas como una sola clase, los tenedores de la mayoría de las Acciones Ordinarias en circulación de la Sociedad Anónima, votando como una clase separada, los tenedores de por lo menos el 60% de las Acciones Preferidas Convertibles de la Serie A en circulación de la Sociedad Anónima, votando como una clase separada, los tenedores de por lo menos el 71% de las Acciones Preferidas Convertibles de la Serie B en circulación votando como una clase separada, los tenedores de por lo menos el 66 2/3% de las Acciones Preferidas Convertibles de la Serie C en circulación de la Sociedad Anónima, votando como una clase separada, y los tenedores de por lo menos el 66 2/3% de las Acciones Preferidas Convertibles de la Serie D en circulación de la Sociedad Anónima votando como una clase separada. Esa votación aprobó la presente Acta Constitutiva Reformada y Declarada Nuevamente de la Sociedad Anónima por el consentimiento dado por escrito de acuerdo con el Artículo 228 de la Ley General de Sociedades Anónimas de Delaware y la Sociedad Anónima notificó por escrito de ello de acuerdo con el Artículo 228 mencionado.----------

EN FE DE LO CUAL, Exelixis, Inc. ha celebrado la presente Acta Constitutiva Reformada y Declarada Nuevamente que deberá ser firmada por su Presidente y Director Ejecutivo y por el Secretario en South San Francisco, California, a los 14 días del mes de abril del año dos mil.----------

EXELIXIS, INC. [Aparece una firma ilegible y un aclaración de firma que reza:] George A. Scangos. Presidente y Director Ejecutivo----------

DOY FE: [Aparece una firma ilegible y una aclaración de firma que reza:] Glen Y. Sato. Secretario----------

CERTIFICO QUE LA QUE ANTECEDE ES TRADUCCIÓN FIEL AL ESPAÑOL DEL DOCUMENTO ORIGINAL REDACTADO EN IDIOMA INGLÉS QUE TUVE A MI VISTA Y AL CUAL ME REMITO EN BUENOS AIRES A LOS NUEVE DÍAS DEL MES DE ABRIL DEL AÑO DOS MIL SIETE----------

MEK INHIBITORS AND METHODS OF THEIR USE

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] This invention relates to certain inhibitors of MEK which are useful in the treatment of hyperproliferative diseases, such as cancer, in mammals. This invention also relates to a method of using such compounds in the treatment of hyperproliferative diseases in mammals, especially humans, and to pharmaceutical compositions containing such compounds.

Cross Reference to Related Applications

[0002] The Applicants claim priority under 35 U.S.C. 119(e) to copending Provisional Applications No. 60/724,578 filed on October 7, 2005 and No. 60/802,840 filed on May 23, 2006, the disclosures of which are incorporated herein by reference in its entirety.

State of the Art

[0003] Improvements in the specificity of agents used to treat cancer is of considerable interest because of the therapeutic benefits which would be realized if the side effects associated with the administration of these agents could be reduced. Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms.

[0004] Protein kinases are enzymes that catalyze the phosphorylation of proteins, in particular, hydroxy groups on tyrosine, serine and threonine residues of proteins. The consequences of this seemingly simple activity are staggering; cell differentiation and proliferation; i.e., virtually all aspects of cell life in one-way or another depend on protein kinase activity. Furthermore, abnormal protein kinase activity has been related to a host of disorders, ranging from relatively non-life threatening diseases such as psoriasis to extremely virulent diseases such as glioblastoma (brain cancer).

[0005] Protein kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases have an extracellular, a transmembrane, and an intracellular portion, while non-receptor type tyrosine kinases are wholly intracellular. They are comprised of a large number of transmembrane receptors with diverse biological activity. In fact, about 20 different subfamilies of receptor-type tyrosine kinases have been identified. One tyrosine kinase subfamily, designated the HER subfamily, is comprised of EGFR (HER1), HER2, HER3, and HER4. Ligands of this subfamily of receptors identified so far include epithelial growth factor, TGF-alpha, amphiregulin, HB-EGF, betacellulin and

heregulin. Another subfamily of these receptor-type tyrosine kinases is the insulin subfamily, which includes INS-R, IGF-IR, and IR-R. The PDGF subfamily includes the PDGF-alpha and beta receptors, CSFIR, c-kit and FLK-II. In addition, there is the FLK family, which is comprised of the kinase insert domain receptor (KDR), fetal liver kinase-1 (FLK-1), fetal liver kinase-4 (FLK-4) and the fms-like tyrosine kinase-1 (flt-1). The PDGF and FLK families are usually considered together due to the similarities of the two groups. For a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al., *DN&P* 7(6): 334-339, 1994, which is hereby incorporated by reference.

[0006] The non-receptor type of tyrosine kinases is also comprised of numerous subfamilies, including Src, Frk, Btk, Csk, Abl, Zap70, Fes/Fps, Fak, Jak, Ack, and LIMK. Each of these subfamilies is further sub-divided into varying receptors. For example, the Src subfamily is one of the largest and includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr, and Yrk. The Src subfamily of enzymes has been linked to oncogenesis. For a more detailed discussion of the non-receptor type of tyrosine kinases, see Bolen, *Oncogene*, **8**:2025-2031 (1993), which is hereby incorporated by reference.

[0007] Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth associated with cancer. In addition to oncological indications, altered kinase signaling is implicated in numerous other pathological diseases. These include, but are not limited to: immunological disorders, cardiovascular diseases, inflammatory diseases, and degenerative diseases. Therefore, both receptor and non-receptor protein kinases are attractive targets for small molecule drug discovery.

[0008] One particularly attractive goal for therapeutic use of kinase modulation relates to oncological indications. For example, modulation of protein kinase activity for the treatment of cancer has been demonstrated successfully with the FDA approval of Gleevec® (imatinib mesylate, produced by Novartis Pharmaceutical Corporation of East Hanover, NJ) for the treatment of Chronic Myeloid Leukemia (CML) and gastrointestinal stroma cancers. Gleevec is a selective Abl kinase inhibitor.

[0009] Modulation (particularly inhibition) of cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. *Drug Disc Technol* **2001** *6*, 1005-1024), is an attractive goal for development of small-molecule drugs. Anti-angiogenic therapy represents a potentially important approach for the treatment of solid tumors and other diseases associated with dysregulated vascularization, including ischemic

coronary artery disease, diabetic retinopathy, psoriasis and rheumatoid arthritis. As well, cell antiproliferative agents are desirable to slow or stop the growth of tumors.

[0010] One particularly attractive target for small-molecule modulation, with respect to antiangiogenic and antiproliferative activity is MEK. Inhibition of MEK1 (MAPK/ERK Kinase) is a promising strategy to control the growth of tumors that are dependent on aberrant ERK/MAPK pathway signaling (Solit et al., 2006; Wellbrock et al., 2004). The MEK-ERK signal transduction cascade is a conserved pathway which regulates cell growth, proliferation, differentiation, and apoptosis in response to growth factors, cytokines, and hormones. This pathway operates downstream of Ras which is often upregulated or mutated in human tumors. It has been demonstrated that MEK is a critical effector of Ras function. The ERK/MAPK pathway is upregulated in 30% of all tumors and oncogenic activating mutations in K-Ras and B-Raf have been identified in 22% and 18% of all cancers respectively (Allen et al., 2003; Bamford S, 2004; Davies et al., 2002; Malumbres and Barbacid, 2003). A large portion of human cancers, including 66% (B-Raf) of malignant melanomas, 60% (K-Ras) and 4% (B-Raf) of pancreatic cancers, 50% of colorectal cancers (colon, in particular, K-Ras: 30%, B-Raf: 15%), 20% (K-Ras) of lung cancers, 27% (B-Raf) papillary and anaplastic thyroid cancer, and 10-20% (B-Raf) of endometriod ovarian cancers, harbor activating Ras and Raf mutations. It has been shown that inhibition of the ERK pathway, and in particular inhibition of MEK kinase activity, results in anti-metastatic and anti-angiogenic effects largely due to a reduction of cell-cell contact and motility as well as downregulation of vascular endothelial growth factor (VEGF) expression. Furthermore, expression of dominant negative MEK, or ERK reduced the transforming ability of mutant Ras as seen in cell culture and in primary and metastatic growth of human tumor xenografts *in vivo*. Therefore, the MEK-ERK signal transduction pathway is an appropriate pathway to target for therapeutic intervention.

[0011] Accordingly, the identification of small-molecule compounds that specifically inhibit, regulate and/or modulate the signal transduction of kinases, particularly MEK, is desirable as a means to treat or prevent disease states associated with cancer and is an object of this invention.

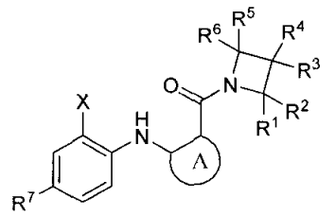
SUMMARY OF THE INVENTION

[0012] The following only summarizes certain aspects of the invention and is not intended to be limiting in nature. These aspects and other aspects and embodiments are described more fully below. All references cited in this specification are hereby incorporated by reference in their entirety. In the event of a discrepancy between the express disclosure of

this specification and the references incorporated by reference, the express disclosure of this specification shall control.

[0013] This invention provides compounds that inhibit, regulate and/or modulate the signal transduction of kinases, particularly MEK. The compounds of the invention are certain azetidin-1-yl(2-(2-fluorophenylamino)cyclic)methanones derivatives that are useful in the treatment of hyperproliferative diseases, such as cancer, in humans. This invention also provides methods of making the compound, methods of using such compounds in the treatment of hyperproliferative diseases in humans and to pharmaceutical compositions containing such compounds.

[0014] In one aspect, the invention provides a compound of Formula I:



I

or a pharmaceutically acceptable salt or solvate, thereof, wherein A, X, R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are as defined in Group A, Group B, Group C, or Group D:

Group A:

A is arylene optionally substituted with one, two, three or four groups selected from R^{10}, R^{12}, R^{14}, and R^{16} where R^{10}, R^{12}, R^{14} and R^{16} are independently hydrogen, alkyl, alkenyl, alkynyl, halo, haloalkoxy, hydroxy, alkoxy, amino, alkylamino, dialkylamino, haloalkyl, $-NHS(O)_2R^8$, -CN, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$ and $-NR^8C(O)R^{8'}$;

X is alkyl, halo, haloalkyl, or haloalkoxy;

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl, where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted

heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; or one of R^1 and R^2 together with the carbon to which they are attached, R^3 and R^4 together with the carbon to which they are attached, and R^5 and R^6 together with the carbon to which they are attached form C(O) or C(=NOH);

m is 0, 1, or 2;

R^7 is hydrogen, halo or alkyl;

R^8, $R^{8'}$ and $R^{8''}$ are independently selected from hydrogen, hydroxy, optionally substituted alkoxy, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl; where the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two three, four, or five groups independently selected from alkyl, halo, hydroxy, hydroxyalkyl, optionally substituted alkoxy, alkoxyalkyl, haloalkyl, carboxy, alkoxycarbonyl, alkenyloxycarbonyl, optionally substituted cycloalkyl, optionally substituted cycloalkyloxycarbonyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted aryloxycarbonyl, optionally substituted arylalkyl, optionally substituted arylalkyloxy, optionally substituted arylalkyloxycarbonyl, nitro, cyano, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, $-S(O)_nR^{31}$ (where n is 0, 1, or 2 and R^{31} is optionally substituted alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), $-NR^{34}SO_2R^{34a}$ (where R^{34} is hydrogen or alkyl and R^{34a} is alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl), $-SO_2NR^{35}R^{35a}$ (where R^{35} is hydrogen or alkyl and R^{35a} is alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl), $-NR^{32}C(O)R^{32a}$ (where R^{32} is hydrogen or alkyl and R^{32a} is alkyl, alkenyl, alkoxy, or cycloalkyl), $-NR^{30}R^{30'}$ (where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl), and $-C(O)NR^{33}R^{33a}$ (where R^{33} is hydrogen or alkyl and R^{33a} is alkyl, alkenyl, alkynyl, or cycloalkyl);

R^9 is alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl; where the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally susbstituted with one, two, three, four, or five groups selected from halo, hydroxy, alkyl, haloalkyl, haloalkoxy, amino, alkylamino, and dialkylamino;

R^{25} and R^{25b} are independently hydrogen, alkyl, alkenyl, optionally sbustituted cycloalkyl, or optionally substituted aryl; and

R^{25a} is hydrogen, alkyl, or alkenyl;

Group B:

A is heteroarylene optionally substituted with one, two, three, or four groups selected from R^{10}, R^{12}, R^{14}, R^{16} and R^{19} where R^{10}, R^{12}, R^{14} and R^{16} are independently hydrogen, alkyl, alkenyl, alkynyl, halo, haloalkoxy, hydroxy, alkoxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkylsulfonylamino, alkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, alkenyloxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, or alkylcarbonylamino; where R^{19} is hydrogen, alkyl, or alkenyl; and where each alkyl and alkenyl, either alone or as part of another group within R^{10}, R^{12}, R^{14}, R^{16}, and R^{19} is independently optionally substituted with halo, hydroxy, or alkoxy;

X is alkyl, halo, haloalkyl, or haloalkoxy;

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl, where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; or one of R^1 and R^2 together with the carbon to which they are attached, R^3 and R^4 together with the carbon to which they are attached, and R^5 and R^6 together with the carbon to which they are attached form C(O) or C(=NOH);

m is 1 or 2;

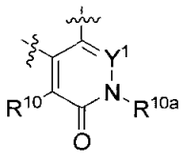
R^7 is hydrogen, halo or alkyl; and

R^8, $R^{8'}$ and $R^{8''}$ are independently selected from hydrogen, hydroxy, optionally substituted alkoxy, alkyl, haloalkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and

heterocycloalkyl, where the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two three, four, or five groups independently selected from alkyl, halo, hydroxy, hydroxyalkyl, optionally substituted alkoxy, alkoxyalkyl, haloalkyl, carboxy, carboxy ester, nitro, cyano, $-S(O)_nR^{31}$ (where n is 0, 1, or 2 and R^{31} is optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), $-NR^{36}S(O)_2R^{36a}$ (where R^{36} is hydrogen, alkyl, or alkenyl and R^{36a} is alkyl, alkenyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), $-S(O)_2NR^{37}R^{37a}$ (where R^{37} is hydrogen, alkyl, or alkenyl and R^{37a} is alkyl, alkenyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted aryloxy, optionally substituted arylalkyloxy, optionally substituted heteroaryl, $-NHC(O)R^{32}$ (where R^{32} is alkyl, alkenyl, alkoxy, or cycloalkyl) and $-NR^{30}R^{30'}$ (where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl), and $-C(O)NHR^{33}$ (where R^{33} is alkyl, alkenyl, alkynyl, or cycloalkyl);

Group C:

A is



(a)

where R^{10} is hydrogen, alkyl, alkenyl, alkynyl, halo, haloalkoxy, hydroxy, alkoxy, amino, alkylamino, dialkylamino, haloalkyl, $-NHS(O)_2R^8$, -CN, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$ and $-NR^8C(O)R^{8'}$;

R^{10a} is hydrogen, alkyl, or alkenyl;

Y^1 is =CH- or =N-;

X is alkyl, halo, haloalkyl, or haloalkoxy;

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$,

$-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl, where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; or one of R^1 and R^2 together with the carbon to which they are attached, R^3 and R^4 together with the carbon to which they are attached, and R^5 and R^6 together with the carbon to which they are attached form C(O) or C(=NOH);

m is 1 or 2;

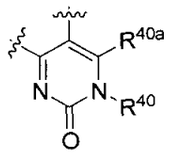
R^7 is hydrogen, halo or alkyl; and

R^8, $R^{8'}$ and $R_{8''}$ are independently selected from hydrogen, hydroxy, optionally substituted alkoxy, alkyl, haloalkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, where the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two three, four, or five groups independently selected from alkyl, halo, hydroxy, hydroxyalkyl, optionally substituted alkoxy, alkoxyalkyl, haloalkyl, carboxy, carboxy ester, nitro, cyano, $-S(O)_nR^{31}$ (where n is 0, 1, or 2 and R^{31} is optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), $-NR^{36}S(O)_2R^{36a}$ (where R^{36} is hydrogen, alkyl, or alkenyl and R^{36a} is alkyl, alkenyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), $-S(O)_2NR^{37}R^{37a}$ (where R^{37} is hydrogen, alkyl, or alkenyl and R^{37a} is alkyl, alkenyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted aryloxy, optionally substituted arylalkyloxy, optionally substituted heteroaryl, $-NHC(O)R^{32}$ (where R^{32} is alkyl, alkenyl, alkoxy, or cycloalkyl) and $-NR^{30}R^{30'}$ (where

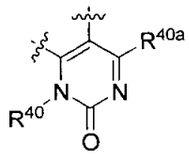
R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl), and $-C(O)NHR^{33}$ (where R^{33} is alkyl, alkenyl, alkynyl, or cycloalkyl); or

Group D:

A is



(b) or



(c)

R^{40} and R^{40a} are independently hydrogen or alkyl;

X is alkyl, halo, haloalkyl, or haloalkoxy;

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl, where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; or one of R^1 and R^2 together with the carbon to which they are attached, R^3 and R^4 together with the carbon to which they are attached, and R^5 and R^6 together with the carbon to which they are attached form C(O) or C(=NOH);

m is 1 or 2;

R^7 is hydrogen, halo or alkyl; and

R^8, $R^{8'}$ and $R_{8''}$ are independently selected from hydrogen, hydroxy, optionally substituted alkoxy, alkyl, haloalkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, where the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two three, four, or five groups independently selected from alkyl, halo, hydroxy, hydroxyalkyl, optionally substituted alkoxy, alkoxyalkyl, haloalkyl, carboxy, carboxy ester, nitro, cyano, $-S(O)_nR^{31}$ (where n is 0, 1, or 2 and R^{31} is optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), $-NR^{36}S(O)_2R^{36a}$ (where R^{36} is hydrogen, alkyl, or alkenyl and R^{36a} is alkyl, alkenyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), $-S(O)_2NR^{37}R^{37a}$ (where R^{37} is hydrogen, alkyl, or alkenyl and R^{37a} is alkyl, alkenyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted aryloxy, optionally substituted arylalkyloxy, optionally substituted heteroaryl, $-NHC(O)R^{32}$ (where R^{32} is alkyl, alkenyl, alkoxy, or cycloalkyl) and $-NR^{30}R^{30'}$ (where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl), and $-C(O)NHR^{33}$ (where R^{33} is alkyl, alkenyl, alkynyl, or cycloalkyl).

[0015] A second aspect of the Invention provides a pharmaceutical composition which comprises a compound of Formula I, or a pharmaceutically acceptable salt or solvate therof, and a pharmaceutically acceptable carrier, excipient, or diluent.

[0016] In a third aspect, the invention is directed to a method of inhibiting MEK comprising administering to a patient a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, and optionally a pharmaceutically acceptable carrier, excipient, or diluent.

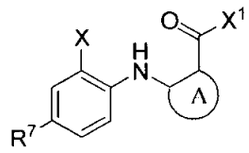
[0017] In a fourth aspect, the invention comprises a method of inhibiting MEK in a cell, comprising contacting a cell with a compound of Formula I or a pharmaceutically acceptable salt or solvate therof, or with a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable carrier, excipient, or diluent.

[0018] A fifth aspect of the Invention provides a method for treating a disease, disorder, or syndrome which method comprises administering to a patient a compound of Formula I or

a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable carrier, excipient, or diluent.

[0019] A sixth aspect of the invention is directed to a process of preparing a compound of Formula I, comprising:

(a) reacting an intermediate of formula 19:



19

where X^1 is OH or halo, specifically chloro or fluoro, and all other groups are as defined in the Summary of the Invention for a compound selected from Group A, Group B, Group C, and Group D; with an intermediate of formula 17:



17

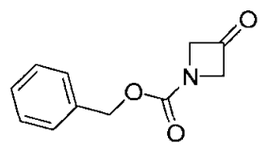
where R^1, R^2, R^3, R^4, R^5, and R^6 are as defined in the Summary of the Invention for a compound selected from Group A, Group B, Group C, and Group D; and

(b) optionally separating indiividual isomers; and

(c) optionally modifying any of the R^1, R^2, R^3, R^4, R^5, and R^6 groups.

[0020] A seventh aspect of the invention is directed to a process of preparing intermediates of formula 3, 4, 5, 6, 10, and 13, comprising:

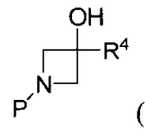
(a) reacting an intermediate of formula 2(a):



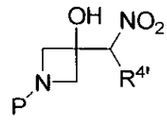
2(a)

with R^4M (where R^4M is a Grignard reagent or organometallic species and R^4 is as defined in the Summary of the Invention for a compound of Group A, Group B, Group C, or Group D); with $R^{4'}CH_2NO_2$ ($R^{4'}$ is hydrogen or alkyl optionally substituted as described for R^4 in the Summary of the Invention for a compound of Group A, Group B, Group C, or Group D); with $R^{4'}R^{4''}C(O)$ ($R^{4'}$ is alkyl optionally substituted as described for R^4 in the Summary of

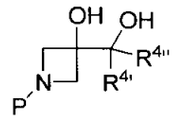
the Invention for a compound of Group A, Group B, Group C, or Group D and $R^{4''}$ is hydrogen or $R^{4'}$); with $R'R''CHP(Ph)_3$ (where R' and R" are independently hydrogen, alkyl, alkenyl, aryl, or heteroaryl and the alkyl, alkenyl, aryl, and heteroaryl are optionally substituted as described for R^4 in the Sumnmary of the Invention for a compound of Group A, Group B, Group C, or Group D); with a chiral oxazolidinone auxiliary and subsequent treatment with a base, such as lithium hydroxide, in aqueous hydrogen peroxide; or with a N-protected heterocycloalkyl group where P^1 is Boc and P^2 is CBz or P^1 is CBz and P^2 is Boc; to yield the intermediates of formula 3, 4, 5, 6, 12, and 13, respectively:



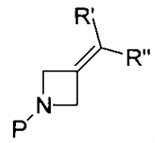
(**3**);



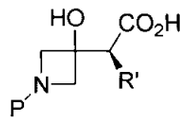
(**4**);



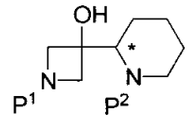
(**5**);



(**6**);

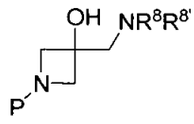


(**10**); and



(**13**);

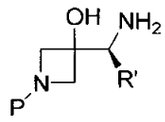
(b) optionally further reacting **6** with *m*-CPBA to form an epoxide and further opening the epoxide with an amine of formula $NHR^8R^{8'}$ to yield an intermediate of formula **8**:



8

where P is a N-protecting group and R^8 and $R^{8'}$ are as defined in the Summary of the Invention for a compound of Group A, Group B, Group C, or Group D;

(c) optionally further subjecting **10** to a Curtius rearrangement and subsequent treatment to yield an intermediate of formula 12:



12

where P is a N-protecting group and R' is an alkyl group such as methyl or ethyl;

(d) optionally further resolving individual isomers; and

(e) optionally modifying any of the R^1, R^2, R^3, R^4, R^5, and R^6 groups.

DETAILED DESCRIPTION OF THE INVENTION

Abbreviations and Definitions

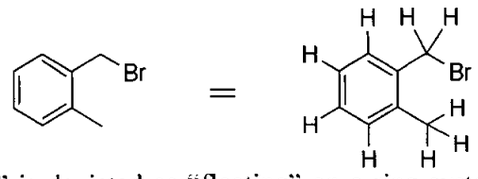
[0021] The following abbreviations and terms have the indicated meanings throughout:

Abbreviation	Meaning
Ac	acetyl
br	broad
°C	degrees Celsius
CBZ	CarboBenZoxy = benzyloxycarbonyl
d	doublet
dd	doublet of doublet
dt	doublet of triplet
DAST	(diethylamino)sulfur trifluoride
DCM	dichloromethane
DIPEA	*N,N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
EI	Electron Impact ionization
Et	ethyl
g	gram(s)
GC	gas chromatography
h or hr	hour(s)
HBTU	2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HOAc	acetic acid
HOBt	hydroxybenzotriazole
HPLC	high pressure liquid chromatography
L	liter(s)
LDA	lithium diiospropylamide
LHMDS	lithium hexamethyldisilazide
M	molar or molarity

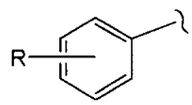
m	multiplet
MCPBA	meta-chloroperbenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz (frequency)
min	minute(s)
mL	milliliter(s)
mM	millimolar
mmol	millimole(s)
mol	mole(s)
MS	mass spectral analysis
N	normal or normality
nM	nanomolar
NMM	*N*-methylmorpholine
NMR	nuclear magnetic resonance spectroscopy
PyBOP	benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate
q	quartet
RT	room temperature
s	singlet
s-	secondary
t-	tertiary
t or tr	triplet
THF	tetrahydrofuran
µL	microliter(s)
µM	micromole(s) or micromolar

[0022] The symbol "-" means a single bond, "=" means a double bond, "≡" means a triple bond, and "---" means a single bond and optionally a double bond. When chemical structures are depicted or described, unless explicitly stated otherwise, all carbons are assumed to have hydrogen substitution to conform to a valence of four.

[0023] When chemical structures are depicted or described, unless explicitly stated otherwise, all carbons are assumed to have hydrogen substitution to conform to a valence of four. For example, in the structure on the left-hand side of the schematic below there are nine hydrogens implied. The nine hydrogens are depicted in the right-hand structure. Sometimes a particular atom in a structure is described in textual formula as having a hydrogen or hydrogens as substitution (expressly defined hydrogen), for example, $-CH_2CH_2-$. It is understood by one of ordinary skill in the art that the aforementioned descriptive techniques are common in the chemical arts to provide brevity and simplicity to description of otherwise complex structures.

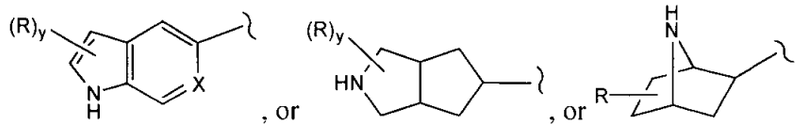


[0024] If a group "R" is depicted as "floating" on a ring system, as for example in the formula:



then, unless otherwise defined, a substituent "R" may reside on any atom of the ring system, assuming replacement of a depicted, implied, or expressly defined hydrogen from one of the ring atoms, so long as a stable structure is formed.

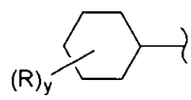
[0025] If a group "R" is depicted as floating on a fused ring system, as for example in the formulae:



, or , or

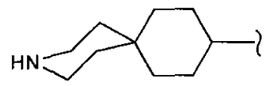
then, unless otherwise defined, a substituent "R" may reside on any atom of the fused ring system, assuming replacement of a depicted hydrogen (for example the -NH- in the formula above), implied hydrogen (for example as in the formula above, where the hydrogens are not shown but understood to be present), or expressly defined hydrogen (for example where in the formula above, "X" equals =CH-) from one of the ring atoms, so long as a stable structure is formed. In the example depicted, the "R" group may reside on either the 5-membered or the 6-membered ring of the fused ring system. In the formula depicted above, when y is 2 for example, then the two "R's" may reside on any two atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring.

[0026] When a group "R" is depicted as existing on a ring system containing saturated carbons, as for example in the formula:



where, in this example, "y" can be more than one, assuming each replaces a currently depicted, implied, or expressly defined hydrogen on the ring; then, unless otherwise defined, where the resulting structure is stable, two "R's" may reside on the same carbon. A simple example is when R is a methyl group; there can exist a geminal dimethyl on a carbon of the depicted ring (an "annular" carbon). In another example, two R's on the same carbon,

including that carbon, may form a ring, thus creating a spirocyclic ring (a "spirocyclyl" group) structure with the depicted ring as for example in the formula:



[0027] "Acyl" means a -C(O)R radical where R is optionally substituted alkyl, optionally substituted alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, or heterocycloalkylalkyl, as defined herein, e.g., acetyl, benzoyl, trifluoromethylcarbonyl, or 2-methoxyethylcarbonyl, and the like.

[0028] "Acylamino" means a -NRR' group where R is acyl, as defined herein, and R' is hydrogen or alkyl.

[0029] "Administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., surgery, radiation, and chemotherapy, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

[0030] "Alkenyl" means a means a linear monovalent hydrocarbon radical of one to six carbon atoms or a branched monovalent hydrocarbon radical of three to 6 carbon atoms which radical contains at least one double bond, e.g., ethenyl, propenyl, 1-but-3-enyl, 1-pent-3-enyl, 1-hex-5-enyl and the like.

[0031] "Alkenylcarbonyl" means a -C(O)R group where R is alkenyl, as defined herein.

[0032] "Alkenyloxycarbonyl" means a -C(O)OR group where R is alkenyl, as defined herein.

[0033] "Alkoxy" means an -OR group where R is alkyl group as defined herein. Examples include methoxy, ethoxy, propoxy, isopropoxy, and the like. Lower-alkoxy refers to groups containing one to six carbons.

[0034] "Alkoxyalkyl" means an alkyl group, as defined herein, substituted with at least one, preferably one, two, or three, alkoxy groups as defined herein. Representative examples include methoxymethyl and the like.

[0035] "Alkoxycarbonyl" means a -C(O)OR group where R is alkyl as defined herein.

[0036] "Alkoxycarbonylamino" means a -NR'R" group where R' is hydrogen, alkyl, hydroxy, or alkoxy and R" is alkoxycarbonyl, as defined herein.

[0037] "Alkyl" means a linear saturated monovalent hydrocarbon radical of one to eight carbon atoms or a branched saturated monovalent hydrocarbon radical of three to eight carbon atoms, e.g., methyl, ethyl, propyl, 2-propyl, butyl (including all isomeric forms), or pentyl (including all isomeric forms), and the like.

[0038] "Alkylamino" means a -NHR radical where R is alkyl as defined herein, or an N-oxide derivative, or a protected derivative thereof, e.g., methylamino, ethylamino, *n*-propylamino, *iso*-propylamino, *n*-butylamino, *iso*-butylamino, *tert*-butylamino, or methylamino-N-oxide, and the like.

[0039] "Alkylaminoalkyl" means an alkyl group substituted with one or two alkylamino groups, as defined herein.

[0040] "Alkylaminocarbonyl" means a -C(O)R group where R is alkylamino, as defined herien.

[0041] "Alkylcarbonyl" means a -C(O)R group where R is alkyl, as defined herein.

[0042] "Alkylcarbonylamino" means a -NRR' group where R is hydrogen or alkyl as defined herein and R' is alkylcarbonyl, as defined herein.

[0043] "Alkylcarbonyloxy" means an -OC(O)R group where R is alkyl, as defined herein.

[0044] "Alkylsulfonylamino" means a $-NRS(O)_2R'$ group where R is hydrogen or alkyl as defined herein, and R' is alkyl, as defined herein.

[0045] "Alkynyl" means a straight or branched hydrocarbon radical having from 2 to 8 carbon atoms and at least one triple bond and includes ethynyl, propynyl, butynyl, pentyn-2-yl and the like.

[0046] "Aminoalkyl" means an alkyl group substiuted with at least one, specifically one, two or three, amino groups.

[0047] "Aminocarbonyl" means a $-C(O)NH_2$ group.

[0048] "Aryl" means a monovalent six- to fourteen-membered, mono- or bi-carbocyclic ring, wherein the monocyclic ring is aromatic and at least one of the rings in the bicyclic ring is aromatic. Unless stated otherwise, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. Representative examples include phenyl, naphthyl, and indanyl, and the like.

[0049] "Arylene" means a divalent six- to fourteen-membered, mono- or bi-carbocyclic ring, wherein the monocyclic ring is aromatic and at least one of the rings in the bicyclic ring is aromatic. Representative examples include phenylene, naphthylene, and indanylene, and the like.

[0050] "Arylalkyl" means an alkyl group, as defined herein, substituted with one or two aryl groups, as defined herein. Examples include benzyl, phenethyl, and the like.

[0051] "Carboxy ester" means a -C(O)OR group where R is lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, aryl or arylalkyl, each of which is defined herein. Representative examples include methoxycarbonyl, ethoxycarbonyl, and benzyloxycarbonyl, and the like.

[0052] "Cycloalkyl" means a monocyclic or fused bicyclic, saturated or partially unsaturated (but not aromatic), monovalent hydrocarbon radical of three to ten carbon ring atoms. Fused bicyclic hydrocarbon radical includes bridged ring systems. Unless stated otherwise, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. One or two ring carbon atoms may be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. More specifically, the term cycloalkyl includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexyl, or cyclohex-3-enyl, and the like.

[0053] "Dialkylamino" means a -NRR' radical where R and R' are alkyl as defined herein, or an N-oxide derivative, or a protected derivative thereof, e.g., dimethylamino, diethylamino, *N,N*-methylpropylamino or *N,N*-methylethylamino, and the like.

[0054] "Dialkylaminoalkyl" means an alkyl group substituted with one or two dialkylamino groups, as defined herein.

[0055] "Dialkylaminocarbonyl" means a -C(O)R group where R is dialkylamino, as defined herien.

[0056] "Fused-polycyclic" or "fused ring system" means a polycyclic ring system that contains fused rings and, unless otherwise indicated, can contain bridged rings; that is, where two rings have more than one shared atom in their ring structures. In this application, fused-polycyclics and fused ring systems are not necessarily all aromatic ring systems. Typically, but not necessarily, fused-polycyclics share a vicinal set of atoms, for example naphthalene or 1,2,3,4-tetrahydro-naphthalene. A spiro ring system is not a fused-polycyclic by this definition, but fused polycyclic ring systems of the invention may themselves have spiro rings attached thereto via a single ring atom of the fused-polycyclic. In some examples, as appreciated by one of ordinary skill in the art, two adjacent groups on an aromatic system may be fused together to form a ring structure. The fused ring structure may contain heteroatoms and may be optionally substituted with one or more groups. It should additionally be noted that saturated carbons of such fused groups (*i.e.* saturated ring structures) can contain two substitution groups.

[0057] "Haloalkoxy" means an -OR' group where R' is haloalkyl as defined herein, e.g., trifluoromethoxy or 2,2,2-trifluoroethoxy, and the like.

[0058] "Halogen" or "halo" means fluoro, chloro, bromo and iodo.

[0059] "Haloalkyl" means an alkyl group, as defined herein, that is substituted with one or more halogens, preferably one to five halo atoms. Representative examples include trifluoromethyl, difluoromethyl, 1-chloro-2-fluoro-ethyl, and the like.

[0060] "Heteroaryl" means a monocyclic, fused bicyclic, or fused tricyclic, monovalent radical of 5 to 14 ring atoms containing one or more, preferably one, two, three, or four ring heteroatoms independently selected from -O-, -$S(O)_n$- (n is 0, 1, or 2), -N-, -$N(R^x)$-, and the remaining ring atoms being carbon, wherein the ring comprising a monocyclic radical is aromatic and wherein at least one of the fused rings comprising a bicyclic or tricyclic radical is aromatic. One or two ring carbon atoms of any nonaromatic rings comprising a bicyclic or tricyclic radical may be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. R^x is hydrogen, alkyl, hydroxy, alkoxy, acyl, or alkylsulfonyl. Unless stated otherwise, the valency may be located on any atom of any ring of the heteroaryl group, valency rules permitting. In particular, when the point of valency is located on the nitrogen, R^x is absent. More specifically, the term heteroaryl includes, but is not limited to, 1,2,4-triazolyl, 1,3,5-triazolyl, phthalimidyl, pyridinyl, pyrrolyl, imidazolyl, thienyl, furanyl, indolyl, 2,3-dihydro-1*H*-indolyl (including, for example, 2,3-dihydro-1*H*-indol-2-yl or 2,3-dihydro-1*H*-indol-5-yl, and the like), isoindolyl, indolinyl, isoindolinyl, benzimidazolyl, benzodioxol-4-yl, benzofuranyl, cinnolinyl, indolizinyl, naphthyridin-3-yl, phthalazin-3-yl, phthalazin-4-yl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, tetrazoyl, pyrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isooxazolyl, oxadiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl (including, for example, tetrahydroisoquinolin-4-yl or tetrahydroisoquinolin-6-yl, and the like), pyrrolo[3,2-c]pyridinyl (including, for example, pyrrolo[3,2-c]pyridin-2-yl or pyrrolo[3,2-c]pyridin-7-yl, and the like), benzopyranyl, thiazolyl, isothiazolyl, thiadiazolyl, benzothiazolyl, benzothienyl, and the derivatives thereof, or N-oxide or a protected derivative thereof.

[0061] "Heteroarylene" means a monocyclic, fused bicyclic, or fused tricyclic, divalent radical of 5 to 14 ring atoms containing one or more, preferably one, two, three, or four ring heteroatoms independently selected from -O-, -$S(O)_n$- (n is 0, 1, or 2), -N-, -$N(R^{19})$-, and the remaining ring atoms being carbon, wherein the ring comprising a monocyclic radical is aromatic and wherein at least one of the fused rings comprising a bicyclic or tricyclic radical is aromatic. One or two ring carbon atoms of any nonaromatic rings comprising a bicyclic or

tricyclic radical may be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. R^{19} is hydrogen, alkyl, or alkenyl. Unless stated otherwise, the valencies may be located on any atom of any ring of the heteroarylene group, valency rules permitting. In particular, when the point of valency is located on the nitrogen, R^x is absent. More specifically, the term heteroaryl includes, but is not limited to, thien-diyl, benzo[*d*]isoxazol-diyl, benzo[*d*]isothiazol-diyl, 1*H*-indazol-diyl (optionally substituted at the N1 position with R^{19}), benzo[*d*]oxazol-diyl, benzo[*d*]thiazol-diyl, 1*H*-benzo[*d*]imidazol-diyl (optionally substituted at the N1 position with R^{19}), 1*H*-benzo[*d*][1,2,3]triazol-diyl (optionally substituted at the N1 position with R^{19}), imidazo[1,2-*a*]pyridin-diyl, cinnolin-diyl, quinolin-diyl, pyridin-diyl, 1-oxido-pyridin-diyl, [1,2,4]triazolo[4,3-a]pyridin-diyl, and 2,3-dihydroimidazo[1,2-a]pyridin-diyl, and the like.

[0062] "Heterocycloalkyl" means a saturated or partially unsaturated (but not aromatic) monovalent monocyclic group of 3 to 8 ring atoms or a saturated or partially unsaturated (but not aromatic) monovalent fused bicyclic group of 5 to 12 ring atoms in which one or more, specifically one, two, three, or four ring heteroatoms independently selected from O, $S(O)_n$ (n is 0, 1, or 2), N, $N(R^y)$ (where R^y is hydrogen, alkyl, hydroxy, alkoxy, acyl, or alkylsulfonyl), the remaining ring atoms being carbon. One or two ring carbon atoms may be replaced by a -C(O)-, -C(S)-, or -C(=NH)- group. Fused bicyclic radical includes bridged ring systems. Unless otherwise stated, the valency of the group may be located on any atom of any ring within the radical, valency rules permitting. When the point of valency is located on a nitrogen atom, R^y is absent. More specifically the term heterocycloalkyl includes, but is not limited to, azetidinyl, pyrrolidinyl, 2-oxopyrrolidinyl, 2,5-dihydro-1*H*-pyrrolyl, piperidinyl, 4-piperidonyl, morpholinyl, piperazinyl, 2-oxopiperazinyl, tetrahydropyranyl, 2-oxopiperidinyl, thiomorpholinyl, thiamorpholinyl, perhydroazepinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, dihydropyridinyl, tetrahydropyridinyl, oxazolinyl, oxazolidinyl, isoxazolidinyl, thiazolinyl, thiazolidinyl, quinuclidinyl, isothiazolidinyl, octahydroindolyl, octahydroisoindolyl, decahydroisoquinolyl, tetrahydrofuryl, and tetrahydropyranyl, and the derivatives thereof and N-oxide or a protected derivative thereof.

[0063] "Hydroxyalkyl" means an alkyl, as defined herein, substituted with at least one, preferably one, two, or three, hydroxy group(s), provided that if two hydroxy groups are present they are not both on the same carbon atom. Representative examples include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-(hydroxymethyl)-2-methylpropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxypropyl, 1-(hydroxymethyl)-2-hydroxyethyl, 2,3-dihydroxybutyl,

3,4-dihydroxybutyl and 2-(hydroxymethyl)-3-hydroxypropyl, preferably 2-hydroxyethyl, 2,3-dihydroxypropyl, and 1-(hydroxymethyl)-2-hydroxyethyl, and the like.

[0064] "Hydroxyamino" means a -NH(OH) group.

[0065] "Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. One of ordinary skill in the art would understand that with respect to any molecule described as containing one or more optional substituents, only sterically practical and/or synthetically feasible compounds are meant to be included. "Optionally substituted " refers to all subsequent modifiers in a term. So, for example, in the term "optionally substituted arylC_{1-8} alkyl," both the "C_{1-8} alkyl" portion and the "aryl" portion of the molecule may or may not be substituted. A list of exemplary optional substitutions is presented below in the definition of "substituted."

[0066] "Optionally substituted alkoxy" means an -OR radical where R is optionally substituted alkyl as defined herein. Representative examples include -$OCH_2CH_2OCH_3$, -OCH_2CH_2OH, -$OCH_2CH(NH_2)CH_3$, and the like.

[0067] "Optionally substituted alkyl" means an alkyl radical, as defined herein, optionally substituted with one or more group(s), specifically one, two, three, four, or five groups, independently selected from alkylcarbonyl, alkenylcarbonyl, cycloalkylcarbonyl, alkylcarbonyloxy, alkenylcarbonyloxy, amino, alkylamino, dialkylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, cyano, cyanoalkylaminocarbonyl, alkoxy, alkenyloxy, halo, hydroxy, hydroxyalkoxy, carboxy, alkylcarbonylamino, alkylcarbonyloxy, -$S(O)_{0-2}$-alkyl, -$S(O)_{0-2}$-alkenyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, -$NR^cS(O)_2$-alkyl (where R^c is hydrogen, alkyl, optionally substituted alkenyl, optionally substituted alkynyl, hydroxy, alkoxy, alkenyloxy, or cyanoalkyl), alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkylaminoalkyloxy, dialkylaminoalkyloxy, alkoxycarbonyl, alkenyloxycarbonyl, alkoxycarbonylamino, alkylaminocarbonylamino, dialkylaminocarbonylamino, alkoxyalkyloxy, and -$C(O)NR^aR^b$ (where R^a and R^b are independently hydrogen, alkyl, optionally substituted alkenyl, optionally substituted alkynyl, hydroxy, alkoxy, alkenyloxy, or cyanoalkyl).

[0068] "Optionally substituted aryl" means an aryl group, as defined herein, which is optionally substituted with one, two, three, four, of five groups selected from halo, haloalkyl, haloalkoxy, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, carboxy, carboxy ester, amino, alkylamino, dialkylamino, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, -C(O)NR'R" (where R' is hydrogen or

alkyl and R" is hydrogen, alkyl, aryl, heteroaryl, or heterocycloalkyl), -NR'C(O)R" (where R' is hydrogen or alkyl and R" is alkyl, aryl, heteroaryl, or heterocycloalkyl), and -NHS(O)$_2$R' (where R' is alkyl, aryl, or heteroaryl).

[0069] "Optionally substituted arylalkyl means an alkyl group substituted with one or two optionally substituted aryl group(s) as defined herein.

[0070] "Optionally substituted arylalkyloxy" means an -OR group where R is optionally substituted arylalkyl, as defined herein.

[0071] "Optionally substituted arylalkyloxycarbonyl" means a -C(O)R group where R is optionally substituted arylalkyloxy, as defined herein.

[0072] "Optionally substituted aryloxy" means an -OR group where R is optionally substituted aryl, as defined herein.

[0073] "Optionally substituted aryloxycarbonyl" means a -C(O)R group where R is optionally substituted aryloxy as defined herein.

[0074] "Optionally substituted cycloalkyl" means a cycloalkyl radical, as defined herein, that is optionally substituted with one, two, three, or four groups independently selected from alkyl, alkenyl, alkynyl, alkoxy, halo, haloalkyl, haloalkoxy, oxo, hydroxy, cyano, nitro, amino, mono(C_1-C_6)alkylamino, dialkylamino, haloalkyl, haloalkoxy, aminoalkyl, alkylaminoalkyl dialkylaminoalkyl, carboxy, carboxy ester, cycloalkyl, hydroxyalkyl, -C(O)NR'R" (where R' is hydrogen, alkyl, hydroxy, or alkoxy and R" is hydrogen, alkyl, aryl, heteroaryl, or heterocycloalkyl), optionally substituted heterocycloalkyl, optionally substituted heteroaryl, -NR'C(O)R" (where R' is hydrogen or alkyl and R" is alkyl, aryl, heteroaryl, or heterocycloalkyl), and -NHS(O)$_2$R' (where R' is alkyl, aryl, or hetercyclyl).

[0075] "Optionally substituted cycloalkyloxycarbonyl" means a -C(O)OR group where R is optionally substituted cycloalkyl as defined herein.

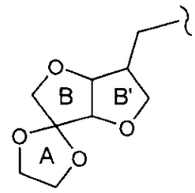
[0076] "Optionally substituted heteroaryl" means a heteroaryl group, as defined herein, optionally substituted with one, two, three, four, or five groups selected from halo, haloalkyl, haloalkoxy, alkyl, alkenyl, alkynyl, alkoxy, hydroxy, oxo (valency rules permitting), carboxy, carboxy ester, amino, alkylamino, dialkylamino, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, heteroaryl, optionally substituted aryl, -C(O)NR'R" (where R' is hydrogen or alkyl and R" is hydrogen, alkyl, aryl, heteroaryl, or heterocycloalkyl), -NR'C(O)R" (where R' is hydrogen or alkyl and R" is alkyl, aryl, heteroaryl, or heterocycloalkyl), and -NHS(O)$_2$R' (where R' is alkyl, aryl, or heteroaryl).

[0077] "Optionally substituted heterocycloalkyl" means a heterocycloalkyl ring, as defined herein, optionally substituted with one, two, three, four, or five groups selected from

halo, haloalkyl, haloalkoxy, hydroxy, oxo, alkyl, alkenyl, alkynyl, alkoxy, optionally substituted cycloalkyl, heterocycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, alkylaminoalkyl, dialkylaminoalkyl, carboxy, alkoxycarbonyl, aryloxycarbonyl, arylalkyloxycarbonyl, cycloalkyloxycarbonyl, cycloalkylalkyloxycarbonyl, -C(O)NR'R" (where R' is hydrogen or alkyl and R" is hydrogen, alkyl, aryl, heteroaryl, or heterocycloalkyl), -NR'C(O)R" (where R' is hydrogen or alkyl and R" is alkyl, aryl, heteroaryl, or heterocycloalkyl), amino, alkylamino, dialkylamino, and -NHS(O)$_2$R' (where R' is alkyl, aryl, or heteroaryl).

[0078] "Saturated bridged ring system" refers to a bicyclic or polycyclic ring system that is not aromatic. Such a system may contain isolated or conjugated unsaturation, but not aromatic or heteroaromatic rings in its core structure (but may have aromatic substitution thereon). For example, hexahydro-furo[3,2-b]furan, 2,3,3a,4,7,7a-hexahydro-1H-indene, 7-aza-bicyclo[2.2.1]heptane, and 1,2,3,4,4a,5,8,8a-octahydro-naphthalene are all included in the class "saturated bridged ring system."

[0079] "Spiro", "Spirocyclyl" or "spiro ring" refers to a ring originating from a particular annular carbon of another ring. For example, as depicted below, a ring atom of a saturated bridged ring system (rings B and B'), but not a bridgehead atom, can be a shared atom between the saturated bridged ring system and a spirocyclyl (ring A) attached thereto.



[0080] "Yield" for each of the reactions described herein is expressed as a percentage of the theoretical yield.

[0081] "Patient" for the purposes of the present invention includes humans and other animals, particularly mammals, and other organisms. Thus the methods are applicable to both human therapy and veterinary applications. In a specific embodiment the patient is a mammal, and in a more specific embodiment the patient is human.

[0082] "Kinase-dependent diseases or conditions" refer to pathologic conditions that depend on the activity of one or more protein kinases. Kinases either directly or indirectly participate in the signal transduction pathways of a variety of cellular activities including proliferation, adhesion, migration, differentiation and invasion. Diseases associated with kinase activities include tumor growth, the pathologic neovascularization that supports solid tumor growth, and associated with other diseases where excessive local vascularization is

involved such as ocular diseases (diabetic retinopathy, age-related macular degeneration, and the like) and inflammation (psoriasis, rheumatoid arthritis, and the like).

[0083] While not wishing to be bound to theory, phosphatases can also play a role in "kinase-dependent diseases or conditions" as cognates of kinases; that is, kinases phosphorylate and phosphatases dephosphorylate, for example protein substrates. Therefore compounds of the invention, while modulating kinase activity as described herein, may also modulate, either directly or indirectly, phosphatase activity. This additional modulation, if present, may be synergistic (or not) to activity of compounds of the invention toward a related or otherwise interdependent kinase or kinase family. In any case, as stated previously, the compounds of the invention are useful for treating diseases characterized in part by abnormal levels of cell proliferation (*i.e.* tumor growth), programmed cell death (apoptosis), cell migration and invasion and angiogenesis associated with tumor growth.

[0084] "Therapeutically effective amount" is an amount of a compound of the invention, that when administered to a patient, ameliorates a symptom of the disease. The amount of a compound of the invention which constitutes a "therapeutically effective amount" will vary depending on the compound, the disease state and its severity, the age of the patient to be treated, and the like. The therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their knowledge and to this disclosure.

[0085] "Cancer" refers to cellular-proliferative disease states, including but not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hanlartoma, inesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinorna, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinorna, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular

carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis defornians), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastorna multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma], fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal Glands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

[0086] A "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, which is incorporated herein by reference or S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977;66:1-19 both of which are incorporated herein by reference.

[0087] Examples of pharmaceutically acceptable acid addition salts include those formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; as well as organic acids such as acetic acid, trifluoroacetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic

acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, 3-(4-hydroxybenzoyl)benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, p-toluenesulfonic acid, and salicylic acid and the like.

[0088] Examples of a pharmaceutically acceptable base addition salts include those formed when an acidic proton present in the parent compound is replaced by a metal ion, such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferable salts are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins. Examples of organic bases include isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, tromethamine, *N*-methylglucamine, polyamine resins, and the like. Exemplary organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine.

[0089] "Prodrug" refers to compounds that are transformed (typically rapidly) *in vivo* to yield the parent compound of the above formulae, for example, by hydrolysis in blood. Common examples include, but are not limited to, ester and amide forms of a compound having an active form bearing a carboxylic acid moiety. Examples of pharmaceutically acceptable esters of the compounds of this invention include, but are not limited to, alkyl esters (for example with between about one and about six carbons) the alkyl group is a straight or branched chain. Acceptable esters also include cycloalkyl esters and arylalkyl esters such as, but not limited to benzyl. Examples of pharmaceutically acceptable amides of the compounds of this invention include, but are not limited to, primary amides, and secondary and tertiary alkyl amides (for example with between about one and about six

carbons). Amides and esters of the compounds of the present invention may be prepared according to conventional methods. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference for all purposes.

[0090] "Metabolite" refers to the break-down or end product of a compound or its salt produced by metabolism or biotransformation in the animal or human body; for example, biotransformation to a more polar molecule such as by oxidation, reduction, or hydrolysis, or to a conjugate (see Goodman and Gilman, "The Pharmacological Basis of Therapeutics" 8.sup.th Ed., Pergamon Press, Gilman et al. (eds), 1990 for a discussion of biotransformation). As used herein, the metabolite of a compound of the invention or its salt may be the biologically active form of the compound in the body. In one example, a prodrug may be used such that the biologically active form, a metabolite, is released *in vivo*. In another example, a biologically active metabolite is discovered serendipitously, that is, no prodrug design *per se* was undertaken. An assay for activity of a metabolite of a compound of the present invention is known to one of skill in the art in light of the present disclosure.

[0091] "Treating" or "treatment" of a disease, disorder, or syndrome, as used herein, includes (i) preventing the disease, disorder, or syndrome from occurring in a human, i.e. causing the clinical symptoms of the disease, disorder, or syndrome not to develop in an animal that may be exposed to or predisposed to the disease, disorder, or syndrome but does not yet experience or display symptoms of the disease, disorder, or syndrome; (ii) inhibiting the disease, disorder, or syndrome, *i.e.*, arresting its development; and (iii) relieving the disease, disorder, or syndrome, *i.e.*, causing regression of the disease, disorder, or syndrome. As is known in the art, adjustments for systemic versus localized delivery, age, body weight, general health, sex, diet, time of administration, drug interaction and the severity of the condition may be necessary, and will be ascertainable with routine experimentation by one of ordinary skill in the art.

Embodiments of the Invention

[0092] In one embodiment of the Invention, R^7 is halo and all other groups are as defined in the Summary of the Invention for Group A, Group B, Group C, or Group D. In a more specific embodiment, R^7 is iodo or bromo. In an even more specific embodiment, R^7 is iodo.

Yet even more specifically, the compound is that where R^7 is iodo or bromo and all other groups are as defined in the Summary of the Invention for Group A.

[0093] In another embodiment of the Invention, X is halo and all other groups are as defined in the Summary of the Invention for Group A, Group B, Group C, or Group D. In a more specific embodiment, X is fluoro or chloro. In an even more specific embodiment, X is fluoro. Yet even more specifically, the compound is that where X is fluoro or chloro and all other groups are as defined in the Summary of the Invention for Group A.

[0094] In another embodiment of the Invention, R^7 and X are halo and all other groups are as defined in the Summary of the Invention for Group A, Group B, Group C, or Group D. More specifcally, R^7 is iodo and X is fluoro. Even more specifically, the compound is that where R^7 is iodo and X is fluoro and all other groups are as defined in the Summary of the Invention for Group A.

[0095] In another embodiment of the Invention, R^1, R^2, R^5, and R^6 are hydrogen and all other groups are as defined in the Summary of the Invention for Group A, Group B, Group C, or Group D. More specifically, R^1, R^2, R^5, and R^6 are hydrogen and all other groups are as defined in the Summary of the Invention for Group A.

[0096] In another embodiment of the Invention, the compound of Formula I is selected from Group A where all groups are as defined in the Summary of the Invention.

[0097] In another embodiment of the invention (A1), X and R^7 are halo and all other groups are as defined in the Summary of the Invention for a compound of Group A.

[0098] In another embodiment (A2), the compound of Formula I is selected from Group A where R^{10} and R^{12} are independently hydrogen or halo. In a more specific embodiment, R^{10} and R^{12} are independently hydrogen or fluoro. More specifically, R^{10} is 3-fluoro and R^{12} is hydrogen. In another more specific embodiment, R^{10} and R^{12} are fluoro, more specifically, 3-fluoro and 4-fluoro, 4-fluoro and 5-fluoro, or 4-fluoro and 6-fluoro.

[0099] In another embodiment of the invention (A3), the compound is that where R^1, R^2, R^5 and R^6 are hydrogen and all other groups are as defined in the Summary of the Invention for Group A.

[00100] In another embodiment (A4), the compound of Formula I is selected from Group A where X, R^7, and A are as defined in the Summary of the Invention; and

one of R^1, R^2, R^3, R^4, R^5, and R^6 is halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, $-CN$, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$,

[00102] A more specific embodiment of embodiment A5 is that where R^1, R^2, R^5 and R^6 are hydrogen.

[00103] In another embodiment of the Invention (A6), the compound of Formula I is selected from Group A where X, R^7, and A are as defined in the Summary of the Invention; and

R^3 and R^4 are independently halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl; where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; or

R^3 and R^4 together with the carbon to which they are attached form C(O) or C(=NOH);

R^1, R^2, R^5 and R^6 are are as defined in the Summary of the Invention.

[00104] A more specific embodiment of embodiment A6 is that where R^1, R^2, R^5 and R^6 are hydrogen.

[00105] In another embodiment of the Invention (A7), the compound of Formula I is selected from Group A where X and R^7 are halo; A is phenylene optionally substituted with R^{10} and R^{12} where R^{10} and R^{12} are independently hydrogen or halo; R^1, R^2, R^5 and R^6 are hydrogen;

R^3 is hydrogen and R^4 is $-NR^8R^{8'}$ (where R^8 is hydrogen, hydroxy, alkyl, alkoxy, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl and $R^{8'}$ is hydroxy, alkoxy, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl), $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, alkenyl, and alkynyl; where the alkenyl and alkynyl are optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted

cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; or

R^3 and R^4 together with the carbon to which they are attached form C(O) or C(=NOH);

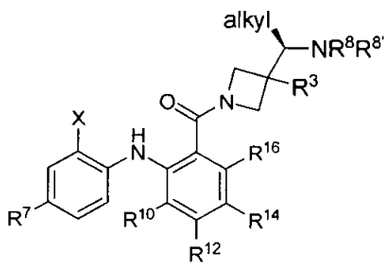
m, $R^{8''}$, and R^9 are as defined in the Summary of the Invention for a compound of Group A; and unless otherwise specified in this embodiment, R^8 and $R^{8'}$ are as defined in the Summary of the Invention for a compound of Group A.

[00106] In another embodiment of the Invention (A8), the compound of Formula I is selected from Group A where R^3 is hydrogen, halo, hydroxy, alkoxy, or amino. More specifically, R^3 is hydrogen, fluoro, hydroxy, methoxy, or amino. Even more specifically, R^3 is hydrogen or hydroxy. Yet even more specifically, R^3 is hydroxy.

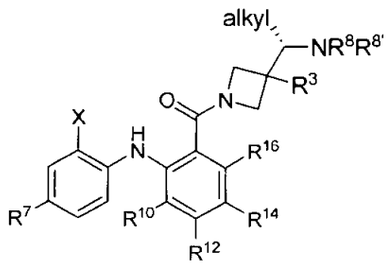
[00107] In a more specific embodiment of embodiment A8, X and R^7 are halo; A is phenylene optionally substituted with R^{10} and R^{12} where R^{10} and R^{12} are independently hydrogen or halo; R^1, R^2, R^5 and R^6 are hydrogen; and R^4, is as defined in the Summary of the Invention for a compound of Group A.

[00108] Another specific embodiment of the Invention (A9) is that where the compound of Formula I is selected from Group A where R^1, R^2, R^5 and R^6 are hydrogen; R^3 is hydrogen, halo, hydroxy, alkoxy, or amino; and R^4 is heterocycloalkyl, heteroaryl, or alkyl substituted with $-NR^8R^{8'}$ where R^8 and $R^{8'}$ and all other groups are as defined in the Summary of the Invention for a compound of Group A.

[00109] Another specific embodiment of embodiment A9 is that where R^4 is alkyl substituted with $-NR^8R^{8'}$ where R^8 and $R^{8'}$ and all other groups are as defined in the Summary of the Invention for a compound of Group A. Specifically, the compound is of Formula I(a) or I(b):



I(a);



I(b)

where R^3 is as defined in A9; X, R^7, R^8, $R^{8'}$, R^{10}, R^{12}, R^{14}, and R^{16} are as defined in the Summary of the Invention for a compound of Group A.

[00110] Another specific embodiment of embodiment A9 is that where R^4 is heterocycloalkyl.

[00111] In a specific embodiment of embodiment A9, the compound is that where X and R^7 are halo; A is phenylene optionally substituted with R^{10} and R^{12} where R^{10} and R^{12} are independently hydrogen or halo; R^3 is hydroxy; and R^4 is alkyl substituted with $-NR^8R^{8'}$ or R^4 is heterocycloalkyl optionally substituted with one, two, or three groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; and where m, R^3, R^8, $R^{8'}$, $R^{8''}$, and R^9 are as defined in the Summary of the Invention for a compound of Group A.

[00112] In another embodiment of the Invention (A10), the compound of Formula I is selected from Group A where

R^4 is

a) hydrogen;
b) $-CH_2N(R^{25})(NR^{25a}R^{25b})$;
c) $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$;
d) $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$;
e) $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$;
f) $-CH_2NR^{25}C(=NH)(R^{25})$;
g) $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$;
h) alkyl;
i) alkyl substituted with one or two $-OR^8$ where R^8 is hydrogen, aryl, or alkyl where the alkyl is substituted with one or two hydroxy;
j) alkyl substituted with one, two, or three halo;
k) alkyl substituted with nitro;
l) alkyl substituted with $-S(O)_mR^9$ (where m is 0 and R^9 is aryl);
m) alkyl substituted with optionally substituted heterocycloalkyl;
n) alkenyl;
o) $-NR^8R^{8'}$ (where R^8 and $R^{8'}$ are independently hydrogen; alkyl; alkenyl; alkyl substituted with one or two hydroxy; alkyl substituted with one or two $-NR^{30}R^{30'}$ where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl; alkyl

substituted with optionally substituted heteroaryl; or alkyl substituted with optionally substituted cycloalkyl);

p) $-C(O)NR^8R^{8'}$ (where R^8 is hydrogen, alkyl, or alkenyl; and $R^{8'}$ is hydrogen; hydroxy; alkyl; alkenyl; alkyl substituted with one or two hydroxy; alkyl substituted with optionally substituted heterocycloalkyl; alkyl substituted with $-NR^{30}R^{30'}$ where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl; or optionally substituted alkoxy);

q) $-NR^8C(O)OR^{8'}$ (where R^8 and $R^{8'}$ are independently hydrogen, alkyl, or alkenyl);

r) alkyl substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen, alkyl, alkenyl, alkynyl, or alkyl substituted with one or two hydroxy; and $R^{8'}$ is hydrogen; hydroxy; alkoxy; alkyl; alkenyl; alkynyl; optionally substituted alkoxy; alkyl substituted with one or two hydroxy; alkyl substituted with one or two alkoxy; alkyl substituted with $-NR^{30}R^{30'}$ where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl; alkyl substituted with one or two hydroxy and one or two $-NR^{30}R^{30'}$ where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl; alkyl substituted with one, two, three, four, or five halo; alkyl substituted with optionally substituted cycloalkyl; alkyl substituted with optionally substituted aryl; alkyl substituted with one or two hydroxy and one optionally substituted aryl; alkyl substituted with optionally substituted heterocycloalkyl; alkyl substituted with optionally substituted heteroaryl; heteroaryl; aryl; aryl substituted with one or two hydroxy; aryl substituted with one or two alkoxy; aryl substituted with one or two halo; aryl substituted with one or two $-NR^{32}C(O)R^{32a}$ where R^{32} is hydrogen or alkyl and R^{32a} is alkyl, alkenyl, alkoxy, or cycloalkyl; aryl substituted with $-NR^{34}SO_2R^{34a}$ where R^{34} is hydrogen or alkyl and R^{34a} is alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl; cycloalkyl; cycloalkyl substituted with one or two hydroxy; cycloalkyl substituted with one or two hydroxy and one or two hydroxyalkyl; cycloalkyl substituted with one or two alkoxy; cycloalkyl substituted with carboxy; cycloalkyl substituted with $-C(O)NR^{33}R^{33a}$ where R^{33} is hydrogen or alkyl and R^{33a} is alkyl, alkenyl, alkynyl, or cycloalkyl; alkyl substituted with $-C(O)NR^{33}R^{33a}$ where R^{33} is hydrogen or alkyl and R^{33a} is alkyl, alkenyl, alkynyl, or cycloalkyl; cycloalkyl substituted with optionally substituted cycloalkyl; heterocycloalkyl; heterocycloalkyl substituted with alkyl; heterocycloalkyl substituted with alkoxycarbonyl; heterocycloalkyl substituted with optionally substituted arylalkyl; heterocycloalkyl substituted with one or two hydroxy; heterocycloalkyl substituted with one or two alkoxy; heterocycloalkyl

2,3-dihydroxypropyl, 3-hydroxy-2-methyl-prop-2-yl, *N*-(1-methoxy-prop-2-yl)-aminomethyl, *N*-(ethoxypropyl)-aminomethyl, *N*-(ethoxyethyl)-aminomethyl, *N*-(2,2-dimethoxyethyl)-aminomethyl, *N*-(methoxyethyl)-aminomethyl, *N*-(isopropxyethyl)-aminomethyl, trifluoromethyl, 1-nitro-ethyl, 1-methyl-1-nitro-ethyl, 1-nitro-propyl, 3-methyl-1-nitro-butyl, phenylthiomethyl, allyl, ethenyl, 2-methylthio-ethylaminomethyl, 3-methylthio-propylaminomethyl, *N*-(*tert*-butoxycarbonylaminopropyl)-aminomethyl, *N*-(1-carboxyethyl)-aminomethyl, *N*-(1*R*-carboxyethyl)-aminomethyl, *N*-(1*S*-carboxyethyl)-aminomethyl, *N*-(1-methoxycarbonylethyl)-aminomethyl, $-NH_2$, $-NH(CH_2)_3CH_3$, $-NHCH_3$, $-NH(CH_2CH_3)$, $-NHCH_2CH(CH_3)_2$, $-NHCH_2CH_2OH$, $-NHCH_2CH_2CH_2NH_2$, $-N(CH_3)CH_2CH_2$(heteroaryl), $-NHCH_2$(cycloalkyl), $-C(O)NH_2$, -C(O)NHOH, $-C(O)NH(OCH_2CH(OH)CH_2OH)$, $-C(O)NH(CH_2)_3CH_3$, $-C(O)NHCH_2CH{=}CH_2$, $-C(O)NHCH_2CH_3$, $-C(O)NHCH_2CH_2OH$, $-C(O)NHCH_2CH(OH)CH_2OH$, $-C(O)NHCH_2CH_2CH(OH)CH_2OH$, $-C(O)NHCH_2CH_2$(piperidin-1-yl), -C(O)NH(phenyl), $-C(O)NHCH_2CH_2N(CH_2CH_3)_2$, $-NHC(O)OC(CH_3)_3$, $-NHC(O)OCH_3$, azetidinylmethyl, pyrrolidinylmethyl, 3-hydroxy-pyrrolidinylmethyl, 2-(methoxymethyl)-pyrrolidinylmethyl, 2*S*-(methoxymethyl)-pyrrolidinylmethyl, 2*R*-(methoxymethyl)-pyrrolidinylmethyl, morpholinylmethyl, hydroxypiperidinylmethyl, 4-alkyl-piperazinylmethyl, 4-alkyl-homopiperazinylmethyl, 4-(heterocycloalkyl)-piperidinylmethyl, 4-(dialkylaminoalkyl)-piperazinylmethyl, *N*-hydroxyaminomethyl, *N*-methoxyaminomethyl, *N*-ethoxyaminomethyl, *N*-ethylaminomethyl, 1-(*N*-ethyl-amino)-ethyl, *N,N*-diethylaminomethyl, *N,N*-dimethylaminomethyl, aminomethyl, 1-amino-ethyl, 1*R*-amino-ethyl, 1*S*-amino-ethyl, 1_(methylamino)-ethyl, 1-(*N,N*-dimethylamino)-ethyl, 1-amino-1-methyl-ethyl, 1-aminopropyl, 1*S*-aminopropyl, 1*R*-aminopropyl, *N*-(n-propyl)-aminomethyl, *N*-(isopropyl)-aminomethyl, 2-(*N*-isopropylamino)-ethyl, 3-(*N*-isopropylamino)-2-methyl-prop-2-yl, 1-(*N*-ethyl-amino)-propyl, 1-(*N,N*-diethyl-amino)-propyl, 1-aminobutyl, 1-amino-isobutyl, *N*-(2-aminoethyl)-aminomethyl, *N*-(n-butyl)-aminomethyl, *N*-isobutylaminomethyl, *tert*-butylaminomethyl, 1-(*tert*-butylamino)-ethyl, *sec*-butylaminomethyl, *N*-(2-methyl-but-3-yl)-aminomethyl, *N*-(3,3-dimethyl-butyl)-aminomethyl, *N*-(3-methylbut-3-yl)-aminomethyl, *N*-(2-methylbutyl)-aminomethyl, *N*-(pent-3-yl)-aminomethyl, n-pentylaminomethyl, isopentylaminomethyl, *sec*-pentylaminomethyl, neopentylaminomethyl, *N*-(2,2,4-trimethyl-pent-4-yl)-aminomethyl, *N*-(2-ethyl-butyl)-aminomethyl, *N*-allyl-aminomethyl, 3-methyl-but-1-yn-3-ylaminomethyl, *N*-(2,3-dihydroxypropyloxy)-aminomethyl, *N*-cyclopropylaminomethyl, *N*-cyclobutylaminomethyl, *N*-cyclopentylaminomethyl, *N*-cyclopenten-4-ylaminomethyl, *N*-(1(*R,S*)-hydroxy-cyclopent-2-yl)-aminomethyl, *N*-(1*S*-hydroxy-cyclopent-2-yl)-

aminomethyl, *N*-(1*R*-hydroxy-cyclopent-2-yl)-aminomethyl, *N*-(1(*R,S*)-hydroxy-1-methyl-cyclopent-2-yl)-aminomethyl, *N*-(1*S*-hydroxy-1-methyl-cyclopent-2-yl)-aminomethyl, *N*-(1*R*-hydroxy-1-methyl-cyclopent-2-yl)-aminomethyl, *N*-(3,4-dihydroxy-cyclopentyl)-aminomethyl, *N*-(1-hydroxymethyl-cyclopent-1-yl)-aminomethyl, *N*-(2,3-dihydroxy-4-hydroxymethyl-cyclopentyl)-aminomethyl, *N*-(1(*R,S*)-methoxy-cyclopent-2-yl)-aminomethyl, *N*-(1*S*-methoxy-cyclopent-2-yl)-aminomethyl, *N*-(1*R*-methoxy-cyclopent-2-yl)-aminomethyl, *N*-(1-carboxy-cyclopentyl)-aminomethyl, *N*-cyclohexylaminomethyl, *N*-(1(*R,S*)-hydroxy-cyclohex-2-yl)-aminomethyl, *N*-(*cis*-4-hydroxy-cyclohexyl)-aminomethyl, *N*-(*trans*-4-hydroxy-cyclohexyl)-aminomethyl, 1-[*N*-(*cis*-4-hydroxy-cyclohexyl)-amino]-ethyl, 1-[*N*-(*trans*-4-hydroxy-cyclohexyl)-amino]-ethyl, *N*-(1(*R*)-hydroxy-cyclohex-2-yl)-aminomethyl, *N*-(1(*S*)-hydroxy-cyclohex-2-yl)-aminomethyl, *N*-(1-hydroxymethyl-cyclohexyl)-aminomethyl, *N*-(2-cyclohexyl-cyclohexyl)-aminomethyl, *N*-{(2*R*,3*S*,4*R*,6*R*)-2-(hydroxymethyl)-3,4-dihydroxy-6-methoxy-tetrahydro-2*H*-pyran-5-yl}-aminomethyl, *N*-(cycloheptyl)-aminomethyl, *N*-(cyclooctyl)-aminomethyl, [(1r,3r,5*R*,7*R*)-tricyclo[3.3.1.1~3,7~]dec-2-ylamino]methyl, *N*-[1-(cyclopropylaminocarbonyl)-cyclopentyl]-aminomethyl, $-CH_2NHC(CH_3)_2C(O)NH$(cyclohexyl), $-CH_2NHC(CH_3)_2C(O)NH(CH_2CH_3)$, *N*-(1-benzyloxy-cyclopent-2-yl)-aminomethyl, *N*-(cyclopropylmethyl)-aminomethyl, *N*-(cyclohexylmethyl)-aminomethyl, *N*-(1-cyclohexylethyl)-aminomethyl, *N*-(imidazolyl)-aminomethyl, *N*-(1,3,5-triazinyl)-aminomethyl, *N*-(5-hydroxy-pyrazol-3-yl)-aminomethyl, *N*-(5-methyl-pyrazol-3-yl)-aminomethyl, *N*-(benzimidazolyl)-aminomethyl, *N*-(pyrimidin-2-yl)-aminomethyl, *N*-(pyridin-2-yl)-aminomethyl, *N*-(pyridin-3-yl)-aminomethyl, *N*-(pyridin-4-yl)-aminomethyl, *N*-indan-1-yl-aminomethyl, *N*-indan-2-yl-aminomethyl, phenylaminomethyl, *N*-(2-hydroxyphenyl)-aminomethyl, *N*-(3-hydroxyphenyl)-aminomethyl, *N*-(4-hydroxyphenyl)-aminomethyl, *N*-(2-methoxyphenyl)-aminomethyl, *N*-(3-methoxyphenyl)-aminomethyl, *N*-(4-methoxyphenyl)-aminomethyl, *N*-(2-fluorophenyl)-aminomethyl, *N*-(3-fluorophenyl)-aminomethyl, *N*-(4-fluorophenyl)-aminomethyl, *N*-(2-chlorophenyl)-aminomethyl, *N*-(3-chlorophenyl)-aminomethyl, *N*-(4-chlorophenyl)-aminomethyl, *N*-(3-methylcarbonylamino-phenyl)-aminomethyl, *N*-(4-methylcarbonylamino-phenyl)-aminomethyl, *N*-(2-aminophenyl)-aminomethyl, *N*-(3-aminophenyl)-aminomethyl, *N*-(4-aminophenyl)-aminomethyl, *N*-(2-methylsulfonylaminophenyl)-aminomethyl, *N*-(3-methylsulfonylaminophenyl)-aminomethyl, *N*-(4-methylsulfonylaminophenyl)-aminomethyl, *N*-(2-fluoro-4-hydroxy-phenyl)-aminomethyl, *N*-(3-fluoro-4-hydroxy-phenyl)-aminomethyl, *N*-(benzyl)-aminomethyl, *N*-(2-hydroxyphenylmethyl)-aminomethyl, *N*-(3-hydroxyphenylmethyl)-aminomethyl, *N*-(4-hydroxyphenylmethyl)-aminomethyl, *N*-(2-(*N*-

methylpiperazin-1-yl)-phenylmethyl)-aminomethyl, *N*-(4-alkyl-phenethyl)-aminomethyl, *N*-(1-hydroxy-3-phenyl-prop-2-yl)-aminomethyl, *N*-(pyrrolidin-2-ylmethyl)-aminomethyl, *N*-(*N*-alkyl-pyrrolidinylmethyl)-aminomethyl, *N*-(*N*-alkyl-pyrrolidinylethyl)-aminomethyl, *N*-(pyrrolidinylpropyl)-aminomethyl, *N*-(1,1-dimethyl-2-pyrrolidin-1-yl-ethyl)-aminomethyl, *N*-(tetrahydrofuranylmethyl)-aminomethyl, *N*-(tetrahydro-2*H*-pyran-4-ylmethyl)-aminomethyl, *N*-(tetrahydro-2*H*-pyranylethyl)-aminomethyl, *N*-(piperidin-4-ylmethyl)-aminomethyl, *N*-(*N*-methylpiperidin-4-ylmethyl)-aminomethyl, *N*-(*N*-*tert*-butoxycarbonylpiperidin-4-ylmethyl)-aminomethyl, *N*-(*N*-methylimidazol-4-ylmethyl)-aminomethyl, *N*-(*N*-methylimidazol-5-ylmethyl)-aminomethyl, *N*-[2-(imidazol-4-yl)-ethyl]-aminomethyl, *N*-[3-(imidazolyl)-propyl]-aminomethyl, *N*-(pyridin-3-ylethyl)-aminomethyl, *N*-(pyridin-4-ylethyl)-aminomethyl, *N*-(thien-2-ylethyl)-aminomethyl, *N*-(furan-2-ylethyl)-aminomethyl, *N*-(5-methyl-1,3,4-oxadiazol-2-ylmethyl)-aminomethyl, *N*-(2-indolin-3-ylethyl)-aminomethyl, 2-(*N,N*-dimethylamino)-ethylaminomethyl, 2-(*N,N*-dimethylamino)-1-methyl-ethylaminomethyl, 3-aminopropylaminomethyl, 3-(*N,N*-dimethylamino)-propylaminomethyl, 3-(*N,N*-diethylamino)-propylaminomethyl, *N*-(*N,N*-diisopropylaminoethyl)-aminomethyl, *N*-(*N,N*-dimethylaminobutyl)-aminomethyl, *N*-(3-hydroxypropyl)-aminomethyl, *N*-(2-hydroxypropyl)-aminomethyl, *N*-(1,2-dihydroxypropyl)-aminomethyl, *N*-(1-amino-2-hydroxy-prop-3-yl)-aminomethyl, *N*-(*N*-ethoxycarbonyl-piperidin-4-yl)-aminomethyl, *N*-(*N*-benzylpiperidin-4-yl)-aminomethyl, *N*-(homopiperidin-3-yl)-aminomethyl, *N*-(*N*-benzylpyrrolidin-3-yl)-aminomethyl, *N*-(*N*-ethylpiperidin-3-yl)aminomethyl, 2,2,2-trifluoroethylaminomethyl, 3,3,3-trifluoropropylaminomethyl, 2,2,3,3,3-pentafluoropropylaminomethyl, $-CH_2N(CH_2CH_2OH)_2$, $-CH_2N(CH_3)(CH_2CH_2OH)$, $-CH_2NH(CH_2CH_2OH)$, $-CH_2NH(CH_2CH_2CH_2CH_2OH)$, $-CH_2N(CH_3)$(*N*-methyl-pyrrolidin-3-yl), $-CH_2NH(C(CH_3)_2CH_2OH)$, $-NHC(O)CH(CH_3)_2$, $-NHC(O)CH_2N(CH_2CH_3)_2$, $-NHC(O)CH_2NH(CH_3)$, -NHC(O)H, $-NHC(O)CH_2CH(OH)CH_2OH$, $-NHC(O)CH_2NH_2$, $-NHC(O)CH_2N(CH_2CH_2OH)_2$, $-NHC(O)CH_2CH_2N(CH_2CH_2OH)_2$, $-NHC(O)CH_2$(4-alkyl-piperazinyl), $-NHC(O)CH_2$(piperidinyl), *N*-(phenyloxyethyl)-aminomethyl, cyclopentyl, 1-amino-cyclopentyl, (*cis,trans*)-2-amino-cyclopentyl, (*cis,trans*)-2-amino-cyclopentyl, *cis*-2-amino-cyclopentyl, *trans*-2-amino-cyclopentyl, (*cis,trans*)-2-hydroxy-cyclohexyl, *cis*-2-hydroxy-cyclohexyl, *trans*-2-hydroxy-cyclohexyl, (*cis,trans*)-2-amino-cyclohexyl, *cis*-2-amino-cyclohexyl, *trans*-2-amino-cyclohexyl, azetidin-3-yl, pyrrolidinyl, *N*-alkyl-pyrrolidinyl, 3-(dialkylamino)-pyrrolidinyl, piperidinyl, 2-methyl-piperidin-6-yl, *N*-*tert*-butoxycarbonylpiperidin-2-yl, piperazinyl, $-CH_2NHC(O)CH_3$, $-CH(CH_3)NHC(O)CH_3$, $-CH(CH_3)NHC(O)C(OCH_3)(CF_3)$phenyl, pyrrol-1-yl, pyrrol-2-yl, pyrrol-3-yl, imidazol-1-yl,

imidazol-2-yl, imidazol-4-yl, imidazol-5-yl, *N*-methyl-imidazol-2-yl, 5-methyl-imidazol-2-yl, 1,2,4-triazol-3-yl, thiazol-2-yl, 2-aminopyrimidin-3-yl, pyridinyl, benzimidazolyl, imidazol-1-ylmethyl, imidazol-2-ylmethyl, triazolylmethyl, (5-amino-3-methylpyrazol-1-yl)-methyl, phenoxymethyl, methylsulfonylaminomethyl, 1-(methoxycarbonylamino)-ethyl, 1-amino-1-phenyl-methyl, or 1-amino-3-hydroxy-propyl.

[00114] A more specific embodiment of embodiment A10 is that wherein X and R^7 are halo; A is phenylene optionally substituted with R^{10} and R^{12} where R^{10} and R^{12} are independently hydrogen or halo; R^1, R^2, R^5 and R^6 are hydrogen; and R^3 is hydrogen, halo, hydroxy, alkoxy, or amino.

[00115] A more specific embodiment of embodiment A10 is that where R^3 is hydrogen and R^4 is

a) hydrogen;

b) $-NR^8R^{8'}$ (where R^8 and $R^{8'}$ are independently hydrogen; alkyl; alkenyl; alkyl substituted with one or two hydroxy; alkyl substituted with one or two $-NR^{30}R^{30'}$ where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl; alkyl substituted with optionally substituted heteroaryl; or alkyl substituted with optionally substituted cycloalkyl);

c) $-C(O)NR^8R^{8'}$ (where R^8 is hydrogen, alkyl, or alkenyl; and $R^{8'}$ is hydrogen; hydroxy; alkyl; alkenyl; alkyl substituted with one or two hydroxy; alkyl substituted with heterocycloalkyl; alkyl substituted with $-NR^{30}R^{30'}$ where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl; or optionally substituted alkoxy);

d) $-NR^8C(O)OR^{8'}$ (where R^8 and $R^{8'}$ are independently hydrogen, alkyl, or alkenyl);

e) $-NR^8C(O)R^{8'}$ (where R^8 is hydrogen, alkyl, or alkenyl; and $R^{8'}$ is hydrogen; alkyl; alkyl substituted with one or two hydroxy; alkyl substituted with optionally substituted heterocycloalkyl; alkyl substituted with $-NR^{30}R^{30'}$ where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, hydroxyalkyl, or alkenyl);

f) alkyl;

g) alkyl substituted with one or two $-OR^8$ (where R^8 is hydrogen);

h) alkyl substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen, alkyl, alkenyl, alkynyl, or alkyl substituted with one or two hydroxy; and $R^{8'}$ is hydrogen; alkyl; alkenyl; alkynyl; alkyl substituted with one or two hydroxy; heterocycloalkyl substituted with alkyl; or alkyl substituted with $-NR^{30}R^{30'}$ where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl);

i) heterocycloalkyl; or

j) heterocycloalkyl substituted with $-NR^8R^{8'}$ (where R^8 and $R^{8'}$ are independently hydrogen, alkyl, or alkenyl).

[00116] Even more specifically, R^3 is hydrogen and R^4 is hydrogen, hydroxymethyl, $-NH_2$, $-NH(CH_2)_3CH_3$, $-NHCH_3$, $-NH(CH_2CH_3)$, $-NHCH_2CH(CH_3)_2$, $-NHCH_2CH_2OH$, $-NHCH_2CH_2CH_2NH_2$, $-N(CH_3)CH_2CH_2$(pyridin-2-yl), $-NHCH_2$(cyclopropyl), $-NHCH_2$(cyclopentyl), $-NHCH_2$(cyclohexyl), $-C(O)NHOH$, $-C(O)NH(OCH_2CH(OH)CH_2OH)$, $-C(O)NH(CH_2)_3CH_3$, $-C(O)NHCH_2CH{=}CH_2$, $-C(O)NHCH_2CH_3$, $-C(O)NHCH_2CH_2OH$, $-C(O)NHCH_2CH(OH)CH_2OH$, $-C(O)NHCH_2CH_2CH(OH)CH_2OH$, $-C(O)NHCH_2CH_2$(piperidin-1-yl), $-C(O)NH$(phenyl), $-C(O)NHCH_2CH_2N(CH_2CH_3)_2$, *N*-(isopropyl)-aminomethyl, *N,N*-dimethylaminomethyl, *N*-(2-aminoethyl)-aminomethyl, $-NHC(O)OC(CH_3)_3$, $-NHC(O)OCH_3$, $-NHC(O)CH(CH_3)_2$, $-NHC(O)CH_2NH_2$, $-NHC(O)CH_2N(CH_2CH_3)_2$, $-NHC(O)CH_2NH(CH_3)$, $-NHC(O)H$, $-NHC(O)CH_2CH(OH)CH_2OH$, $-NHC(O)CH_2N(CH_2CH_2OH)_2$, $-NHC(O)CH_2CH_2N(CH_2CH_2OH)_2$, $-NHC(O)CH_2$(4-alkyl-piperazinyl), $-NHC(O)CH_2$(piperidinyl), pyrrolidinyl, 3-(dialkylamino)-pyrrolidinyl, piperidinyl, 2-methyl-piperidin-6-yl, *N*-methylpiperidin-2-yl, or piperazin-2-yl.

[00117] A more specific embodiment of embodiment A10 is that where R^3 is alkoxy and R^4 is alkyl substituted with $-NR^8R^{8'}$ (where R^8 and $R^{8'}$ are independently hydrogen, alkyl, or alkenyl). More specifically, R^3 is methoxy and R^4 is alkyl substituted with $-NR^8R^{8'}$ (where R^8 and $R^{8'}$ are independently hydrogen, alkyl, or alkenyl).

[00118] A more specific embodiment of embodiment A10 is that where R^3 is halo and R^4 is alkyl substituted with $-NR^8R^{8'}$ (where R^8 and $R^{8'}$ are independently hydrogen, alkyl, or alkenyl). More specifically, R^3 is fluoro and R^4 is alkyl substituted with $-NR^8R^{8'}$ (where R^8 and $R^{8'}$ are independently hydrogen, alkyl, or alkenyl).

[00119] A more specific embodiment of embodiment A10 is that where R^3 is amino and R^4 is alkyl substituted with $-NR^8R^{8'}$ (where R^8 and $R^{8'}$ are independently hydrogen, alkyl, or alkenyl).

[00120] A more specific embodiment of embodiment A10 is that where R^3 is hydroxy and R^4 is

a) hydrogen;

b) $-CH_2N(R^{25})(NR^{25a}R^{25b})$;

c) $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$;

d) $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$;

e) $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$;

f) $-CH_2NR^{25}C(=NH)(R^{25})$;

g) $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$;

h) alkyl;

i) alkenyl;

j) alkyl substituted with one or two $-OR^8$ where R^8 is hydrogen, aryl, or alkyl where the alkyl is substituted with one or two hydroxy;

k) alkyl substituted with one, two, or three halo;

l) alkyl substituted with nitro;

m) alkyl substituted with $-S(O)_mR^9$ (where m is 0 and R^9 is aryl);

n) alkyl substituted with optionally substituted heterocycloalkyl;

o) alkyl substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen, alkyl, alkenyl, alkynyl, or alkyl substituted with one or two hydroxy; and $R^{8'}$ is hydrogen; hydroxy; alkoxy; alkyl; alkenyl; alkynyl; optionally substituted alkoxy; alkyl substituted with one or two hydroxy; alkyl substituted with $-NR^{30}R^{30'}$ where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl; alkyl substituted with one or two hydroxy and one or two $-NR^{30}R^{30'}$ where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl; heterocycloalkyl substituted with alkyl, alkoxycarbonyl, or optionally substituted arylalkyl; alkyl substituted with one, two, three, four, or five halo; alkyl substituted with optionally substituted cycloalkyl; alkyl substituted with optionally substituted aryl; alkyl substituted with one or two hydroxy and one optionally substituted aryl; alkyl substituted with optionally substituted heterocycloalkyl; alkyl substituted with optionally substituted heteroaryl; heteroaryl; aryl; aryl substituted with one or two hydroxy; aryl substituted with one or two alkoxy; aryl substituted with one or two halo; aryl substituted with one or two $-NR^{32}C(O)R^{32a}$ where R^{32} is hydrogen or alkyl and R^{32a} is alkyl, alkenyl, alkoxy, or cycloalkyl; aryl substituted with $-NR^{34}SO_2R^{34a}$ where R^{34} is hydrogen or alkyl and R^{34a} is alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl; cycloalkyl; cycloalkyl substituted with one or two hydroxy; cycloalkyl substituted with one or two hydroxy and one or two hydroxyalkyl; cycloalkyl substituted with one or two alkoxy; cycloalkyl substituted with carboxy; cycloalkyl substituted with $-C(O)NR^{33}R^{33a}$ where R^{33} is hydrogen or alkyl and R^{33a} is alkyl, alkenyl, alkynyl, or cycloalkyl; cycloalkyl substituted with optionally substituted cycloalkyl; heterocycloalkyl; heterocycloalkyl substituted with one or two hydroxy; heterocycloalkyl substituted with one or two alkoxy; heterocycloalkyl substituted with one or two hydroxyalkyl; heterocycloalkyl

substituted with one or two hydroxy, one or two alkoxy, and one or two hydroxyalkyl; alkyl substituted with $-C(O)NR^{33}R^{33a}$ where R^{33} is hydrogen or alkyl and R^{33a} is alkyl, alkenyl, alkynyl, or cycloalkyl; alkyl substituted with optionally substituted aryloxy; alkyl substituted with $-S(O)_nR^{31}$ where n is 0 and R^{31} is alkyl; alkyl substituted with carboxy; alkyl substituted with alkoxycarbonyl; or alkyl substituted with $-NR^{32}C(O)R^{32a}$ where R^{32} is hydrogen or alkyl and R^{32a} is alkyl, alkenyl, alkoxy, or cycloalkyl);

p) heterocycloalkyl;

q) $-C(O)NR^8R^{8'}$ (where R^8 is hydrogen, alkyl, or alkenyl; and $R^{8'}$ is hydrogen; alkyl; alkyl; alkenyl; or substituted with one or two hydroxy;);

r) alkyl substituted with $-NR^8C(O)R^{8'}$ (where R^8 is hydrogen, alkyl, or alkenyl and $R^{8'}$ is alkyl; alkenyl; or alkyl substituted with alkoxy, aryl, and one, two, or three halo);

s) cycloalkyl;

t) cycloalkyl substituted with $-NR^8R^{8'}$ where R^8 and $R^{8'}$ are independently hydrogen, alkyl, or alkenyl;

u) cycloalkyl substituted with $-C(O)NR^{33}R^{33a}$ where R^{33} is hydrogen or alkyl and R^{33a} is alkyl, alkenyl, alkynyl, or cycloalkyl;

v) heterocycloalkyl;

w) heterocycloalkyl substituted with one or two alkyl;

x) heterocylcloalkyl substituted with $-C(O)OR^8$ where R^8 is alkyl or alkenyl;

y) heteroaryl;

z) heteroaryl optionally substituted with $-NR^8R^{8'}$ where R^8 and $R^{8'}$ are independently hydrogen, alkyl, or alkenyl;

aa) alkyl substituted with optionally substituted heteroaryl;

bb) alkyl substituted with $-NR^8S(O)_2R^9$ where R^8 is hydrogen, alkyl, or alkenyl and R^9 is alkyl or alkenyl;

cc) alkyl substituted with $-NR^8C(O)OR^{8'}$ where R^8 and $R^{8'}$ are independently hydrogen, alkyl, or alkenyl;

dd) alkyl substituted with one aryl and one $-NR^8R^{8'}$ where R^8 and $R^{8'}$ are independently hydrogen, alkyl, or alkenyl; or

ee) alkyl substituted with one or two $-OR^8$ (where R^8 is hydrogen) and one or two $-NR^8R^{8'}$ where R^8 and $R^{8'}$ are independently hydrogen, alkyl, or alkenyl.

[00121] Even more specifically, R^3 is hydroxy and R^4 is hydrogen, $-CH_2N(H)(NHCH_3)$, $-CH_2NHC(=NH)(NH_2)$, $-CH_2NHC(=NH)(NHNO_2)$, $-CH_2NHC(=NH)(NHCN)$,

-$CH_2NHC(=NH)$(phenyl), -$CH_2NHC(NH_2)=CH(NO_2)$, methyl, ethyl, hydroxymethyl, 2,3-dihydroxypropyl, 3-hydroxy-2-methyl-prop-2-yl, *N*-(1-methoxy-prop-2-yl)-aminomethyl, *N*-(ethoxypropyl)-aminomethyl, *N*-(ethoxyethyl)-aminomethyl, *N*-(2,2-dimethoxyethyl)-aminomethyl, *N*-(methoxyethyl)-aminomethyl, *N*-(isopropxyethyl)-aminomethyl, trifluoromethyl, 1-nitro-ethyl, 1-methyl-1-nitro-ethyl, 1-nitro-propyl, 3-methyl-1-nitro-butyl, phenylthiomethyl, allyl, ethenyl, 2-methylthio-ethylaminomethyl, 3-methylthio-propylaminomethyl, *N*-(*tert*-butoxycarbonylaminopropyl)-aminomethyl, *N*-(1-carboxyethyl)-aminomethyl, *N*-(1*R*-carboxyethyl)-aminomethyl, *N*-(1*S*-carboxyethyl)-aminomethyl, *N*-(1-methoxycarbonylethyl)-aminomethyl, azetidinylmethyl, pyrrolidinylmethyl, 3-hydroxy-pyrrolidinylmethyl, 2-(methoxymethyl)-pyrrolidinylmethyl, 2*S*-(methoxymethyl)-pyrrolidinylmethyl, 2*R*-(methoxymethyl)-pyrrolidinylmethyl, morpholinylmethyl, 4-hydroxypiperidinylmethyl, 4-methyl-piperazinylmethyl, 4-methyl-homopiperazinylmethyl, 4-(piperidinyl)-piperidinylmethyl, 4-[2-(*N,N*-diethylamino)-ethyl]-piperazinylmethyl, *N*-hydroxyaminomethyl, *N*-methoxyaminomethyl, *N*-ethoxyaminomethyl, *N*-ethylaminomethyl, 1-(*N*-ethyl-amino)-ethyl, *N,N*-diethylaminomethyl, *N,N*-dimethylaminomethyl, aminomethyl, 1-amino-ethyl, 1*R*-amino-ethyl, 1*S*-amino-ethyl, 1-(methylamino)-ethyl, 1-(*N,N*-dimethylamino)-ethyl, 1-amino-1-methyl-ethyl, 1-aminopropyl, 1*S*-aminopropyl, 1*R*-aminopropyl, *N*-(n-propyl)-aminomethyl, *N*-(isopropyl)-aminomethyl, 2-(*N*-isopropylamino)-ethyl, 3-(*N*-isopropylamino)-2-methyl-prop-2-yl, 1-(*N*-ethyl-amino)-propyl, 1-(*N,N*-diethyl-amino)-propyl, 1-aminobutyl, 1-amino-isobutyl, *N*-(n-butyl)-aminomethyl, *N*-isobutylaminomethyl, *tert*-butylaminomethyl, 1-(*tert*-butylamino)-ethyl, *sec*-butylaminomethyl, *N*-(2-methyl-but-3-yl)-aminomethyl, *N*-(3,3-dimethyl-butyl)-aminomethyl, *N*-(3-methylbut-3-yl)-aminomethyl, *N*-(2-methylbutyl)-aminomethyl, *N*-(pent-3-yl)-aminomethyl, n-pentylaminomethyl, isopentylaminomethyl, *sec*-pentylaminomethyl, neopentylaminomethyl, *N*-(2,2,4-trimethyl-pent-4-yl)-aminomethyl, *N*-(2-ethyl-butyl)-aminomethyl, *N*-allyl-aminomethyl, 3-methyl-but-1-yn-3-ylaminomethyl, *N*-(2,3-dihydroxypropyloxy)-aminomethyl, *N*-cyclopropylaminomethyl, *N*-cyclopentylaminomethyl, *N*-cyclopenten-4-ylaminomethyl, *N*-(1(*R,S*)-hydroxy-cyclopent-2-yl)-aminomethyl, *N*-(1*S*-hydroxy-cyclopent-2-yl)-aminomethyl, *N*-(1*R*-hydroxy-cyclopent-2-yl)-aminomethyl, *N*-(1(*R,S*)-hydroxy-1-methyl-cyclopent-2-yl)-aminomethyl, *N*-(1*S*-hydroxy-1-methyl-cyclopent-2-yl)-aminomethyl, *N*-(1*R*-hydroxy-1-methyl-cyclopent-2-yl)-aminomethyl, *N*-(3,4-dihydroxy-cyclopentyl)-aminomethyl, *N*-(1-hydroxymethyl-cyclopent-1-yl)-aminomethyl, *N*-(2,3-dihydroxy-4-hydroxymethyl-cyclopentyl)-aminomethyl, *N*-(1(*R,S*)-methoxy-cyclopent-2-yl)-aminomethyl, *N*-(1*S*-methoxy-cyclopent-2-yl)-aminomethyl, *N*-(1*R*-methoxy-

cyclopent-2-yl)-aminomethyl, *N*-(1-carboxy-cyclopentyl)-aminomethyl, *N*-cyclohexylaminomethyl, *N*-(1(*R,S*)-hydroxy-cyclohex-2-yl)-aminomethyl, *N*-(1(*R*)-hydroxy-cyclohex-2-yl)-aminomethyl, *N*-(1(*S*)-hydroxy-cyclohex-2-yl)-aminomethyl, *N*-(*cis*-4-hydroxy-cyclohexyl)-aminomethyl, *N*-(*trans*-4-hydroxy-cyclohexyl)-aminomethyl, 1-[*N*-(*cis*-4-hydroxy-cyclohexyl)-amino]-ethyl, 1-[*N*-(*trans*-4-hydroxy-cyclohexyl)-amino]-ethyl, *N*-(1-hydroxymethyl-cyclohexyl)-aminomethyl, *N*-(2-cyclohexyl-cyclohexyl)-aminomethyl, *N*-{(2*R*,3*S*,4*R*,6*R*)-2-(hydroxymethyl)-3,4-dihydroxy-6-methoxy-tetrahydro-2*H*-pyran-5-yl}-aminomethyl, *N*-(cycloheptyl)-aminomethyl, *N*-(cyclooctyl)-aminomethyl, [(1r,3r,5*R*,7*R*)-tricyclo[3.3.1.1~3,7~]dec-2-ylamino]methyl, *N*-(1-benzyloxy-cyclopent-2-yl)-aminomethyl, *N*-[1-(cyclopropylaminocarbonyl)-cyclopentyl]-aminomethyl, $-CH_2NHC(CH_3)_2C(O)NH$(cyclohexyl), $-CH_2NHC(CH_3)_2C(O)NH(CH_2CH_3)$, *N*-(cyclopropylmethyl)-aminomethyl, *N*-(cyclohexylmethyl)-aminomethyl, *N*-(1-cyclohexylethyl)-aminomethyl, *N*-(imidazolyl)-aminomethyl, *N*-(1,3,5-triazinyl)-aminomethyl, *N*-(5-hydroxy-pyrazol-3-yl)-aminomethyl, *N*-(5-methyl-pyrazol-3-yl)-aminomethyl, *N*-(benzimidazolyl)-aminomethyl, *N*-(pyrimidin-2-yl)-aminomethyl, *N*-(pyridin-2-yl)-aminomethyl, *N*-(pyridin-3-yl)-aminomethyl, *N*-(pyridin-4-yl)-aminomethyl, *N*-indan-1-yl-aminomethyl, *N*-indan-2-yl-aminomethyl, phenylaminomethyl, *N*-(2-hydroxyphenyl)-aminomethyl, *N*-(3-hydroxyphenyl)-aminomethyl, *N*-(4-hydroxyphenyl)-aminomethyl, *N*-(2-methoxyphenyl)-aminomethyl, *N*-(3-methoxyphenyl)-aminomethyl, *N*-(4-methoxyphenyl)-aminomethyl, *N*-(2-fluorophenyl)-aminomethyl, *N*-(3-fluorophenyl)-aminomethyl, *N*-(4-fluorophenyl)-aminomethyl, *N*-(2-chlorophenyl)-aminomethyl, *N*-(3-chlorophenyl)-aminomethyl, *N*-(4-chlorophenyl)-aminomethyl, *N*-(3-methylcarbonylamino-phenyl)-aminomethyl, *N*-(4-methylcarbonylamino-phenyl)-aminomethyl, *N*-(2-aminophenyl)-aminomethyl, *N*-(3-aminophenyl)-aminomethyl, *N*-(4-aminophenyl)-aminomethyl, *N*-(2-methylsulfonylaminophenyl)-aminomethyl, *N*-(3-methylsulfonylaminophenyl)-aminomethyl, *N*-(4-methylsulfonylaminophenyl)-aminomethyl, *N*-(2-fluoro-4-hydroxy-phenyl)-aminomethyl, *N*-(3-fluoro-4-hydroxy-phenyl)-aminomethyl, *N*-(benzyl)-aminomethyl, *N*-(2-hydroxyphenylmethyl)-aminomethyl, *N*-(3-hydroxyphenylmethyl)-aminomethyl, *N*-(4-hydroxyphenylmethyl)-aminomethyl, *N*-(2-(*N*-methylpiperazin-1-yl)-phenylmethyl)-aminomethyl, *N*-(4-methyl-phenethyl)-aminomethyl, *N*-(1-hydroxy-3-phenyl-prop-2-yl)-aminomethyl, *N*-(pyrrolidin-2-ylmethyl)-aminomethyl, *N*-(*N*-ethyl-pyrrolidinylmethyl)-aminomethyl, *N*-(*N*-methyl-pyrrolidin-2-ylethyl)-aminomethyl, *N*-(pyrrolidinylpropyl)-aminomethyl, *N*-(1,1-dimethyl-2-pyrrolidin-1-yl-ethyl)-aminomethyl, *N*-(tetrahydrofuranylmethyl)-aminomethyl, *N*-(tetrahydro-2*H*-pyran-4-ylmethyl)-

aminomethyl, *N*-(tetrahydro-2*H*-pyranylethyl)-aminomethyl, *N*-(piperidin-4-ylmethyl)-aminomethyl, *N*-(*N*-methylpiperidin-4-ylmethyl)-aminomethyl, *N*-(*N*-*tert*-butoxycarbonylpiperidin-4-ylmethyl)-aminomethyl, *N*-(*N*-methylimidazol-5-ylmethyl)-aminomethyl, *N*-(*N*-methylimidazol-4-ylmethyl)-aminomethyl, *N*-[2-(imidazol-4-yl)-ethyl]-aminomethyl, *N*-[3-(imidazolyl)-propyl]-aminomethyl, *N*-(pyridin-3-ylethyl)-aminomethyl, *N*-(pyridin-4-ylethyl)-aminomethyl, *N*-(thien-2-ylethyl)-aminomethyl, *N*-(furan-2-ylethyl)-aminomethyl, *N*-(5-methyl-1,3,4-oxadiazol-2-ylmethyl)-aminomethyl, *N*-(2-indolin-3-ylethyl)-aminomethyl, 2-(*N,N*-dimethylamino)-ethylaminomethyl, 2-(*N,N*-dimethylamino)-1-methyl-ethylaminomethyl, 3-aminopropylaminomethyl, 3-(*N,N*-dimethylamino)-propylaminomethyl, 3-(*N,N*-diethylamino)-propylaminomethyl, *N*-(*N,N*-diisopropylaminoethyl)-aminomethyl, *N*-(*N,N*-dimethylaminobutyl)-aminomethyl, 3-hydroxypropylaminomethyl, *N*-(1,2-dihydroxypropyl)-aminomethyl, *N*-(1-amino-2-hydroxy-prop-3-yl)-aminomethyl, *N*-(*N*-ethoxycarbonyl-piperidin-4-yl)-aminomethyl, *N*-(*N*-benzylpiperidin-4-yl)-aminomethyl, *N*-(homopiperidin-3-yl)-aminomethyl, *N*-(*N*-benzylpyrrolidin-3-yl)-aminomethyl, *N*-(*N*-ethylpiperidin-3-yl)aminomethyl, 2,2,2-trifluoroethylaminomethyl, 3,3,3-trifluoropropylaminomethyl, 2,2,3,3,3-pentafluoropropylaminomethyl, $-CH_2N(CH_2CH_2OH)_2$, $-CH_2N(CH_3)(CH_2CH_2OH)$, $-CH_2NH(CH_2CH_2OH)$, $-CH_2NH(CH_2CH_2CH_2CH_2OH)$, $-CH_2NH(C(CH_3)_2CH_2OH)$, $-CH_2N(CH_3)$(*N*-methyl-pyrrolidin-3-yl), $-C(O)NH_2$, $-C(O)NHCH_2CH{=}CH_2$, $-C(O)NHCH_2CH(OH)CH_2OH$, *N*-(phenyloxyethyl)-aminomethyl, $-CH_2NHC(O)CH_3$, $-CH(CH_3)NHC(O)CH_3$, $-CH(CH_3)NHC(O)C(OCH_3)(CF_3)$phenyl, cyclopentyl, 1-amino-cyclopentyl, (*cis,trans*)-2-amino-cyclopentyl, (*cis,trans*)-2-amino-cyclopentyl, *cis*-2-amino-cyclopentyl, *trans*-2-amino-cyclopentyl, (*cis,trans*)-2-hydroxy-cyclohexyl, *cis*-2-hydroxy-cyclohexyl, *trans*-2-hydroxy-cyclohexyl, (*cis,trans*)-2-amino-cyclohexyl, *cis*-2-amino-cyclohexyl, *trans*-2-amino-cyclohexyl, azetidin-3-yl, pyrrolidinyl, *N*-methyl-pyrrolidin-2-yl, *N*-ethyl-pyrrolidin-2-yl, 3-(dimethylamino)-pyrrolidinyl, piperidinyl, 2-methyl-piperidin-6-yl, *N*-methylpiperidin-2-yl, *N*-*tert*-butoxycarbonylpiperidin-2-yl, piperazin-2-yl, pyrrol-1-yl, pyrrol-2-yl, pyrrol-3-yl, imidazol-1-yl, imidazol-2-yl, imidazol-4-yl, imidazol-5-yl, *N*-methyl-imidazol-2-yl, 5-methyl-imidazol-2-yl, 1,2,4-triazol-3-yl, thiazol-2-yl, 2-aminopyrimidin-3-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, benzimidazolyl, imidazol-1-ylmethyl, imidazol-2-ylmethyl, triazol-1-ylmethyl, (5-amino-3-methyl-pyrazol-3-yl)-methyl, phenoxymethyl, 2-hydroxyethyloxymethyl, methylsulfonylaminomethyl, 1-(methoxycarbonylamino)-ethyl, 1-amino-1-phenyl-methyl, or 1-amino-3-hydroxy-propyl.

[00122] Another specific embodiment of the Invention (A11) is that where the compound of Formula I is selected from Group A where R^3 and R^4 together with the carbon to which they are attached form C(O) or C(=NOH). More specifically, X and R^7 are halo; A is phenylene optionally substituted with R^{10} and R^{12} where R^{10} and R^{12} are independently hydrogen or halo; R^1, R^2, R^5 and R^6 are hydrogen; and R^3 and R^4 together with the carbon to which they are attached form C(O) or C(=NOH).

[00123] Another specific embodiment of the Invention (A12) is that where the compound of Formula I is selected from Group A where X and R^7 are halo; A is phenylene optionally substituted with R^{10} and R^{12} where R^{10} and R^{12} are independently hydrogen or halo; and R^1, R^2, R^4, R^5 and R^6 are hydrogen.

[00124] Another specific embodiment of the Invention (A13) is that where the compound of Formula I is selected from Group A where A is phenylene.

[00125] Another specific embodiment of the Invention (A14) is that where the compound of Formula I is selected from Group A where R^1 is hydrogen and R^2 is alkyl substituted with $-NR^8R^{8'}$ where R^8 and $R^{8'}$ and all other groups are as defined in the Summary of the Invention for a compound of Group A.

[00126] Another specific embodiment of the Invention (A15) is that where the compound of Formula I is selected from Group A where A is phenylene; R^7 is iodo or bromo; X is fluoro or chloro; and R^1, R^2, R^5, and R^6 are hydrogen; and R^{10}, R^{12}, R^{14}, and R^{16} are independently hydrogen or fluoro. More specifically, R^{10} is 3-fluoro and R^{12}, R^{14}, and R^{16} are hydrogen or halo; R^{10} is 3-fluoro, R^{12} is 4-fluoro, and R^{14} and R^{16} are hydrogen; R^{10} is 4-fluoro, R^{12} is 5-fluoro, and R^{14} and R^{16} are hydrogen; R^{10} is 4-fluoro, R^{12} is 6-fluoro, and R^{14} and R^{16} are hydrogen; or R^{12} is 4-fluoro and R^{10}, R^{14}, and R^{16} are hydrogen.

[00127] In another embodiment of the invention is a compound of Formula selected form Group A where R^3 is hydroxy and R^4 is heterocycloalkyl, alkyl, or heteroaryl, where the alkyl is optionally substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen or alkyl and $R^{8'}$ is hydrogen, alkyl, or cycloalkyl where the cycloalkyl is optionally substituted with groups independently selected from hydroxy and alkyl) and the heteroaryl is optionally substituted with alkyl. Specifically, R^3 is hydroxy and R^4 is heterocycloalkyl or alkyl, where the alkyl is optionally substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen or alkyl and $R^{8'}$ is hydrogen, alkyl, or cycloalkyl where the cycloalkyl is optionally substituted with groups independently selected from hydroxy and alkyl).

[00128] In another embodiment of the Invention (B1) the compound of Formula I is selected from Group B where all groups are as defined in the Summary of the Invention.

[00129] In another embodiment of the invention (B2), X and R^7 are halo; and all other groups are as defined in the Summary of the Invention for a compound of Group B. Specifically, X is fluoro or chloro and R^7 is iodo or bromo.

[00130] In another embodiment of the invention (B3), the compound is selected from Group B where R^3 is halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl; where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$ and R^4 is as defined in the Summary of the Invention; or R^3 and R^4 together with the carbon to which they are attached form C(O) or C(=NOH); and all other groups are as defined in the Summary of the Invention for a compound of Group B. More specifically, R^1, R^2, R^5 and R^6 are hydrogen; and X and R^7 are halo.

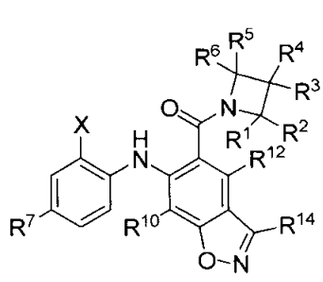
[00131] In another embodiment of the invention (B4), the compound is selected from Group B where R^3 and R^4 are independently halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl; where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; or R^3 and R^4 together

with the carbon to which they are attached form C(O) or C(=NOH); and all other groups are as defined in the Summary of the Invention for a compound of Group B. More specifically, R^1, R^2, R^5 and R^6 are hydrogen; and X and R^7 are halo.

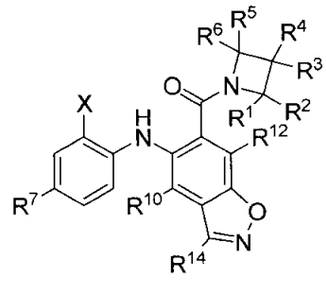
[00132] In another embodiment of the invention (B5), A is heteroarylene selected from thien-diyl, benzo[*d*]isoxazol-diyl, benzo[*d*]isothiazol-diyl, 1*H*-indazol-diyl (optionally substituted at the N1 position with R^{19} where R^{19} is as defined in the Summary of the Invention for a compound of Group B), benzo[*d*]oxazol-diyl, benzo[*d*]thiazol-diyl, 1*H*-benzo[*d*]imidazol-diyl (optionally substituted at the N1 position with R^{19} where R^{19} is as defined in the Summary of the Invention for a compound of Group B), 1*H*-benzo[*d*][1,2,3]triazol-diyl (optionally substituted at the N1 position with R^{19} where R^{19} is as defined in the Summary of the Invention for a compound of Group B), imidazo[1,2-*a*]pyridin-diyl, cinnolin-diyl, quinolin-diyl, pyridin-diyl, 1-oxido-pyridin-diyl, [1,2,4]triazolo[4,3-a]pyridin-diyl, and 2,3-dihydroimidazo[1,2-a]pyridin-diyl; and A is further optionally substituted with one, two, three, or four groups selected from R^{10}, R^{12}, R^{14}, and R^{16} where R^{10}, R^{12}, R^{14}, and R^{16} and all other groups are as defined in the Summary of the Invention for a compound of Group B. More specifically A is selected from thien-3,4-diyl, benzo[*d*]isoxazol-5,6-diyl, benzo[*d*]isothiazol-5,6-diyl, 1*H*-indazol-5,6-diyl (optionally substituted at the N1 position with R^{19} where R^{19} is alkyl or alkenyl), benzo[*d*]oxazol-5,6-diyl, benzo[*d*]thiazol-5,6-diyl, 1*H*-benzo[d]imidazol-5,6-diyl (optionally substituted at the N1 position with R^{19} where R^{19} is alkyl or alkenyl), 1*H*-benzo[*d*][1,2,3]triazol-5,6-diyl (optionally substituted at the N1 position with R^{19} where R^{19} is alkyl or alkenyl), imidazo[1,2-*a*]pyridin-5,6-diyl, cinnolin-6,7-diyl, quinolin-6,7-diyl, pyridin-3,4-diyl, 1-oxido-pyridin-3,4-diyl, [1,2,4]triazolo[4,3-a]pyridin-6,7-diyl, and 2,3-dihydroimidazo[1,2-a]pyridin-6,7-diyl.

[00133] In another embodiment of the Invention (B6), the compound of Formula I is selected from Group B where A is thien-diyl and X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, and R^{12} are as defined in the Summary of the Invention for a compound of Group B. More specifically A is thien-3,4-diyl; R^{10} and R^{12} are hydrogen; X and R^7 are halo; and R^1, R^2, R^5, and R^6 are hydrogen. Even more specifically, X is fluoro or chloro; R^7 is iodo or bromo; R^3 is hydrogen or hydroxy; and R^4 is $-NR^8R^{8'}$ (where R^8 and $R^{8'}$ are independently hydrogen or alkyl), heterocycloalkyl, heteroaryl (optionally substituted with alkyl), or alkyl where the alkyl is optionally substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen or alkyl and $R^{8'}$ is hydrogen, alkyl, or cycloalkyl where the cycloalkyl is optionally substituted with one or two groups independently selected from hydroxy and alkyl).

[00134] In another embodiment (B7), the compound is of Formula I(c) or I(d)



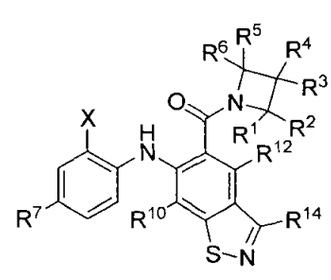
I(c);



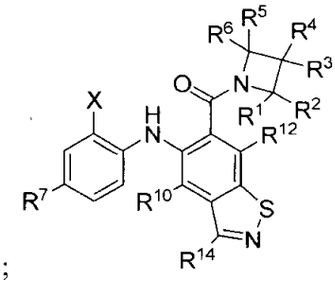
I(d);

where X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{12} and R^{14} are as defined in the Summary of the Invention for a compound of Group B. More specifically, R^1, R^2, R^5, and R^6 are hydrogen; X and R^7 are halo; R^3 and R^4 are as defined in the Summary of the Invention for Group B; and R^{10}, R^{12}, and R^{14} are independently hydrogen, halo, or alkyl. Even more specifically, X is fluoro or chloro and R^7 is iodo or bromo; R^{10} is hydrogen or halo, more specifically hydrogen or fluoro; R^{12} is hydrogen; R^{14} is hydrogen or alkyl; and R^3 is hydroxy. Yet even more specifically, R^4 is heterocycloalkyl, alkyl, or heteroaryl, where the alkyl is optionally substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen or alkyl and $R^{8'}$ is hydrogen, alkyl, or cycloalkyl where the cycloalkyl is optionally substituted with groups independently selected from hydroxy and alkyl) and the heteroaryl is optionally substituted with alkyl. Yet even more specifically, R^4 is piperidinyl, pyrrolidinyl, 1(*R,S*)-amino-ethyl, 1(*R*)-amino-ethyl, 1(*S*)-amino-ethyl, 1(*R,S*)-(methylamino)-ethyl, 1(*R*)-(methylamino)-ethyl, 1(*S*)-(methylamino)-ethyl, 1(*R.S*)-(dimethylamino)-ethyl, 1(*R*)-(dimethylamino)-ethyl, 1(*S*)-(dimethylamino)-ethyl, 1(*R,S*)-(3,4-*cis*-dihydroxy-cyclopentylamino)-ethyl, 1(*R*)-(3,4-*cis*-dihydroxy-cyclopentylamino)-ethyl, or 1(*S*)-(3,4-*cis*-dihydroxy-cyclopentylamino)-ethyl.

[00135] In another embodiment of the Invention (B8), the compound is of Formula I(e) or I(f):



I(e);

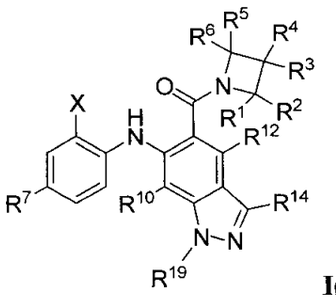


I(f);

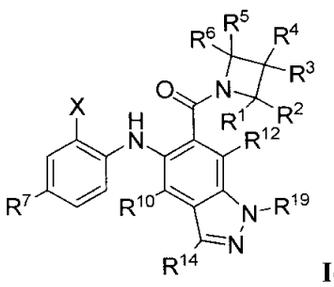
where X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{12} and R^{14} are as defined in the Summary of the Invention for a compound of Group B. More specifically, R^1, R^2, R^5, and R^6 are hydrogen; X and R^7 are halo; R^3 and R^4 are as defined in the Summary of the Invention for Group B; and R^{10}, R^{12}, and R^{14} are independently hydrogen, halo, or alkyl. Even more specifically, X is

fluoro or chloro and R^7 is iodo or bromo; R^{10} is hydrogen or halo, more specifically hydrogen or fluoro; R^{12} and R^{14} are hydrogen; R^3 is hydroxy; and R^4 is heterocycloalkyl, alkyl, or heteroaryl, where the alkyl is optionally substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen or alkyl and $R^{8'}$ is hydrogen, alkyl, or cycloalkyl where the cycloalkyl is optionally substituted with one or two groups independently selected from hydroxy and alkyl) and the heteroaryl is optionally substituted with alkyl.

[00136] In another embodiment of the Invention (B9), the compound is of Formula I(g) or I(h):



I(g);



I(h);

where X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{12}, R^{14}, and R^{19} are as defined in the Summary of the Invention for a compound of Group B.

[00137] In a more specific embodiment of embodiment B9, the compound is of formula I(g) or I(h) where

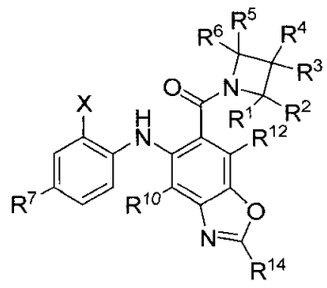
R^3 is halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, cycloalkyl, heteroaryl, or heterocycloalkyl; where the cycloalkyl, heteroaryl, and heterocycloalkyl are optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; and R^4 is as defined in the Summary of the Invention; or R^3 and R^4 together with the carbon to which they are attached form C(O) or C(=NOH); and

all other groups are as defined in the Summary of the Invention for a compound of Group B.

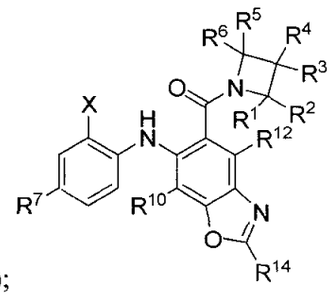
[00138] In a more specific em bodiment of embodiment B9, the compound is of formula I(g) or I(h) where R^3 is hydroxy and all other groups are as defined in the Summary of the Invention for a compound of Group B.

[00139] In a more specific embodiment of embodiment B9, the compound is of formula I(g) or I(h) where R^1, R^2, R^5, and R^6 are hydrogen; X and R^7 are halo; R^3 and R^4 are as defined in the Summary of the Invention for Group B; R^{10}, R^{12}, and R^{14} are independently hydrogen, halo, or alkyl; and R^{19} is hydrogen or methyl. Even more specifically, X is fluoro or chloro and R^7 is iodo or bromo; R^{10} is hydrogen or halo, more specifically hydrogen or fluoro; R^{12} and R^{14} are hydrogen; R^3 is hydroxy; and R^4 is heterocycloalkyl, alkyl, or heteroaryl, where the alkyl is optionally substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen or alkyl and $R^{8'}$ is hydrogen, alkyl, or cycloalkyl where the cycloalkyl is optionally substituted with one or two groups independently selected from hydroxy and alkyl) and the heteroaryl is optionally substituted with alkyl.

[00140] In another embodiment of the Invention (B10), the compound is of Formula I(i) or I(j):



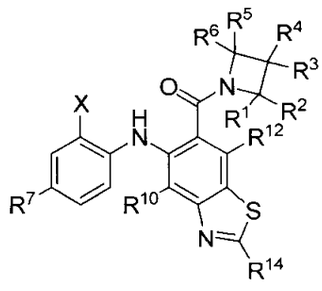
I(i);



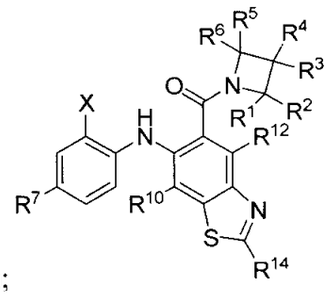
I(j);

where X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{12} and R^{14} are as defined in the Summary of the Invention for a compound of Group B. More specifically, R^1, R^2, R^5, and R^6 are hydrogen; X and R^7 are halo; R^3 and R^4 are as defined in the Summary of the Invention for Group B; and R^{10}, R^{12}, and R^{14} are independently hydrogen, halo, or alkyl. Even more specifically, X is fluoro or chloro and R^7 is iodo or bromo; R^{10} is hydrogen or halo, more specifically hydrogen or fluoro; R^{12} and R^{14} are hydrogen; R^3 is hydroxy; and R^4 is heterocycloalkyl, alkyl, or heteroaryl, where the alkyl is optionally substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen or alkyl and $R^{8'}$ is hydrogen, alkyl, or cycloalkyl where the cycloalkyl is optionally substituted with one or two groups independently selected from hydroxy and alkyl) and the heteroaryl is optionally substituted with alkyl.

[00141] In another embodiment of the Invention (B11), the compound is of Formula I(k) or I(m):



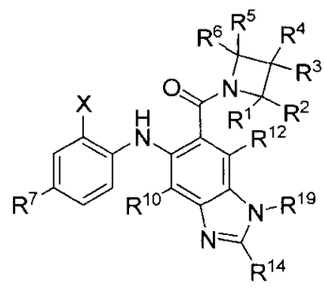
I(k);



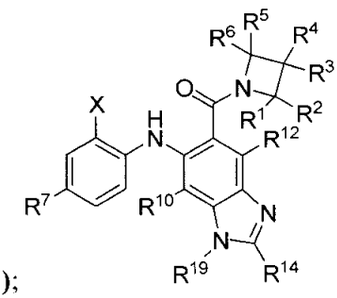
I(m);

where X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{12} and R^{14} are as defined in the Summary of the Invention for a compound of Group B. More specifically, R^1, R^2, R^5, and R^6 are hydrogen; X and R^7 are halo; R^3 and R^4 are as defined in the Summary of the Invention for Group B; and R^{10}, R^{12}, and R^{14} are independently hydrogen, halo, or alkyl. Even more specifically, X is fluoro or chloro and R^7 is iodo or bromo; R^{10} is hydrogen or halo, more specifically hydrogen or fluoro; R^{12} and R^{14} are hydrogen; R^3 is hydroxy; and R^4 is heterocycloalkyl, alkyl, or heteroaryl, where the alkyl is optionally substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen or alkyl and $R^{8'}$ is hydrogen, alkyl, or cycloalkyl where the cycloalkyl is optionally substituted with one or two groups independently selected from hydroxy and alkyl) and the heteroaryl is optionally substituted with alkyl.

[00142] In another embodiment of the Invention (B12), the compound is of Formula I(n) or I(o):



I(n);



I(o);

where X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{12}, R^{14}, and R^{19} are as defined in the Summary of the Invention for a compound of Group B.

[00143] In a more specific embodiment of embodiment B12, the compound is of formula I(n) or I(o) where R^7 is halo or alkyl; and all other groups are as defined in the Summary of the Invention for a compound of Group B. More specifically, R^7 is iodo or bromo.

[00144] In a more specific embodiment of embodiment B12, the compound is of formula I(n) or I(o) where X is halo, haloalkyl, or haloalkoxy; and all other groups are as defined in

the Summary of the Invention for a compound of Group B. More specifically, X is halo. Even more specifically X is fluoro or chloro.

[00145] In a more specific embodiment of embodiment B12, the compound is of formula I(n) or I(o) where

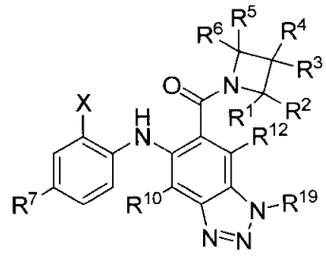
R^3 is halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl; where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; and R^4 is as defined in the Summary of the Invention; or

R^3 and R^4 together with the carbon to which they are attached form C(O) or C(=NOH); and unless otherwise indicated, R^8 and $R^{8'}$ are as defined in the Summary of the Invention; and all other groups are as defined in the Summary of the Invention for a compound of Group B.

[00146] In a more specific embodiment of embodiment B12, the compound is of formula I(n) or I(o) where R^{19} is alkyl; R^1, R^2, R^5, and R^6 are hydrogen; X and R^7 are halo; R^3 and R^4 are as defined in the Summary of the Invention for Group B; and R^{10}, R^{12}, and R^{14} are independently hydrogen or halo. Even more specifically, R^{19} is methyl; X is fluoro or chloro and R^7 is iodo or bromo; R^{10} is hydrogen or fluoro; R^{12} and R^{14} are hydrogen; and R^3 is hydroxy. Yet even more specifically, R^4 is heterocycloalkyl, alkyl, or heteroaryl, where the alkyl is optionally substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen or alkyl and $R^{8'}$ is hydrogen, alkyl, or cycloalkyl where the cycloalkyl is optionally substituted with one or two groups independently selected from hydroxy and alkyl) and the heteroaryl is optionally substituted with alkyl. Yet even more specifically, R^4 is piperidinyl, pyrrolidinyl, 1(*R,S*)-amino-ethyl, 1(*R*)-amino-ethyl, 1(*S*)-amino-ethyl, 1(*R,S*)-(methylamino)-ethyl, 1(*R*)-(methylamino)-ethyl, 1(*S*)-(methylamino)-ethyl, 1(*R,S*)-(dimethylamino)-ethyl, 1(*R*)-(dimethylamino)-ethyl, 1(*S*)-(dimethylamino)-ethyl, 1(*R,S*)-(3,4-cis-dihydroxy-

cyclopentylamino)-ethyl, 1(*R*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl, or 1(*S*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl.

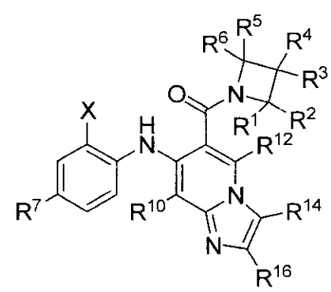
[00147] In another embodiment of the Invention (B13), the compound is of Formula I(p):



I(p)

where X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{12}, and R^{19} are as defined in the Summary of the Invention for a compound of Group B. More specifically, R^1, R^2, R^5, and R^6 are hydrogen; X and R^7 are halo; R^3 and R^4 are as defined in the Summary of the Invention for Group B; and R^{10} and R^{12} are independently hydrogen, halo, or alkyl. Even more specifically, X is fluoro or chloro; R^7 is iodo or bromo; R^{10} is hydrogen or halo, more specifically hydrogen or fluoro; R^{12} is hydrogen; R^{19} is hydrogen or alkyl, more specifically hydrogen or methyl; R^3 is hydroxy. Even more specifically, R^4 is heterocycloalkyl, alkyl, or heteroaryl, where the alkyl is optionally substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen or alkyl and $R^{8'}$ is hydrogen, alkyl, or cycloalkyl where the cycloalkyl is optionally substituted with one or two groups independently selected from hydroxy and alkyl) and the heteroaryl is optionally substituted with alkyl. Yet even more specifically, R^4 is piperidinyl, pyrrolidinyl, 1(*R,S*)-amino-ethyl, 1(*R*)-amino-ethyl, 1(*S*)-amino-ethyl, 1(*R,S*)-(methylamino)-ethyl, 1(*R*)-(methylamino)-ethyl, 1(*S*)-(methylamino)-ethyl, 1(*R,S*)-(dimethylamino)-ethyl, 1(*R*)-(dimethylamino)-ethyl, 1(*S*)-(dimethylamino)-ethyl, 1(*R,S*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl, 1(*R*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl, or 1(*S*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl.

[00148] In another embodiment of the Invention (B14), the compound is of Formula I(q):



I(q)

where X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{12} R^{14}, and R^{16} are as defined in the Summary of the Invention for a compound of Group B.

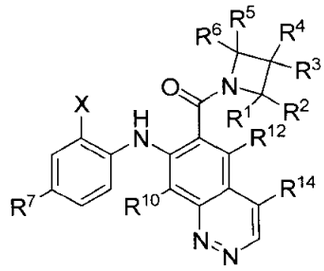
[00149] In a more specific embodiment of embodiment B14, the compound is of formula I(q) where

R^3 is halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl; where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; and R^4 is as defined in the Summary of the Invention; or

R^3 and R^4 together with the carbon to which they are attached form C(O) or C(=NOH); and all other groups are as defined in the Summary of the Invention for a compound of Group B.

[00150] In a more specific embodiment of embodiment B14, the compound is of formula I(q) where R^1, R^2, R^5, and R^6 are hydrogen; X and R^7 are halo; R^3 and R^4 are as defined in the Summary of the Invention for Group B; and R^{10}, R^{12}, R^{14}, and R^{16} are independently hydrogen or halo. Even more specifically, R^{10} is halo and R^{12}, R^{14}, and R^{16} are hydrogen. Even more specifically, X is fluoro or chloro; R^7 is iodo or bromo; R^{10} is chloro; and R^3 is hydroxy. Even more specifically, R^4 is heterocycloalkyl, alkyl, or heteroaryl, where the alkyl is optionally substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen or alkyl and $R^{8'}$ is hydrogen, alkyl, or cycloalkyl where the cycloalkyl is optionally substituted with one or two groups independently selected from hydroxy and alkyl) and the heteroaryl is optionally substituted with alkyl. Yet even more specifically, R^4 is piperidinyl, pyrrolidinyl, benzimidazolyl, 1(*R,S*)-amino-ethyl, 1(*R*)-amino-ethyl, 1(*S*)-amino-ethyl, 1(*R,S*)-(methylamino)-ethyl, 1(*R*)-(methylamino)-ethyl, 1(*S*)-(methylamino)-ethyl, 1(*R,S*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl, 1(*R*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl, or 1(*S*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl.

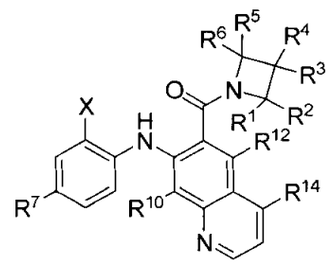
[00151] In another embodiment of the Invention (B15), the compound is of Formula I(r):



I(r)

where X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{12} and R^{14} are as defined in the Summary of the Invention for a compound of Group B. More specifically, R^1, R^2, R^5, and R^6 are hydrogen; X and R^7 are halo; R^3 and R^4 are as defined in the Summary of the Invention for Group B; R^{10} and R^{12} are independently hydrogen, halo, or alkyl; and R^{14} is hydrogen, halo, alkyl, or amino. Even more specifically, X is fluoro or chloro; R^7 is iodo or bromo; R^{10} is hydrogen or halo, more specifically hydrogen or fluoro; R^{12} is hydrogen; R^{14} is hydrogen, alkyl, or amino, more specifically hydrogen, methyl, or amino; R^3 is hydroxy. Even more specifically, R^4 is heterocycloalkyl, alkyl, or heteroaryl, where the alkyl is optionally substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen or alkyl and $R^{8'}$ is hydrogen, alkyl, or cycloalkyl where the cycloalkyl is optionally substituted with one or two groups independently selected from hydroxy and alkyl) and the heteroaryl is optionally substituted with alkyl. Yet even more specifically, R^4 is piperidinyl, pyrrolidinyl, 1(*R,S*)-amino-ethyl, 1(*R*)-amino-ethyl, 1(*S*)-amino-ethyl, 1(*R,S*)-(methylamino)-ethyl, 1(*R*)-(methylamino)-ethyl, 1(*S*)-(methylamino)-ethyl, 1(*R,S*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl, 1(*R*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl, or 1(*S*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl.

[00152] In another embodiment of the Invention (B16), the compound is of Formula I(s):

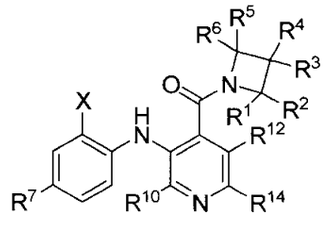


I(s)

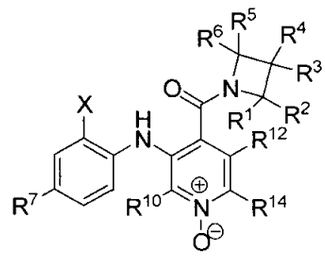
where X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{12} and R^{14} are as defined in the Summary of the Invention for a compound of Group B. More specifically, R^1, R^2, R^5, and R^6 are hydrogen; X and R^7 are halo; R^3 and R^4 are as defined in the Summary of the Invention for Group B; and

R^{10} and R^{12} are independently hydrogen, halo, or alkyl; and R^{14} is hydrogen, halo, alkyl, or amino. Even more specifically, X is fluoro or chloro and R^7 is iodo or bromo; R^{10} is hydrogen or halo, more specifically hydrogen or fluoro; R^{12} is hydrogen; R^{14} is hydrogen, methyl, or amino; R^3 is hydroxy; and R^4 is heterocycloalkyl, alkyl, or heteroaryl, where the alkyl is optionally substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen or alkyl and $R^{8'}$ is hydrogen, alkyl, or cycloalkyl where the cycloalkyl is optionally substituted with one or two groups independently selected from hydroxy and alkyl) and the heteroaryl is optionally substituted with alkyl.

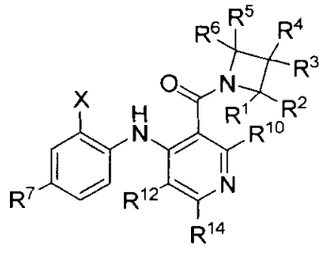
[00153] In another embodiment of the Invention (B18), the compound is of Formula I(u), I(v), I(w), or I(x):



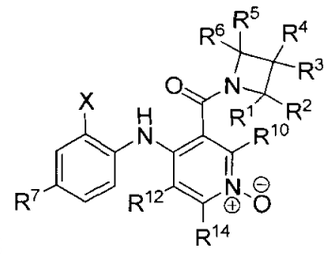
I(u);



I(v);



I(w);



I(x);

where X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{12} and R^{14} are as defined in the Summary of the Invention for a compound of Group B.

[00154] In a more specific embodiment of embodiment B18, the compound is of formula I(u), I(v), I(w), or I(x) where R^3 is halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl; where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted

heteroarylalkyl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; and R^4 is as defined in the Summary of the Invention for a compound of Group B; or R^3 and R^4 together with the carbon to which they are attached form C(O) or C(=NOH); and all other groups are as defined in the Summary of the Invention for a compound of Group B.

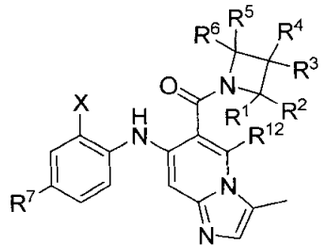
[00155] In a more specific embodiment of embodiment B18, the compound is of formula I(t), I(u), I(v), or I(w) where R^3 and R^4 are independently halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl; where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; or R^3 and R^4 together with the carbon to which they are attached form C(O) or C(=NOH); and all other groups are as defined in the Summary of the Invention for a compound of Group B.

[00156] In a more specific embodiment of embodiment B18, the compound is of formula I(u), I(v), I(w), or I(x) where R^4 is heterocycloalkyl, heteroaryl (optionally substituted with alkyl), or alkyl where the alkyl is optionally substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen or alkyl and $R^{8'}$ is hydrogen, alkyl, or cycloalkyl where the cycloalkyl is optionally substituted with one or two groups independently selected from hydroxy and alkyl). More specifically, R^4 is piperidinyl, pyrrolidinyl, 1(*R,S*)-amino-propyl, 1(*R*)-amino-propyl, 1(*S*)-amino-propyl, 1(*R,S*)-(methylamino)-propyl, 1(*R*)-(methylamino)-propyl, 1(*S*)-(methylamino)-propyl, 1(*R.S*)-(3,4-cis-dihydroxy-cyclopentylamino)-propyl, 1(*R*)-(3,4-*cis*-dihydroxy-cyclopentylamino)-propyl, or 1(*S*)-(3,4-cis-dihydroxy-cyclopentylamino)-propyl.

[00157] In a more specific embodiment of embodiment B18, the compound is of formula I(u), I(v), I(w), or I(x) where R^1, R^2, R^5, and R^6 are hydrogen; X and R^7 are halo; R^3 and R^4 are as defined in the Summary of the Invention for Group B; and R^{10}, R^{12}, and R^{14} are

independently hydrogen, halo, or alkyl. Even more specifically, X is fluoro or chloro; R^7 is iodo or bromo; R^{10} is hydrogen or halo, more specifically hydrogen or fluoro; R^{12} and R^{14} are hydrogen; and R^3 is hydroxy. Even more specifically R^4 is heterocycloalkyl, alkyl, or heteroaryl, where the alkyl is optionally substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen or alkyl and $R^{8'}$ is hydrogen, alkyl, or cycloalkyl where the cycloalkyl is optionally substituted with one or two groups independently selected from hydroxy and alkyl) and the heteroaryl is optionally substituted with alkyl.

[00158] In another embodiment of the Invention (B19), the compound is of Formula I(cc)



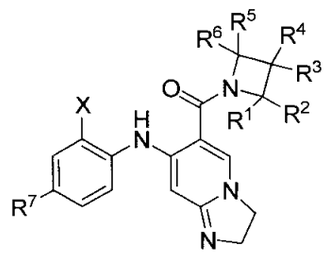
I(cc)

where X, R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are as defined in the Summary of the Invention for a compound of Group B. Specifically, R^1, R^2, R^5, and R^6 are hydrogen; and X and R^7 are halo. More specifically, X is fluoro or chloro; and R^3 is hydrogen or hydroxy; R^7 is iodo or bromo. Even more specifically, R^4 is heterocycloalkyl, alkyl, or heteroaryl, where the alkyl is optionally substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen or alkyl and $R^{8'}$ is hydrogen, alkyl, or cycloalkyl where the cycloalkyl is optionally substituted with one or two groups independently selected from hydroxy and alkyl) and the heteroaryl is optionally substituted with alkyl. Yet even more specifically, R^4 is piperidinyl, pyrrolidinyl, benzimidazolyl, *N*-methyl-benzimidazolyl, methylaminomethyl, 1(*R,S*)-amino-ethyl, 1(*R*)-amino-ethyl, 1(*S*)-amino-ethyl, 1(*R,S*)-(methylamino)-ethyl, 1(*R*)-(methylamino)-ethyl, 1(*S*)-(methylamino)-ethyl, 1(*R,S*)-(dimethylamino)-ethyl, 1(*R*)-(dimethylamino)-ethyl, 1(*S*)-(dimethylamino)-ethyl, 1(*R,S*)-amino-propyl, 1(*R*)-amino-propyl, 1(*S*)-amino-propyl, 1(*R,S*)-(methylamino)-propyl, 1(*R*)-(methylamino)-propyl, 1(*S*)-(methylamino)-propyl, 1(*R,S*)-(dimethylamino)-propyl, 1(*R*)-(dimethylamino)-propyl, 1(*S*)-(dimethylamino)-propyl, 1(*R,S*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl, 1(*R*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl, or 1(*S*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl.

[00159] In a specific embodiment (B19a) of embodiment B19 is that where R^4 is heterocycloalkyl or alkyl where the alkyl is optionally substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen or alkyl and $R^{8'}$ is hydrogen, alkyl, or cycloalkyl where the cycloalkyl is optionally

substituted with one or two groups independently selected from hydroxy and alkyl). Specifically, R^4 is piperidinyl, pyrrolidinyl, methylaminomethyl, 1(*R,S*)-amino-ethyl, 1(*R*)-amino-ethyl, 1(*S*)-amino-ethyl, 1(*R,S*)-(methylamino)-ethyl, 1(*R*)-(methylamino)-ethyl, 1(*S*)-(methylamino)-ethyl, 1(*R,S*)-(dimethylamino)-ethyl, 1(*R*)-(dimethylamino)-ethyl, 1(*S*)-(dimethylamino)-ethyl, 1(*R,S*)-amino-propyl, 1(*R*)-amino-propyl, 1(*S*)-amino-propyl, 1(*R,S*)-(methylamino)-propyl, 1(*R*)-(methylamino)-propyl, 1(*S*)-(methylamino)-propyl, 1(*R,S*)-(dimethylamino)-propyl, 1(*R*)-(dimethylamino)-propyl, 1(*S*)-(dimethylamino)-propyl, 1(*R,S*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl, 1(*R*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl, or 1(*S*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl.

[00160] In another embodiment of the Invention (B20), the compound is of Formula I(dd)



I(dd)

where X, R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are as defined in the Summary of the Invention for a compound of Group B. Specifically, R^1, R^2, R^5, and R^6 are hydrogen; and X and R^7 are halo. More specifically, X is fluoro or chloro; and R^3 is hydrogen or hydroxy; R^7 is iodo or bromo. Even more specifically, R^4 is heterocycloalkyl, alkyl, or heteroaryl, where the alkyl is optionally substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen or alkyl and $R^{8'}$ is hydrogen, alkyl, or cycloalkyl where the cycloalkyl is optionally substituted with one or two groups independently selected from hydroxy and alkyl) and the heteroaryl is optionally substituted with alkyl. Yet even more specifically, R^4 is piperidinyl, pyrrolidinyl, benzimidazolyl, *N*-methyl-benzimidazolyl, methylaminomethyl, 1(*R,S*)-amino-ethyl, 1(*R*)-amino-ethyl, 1(*S*)-amino-ethyl, 1(*R,S*)-(methylamino)-ethyl, 1(*R*)-(methylamino)-ethyl, 1(*S*)-(methylamino)-ethyl, 1(*R,S*)-(dimethylamino)-ethyl, 1(*R*)-(dimethylamino)-ethyl, 1(*S*)-(dimethylamino)-ethyl, 1(*R,S*)-amino-propyl, 1(*R*)-amino-propyl, 1(*S*)-amino-propyl, 1(*R,S*)-(methylamino)-propyl, 1(*R*)-(methylamino)-propyl, 1(*S*)-(methylamino)-propyl, 1(*R,S*)-(dimethylamino)-propyl, 1(*R*)-(dimethylamino)-propyl, 1(*S*)-(dimethylamino)-propyl, 1(*R,S*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl, 1(*R*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl, or 1(*S*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl.

[00161] In a specific embodiment (B20a) of embodiment B20 is that where R^4 is heterocycloalkyl or alkyl where the alkyl is optionally substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen or alkyl and $R^{8'}$ is hydrogen, alkyl, or cycloalkyl where the cycloalkyl is optionally substituted with one or two groups independently selected from hydroxy and alkyl). Specifically, R^4 is piperidinyl, pyrrolidinyl, methylaminomethyl, 1(*R,S*)-amino-ethyl, 1(*R*)-amino-ethyl, 1(*S*)-amino-ethyl, 1(*R,S*)-(methylamino)-ethyl, 1(*R*)-(methylamino)-ethyl, 1(*S*)-(methylamino)-ethyl, 1(*R,S*)-(dimethylamino)-ethyl, 1(*R*)-(dimethylamino)-ethyl, 1(*S*)-(dimethylamino)-ethyl, 1(*R,S*)-amino-propyl, 1(*R*)-amino-propyl, 1(*S*)-amino-propyl, 1(*R,S*)-(methylamino)-propyl, 1(*R*)-(methylamino)-propyl, 1(*S*)-(methylamino)-propyl, 1(*R,S*)-(dimethylamino)-propyl, 1(*R*)-(dimethylamino)-propyl, 1(*S*)-(dimethylamino)-propyl, 1(*R,S*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl, 1(*R*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl, or 1(*S*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl.

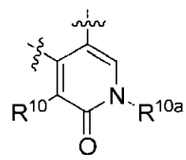
[00162] In one embodiment of the Invention (C1), the compound of Formula I is selected from Group C where all groups are as defined in the Summary of the Invention.

[00163] In another embodiment of the invention (C2), X and R^7 are halo; and all other groups are as defined for a compound selected from Group C.

[00164] In another embodiment of the invention (C3), the compound is selected from Group C where R^3 is halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl; where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; and R^4 is as defined in the Summary of the Invention; or R^3 and R^4 together with the carbon to which they are attached form C(O) or C(=NOH); and all other groups are as defined in the Summary of the Invention for a compound of Group C. More specifically, R^1, R^2, R^5 and R^6 are hydrogen; and X and R^7 are halo.

[00165] In another embodiment of the invention (C4), the compound is selected from Group C where R^3 and R^4 are independently halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl; where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; or R^3 and R^4 together with the carbon to which they are attached form C(O) or C(=NOH); and all other groups are as defined in the Summary of the Invention for a compound of Group C. More specifically, R^1, R^2, R^5 and R^6 are hydrogen; and X and R^7 are halo.

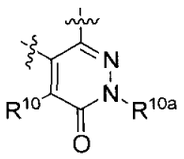
[00166] In another embodiment of the invention (C5), A is



and X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, and R^{10a} are as defined in the Summary of the invention for a compound of Group C. More specifically, R^1, R^2, R^5, and R^6 are hydrogen; X and R^7 are halo; R^{10} is hydrogen or halo; and R^{10a} is alkyl. Even more specifically, X is fluoro or chloro; R^3 is hydroxy; R^7 is iodo or bromo; R^{10} is hydrogen or fluoro; and R^{10a} is methyl. Even more specifically, R^4 is heterocycloalkyl, alkyl, or heteroaryl, where the alkyl is optionally substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen or alkyl and $R^{8'}$ is hydrogen, alkyl, or cycloalkyl where the cycloalkyl is optionally substituted with one or two groups independently selected from hydroxy and alkyl) and the heteroaryl is optionally substituted with alkyl. Yet even more specifically, R^4 is piperidinyl, pyrrolidinyl, benzimidazolyl, *N*-methyl-benzimidazolyl, methylaminomethyl, 1(*R,S*)-amino-ethyl, 1(*R*)-amino-ethyl, 1(*S*)-amino-ethyl, 1(*R,S*)-(methylamino)-ethyl, 1(*R*)-(methylamino)-ethyl, 1(*S*)-(methylamino)-ethyl, 1(*R,S*)-(dimethylamino)-ethyl, 1(*R*)-(dimethylamino)-ethyl,

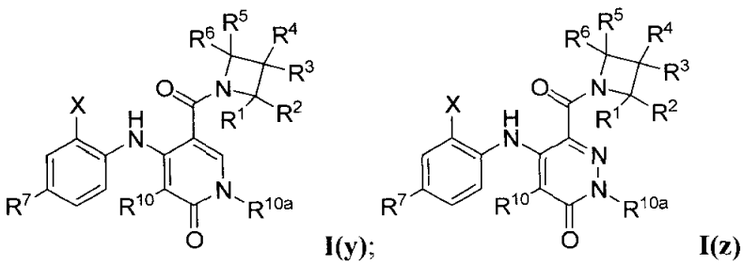
1(*S*)-(dimethylamino)-ethyl, 1(*R,S*)-amino-propyl, 1(*R*)-amino-propyl, 1(*S*)-amino-propyl, 1(*R,S*)-(methylamino)-propyl, 1(*R*)-(methylamino)-propyl, 1(*S*)-(methylamino)-propyl, 1(*R,S*)-(dimethylamino)-propyl, 1(*R*)-(dimethylamino)-propyl, 1(*S*)-(dimethylamino)-propyl, 1(*R,S*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl, 1(*R*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl, or 1(*S*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl.

[00167] In another embodiment of the invention (C6), A is



and X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, and R^{10a} are as defined in the Summary of the invention for a compound of Group C. More specifically, R^1, R^2, R^5, and R^6 are hydrogen; X and R^7 are halo; R^{10} is hydrogen or halo; and R^{10a} is alkyl. Even more specifically, X is fluoro or chloro; R^3 is hydroxy; R^7 is iodo or bromo; R^{10} is hydrogen or fluoro; and R^{10a} is methyl. Even more specifically, R^4 is heterocycloalkyl, alkyl, or heteroaryl, where the alkyl is optionally substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen or alkyl and $R^{8'}$ is hydrogen, alkyl, or cycloalkyl where the cycloalkyl is optionally substituted with one or two groups independently selected from hydroxy and alkyl) and the heteroaryl is optionally substituted with alkyl. Yet even more specifically, R^4 is piperidinyl, pyrrolidinyl, benzimidazolyl, *N*-methylbenzimidazolyl, 1(*R,S*)-amino-ethyl, 1(*R*)-amino-ethyl, 1(*S*)-amino-ethyl, 1(*R,S*)-amino-propyl, 1(*R*)-amino-propyl, 1(*S*)-amino-propyl, 1(*R,S*)-(methylamino)-propyl, 1(*R*)-(methylamino)-propyl, 1(*S*)-(methylamino)-propyl, 1(*R,S*)-(3,4-cis-dihydroxy-cyclopentylamino)-propyl, 1(*R*)-(3,4-cis-dihydroxy-cyclopentylamino)-propyl, 1(*S*)-(3,4-cis-dihydroxy-cyclopentylamino)-propyl, 1(*R,S*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl, 1(*R*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl, or 1(*S*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl.

[00168] In another embodiment of the Invention (C7), the compound is of Formula I(y) or I(z):



I(y); **I(z)**

where R^1, R^2, R^5, and R^6 are hydrogen; X and R^7 are halo; R^3, R^4, R^{10}, R^{10a}, and Y^1 are as defined in the Summary of the Invention for a compound of Group C. In a more specific embodiment, X is fluoro or chloro; R^7 is iodo or bromo; R^{10} is hydrogen, halo, or alkyl, more specifically hydrogen or halo; and R^{10a} is alkyl, more specifically methyl. Even more specifically R^{10} is hydrogen or fluoro; R^3 is hydroxy; and R^4 is heterocycloalkyl, alkyl, or heteroaryl, where the alkyl is optionally substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen or alkyl and $R^{8'}$ is hydrogen, alkyl, or cycloalkyl where the cycloalkyl is optionally substituted with one or two groups independently selected from hydroxy and alkyl) and the heteroaryl is optionally substituted with alkyl.

[00169] In one embodiment of the Invention (D), the compound of Formula I is selected from Group D where all groups are as defined in the Summary of the Invention.

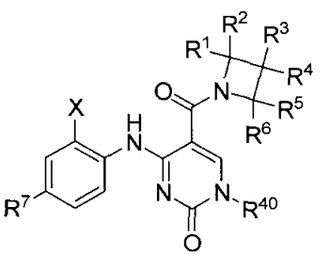
[00170] In another embodiment of the invention (D1), X and R^7 are halo; and all other groups are as defined for a compound selected from Group D.

[00171] In another embodiment of the invention (D2), the compound is selected from Group D where R^3 is halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl; where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; and R^4 is as defined in

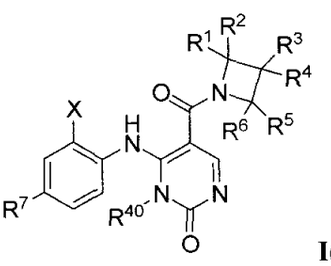
the Summary of the Invention; or R^3 and R^4 together with the carbon to which they are attached form C(O) or C(=NOH); and all other groups are as defined in the Summary of the Invention for a compound of Group C. More specifically, R^1, R^2, R^5 and R^6 are hydrogen; and X and R^7 are halo.

[00172] In another embodiment of the invention (D3), the compound is selected from Group D where R^3 and R^4 are independently halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl; where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; or R^3 and R^4 together with the carbon to which they are attached form C(O) or C(=NOH); and all other groups are as defined in the Summary of the Invention for a compound of Group C. More specifically, R^1, R^2, R^5 and R^6 are hydrogen; and X and R^7 are halo.

[00173] In another embodiment of the invention (D4), A is



I(aa) or



I(bb)

where R^{40} is hydrogen or methyl (specifically, R^{40} is hydrogen) and all other groups are as defined in the Summary of the Invention. Specifically, R^1, R^2, R^5, and R^6 are hydrogen; X and R^7 are halo; and R^{40} is hydrogen or methyl. More specifically, X is fluoro or chloro; and R^3 is hydrogen or hydroxy; R^7 is iodo or bromo. Even more specifically, R^4 is heterocycloalkyl, alkyl, or heteroaryl, where the alkyl is optionally substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen or alkyl and $R^{8'}$ is hydrogen, alkyl, or cycloalkyl where the cycloalkyl

is optionally substituted with one or two groups independently selected from hydroxy and alkyl) and the heteroaryl is optionally substituted with alkyl. Yet even more specifically, R^4 is piperidinyl, pyrrolidinyl, benzimidazolyl, *N*-methyl-benzimidazolyl, methylaminomethyl, 1(*R,S*)-amino-ethyl, 1(*R*)-amino-ethyl, 1(*S*)-amino-ethyl, 1(*R,S*)-(methylamino)-ethyl, 1(*R*)-(methylamino)-ethyl, 1(*S*)-(methylamino)-ethyl, 1(*R,S*)-(dimethylamino)-ethyl, 1(*R*)-(dimethylamino)-ethyl, 1(*S*)-(dimethylamino)-ethyl, 1(*R,S*)-amino-propyl, 1(*R*)-amino-propyl, 1(*S*)-amino-propyl, 1(*R,S*)-(methylamino)-propyl, 1(*R*)-(methylamino)-propyl, 1(*S*)-(methylamino)-propyl, 1(*R,S*)-(dimethylamino)-propyl, 1(*R*)-(dimethylamino)-propyl, 1(*S*)-(dimethylamino)-propyl, 1(*R,S*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl, 1(*R*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl, or 1(*S*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl.

[00174] In a specific embodiment (D4a) of the invention of D4 is that where R^4 is heterocycloalkyl or alkyl where the alkyl is optionally substituted with $-NR^8R^{8'}$ (where R^8 is hydrogen or alkyl and $R^{8'}$ is hydrogen, alkyl, or cycloalkyl where the cycloalkyl is optionally substituted with one or two groups independently selected from hydroxy and alkyl). Specifically, R^4 is piperidinyl, pyrrolidinyl, methylaminomethyl, 1(*R,S*)-amino-ethyl, 1(*R*)-amino-ethyl, 1(*S*)-amino-ethyl, 1(*R,S*)-(methylamino)-ethyl, 1(*R*)-(methylamino)-ethyl, 1(*S*)-(methylamino)-ethyl, 1(*R,S*)-(dimethylamino)-ethyl, 1(*R*)-(dimethylamino)-ethyl, 1(*S*)-(dimethylamino)-ethyl, 1(*R,S*)-amino-propyl, 1(*R*)-amino-propyl, 1(*S*)-amino-propyl, 1(*R,S*)-(methylamino)-propyl, 1(*R*)-(methylamino)-propyl, 1(*S*)-(methylamino)-propyl, 1(*R,S*)-(dimethylamino)-propyl, 1(*R*)-(dimethylamino)-propyl, 1(*S*)-(dimethylamino)-propyl, 1(*R,S*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl, 1(*R*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl, or 1(*S*)-(3,4-cis-dihydroxy-cyclopentylamino)-ethyl.

[00175] Another embodiment of the Invention (E) is directed to a Compound selected from Group A, Group B, and Group C where

Group A

A is phenylene optionally substituted with one or two groups selected from R^{10}, R^{12}, R^{14}, and R^{16} where R^{10}, R^{12}, R^{14} and R^{16} are independently hydrogen or halo;

X is halo;

R^1, R^2, R^5 and R^6 are hydrogen;

R^3 is hydrogen, halo, hydroxy, alkoxy, or amino;

R^4 is hydrogen, $-NR^8R^{8'}$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl,

cycloalkyl, heterocycloalkyl, or heteroaryl; where the R^4 alkyl is optionally substituted with one, two, or three groups independently selected from $-OR^8$, halo, nitro, $-S(O)_mR^9$, optionally substituted heterocycloalkyl, $-NR^8R^{8'}$, $-NR^8C(O)R^{8'}$, $-NR^8S(O)_2R^9$, $-NR^8C(O)OR^{8'}$, and aryl; where the R^4 cycloalkyl is optionally substituted with one or two groups selected from $-OR^8$ and $-NR^8R^{8'}$; where the R^4 heterocycloalkyl is optionally substituted with one or two groups independently selected from alkyl and $-C(O)OR^8$; and where the R^4 heteroaryl is optionally substituted with $-NR^8R^{8'}$; or

R^3 and R^4 together with the carbon to which they are attached form C(O) or C(=NOH);

m is 0;

R^7 is halo;

R^8 and $R^{8'}$ are independently selected from hydrogen, hydroxy, alkyl, alkenyl, alkynyl, aryl, heterocycloalkyl, heteroaryl, and cycloalkyl;

where the R^8 and $R^{8'}$ alkyl are independently optionally substituted with one, two, or three groups indendently selected from hydroxy, $-NR^{30}R^{30'}$ (where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl), optionally substituted heteroaryl, optionally substituted cycloalkyl), optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, $-C(O)NR^{33}R^{33a}$ (where R^{33} is hydrogen or alkyl and R^{33a} is alkyl, alkenyl, alkynyl, or cycloalkyl), optionally substituted aryloxy, $-S(O)_nR^{31}$ (where n is 0 and R^{31} is alkyl), carboxy, alkoxycarbonyl, and $-NR^{32}C(O)R^{32a}$ (where R^{32} is hydrogen or alkyl and R^{32a} is alkyl, alkenyl, alkoxy, or cycloalkyl); or where the alkyl is optionally substituted with one, two, three, four, or five halo;

where the R^8 and $R^{8'}$ heteroaryl are independently optionally substituted with one or two groups indendently selected from amino and alkyl;

where the R^8 and $R^{8'}$ heterocycloalkyl are independently optionally substituted with one, two, or three groups indendently selected from alkyl, alkoxycarbonyl, optionally substituted arylalkyl, hydroxy, alkoxy, and hydroxyalkyl;

where the R^8 and $R^{8'}$ aryl are independently optionally substituted with one or two groups indendently selected from hydroxy, alkoxy, halo, $-NR^{32}C(O)R^{32a}$ (where R^{32} is hydrogen or alkyl and R^{32a} is alkyl, alkenyl, alkoxy, or cycloalkyl), and $-NR^{34}SO_2R^{34a}$ (where R^{34} is hydrogen or alkyl and R^{34a} is alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl); and

where the R^8 and $R^{8'}$ cycloalkyl are independently optionally substituted with one, two, or three groups indendently selected from hydroxy, hydroxyalkyl, alkoxy, carboxy, $-C(O)NR^{33}R^{33a}$ (where R^{33} is hydrogen or alkyl and R^{33a} is alkyl, alkenyl, alkynyl, or cycloalkyl), and optionally substituted cycloalkyl; and

R^9 is alkyl or aryl;

Group B

A is thien-3,4-diyl, benzo[*d*]isoxazol-5,6-diyl, 1*H*-indazol-5,6-diyl (optionally substituted at the N1 position with R^{19} where R^{19} is alkyl or alkenyl), benzo[*d*]oxazol-5,6-diyl, benzo[*d*]thiazol-5,6-diyl, 1*H*-benzo[d]imidazol-5,6-diyl (optionally substituted at the N1 position with R^{19} where R^{19} is alkyl or alkenyl), 1*H*-benzo[*d*][1,2,3]triazol-5,6-diyl (optionally substituted at the N1 position with R^{19} where R^{19} is alkyl or alkenyl), imidazo[1,2-*a*]pyridin-6,7-diyl, cinnolin-6,7-diyl, quinolin-6,7-diyl, pyridin-3,4-diyl, or 1-oxido-pyridin-3,4-diyl; where A is optionally substituted with one, two, or three groups independently selected from R^{10}, R^{12}, R^{14}, R^{16} and R^{19} where R^{10}, R^{12}, R^{14} and R^{16} are independently hydrogen, alkyl, halo, or amino; and R^{19} is hydrogen or alkyl;

X is halo;

R^1, R^2, R^5 and R^6 are hydrogen;

R^3 is hydrogen or hydroxy;

R^4 is $-NR^8R^{8'}$, heterocycloalkyl, heteroaryl, or alkyl; where the alkyl is optionally substituted with $-NR^8R^{8'}$ and where the heteroaryl is optionaly substituted with alkyl;

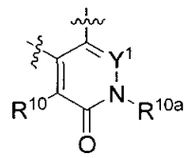
R^7 is halo;

R^8 is hydrogen or alkyl; and

$R^{8'}$ is hydrogen, alkyl, or cycloalkyl; where the cycloalkyl is optionally substituted with one or two groups independently selected from hydroxy and alkyl;

Group C

A is



(a)

where R^{10} is hydrogen or halo;

R^{10a} is hydrogen or alkyl;

Y^1 is =CH- or =N-;

X is halo;

R^1, R^2, R^5 and R^6 are hydrogen;

R^3 is hydrogen or hydroxy;

R^4 is $-NR^8R^{8'}$, heterocycloalkyl, heteroaryl, or alkyl; where the alkyl is optionally substituted with $-NR^8R^{8'}$ and where the heteroaryl is optionaly substituted with alkyl;

R^7 is halo;

R^8 is hydrogen or alkyl; and

$R^{8'}$ is hydrogen, alkyl, or cycloalkyl; where the cycloalkyl is optionally substituted with one or two groups independently selected from hydroxy and alkyl.

[00176] One embodiment of the invention provides a pharmaceutical composition which comprises a compound of Formula I selected from Group A, or a pharmaceutically acceptable salt or solvate therof and a pharmaceutically acceptable carrier, excipient, or diluent.

[00177] Another embodiment of the invention provides a pharmaceutical composition which comprises a compound of Formula I selected from Group B, or a pharmaceutically acceptable salt or solvate therof and a pharmaceutically acceptable carrier, excipient, or diluent. Specifically, the compound is of Formula I(c), I(d), I(e), I(f), I(g), I(h), I(i), I(j), I(k), I(m), I(n), I(o), I(p), I(q), I(r), I(s), I(t), I(u), I(v), I(w), I(x), I(cc), or I(dd).

[00178] Another embodiment of the invention provides a pharmaceutical composition which comprises a compound of Formula I selected from Group C, or a pharmaceutically acceptable salt or solvate therof and a pharmaceutically acceptable carrier, excipient, or diluent.

[00179] Another embodiment of the invention provides a pharmaceutical composition which comprises a compound of Formula I selected from Group D, or a pharmaceutically acceptable salt or solvate therof and a pharmaceutically acceptable carrier, excipient, or diluent.

[00180] In another embodiment, the invention comprises a method of inhibiting MEK in a cell, comprising contacting a cell with a compound of Formula I selected from Group A or a pharmaceutically acceptable salt or solvate therof, or with a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I selected from Group A and a pharmaceutically acceptable carrier, excipient, or diluent.

[00181] In another embodiment, the invention comprises a method of inhibiting MEK in a cell, comprising contacting a cell with a compound of Formula I selected from Group B or a pharmaceutically acceptable salt or solvate therof, or with a pharmaceutical composition

comprising a therapeutically effective amount of a compound of Formula I selected from Group B and a pharmaceutically acceptable carrier, excipient, or diluent.

[00182] In another embodiment, the invention comprises a method of inhibiting MEK in a cell, comprising contacting a cell with a compound of Formula I selected from Group C or a pharmaceutically acceptable salt or solvate therof, or with a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I selected from Group C and a pharmaceutically acceptable carrier, excipient, or diluent.

[00183] In another embodiment, the invention comprises a method of inhibiting MEK in a cell, comprising contacting a cell with a compound of Formula I selected from Group D or a pharmaceutically acceptable salt or solvate therof, or with a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I selected from Group D and a pharmaceutically acceptable carrier, excipient, or diluent.

[00184] Another embodiment of the Invention provides a method for treating a proliferative disease which method comprises administering to a patient a compound of Formula I or a pharmaceutically acceptable salt or solvate therof, or administering a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable carrier, excipient, or diluent. In a specific embodiment, the disease is cancer. More specifically, the cancer is selected from malignant melanoma, colorectal cancer, pancreatic cancer, breast cancer, non-small cell lung cancer, small cell lung cancer, papillary and anaplastic thyroid cancer, and endometriod ovarian cancers.

[00185] One of ordinary skill in the art would understand that certain crystallized, protein-ligand complexes and their corresponding x-ray structure coordinates can be used to reveal new structural information useful for understanding the biological activity of kinases as described herein. As well, the key structural features of the aforementioned proteins, particularly, the shape of the ligand binding site, are useful in methods for designing or identifying selective modulators of kinases and in solving the structures of other proteins with similar features. Such protein-ligand complexes, having compounds of the invention as their ligand component, are an aspect of the invention.

[00186] As well, one of ordinary skill in the art would appreciate that such suitable x-ray quality crystals can be used as part of a method of identifying a candidate agent capable of binding to and modulating the activity of kinases. Such methods may be characterized by the following aspects: a) introducing into a suitable computer program, information defining a ligand binding domain of a kinase in a conformation (*e.g.* as defined by x-ray structure

coordinates obtained from suitable x-ray quality crystals as described above) wherein the computer program creates a model of the three dimensional structures of the ligand binding domain, b) introducing a model of the three dimensional structure of a candidate agent in the computer program, c) superimposing the model of the candidate agent on the model of the ligand binding domain, and d) assessing whether the candidate agent model fits spatially into the ligand binding domain. Aspects a-d are not necessarily carried out in the aforementioned order. Such methods may further entail: performing rational drug design with the model of the three-dimensional structure, and selecting a potential candidate agent in conjunction with computer modeling.

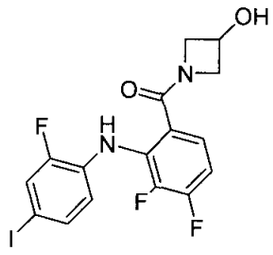
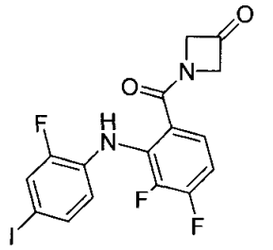
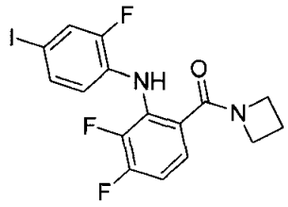
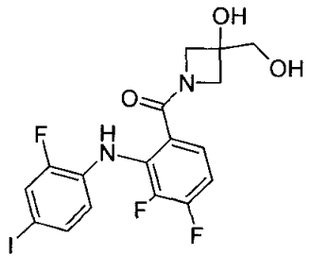
[00187] Additionally, one skilled in the art would appreciate that such methods may further entail: employing a candidate agent, so-determined to fit spatially into the ligand binding domain, in a biological activity assay for kinase modulation, and determining whether said candidate agent modulates kinase activity in the assay. Such methods may also include administering the candidate agent, determined to modulate kinase activity, to a mammal suffering from a condition treatable by kinase modulation, such as those described above.

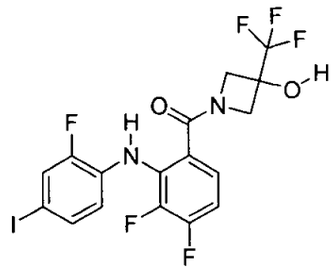
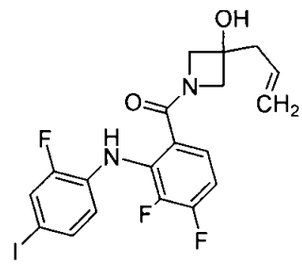
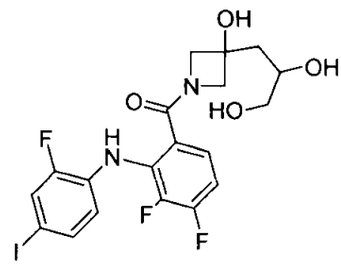
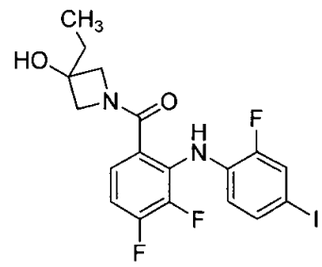
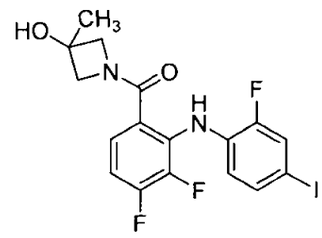
[00188] Also, one skilled in the art would appreciate that compounds of the invention can be used in a method of evaluating the ability of a test agent to associate with a molecule or molecular complex comprising a ligand binding domain of a kinase. Such a method may be characterized by the following aspects: a) creating a computer model of a kinase binding pocket using structure coordinates obtained from suitable x-ray quality crystals of the kinase, b) employing computational algorithms to perform a fitting operation between the test agent and the computer model of the binding pocket, and c) analyzing the results of the fitting operation to quantify the association between the test agent and the computer model of the binding pocket.

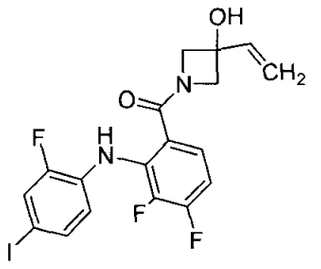
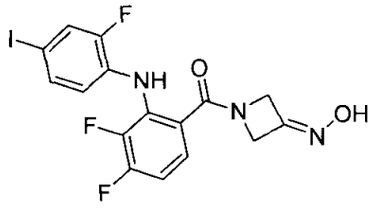
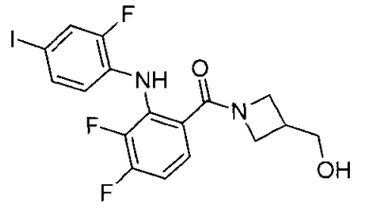
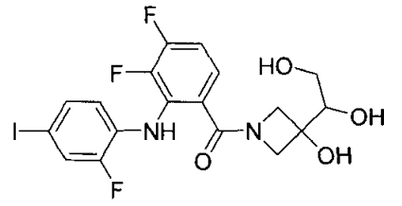
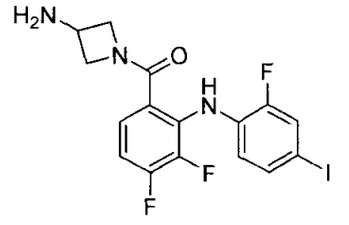
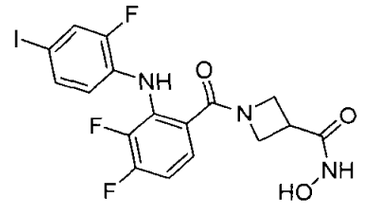
Representative Compounds

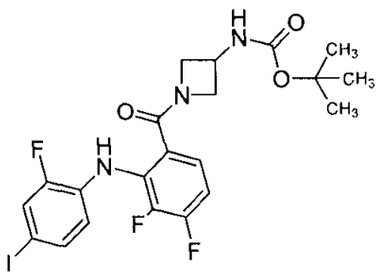
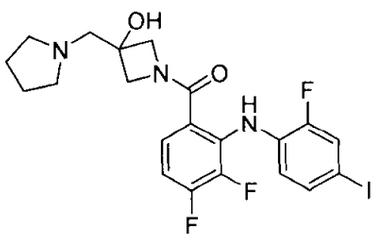
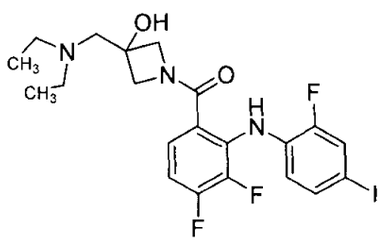
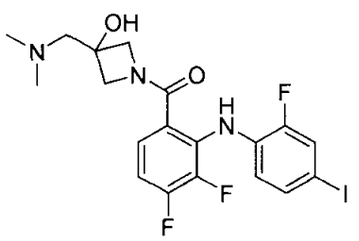
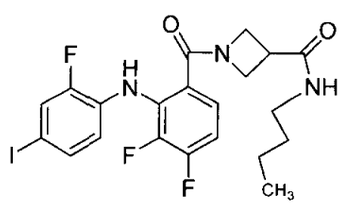
[00189] Representative compounds of Formula I are depicted below. The examples are merely illustrative and do not limit the scope of the invention in any way. Compounds of the invention are named according to systematic application of the nomenclature rules agreed upon by the International Union of Pure and Applied Chemistry (IUPAC), International Union of Biochemistry and Molecular Biology (IUBMB), and the Chemical Abstracts Service (CAS). Names were generated using ACD/Labs naming software 8.00 release, product version 8.08.

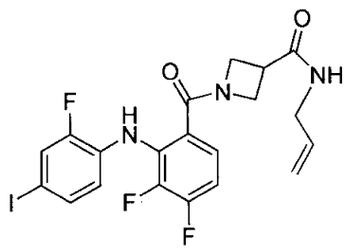
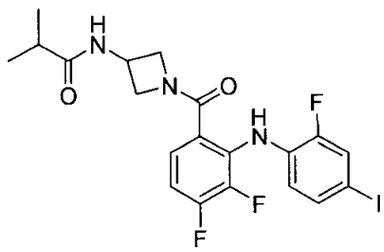
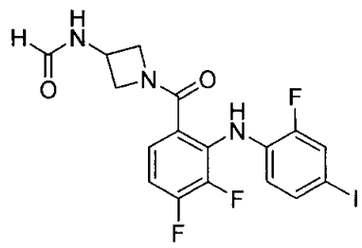
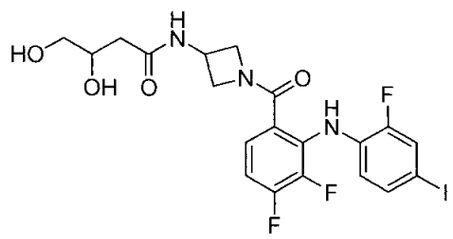
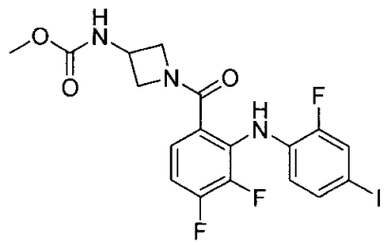
Table 1

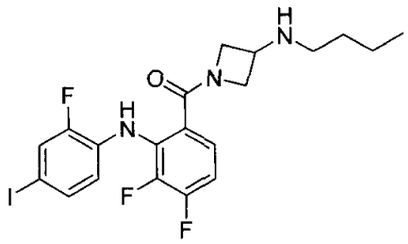
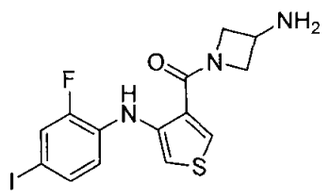
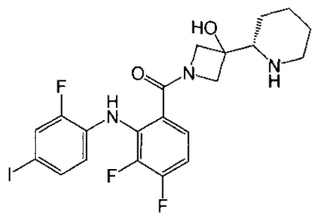
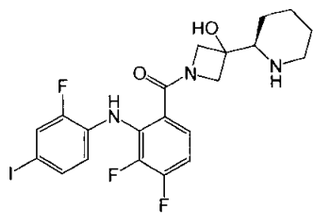
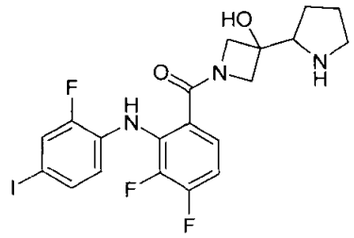
Cmpd No.	Structure	Name
1		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}-carbonyl)azetidin-3-ol
2		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl) azetidin-3-one
3		6-(azetidin-1-ylcarbonyl)-2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)aniline
4		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl) -3-(hydroxymethyl)azetidin-3-ol

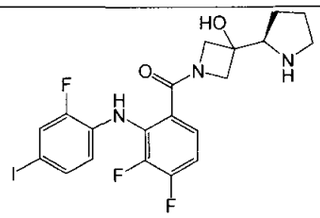
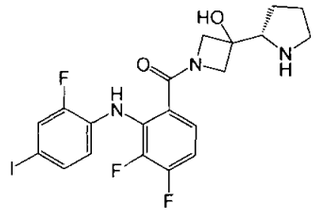
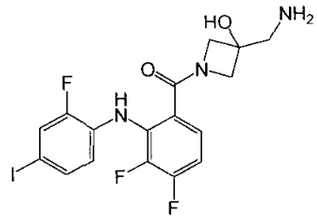
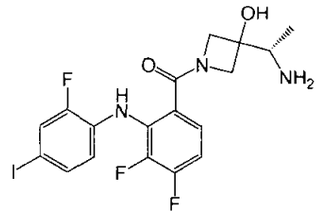
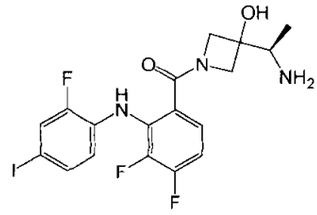
Cmpd No.	Structure	Name
5		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(trifluoromethyl)azetidin-3-ol
6		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-prop-2-en-1-ylazetidin-3-ol
7		3-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]propane-1,2-diol
8		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-ethylazetidin-3-ol
9		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-methylazetidin-3-ol

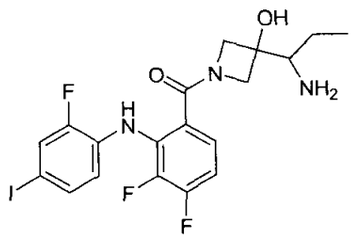
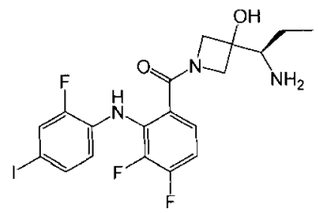
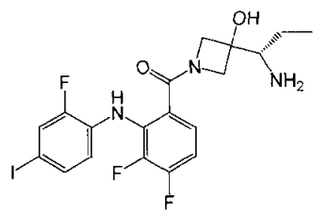
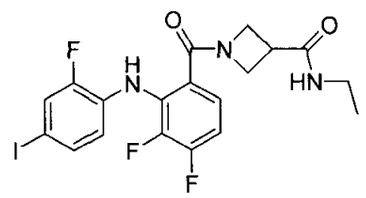
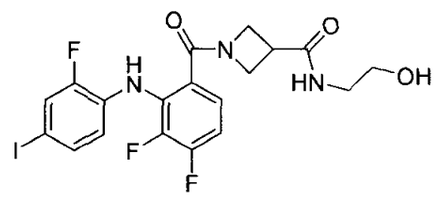
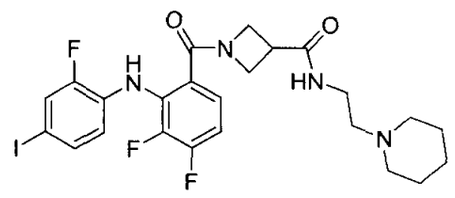
Cmpd No.	Structure	Name
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11		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-one oxime
12		[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]methanol
13		1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethane-1,2-diol
14		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine
15		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-hydroxyazetidine-3-carboxamide

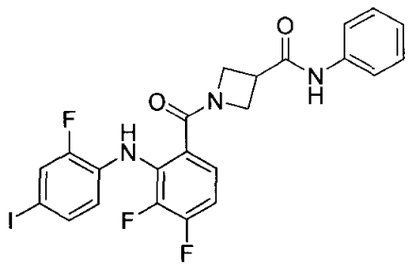
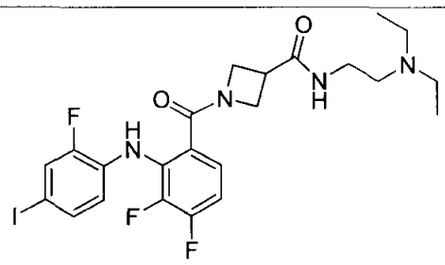
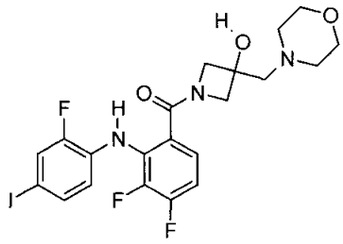
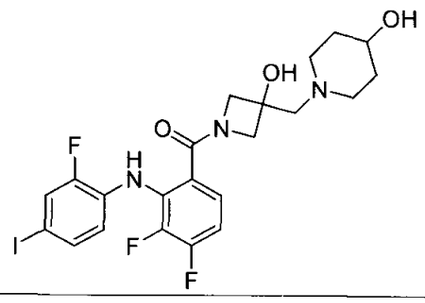
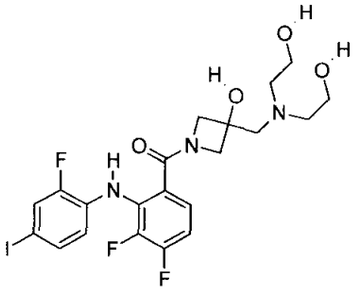
Cmpd No.	Structure	Name
16		1,1-dimethylethyl [1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl) azetidin-3-yl]carbamate
17		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl) -3-(pyrrolidin-1-ylmethyl)azetidin-3-ol
18		3-[(diethylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl) azetidin-3-ol
19		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl) -3-[(dimethylamino)methyl]azetidin-3-ol
20		*N*-butyl-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl) azetidine-3-carboxamide

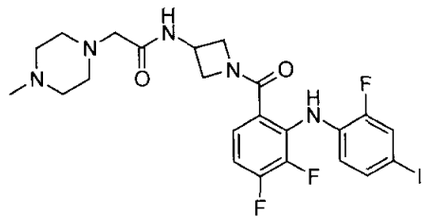
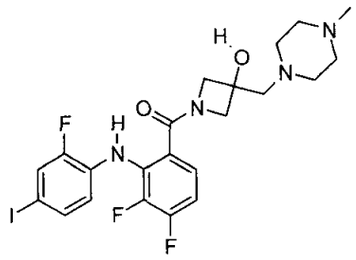
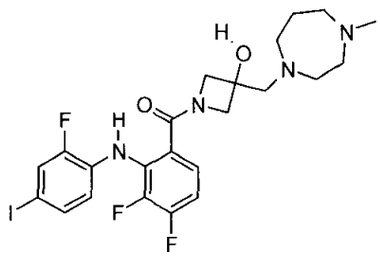
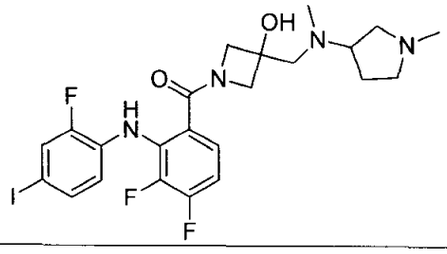
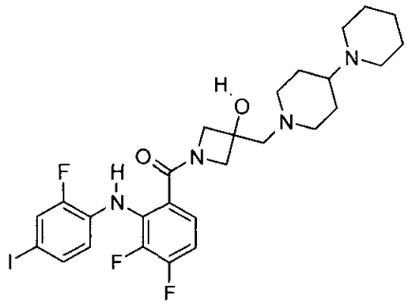
Cmpd No.	Structure	Name
21		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-prop-2-en-1-ylazetidine-3-carboxamide
22		*N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-2-methylpropanamide
23		*N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]formamide
24		*N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-3,4-dihydroxybutanamide
25		methyl [1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]carbamate

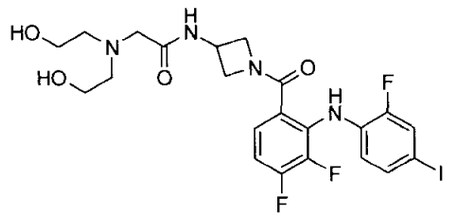
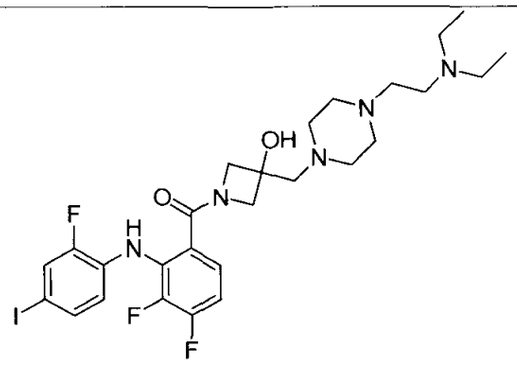
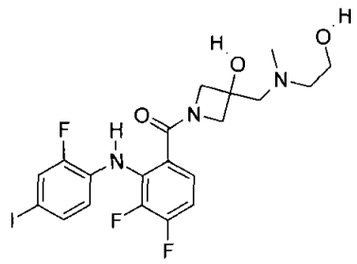
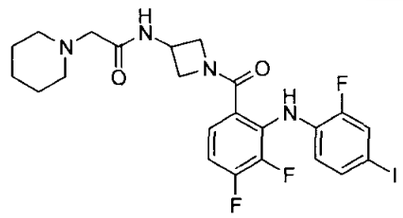
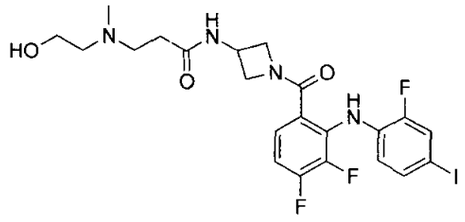
Cmpd No.	Structure	Name
26		*N*-butyl-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl) azetidin-3-amine
27		1-({4-[(2-fluoro-4-iodophenyl)amino]-3-thienyl}carbonyl)azetidin-3-amine
28		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl) -3-[(2*S*)-piperidin-2-yl]azetidin-3-ol
29		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl) -3-[(2*R*)-piperidin-2-yl]azetidin-3-ol
30		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl) -3-pyrrolidin-2-ylazetidin-3-ol
31		(*R*)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl) -3-pyrrolidin-2-ylazetidin-3-ol

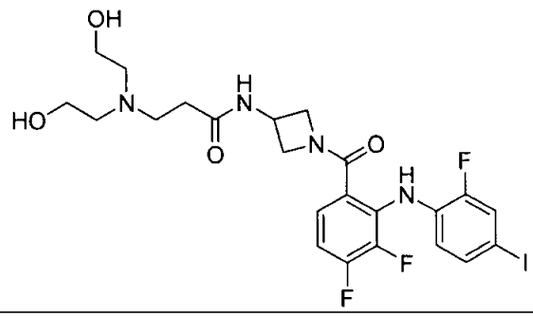
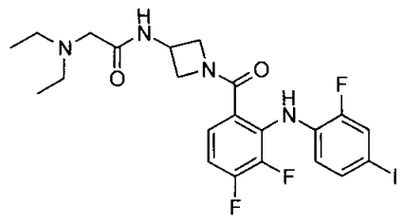
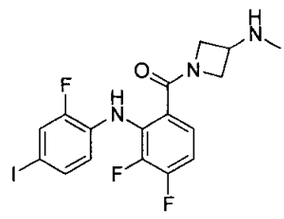
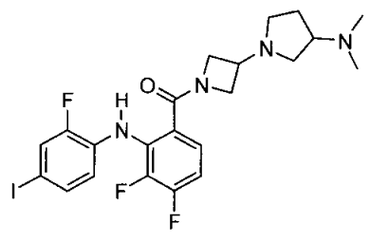
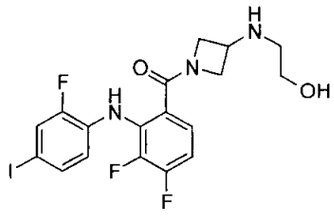
Cmpd No.	Structure	Name
		
32		(*S*)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-pyrrolidin-2-ylazetidin-3-ol
33		3-(aminomethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
34		3-[(1*S*)-1-aminoethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
35		3-[(1*R*)-1-aminoethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol

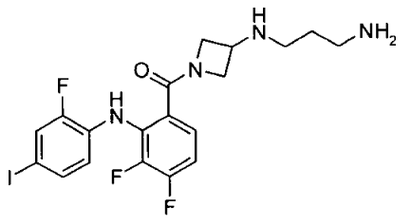
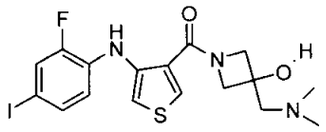
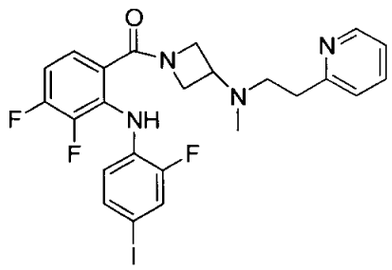
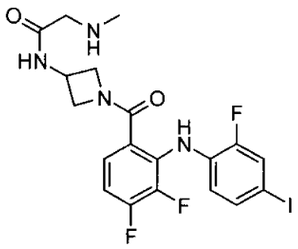
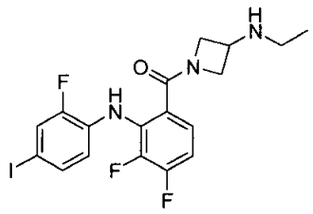
Cmpd No.	Structure	Name
36		(3-(1-aminopropyl)-3-hydroxyazetidin-1-yl)(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)methanone
37		(*R*)-(3-(1-aminopropyl)-3-hydroxyazetidin-1-yl)(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)methanone
38		(*S*)-(3-(1-aminopropyl)-3-hydroxyazetidin-1-yl)(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)methanone
39		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-ethylazetidine-3-carboxamide
40		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(2-hydroxyethyl)azetidine-3-carboxamide
41		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(2-piperidin-1-ylethyl)azetidine-3-carboxamide

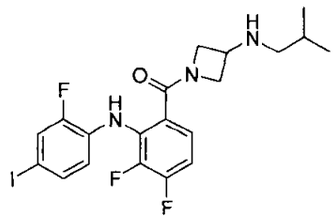
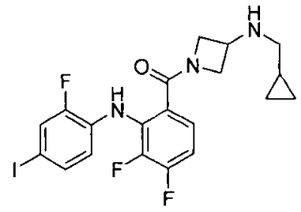
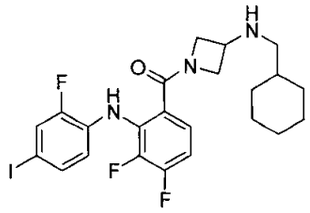
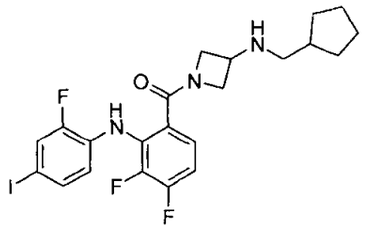
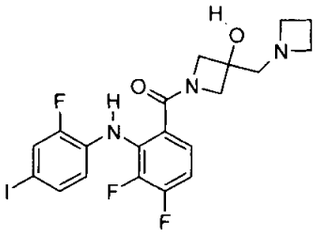
Cmpd No.	Structure	Name
42		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-phenylazetidine-3-carboxamide
43		*N*-[2-(diethylamino)ethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidine-3-carboxamide
44		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(morpholin-4-ylmethyl)azetidin-3-ol
45		1-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}piperidin-4-ol
46		3-{[bis(2-hydroxyethyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol

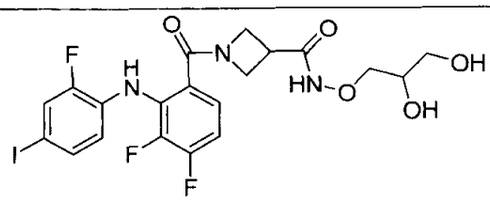
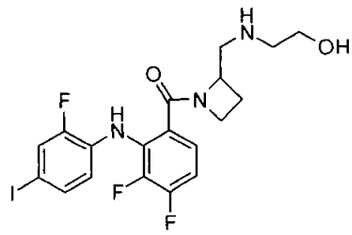
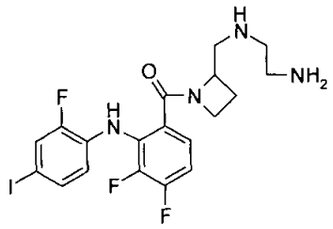
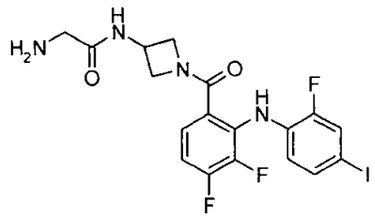
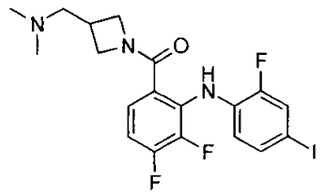
Cmpd No.	Structure	Name
47		*N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-2-(4-methylpiperazin-1-yl)acetamide
48		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(4-methylpiperazin-1-yl)methyl]azetidin-3-ol
49		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(4-methyl-1,4-diazepan-1-yl)methyl]azetidin-3-ol
50		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[methyl(1-methylpyrrolidin-3-yl)amino]methyl}azetidin-3-ol
51		3-(1,4'-bipiperidin-1'-ylmethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol

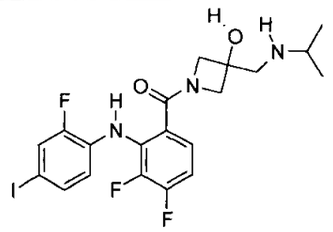
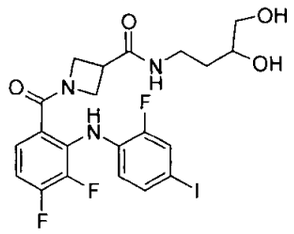
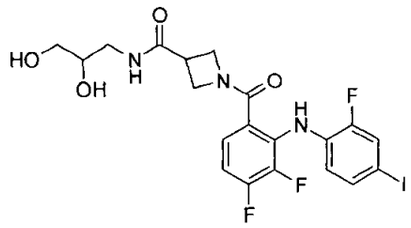
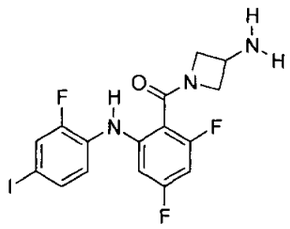
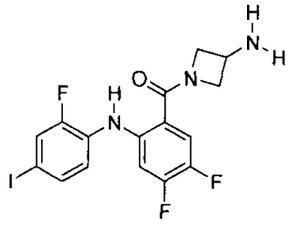
Cmpd No.	Structure	Name
52		*N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-*N*,*N*-bis(2-hydroxyethyl)glycinamide
53		3-({4-[2-(diethylamino)ethyl]piperazin-1-yl}methyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
54		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxyethyl)(methyl)amino]methyl}azetidin-3-ol
55		*N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-2-*piperidin*-1-ylacetamide
56		*N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-*N*3-(2-hydroxyethyl)-*N*3-methyl-beta-alaninamide

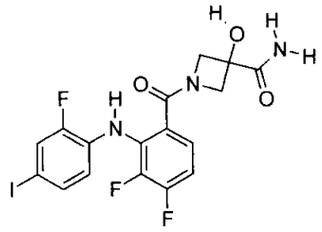
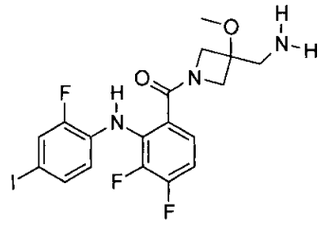
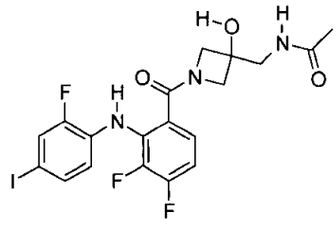
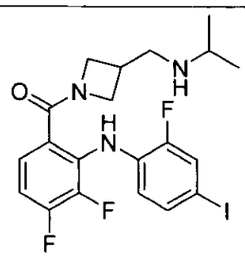
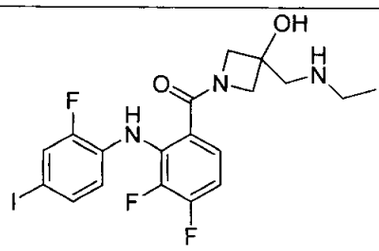
Cmpd No.	Structure	Name
57		*N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-*N*3,*N*3-bis(2-hydroxyethyl)-beta-alaninamide
58		*N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-*N*2,*N*2-diethylglycinamide
59		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-methylazetidin-3-amine
60		1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-*N*,*N*-dimethylpyrrolidin-3-amine
61		2-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]amino}ethanol

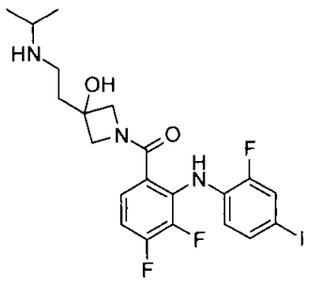
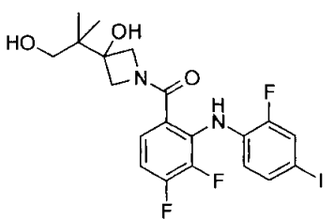
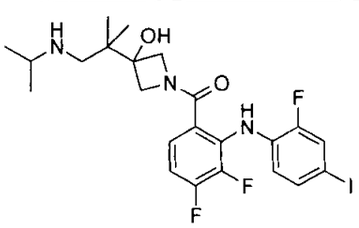
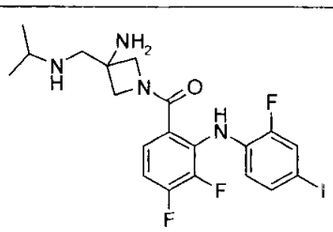
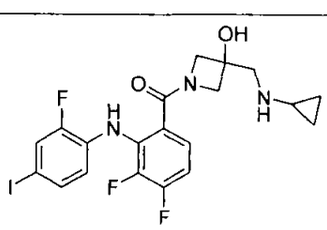
Cmpd No.	Structure	Name
62		*N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]propane-1,3-diamine
63		3-[(dimethylamino)methyl]-1-({4-[(2-fluoro-4-iodophenyl)amino]-3-thienyl}carbonyl)azetidin-3-ol
64		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-methyl-*N*-(2-pyridin-2-ylethyl)azetidin-3-amine
65		*N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-*N*2-methylglycinamide
66		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-ethylazetidin-3-amine

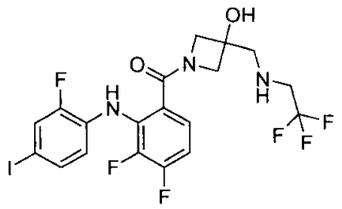
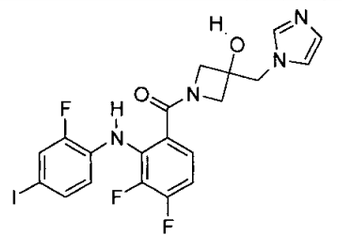
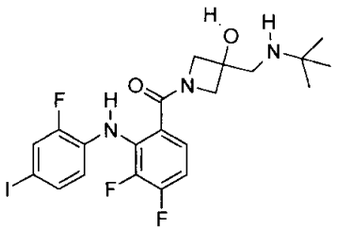
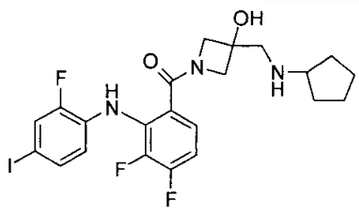
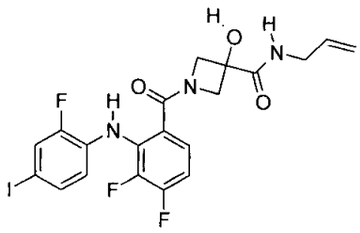
Cmpd No.	Structure	Name
67		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(2-methylpropyl)azetidin-3-amine
68		*N*-(cyclopropylmethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine
69		*N*-(cyclohexylmethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine
70		*N*-(cyclopentylmethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine
71		3-(azetidin-1-ylmethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol

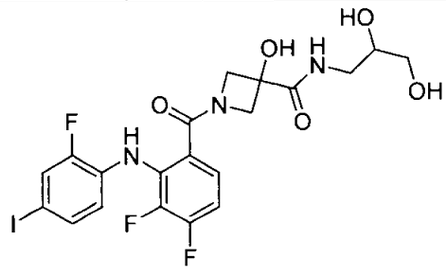
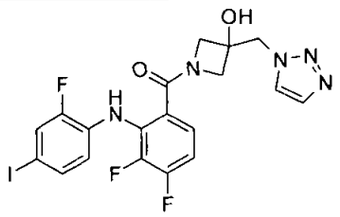
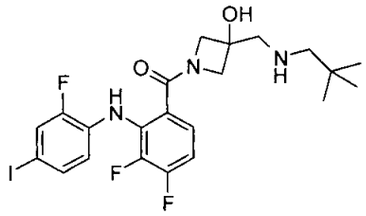
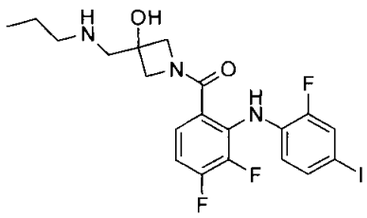
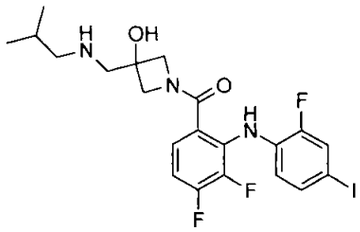
Cmpd No.	Structure	Name
72		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-[(2,3-dihydroxypropyl)oxy]azetidine-3-carboxamide
73		2-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-2-yl]methyl}amino)ethanol
74		*N*-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-2-yl]methyl}ethane-1,2-diamine
75		*N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]glycinamide
76		6-({3-[(dimethylamino)methyl]azetidin-1-yl}carbonyl)-2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)aniline

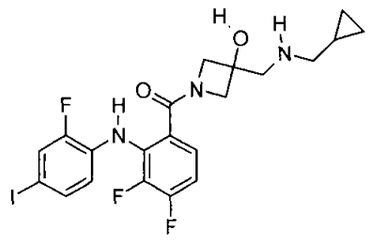
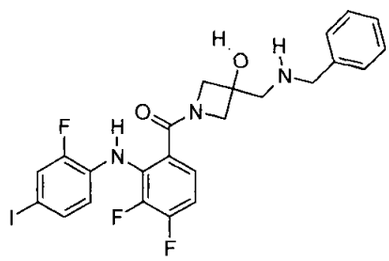
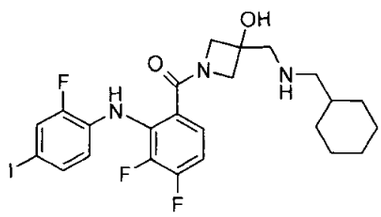
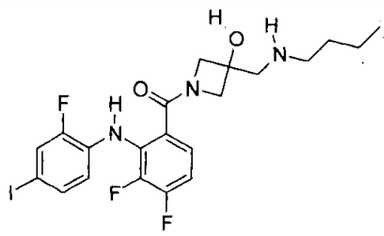
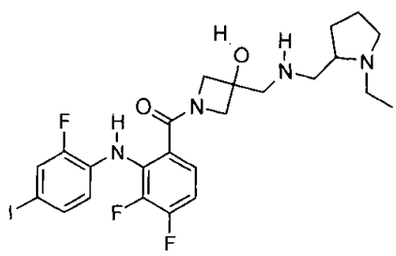
Cmpd No.	Structure	Name
77		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1-methylethyl)amino]methyl}azetidin-3-ol
78		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(3,4-dihydroxybutyl)azetidine-3-carboxamide
79		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(2,3-dihydroxypropyl)azetidine-3-carboxamide
80		1-({2,4-difluoro-6-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine
81		1-({4,5-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine

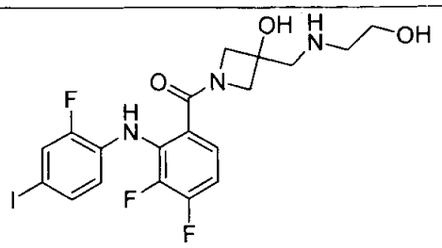
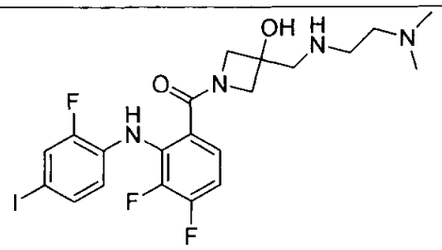
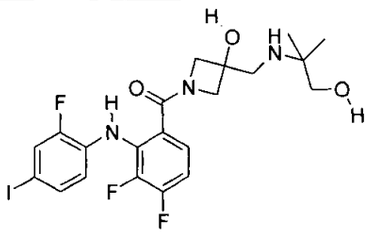
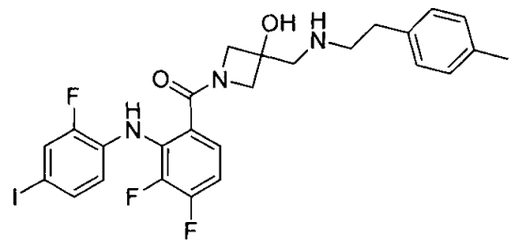
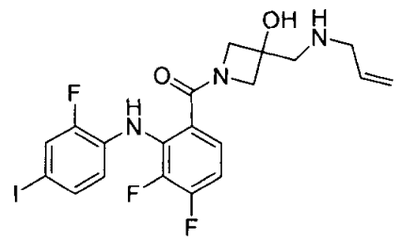
Cmpd No.	Structure	Name
82		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidine-3-carboxamide
83		6-{[3-(aminomethyl)-3-(methyloxy)azetidin-1-yl]carbonyl}-2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)aniline
84		*N*-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}acetamide
85		2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)-6-[(3-{[(1-methylethyl)amino]methyl}azetidin-1-yl)carbonyl]aniline
86		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(ethylamino)methyl]azetidin-3-ol

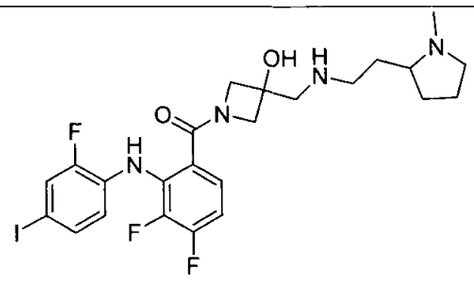
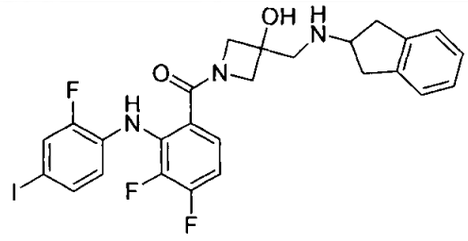
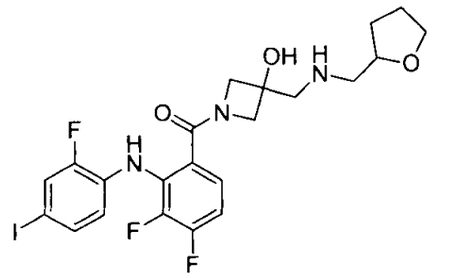
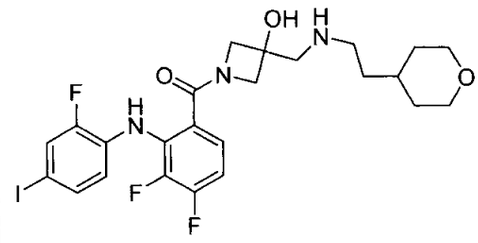
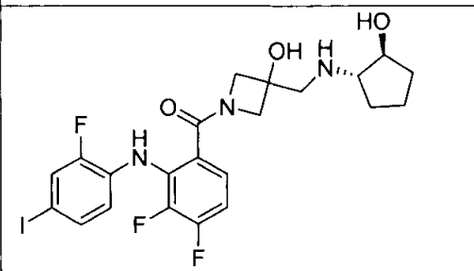
Cmpd No.	Structure	Name
87		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{2-[(1-methylethyl)amino]ethyl}azetidin-3-ol
88		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(2-hydroxy-1,1-dimethylethyl)azetidin-3-ol
89		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{1,1-dimethyl-2-[(1-methylethyl)amino]ethyl}azetidin-3-ol
90		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1-methylethyl)amino]methyl}azetidin-3-amine
91		3-[(cyclopropylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol

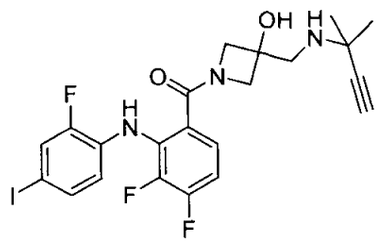
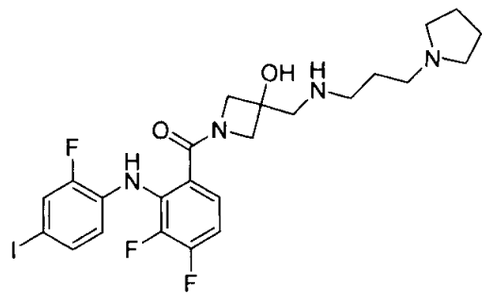
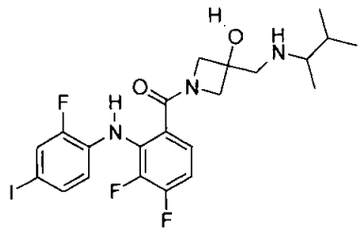
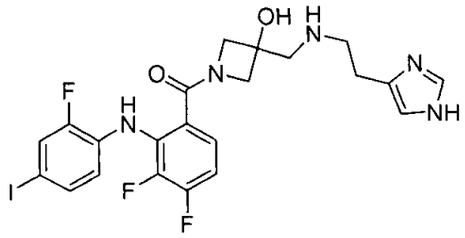
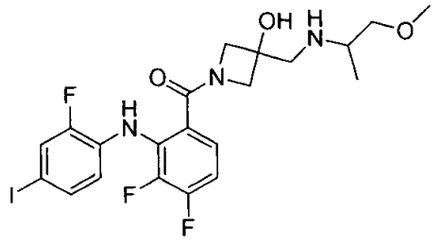
Cmpd No.	Structure	Name
92		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2,2,2-trifluoroethyl)amino]methyl}azetidin-3-ol
93		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1*H*-imidazol-1-ylmethyl)azetidin-3-ol
94		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1,1-dimethylethyl)amino]methyl}azetidin-3-ol
95		3-[(cyclopentylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
96		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxy-*N*-prop-2-en-1-ylazetidine-3-carboxamide

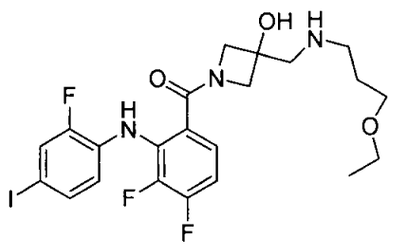
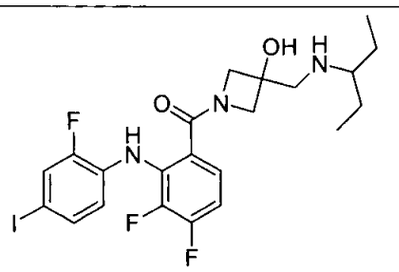
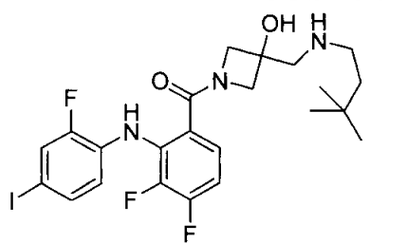
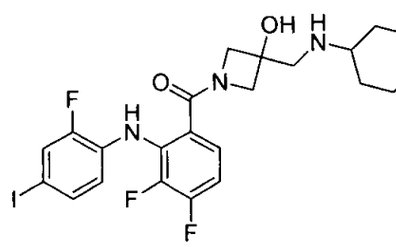
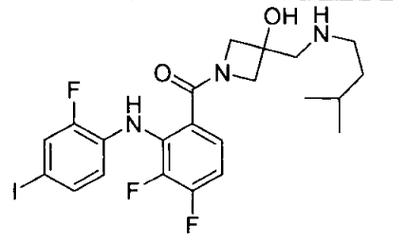
Cmpd No.	Structure	Name
97		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(2,3-dihydroxypropyl)-3-hydroxyazetidine-3-carboxamide
98		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1*H*-1,2,3-triazol-1-ylmethyl)azetidin-3-ol
99		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2,2-dimethylpropyl)amino]methyl}azetidin-3-ol
100		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(propylamino)methyl]azetidin-3-ol
101		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-methylpropyl)amino]methyl}azetidin-3-ol

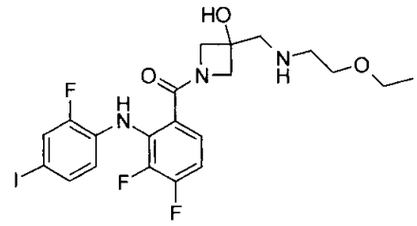
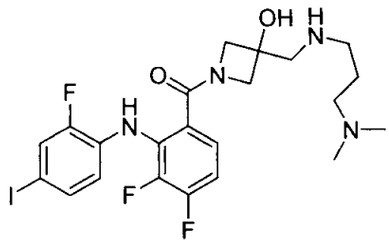
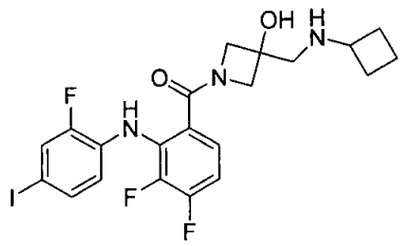
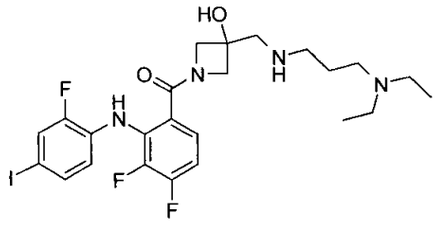
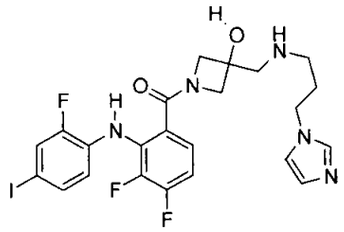
Cmpd No.	Structure	Name
102		3-{[(cyclopropylmethyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
103		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(phenylmethyl)amino]methyl}azetidin-3-ol
104		3-{[(cyclohexylmethyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
105		3-[(butylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
106		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(1-ethylpyrrolidin-2-yl)methyl]amino}methyl)azetidin-3-ol

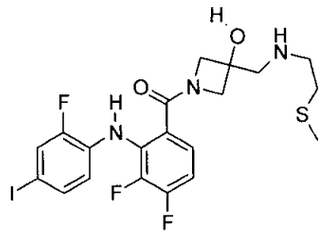
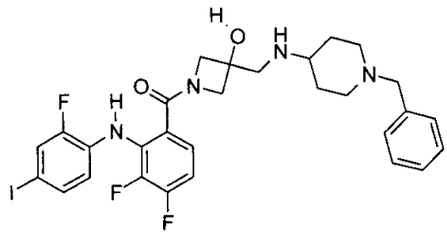
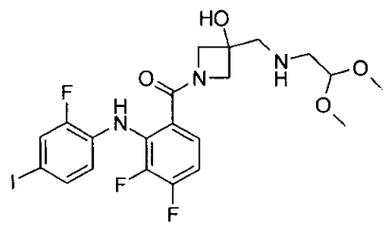
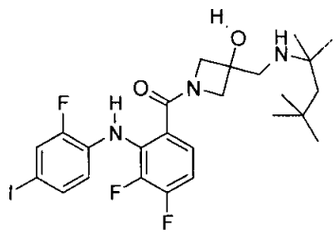
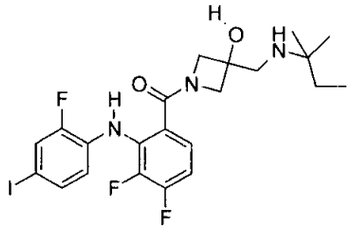
Cmpd No.	Structure	Name
107		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxyethyl)amino]methyl}azetidin-3-ol
108		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(dimethylamino)ethyl]amino}methyl)azetidin-3-ol
109		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxy-1,1-dimethylethyl)amino]methyl}azetidin-3-ol
110		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(4-methylphenyl)ethyl]amino}methyl)azetidin-3-ol
111		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(prop-2-en-1-ylamino)methyl]azetidin-3-ol

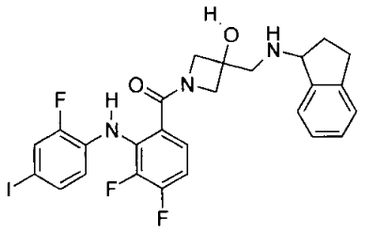
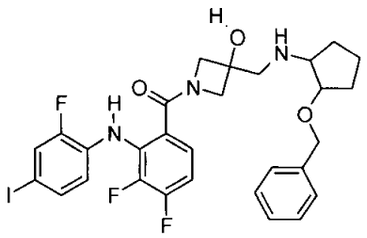
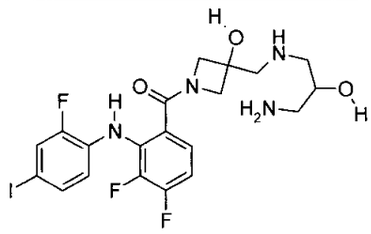
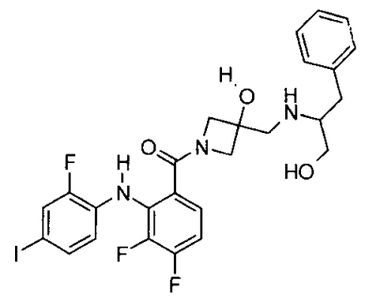
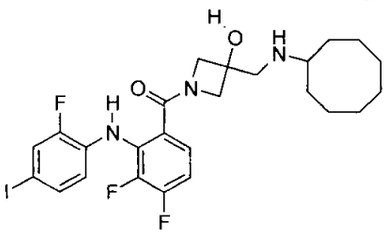
Cmpd No.	Structure	Name
112		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(1-methylpyrrolidin-2-yl)ethyl]amino}methyl)azetidin-3-ol
113		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2,3-dihydro-1*H*-inden-2-ylamino)methyl]azetidin-3-ol
114		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(tetrahydrofuran-2-ylmethyl)amino]methyl}azetidin-3-ol
115		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(tetrahydro-2*H*-pyran-4-yl)ethyl]amino}methyl)azetidin-3-ol
116		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(1*S*,2*S*)-2-hydroxycyclopentyl]amino}methyl)azetidin-3-ol

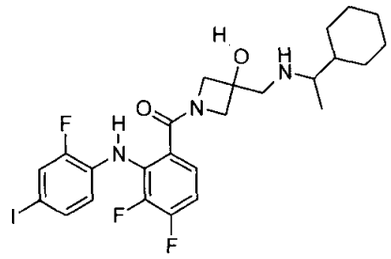
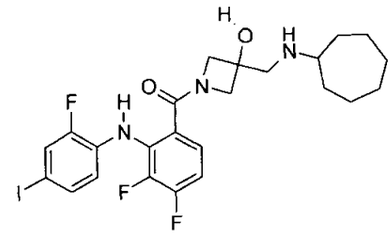
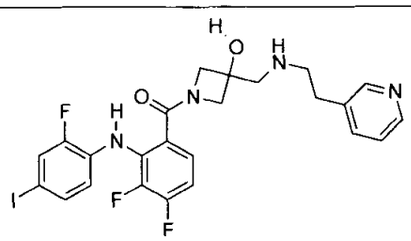
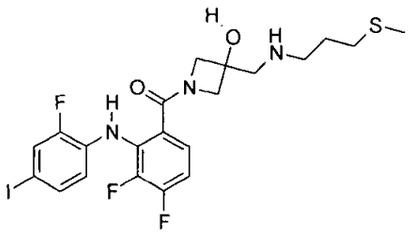
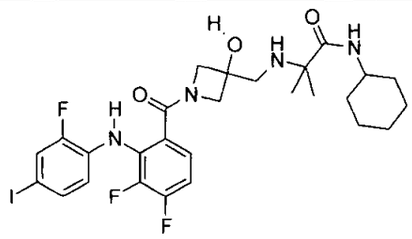
Cmpd No.	Structure	Name
117		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1,1-dimethylprop-2-yn-1-yl)amino]methyl}azetidin-3-ol
118		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(3-pyrrolidin-1-ylpropyl)amino]methyl}azetidin-3-ol
119		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1,2-dimethylpropyl)amino]methyl}azetidin-3-ol
120		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(1*H*-imidazol-4-yl)ethyl]amino}methyl)azetidin-3-ol
121		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[1-methyl-2-(methyloxy)ethyl]amino}methyl)azetidin-3-ol

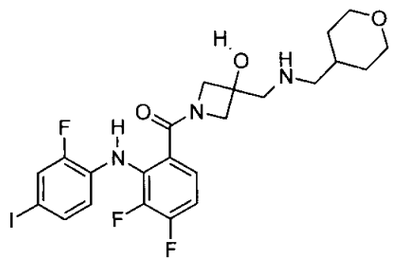
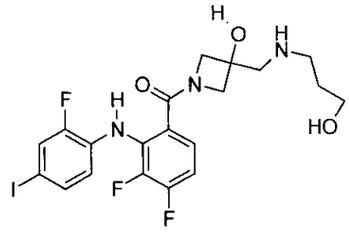
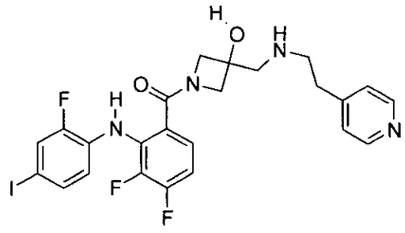
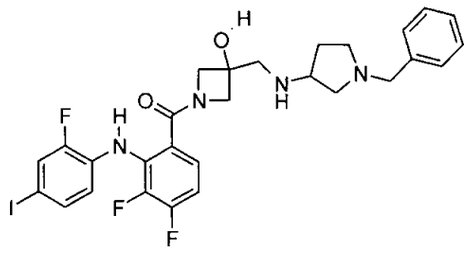
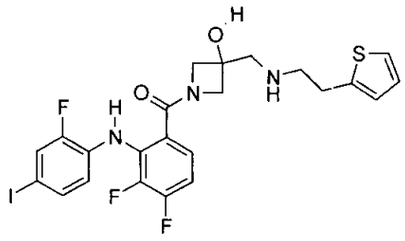
Cmpd No.	Structure	Name
122		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[3-(ethyloxy)propyl]amino}methyl)azetidin-3-ol
123		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1-ethylpropyl)amino]methyl}azetidin-3-ol
124		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(3,3-dimethylbutyl)amino]methyl}azetidin-3-ol
125		ethyl 4-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)piperidine-1-carboxylate
126		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(3-methylbutyl)amino]methyl}azetidin-3-ol

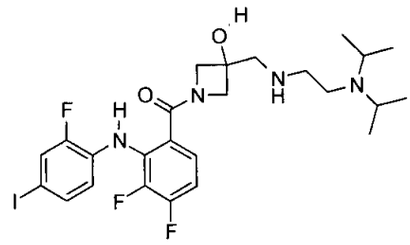
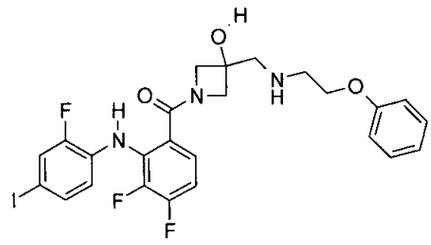
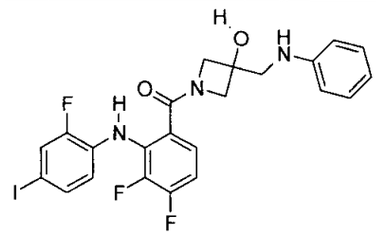
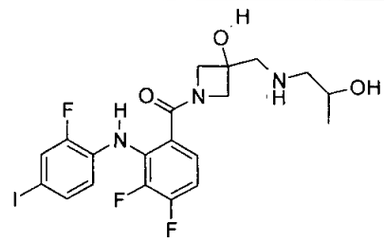
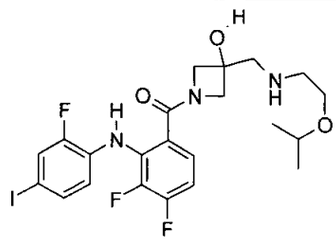
Cmpd No.	Structure	Name
127		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(ethyloxy)ethyl]amino}methyl)azetidin-3-ol
128		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[3-(dimethylamino)propyl]amino}methyl)azetidin-3-ol
129		3-[(cyclobutylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
130		3-({[3-(diethylamino)propyl]amino}methyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
131		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[3-(1*H*-imidazol-1-yl)propyl]amino}methyl)azetidin-3-ol

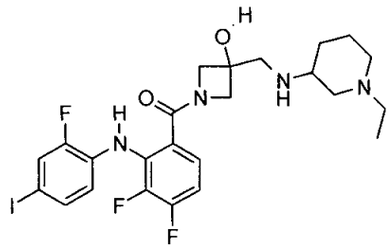
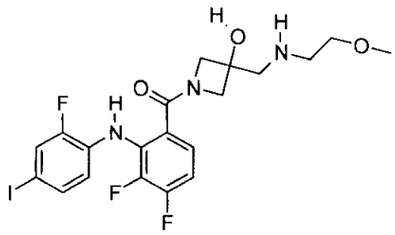
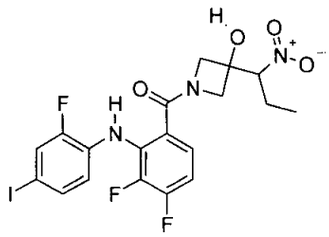
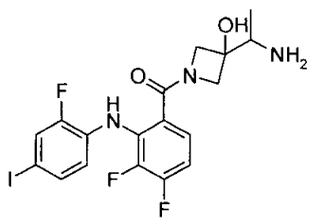
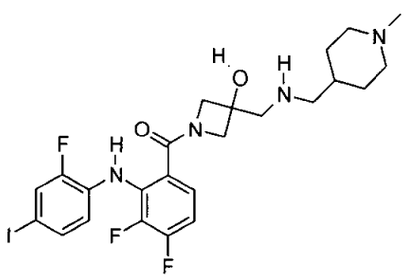
Cmpd No.	Structure	Name
132		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(methylthio)ethyl]amino}methyl)azetidin-3-ol
133		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[1-(phenylmethyl)piperidin-4-yl]amino}methyl)azetidin-3-ol
134		3-({[2,2-bis(methyloxy)ethyl]amino}methyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
135		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1,1,3,3-tetramethylbutyl)amino]methyl}azetidin-3-ol
136		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1,1-dimethylpropyl)amino]methyl}azetidin-3-ol

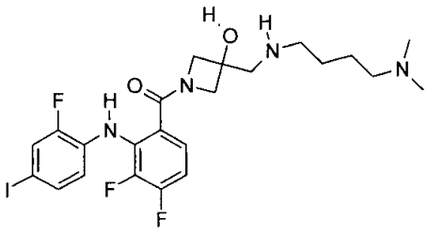
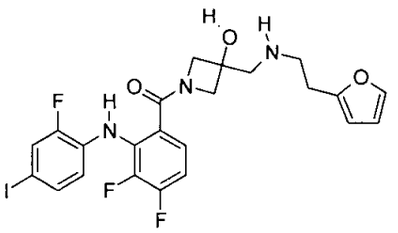
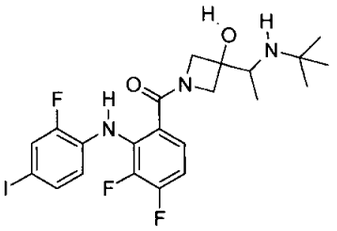
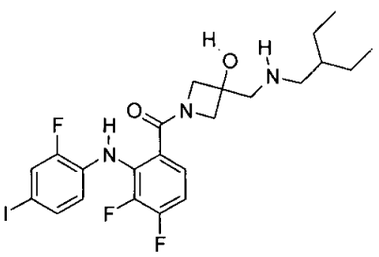
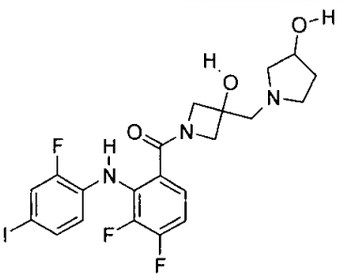
Cmpd No.	Structure	Name
137		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2,3-dihydro-1*H*-inden-1-ylamino)methyl]azetidin-3-ol
138		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[({2-[(phenylmethyl)oxy]cyclopentyl}amino)methyl]azetidin-3-ol
139		3-{[(3-amino-2-hydroxypropyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
140		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-hydroxy-1-(phenylmethyl)ethyl]amino}methyl)azetidin-3-ol
141		3-[(cyclooctylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol

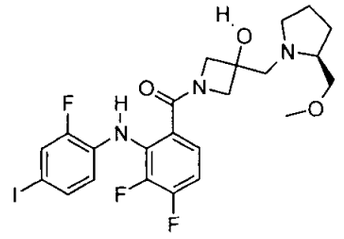
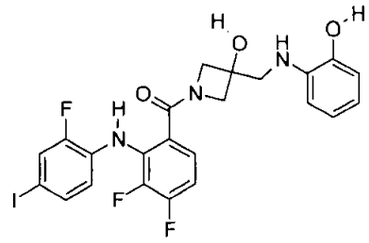
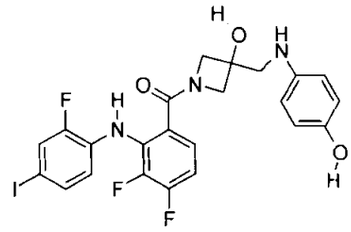
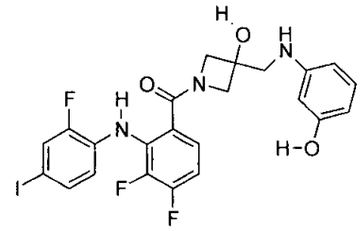
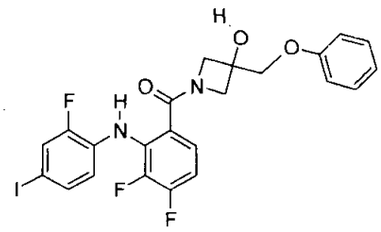
Cmpd No.	Structure	Name
142		3-{[(1-cyclohexylethyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
143		3-[(cycloheptylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
144		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-pyridin-3-ylethyl)amino]methyl}azetidin-3-ol
145		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[3-(methylthio)propyl]amino}methyl)azetidin-3-ol
146		*N*-cyclohexyl-*N*~2~-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}-2-methylalaninamide

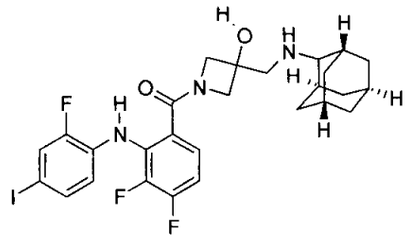
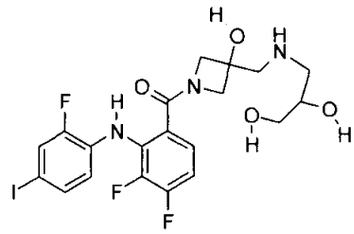
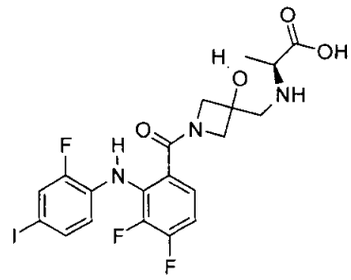
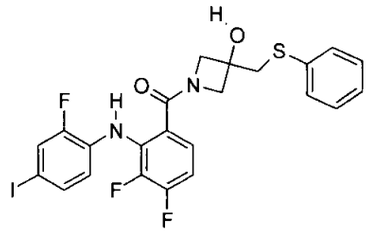
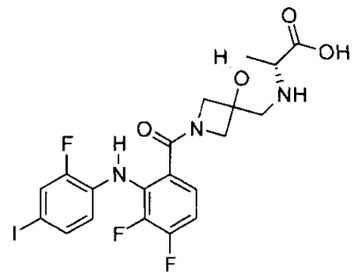
Cmpd No.	Structure	Name
147		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]methyl}azetidin-3-ol
148		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(3-hydroxypropyl)amino]methyl}azetidin-3-ol
149		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-pyridin-4-ylethyl)amino]methyl}azetidin-3-ol
150		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[1-(phenylmethyl)pyrrolidin-3-yl]amino}methyl)azetidin-3-ol
151		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(2-thienyl)ethyl]amino}methyl)azetidin-3-ol

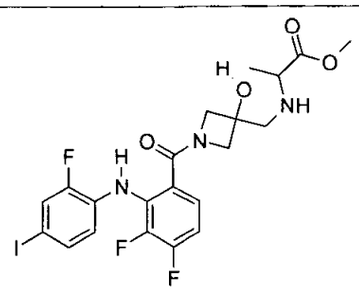
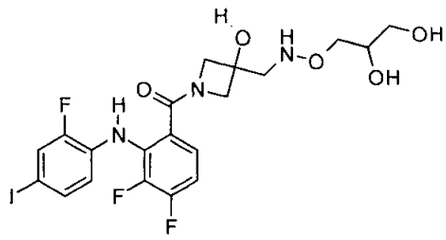
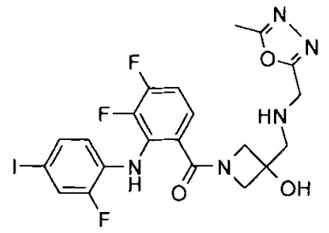
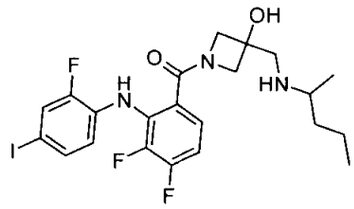
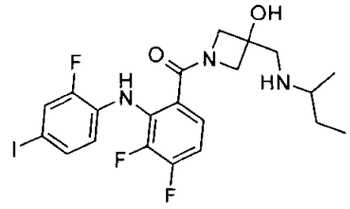
Cmpd No.	Structure	Name
152		3-[({2-[bis(1-methylethyl)amino]ethyl}amino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
153		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(phenyloxy)ethyl]amino}methyl)azetidin-3-ol
154		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(phenylamino)methyl]azetidin-3-ol
155		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxypropyl)amino]methyl}azetidin-3-ol
156		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[({2-[(1-methylethyl)oxy]ethyl}amino)methyl]azetidin-3-ol

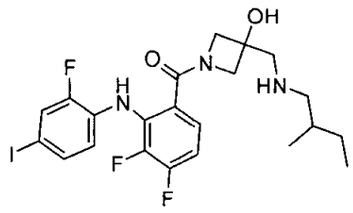
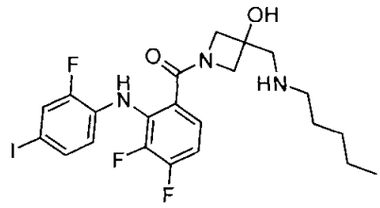
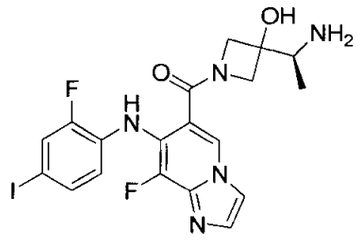
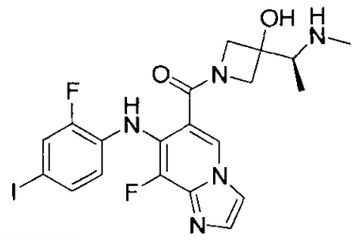
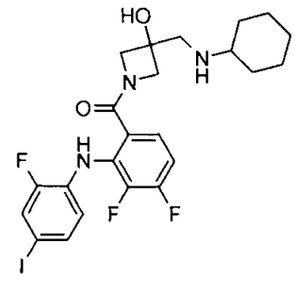
Cmpd No.	Structure	Name
157		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1-ethylpiperidin-3-yl)amino]methyl}azetidin-3-ol
158		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(methyloxy)ethyl]amino}methyl)azetidin-3-ol
159		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-nitropropyl)azetidin-3-ol
160		3-(1-aminoethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
161		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(1-methylpiperidin-4-yl)methyl]amino}methyl)azetidin-3-ol

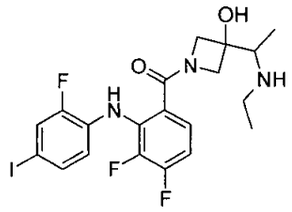
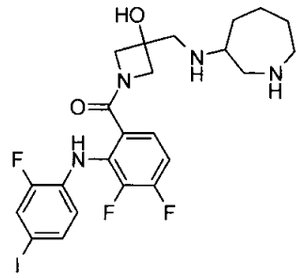
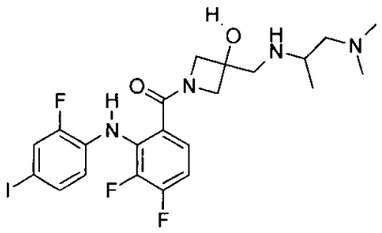
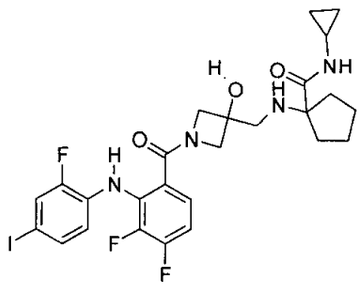
Cmpd No.	Structure	Name
162		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[4-(dimethylamino)butyl]amino}methyl)azetidin-3-ol
163		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-furan-2-ylethyl)amino]methyl}azetidin-3-ol
164		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{1-[(1,1-dimethylethyl)amino]ethyl}azetidin-3-ol
165		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-ethylbutyl)amino]methyl}azetidin-3-ol
166		1-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}pyrrolidin-3-ol

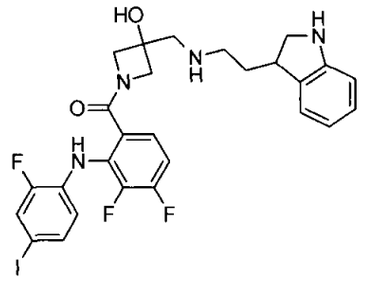
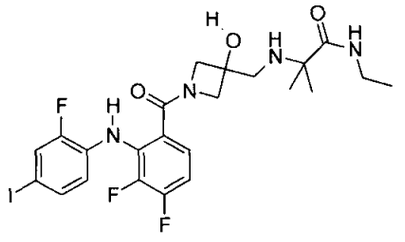
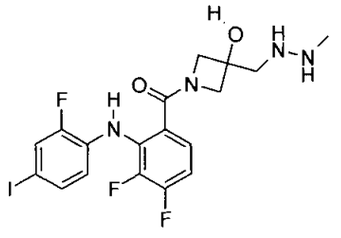
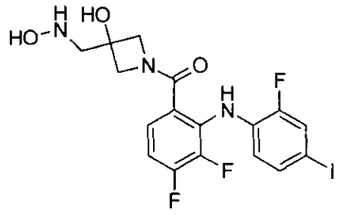
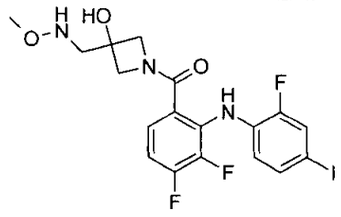
Cmpd No.	Structure	Name
167		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({(2*S*)-2-[(methyloxy)methyl]pyrrolidin-1-yl}methyl)azetidin-3-ol
168		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxyphenyl)amino]methyl}azetidin-3-ol
169		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(4-hydroxyphenyl)amino]methyl}azetidin-3-ol
170		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(3-hydroxyphenyl)amino]methyl}azetidin-3-ol
171		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(phenyloxy)methyl]azetidin-3-ol

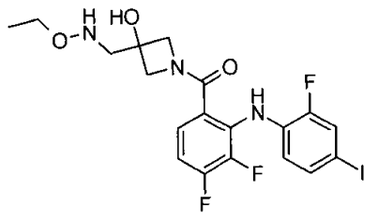
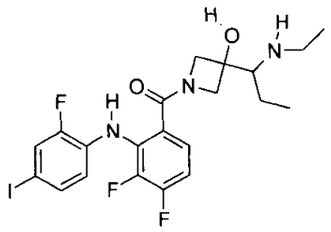
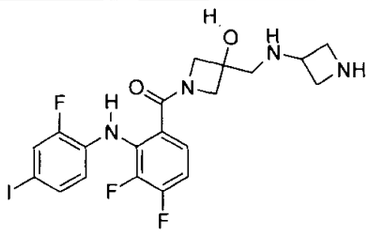
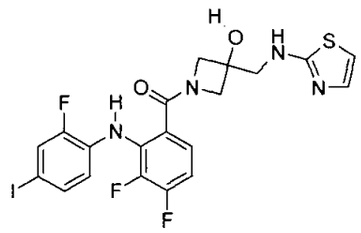
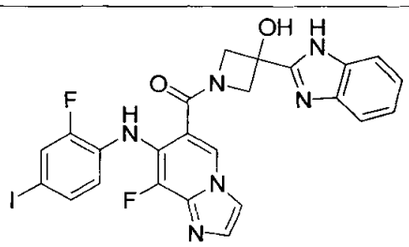
Cmpd No.	Structure	Name
172		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1r,3r,5*R*,7*R*)-tricyclo[3.3.1.1~3,7~]dec-2-ylamino]methyl}azetidin-3-ol
173		3-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)propane-1,2-diol
174		*N*-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}-L-alanine
175		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(phenylthio)methyl]azetidin-3-ol
176		*N*-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}-D-alanine

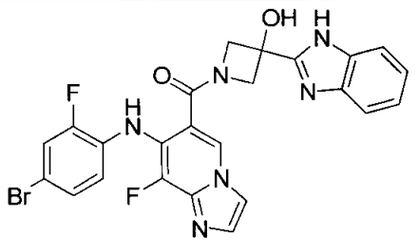
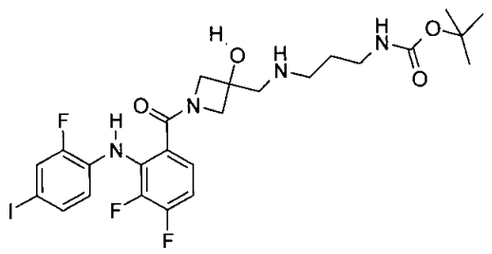
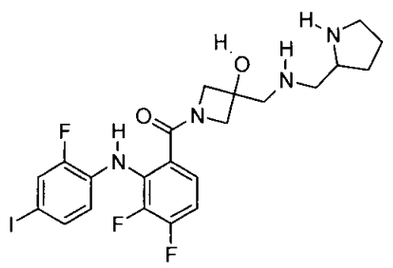
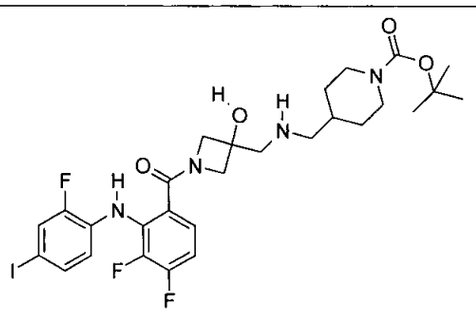
Cmpd No.	Structure	Name
177		methyl *N*-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}alaninate
178		3-[({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)oxy]propane-1,2-diol
179		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]amino}methyl)azetidin-3-ol
180		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1-methylbutyl)amino]methyl}azetidin-3-ol
181		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1-methylpropyl)amino]methyl}azetidin-3-ol

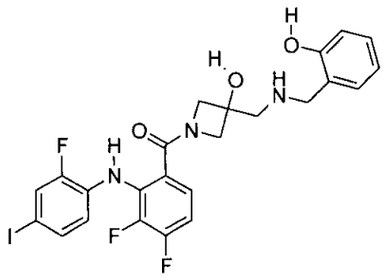
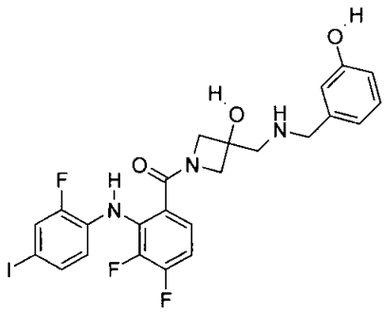
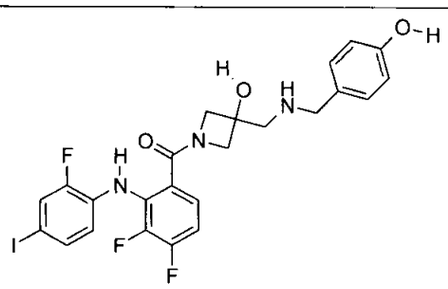
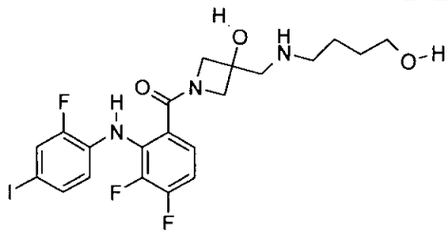
Cmpd No.	Structure	Name
182		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-methylbutyl)amino]methyl}azetidin-3-ol
183		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(pentylamino)methyl]azetidin-3-ol
184		3-[(1*S*)-1-aminoethyl]-1-({8-fluoro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-*a*]pyridin-6-yl}carbonyl)azetidin-3-ol
185		1-({8-fluoro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-*a*]pyridin-6-yl}carbonyl)-3-[(1*S*)-1-(methylamino)ethyl]azetidin-3-ol
186		3-[(cyclohexylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol

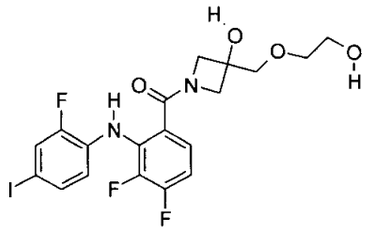
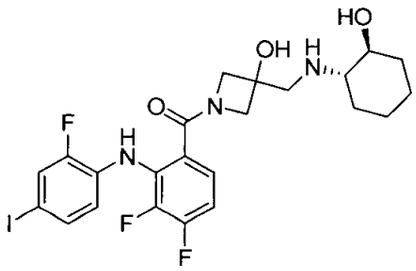
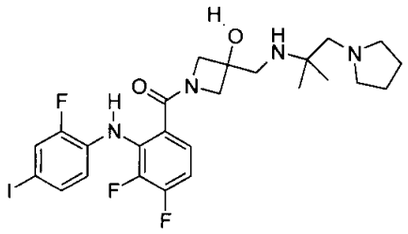
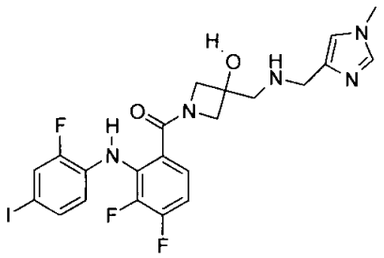
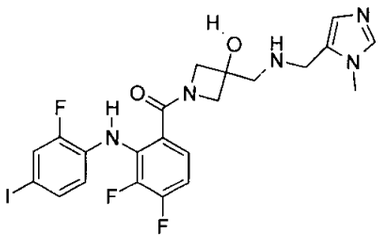
Cmpd No.	Structure	Name
187		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[1-(ethylamino)ethyl]azetidin-3-ol
188		3-[(azepan-3-ylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
189		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(dimethylamino)-1-methylethyl]amino}methyl)azetidin-3-ol
190		*N*-cyclopropyl-1-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)cyclopentanecarboxamide

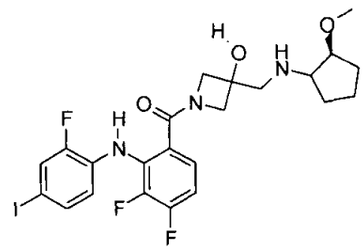
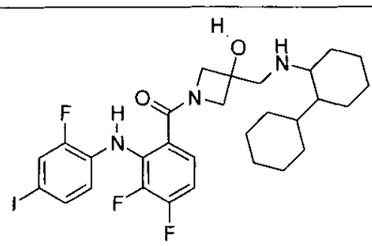
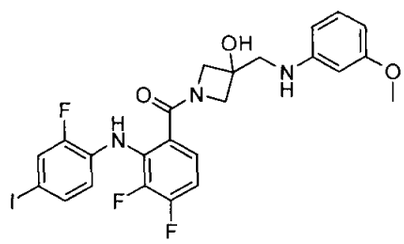
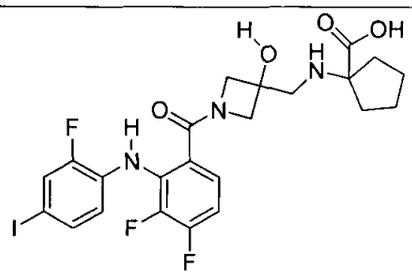
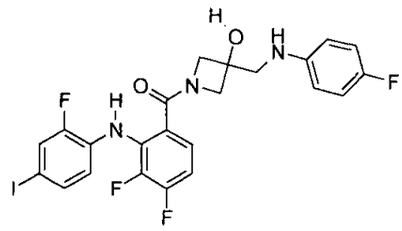
Cmpd No.	Structure	Name
191		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(2,3-dihydro-1*H*-indol-3-yl)ethyl]amino}methyl)azetidin-3-ol
192		*N*~2~-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}-*N*-ethyl-2-methylalaninamide
193		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2-methylhydrazino)methyl]azetidin-3-ol
194		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(hydroxyamino)methyl]azetidin-3-ol
195		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(methyloxy)amino]methyl}azetidin-3-ol

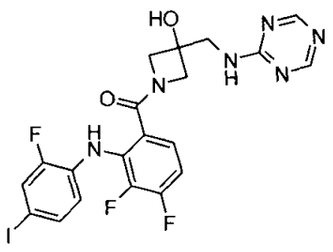
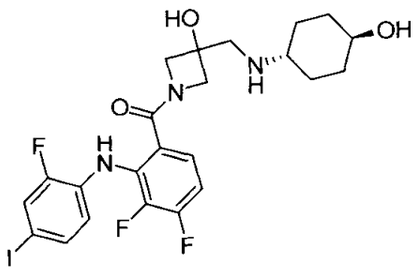
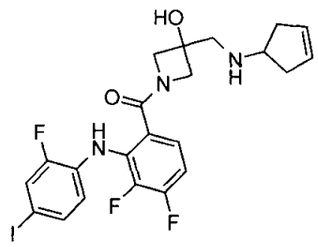
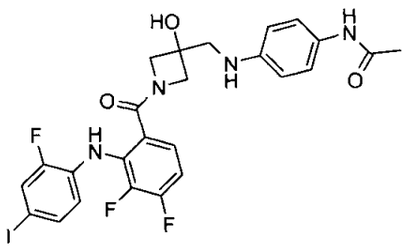
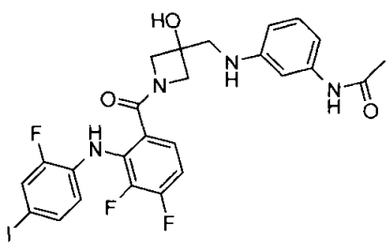
Cmpd No.	Structure	Name
196		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(ethyloxy)amino]methyl}azetidin-3-ol
197		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[1-(ethylamino)propyl]azetidin-3-ol
198		3-[(azetidin-3-ylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
199		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(1,3-thiazol-2-ylamino)methyl]azetidin-3-ol
200		3-(1*H*-benzimidazol-2-yl)-1-({8-fluoro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-*a*]pyridin-6-yl}carbonyl)azetidin-3-ol

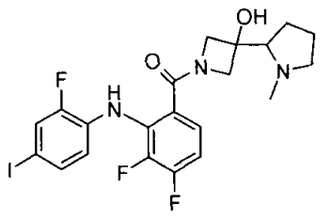
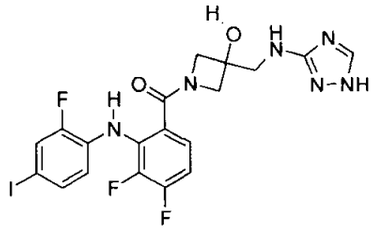
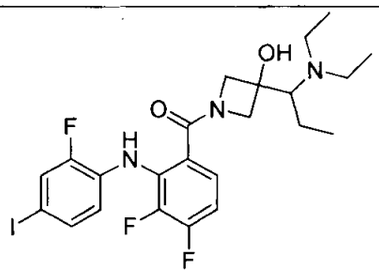
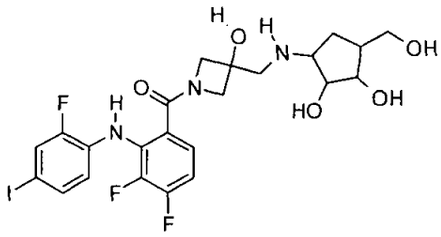
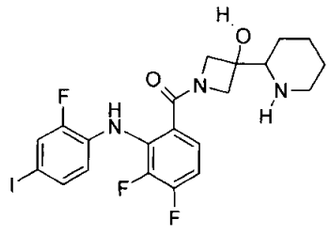
Cmpd No.	Structure	Name
201		3-(1*H*-benzimidazol-2-yl)-1-({7-[(4-bromo-2-fluorophenyl)amino]-8-fluoroimidazo[1,2-*a*]pyridin-6-yl}carbonyl)azetidin-3-ol
202		1,1-dimethylethyl [3-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)propyl]carbamate
203		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(pyrrolidin-2-ylmethyl)amino]methyl}azetidin-3-ol
204		1,1-dimethylethyl 4-[({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)methyl]piperidine-1-carboxylate

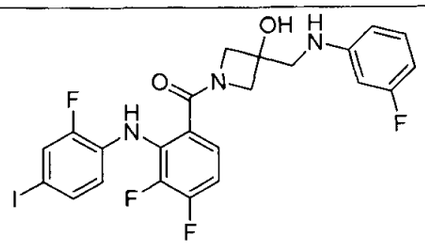
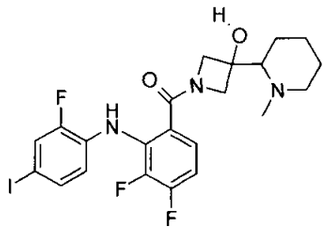
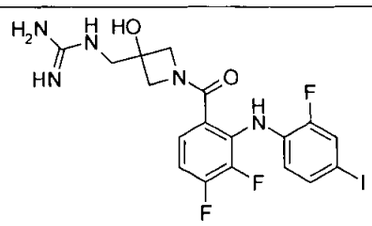
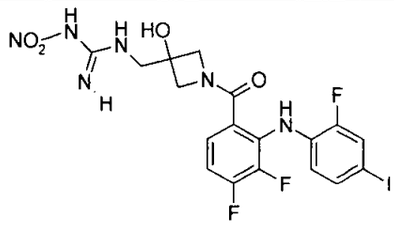
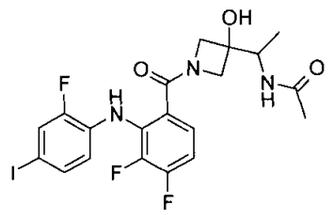
Cmpd No.	Structure	Name
205		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(2-hydroxyphenyl)methyl]amino}methyl) azetidin-3-ol
206		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(3-hydroxyphenyl)methyl]amino}methyl) azetidin-3-ol
207		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(4-hydroxyphenyl)methyl]amino}methyl) azetidin-3-ol
208		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(4-hydroxybutyl)amino]methyl}azetidin-3-ol

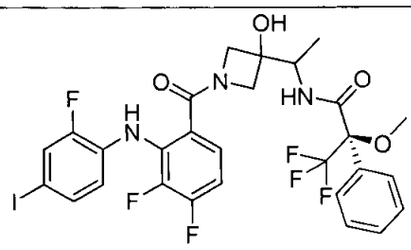
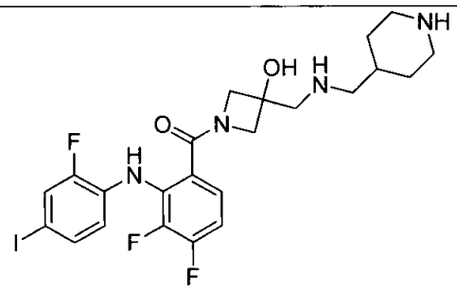
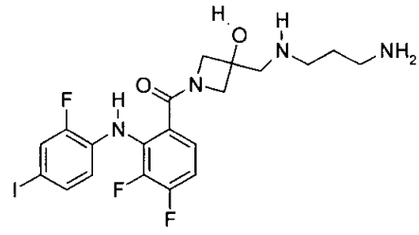
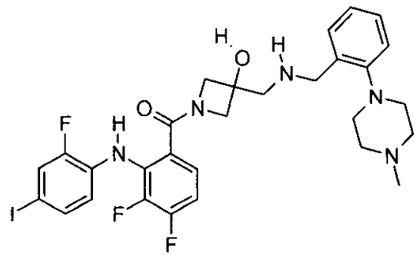
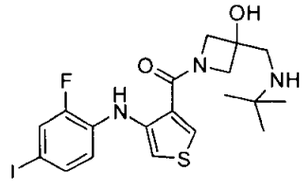
Cmpd No.	Structure	Name
209		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxyethyl)oxy]methyl}azetidin-3-ol
210		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(1*S*,2*S*)-2-hydroxycyclohexyl]amino}methyl)azetidin-3-ol
211		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1,1-dimethyl-2-pyrrolidin-1-ylethyl)amino]methyl}azetidin-3-ol
212		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(1-methyl-1*H*-imidazol-4-yl)methyl]amino}methyl)azetidin-3-ol
213		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(1-methyl-1*H*-imidazol-5-yl)methyl]amino}methyl)azetidin-3-ol

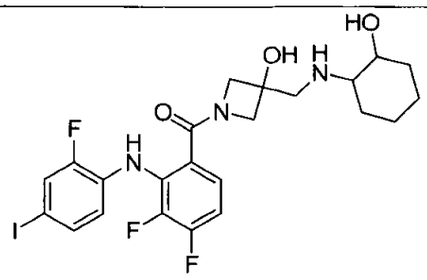
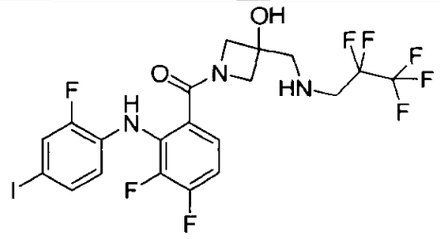
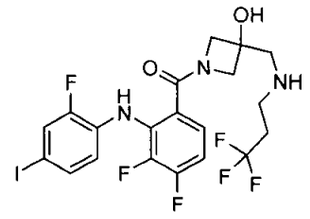
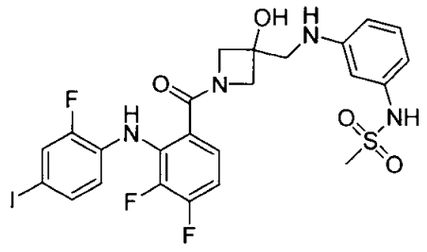
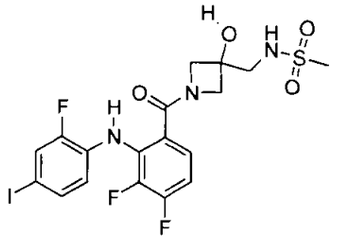
Cmpd No.	Structure	Name
214		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(2*S*)-2-(methyloxy)cyclopentyl]amino}methyl)azetidin-3-ol
215		3-{[1,1'-bi(cyclohexyl)-2-ylamino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
216		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[3-(methyloxy)phenyl]amino}methyl)azetidin-3-ol
217		1-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)cyclopentanecarboxylic acid
218		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(4-fluorophenyl)amino]methyl}azetidin-3-ol

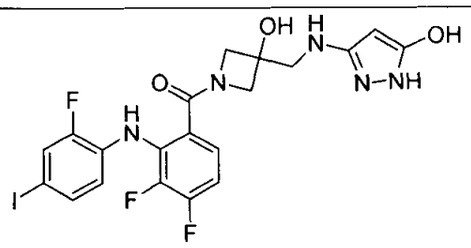
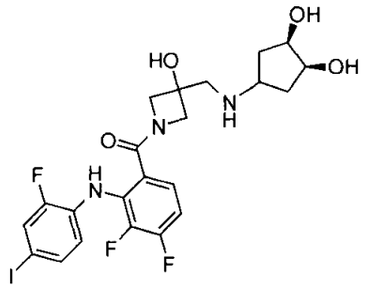
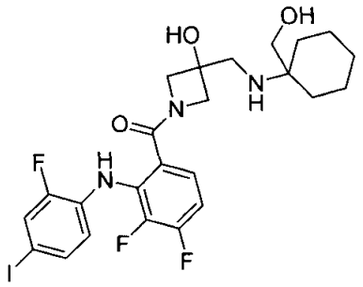
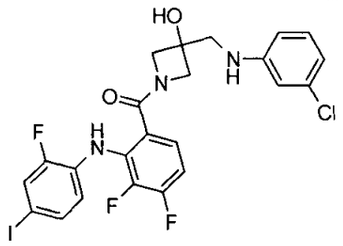
Cmpd No.	Structure	Name
219		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(1,3,5-triazin-2-ylamino)methyl]azetidin-3-ol
220		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(*trans*-4-hydroxycyclohexyl)amino]methyl}azetidin-3-ol
221		3-[(cyclopent-3-en-1-ylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
222		*N*-[4-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)phenyl]acetamide
223		*N*-[3-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)phenyl]acetamide

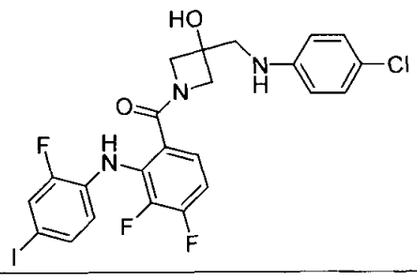
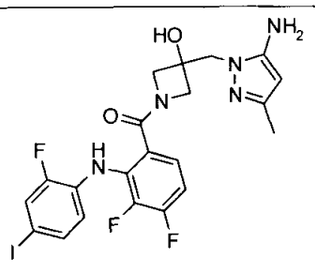
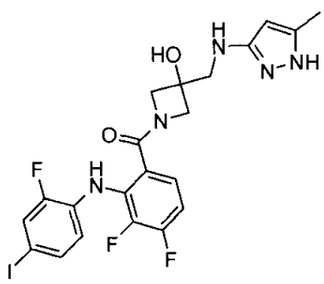
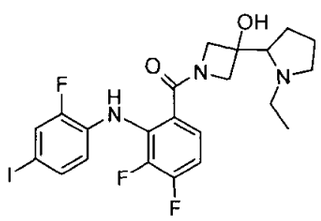
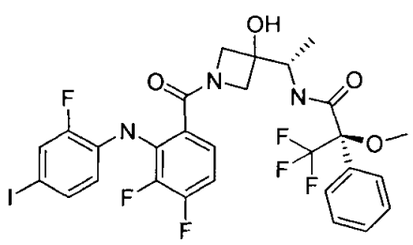
Cmpd No.	Structure	Name
224		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-methylpyrrolidin-2-yl)azetidin-3-ol
225		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(1*H*-1,2,4-triazol-3-ylamino)methyl]azetidin-3-ol
226		3-[1-(diethylamino)propyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
227		3-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)-5-(hydroxymethyl)cyclopentane-1,2-diol
228		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-piperidin-2-ylazetidin-3-ol

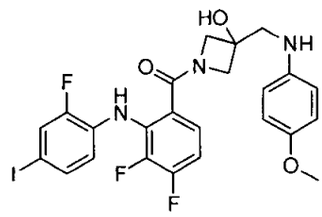
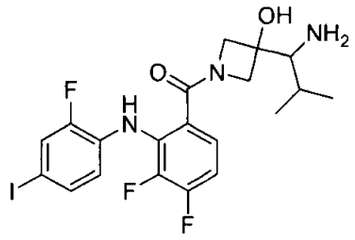
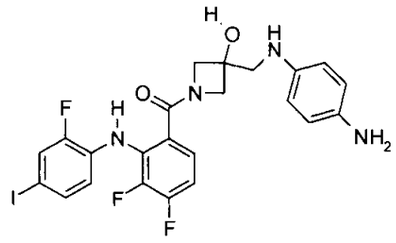
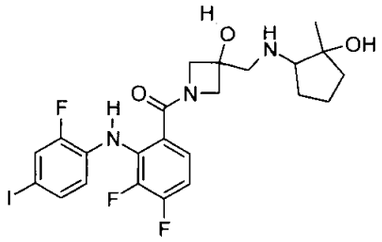
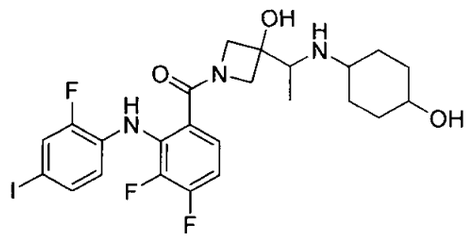
Cmpd No.	Structure	Name
229		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(3-fluorophenyl)amino]methyl}azetidin-3-ol
230		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-methylpiperidin-2-yl)azetidin-3-ol
231		1-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}guanidine
232		1-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}-3-nitroguanidine
233		*N*-{1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}acetamide

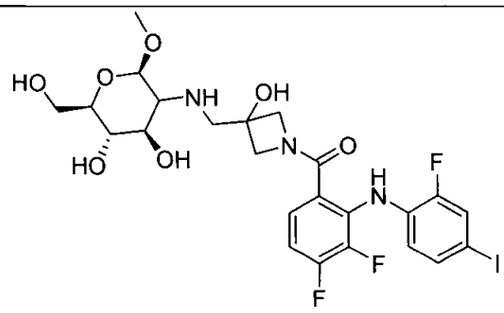
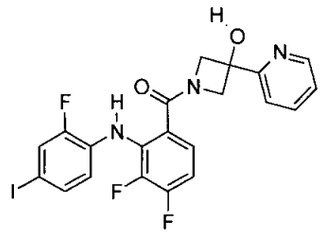
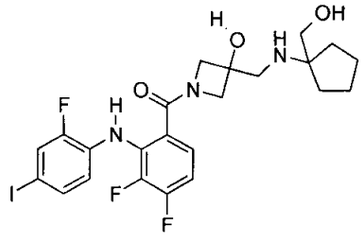
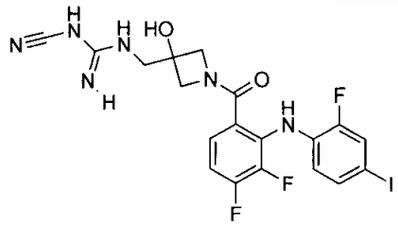
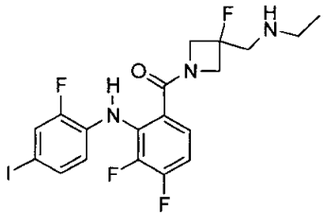
Cmpd No.	Structure	Name
234		(2*R*)-*N*-{1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanamide
235		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(piperidin-4-ylmethyl)amino]methyl}azetidin-3-ol
236		3-{[(3-aminopropyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
237		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[({[2-(4-methylpiperazin-1-yl)phenyl]methyl}amino)methyl]azetidin-3-ol
238		3-{[(1,1-dimethylethyl)amino]methyl}-1-({4-[(2-fluoro-4-iodophenyl)amino]-3-thienyl}carbonyl)azetidin-3-ol

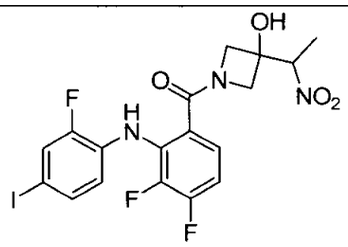
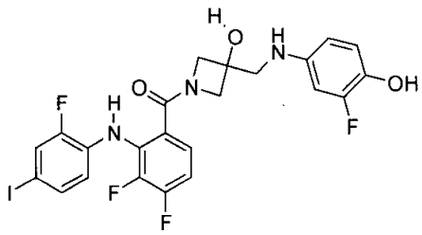
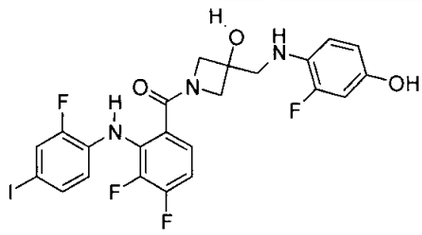
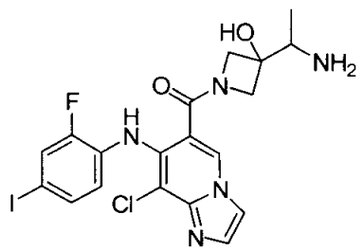
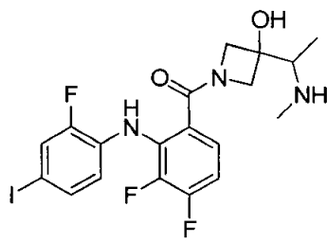
Cmpd No.	Structure	Name
239		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxycyclohexyl)amino]methyl}azetidin-3-ol
240		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2,2,3,3,3-pentafluoropropyl)amino]methyl}azetidin-3-ol
241		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(3,3,3-trifluoropropyl)amino]methyl}azetidin-3-ol
242		*N*-[3-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)phenyl]methanesulfonamide
243		*N*-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}methanesulfonamide

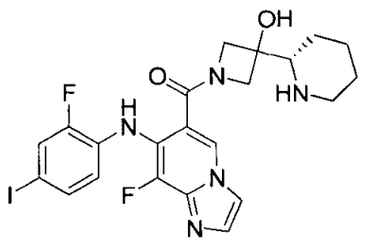
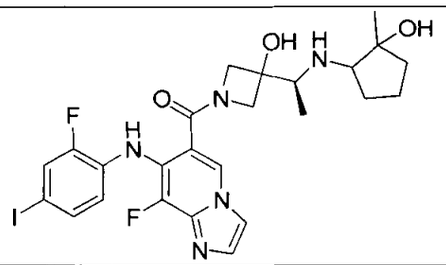
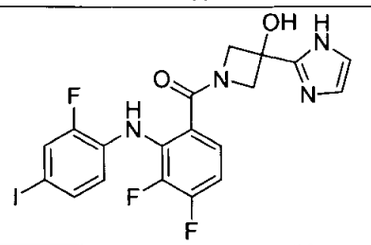
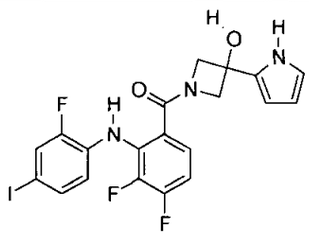
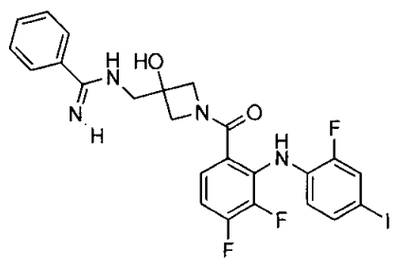
Cmpd No.	Structure	Name
244		3-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)-1*H*-pyrazol-5-ol
245		(1*R*,2*S*)-4-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)cyclopentane-1,2-diol
246		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[1-(hydroxymethyl)cyclohexyl]amino}methyl)azetidin-3-ol
247		3-{[(3-chlorophenyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol

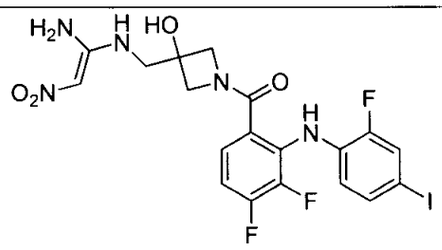
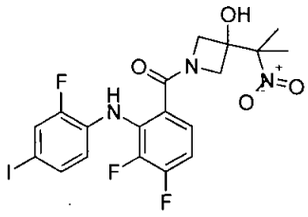
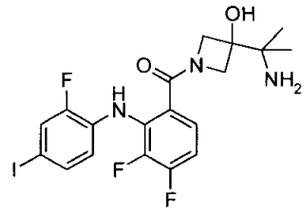
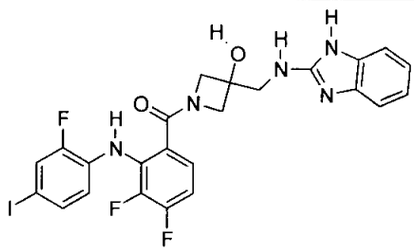
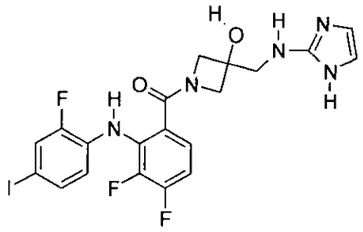
Cmpd No.	Structure	Name
248		3-{[(4-chlorophenyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
249		3-[(5-amino-3-methyl-1*H*-pyrazol-1-yl)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
250		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(5-methyl-1*H*-pyrazol-3-yl)amino]methyl}azetidin-3-ol
251		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-ethylpyrrolidin-2-yl)azetidin-3-ol
252		(2*R*)-*N*-{(1*S*)-1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanamide

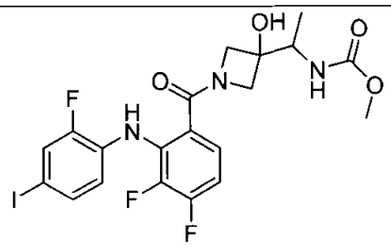
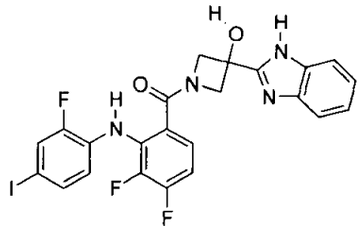
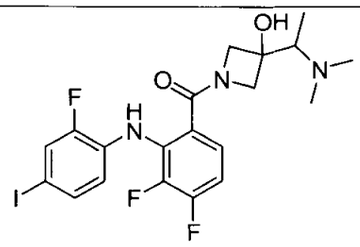
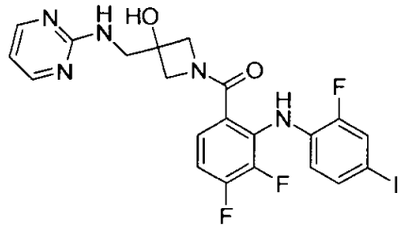
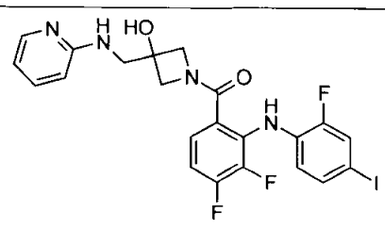
Cmpd No.	Structure	Name
253		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[4-(methyloxy)phenyl]amino}methyl)azetidin-3-ol
254		3-(1-amino-2-methylpropyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
255		3-{[(4-aminophenyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
256		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxy-2-methylcyclopentyl)amino]methyl}azetidin-3-ol
257		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{1-[(4-hydroxycyclohexyl)amino]ethyl}azetidin-3-ol

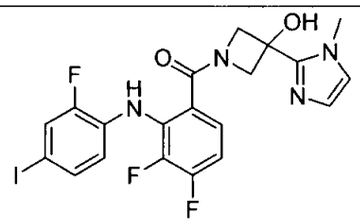
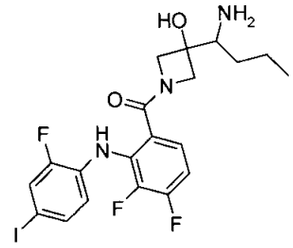
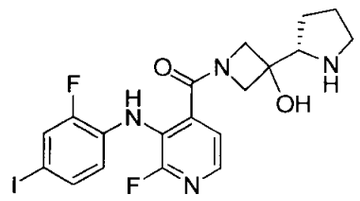
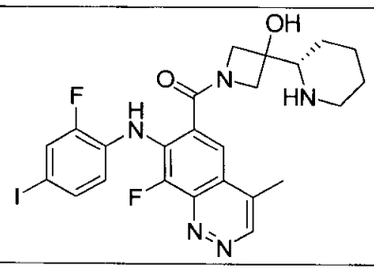
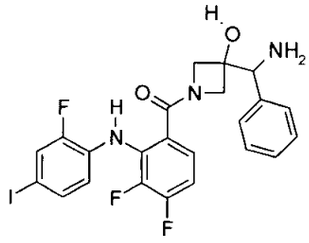
Cmpd No.	Structure	Name
258		methyl (2xi)-2-deoxy-2-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)-beta-D-arabino-hexopyranoside
259		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-pyridin-2-ylazetidin-3-ol
260		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[1-(hydroxymethyl)cyclopentyl]amino}methyl)azetidin-3-ol
261		1-cyano-3-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}guanidine
262		6-({3-[(ethylamino)methyl]-3-fluoroazetidin-1-yl}carbonyl)-2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)aniline

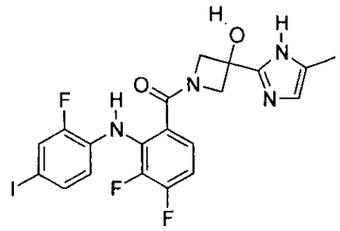
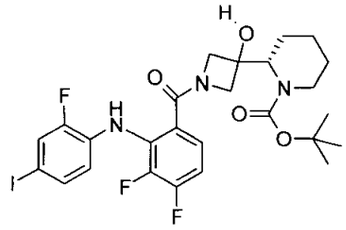
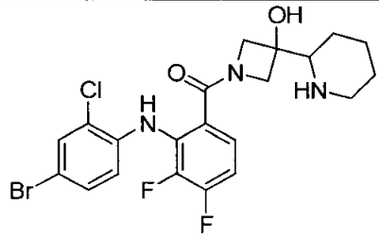
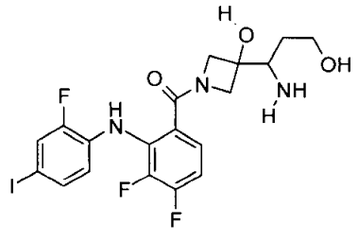
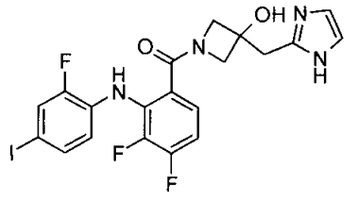
Cmpd No.	Structure	Name
263		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-nitroethyl)azetidin-3-ol
264		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(3-fluoro-4-hydroxyphenyl)amino]methyl}azetidin-3-ol
265		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-fluoro-4-hydroxyphenyl)amino]methyl}azetidin-3-ol
266		3-(1-aminoethyl)-1-({8-chloro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-a]pyridin-6-yl}carbonyl)azetidin-3-ol
267		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[1-(methylamino)ethyl]azetidin-3-ol

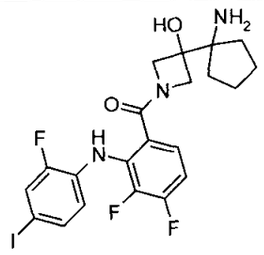
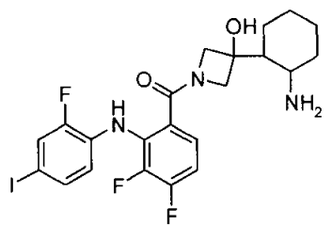
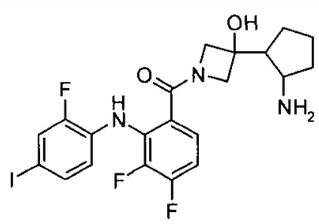
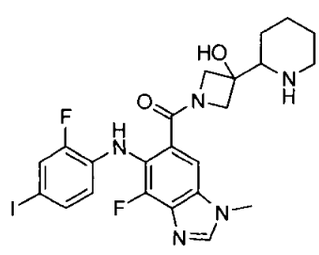
Cmpd No.	Structure	Name
268		1-({8-fluoro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-*a*]pyridin-6-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol
269		1-({8-fluoro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-*a*]pyridin-6-yl}carbonyl)-3-{(1*S*)-1-[(2-hydroxy-2-methylcyclopentyl)amino]ethyl}azetidin-3-ol
270		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1*H*-imidazol-2-yl)azetidin-3-ol
271		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1*H*-pyrrol-2-yl)azetidin-3-ol
272		*N*-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}benzenecarboximidamide

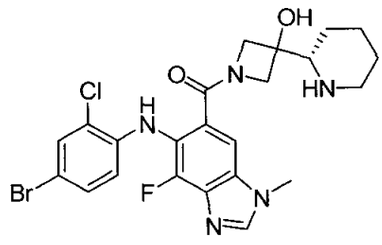
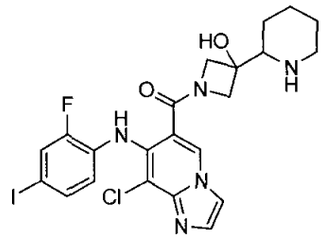
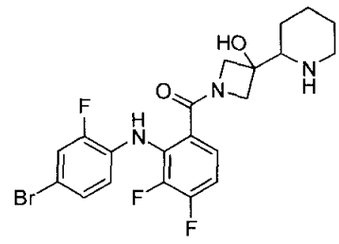
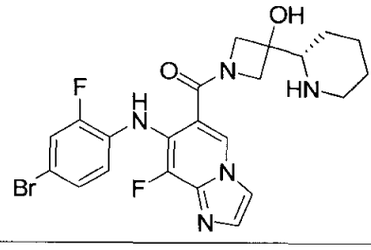
Cmpd No.	Structure	Name
273		3-({[(E)-1-amino-2-nitroethenyl]amino}methyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
274		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-methyl-1-nitroethyl)azetidin-3-ol
275		3-(1-amino-1-methylethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
276		3-[(1*H*-benzimidazol-2-ylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
277		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(1*H*-imidazol-2-ylamino)methyl]azetidin-3-ol

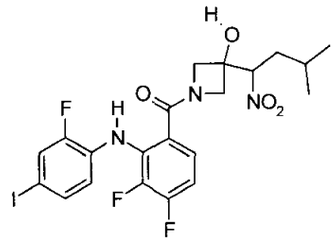
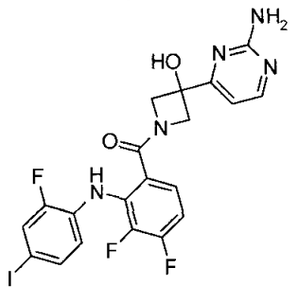
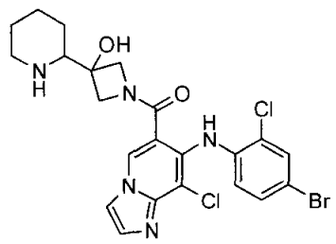
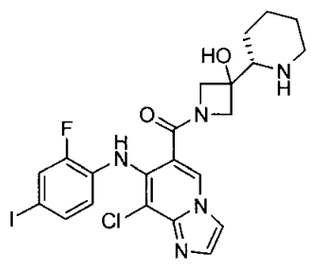
Cmpd No.	Structure	Name
278		methyl {1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}carbamate
279		3-(1*H*-benzimidazol-2-yl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
280		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[1-(dimethylamino)ethyl]azetidin-3-ol
281		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(pyrimidin-2-ylamino)methyl]azetidin-3-ol
282		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(pyridin-2-ylamino)methyl]azetidin-3-ol

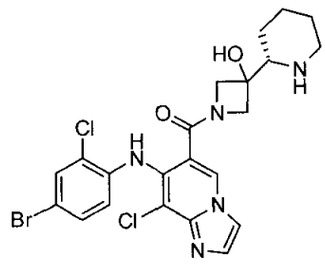
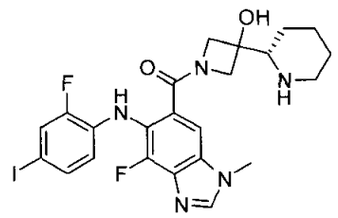
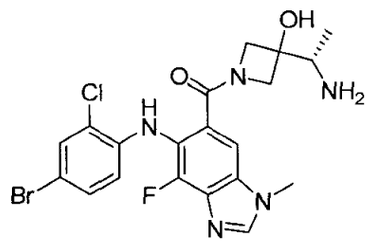
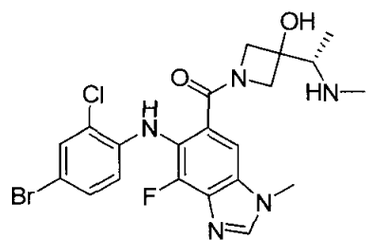
Cmpd No.	Structure	Name
283		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-methyl-1*H*-imidazol-2-yl)azetidin-3-ol
284		3-(1-aminobutyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
285		1-({2-fluoro-3-[(2-fluoro-4-iodophenyl)amino]pyridin-4-yl}carbonyl)-3-[(2*S*)-pyrrolidin-2-yl]azetidin-3-ol
286		1-({8-fluoro-7-[(2-fluoro-4-iodophenyl)amino]-4-methylcinnolin-6-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol
287		3-[amino(phenyl)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol

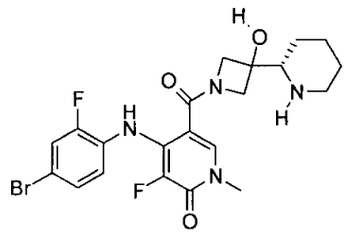
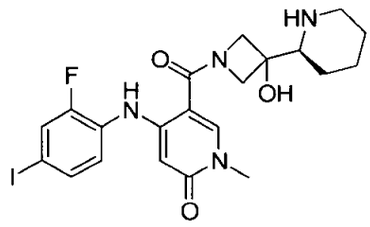
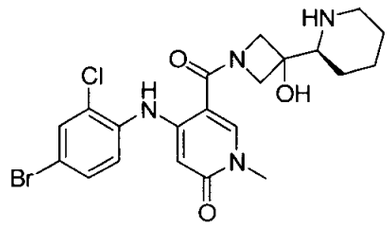
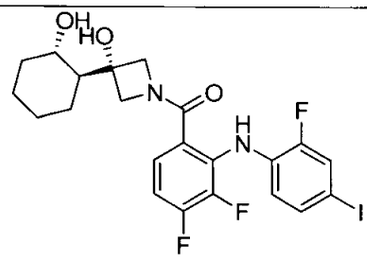
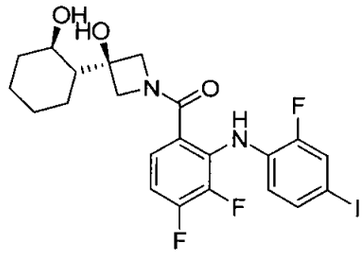
Cmpd No.	Structure	Name
288		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(5-methyl-1*H*-imidazol-2-yl)azetidin-3-ol
289		1,1-dimethylethyl (2*S*)-2-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]piperidine-1-carboxylate
290		1-({2-[(4-bromo-2-chlorophenyl)amino]-3,4-difluorophenyl}carbonyl)-3-piperidin-2-ylazetidin-3-ol
291		3-(1-amino-3-hydroxypropyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
292		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1*H*-imidazol-2-ylmethyl)azetidin-3-ol

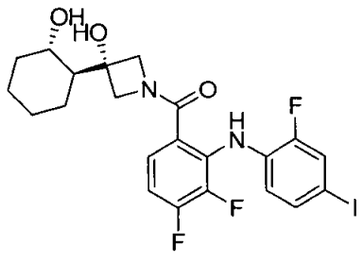
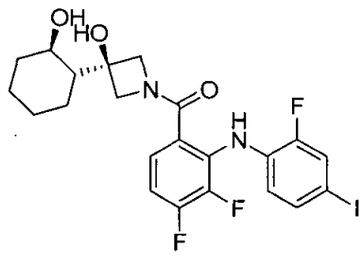
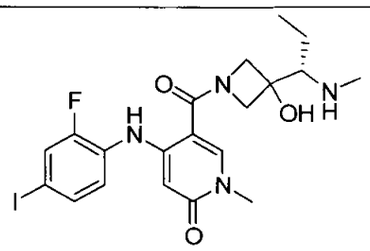
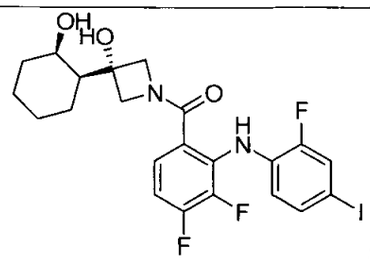
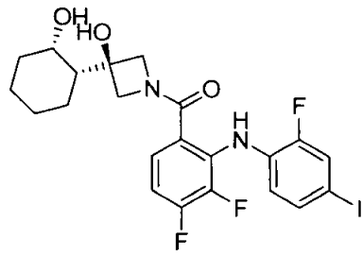
Cmpd No.	Structure	Name
293		3-(1-aminocyclopentyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
294		3-(2-aminocyclohexyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
295		3-(2-aminocyclopentyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-azetidin-3-ol
296		1-({4-fluoro-5-[(2-fluoro-4-iodophenyl)amino]-1-methyl-1*H*-benzimidazol-6-yl}carbonyl)-3-piperidin-2-ylazetidin-3-ol

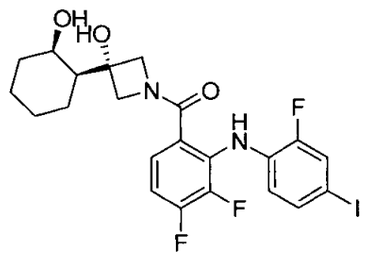
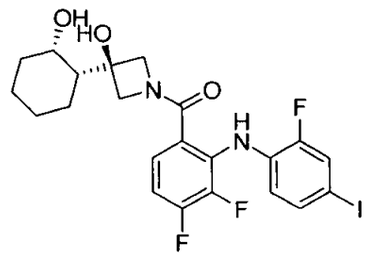
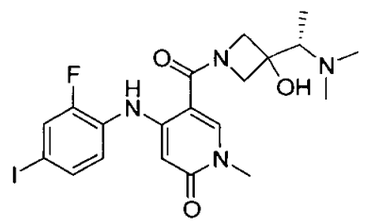
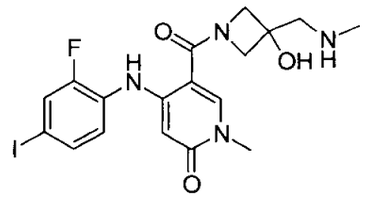
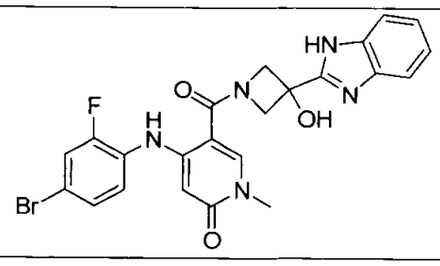
Cmpd No.	Structure	Name
297		1-({5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-1-methyl-1*H*-benzimidazol-6-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol
298		1-({8-chloro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-a]pyridin-6-yl}carbonyl)-3-piperidin-2-ylazetidin-3-ol
299		1-({2-[(4-bromo-2-fluorophenyl)amino]-3,4-difluorophenyl}carbonyl)-3-piperidin-2-ylazetidin-3-ol
300		1-({7-[(4-bromo-2-fluorophenyl)amino]-8-fluoroimidazo[1,2-*a*]pyridin-6-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol

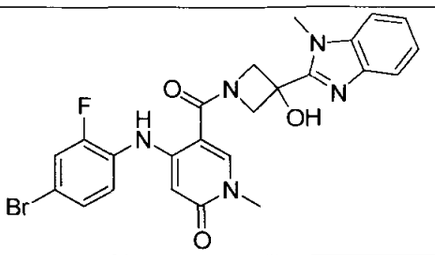
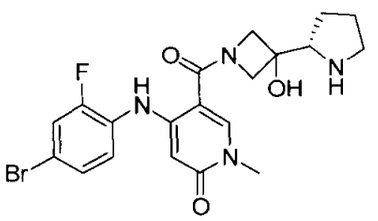
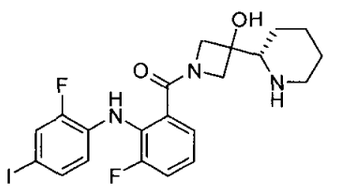
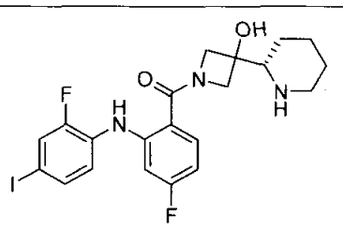
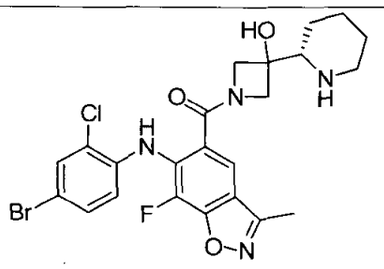
Cmpd No.	Structure	Name
301		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(3-methyl-1-nitrobutyl)azetidin-3-ol
302		3-(2-aminopyrimidin-4-yl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol
303		1-({7-[(4-bromo-2-chlorophenyl)amino]-8-chloroimidazo[1,2-a]pyridin-6-yl}carbonyl)-3-piperidin-2-ylazetidin-3-ol
304		1-({8-chloro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-a]pyridin-6-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol

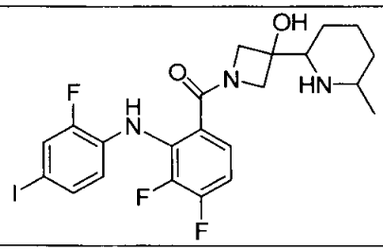
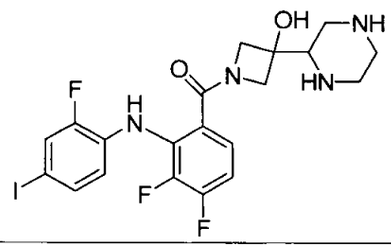
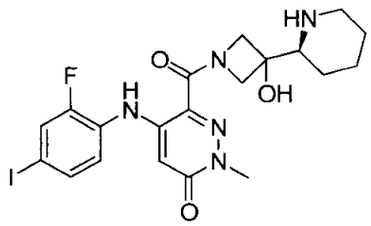
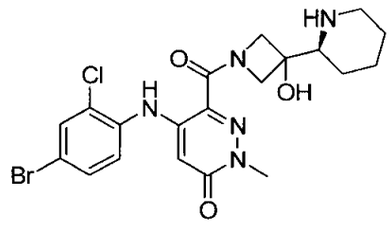
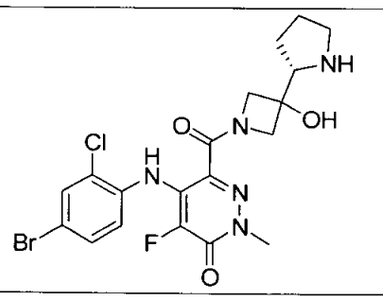
Cmpd No.	Structure	Name
305		1-({7-[(4-bromo-2-chlorophenyl)amino]-8-chloroimidazo[1,2-a]pyridin-6-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol
306		1--({4-fluoro-5-[(2-fluoro-4-iodophenyl)amino]-1-methyl-1*H*-benzimidazol-6-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol
307		3-[(1*S*)-1-aminoethyl]-1-({5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-1-methyl-1*H*-benzimidazol-6-yl}carbonyl)azetidin-3-ol
308		1-({5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-1-methyl-1*H*-benzimidazol-6-yl}carbonyl)-3-[(1*S*)-1-(methylamino)ethyl]azetidin-3-ol

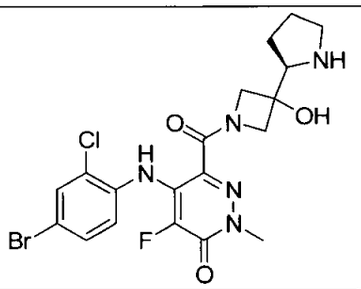
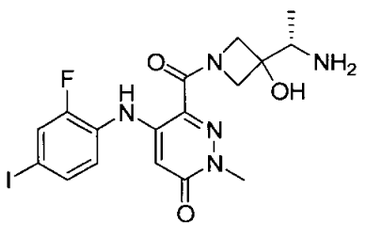
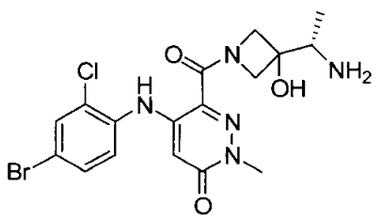
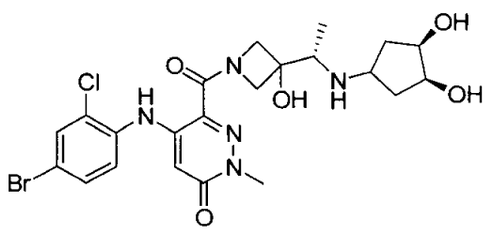
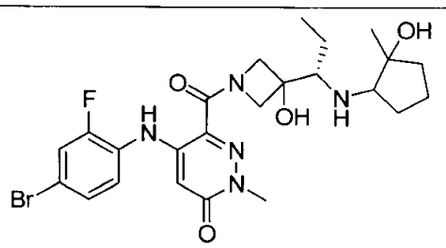
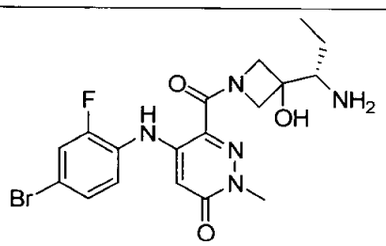
Cmpd No.	Structure	Name
309		4-[(4-bromo-2-fluorophenyl)amino]-3-fluoro-5-({3-hydroxy-3-[(2*S*)-piperidin-2-yl]azetidin-1-yl}carbonyl)pyridin-2(1*H*)-one
310		4-[(2-fluoro-4-iodophenyl)amino]-5-({3-hydroxy-3-[(2*S*)-piperidin-2-yl]azetidin-1-yl}carbonyl)-1-methylpyridin-2(1*H*)-one
311		4-[(2-fluoro-4-iodophenyl)amino]-5-({3-hydroxy-3-[(2*S*)-piperidin-2-yl]azetidin-1-yl}carbonyl)-1-methylpyridin-2(1*H*)-one
312	 and 	(±)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(*trans*)-2-hydroxycyclohexyl]azetidin-3-ol

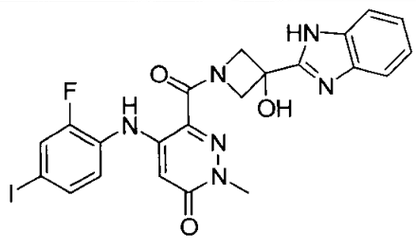
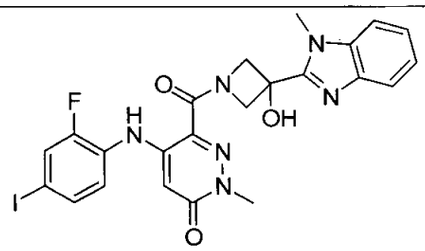
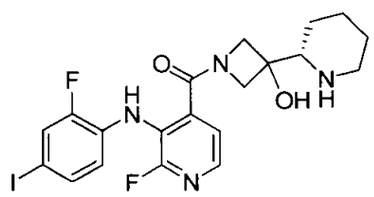
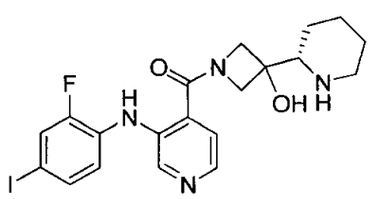
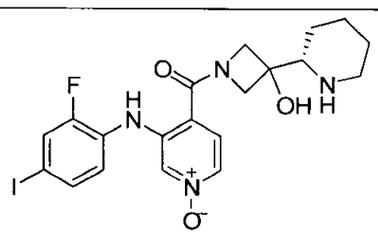
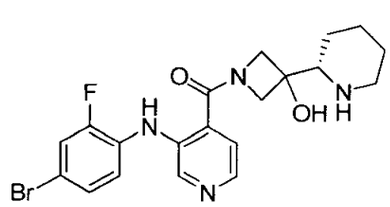
Cmpd No.	Structure	Name
313		(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)(3-hydroxy-3-((1*S*,2*S*)-2-hydroxycyclohexyl)azetidin-1-yl)methanone
314		(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)(3-hydroxy-3-((1*S*,2*R*)-2-hydroxycyclohexyl)azetidin-1-yl)methanone
315		4-[(2-fluoro-4-iodophenyl)amino]-5-({3-hydroxy-3-[(1*S*)-1-(methylamino)propyl]azetidin-1-yl}carbonyl)-1-methylpyridin-2(1*H*)-one
316	 and 	(±)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(*cis*)-2-hydroxycyclohexyl]azetidin-3-ol

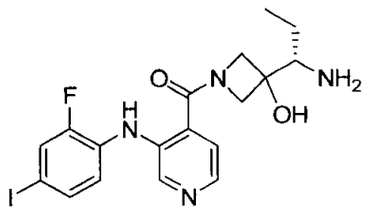
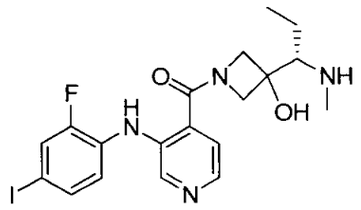
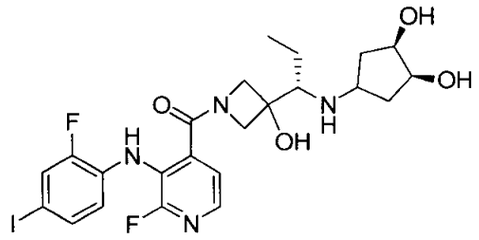
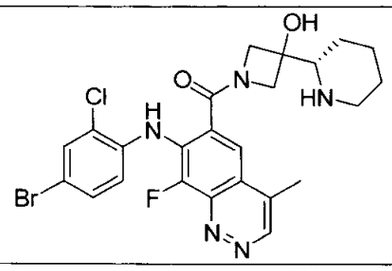
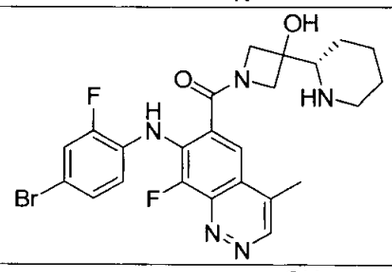
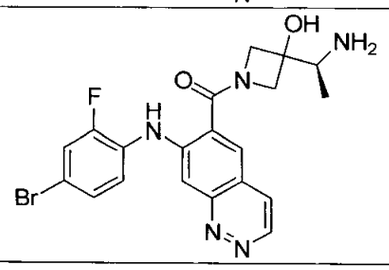
Cmpd No.	Structure	Name
317		(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)(3-hydroxy-3-((1*S*,2*R*)-2-hydroxycyclohexyl)azetidin-1-yl)methanone
318		(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)(3-hydroxy-3-((1*R*,2*S*)-2-hydroxycyclohexyl)azetidin-1-yl)methanone
319		5-({3-[(1*S*)-1-(dimethylamino)ethyl]-3-hydroxyazetidin-1-yl}carbonyl)-4-[(2-fluoro-4-iodophenyl)amino]-1-methylpyridin-2(1*H*)-one
320		4-[(2-fluoro-4-iodophenyl)amino]-5-({3-hydroxy-3-[(methylamino)methyl]azetidin-1-yl}carbonyl)-1-methylpyridin-2(1*H*)-one
321		5-{[3-(1*H*-benzimidazol-2-yl)-3-hydroxyazetidin-1-yl]carbonyl}-4-[(4-bromo-2-fluorophenyl)amino]-1-methylpyridin-2(1*H*)-one

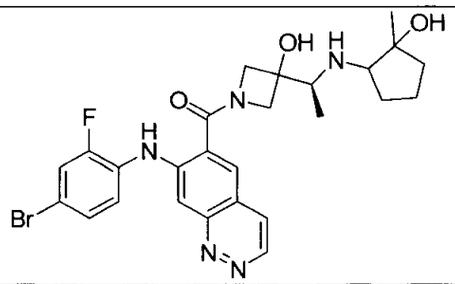
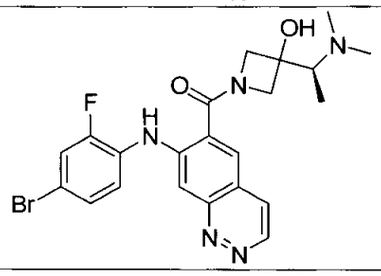
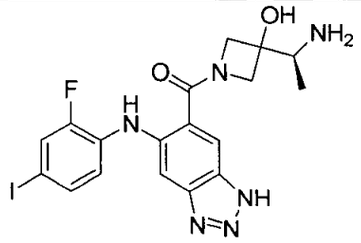
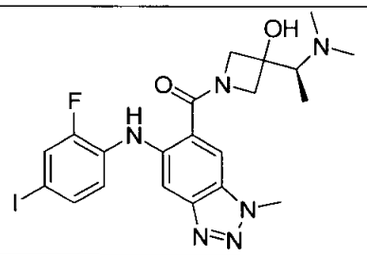
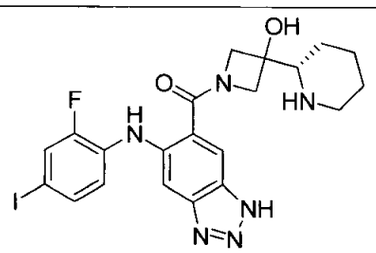
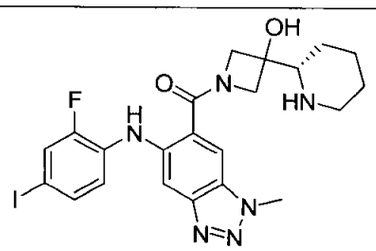
Cmpd No.	Structure	Name
322		4-[(4-bromo-2-fluorophenyl)amino]-5-{[3-hydroxy-3-(1-methyl-1*H*-benzimidazol-2-yl)azetidin-1-yl]carbonyl}-1-methylpyridin-2(1*H*)-one
323		4-[(4-bromo-2-fluorophenyl)amino]-5-({3-hydroxy-3-[(2*S*)-pyrrolidin-2-yl]azetidin-1-yl}carbonyl)-1-methylpyridin-2(1*H*)-one
324		1-({3-fluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol
325		1-({4-fluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol
326		1-({6-[(4-bromo-2-chlorophenyl)amino]-7-fluoro-3-methyl-1,2-benzisoxazol-5-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol
327		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(6-methylpiperidin-2-yl)azetidin-3-ol

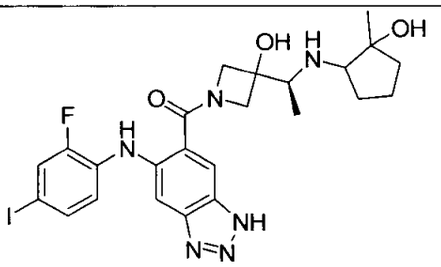
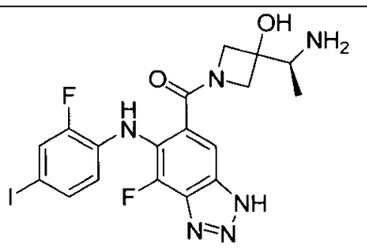
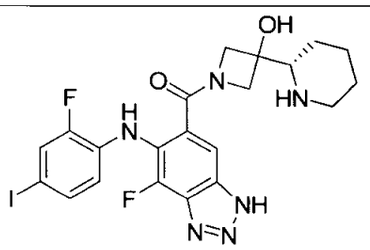
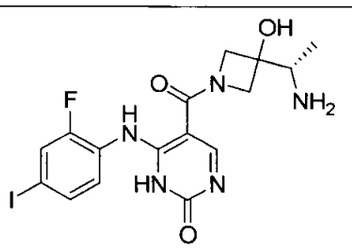
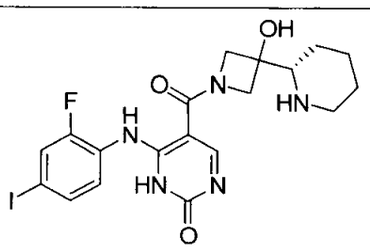
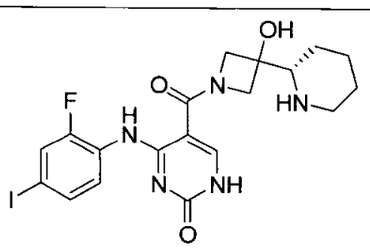
Cmpd No.	Structure	Name
		
328		1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-piperazin-2-ylazetidin-3-ol
329		5-[(2-fluoro-4-iodophenyl)amino]-6-({3-hydroxy-3-[(2*S*)-piperidin-2-yl]azetidin-1-yl}carbonyl)-2-methylpyridazin-3(2*H*)-one
330		5-[(4-bromo-2-chlorophenyl)amino]-6-({3-hydroxy-3-[(2*S*)-piperidin-2-yl]azetidin-1-yl}carbonyl)-2-methylpyridazin-3(2*H*)-one
331		5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-6-({3-hydroxy-3-[(2*S*)-pyrrolidin-2-yl]azetidin-1-yl}carbonyl)-2-methylpyridazin-3(2*H*)-one

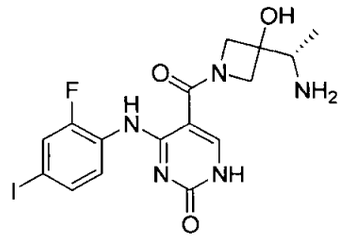
Cmpd No.	Structure	Name
332		5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-6-({3-hydroxy-3-[(2*R*)-pyrrolidin-2-yl]azetidin-1-yl}carbonyl)-2-methylpyridazin-3(2*H*)-one
333		6-({3-[(1*S*)-1-aminoethyl]-3-hydroxyazetidin-1-yl}carbonyl)-5-[(2-fluoro-4-iodophenyl)amino]-2-methylpyridazin-3(2*H*)-one
334		6-({3-[(1*S*)-1-aminoethyl]-3-hydroxyazetidin-1-yl}carbonyl)-5-[(4-bromo-2-chlorophenyl)amino]-2-methylpyridazin-3(2*H*)-one
335		5-[(4-bromo-2-chlorophenyl)amino]-6-{[3-((1*S*)-1-{[(3*R*,4*S*)-3,4-dihydroxycyclopentyl]amino}ethyl)-3-hydroxyazetidin-1-yl]carbonyl}-2-methylpyridazin-3(2*H*)-one
336		5-[(4-bromo-2-fluorophenyl)amino]-6-[(3-hydroxy-3-{(1*S*)-1-[(2-hydroxy-2-methylcyclopentyl)amino]propyl}azetidin-1-yl)carbonyl]-2-methylpyridazin-3(2*H*)-one
337		6-({3-[(1*S*)-1-aminopropyl]-3-hydroxyazetidin-1-yl}carbonyl)-5-[(4-bromo-2-fluorophenyl)amino]-2-methylpyridazin-3(2*H*)-one

Cmpd No.	Structure	Name
338		6-{[3-(1*H*-benzimidazol-2-yl)-3-hydroxyazetidin-1-yl]carbonyl}-5-[(2-fluoro-4-iodophenyl)amino]-2-methylpyridazin-3(2*H*)-one
339		5-[(2-fluoro-4-iodophenyl)amino]-6-{[3-hydroxy-3-(1-methyl-1*H*-benzimidazol-2-yl)azetidin-1-yl]carbonyl}-2-methylpyridazin-3(2*H*)-one
340		1-({2-fluoro-3-[(2-fluoro-4-iodophenyl)amino]pyridin-4-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol
341		1-({3-[(2-fluoro-4-iodophenyl)amino]pyridin-4-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol
342		1-({3-[(2-fluoro-4-iodophenyl)amino]-1-oxidopyridin-4-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol
343		1-({2-fluoro-3-[(2-fluoro-4-bromophenyl)amino]pyridin-4-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol

Cmpd No.	Structure	Name
344		3-[(1*S*)-1-aminopropyl]-1-({3-[(2-fluoro-4-iodophenyl)amino]pyridin-4-yl}carbonyl)azetidin-3-ol
345		1-({3-[(2-fluoro-4-iodophenyl)amino]pyridin-4-yl}carbonyl)-3-[(1*S*)-1-(methylamino)propyl]azetidin-3-ol
346		(1*R*,2*S*)-4-({(1*S*)-1-[1-({2-fluoro-3-[(2-fluoro-4-iodophenyl)amino]pyridin-4-yl}carbonyl)-3-hydroxyazetidin-3-yl]propyl}amino)cyclopentane-1,2-diol
347		1-({7-[(4-bromo-2-chlorophenyl)amino]-8-fluoro-4-methylcinnolin-6-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol
348		1-({7-[(4-bromo-2-fluorophenyl)amino]-8-fluoro-4-methylcinnolin-6-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol
349		3-[(1*S*)-1-aminoethyl]-1-({7-[(4-bromo-2-fluorophenyl)amino]cinnolin-6-yl}carbonyl)azetidin-3-ol

Cmpd No.	Structure	Name
350		1-({7-[(4-bromo-2-fluorophenyl)amino]cinnolin-6-yl}carbonyl)-3-{(1*S*)-1-[(2-hydroxy-2-methylcyclopentyl)amino]ethyl}azetidin-3-ol
351		1-({7-[(4-bromo-2-fluorophenyl)amino]cinnolin-6-yl}carbonyl)-3-[(1*S*)-1-(dimethylamino)ethyl]azetidin-3-ol
352		3-[(1*S*)-1-aminoethyl]-1-({5-[(2-fluoro-4-iodophenyl)amino]-1*H*-1,2,3-benzotriazol-6-yl}carbonyl)azetidin-3-ol
353		3-[(1*S*)-1-(dimethylamino)ethyl]-1-({5-[(2-fluoro-4-iodophenyl)amino]-1-methyl-1*H*-1,2,3-benzotriazol-6-yl}carbonyl)azetidin-3-ol
354		1-({5-[(2-fluoro-4-iodophenyl)amino]-1*H*-1,2,3-benzotriazol-6-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol
355		1-({5-[(2-fluoro-4-iodophenyl)amino]-1-methyl-1*H*-1,2,3-benzotriazol-6-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol

Cmpd No.	Structure	Name
356		1-({5-[(2-fluoro-4-iodophenyl)amino]-1*H*-1,2,3-benzotriazol-6-yl}carbonyl)-3-{(1*S*)-1-[(2-hydroxy-2-methylcyclopentyl)amino]ethyl}azetidin-3-ol
357		3-[(1*S*)-1-aminoethyl]-1-({4-fluoro-5-[(2-fluoro-4-iodophenyl)amino]-1*H*-1,2,3-benzotriazol-6-yl}carbonyl)azetidin-3-ol
358		1-({4-fluoro-5-[(2-fluoro-4-iodophenyl)amino]-1*H*-1,2,3-benzotriazol-6-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol
359		5-({3-[(1*S*)-1-aminoethyl]-3-hydroxyazetidin-1-yl}carbonyl)-6-[(2-fluoro-4-iodophenyl)amino]pyrimidin-2(1*H*)-one
360		6-[(2-fluoro-4-iodophenyl)amino]-5-({3-hydroxy-3-[(2*S*)-piperidin-2-yl]azetidin-1-yl}carbonyl)pyrimidin-2(1*H*)-one
361		4-[(2-fluoro-4-iodophenyl)amino]-5-({3-hydroxy-3-[(2*S*)-piperidin-2-yl]azetidin-1-yl}carbonyl)pyrimidin-2(1*H*)-one

Cmpd No.	Structure	Name
362		5-({3-[(1*S*)-1-aminoethyl]-3-hydroxyazetidin-1-yl}carbonyl)-4-[(2-fluoro-4-iodophenyl)amino]pyrimidin-2(1*H*)-one

General Administration

[00190] In one aspect, the invention provides pharmaceutical compositions comprising an inhibitor of MEK according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent. In certain other embodiments, administration may preferably be by the oral route. Administration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally (intravenous, intramuscular, or subcutaneous), topically, transdermally, intravaginally, intravesically, intracistemally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages.

[00191] The compositions will include a conventional pharmaceutical carrier or excipient and a compound of the invention as the/an active agent, and, in addition, may include carriers and adjuvants, etc.

[00192] Adjuvants include preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

[00193] If desired, a pharmaceutical composition of the invention may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents,

antioxidants, and the like, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, butylalted hydroxytoluene, etc.

[00194] The choice of formulation depends on various factors such as the mode of drug administration (e.g., for oral administration, formulations in the form of tablets, pills or capsules are preferred) and the bioavailability of the drug substance. Recently, pharmaceutical formulations have been developed especially for drugs that show poor bioavailability based upon the principle that bioavailability can be increased by increasing the surface area i.e., decreasing particle size. For example, U.S. Pat. No. 4,107,288 describes a pharmaceutical formulation having particles in the size range from 10 to 1,000 nm in which the active material is supported on a crosslinked matrix of macromolecules. U.S. Pat. No. 5,145,684 describes the production of a pharmaceutical formulation in which the drug substance is pulverized to nanoparticles (average particle size of 400 nm) in the presence of a surface modifier and then dispersed in a liquid medium to give a pharmaceutical formulation that exhibits remarkably high bioavailability.

[00195] Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

[00196] One specific route of administration is oral, using a convenient daily dosage regimen that can be adjusted according to the degree of severity of the disease-state to be treated.

[00197] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, cellulose derivatives, starch, alignates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution

retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

[00198] Solid dosage forms as described above can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain pacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedded compositions that can be used are polymeric substances and waxes. The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

[00199] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. Such dosage forms are prepared, for example, by dissolving, dispersing, etc., a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like; solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide; oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan; or mixtures of these substances, and the like, to thereby form a solution or suspension.

[00200] Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

[00201] Compositions for rectal administrations are, for example, suppositories that can be prepared by mixing the compounds of the present invention with for example suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt while in a suitable body cavity and release the active component therein.

[00202] Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile

conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

[00203] Compressed gases may be used to disperse a compound of this invention in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, etc.

[00204] Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and 99% to 1% by weight of a suitable pharmaceutical excipient. In one example, the composition will be between about 5% and about 75% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, with the rest being suitable pharmaceutical excipients.

[00205] Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, for treatment of a disease-state in accordance with the teachings of this invention.

[00206] The compounds of the invention, or their pharmaceutically acceptable salts or hydrates, are administered in a therapeutically effective amount which will vary depending upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of the compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular disease-states, and the host undergoing therapy. The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day. For a normal human adult having a body weight of about 70 kilograms, a dosage in the range of about 0.01 to about 100 mg per kilogram of body weight per day is an example. The specific dosage used, however, can vary. For example, the dosage can depend on a number of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well known to one of ordinary skill in the art.

[00207] If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described above and the other pharmaceutically

Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition) and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989). These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure. The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

[00214] Unless specified to the contrary, the reactions described herein take place at atmospheric pressure and over a temperature range from about -78 °C to about 150 °C, more preferably from about 0 °C to about 125 °C and most preferably at about room (or ambient) temperature, e.g., about 20 °C. Unless otherwise stated (as in the case of an hydrogenation), all reactions are performed under an atmosphere of nitrogen.

[00215] Prodrugs can be prepared by techniques known to one skilled in the art. These techniques generally modify appropriate functional groups in a given compound. These modified functional groups regenerate original functional groups by routine manipulation or *in vivo*. Amides and esters of the compounds of the present invention may be prepared according to conventional methods. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference for all purposes.

[00216] The compounds of the invention, or their pharmaceutically acceptable salts, may have asymmetric carbon atoms or quaternized nitrogen atoms in their structure. Compounds of Formula I that may be prepared through the syntheses described herein may exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. The compounds may also exist as geometric isomers. All such single stereoisomers, racemates and mixtures thereof, and geometric isomers are intended to be within the scope of this invention. Some of the compounds of the invention may exist as tautomers. For example, where a ketone or aldehyde is present, the molecule may exist in the enol form; where an amide is present, the

molecule may exist as the imidic acid; and where an enamine is present, the molecule may exist as an imine. All such tautomers are within the scope of the invention.

[00217] The present invention also includes N-oxide derivatives and protected derivatives of compounds of Formula I. For example, when compounds of Formula I contain an oxidizable nitrogen atom, the nitrogen atom can be converted to an N-oxide by methods well known in the art. When compounds of Formula I contain groups such as hydroxy, carboxy, thiol or any group containing a nitrogen atom(s), these groups can be protected with a suitable "protecting group" or "protective group". A comprehensive list of suitable protective groups can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1991, the disclosure of which is incorporated herein by reference in its entirety. The protected derivatives of compounds of Formula I can be prepared by methods well known in the art.

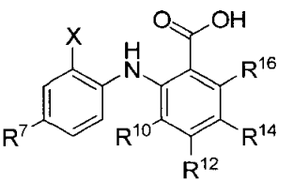
[00218] Methods for the preparation and/or separation and isolation of single stereoisomers from racemic mixtures or non-racemic mixtures of stereoisomers are well known in the art. For example, optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. Enantiomers (R- and S-isomers) may be resolved by methods known to one of ordinary skill in the art, for example by: formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallization; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallization, selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, such as silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where a desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step may be required to liberate the desired enantiomeric form. Alternatively, specific enantiomer may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents or by converting on enantiomer to the other by asymmetric transformation. For a mixture of enantiomers, enriched in a particular enantiomer, the major component enantiomer may be further enriched (with concomitant loss in yield) by recrystallization.

[00219] In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the

like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

[00220] The chemistry for the preparation of the compounds of this invention is known to those skilled in the art.

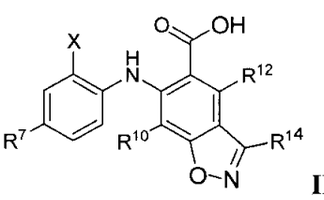
[00221] An intermediate of Formula II:



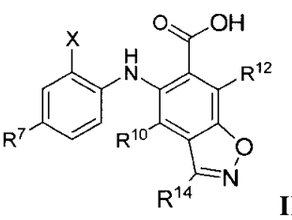
II

where R^7, X, R^{10}, R^{12}, R^{14}, and R^{16} are as defined in the Summary of the Invention for Group A can be prepared using procedures known to one of ordinary skill in the art. In particular, see (for example) US 7,019,033, WO 2002006213, WO 2003062191, WO 2003062189, WO 2002018319, WO2001005392, WO 2000064856, WO 2001005392, WO 9901421, WO 2004056789, Davis, E. M. et al. *Org. Process Res. & Dev.* **2005**, 9, 843-6, and Shapiro, N. *et al. Synthetic Commun.* **2005**, 35, 2265-9 which are incorporated by reference herein. The following intermediates were prepared using similar procedures as described in the above references: 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid; 2-[(2-chloro-4-iodophenyl)amino]-3,4-difluorobenzoic acid; 4-fluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid; 4,5-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid; and 2-[(4-bromo-2-fluorophenyl)amino]-3,4-difluorobenzoic acid.

[00222] An intermediate of Formula III(a) or III(b):



III(a);

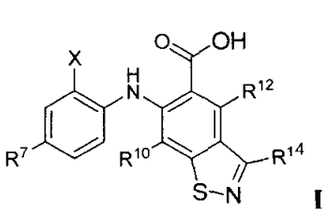


III(b)

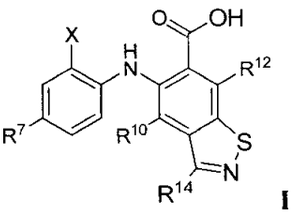
where R^7, X, R^{10}, R^{12}, and R^{14} are as defined in the Summary of the Invention for Group B can be prepared using procedures known to one of ordinary skill in the art. In particular for formula III(a), where R^{14} is amino or alkyl (particularly methyl); R^{10} is halo (particularly fluoro); R^7 is hydrogen or halo (particularly bromo or chloro); X is halo (particularly chloro); and R^{12} is hydrogen see for example WO2006030610, US2005049419, and US2005/0054701 which are incorporated by reference herein. 6-[(4-bromo-2-chlorophenyl)amino]-7-fluoro-3-

methyl-1,2-benzisoxazole-5-carboxylic acid was prepared using methods similar to those disclosed in WO2006030610, US2005049419, and US2005/0054701.

[00223] An intermediate of Formula IV(a) or IV(b):



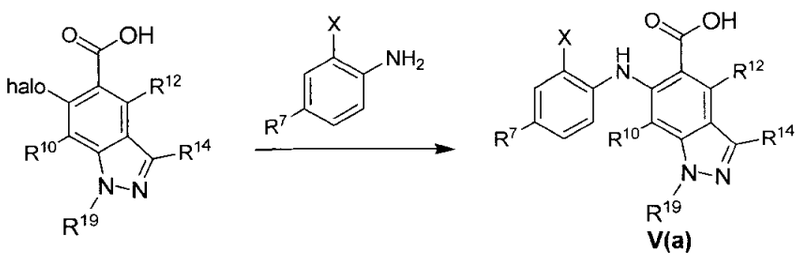
IV(a);



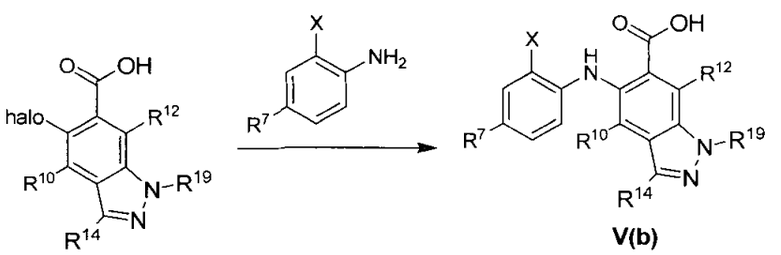
IV(b)

where R^7, X, R^{10}, R^{12}, and R^{14} are as defined in the Summary of the Invention for Group B can be prepared using procedures known to one of ordinary skill in the art.

[00224] An intermediate of Formula V(a) or V(b):



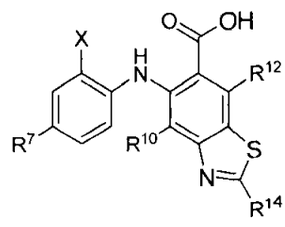
V(a)



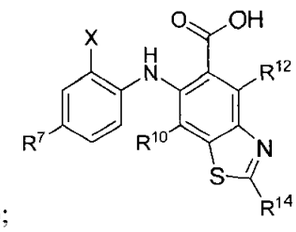
V(b)

where R^7, X, R^{10}, R^{12}, R^{14}, and R^{19} are as defined in the Summary of the Invention for Group B can be prepared using procedures known to one of ordinary skill in the art. In particular the halo precursor of V(a) can be prepared using, for example, WO2003101968 and WO2002083648 which are incorporated by reference herein. In particular the halo precursor of V(b) can be prepared using, for example, US2004192653, US2004180896, US2004176325 which are incorporated by reference herein. The halo precursors are then reacted with an appropriate aniline to yield the intermediates of Formula V(a) and V(b).

[00225] An intermediate of Formula VI(a) or VI(b):



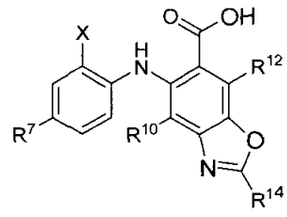
VI(a);



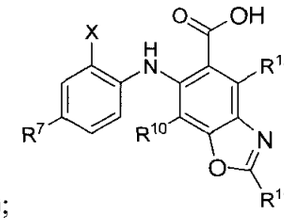
VI(b)

where R^7, X, R^{10}, R^{12}, and R^{14} are as defined in the Summary of the Invention for Group B can be prepared using procedures known to one of ordinary skill in the art. In particular, for VI(b) see for example WO2000042022 and WO2001005390 which are incorporated by reference herein.

[00226] An intermediate of Formula VII(a) or VII(b):



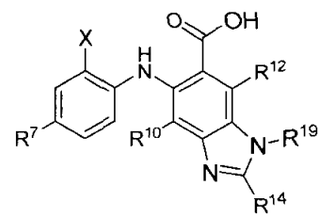
VII(a);



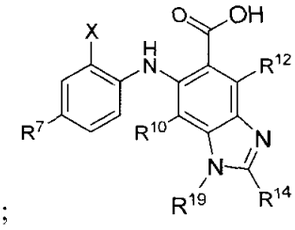
VII(b)

where R^7, X, R^{10}, R^{12}, and R^{14} are as defined in the Summary of the Invention for Group B can be prepared using procedures known to one of ordinary skill in the art. For intermediate VII(b) see, for example, WO2001005390 and WO2000042022 which are incorporated by reference herein.

[00227] An intermediate of Formula VIII(a) or VIII(b):



VIII(a);

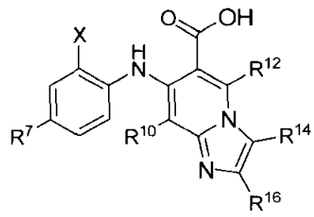


VIII(b)

where R^7, X, R^{10}, R^{12}, R^{14}, and R^{19} are as defined in the Summary of the Invention for Group B can be prepared using procedures known to one of ordinary skill in the art. In particular for formula VIII(b) where R^{10} is halo (particularly fluoro), R^{12} is hydrogen, R^{14} is hydrogen, and R^{19} is hydrogen or alkyl (particularly methyl) or alkenyl (particularly allyl), see WO 05/023251, WO2005009975, and WO2001005390 which are incorporated by reference herein. In particular for VIII(a) where X is halo (particularly chloro or fluoro) or alkyl (particularly methyl), R^7 is halo (particularly iodo, bromo, or chloro) or haloalkoxy (particularly trifluormethoxy), R^{10} is halo (particularly fluoro or chloro), R^{14} is hydrogen or alkyl (particularly methyl), and R^{19} is hydrogen or alkyl (particularly methyl), see for

example US 2004/0116710, WO 03/077914, WO 03/077855, WO 00/42022, WO2005009975, and WO2001005390 which are incorporated by reference herein. The following intermediates were prepared using similar procedures described in US 2004/0116710, WO 03/077914, WO 03/077855, WO 00/42022, WO2005009975, and WO2001005390: 5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-1-methyl-1*H*-benzimidazole-6-carboxylic acid and 4-fluoro-5-[(2-fluoro-4-iodophenyl)amino]-1-methyl-1*H*-benzimidazole-6-carboxylic acid.

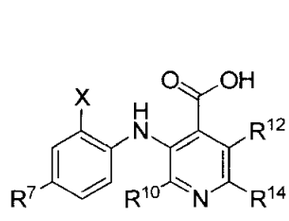
[00228] An intermediate of Formula IX:



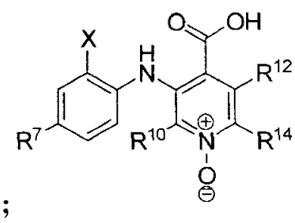
IX

where R^7, X, R^{10}, R^{12}, R^{14}, and R^{16} are as defined in the Summary of the Invention for Group B can be prepared using procedures known to one of ordinary skill in the art. In particular, where R^{10} is hydrogen or halo (particularly chloro or fluoro); R^{12} is hydrogen; R^{14} is hydrogen, amino, alkylamino, or dialkylamino; R^{16} is hydrogen; X is halo (particularly chloro); and R^7 is halo (particularly bromo) see for example WO 05/023759, US 2005/0054701, US 2006030610, US 2005049419, and US 2005049276 which are incorporated by reference herein. The following intermediates were prepared using similar procedures as those described in WO 05/023759, as well as US 2006030610 and US 2005/0054701: 7-[(4-bromo-2-chlorophenyl)amino]-8-chloroimidazo[1,2-a]pyridine-6-carboxylic acid and 8-chloro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-a]pyridine-6-carboxylic acid. The following intermediates can be prepared using similar procedures described in the references given above: 8-Fluoro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-*a*]pyridine-6-carboxylic acid and 7-[(4-Bromo-2-fluorophenyl)amino]-8-fluoroimidazo[1,2-*a*]pyridine-6-carboxylic acid.

[00229] An intermediate of Formula X(a) and X(b):



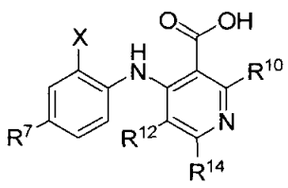
X(a);



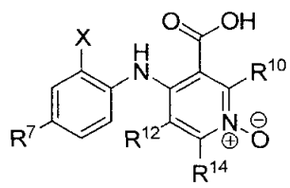
X(b)

where R^7, X, R^{10}, R^{12}, and R^{14} are as defined in the Summary of the Invention for Group B can be prepared using procedures known to one of ordinary skill in the art. In particular, where R^{10} is hydrogen, halo (specifically chloro), or alkyl (specifically methyl), R^{12} is hydrogen, and R^{14} is hydrogen, halo (specifically bromo), see for example WO 06/045514 which is incorporated by reference herein. To prepare the intermediate of Formula X(b), the nitrogen in the pyridine ring of X(a) can then be oxidized with an agent such as MCPBA or H_2O_2. The following X(a) and X(b) intermediates were prepared using similar methods as disclosed in WO 06/045514: 3-[(2-Fluoro-4-iodophenyl)amino]pyridine-4-carboxylic acid and 3-[(2-Fluoro-4-iodophenyl)amino]pyridine-4-carboxylic acid 1-oxide. The following X(a) intermediates can be prepared using similar methods as disclosed in WO 06/045514: 2-Fluoro-3-[(2-fluoro-4-iodophenyl)amino]pyridine-4-carboxylic acid and 3-[(4-Bromo-2-fluorophenyl)amino]pyridine-4-carboxylic acid.

[00230] An intermediate of Formula XI(a):



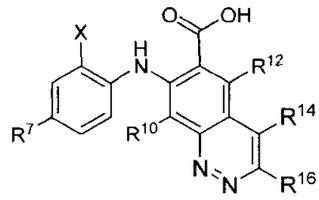
XI(a);



XI(b)

where R^7, X, R^{10}, R^{12}, and R^{14} are as defined in the Summary of the Invention for Group B can be prepared using procedures known to one of ordinary skill in the art. In particular, where R^{10} is hydrogen, R^{12} is hydrogen or halo (particularly chloro or fluoro), R^{14} is amino or halo (particularly chloro), X is halo (particularly chloro), and R^7 is halo (particularly bromo) see for example US 2005/0054701, US 200549419, and US 2006030610 which are incorporated by reference herein. The intermediate of Formula XI(b) can be prepared by oxidizing the nitrogen in the pyridine ring of XI(a) with an agent such as MCPBA or H_2O_2.

[00231] An intermediate of Formula XII:



XII

where R^7, X, R^{10}, R^{12}, R^{14}, and R^{16} are as defined in the Summary of the Invention for Group B can be prepared using procedures known to one of ordinary skill in the art. In particular, see for example WO 05/051302 which is incorporated by reference herein. The following intermediates can be prepared using similar methods as disclosed in WO 05/051302:

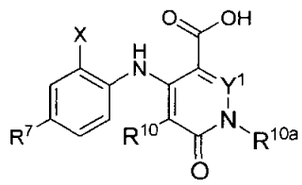
8-Fluoro-7-[(2-fluoro-4-iodophenyl)amino]-4-methylcinnoline-6-carboxylic acid;

7-[(4-Bromo-2-chlorophenyl)amino]-8-fluoro-4-methylcinnoline-6-carboxylic acid;

7-[(4-Bromo-2-fluorophenyl)amino]-8-fluoro-4-methylcinnoline-6-carboxylic acid; and

7-[(4-Bromo-2-fluorophenyl)amino]cinnoline-6-carboxylic acid.

[00232] An intermediate of Formula XIII:



XIII

where R^7, X, R^{10}, R^{10a}, and Y^1 are as defined in the Summary of the Invention for Group C can be prepared using procedures known to one of ordinary skill in the art, including for example the procedures in US 05/0256123, Wallace, E. M. *et al. J. Med. Chem.* **2006**, 49, 441-4, WO 2005000818, and WO 2005051301 (where Y^1 is carbon) which are incorporated by reference herein. 4-[(4-Bromo-2-fluorophenyl)amino]-5-fluoro-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid was prepared using similar procedures to those disclosed in US 05/0256123 and WO 2005051301. 4-Chloro-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid was prepared using similar procedures to those disclosed in US 2005256123. The following intermediates can be prepared using the methods disclosed in the above references:

4-[(2-Fluoro-4-iodophenyl)amino]-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid;

4-[(4-Bromo-2-chlorophenyl)amino]-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid;

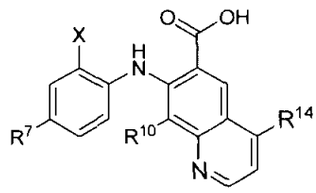
4-[(4-Bromo-2-fluorophenyl)amino]-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid;

4-[(4-Bromo-2-chlorophenyl)amino]-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid;

4-[(4-Bromo-2-chlorophenyl)amino]-5-fluoro-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid; and

4-[(4-Bromo-2-fluorophenyl)amino]-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid.

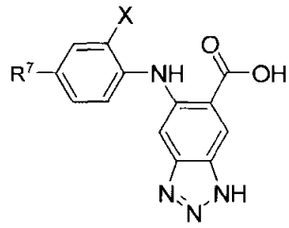
[00233] An intermediate of Formula XIV:



XIV

where R^7, X, R^{10}, and R^{14} are as defined in the Summary of the Invention for Group B can be prepared using procedures known to one of ordinary skill in the art. In particular, see for example WO 05/051302 which is incorporated by reference herein.

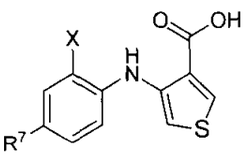
[00234] An intermediate of Formula XVI



XVI

where X and R^7 are as defined in the Summary of the Invention for a Compound of Group B can be prepared using procedures known to one of ordinary skill in the art. In particular, see for example WO 2001005390 and WO 2000042022 for procedures that can be used to prepare the following: 5-[(2-Fluoro-4-iodophenyl)amino]-1*H*-benzotriazole-6-carboxylic acid; 5-[(2-Fluoro-4-iodophenyl)amino]-1-methyl-1*H*-benzotriazole-6-carboxylic acid; and 4-Fluoro-5-[(2-fluoro-4-iodophenyl)amino]-1*H*-benzotriazole-6-carboxylic acid.

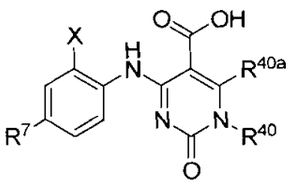
[00235] An intermediate of Formula XVII



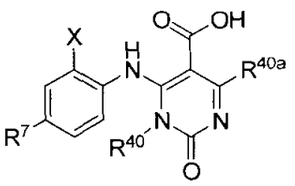
XVII

where X and R^7 are as defined in the Summary of the Invention for a Compound of Group B can be prepared using procedures known to one of ordinary skill in the art. In particular, see Example 29.

[00236] An intermediate of Formula XVIII(a) or XVIII(b)

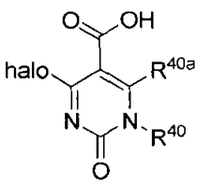


XVIII(a)

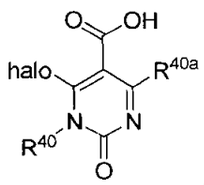


XVIII(b)

where X, R^7, R^{40}, and R^{40a} are as defined in the Summary of the Invention for a Compound of Group D can be prepared using procedures known to one of ordinary skill in the art. In particular, the halo precursors to XVIII(a) and XVIII(b)

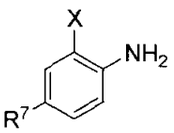


and



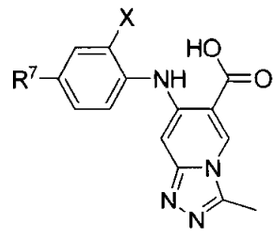
, respectively

can be prepared using procedures similar to those described in Machon and Dlugosz *Acta Poloniae Pharmaceutica* **1983,** *40(1),* 1-6 and von Angerer, *Science of Synthesis* **2004,** *16,* 379-572 (General Review written in English). The halo precursors are then reacted with



using procedures known to one of ordinary skill in the art and the synthetic methods disclosed herein. The following intermediates can be prepared as described above: 6-[(2-fluoro-4-iodophenyl)amino]-2-oxo-1,2-dihydropyrimidine-5-carboxylic acid and 4-[(2-fluoro-4-iodophenyl)amino]-2-oxo-1,2-dihydropyrimidine-5-carboxylic acid.

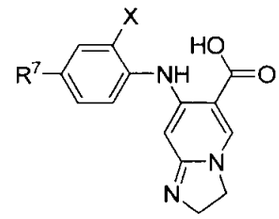
[00237] An intermediate of Formula XIX



XIX

where X and R^7 are as defined in the Summary of the Invention for a Compound of Group C can be prepared using methods known to one of ordinary skill in the art. In particular see US 2005049276.

[00238] An intermediate of Formula XX

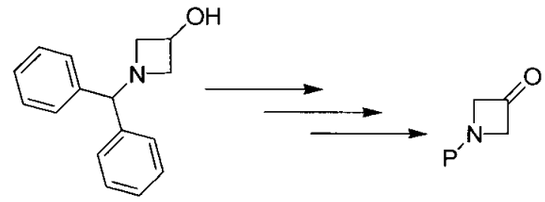


XX

where X and R^7 are as defined in the Summary of the Invention for a Compound of Group C can be prepared using methods known to one of ordinary skill in the art. In particular see US 2005049276.

[00239] The synthesis of azetidines substituted at the 3-position can be conveniently carried out according to Scheme 1:

Scheme 1

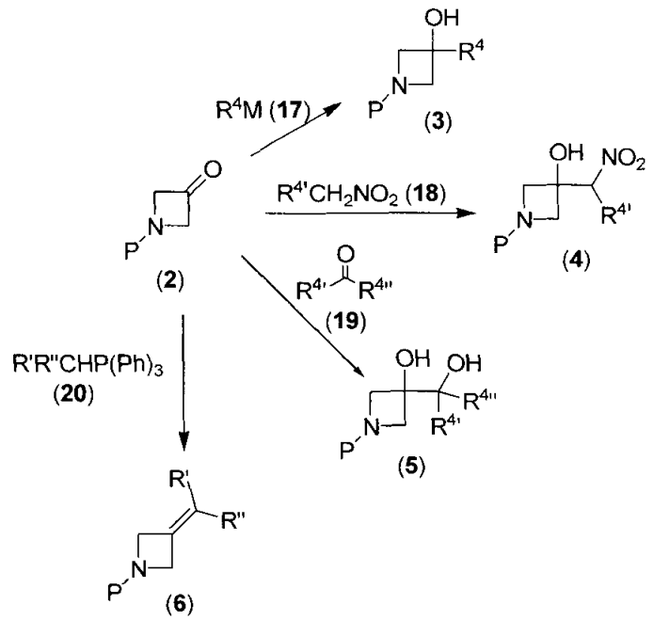


(1) (2)

starting from the *N*-diphenylmethyl protected azetidin-3-ol (**1**), readily prepared by reaction of epichlorohydrin and diphenylmethylamine (Chatterjee, Shym S.; Triggle, D. *J. Chemical Communications (London)* **1968,** *2,* 93). Protecting group exchange, from Boc to CBz, on the azetidine is carried out according to literature protocols (Greene, T.W., Wuts, P.G. Protective Groups in Organic Synthesis, Wiley-Interscience) and subsequent oxidation to the azetidinone (**2**) where P is CBz provides a useful intermediate for the preparation of compounds of the invention.

[00240] For example, the ketone intermediates of formula **2** can be broadly functionalized at the 3-position according to Scheme 2.

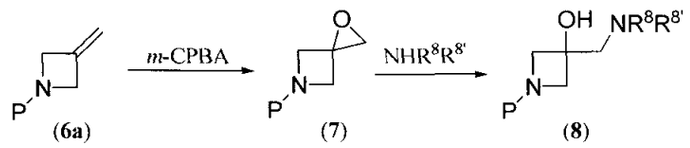
Scheme 2



An intermediate of formula (**3**), where R^4 is as defined in the Summary of the Invention for a compound of Group A, Group B, Group C, or Group D can be prepared by reacting the intermediate **2** with Grignard reagents or other organometallic species of formula **17**, such as organolithiums. Alternatively, the intermediate **2** can be reacted with nitroalkane anions of formula **18** prepared *in-situ* as in the Henry reaction (The Henry reaction, recent examples: Luzzio, F. A. *Tetrahedron* **2001,** *57(6),* 915-945) to give (**4**) where $R^{4'}$ is hydrogen or alkyl optionally substituted as described for R^4 in the Summary of the Invention for a compound of Group A, Group B, Group C, or Group D. Alternatively, the intermediate **2** can be reacted with ketone or aldehyde anions of formula **19** in a Claisen-type condensation to give (**5**) where $R^{4'}$ is alkyl optionally substituted as described for R^4 in the Summary of the Invention for a compound of Group A, Group B, Group C, or Group D and $R^{4''}$ is hydrogen or $R^{4'}$. In addition, **2** can be reacted with Wittig reagents of formula **20** (where R' and R" are independently hydrogen, alkyl, alkenyl, aryl, or heteroaryl and the alkyl, alkenyl, aryl, and heteroaryl are optionally substituted as described for R^4 in the Sumnmary of the Invention for a compound of Group A, Group B, Group C, or Group D) to prepare intermediates of formula **6**, which are also useful as precursors for compounds of the invention.

[00241] According to Scheme 3, intermediates of formula (**6**) where where (R' and R" are hydrogen and P is a nitrogen-protecting group such as CBz or Boc)

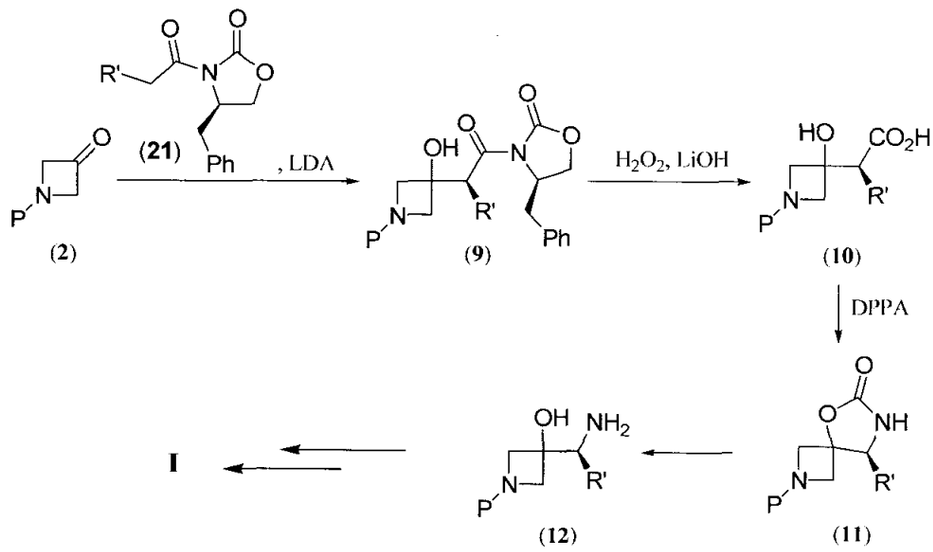
Scheme 3



can be further converted to the corresponding epoxide (**7**) and subsequent reaction with a suitable nitrogen base or other nucleophiles may be carried out to give access to a broad range of azetidin-3-ol derivatives such as (**8**), where R^8 and $R^{8'}$ are as defined in the Summary of the Invention.

[00242] In some cases the preparation of optically pure compounds is desired where the azetidine contains one or more stereocenters. Numerous techniques for the preparation of optically pure compounds through both resolution techniques and asymmetric synthesis are well known in the art. In one such case, an asymmetric synthesis methodology can be employed where an azetidine precursor of formula (**2**) is reacted with an intermediate of formula **21** where R' is not hydrogen, as depicted in Scheme 4.

Scheme 4

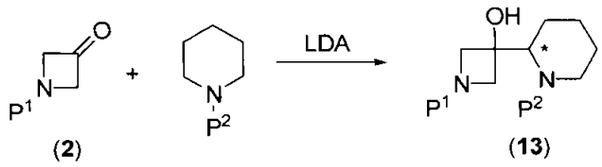


One such useful approach makes use of Evans oxazolidinone methodology (Diastereoselective aldol condensation using a chiral oxazolidinone auxiliary. Gage, James R.; Evans, David A. *Organic Syntheses* **1990,** *68,* 83-91). The condensation of an azetidinone (**2**) with the a chiral oxazolidinone in the presence of a base such as LDA affords an intermediate oxazolidinone (**9**), where P is a nitrogen-protecting group such as CBz or

Boc, with diastereoselectivity. Treatment with lithium hydroxide in aqueous hydrogen peroxide gives carboxylic acid (**10**) which can be subject to Curtius rearrangement to provide the chiral oxazolidinone (**11**) then carried forward as required to a useful intermediate (**12**). Further protecting group manipulation and derivatization as required can be employed to prepare compounds of Formula I.

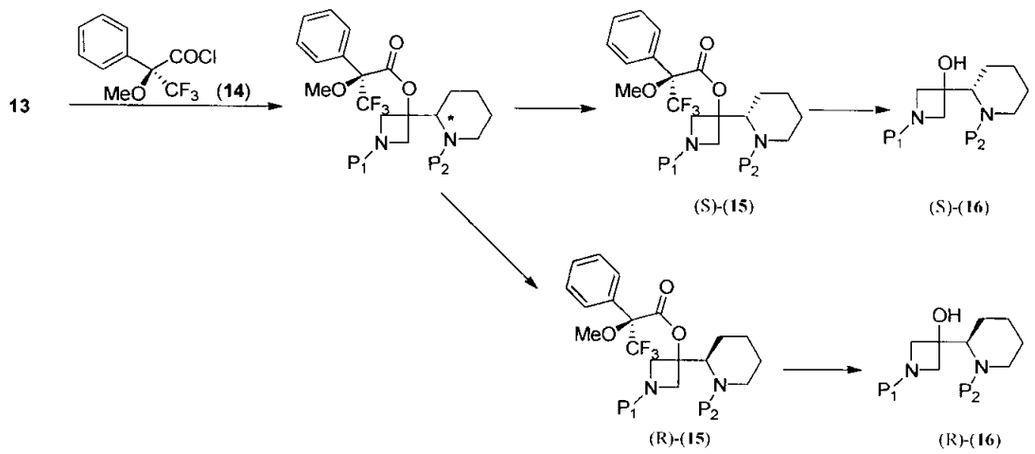
[00243] Alternatively, a racemic mixture of an intermediate of formula (**13**), useful to prepare a compound of Formula I where R^3 is hydroxy and R^4 is heterocycloalkyl (in particular, where R^4 is a N-protected piperidine), can be prepared according to Scheme 5.

Scheme 5



In the reaction schemes P^1 and P^2 are orthogonal nitrogen-protecting groups. For example, P^1 is Boc and P^2 is CBz or P^1 is CBz and P^2 is Boc. The reaction is carried out *in-situ* by treating **22** to generate the lithated amine and by subsequently treating it with a ketone such as (**2**) according to the method of Peter Beak (Beak, Peter; Lee, Won Koo α-Lithioamine synthetic equivalents: syntheses of diastereoisomers from the Boc-piperidines. Journal of Organic Chemistry 1990, 55(9), 2578-80). The racemate (**13**) thus prepared can be resolved by functionalization, as depicted in Scheme 6, with a chiral acid such as the readily-available Mosher acid (**14**).

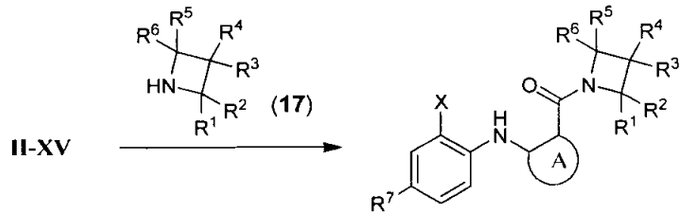
Scheme 6



The resulting diastereomeric esters (**15**) can be separated by chromatographic means and then carried forward individually as the enantiomerically pure intermediates (R)-(**16**) and (S)-(**16**).

[00244] Compounds of the Invention can be prepared by reacting an intermediate of Formula II, III(a), III(b), IV(a), IV(b), V(a), V(b), VI(a), VI(b), VII(a), VII(b), VIII(a), VIII(b), IX, X(a), X(b), XI(a), XI(b), XII, XIII, XIV, XVI, XVII, XVIII(a), XVIII(b), XIX, or XX with intermediate 17 according to Scheme 7:

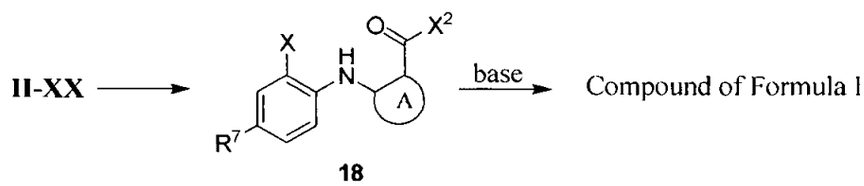
Scheme 7



The reaction is carried out in a solvent such as DMF, THF, or DCM in the presence of a base such as DIPEA, *N*-methylmorpholine, DMAP, or triethylamine and optionally in the presence of a coupling agent such as PyBOP, HBTU, or EDCI.

[00245] Alternatively an intermediate of Formula II, III(a), III(b), IV(a), IV(b), V(a), V(b), VI(a), VI(b), VII(a), VII(b), VIII(a), VIII(b), IX, X(a), X(b), XI(a), XI(b), XII, XIII, XIV, XVI, XVII, XVIII(a), XVIII(b), XIX, or XX can be converted into an acid halide according to Scheme 8

Scheme 8



where X^2 is halo, such as chloro or fluoro, and all other groups are as defined in the Summary of the Invention for a compound of Group A, Group B, Group C, or Group D. The reaction is carried out in a solvent such as dioxane, THF, or DCM in the presence of a base such as DIPEA, sodium bicarbonate. The acid halide of formula **18** can then be reacted with an azetidine intermediate of formula **17** to prepare a compound of Formula I.

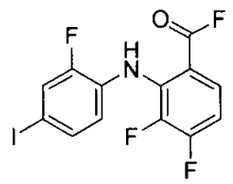
SYNTHETIC EXAMPLES

[00246] Generally, the compounds listed below were identified by LC-MS, and/or isolated, and characterized by ^{1}H-NMR (most typically 400 MHz). Liquid chromatography-mass spectral (LC-MS) analyses were performed using at least one of: a Hewlett-Packard Series 1100 MSD, an Agilent 1100 Series LC/MSD (available from Agilent Technologies Deutschland GmbH of Waldbronn Germany), or a Waters 8-Channel MUX System (available

from Waters Corporation of Milford, Massachusetts). Compounds were identified according to either their observed mass [MH^+] or [MNa^+] ion (positive mode) or [MH^-] ion (negative mode). ^{1}H-NMR data for compounds was taken with a Varian AS400 Spectrometer (400MHz, available from Varian GmbH, Darmstadt, Germany). Starting materials and intermediates used to prepare a compound of the invention are either commercially available or can be prepared by one of ordinary skill in the art.

REFERENCE 1

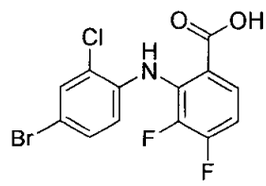
3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino] benzoyl fluoride



[00247] To a stirred mixture of 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino] benzoic acid (12 g, 30.5 mmol), prepared using procedures similar to those described in US 7,019,033, in dichloromethane (70 mL) at 0 °C was added pyridine (2.5 mL, 30.8 mmol) followed by dropwise addition of cyanuric fluoride (2.8 mL, 33.6 mmol). The reaction mixture was stirred at 0 °C for 10 minutes and then warmed to room temperature and stirred for 2 hours. The reaction mixture was diluted with water and extracted with dichloromethane (100 mL). The aqueous layer was extracted once with dichloromethane (50 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution, brine, dried over anhydrous sodium sulfate and concentrated *in vacuo* to give crude product as a brownish solid. Crude product was purified by flash chromatography (plug, 25% ethyl acetate in hexanes) to afford 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino] benzoyl fluoride as a beige solid (11.8 g, 97% yield). ^{1}H NMR (400MHz, CD_3OD): 8.41 (s, 1H), 7.80-7.81 (m, 1H), 7.52 (dd, 1H), 7.43-7.47 (m, 1H), 6.96-7.03 (m, 1H), 6.85-6.92 (m, 1H).

REFERENCE 2

2-[(4-bromo-2-chlorophenyl)amino]-3,4-difluorobenzoic acid



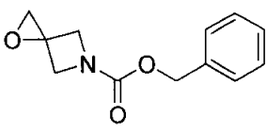
[00248] To a solution of 2,3,4-trifluorobenzoic acid (1 g, 5.68 mmol) and 4-bromo-2-chloroaniline (1.2 g, 5.68 mmol) in acetonitrile (10 mL) was added lithium amide (0.39 g,

17.04 mmol) and the reaction stirred at 60 °C for 1.5 hours. The mixture was cooled to room temperature and then to 0 °C and acidified with aq. hydrochloric acid. The obtained precipitate was collected by filtration and washed with cold water and dried *in vacuo* to afford 2-[(4-bromo-2-chlorophenyl)amino]-3,4-difluorobenzoic acid (1.92 g, 94% yield) as a beige solid. MS (EI) for $C_{13}H_7BrClF_2NO_2$: 363 (MH^+).

[00249] Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, 2-[(4-iodo-2-fluorophenyl)amino]-3-fluorobenzoic acid was prepared. MS (EI) for $C_{13}H_8F_2INO_2$: 376 (MH^+).

REFERENCE 3

Phenylmethyl 1-oxa-5-azaspiro[2.3]hexane-5-carboxylate



[00250] To a solution of azetidin-3-ol hydrochloride in tetrahydrofuran (90 mL) and water (10 mL) was added triethylamine (15 mL, 0.106 mol) followed by slow addition of benzyl chloroformate (8.0 mL, 0.056 mol) at room temperature. The reaction mixture was stirred at room termperature for 16 hours then partitioned with water and ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by flash chromatography (SiO_2, 25-50% ethyl acetate in hexanes) to afford phenylmethyl 3-hydroxyazetidine-1-carboxylate (3.56 g, 33% yield) as a clear and colorless oil. ^1H NMR (400 MHz, $CDCl_3$): 7.36-7.31 (m, 5H), 5.09 (s, 2H), 4.64-4.57 (m, 1H), 4.22 (dd, 2H), 3.88 (dd, 2H), 2.61 (d, 1H, J=4.0 Hz). MS (EI) for $C_{11}H_{13}NO_3$: 208 (MH^+).

[00251] To a solution of phenylmethyl 3-hydroxyazetidine-1-carboxylate (3.5 g, 0.0168 mol) in dichloromethane (100 mL) was added Dess-Martin periodinane (10.7 g, 0.0.25 mol) at room temperature and stirred for 5 h. The reaction mixture was quenched with 1:1 ratio of saturated aqueous sodium bicarbonate and 1M sodium thiosulfate (200 mL) and then partitioned with dichloromethane. The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford phenylmethyl 3-oxoazetidine-1-carboxylate (3.43 g, 99% yield) as a clear and colorless oil without further purification. ^1H NMR (400 MHz, $CDCl_3$): 7.39-7.31 (m, 5H), 5.17 (s, 2H), 4.77 (s, 4H). MS (EI) for $C_{11}H_{11}NO_3$: 205 (M^+).

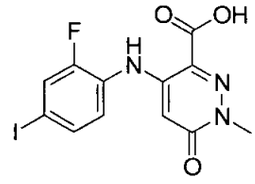
[00252] A suspension of methyltriphenylphosphonium bromide (23.0 g, 0.0649 mol) and potassium *tert*-butoxide (7.3 g, 0.0649 mol) in diethyl ether (140 mL) was stirred at room temperature for 20 min, and then heated to 35 °C for 1 h. To this bright yellow reaction

mixture was slowly added a dilute solution of phenylmethyl 3-oxoazetidine-1-carboxylate (3.33 g, 0.0162 mol) in diethyl ether (50 mL). The reaction mixture was stirred at 35 °C for 12 hours then filtered through a bed of celite and rinsed with ethyl ether. The filtrate was washed with water and brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by flash chromatography (SiO_2, 5-10% ethyl acetate in hexanes) to afford phenylmethyl 3-methylideneazetidine-1-carboxylate (2.46 g, 75% yield) as a clear and colorless oil). ^{1}H NMR (400 MHz, $CDCl_3$): 7.27-7.22 (m, 5H), 5.02 (s, 2H), 4.93-4.90 (m, 2H), 4.48-4.47 (m, 4H). MS (EI) for $C_{12}H_{13}NO_2$: 203 (M^+).

[00253] To a solution of phenylmethyl 3-methylideneazetidine-1-carboxylate (2.46 g, 0.0121 mol) in chloroform (100 mL) was added 3-chloroperoxybenzoic acid (12.5 g, 0.0726 mol) at 0 °C. The reaction mixture was allowed to warm up to room temperature over a period of 12 hours then quenched with 1 M sodium thiosulfate / saturated aqueous sodium bicarbonate (1:1). The layers were separated and the organic layer was dried over anhydrous magnesium sulfate then concentrated. The residue was purified by flash chromatography (5-15% ethyl acetate in hexanes) to afford phenylmethyl 1-oxa-5-azaspiro[2.3]hexane-5-carboxylate (2.2 g, 83% yield) as clear and colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): 7.37-7.29 (m, 5H), 5.12 (s, 2H), 4.35-4.26 (m, 4H), 2.85 (s, 2H). MS (EI) for $C_{12}H_{13}NO_3$: 220 (MH^+).

REFERENCE 4

4-(2-fluoro-4-iodophenylamino)-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid



[00254] 4-chloro-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid was prepared using procedures similar to those disclosed in US 2005256123.

[00255] To a solution of 4-chloro-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid (350 mg, 1.855 mmol) and 2-fluoro-4-iodoaniline (1.06 g, 4.453 mmol) in tetrahydrofuran (13.3 mL) was sparged with nitrogen for 5 minutes followed by the slow addition of lithium bis(trimethylsilyl)amide, 1.0 M in THF (7.4 mL). The reaction mixture stirred for an additional 4 hours at room temperature. The mixture was quenched with 1 N HCl and concentrated *in vacuo*. The residue was partitioned between ethyl acetate and 1 N

aqueous HCl. The aqueous layer was extracted (3x) with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to afford 4-(2-fluoro-4-iodophenylamino)-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid (939 mg, 100% yield). ^{1}H NMR ($CDCl_3$): 7.27 (dd, 1H), 7.21 (d, 1H), 6.54 (t, 1H), 4.84 (broad s, 2H), 2.09 (s, 1H), 1.26 (t, 3H); MS (EI) for $C_{12}H_9N_3O_3FI$: 389 (MH^+).

[00256] A solution of 4-(2-fluoro-4-iodophenylamino)-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid (939 mg, 2.413 mmol) in dichloromethane (60 mL) in the presence of dimethylformamide (8.0 mL) was cooled to 0 °C. Malonyl chloride (1.26 mL, 14.48 mmol) was added and stirred at room temperature for 1 hour. The reaction mixture was evaporated and partitioned between ethyl acetate and 1M aqueous ammonium chloride. The aqueous layer was extracted 1x with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford 4-(2-fluoro-4-iodophenylamino)-1-methyl-6-oxo-1,6-dihydropyridazine-3-carbonyl chloride. This crude material was taken into the next step without further purification. MS (EI) for $C_{12}H_8N_3O_2ClFI$: 408 (MH^+).

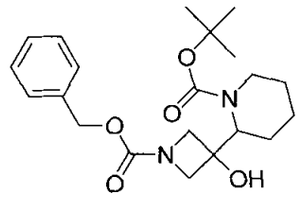
[00257] To a solution of 4-(2-fluoro-4-iodophenylamino)-1-methyl-6-oxo-1,6-dihydropyridazine-3-carbonyl chloride in methanol (15 mL) and benzene (12 mL) was added dropwise trimethylsilyl diazomethane (1 mL) and stirred at room temperature for 15 minutes. The reaction mixture was quenched with acetic acid and evaporated. The residue was partitioned between ethyl acetate and brine. The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified on silica gel chromatography column (7:3 hexanes/ethyl acetate) to afford methyl 4-(2-fluoro-4-iodophenylamino)-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylate (84.9 mg, 8.7% yield). ^{1}H NMR ($CDCl_3$): 7.49-7.56 (m, 3H), 7.12 (t, 1H), 6.13 (d, 1H), 4.00 (s, 3H), 3.83 (s, 3H); MS (EI) for $C_{13}H_{11}N_3O_3FI$: 404 (MH^+).

[00258] Methyl 4-(2-fluoro-4-iodophenylamino)-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylate (84.9 mg, 0.211 mmol) was dissolved in tetrahydrofuran (5 mL), methanol (2.5 mL) and water (2.5 mL). Aqueous 2 M lithium hydroxide (200 μL) was added at room temperature. After 10 minutes, the reaction mixture was heated to 50 °C for 30 minutes and continued to stir at room temperature for 16 hours at which time the solvents were evaporated. The residue was made acidic with 2 M aqueous hydrochloric acid to pH 2 and extracted with ethyl acetate. The organic layer separated, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to provide 4-(2-fluoro-4-iodophenylamino)-1-

methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid (54.0 mg, 66% yield). MS (EI) for $C_{12}H_9N_3O_3FI$: 390 (MH^+).

REFERENCE 5

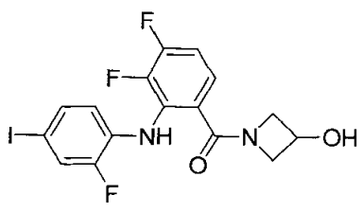
1,1-dimethylethyl 2-(3-hydroxy-1-{[(phenylmethyl)oxy]carbonyl}azetidin-3-yl)piperidine-1-carboxylate



[00259] To a solution of 1,1-dimethylethyl piperidine-1-carboxylate (0.50 g, 2.7 mmol) in anhydrous diethyl ether (9.0 mL) under anhydrous nitrogen gas was added *N,N,N',N'*-tetramethylethane-1,2-diamine (0.41 mL, 2.7 mmol), and the solution was cooled to -78°C. To this solution was added (2-methylpropyl)lithium (2.1 mL, 1.4 M in cyclohexane, 3.0 mmol) in small portions. To this anion solution was added phenylmethyl 3-oxoazetidine-1-carboxylate (1.0 g, 5.4 mmol), prepared using procedures as described in Reference 3, in anhydrous ether (2.0 mL), while maintaining the internal temperature at less than -60°C. The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water, and partitioned between water and diethyl ether. The layers were separated and the aqueous layer was extracted with diethyl ether twice. The combined organic layers were dried (magnesium sulfate), filtered and concentrated *in vacuo*. Chromatography (silica gel, 3:1 hexanes/ethyl acetate) gave 0.13 g (13%) of 1,1-dimethylethyl 2-(3-hydroxy-1-{[(phenylmethyl)oxy]carbonyl}azetidin-3-yl)piperidine-1-carboxylate. ^{1}H NMR (400 MHz, $CDCl_3$): 7.31 (m, 5H), 5.08 (s, 2H), 4.05 (d, 1H), 4.00 (d, 1H), 3.84 (d, 2H), 3.80 (broad s, 1H), 3.55 (broad s, 1H), 3.10 (broad s, 1H), 1.92 (m, 1H), 1.45-1.62 (m, 6H), 1.43 (s, 9H). MS (EI) for $C_{21}H_{30}N_2O_5$: 335 (M-tBu), 315 (M-OtBu).

EXAMPLE 1

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol



[00260] 3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid (2.1 g, 5.3 mmol), prepared using procedures similar to those in US 7,019,033, was taken into DMF (10 mL) followed by addition of PyBOP (2.6 g, 5.3 mmol) and the mixture was allowed to stir at room temperature over 15 minutes. Azetidin-3-ol hydrochloride (870 mg, 8.0 mmol) and DIPEA (1.85 mL, 11.2 mmol) was then added and the mixture was allowed to stir an additional hour at room temperature. The mixture was then partitioned with ethyl acetate and 0.5 M aqueous sodium hydroxide solution. The organic layer was then washed with water (3x) then brine and dried over anhydrous sodium sulfate. Filtration and concentration followed by silica gel flash chromatography using ethyl acetate: hexanes (5:1) eluent afforded 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol (2.09 g, 87% yield) as a colorless amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): 8.47 (s, 1H), 7.39 (dd, 1H), 7.32 (d, 1H), 7.13-7.09 (m, 1H), 6.84-6.78 (m, 1H), 6.63-6.57 (m, 1H), 4.74-4.67 (m, 1H), 4.43-4.39 (m, 2H), 4.20-3.96 (br d, 2H), 2.50 (d, 1H).

[00261] Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, the compounds in Examples 1(a)-(e) were prepared.

EXAMPLE 1(a). 1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}-carbonyl)azetidin-3-yl]-*N,N*-dimethylpyrrolidin-3-amine. The title compound was prepared by reacting 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid with *N*-methyl-*N*-(2-(pyridin-2-yl)ethyl)azetidin-3-amine. The azetidine intermediate was prepared using procedures similar to those described in Abdel-Magid, et.al., *Tetrahedron Letters* **1990,** *31(39),* 5595 starting with *tert*-butyl 3-oxoazetidine-1-carboxylate, which itself was prepared as described in Example 3. The title compound: ^{1}H NMR (400 MHz, d_6-DMSO): 8.56 (s, 1H), 7.58 (m, 1H), 7.38 (d, 1H), 7.31 (m, 1H), 7.16 (m, 1H), 6.67 (m, 1H), 4.16 (m, 1H), 3.97 (m, 2H), 3.77 (m, 1H), 3.26 (br s, 4H), 2.63 (m, 1H), 2.42 (br s, 6H), 1.99 (br s, 1H), 1.74 (br s, 1H). MS (EI) for $C_{22}H_{24}F_3IN_4O$: 545 (MH^+).

EXAMPLE 1(b). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-methyl-*N*-(2-pyridin-2-ylethyl)azetidin-3-amine. The title compound was prepared by reacting 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid with 1-(azetidin-3-yl)-N,N-dimethylpyrrolidin-3-amine. The azetidine intermediate was preparedusing procedures similar to those described in Abdel-Magid, et.al., *Tetrahedron Letters* **1990,** *31(39),* 5595 starting with *tert*-butyl 3-oxoazetidine-1-carboxylate, which itself was prepared as described in Example 3. The title compound: ^{1}H NMR(400 MHz, CD_3OD): 8.50 (d, 1H), 7.94 (t, 1H), 7.50-7.30 (m, 5H), 7.07 (q, 1H), 6.66- 6.61 (m, 1H), 4.52-4.48 (m, 2H), 4.31(s, 2H), 4.23-

4.18 (m, 1H), 3.48- 3.46 (m, 2H), 3.17-3.13 (m, 2H), 2.88 (s, 3H); MS(EI) for $C_{24}H_{22}F_3IN_4O$: 567 (MH^+).

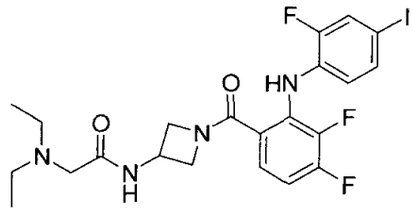
EXAMPLE 1(c). 6-(Azetidin-1-ylcarbonyl)-2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)aniline: ^1H NMR (400 MHz, $CDCl_3$): 8.57 (s, 1H), 7.41-7.38 (dd, 1H), 7.34-7.31 (dt, 1H), 7.13-7.09 (m, 1H), 6.83-6.77 (m, 1H), 6.64-6.58 (m, 1H), 4.27 (b, 2H), 4.18 (b, 2H), 2.38-2.30 (p, 2H); MS (EI) for $C_{16}H_{12}F_3IN_3O$: 433 (MH^+).

EXAMPLE 1(d). [1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]methanol: ^1H NMR (400 MHz, $CDCl_3$): 8.52 (s, 1H), 7.41-7.38 (dd, 1H), 7.34-7.31 (dt, 1H), 7.15-7.11 (m, 1H), 6.83-6.77 (m, 1H), 6.64-6.58 (m, 1H), 4.29-4.20 (m, 2H), 4.09 (b, 1H), 3.93 (b, 1H), 3.82-3.81 (d, 2H), 2.89-2.75 (m, 1H); MS (EI) for $C_{17}H_{14}F_3IN_2O_2$: 463 (MH^+).

EXAMPLE 1(e). 1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidine-3-carboxylic acid: ^1H NMR (400 MHz, $CDCl_3$): 7.79 (b, 2H), 7.42-7.38 (dd, 1H), 7.34-7.32 (dt, 1H), 7.15-7.11 (m, 1H), 6.89-6.83 (m, 1H), 6.65-6.60 (m, 1H), 4.46-4.29 (m, 4H), 3.55-3.47 (m, 1H); MS (EI) for $C_{17}H_{12}F_3IN_2O_3$: 477 (MH^+).

EXAMPLE 2

N-[1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-*N2,N2*-diethylglycinamide



[00262] A solution of 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid (200 mg, 0.51 mmol), prepared using procedures similar to those in US 7,019,033, PyBOP (256 mg, 0.51 mmol), commercially available *tert*-butyl azetidin-3-ylcarbamate (131 mg, 0.77 mmol) and *N,N*-diisopropylethylamine (180 µL, 1.02 mmol) in dimethylformamide (3 mL) was stirred at room temperature for 15 hours. The reaction mixture was partitioned between 5% aqueous lithium chloride and ethyl acetate. The organic portion was washed with 20% aqueous citric acid, saturated aqueous sodium bicarbonate, brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a brown residue which was purified by silica gel column chromatography eluting with 30% ethyl acetate in hexanes to afford 1,1-

dimethylethyl [1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]carbamate (225 mg, 80% yield) as a colorless oil. ^{1}H NMR (400 MHz, DMSO): 8.56 (s, 1H), 7.60-7.55 (m, 2H), 7.38 (d, 1H), 7.30-7.26 (m, 1H), 7.20-7.13 (m, 1H), 6.71-6.66 (m, 1H), 4.37-4.20 (m, 2H), 4.18-4.06 (m, 1H), 3.98-3.93 (m, 1H), 3.82-3.75 (m, 1H), 1.37 (s, 9H). MS (EI) $C_{21}H_{21}N_3O_3F_3I$: 548 (MH^+).

[00263] A solution of 1,1-dimethylethyl [1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]carbamate (113 mg, 0.20 mmol) and trifluoroacetic acid (500 μL) in dichloromethane (2 mL) was added stirred at room temperature for one hour then was partitioned between saturated aqueous sodium bicarbonate, and dichloromethane. The organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to afford a colorless residue which was purified by column chromatography eluting with 10% methanol in dichloromethane to afford 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine (85 mg, 95% yield) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$): 8.53 (s, 1H), 7.39 (d, 1H), 7.32 (d, 1H), 7.13-7.09 (m, 1H), 6.84-6.77 (m, 1H), 6.63-6.57 (m, 1H), 4.46-4.39 (m, 2H), 3.98-3.75(br m, 4H); MS (EI) for $C_{16}H_{13}F_3IN_3O$: 448 (MH^+).

[00264] A solution of 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine (100 mg, 0.22 mmol), PyBOP (131 mg, 0.25 mmol), *N,N*-diisopropylethylamine (80 μL, 0.44 mol) and bromoacetic acid (35 mg, 0.25 mmol) in dimethylformamide (1 mL) was stirred at room temperature for 15 hours. The reaction mixture was concentrated *in vacuo* and the resultant residue was purified by column chromatography eluting with 80% ethyl acetate in hexanes to afford 2-bromo-*N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]acetamide (102 mg, 82% yield) as a white foam. MS (EI) for $C_{18}H_{14}BrF_3IN_3O_2$: 568.

[00265] A solution of 2-bromo-*N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]acetamide (30 mg, 0.05 mmol) and *N,N*-diethylamine (100 μL, excess) in dichloromethane (2 mL) was stirred at room temperature for 15 hours. The reaction mixture was concentrated *in vacuo* and purified by preparative reverse phase HPLC (CH_3CN/H_2O with 0.1% TFA). Isolated product was concentrated *in vacuo* to afford *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-*N2,N2*-diethylglycinamide trifluoroacetate salt (13.0 mg, 38% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): 9.36 (br s, 1H), 9.25 (d, 1H), 8.60 (s, 1H), 7.60 (d, 1H), 7.40 (d, 1H), 7.33-7.27 (m, 1H), 7.22-7.15 (m, 1H),

6.73-6.66 (m, 1H), 4.54-4.40 (m, 2H), 4.25-4.20 (m, 1H), 4.04-3.82 (m, 4H), 3.17-3.12 (m, 4H), 1.18-1.15 (m, 6H); MS (EI) $C_{22}H_{24}F_3IN_4O_2$: 561 (MH^+).

[00266] Using the same or analogous synthetic techniques and/or substituting with alternative reagents, the compounds in Examples 2(a)-(n) were prepared.

EXAMPLE 2(a). 1,1-Dimethylethyl [1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]carbamate: ^{1}H NMR (400 MHz, $CDCl_3$): 8.52 (br s, 1H), 7.40 (dd, 1H), 7.33 (dt, 1H), 7.13-7.07 (m, 1H), 6.80 (ddd, 1H), 6.61 (ddd, 1H), 5.01-4.88 (br, 1H), 4.55-4.37 (br, 4H), 4.05 (br d, 1H), 1.43 (s, 9H); MS (EI) for $C_{21}H_{21}F_3IN_3O_3S$: 548 (MH^+).

EXAMPLE 2(b). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine trifluoroacetate salt: ^{1}H NMR (400 MHz, $CDCl_3$): 8.53 (s, 1H), 7.39 (d, 1H), 7.32 (d, 1H), 7.13-7.09 (m, 1H), 6.84-6.77 (m, 1H), 6.63-6.57 (m, 1H), 4.46-4.39 (m, 2H), 3.98-3.75(br m, 4H); MS (EI) for $C_{16}H_{13}F_3IN_3O$: 448 (MH^+).

EXAMPLE 2(c). *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-2-methylpropanamide: ^{1}H NMR (400 MHz, DMSO): 8.60 (s, 1H), 8.38 (d, 1H), 7.59 (d, 1H), 7.38 (d, 1H), 7.32-7.28 (m, 1H), 7.18-7.13 (m, 1H), 6.72-6.66 (m, 1H), 4.45-4.35 (m, 1H), 4.18-3.77 (m, 4H), 2.36-2.28 (m, 1H), 0.99 (d, 6H); MS (EI) $C_{20}H_{19}F_3IN_3O_2$: 518 (MH^+).

EXAMPLE 2(d). *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]formamide: ^{1}H NMR (400 MHz, DMSO): 8.69 (d, 1H), 8.58 (s, 1H), 8.02 (s, 1H), 7.59 (d, 1H), 7.39 (d, 1H), 7.31-7.27 (m, 1H), 7.19-7.13 (m, 1H), 6.70-6.66 (m, 1H), 4.55-4.46 (m, 1H), 4.42-4.36 (m, 1H), 4.20-4.16 (m, 1H), 4.01-3.97 (m, 1H), 3.82-3.79 (m, 1H); MS (EI) $C_{17}H_{13}F_3IN_3O_2$: 476 (MH^+).

EXAMPLE 2(e). *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-3,4-dihydroxybutanamide: ^{1}H NMR (400 MHz, DMSO): 8.60 (s, 1H), 8.47 (d, 1H), 7.59 (d, 1H), 7.39 (d, 1H), 7.31-7.28 (m, 1H), 7.20-7.14 (m, 1H), 6.72-6.66 (m, 1H), 4.45-4.35 (m, 2H), 4.18-4.14 (m, 1H), 4.00-3.92 (m, 1H), 3.84-3.78 (m, 2H), 3.31-3.18 (m, 2H), 2.38-2.18 (m, 1H), 2.09-2.03 (m, 1H); MS (EI) $C_{20}H_{19}F_3IN_3O_4$: 550 (MH^+).

EXAMPLE 2(f). methyl [1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]carbamate: ^{1}H NMR (400 MHz, DMSO): 8.58 (s, 1H), 7.84 (d, 1H), 7.59 (d, 1H), 7.39 (d, 1H), 7.35-7.27 (m, 1H), 7.20-7.13 (m, 1H),

6.71-6.66 (m, 1H), 4.38-4.25 (m, 2H), 4.17-4.12 (m, 1H), 4.00-3.97 (m, 1H), 3.83-3.78 (m, 1H), 3.53 (s, 3H); MS (EI) $C_{18}H_{15}F_3IN_3O_3$: 506 (MH^+).

EXAMPLE 2(g). *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-2-(4-methylpiperazin-1-yl)acetamide trifluoroacetate salt: ^{1}H NMR (400 MHz, DMSO): 8.64 (s, 1H), 8.54 (d, 1H), 7.60 (d, 1H), 7.39 (d, 1H), 7.32-7.29 (m, 1H), 7.21-7.15 (m, 1H), 6.72-6.66 (m, 1H), 4.54-4.28 (m, 2H), 4.19-4.15 (m, 1H), 4.06-4.00 (m, 1H), 3.91-3.84 (m, 1H), 3.44-3.24 (m, 2H), 3.16-2.92 (m, 6H), 2.78 (s, 3H), 2.62-2.50 (m, 2H); MS (EI) $C_{23}H_{25}F_3IN_5O_2$: 588 (MH^+).

EXAMPLE 2(h). *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-*N*,*N*-bis(2-hydroxyethyl)glycinamide trifluoroacetate salt: ^{1}H NMR (400 MHz, DMSO): 9.19 (d, 1H), 7.60 (d, 1H), 7.41 (d, 1H), 7.31-7.27 (m, 1H), 7.21-7.15 (m, 1H), 6.73-6.66 (m, 1H), 4.51-4.40 (m, 2H), 4.23-4.18 (m, 1H), 4.05-3.98 (m, 3H), 3.86-3.82 (m, 1H), 3.75-3.69 (m, 3H), 3.32 (br s, 4H) $C_{22}H_{24}F_3IN_4O_4$: 593 (MH^+).

EXAMPLE 2(i). *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-2-piperidin-1-ylacetamide trifluoroacetate salt: ^{1}H NMR (400 MHz, DMSO): 9.20 (d, 1H), 7.60 (d, 1H), 7.41 (d, 1H), 7.31-7.27 (m, 1H), 7.21-7.15 (m, 1H), 6.73-6.66 (m, 1H), 4.52-4.40 (m, 2H), 4.24-4.18 (m, 1H), 4.05-4.00 (m, 1H), 3.87-3.80 (m, 3H), 3.40-3.32 (m, 2H), 3.00-2.91 (m, 2H), 1.82-1.66 (m, 6H); MS (EI) $C_{23}H_{24}F_3IN_4O_2$: 573 (MH^+).

EXAMPLE 2(j). *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-N3-(2-hydroxyethyl)-N3-methyl-beta-alaninamide hydrochloride: ^{1}H NMR (400 MHz, DMSO): 9.36 (br s, 1H), 8.86 (d, 1H), 8.60 (s, 1H), 7.59 (d, 1H), 7.39 (d, 1H), 7.32-7.26 (m, 1H), 7.21-7.14 (m, 1H), 6.72-6.66 (m, 1H), 5.35-5.33 (m, 1H), 4.48-4.37 (m, 2H), 4.20-4.15 (m, 1H), 4.02-3.96 (m, 1H), 3.84-3.79 (m, 1H), 3.74-3.68 (m, 2H), 3.42-3.06 (m, 4H), 2.75 (s, 3H), 2.65-2.60 (m, 2H); MS (EI) $C_{22}H_{24}F_3IN_4O_3$: 577 (MH^+).

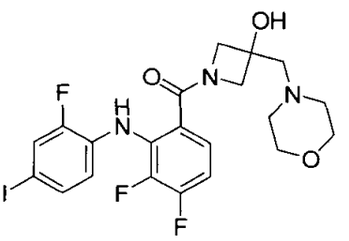
EXAMPLE 2(k). *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-N3,N3-bis(2-hydroxyethyl)-beta-alaninamide hydrochloride: ^{1}H NMR (400 MHz, DMSO): 9.39 (br s, 1H), 8.91 (d, 1H), 8.61 (s, 1H), 7.59 (d, 1H), 7.39 (d, 1H), 7.31-7.27 (m, 1H), 7.21-7.14 (m, 1H), 6.72-6.66 (m, 1H), 5.31 (br s, 2H), 4.46-4.36 (m, 2H), 4.20-4.15 (m, 1H), 4.02-3.97 (m, 1H), 3.85-3.72 (m, 5H), 3.30-3.17 (m, 4H), 2.68-2.63 (m, 2H); MS (EI) $C_{23}H_{26}F_3IN_4O_4$: 607 (MH^+).

EXAMPLE 2(m). *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-N2-methylglycinamide trifluoroacetate salt: ^{1}H NMR (400 MHz, DMSO): 9.09 (d, 1H), 8.69 (br s, 2H), 8.60 (s, 1H), 7.60 (d, 1H), 7.39 (d, 1H), 7.31-7.27 (m, 1H), 7.22-7.15 (m, 1H), 6.73-6.66 (m, 1H), 4.54-4.41 (m, 2H), 4.25-4.19 (m, 1H), 3.99-3.96 (m, 1H), 3.84-3.78 (m, 1H), 3.72-3.67 (m, 2H), 2.58-2.54 (m, 3H); MS (EI) $C_{19}H_{18}F_3IN_4O_2$: 519 (MH^+).

EXAMPLE 2(n). *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]glycinamide trifluoroacetate salt: ^{1}H NMR (400 MHz, DMSO): 8.59 (s, 1H), 8.46 (br s, 1H), 7.59 (d, 1H), 7.39 (d, 1H), 7.32-7.28 (m, 1H), 7.20-7.13 (m, 1H), 6.72-6.66 (m, 1H), 4.49 (br s, 1H), 4.40-4.35 (m, 1H), 4.18-4.13 (m, 1H), 4.05-4.01 (m, 1H), 3.86-3.81 (m, 1H), 3.07 (s, 2H); MS (EI) $C_{18}H_{16}F_3IN_4O_2$: 505 (MH^+).

EXAMPLE 3

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(morpholin-4-ylmethyl)azetidin-3-ol



[00267] A mixture of 3-azetidinol hydrochloride (10 g, 91 mmol), di-*tert*-butyl dicarbonate (18.8 g, 86.3 mmol) and sodium bicarbonate (15.3 g, 182 mmol) in dioxane:water (400 mL, 1:1) was stirred at room temperature for 15 hours. The organic portion was removed *in vacuo* and the aqueous portion was extracted with ethyl acetate three times. The combined organic portion was washed with 5% aqueous HCl, water, brine, dried over sodium sulfate, filtered and concentrated *in-vacuo* to afford 12.8 g, 74 mmol (81%) of 1,1-dimethylethyl 3-hydroxyazetidine-1-carboxylate as a colorless oil without further purification. ^{1}H NMR (400 MHz, DMSO): 5.62 (d, 1H), 4.40-4.33 (m, 1H), 4.02-3.95 (m, 2H), 3.62-3.54 (m, 2H), 1.37 (s, 9H). GC/MS for $C_8H_{15}NO_3$: 173.

[00268] A solution of oxalyl chloride (545 μL, 6.36 mmol) in dichloromethane (25 mL) was cooled to -78 °C. While maintaining an internal temperature of -78 °C, the dropwise addition of DMSO (903 μL, 12.7 mmol) followed by 1,1-dimethylethyl 3-hydroxyazetidine-

1-carboxylate (1 g, 5.78 mmol in 30 mL of dichloromethane) and finally triethylamine (3.25 mL, 23.1 mmol in 20 mL of dichloromethane) was performed. The mixture was allowed to warm to room temperature and was stirred for 15 hours. The reaction mixture was diluted with water and partitioned and the organic portion was washed twice with water. The combined aqueous portion was extracted once with dichloromethane. The combined organic portion was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a yellow oil which was purified by column chromatography. Eluting with 30% ethyl acetate in hexanes, isolated product was concentrated *in vacuo* to afford 893 mg, 5.20 mmol (90%) of 1,1-dimethylethyl 3-oxoazetidine-1-carboxylate as a colorless oil, which solidified upon standing. ^{1}H NMR (400 MHz, DMSO): 4.67 (s, 4H), 1.42 (s, 9H). GC/MS for $C_8H_{13}NO_3$: 171.

[00269] A mixture of potassium *tert*-butoxide (15.5 g, 137 mmol) and methyltriphenylphosphine bromide (49 g, 137 mmol) in diethyl ether (300 mL) was stirred at room temperature for 1 hour, followed by the addition of 1,1-dimethylethyl 3-oxoazetidine-1-carboxylate (10 g, 58 mmol in 100 mL diethyl ether). The mixture was stirred at 35 °C for 2 hours and then allowed to cool to room temperature. The mixture was filtered through a pad of celite, washing with diethyl ether. The filtrate was partitioned with water and washed twice with water, brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to give an orange oil which was purified by column chromatography. Eluting with 10% ethyl acetate in hexanes, isolated product was concentrated *in vacuo* to afford 9.80 g, 58 mmol (100%) of 1,1-dimethylethyl 3-methylideneazetidine-1-carboxylate as a colorless oil. ^{1}H NMR (400 MHz, DMSO): 5.05-4.85 (m, 2H), 4.95-4.63 (m, 4H), 1.45 (s, 9H). GC-MS for $C_9H_{15}NO_2$: 169.

[00270] To a solution of 1,1-dimethylethyl 3-methylideneazetidine-1-carboxylate (2.96 g, 17.5 mmol) in chloroform (180 mL) was added 3-chloroperoxybenzoic acid (77%, 13.9 g, 62.0 mmol), and the resulting mixture was stirred at room temperature for 2 days. The reaction mixture was quenched with a 1:1 mixture (150 mL) of 10% sodium thiosulfate and saturated sodium bicarbonate solutions. The organic portion was isolated, dried over sodium sulfate, filtered and concentrated to give an oily residue which was then purified by flash chromatography (15-50% ethyl acetate-hexanes) to give 1,1-dimethylethyl 1-oxa-5-azaspiro[2.3]hexane-5-carboxylate (1.65g, 51%), GC-MS for $C_9H_{15}NO_3$: 185.

[00271] 1,1-Dimethylethyl 1-oxa-5-azaspiro[2.3]hexane-5-carboxylate (51 mg, 0.28 mmol) was taken into THF (1 mL) followed by addition of morpholine (123 μL, 1.4 mmol) and the mixture was stirred for one hour at room temperature. The solution was then

concentrated and the residue partitioned with ethyl acetate and water. The organic layer was washed once with water then brine and the organic layer dried over anhydrous sodium sulfate. Filtration and concentration gave a colorless oil that was purified by silica gel flash chromatography using ethyl acetate to 10% methanol in dichloromethane as eluents. The combined pure fractions were concentrated and the residue treated with neat TFA (1 mL) for 5 minutes then concentrated. The residue was taken into methanol (2 mL) and basified to pH > 10 by addition of Biorad AG-1X hydroxide form resin. Filtration and concentration afforded 3-(morpholin-4-ylmethyl)azetidin-3-ol (11.6 mg, 24% yield) as a colorless oil. ^{1}H NMR (400 MHz, CD_3OD): 3.69-3.66 (m, 4H), 3.55 (d, 2H), 3.49 (d, 2H), 2.66 (s, 2H), 2.57-2.55 (m, 4H).

[00272] 3-(Morpholin-4-ylmethyl)azetidin-3-ol (11.6 mg, 0.07 mmol) was taken into DMF (1 mL) followed by addition of DIPEA (35 μL, 0.21 mmol) and 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoyl fluoride (28 mg, 0.07 mmol), prepared using procedures similar to those described in Reference 1, and the mixture was stirred for 30 minutes at room temperature. The solution was then concentrated *in vacuo* and the residue purified by preparative reverse phase HPLC. Lyophillization of the combined fractions gave 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(morpholin-4-ylmethyl)azetidin-3-ol trifluoroacetate salt (6.3 mg) as a colorless amorphous solid. ^{1}H NMR (400 MHz, CD_3OD): 7.48 (d, 1H), 7.36 (d, 1H), 7.33-7.29 (m, 1H), 7.08-7.02 (m, 1H), 6.65-6.60 (m, 1H), 4.39 (br d, 1H), 4.24-4.18 (br, 2H), 4.08-3.96 (br m, 3H), 3.80 (br s, 2H), 3.51 (d, 2H), 3.40 (br s, 2H), 3.24 (br s, 2H).

[00273] Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, the following compounds were prepared.

EXAMPLE 3(a). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(pyrrolidin-1-ylmethyl)azetidin-3-ol: MS (EI) for $C_{21}H_{21}F_3IN_3O_2$: 532 (MH^+).

EXAMPLE 3(b). 1-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}piperidin-4-ol: MS (EI) for $C_{22}H_{23}F_3IN_3O_3$: 562 (MH^+).

EXAMPLE 3(c). 3-{[bis(2-hydroxyethyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: MS (EI) for $C_{21}H_{23}F_3IN_3O_4$: 566 (MH^+).

EXAMPLE 3(d). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(4-methylpiperazin-1-yl)methyl]azetidin-3-ol: MS (EI) for $C_{22}H_{24}F_3IN_4O_2$: 561 (MH^+).

EXAMPLE 3(e). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(4-methyl-1,4-diazepan-1-yl)methyl]azetidin-3-ol: MS (EI) for $C_{23}H_{26}F_3IN_4O_2$: 575 (MH^+).

EXAMPLE 3(f). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[methyl(1-methylpyrrolidin-3-yl)amino]methyl}azetidin-3-ol: MS (EI) for $C_{23}H_{26}F_3IN_4O_2$: 575 (MH^+).

EXAMPLE 3(g). 3-(1,4'-bipiperidin-1'-ylmethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: MS (EI) for $C_{27}H_{32}F_3IN_3O_2$: 629 (MH^+).

EXAMPLE 3(h). 3-({4-[2-(diethylamino)ethyl]piperazin-1-yl}methyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: MS (EI) for $C_{27}H_{35}F_3IN_3O_2$: 647 (MH^+).

EXAMPLE 3(i). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxyethyl)(methyl)amino]methyl}azetidin-3-ol: MS (EI) for $C_{20}H_{21}F_3IN_3O_3$: 536 (MH^+).

EXAMPLE 3(j). 3-(azetidin-1-ylmethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: MS (EI) for $C_{20}H_{19}F_3IN_3O_2$: 518 (MH^+).

EXAMPLE 3(k). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1-methylethyl)amino]methyl}azetidin-3-ol: MS (EI) for $C_{20}H_{21}F_3IN_3O_2$: 520 (MH^+).

EXAMPLE 3(m). 3-(aminomethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: MS (EI) for $C_{17}H_{15}F_3IN_3O_2$: 478 (MH^+).

EXAMPLE 3(n). *N*-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}acetamide: MS (EI) for $C_{19}H_{17}F_3IN_3O_3$: 520 (MH^+).

EXAMPLE 3(o). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1,1-dimethylethyl)amino]methyl}azetidin-3-ol: MS (EI) for $C_{21}H_{23}F_3IN_3O_4$: 534 (MH^+).

EXAMPLE 3(q). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(hydroxyamino)methyl]azetidin-3-ol: ^{1}H NMR (400 MHz, d_4-MeOH): 7.45 (2d, 1H), 7.35 (m, 1H), 7.28 (m, 1H), 7.03 (m, 1H), 6.63 (m, 1H), 4.32 (d, 1H), 4.05 (dd, 2H), 3.85 (d, 1H), 3.00 (s, 2H); MS (EI) for $C_{17}H_{15}F_3IN_3O_3$: 494 (MH^+).

EXAMPLE 3(r). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(methyloxy)amino]methyl}azetidin-3-ol: ^{1}H NMR (400 MHz, d_4-MeOH): 7.45 (2d, 1H), 7.35 (m, 1H), 7.27 (m, 1H), 7.04 (m, 1H), 6.62 (m, 1H), 4.26 (d, 1H), 4.08 (d, 1H), 4.00 (d, 1H), 3.84 (d, 1H), 3.30 (s, 3H), 3.00 (d, 2H); MS (EI) for $C_{18}H_{17}F_3IN_3O_3$: 508 (MH^+).

EXAMPLE 3(s). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(ethyloxy)amino]methyl}azetidin-3-ol: ^{1}H NMR (400 MHz, d_4-MeOH): 7.45 (2d, 1H), 7.34 (m, 1H), 7.26 (m, 1H), 7.03 (m, 1H), 6.63 (m, 1H), 4.26 (d, 1H), 4.12 (d, 1H), 4.00 (d, 1H), 3.84 (d, 1H), 3.61 (dd, 2H), 3.00 (s, 2H), 1.06 (t, 3H); MS (EI) for $C_{19}H_{19}F_3IN_3O_3$: 522 (MH^+).

EXAMPLE 3(t). 1-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}guanidine acetate salt: ^{1}H NMR (400 MHz, d_4-MeOH): 7.46 (2d, 1H), 7.36 (m, 1H), 7.30 (m, 1H), 7.04 (m, 1H), 6.62 (m, 1H), 4.18 (d, 1H), 4.08 (d, 1H), 4.02 (d, 1H), 3.88 (1*H*), 3.40 (s, 2H); MS (EI) for $C_{18}H_{17}F_3IN_5O_2$: 520 (MH^+).

EXAMPLE 3(u). *N*-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}benzenecarboximidamide hydrochloride: ^{1}H NMR (400 MHz, d_4-MeOH): 7.70 (d, 3H), 7.58 (m, 2H), 7.46 (dd, 1H), 7.36 (m, 1H), 7.31 (m, 1H), 7.04 (m, 1H), 6.62 (m, 1H), 4.28 (m, 1H), 4.15 (m, 2H), 3.96 (m, 1H), 3.78 (s, 2H); MS (EI) for $C_{24}H_{20}F_3IN_4O_2$: 581 (MH^+).

EXAMPLE 3(v). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(pyrimidin-2-ylamino)methyl]azetidin-3-ol hydrochloride: ^{1}H NMR (400 MHz, d_4-MeOH): 8.48 (s, 2H), 7.46 (2d, 1H), 7.36 (m, 1H), 7.28 (m, 1H), 7.04 (m, 1H), 6.85 (t, 1H), 6.61 (m, 1H), 4.24 (d, 1H), 4.06 (t, 2H), 3.87 (d, 1H), 3.75 (d, 2H); MS (EI) for $C_{21}H_{17}F_3IN_5O_2$: 556 (MH^+).

EXAMPLE 3(w). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(pyridin-2-ylamino)methyl]azetidin-3-ol hydrochloride: ^{1}H NMR (400 MHz, d_4-MeOH): 7.87 (dd, 1H), 7.85 (dd, 1H), 7.46 (2d, 1H), 7.36 (m, 2H), 7.06 (m, 2H), 6.89 (m, 1H), 6.61 (m, 1H), 4.53 (d, 2H), 4.46 (m, 1H), 4.28 (m, 1H), 4.16 (m, 1H), 3.96 (m, 1H); MS (EI) for $C_{22}H_{18}F_3IN_4O_2$: 555 (MH^+).

EXAMPLE 3(x). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(ethylamino)methyl]azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8.61 (s, 2H), 7.59 (d, 1H), 7.40 (d, 1H), 7.36-7.33 (m, 1H), 7.23-7.18 (m, 1H), 6.71 (s, 2H), 4.31-4.26 (m, 1H), 4.13-4.05 (m, 2H), 3.88-3.84 (m, 1H), 3.21 (br m, 2H), 2.97-2.90 (m, 2H), 1.19 (t, 3H). MS (EI) for $C_{19}H_{19}F_3IN_3O_2$: 506 (MH^+).

EXAMPLE 3(y). 3-[(cyclopropylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8.99 (br s, 2H), 8.60 (s, 1H), 7.58 (d, 1H), 7.39 (d, 1H), 7.36-7.33 (m, 1H), 7.23-7.16 (m, 1H), 6.72 (s, 2H), 4.34-4.29 (m, 1H), 4.14-4.04 (m, 2H), 3.88-3.84 (m, 1H), 2.70-2.64 (m, 1H), 0.89 (br s, 2H), 0.74-0.69 (br s, 2H). MS (EI) for $C_{20}H_{19}F_3IN_3O_2$: 518 (MH^+).

EXAMPLE 3(z). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2,2,2-trifluoroethyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8.60 (s, 1H), 7.58 (d, 1H), 7.38 (d, 1H), 7.35-7.30 (m, 1H), 7.22-7.17 (m, 1H), 6.72-6.67 (m, 1H), 4.25-4.19 (m, 1H), 4.07-3.98 (m, 2H), 3.86-3.77 (m, 2H), 3.19-3.09 (m, 2H). MS (EI) for $C_{19}H_{16}F_6IN_3O_2$: 560 (MH^+).

EXAMPLE 3(aa). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1*H*-1,2,3-triazol-1-ylmethyl)azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8.55 (s, 1H), 8.04 (s, 1H), 7.66 (s, 1H), 7.58 (d, 1H), 7.39 (d, 1H), 7.34-7.29 (m, 1H), 7.22-7.15 (m, 1H), 6.72-6.66 (m, 1H), 6.29 (s, 1H), 4.64 (s, 2H), 4.29-4.25 (m, 1H), 4.13-4.09 (m, 1H), 4.00-3.96 (m, 1H), 3.77-3.73 (m, 1H), 3.16 (d, 1H). MS (EI) for $C_{19}H_{15}F_3IN_5O_2$: 530 (MH^+).

EXAMPLE 3(bb). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2,2-dimethylpropyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8.61 (s, 1H), 8.30 (s, 2H), 7.59 (d, 1H), 7.39 (d, 1H), 7.36-7.17 (m, 4H), 6.77-6.66 (m, 4H), 4.35-4.30 (m, 1H), 4.16-4.08 (m, 2H), 3.92-3.87 (m, 1H), 3.31-3.27 (m, 2H), 2.78-2.74 (m, 2H), 1.76 (s, 4H), 0.99 (s, 9H). MS (EI) for $C_{22}H_{25}F_3IN_3O_2$: 548 (MH^+).

EXAMPLE 3(cc). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(4-methylphenyl)ethyl]amino}methyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, $CDCl_3$): 8.48 (s, 1H), 7.39 (dd, 1H), 7.31-7.34 (m, 1H), 7.08 (dd, 5H), 6.77-6.83 (m, 1H), 6.58-6.63 (m, 1H), 4.20 (br s, 1H), 4.01 (d, 1H), 2.87 (t, 4H), 2.75 (t, 4H), 2.5 (br s, 2H), 2.33 (s, 3H), 2.08 (s, 2H). MS (EI) for $C_{26}H_{25}F_3IN_3O_2$: 594 (M-H).

EXAMPLE 3(dd). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2,3-dihydro-1*H*-inden-2-ylamino)methyl]azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, $CDCl_3$): 8.48 (s, 1H), 7.40 (dd, 1H), 7.32-7.34 (m, 1H), 7.15-7.22 (m, 4H), 7.10-7.14 (m, 1H), 6.77-6.83 (m, 1H), 6.58-6.64 (m, 1H), 4.22 (br s, 1H), 4.04 (d, 1H), 3.57-3.63 (m, 1H), 3.17 (dd, 2H), 2.94 (s, 2H), 2.75 (dd, 2H), 2.48 (br s, 4H), 2.08 (s, 2H). MS (EI) for $C_{26}H_{23}F_3IN_3O_2$: 592 (M-H).

EXAMPLE 3(ee). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(1S,2S)-2-hydroxycyclopentyl]amino}methyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.46 (dd, 1H), 7.33-7.37 (m, 1H), 7.26-7.31 (m, 1H), 7.00-7.08 (m, 1H), 6.58-6.65 (m, 1H), 4.2 (t, 1H), 3.86-4.06 (m, 4H), 2.92-3.10 (m, 3H), 2.00-2.10 (m, 1H), 1.91-1.97 (m, 3H), 1.66-1.78 (m, 2H), 1.52-1.61 (m, 1H), 1.32-1.44 (m, 1H). MS (EI) for $C_{22}H_{23}F_3IN_3O_3$: 560 (M-H).

EXAMPLE 3(ff). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1,2-dimethylpropyl)amino]methyl}azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.45 (dd, 1H), 7.33-7.37 (m, 1H), 7.26-7.31 (m, 1H), 7.01-7.08 (m, 1H), 6.59-6.64 (m, 1H), 4.14-4.22 (m, 1H), 3.98-4.06 (m, 2H), 3.84-3.90 (m, 1H), 2.86-3.20 (m, 2H), 2.65 (br s, 1H), 1.92 (s, 2H), 1.76-1.86 (m, 1H), 1.06 (d, 3H), 0.91 (dd, 6H). MS (EI) for $C_{22}H_{25}F_3I\,N_3O_2$: 546 (M-H).

EXAMPLE 3(gg). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[1-methyl-2-(methyloxy)ethyl]amino}methyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.55 (dd, 1H), 7.33-7.36 (m, 1H), 7.26-7.31 (m, 1H), 7.01-7.09 (m, 1H), 6.59-6.65 (m, 1H), 4.14-4.22 (m, 1H), 3.96-4.06 (m, 2H), 3.85-3.92 (m, 1H), 3.40-3.48 (m, 1H), 3.34 (s, 3H), 2.90-3.15 (m, 3H), 1.94 (s, 3H), 1.11 (d, 3H). MS (EI) for $C_{21}H_{23}F_3IN_3O_3$: 548 (M-H).

EXAMPLE 3(hh). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1-ethylpropyl)amino]methyl}azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.45 (dd, 1H), 7.33-7.36 (m, 1H), 7.26-7.31 (m, 1H), 7.01-7.09 (m, 1H), 6.58-6.65 (m, 1H), 4.15-4.20 (m, 1H), 3.99-4.06 (m, 2H), 3.86-3.91 (m, 1H), 2.94 (s, 2H), 2.55-2.63 (m, 1H), 1.92 (s, 2H), 1.48-1.58 (m, 4H), 0.92 (t, 6H). MS (EI) for $C_{22}H_{25}F_3IN_3O_2$: 546 (M-H).

EXAMPLE 3(ii). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1*H*-imidazol-1-ylmethyl)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7.67 (br s, 1H), 7.48 (m, 1H), 7.36 (m, 1H), 6.91 (br s, 1H), 6.63 (m, 1H), 4.25 (s, 2H), 4.22 (m, 1H), 4.02 (m, 2H), 3.82 (m, 1H). MS (EI) for $C_{20}H_{16}F_3IN_4O_2$: 529 (MH^+).

EXAMPLE 3(jj). 3-{[(cyclopropylmethyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7.47 (m, 1H), 7.36 (m, 1H), 7.31 (m, 1H), 7.05 (m, 1H), 6.62 (m, 1H), 4.30 (m, 1H), 4.24 (m, 2H), 3.99 (m, 1H), 3.66 (m, 2H), 2.91 (d, 2H), 1.08 (m, 1H), 0.71 (m, 2H), 0.40 (m, 2H). MS (EI) for $C_{21}H_{21}F_3IN_3O_2$: 532 (MH^+).

EXAMPLE 3(kk). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(phenylmethyl)amino]methyl}azetidin-3-ol hydrochloride: ^{1}H NMR (400 MHz, CD_3OD): 7.47 (m, 5H), 7.43 (m, 1H), 7.35 (m, 1H), 7.27 (m, 1H), 7.04 (m, 1H), 6.61 (m, 1H), 4.24 (m, 3H), 4.08 (m, 2H), 3.96 (m, 1H). MS (EI) for $C_{24}H_{21}F_3IN_3O_2$: 568 (MH^+).

EXAMPLE 3(mm). 3-[(butylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.56 (s, 1H), 7.57 (dd, 1H), 7.36 (d, 1H), 7.31 (t, 1H), 7.17 (q, 1H), 6.67 (dt, 1H), 4.04 (d, 1H), 3.88 (q, 2H), 3.69 (d, 1H), 2.59 (s, 2H), 1.90 (s, 2H), 1.22-1.33 (m, 4H), 0.84 (t, 3H); MS (EI) for $C_{21}H_{23}F_3IN_3O_2$: 534 (MH^+).

EXAMPLE 3(nn). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(1-ethylpyrrolidin-2-yl)methyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.59 (s, 1H), 7.57 (dd, 1H), 7.36 (d, 1H), 7.31 (t, 1H), 7.17 (q, 1H), 6.68 (dt, 1H), 4.02 (t, 1H), 3.89 (q, 2H), 3.69 (d, 1H), 2.98 (s, 1H), 2.67-2.76 (m, 1H), 2.62 (s, 1H), 2.39-

2.45 (m, 1H), 2.29 (s, 1H), 1.97-2.13 (m, 2H), 1.69 (s, 1H), 1.54 (s, 3H), 0.97 (t, 3H); MS (EI) for $C_{24}H_{28}F_3IN_4O_2$: 589 (MH^+).

EXAMPLE 3(oo). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxyethyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.57 (s, 1H), 7.57 (dd, 1H), 7.37 (d, 1H), 7.32 (t, 1H), 7.18 (q, 1H), 6.68 (dt, 1H), 4.06 (d, 1H), 3.87 (d, 2H), 3.70 (d, 1H), 3.42 (t, 2H), 2.65 (s, 2H), 2.56 (dt, 2H). 1.91 (s, 2H); MS (EI) for $C_{19}H_{19}F_3IN_3O_3$: 522 (MH^+).

EXAMPLE 3(pp). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(dimethylamino)ethyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.58 (s, 1H), 7.57 (dd, 1H), 7.36 (d, 1H), 7.31 (t, 1H), 7.17 (q, 1H), 6.68 (dt, 1H), 4.02 (d, 1H), 3.87 (t, 2H), 3.70 (d, 1H), 2.62 (s, 1H), 2.54 (t, 1H), 2.23 (t, 1H), 2.09 (s, 4H), 7.85 (s, 6H); MS (EI) for $C_{21}H_{24}F_3IN_4O_2$: 549 (MH^+).

EXAMPLE 3(qq). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(1-methylpyrrolidin-2-yl)ethyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.58 (s, 1H), 7.57 (dt, 1H), 7.36 (d, 1H), 7.31 (t, 1H), 7.17 (q, 1H), 6.68 (dt, 1H), 4.04 (d, 1H), 3.89 (d, 2H), 3.79 (d, 1H), 2.88-2.92 (m, 1H), 2.61 (s, 2H), 2.15 (s, 3H), 1.93-2.04 (m, 2H), 1.75-1.83 (m, 3H), 1.54-1.70 (m, 3H), 1.20-1.37 (m, 2H); MS (EI) for $C_{24}H_{28}F_3IN_4O_2$: 589 (MH^+).

EXAMPLE 3(rr). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(tetrahydrofuran-2-ylmethyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.58 (s, 1H), 7.57 (dd, 1H), 7.37 (d, 1H), 7.31 (t, 1H), 7.14 (q, 1H), 6.68 (dt, 1H), 5.75 (s, 1H), 4.03 (t, 1H), 3.87 (t, 2H), 3.76 (q, 1H), 3.68 (q, 2H), 3.54-3.58 (m, 1H), 2.63 (s, 2H), 1.91 (s, 2H), 1.71-1.87 (m, 3H), 1.40-1.48 (m, 1H); MS (EI) for $C_{22}H_{23}F_3IN_3O_3$: 562 (MH^+).

EXAMPLE 3(ss). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(3-pyrrolidin-1-ylpropyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.58 (s, 1H), 7.57 (dd, 1H), 7.36 (d, 1H), 7.31 (t, 1H), 7.17 (q, 1H), 6.68 (dt, 1H), 4.04 (d, 1H), 3.89 (d, 2H), 3.69 (d, 1H), 2.60 (s, 1H), 2.34-2.37 (m, 4H), 1.86 (s, 8H), 1.64 (s, 2H), 1.46-1.53 (m, 1H); MS (EI) for $C_{24}H_{28}F_3IN_4O_2$: 589 (MH^+).

EXAMPLE 3(tt). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(methyloxy)ethyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): ^{1}H NMR (400MHz, d_6-DMSO): 8.57 (s, 1H), 7.57 (dd, 1H), 7.37 (d, 1H), 7.31 (t, 1H), 7.17 (q, 1H), 6.68 (dt, 1H), 4.03 (d, 1H), 3.86 (d, 2H), 3.70 (d, 1H), 3.21 (s, 3H), 2.63 (s, 4H), 1.88 (s, 2H); MS (EI) for $C_{20}H_{21}F_3IN_3O_3$: 536 (MH^+).

EXAMPLE 3(uu). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(1-methylpiperidin-4-yl)methyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.58 (s, 1H), 7.57 (d, 1H), 7.37 (d, 1H), 7.31 (t, 1H), 7.17 (q, 1H), 6.68 (t, 1H), 4.03 (d, 1H), 3.89 (t, 2H), 3.69 (d, 1H), 2.68 (d, 2H), 2.57 (s, 1H), 2.34 (d, 2H), 1.88 (s, 4H), 1.73 (t, 2H), 1.57 (d, 2H), 1.23 (s, 1H), 1.05 (q, 2H); MS (EI) for $C_{24}H_{28}F_3IN_4O_3$: 589 (MH^+).

EXAMPLE 3(vv). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[4-(dimethylamino)butyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 7.57 (dd, 1H), 7.36 (d, 1H), 7.31 (t, 1H), 7.18 (q, 1H), 6.68 (dt, 1H), 4.03 (t, 2H), 3.88 (t, 2H), 3.70 (d, 1H), 3.08 (s, 1H), 2.60 (s, 1H), 2.44-2.47 (m, 2H), 2.28-2.33 (m, 1H), 2.07-2.16 (m, 6H), 1.29-1.35 (m, 4H); MS (EI) for $C_{23}H_{28}F_3IN_4O_2$: 577 (MH^+).

EXAMPLE 3(ww). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-furan-2-ylethyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.58 (s, 1H), 7.57 (d, 1H), 7.49 (s, 1H), 7.36 (d, 1H), 7.31 (t, 1H), 7.17 (q, 1H), 6.68 (t, 1H), 6.33 (s, 1H), 6.08 (s, 1H), 5.72 (s, 1H), 4.04 (d, 1H), 3.87 (d, 2H), 3.70 (d, 1H), 2.74 (d, 2H), 2.69 (d, 2H), 2.64 (s, 2H); MS (EI) for $C_{23}H_{21}F_3IN_3O_3$: 572 (MH^+).

EXAMPLE 3(xx). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-ethylbutyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.58 (s, 1H), 7.56 (dd, 1H), 7.36 (d, 1H), 7.31 (t, 1H), 7.17 (q, 1H), 6.67 (dt, 1H), 4.03 (d, 1H), 3.90 (d, 2H), 3.69 (d, 1H), 2.58 (s, 2H), 2.37 (d, 2H), 1.17-1.27 (m, 5H), 0.78 (t, 6H); MS (EI) for $C_{23}H_{27}F_3IN_3O_2$: 562 (MH^+).

EXAMPLE 3(yy). 1,1-dimethylethyl [3-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)propyl]carbamate: ^{1}H NMR (400MHz, d_6-DMSO): 8.58 (s, 1H), 7.57 (d, 1H), 7.30-7.38 (m, 3H), 7.17 (q, 1H), 6.82 (t, 1H), 6.68 (dt, 1H), 4.07 (d, 1H), 3.89 (d, 2H), 3.70 (d, 1H), 3.36 (s, 2H), 2.93 (q, 2H), 2.61 (s, 2H), 1.46 (t, 2H), 1.36 (s, 9H); MS (EI) for $C_{25}H_{30}F_3IN_4O_4$: 635 (MH^+).

EXAMPLE 3(zz). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(pyrrolidin-2-ylmethyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.53 (s, 1H), 7.58 (dd, 1H), 7.37 (d, 1H), 7.33 (d, 1H), 7.18 (q, 1H), 6.67 (dt, 1H), 6.25 (s, 1H), 4.07 (d, 1H), 3.96 (q, 2H), 3.78 (s, 3H), 3.34 (s, 6H), 1.73 (s, 1H), 1.35-1.39 (m, 1H); MS (EI) for $C_{22}H_{24}F_3IN_4O_2$: 561 (MH^+).

EXAMPLE 3(aaa). 1,1-dimethylethyl 4-[({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)methyl]piperidine-1-carboxylate: ^{1}H NMR (400MHz, d_6-DMSO): 8.56 (s,

1H), 7.56 (dd, 1H), 7.36 (d, 1H), 7.30 (t, 1H), 7.17 (q, 1H), 6.68 (dt, 1H), 4.03 (d, 1H), 3.88 (t, 4H), 3.69 (d, 1H), 2.58 (s, 2H), 2.35 (d, 2H), 1.60 (d, 2H), 1.47 (s, 1H), 1.39 (s, 10H), 0.90 (q, 2H); MS (EI) for $C_{28}H_{34}F_3IN_4O_4$: 675 (MH^+).

EXAMPLE 3(bbb). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(2-hydroxyphenyl)methyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.56 (s, 1H), 7.54 (dd, 1H), 7.35 (d, 1H), 7.30 (t, 1H), 7.17 (q, 1H), 7.05 (t, 2H), 6.64-6.72 (m, 3H), 4.07 (d, 1H), 3.90 (t, 2H), 3.78 (s, 2H), 3.72 (d, 1H), 2.65 (s, 2H); MS (EI) for $C_{24}H_{21}F_3IN_3O_3$: 584 (MH^+).

EXAMPLE 3(ccc). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(3-hydroxyphenyl)methyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.58 (s, 1H), 7.56 (d, 1H), 7.35 (d, 1H), 7.29 (t, 1H), 7.16 (q, 1H), 7.06 (t, 1H), 6.64-6.72 (m, 3H), 6.60 (dd, 1H), 4.07 (d, 1H), 3.88 (t, 2H), 3.69 (d, 1H), 3.60 (s, 2H), 2.58 (d, 2H); MS (EI) for $C_{24}H_{21}F_3IN_3O_3$: 584 (MH^+).

EXAMPLE 3(ddd). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(4-hydroxyphenyl)methyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.57 (s, 1H), 7.55 (dd, 1H), 7.35 (d, 1H), 7.27 (t, 1H), 7.16 (q, 1H), 7.06 (d, 2H), 6.64-6.70 (m, 3H), 4.04 (d, 1H), 3.85 (t, 2H), 3.68 (d, 1H), 3.55 (s, 2H), 2.56 (d, 2H); MS (EI) for $C_{24}H_{21}F_3IN_3O_3$: 584 (MH^+).

EXAMPLE 3(eee). 3-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)-5-(hydroxymethyl)cyclopentane-1,2-diol: ^{1}H NMR (400MHz, d_6-DMSO): 8.60 (broad s, 1H), 7.57 (dd, 1H), 7.37 (d, 1H), 7.32 (t, 1H), 7.16 (q, 1H), 6.68 (t, 1H), 4.06 (q, 2H), 3.86 (t, 3H), 3.72 (dd, 1H), 3.60 (t, 1H), 3.36-3.43 (m, 2H), 3.30 (dd, 1H), 2.80 (q, 1H), 2.62-2.72 (m, 2H), 1.88-1.95 (m, 1H), 0.82-0.90 (m, 1H); MS (EI) for $C_{23}H_{25}F_3IN_3O_5$: 608 (MH^+).

EXAMPLE 3(fff). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(piperidin-4-ylmethyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.59 (broad s, 1H), 7.57 (dd, 1H), 7.37 (d, 1H), 7.30 (t, 1H), 7.17 (q, 1H), 6.68 (dt, 1H), 4.03 (d, 1H), 3.87 (d, 2H), 3.69 (d, 1H), 3.01 (d, 2H), 2.59 (s, 2H), 2.43-2.56 (m, 1H), 2.35 (d, 2H), 1.65 (d, 2H), 1.47 (s, 1H), 1.07 (q, 2H); MS (EI) for $C_{23}H_{26}F_3IN_4O_2$: 575 (MH^+).

EXAMPLE 3(ggg). 3-{[(3-aminopropyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 7.57 (dd, 1H), 7.37 (d, 1H), 7.31 (t, 1H), 7.17 (q, 1H),, 6.68 (dt, 1H), 4.05 (d, 1H), 3.88 (d, 2H), 3.69 (d, 1H), 2.61 (t, 3H), 2.53-2.56 (m, 1H), 1.49 (t, 1.49); MS (EI) for $C_{23}H_{26}F_3IN_4O_2$: 535 (MH^+).

EXAMPLE 3(hhh). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[({[2-(4-methylpiperazin-1-yl)phenyl]methyl}amino)methyl]azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.59 (broad s, 1H), 7.55 (dd, 1H), 7.34 (t, 2H), 7.28 (d, 1H), 7.13-7.20 (m, 1H), 7.05 (d, 1H), 6.99 (t, 1H), 6.66 (dt, 1H), 4.03 (d, 1H), 3.90 (t, 2H), 3.71 (d, 3H), 2.83 (s, 5H), 2.60 (s, 2H), 2.42 (s, 3H), 2.20 (s, 3H); MS (EI) for $C_{29}H_{31}F_3IN_5O_2$: 666 (MH^+).

EXAMPLE 3(iii). 3-[(1*H*-benzimidazol-2-ylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8.04 (s, 2H), 7.28-7.35 (m, 2H), 7.23-7.26 (m, 2H), 7.09-7.12 (m, 2H), 6.80 (q, 1H), 6.57-6.63 (m, 1H), 5.28 (broad s, 2H), 4.38 (s, 3H), 4.25 (s, 1H), 4.21 (d, 2H); MS (EI) for $C_{24}H_{19}F_3IN_5O_2$: 594 (MH^+).

EXAMPLE 3(jjj). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(1*H*-imidazol-2-ylamino)methyl]azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 12.12 (s, 1H), 8.68 (s, 1H), 7.57-7.61 (m, 3H), 7.36-7.41 (m, 2H), 7.19 (q, 1H), 6.99 (s, 1H), 6.91 (s, 1H), 6.71 (dt, 1H), 6.45 (s, 1H), 4.28 (d, 1H), 4.06 (d, 1H), 4.03 (d, 1H), 3.82 (d, 2H); MS (EI) for $C_{24}H_{17}F_3IN_5O_2$: 544 (MH^+).

EXAMPLE 3(kkk). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{2-[(2,2,3,3,3-pentafluoropropyl)amino]ethyl}azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8.58 (br s, 1H), 7.56 (dd, 1H), 7.37 (dd, 1H), 7.34-7.28 (m, 1H), 7.22-7.13 (m, 1H), 6.68 (ddd, 1H), 5.82 (br s, 1H), 4.06 (d, 1H), 3.91 (t, 2H), 3.70 (d, 1H), 3.40-3.25 (m, 2H), 2.76 (d, 2H), 2.40-2.31 (m, 1H); MS (EI) for $C_{20}H_{16}F_8IN_3O_2$: 610 (MH^+).

EXAMPLE 3(mmm). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{2-[(3,3,3-trifluoropropyl)amino]ethyl}azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8.58 (br s, 1H), 7.57 (dd, 1H), 7.37 (dd, 1H), 7.34-7.28 (m, 1H), 7.22-7.13 (m, 1H), 6.68 (ddd, 1H), 5.76 (br s, 1H), 4.05 (d, 1H), 3.88 (d, 2H), 3.70 (d, 1H), 2.71 (t, 2H), 2.63 (s, 2H), 2.41-2.26 (m, 2H); MS (EI) for $C_{20}H_{18}F_6IN_3O_2$: 574 (MH^+).

EXAMPLE 3(nnn). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2,3-dihydro-1*H*-inden-1-ylamino)methyl]azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, DMSO): 8.61-8.56 (m, 1H), 7.55 (d, 1H), 7.37-7.07 (m, 8H), 6.71-6.64 (m, 1H), 4.16-4.05 (m, 2H), 3.98-3.85 (m, 2H), 3.72-3.68 (m, 1H), 2.90-2.82 (m, 1H), 2.74-2.64 (m, 2H), 1.91 (s, 3H), 1.73-1.63 (m, 1H); MS (EI) for $C_{26}H_{23}F_3IN_3O_2$: 594 (MH^+).

EXAMPLE 3(ooo). 3-[(cyclooctylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, DMSO): 8.56 (s, 1H), 7.55 (d, 1H), 7.20-7.14 (m, 2H), 6.70-6.66 (m, 1H), 4.03-3.98 (m, 1H), 3.92-

3.86 (m, 2H), 3.72-3.67 (m, 1H), 2.60 (s, 2H), 1.90 (s, 3H), 1.64-1.22 (m, 15H); MS (EI) for $C_{25}H_{29}F_3IN_3O_2$: 588 (MH^+).

EXAMPLE 3(ppp). 3-[(cycloheptylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, DMSO): 8.55 (s, 1H), 7.55 (d, 1H), 7.36-7.28 (m, 2H), 7.21-7.14 (m, 1H), 6.70-6.66 (m, 1H), 4.04-4.00 (m, 1H), 3.92-3.85 (m, 2H), 3.71-3.66 (m, 1H), 2.60 (s, 2H), 1.90 (s, 3H), 1.70-1.13 (m, 13H); MS (EI) for $C_{24}H_{27}F_3IN_3O_2$: 574 (MH^+).

EXAMPLE 3(qqq). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-pyridin-3-ylethyl)amino]methyl}azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, DMSO): 8.58 (s, 1H), 8.42-8.37 (m, 2H), 7.62-7.54 (m, 2H), 7.38-7.27 (m, 3H), 7.21-7.14 (m, 1H), 6.71-6.66 (m, 1H), 4.06-4.02 (m, 1H), 3.90-3.86 (m, 2H), 3.72-3.68 (m, 1H), 2.80-2.64 (m, 6H), 1.90 (s, 3H); MS (EI) for $C_{24}H_{22}F_3IN_4O_2$: 583 (MH^+).

EXAMPLE 3(rrr). *N*-cyclohexyl-N2-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}-2-methylalaninamide acetate salt: ^{1}H NMR (400 MHz, DMSO): 8.66 (br s 1H), 8.55 (s, 1H), 7.93-7.90 (m, 1H), 7.58 (d, 1H), 7.40-7.31 (m, 2H), 7.24-7.17 (m, 1H), 6.71-6.66 (m, 1H), 6.60 (br s, 1H), 4.28-4.23 (m, 1H), 4.14-4.02 (m, 2H), 3.89-3.83 (m, 1H), 3.12 (br s, 2H), 1.90 (s, 3H), 1.74-1.42 (m, 11H), 1.31-1.02 (m, 6H); MS (EI) for $C_{27}H_{32}F_3IN_4O_3$: 645 (MH^+).

EXAMPLE 3(sss). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(tetrahydro-2H-pyran-4-ylmethyl)amino]methyl}azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, DMSO): 8.56 (s, 1H), 7.56 (d, 1H), 7.38-7.27 (m, 2H), 7.20-7.14 (m, 1H), 6.71-6.66 (m, 1H), 4.05-4.01 (m, 1H), 3.91-3.78 (m, 4H), 3.71-3.67 (m, 1H), 3.25-3.18 (m, 2H), 2.60 (s, 2H), 2.36 (d, 2H), 1.90 (s, 3H), 1.57-1.50 (m, 3H), 1.13-1.02 (m, 2H); MS (EI) for $C_{23}H_{25}F_3IN_3O_3$: 576 (MH^+).

EXAMPLE 3(ttt). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(dimethylamino)-1-methylethyl]amino}methyl)azetidin-3-ol trifluoroacetate salt: ^{1}H NMR (400 MHz, DMSO): 8.59-8.54 (m, 1H), 7.56 (d, 1H), 7.38-7.28 (m, 2H), 7.21-7.13 (m, 1H), 6.71-6.63 (m, 1H), 4.04-3.95 (m, 1H), 3.88-3.78 (m, 2H), 3.73-3.68 (m, 1H), 2.70-2.50 (m, 3H), 2.08 (s, 6H), 1.88 (s, 2H), 0.85-0.82 (m, 3H); MS (EI) for $C_{22}H_{26}F_3IN_4O_2$: 563 (MH^+).

EXAMPLE 3(uuu). *N*-cyclopropyl-1-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)cyclopentanecarboxamide trifluoroacetate salt: ^{1}H NMR (400 MHz, DMSO): 8.80 (br s, 1H), 8.58 (s, 1H), 8.04 (s, 1H), 7.59 (d, 1H), 7.40-7.31 (m, 2H), 7.25-

7.16 (m, 1H), 6.74-6.58 (m, 2H), 4.26-3.82 (m, 4H), 3.10 (br s, 2H), 2.69-2.64 (m, 1H), 2.11-1.88 (m, 4H), 1.82-1.61 (m, 4H), 0.67-0.62 (m, 2H), 0.52-0.48 (m, 2H); MS (EI) for $C_{26}H_{28}F_3IN_4O_3$: 629 (MH^+).

EXAMPLE 3(vvv). N2-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}-*N*-ethyl-2-methylalaninamide acetate salt: ^{1}H NMR (400 MHz, DMSO): 8.60 (s, 1H), 7.60-7.72 (m, 1H), 7.56 (d, 1H), 7.38-7.30 (m, 2H), 7.22-7.14 (m, 1H), 6.69-6.63 (m, 1H), 4.07-4.04 (m, 1H), 3.95-3.90 (m, 2H), 3.72-3.68 (m, 1H), 3.05-3.01 (m, 2H), 2.47 (br s, 2H), 1.90 (s, 3H), 1.09 (s, 6H), 0.94 (t, 3H); MS (EI) for $C_{23}H_{26}F_3IN_4O_3$: 591 (MH^+).

EXAMPLE 3(www). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2-methylhydrazino)methyl]azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, DMSO): 8.54 (s, 1H), 7.57 (d, 1H), 7.38-7.30 (m, 2H), 7.19-7.12 (m, 1H), 6.69-6.63 (m, 1H), 4.04-4.01 (m, 1H), 3.92-3.84 (m, 2H), 3.68-3.63 (m, 1H), 2.55 (s, 2H), 2.39 (s, 3H), 1.90 (s, 3H); MS (EI) for $C_{18}H_{18}F_3IN_4O_2$: 507 (MH^+).

EXAMPLE 3(xxx). 3-[(azetidin-3-ylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, DMSO): 7.57 (d, 1H), 7.39-7.30 (m, 2H), 7.20-7.13 (m, 1H), 6.70-6.65 (m, 1H), 4.10-4.04 (m, 1H), 3.90-3.83 (m, 2H), 3.78-3.67 (m, 3H), 3.61-3.53 (m, 1H), 3.48-3.42 (m, 2H), 2.61-2.54 (m, 2H), 1.90 (s, 3H); MS (EI) for $C_{20}H_{20}F_3IN_4O_2$: 533 (MH^+).

EXAMPLE 3(yyy). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(1,3-thiazol-2-ylamino)methyl]azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, DMSO): 8.60 (s, 1H), 7.57 (d, 1H), 7.38-7.28 (m, 2H), 7.20-7.13 (m, 1H), 6.75 (d, 1H), 6.70-6.64 (m, 1H), 5.93 (d, 1H), 4.26-4.22 (m, 1H), 4.11-4.08 (m, 1H), 4.00-3.88 (m, 3H), 3.74-3.70 (m, 1H), 1.90 (s, 3H); MS (EI) for $C_{20}H_{16}F_3IN_4O_2S$: 561 (MH^+).

EXAMPLE 3(zzz). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[3-(methyloxy)phenyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400 MHz, DMSO): 8.57 (s, 1H), 7.56 (d, 1H), 7.38-7.30 (m, 2H), 7.20-7.12 (m, 1H), 6.95-6.91 (m, 1H), 6.70-6.66 (m, 1H), 6.21-6.17 (m, 2H), 6.14-6.10 (m, 1H), 5.94 (s, 1H), 5.49-5.44 (m, 1H), 4.14-4.10 (m, 1H), 3.98-3.93 (m, 2H), 3.78-3.75 (m, 1H), 3.65 (s, 3H), 3.21 (d, 2H); MS (EI) for $C_{24}H_{21}F_3IN_3O_3$: 584 (MH^+).

EXAMPLE 3(ab). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[4-(methyloxy)phenyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400 MHz, DMSO): 8.56 (s, 1H), 7.58 (d, 1H), 7.39-7.30 (d, 2H), 7.20-7.13 (m, 1H), 6.71-6.66 (m, 3H), 6.55 (d, 2H), 5.93

(s, 1H), 5.00-4.95 (m, 1H), 4.14-4.08 (m, 1H), 3.98-3.92 (m, 2H), 3.79-3.74 (m, 1H), 3.63 (s, 3H), 3.13 (d, 2H); MS (EI) for $C_{24}H_{21}F_3IN_3O_3$: 584 (MH^+).

EXAMPLE 3(ac). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(ethyloxy)ethyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.36-7.33 (d, 1H), 7.31-7.26 (m, 1H), 7.08-7.00 (q, 1H), 6.65-6.58 (t, 1H), 4.24-4.16 (d, 1H), 4.08-3.98 (t, 2H), 3.92-3.85 (d, 1H), 3.60-3.55 (t, 2H), 3.54-3.47 (q, 2H), 3.01-2.96 (s, 2H), 2.94-2.89 (t, 2H), 1.20-1.15 (t, 3H); MS (EI) for $C_{21}H_{23}F_3IN_3O_3$: 550 (MH^+).

EXAMPLE 3(ad). 3-({[2,2-bis(methyloxy)ethyl]amino}methyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.37-7.32 (d, 1H), 7.30-7.24 (m, 1H), 7.08-7.00 (q, 1H), 6.65-6.57 (t, 1H), 4.48-4.42 (t, 1H), 4.20-4.11 (d, 1H), 4.02-3.93 (t, 2H), 3.86-3.80 (d, 1H), 3.38-3.34 (s, 6H), 2.84-2.80 (s, 2H), 2.75-2.70 (d, 2H),1.93-1.87 (s, 3H); MS (EI) for $C_{21}H_{23}F_3IN_3O_4$: 566 (MH^+).

EXAMPLE 3(ae). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(3-hydroxypropyl)amino]methyl}azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.38-7.33 (d, 1H), 7.32-7.26 (m, 1H), 7.09-7.00 (q, 1H), 6.66-6.58 (t, 1H), 4.31-4.23 (d, 1H), 4.16-4.05 (t, 2H), 3.99-3.89 (d, 1H), 3.70-3.64 (t, 2H), 3.26-3.22 (s, 2H), 3.11-3.04 (t, 2H), 1.93-1.89 (s, 3H), 1.89-1.82 (t, 3H); MS (EI) for $C_{20}H_{21}F_3IN_3O_3$: 536 (MH^+).

EXAMPLE 3(af). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-pyridin-4-ylethyl)amino]methyl}azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 8.36-8.32 (d, 2H), 7.38-7.33 (d, 1H), 7.26-7.14 (m, 3H), 7.00-6.91 (q, 1H), 4.12-4.04 (d, 1H), 3.96-3.88 (t, 2H), 3.80-3.73 (d, 2H), 2.92-2.74 (m, 6H), 1.87-1.84 (s, 3H); MS (EI) for $C_{24}H_{22}F_3IN_4O_2$: 583 (MH^+).

EXAMPLE 3(ag). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[1-(phenylmethyl)pyrrolidin-3-yl]amino}methyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.47-7.24 (m, 8H), 7.08-7.00 (q, 1H), 6.64-6.57 (t, 1H), 4.19-4.11 (d, 1H), 4.05-3.81 (m, 5H), 3.52-3.44 (m, 1H), 3.09-2.99 (m, 2H), 2.91-2.76 (m, 3H), 1.93-1.91 (s, 3H), 1.82-1.71 (m, 1H); MS (EI) for $C_{28}H_{28}F_3IN_4O_2$: 637 (MH^+).

EXAMPLE 3(ah). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(2-thienyl)ethyl]amino}methyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.47-7.42 (d, 1H), 7.36-7.31 (d, 1H), 7.30-7.24 (m, 1H), 7.21-7.17 (d, 1H), 7.08-7.00 (q, 1H), 6.93-6.89 (t, 1H), 6.86-6.83 (d, 1H), 6.64-6.57 (t, 1H), 4.18-4.11 (d, 1H), 4.01-3.93 (t, 2H),

3.85-3.78 (d, 1H), 3.04-2.97 (t, 2H), 2.92-2.87 (t, 2H), 2.82-2.78 (s, 2H), 1.92-1.87 (s, 3H); MS (EI) for $C_{23}H_{21}F_3IN_3O_2S$: 588 (MH^+).

EXAMPLE 3(ai). 3-[({2-[bis(1-methylethyl)amino]ethyl}amino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^1H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.36-7.33 (d, 1H), 7.31-7.26 (m, 1H), 7.08-7.00 (q, 1H), 6.65-6.58 (t, 1H), 4.18-4.13 (d, 1H), 4.06-3.98 (t, 2H), 3.88-3.82 (d, 2H), 3.57-3.47 (q, 2H), 3.05-2.99 (t, 2H), 2.92-2.85 (t, 4H), 1.92-1.88 (s, 3H), 1.28-1.22 (d, 12H); MS (EI) for $C_{25}H_{32}F_3IN_4O_2$: 605 (MH^+).

EXAMPLE 3(aj). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(phenyloxy)ethyl]amino}methyl)azetidin-3-ol acetate salt: ^1H NMR (400 MHz, CD_3OD): 7.36-7.31 (d, 1H), 7.26-7.22 (d, 1H), 7.20-7.13 (m, 3H), 6.97-6.89 (t, 1H), 6.86-6.80 (m, 3H), 6.54-6.47 (t, 1H), 4.13-4.07 (d, 1H), 4.01-3.96 (t, 2H), 3.79-3.74 (d, 1H), 2.97-2.91 (t, 2H), 2.84-2.79 (s, 2H), 1.84-1.81 (s, 3H); MS (EI) for $C_{25}H_{23}F_3IN_3O_3$: 598 (MH^+).

EXAMPLE 3(ak). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxypropyl)amino]methyl}azetidin-3-ol acetate salt: ^1H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.36-7.33 (d, 1H), 7.31-7.26 (m, 1H), 7.08-7.00 (q, 1H), 6.65-6.58 (t, 1H), 4.27-4.19 (d, 1H), 4.10-4.00 (m, 2H), 3.15-3.00 (t, 2H), 3.57-3.47 (q, 2H), 3.15-3.00 (t, 2H), 2.87-2.81 (d, 1H), 2.72-2.64 (t, 1H), 1.94-1.91 (s, 3H), 1.19-1.15 (d, 3H); MS (EI) for $C_{20}H_{21}F_3IN_3O_3$: 536 (MH^+).

EXAMPLE 3(am). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[({2-[(1-methylethyl)oxy]ethyl}amino)methyl]azetidin-3-ol acetate salt: ^1H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.36-7.33 (d, 1H), 7.31-7.26 (m, 1H), 7.08-7.00 (q, 1H), 6.65-6.58 (t, 1H), 4.21-4.13 (d, 1H), 4.04-3.95 (t, 2H), 3.88-3.82 (d, 1H), 3.64-3.51 (m, 3H), 2.89-2.84 (s, 2H), 2.83-2.77 (t, 2H), 1.91-1.89 (s, 3H), 1.15-1.12 (d, 6H); MS (EI) for $C_{22}H_{25}F_3IN_3O_3$: 564 (MH^+).

EXAMPLE 3(an). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1-ethylpiperidin-3-yl)amino]methyl}azetidin-3-ol acetate salt: ^1H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.36-7.33 (d, 1H), 7.31-7.26 (m, 1H), 7.08-7.00 (q, 1H), 6.65-6.58 (t, 1H), 4.17-4.10 (d, 1H), 4.04-3.95 (t, 2H), 3.88-3.82 (d, 1H), 3.24-3.06 (m, 2H), 2.95-2.75 (m, 6H), 2.76-2.46 (m, 2H), 1.93-1.90 (s, 3H), 1.74-1.62 (m, 1H), 1.44-1.31 (m, 1H), 1.28-1.20 (t, 3H); MS (EI) for $C_{24}H_{28}F_3IN_4O_2$: 589 (MH^+).

EXAMPLE 3(ao). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]amino}methyl)azetidin-3-ol acetate salt: ^1H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.36-7.33 (d, 1H), 7.31-7.26 (m, 1H), 7.08-7.00 (q,

1H), 6.65-6.58 (t, 1H), 4.20-4.13 (d, 1H), 4.00-3.90 (t, 2H), 3.83-3.75 (d, 1H), 2.84-2.78 (s, 2H), 2.53-2.48 (s, 2H), 1.93-1.87 (s, 3H); MS (EI) for $C_{21}H_{19}F_3IN_5O_3$: 574 (MH^+).

EXAMPLE 3(ap). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1-methylbutyl)amino]methyl}azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.38-7.33 (d, 1H), 7.32-7.27 (m, 1H), 7.09-7.01 (q, 1H), 6.65-6.58 (t, 1H), 4.25-4.19 (d, 1H), 4.12-4.02 (t, 2H), 3.96-3.90 (d, 1H), 3.16-2.96 (m, 3H), 1.91-1.89 (s, 3H), 1.68-1.57 (m, 1H), 1.49-1.29 (m, 3H), 1.23-1.18 (d, 3H), 0.99-0.92 (t, 3H); MS (EI) for $C_{22}H_{25}F_3IN_3O_2$: 548 (MH^+).

EXAMPLE 3(aq). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1-methylpropyl)amino]methyl}azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.37-7.33 (d, 1H), 7.32-7.26 (m, 1H), 7.09-7.01 (q, 1H), 6.65-6.58 (t, 1H), 4.27-4.20 (d, 1H), 4.14-4.03 (t, 2H), 3.98-3.92 (d, 1H), 3.20-3.16 (s, 2H), 3.07-2.97 (m, 1H), 1.91-1.89 (s, 3H), 1.80-1.70 (m, 1H), 1.54-1.41 (m, 1H), 1.26-1.22 (d, 3H), 1.00-0.94 (t, 3H); MS (EI) for $C_{21}H_{23}F_3IN_3O_2$: 534 (MH^+).

EXAMPLE 3(ar). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-methylbutyl)amino]methyl}azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.37-7.33 (d, 1H), 7.32-7.26 (m, 1H), 7.09-7.01 (q, 1H), 6.65-6.58 (t, 1H), 4.26-4.19 (d, 1H), 4.10-4.01 (t, 2H), 3.94-3.87 (d, 1H), 3.05-2.99 (s, 2H), 2.77-2.70 (m, 1H), 2.61-2.54 (m, 1H), 1.91-1.89 (s, 3H), 1.73-1.61 (m, 1H), 1.49-1.39 (m, 1H), 1.24-1.12 (m, 1H), 0.94-0.84 (m, 6H); MS (EI) for $C_{22}H_{25}F_3IN_3O2$: 548 (MH^+).

EXAMPLE 3(as). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(pentylamino)methyl]azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.37-7.33 (d, 1H), 7.32-7.26 (m, 1H), 7.09-7.01 (q, 1H), 6.65-6.58 (t, 1H), 4.29-4.23 (d, 1H), 4.15-4.05 (t, 2H), 3.98-3.90 (d, 1H), 3.21-3.18 (s, 2H), 2.93-2.86 (m, 2H), 1.91-1.89 (s, 3H), 1.70-1.60 (m, 2H), 1.42-1.29 (m, 4H), 0.97-0.90 (t, 3H); MS (EI) for $C_{22}H_{25}F_3IN_3O_2$: 548 (MH^+).

EXAMPLE 3(at). 3-[(cyclohexylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.38-7.34 (d, 1H), 7.33-7.27 (m, 1H), 7.09-7.01 (q, 1H), 6.65-6.58 (t, 1H), 4.25-4.19 (d, 1H), 4.14-4.03 (t, 2H), 3.98-3.90 (d, 1H), 3.21-3.18 (s, 2H), 2.93-2.86 (m, 1H), 2.07-2.00 (d, 2H), 1.92-1.90 (s, 3H), 1.89-1.82 (d, 2H), 1.73-1.66 (d, 1H), 1.42-1.14 (m, 5H); MS (EI) for $C_{23}H_{25}F_3IN_3O_2$: 560 (MH^+).

EXAMPLE 3(au). 3-[(azepan-3-ylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD):

7.48-7.43 (d, 1H), 7.37-7.33 (d, 1H), 7.32-7.26 (m, 1H), 7.09-7.01 (q, 1H), 6.65-6.58 (t, 1H), 4.19-4.13 (d, 1H), 4.05-3.95 (t, 2H), 3.90-3.81 (d, 1H), 3.37-3.34 (s, 2H), 3.22-3.03 (m, 2H), 2.91-2.64 (m, 3H), 1.93-1.89 (s, 3H), 1.88-1.52 (m, 6H); MS (EI) for $C_{23}H_{26}F_3IN_4O_2$: 575 (MH^+).

EXAMPLE 3(av). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(2,3-dihydro-1*H*-indol-3-yl)ethyl]amino}methyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.58-7.54 (d, 1H), 7.48-7.43 (d, 1H), 7.36-7.33 (d, 1H), 7.31-7.26 (m, 1H), 7.14-6.99 (m, 4H), 6.65-6.58 (t, 1H), 4.25-4.19 (d, 1H), 4.10-4.02 (t, 2H), 3.95-3.88 (d, 1H), 3.23-3.03 (m, 9H), 1.94-1.92 (s, 3H); MS (EI) for $C_{27}H_{26}F_3IN_4O_2$: 623 (MH^+).

EXAMPLE 3(aw). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(1,3,5-triazin-2-ylamino)methyl]azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 8.48-8.46 (s, 1H), 8.36-8.34 (s, 1H), 7.48-7.43 (d, 1H), 7.37-7.33 (d, 1H), 7.28-7.22 (m, 1H), 7.06-6.98 (q, 1H), 6.65-6.58 (t, 1H), 4.24-4.18 (d, 1H), 4.10-3.96 (t, 2H), 3.84-3.78 (d, 1H), 3.69-3.67 (s, 2H), 1.99-1.97 (s, 3H); MS (EI) for $C_{20}H_{16}F_3IN_6O_2$: 557 (MH^+).

EXAMPLE 3(ax). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(4-hydroxycyclohexyl)amino]methyl}azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.37-7.33 (d, 1H), 7.32-7.26 (m, 1H), 7.09-7.01 (q, 1H), 6.65-6.58 (t, 1H), 4.22-4.15 (d, 1H), 4.08-3.99 (t, 2H), 3.93-3.87 (d, 1H), 3.56-3.47 (m, 1H), 3.05-3.02 (s, 2H), 2.76-2.68 (m, 1H), 2.03-1.96 (m, 4H), 1.93-1.89 (s, 3H), 1.35-1.23 (m, 4H); MS (EI) for $C_{23}H_{25}F_3IN_3O_3$: 576 (MH^+).

EXAMPLE 3(ay). 3-[(cyclopent-3-en-1-ylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.37-7.33 (d, 1H), 7.32-7.26 (m, 1H), 7.09-7.01 (q, 1H), 6.65-6.58 (t, 1H), 5.70-5.65 (s, 2H), 4.20-4.14 (d, 1H), 4.03-3.95 (t, 2H), 3.90-3.81 (d, 1H), 3.58-3.50 (m, 1H), 2.90-2.86 (s, 2H), 2.68-2.58 (m, 2H), 2.26-2.16 (m, 2H), 1.93-1.89 (s, 3H); MS (EI) for $C_{22}H_{21}F_3IN_3O_2$: 544 (MH^+).

EXAMPLE 3(az). *N*-[4-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)phenyl]acetamide acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.37-7.33 (d, 1H), 7.27-7.20 (m, 3H), 7.09-7.01 (q, 1H), 6.65-6.55 (m, 3H), 4.22-4.16 (d, 1H), 4.08-3.98 (t, 2H), 3.88-3.82 (d, 1H), 3.28-3.24 (s, 2H), 2.08-2.05 (s, 3H), 2.91-2.64 (m, 3H), 1.93-1.89 (s, 3H); MS (EI) for $C_{25}H_{22}F_3IN_4O_3$: 611 (MH^+).

EXAMPLE 3(ba). *N*-[3-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-

yl]methyl}amino)phenyl]acetamide acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.36-7.33 (d, 1H), 7.27-7.20 (m, 1H), 7.04-6.96 (m, 3H), 6.72-6.68 (d, 1H), 6.65-6.58 (t, 1H), 6.40-6.35 (d, 1H), 4.24-4.18 (d, 1H), 4.08-3.98 (t, 2H), 3.87-3.81 (d, 1H), 3.28-3.25 (s, 2H), 2.10-2.07 (s, 3H), 1.97-1.95 (s, 3H); MS (EI) for $C_{25}H_{22}F_3IN_4O_3$: 611 (MH^+).

EXAMPLE 3(bc). (1R,2S)-4-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)cyclopentane-1,2-diol acetate salt: ^{1}H NMR (400 MHz, DMSO): 8.58-8.54 (s, 1H), 7.61-7.53 (d, 1H), 7.39-7.28 (m, 2H), 7.21-7.13 (m, 1H), 6.71-6.63 (t, 1H), 5.58-5.64 (s, 1H), 5.63-5.58 (s, 1H), 4.06-4.01 (d, 1H), 3.90-3.84 (t, 2H), 3.72-3.66 (d, 1H), 3.31-3.26 (m, 3H), 2.61-2.57 (s, 2H), 2.46-2.36 (m, 2H), 2.02-1.93 (dd, 2H), 1.91-1.88 (s, 3H); MS (EI) for $C_{22}H_{23}F_3IN_3O_4$: 578 (MH^+).

EXAMPLE 3(bd). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[1-(hydroxymethyl)cyclohexyl]amino}methyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.37-7.33 (d, 1H), 7.32-7.26 (m, 1H), 7.09-7.01 (q, 1H), 6.65-6.58 (t, 1H), 4.22-4.15 (d, 1H), 4.08-3.99 (t, 2H), 3.89-3.83 (d, 1H), 3.49-3.45 (s, 2H), 2.86-2.80 (s, 2H), 1.91-1.89 (s, 3H), 1.67-1.34 (m, 10H); MS (EI) for $C_{24}H_{27}F_3IN_3O_3$: 590 (MH^+).

EXAMPLE 3(be). 3-{[(3-chlorophenyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.37-7.33 (d, 1H), 7.32-7.26 (m, 1H), 7.08-6.98 (m, 2H), 6.65-6.55 (m, 3H), 6.53-6.44 (d, 1H), 4.22-4.15 (d, 1H), 4.06-3.98 (t, 2H), 3.88-3.82 (d, 1H), 3.27-3.24 (s, 2H), 1.91-1.89 (s, 3H); MS (EI) for $C_{23}H_{18}ClF_3IN_3O_2$: 588 (MH^+).

EXAMPLE 3(bf). 3-{[(4-chlorophenyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.45-7.40 (d, 1H), 7.35-7.30 (d, 1H), 7.28-7.22 (m, 1H), 7.06-6.97 (m, 3H), 6.62-6.54 (m, 3H), 6.53-6.44 (d, 1H), 4.22-4.15 (d, 1H), 4.06-3.98 (t, 2H), 3.88-3.82 (d, 1H), 3.26-3.22 (s, 2H), 1.96-1.94 (s, 3H); MS (EI) for $C_{23}H_{18}ClF_3IN_3O_2$: 588 (MH^+).

EXAMPLE 3(bg). 3-[(5-amino-3-methyl-1*H*-pyrazol-1-yl)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.38-7.33 (d, 1H), 7.28-7.24 (d, 1H), 7.21-7.15 (m, 1H), 6.98-6.90 (q, 1H), 6.56-6.49 (t, 1H), 5.16-5.14 (s, 1H), 4.36-4.30 (d, 1H), 4.22-4.16 (d, 1H), 3.99-3.97 (s, 1H), 3.95-3.90 (d, 1H), 3.77-3.71 (d, 1H), 1.96-1.92 (s, 3H), 1.85-1.82 (s, 3H); MS (EI) for $C_{21}H_{19}F_3IN_5O_2$: 558 (MH^+).

EXAMPLE 3(bh). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(5-methyl-1*H*-pyrazol-3-yl)amino]methyl}azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.38-7.33 (d, 1H), 7.28-7.24 (d, 1H), 7.21-7.15 (m, 1H), 6.98-6.90 (q, 1H), 6.56-6.49 (t, 1H), 5.22-5.19 (s, 1H), 4.15-4.08 (d, 1H), 4.02-3.88 (m, 2H), 3.75-3.68 (d, 1H), 3.20-3.18 (s, 2H), 2.07-2.05 (s, 3H), 1.85-1.82 (s, 3H); MS (EI) for $C_{21}H_{19}F_3IN_5O_2$: 558 (MH^+).

EXAMPLE 3(bi). 3-[(diethylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8.54 (s, 1H), 7.58-7.55 (dd, 1H), 7.38-7.35 (dt, 1H), 7.33-7.31 (m, 1H), 7.22-7.15 (m, 1H), 6.69-6.64 (m, 1H), 5.56 (b, 1H), 4.06-4.04 (d, 1H), 3.90-3.88 (m, 2H), 3.72-3.69 (d 1H), 2.51-2.49 (m, 6H), 0.86-0.83 (t, 6H); MS (EI) for $C_{21}H_{23}F_3IN_3O_2$: 534 (MH^+).

EXAMPLE 3(bj). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(dimethylamino)methyl]azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO):
8.56 (s, 1H), 7.59-7.56 (dd, 1H), 7.38-7.36 (dt, 1H), 7.34-7.33 (m, 1H), 7.21-7.14 (m, 1H), 6.71-6.65 (m, 1H), 5.55 (b, 1H), 4.07-4.05 (d, 1H), 3.89-3.84 (t, 2H), 3.74-3.719 (d, 1H), 2.46 (m, 2H), 2.19 (br s, 6H); MS (EI) for $C_{19}H_{19}F_3IN_3O_2$: 506 (MH^+).

EXAMPLE 3(bk). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxy-1,1-dimethylethyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8.40 (s, 1H), 7.38 (dd, 1H), 7.33-7.30 (m, 1H), 7.12 (m, 1H), 6.85-6.79 (m, 1H), 6.63-6.57 (m, 1H), 4.22-4.11(br m, 4H), 3.55 (s, 2H), 3.15 (s, 2H), 1.32 (s, 6H); MS (EI) for $C_{21}H_{23}F_3IN_3O_3$: 550 (MH^+).

EXAMPLE 3(bm). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(prop-2-en-1-ylamino)methyl]azetidin-3-ol): ^{1}H NMR (400MHz, $CDCl_3$): 8.47 (s, 1H), 7.40 (dd, 1H), 7.34-7.31 (m, 1H), 7.12 (m, 1H), 6.83-6.77 (m, 1H), 6.64-6.59 (m, 1H), 6.64-6.59 (m, 1H), 5.88-5.78 (m, 1H), 5.00-5.12 (m, 2H), 4.13 (br m, 4H), 3.26 (d, 2H), 2.88 (d, 2H), 2.02 (s, 1H); MS (EI) for $C_{21}H_{19}F_3IN_3O_2$: 518 (MH^+).

EXAMPLE 3(bn). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(tetrahydro-2H-pyran-4-yl)ethyl]amino}methyl)azetidin-3-ol): ^{1}H NMR (400MHz, $CDCl_3$): 8.45 (s, 1H), 7.39 (dd, 1H), 7.34-7.31 (m, 1H), 7.14-7.10 (m, 1H), 6.84-6.77 (m, 1H), 6.63-6.58 (m, 1H), 4.26-4.04 (m, 4H), 3.95 (dd, 2H), 3.35 (t, 2H), 2.92 (d, 2H), 2.67 (m, 2H), 1.40-1.25 (m, 8H); MS (EI) for $C_{24}H_{27}F_3IN_3O_3$: 590 (MH^+).

EXAMPLE 3(bo). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1,1-dimethylprop-2-yn-1-yl)amino]methyl}azetidin-3-ol): ^{1}H NMR (400MHz, $CDCl_3$): 8.46 (s, 1H), 7.39 (dd, 1H), 7.33-7.30 (m, 1H), 7.15-7.11 (m, 1H), 6.84-6.77 (m, 1H), 6.64-

6.58 (m, 1H), 4.20 (br, 1H), 4.07 (br, 1H), 2.92 (s, 2H), 1.58 (m, 4H), 0.92 (dd, 6h); MS (EI) for $C_{22}H_{21}F_3IN_3O_2$: 572 (MH^+).

EXAMPLE 3(bp). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(1*H*-imidazol-4-yl)ethyl]amino}methyl)azetidin-3-ol): ^{1}H NMR (400MHz, $CDCl_3$): 8.44 (s, 1H), 7.33-7.14 (m, 3H), 7.00 (m, 1H), 6.67 (dd, 1H), 6.59 (s, 1H), 6.44 (m, 1H), 3.93 (d, 2H), 2.75 (m, 2H), 2.60 (m, 1H), 2.42 (m, 1H) 2.02 (AcOH; s, 3H), 1.86 (m, 4H); MS (EI) for $C_{22}H_{21}F_3IN_5O_2$: 572 (MH^+).

EXAMPLE 3(bq). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[3-(ethyloxy)propyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8.49 (s, 1H), 7.39 (dd, 1H), 7.34-7.31 (m, 1H), 7.14-7.10 (m, 1H), 6.83-6.76 (m, 1H), 6.64-6.58 (m, 1H), 4.26-4.03 (br m, 4H), 3.53-3.44 (m, 4H), 2.92-2.73 (m, 4H), 1.72 (m, 2H) 1.18 (t, 3H); MS (EI) for $C_{22}H_{23}F_3IN_3O_3$: 564 (MH^+).

EXAMPLE 3(br). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(3,3-dimethylbutyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8.46 (s, 1H), 7.39 (dd, 1H), 7.34-7.31 (m, 1H), 7.14-7.10 (m, 1H), 6.84-6.77 (m, 1H), 6.63-6.58 (m, 1H), 4.18 (br, 3H), 3.15 (s, 2H), 2.71 (m, 2H) 2.05 (AcOH; s, 3H), 1.43 (m, 2H), 0.90 (s, 9H); MS (EI) for $C_{23}H_{27}F_3IN_3O_2$: 562 (MH^+).

EXAMPLE 3(bs). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(3-methylbutyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8.46 (s, 1H), 7.39 (dd, 1H), 7.34-7.30 (m, 1H), 7.14-7.11 (m, 1H), 6.84-6.77 (m, 1H), 6.63-6.59 (m, 1H), 4.27-3.61 (br m, 6H), 2.98 (m, 2H), 2.72 (t, 2H) 2.05 (AcOH; s, 3H), 1.61 (m,1H), 1.43 (m, 2H), 0.90 (d, 6H); MS (EI) for $C_{22}H_{25}F_3IN_3O_2$: 547 (MH^+).

EXAMPLE 3(bt). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[3-(dimethylamino)propyl]amino}methyl)azetidin-3-ol: MS (EI) for $C_{22}H_{26}F_3IN_4O_2$: 563 (MH^+).

EXAMPLE 3(bu). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[3-(1*H*-imidazol-1-yl)propyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8.46 (s, 1H), 7.53 (s, 1H), 7.40 (dd, 1H), 7.34-7.30 (m, 1H), 7.14-7.09 (m, 1H), 7.05 (s, 1H), 6.89 (s, 1H), 6.84-6.77 (m, 1H), 6.63-6.59 (m, 1H), 4.24-4.00 (br m, 6H), 2.84 (m, 2H), 2.61 (m, 2H), 1.94 (m, 2H); MS (EI) for $C_{23}H_{21}F_3IN_5O_2$: 586 (MH^+).

EXAMPLE 3(bv). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(methylthio)ethyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$):

8.49 (s, 1H), 7.39 (dd, 1H), 7.34-7.31 (m, 1H), 7.14-7.11 (m, 1H), 6.83-6.77 (m, 1H), 6.63-6.59 (m, 1H), 4.26-4.03 (br m, 4H), 2.88 (s, 2H), 2.82 (t, 2H), 2.62 (t, 2H), 2.08 (s, 3H); MS (EI) for $C_{23}H_{21}F_3IN_3O_2S$: 552 (MH^+).

EXAMPLE 3(bw). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1,1,3,3-tetramethylbutyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8.49 (s, 1H), 7.38 (dd, 1H), 7.34-7.30 (m, 1H), 7.14-7.11 (m, 1H), 6.83-6.77 (m, 1H), 6.64-6.59 (m, 1H), 4.25-4.01 (br m, 4H), 2.82 (s, 2H), 1.45 (s, 2H), 1.15 (s, 6H), 0.90 (s, 9H); MS (EI) for $C_{25}H_{31}F_3IN_3O_2$: 590 (MH^+).

EXAMPLE 3(bx). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1,1-dimethylpropyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8.50 (s, 1H), 7.39 (dd, 1H), 7.35-7.30 (m, 1H), 7.15-7.11 (m, 1H), 6.83-6.77 (m, 1H), 6.65-6.59 (m, 1H), 4.27-4.01 (br m, 4H), 2.82 (s, 2H), 1.46 (s, 2H), 1.08 (s, 6H), 0.89 (s, 3H); MS (EI) for $C_{22}H_{21}F_3IN_4O_3$: 548 (MH^+).

EXAMPLE 3(by). 3-{[(3-amino-2-hydroxypropyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: MS (EI) for $C_{23}H_{22}F_3IN_4O_3$: 551 (MH^+).

EXAMPLE 3(bz). 1-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}pyrrolidin-3-ol: MS (EI) for $C_{21}H_{21}F_3IN_3O_3$: 548 (MH^+).

EXAMPLE 3(ca). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({(2S)-2-[(methyloxy)methyl]pyrrolidin-1-yl}methyl)azetidin-3-ol: MS (EI) for $C_{23}H_{25}F_3IN_3O_3$: 576 (MH^+).

EXAMPLE 3(cb). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxyphenyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8.46 (s, 1H), 7.41 (dd, 1H), 7.35-7.30 (m, 1H), 7.15-7.11 (m, 1H), 6.89-5.98 (m, 6H), 4.92 (s, 1H), 4.28-4.05 (br m, 4H), 3.44 (s, 2H); MS (EI) for $C_{23}H_{19}F_3IN_3O_3$: 570 (MH^+).

EXAMPLE 3(cd). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(4-hydroxyphenyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8.46 (s, 1H), 7.78 (s, 1H), 7.40-7.05 (m, 4H), 6.72 (m, 1H), 6.62 (d, 1H), 6.50 (m, 1H), 6.42 (d, 1H) 4.04-3.98 (m, 4H), 3.18 (s, 2H); MS (EI) for $C_{23}H_{19}F_3IN_3O_3$: 570 (MH^+).

EXAMPLE 3(ce). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(3-hydroxyphenyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8.52 (s, 1H), 8.22 (s, 1H), 7.39 (dd, 1H), 7.34-7.31 (m, 1H), 7.14-7.11 (m, 1H), 6.85 (dd, 1H), 6.84-6.77 (m, 1H), 6.63-6.59 (m, 1H), 6.15 (d, 1H) 6.09-6.01 (m, 3H), 4.16-3.95 (br m, 4H), 3.22 (d, 2H) 2.15 (AcOH; s, 3H); MS (EI) for $C_{23}H_{19}F_3IN_3O_3$: 570 (MH^+).

EXAMPLE 3(cf). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(phenyloxy)methyl]azetidin-3-ol: MS (EI) for $C_{23}H_{18}F_3IN_2O_3$: 555 (MH^+).

EXAMPLE 3(cg). 3-({[1-({3, 4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)propane-1,2-diol: MS (EI) for $C_{20}H_{21}F_3IN_3O_4$: 552 (MH^+).

EXAMPLE 3(ch). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(phenylthio)methyl]azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$):
8.46 (s, 1H), 7.45-7.23 (m, 5H), 7.14-7.05 (m, 1H), 6.78 (dd, 1H), 6.60 (m, 1H), 4.14-3.92 (br m, 4H), 3.33 (s, 2H); MS (EI) for $C_{23}H_{18}F_3IN_2O_2$: 571 (MH^+).

EXAMPLE 3(ci). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(4-hydroxybutyl)amino]methyl}azetidin-3-ol): ^{1}H NMR (400MHz, $CDCl_3$): 8.43 (s, 1H), 7.38 (dd, 1H), 7.34-7.30 (m, 1H), 7.14-7.10 (m, 1H), 6.84-6.77 (m, 1H), 6.63-6.58 (m, 1H), 4.26-4.04 (m, 4H), 3.61 (m, 2H), 2.96 (s, 2H), 2.73 (s, 2H); MS (EI) for $C_{21}H_{23}F_3IN_3O_3$: 550 (MH^+).

EXAMPLE 3(cj). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxyethyl)oxy]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$):
8.51 (s, 1H), 7.39 (dd, 1H), 7.35-7.31 (m, 1H), 7.14-7.11 (m, 1H), 6.84-6.77 (m, 1H), 6.63-6.59 (m, 1H), 4.21-4.05 (br m, 4H), 3.77 (m, 2H), 3.66 (m, 2H); MS (EI) for $C_{19}H_{18}F_3IN_2O_4$: 523 (MH^+).

EXAMPLE 3(ck). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(1S,2S)-2-hydroxycyclohexyl]amino}methyl)azetidin-3-ol): MS (EI) for $C_{23}H_{25}F_3IN_3O_3$: 576 (MH^+).

EXAMPLE 3(cm). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1,1-dimethyl-2-pyrrolidin-1-ylethyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$):
8.49 (s, 1H), 7.39 (dd, 1H), 7.34-7.29 (m, 1H), 7.14-7.11 (m, 1H), 6.83-6.77 (m, 1H), 6.64-6.59 (m, 1H), 4.25-4.07 (br m, 4H), 2.88 (d, 2H), 2.62 (m, 4H), 2.58 (m, 2H), 1.78 (m, 4H), 2.05 (AcOH; s, 3H); MS (EI) for $C_{25}H_{30}F_3IN_4O_2$: 603 (MH^+).

EXAMPLE 3(cn). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(1-methyl-1*H*-imidazol-4-yl)methyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8.50 (s, 1H), 7.41-7.11 (m, 3H), 7.12 (m, 1H), 6.85-6.79 (m, 2H), 4.12-3.98 (br m, 4H), 3.78 (s, 2H), 3.66 (s, 3H), 2.95 (s, 2H), 2.08 (AcOH; s, 4H) ,2.05 (AcOH; s, 3H); MS (EI) for $C_{22}H_{21}F_3IN_5O_2$: 572 (MH^+).

EXAMPLE 3(co). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(1-methyl-1*H*-imidazol-5-yl)methyl]amino}methyl)azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8.45 (s, 1H), 7.47 (s, 1H), 7.39 (dd, 1H), 7.33-7.30 (m, 1H), 7.15-7.10 (m, 1H), 6.91 (s, 1H), 6.87-6.77 (m, 1H), 6.63-6.58 (m, 1H), 4.18-4.02 (m, 4H), 3.3.80 (s, 2H), 3.62 (s, 3H), 2.90 (s, 1H), 2.05 (AcOH; s, 3H); MS (EI) for $C_{22}H_{21}F_3IN_5O_2$: 572 (MH^+).

EXAMPLE 3(cp). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(2S)-2-(methyloxy)cyclopentyl]amino}methyl)azetidin-3-ol): MS (EI) for $C_{23}H_{25}F_3IN_3O_3$: 576 (MH^+).

EXAMPLE 3(cq). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(1R)-2-hydroxycyclohexyl]amino}methyl)azetidin-3-ol): MS (EI) for $C_{23}H_{25}F_3IN_3O_3$: 576 (MH^+).

EXAMPLE 3(cr). *N*-[3-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)phenyl]methanesulfonamide: ^{1}H NMR (400MHz, $CDCl_3$): 7.33 (dd, 1H), 7.22 (m, 1H), 7.08 (dd, 1H), 6.83-6.77 (m, 1H), 6.03-5.98 (m, 2H), 6.64-6.59 (m, 1H), 4.08-3.77 (br m, 5H), 2.88 (s, 3H); MS (EI) for $C_{24}H_{22}F_3IN_4O_4S$: 647 (MH^+).

EXAMPLE 3(cs). 3-{[(4-aminophenyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8.44 (s, 1H), 7.39 (dd, 1H), 7.34-7.30 (m, 1H), 7.14-7.10 (m, 1H), 6.84-6.77 (m, 1H), 6.64-6.53 (m, 5H), 4.22-4.04 (br m, 4H), 3.34 (s, 2H); MS (EI) for $C_{23}H_{20}F_3IN_4O_2$: 569 (MH^+).

EXAMPLE 3(ct). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxy-2-methylcyclopentyl)amino]methyl}azetidin-3-ol: MS (EI) for $C_{23}H_{25}F_3IN_3O_3$: 576 (MH^+).

EXAMPLE 3(cu). 3-[(cyclopentylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7.44 (dd, 1H), 7.36-7.31 (m, 1H), 7.30-7.24 (m, 1H), 7.09-6.99 (m, 1H), 6.64-6.57 (m, 1H), 4.17-4.10 (m,1H), 4.01-3.91 (m, 2H), 3.87-3.79 (m, 1H), 3.07-2.97 (m, 1H), 2.75 (s, 2H), 1.92-1.79 (m, 2H), 1.75-1.62 (m, 2H), 1.61-1.47 (m, 2H), 1.37-1.22 (m, 2H). MS (EI) for $C_{22}H_{23}F_3IN_3O_2$: 546 (MH^+)

EXAMPLE 3(cv). 3-{[(cyclohexylmethyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate (salt): ^{1}H NMR (400 MHz, CD_3OD): 7.46 (dd, 1H), 7.39-7.32 (m, 1H), 7.31-7.25 (m, 1H), 7.11-6.99 (m, 1H), 6.67-6.57 (m, 1H), 4.27-4.15 (m, 1H), 4.12-3.97 (m, 2H), 3.96-3.85 (m, 1H), 3 (s,2H), 2.62 (d, 2H),

1.90 (s, 3H), 1.82-1.45 (m, 6H), 1.40-1.07 (m, 3H), 1.04-0.80 (m, 2H). MS (EI) for $C_{24}H_{27}F_3IN_3O_2$: 574 (MH^+).

EXAMPLE 3(cw). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(propylamino)methyl]azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.56 (s, 1H), 7.57 (dd, 1H), 7.37 (dd, 1H), 7.32 (m, 1H), 7.18 (m, 1H), 6.67 (m, 1H), 4.03 (d, 1H), 3.89 (m, 2H), 3.69 (d, 1H), 2.59 (s, 2H), 2.42 (t, 2H), 1.90 (s, 3H), 1.32 (m, 2H), 0.81 (t, 3H); MS (EI) for $C_{20}H_{21}F_3IN_3O_2$: 520 (MH^+).

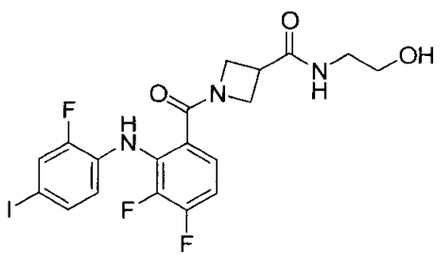
EXAMPLE 3(cx). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-methylpropyl)amino]methyl}azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.56 (s, 1H), 7.56 (dd, 1H), 7.36 (dd, 1H), 7.31 (m, 1H), 7.18 (m, 1H), 6.67 (m, 1H), 4.02 (d, 1H), 3.89 (m, 2H), 3.70 (d, 1H), 2.57 (s, 2H), 2.27 (d, 2H), 1.91 (s, 3H), 1.55 (m, 1H), 0.79 (d, 6H); MS (EI) for $C_{21}H_{23}F_3IN_3O_2$: 534 (MH^+).

EXAMPLE 3(cy). methyl (2xi)-2-deoxy-2-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)-beta-D-arabino-hexopyranoside: ^{1}H NMR (400 MHz, d_4-methanol, ~3:1 mixture of anomers): δ 7.46 (d, 1H), 7.34 (d, 1H), 7.28 (m, 1H), 7.04 (q, 1H), 6.62 (m, 1H), 4.19-5.92 (m, 4H), 3.87-3.78 (m, 2H), 3.68 (m, 1H), 3.56-3.18 (m, 5H), 2.99-2.82 (m, 3H), 2.56 (m, 0.25H), 2.29 (m, 0.75H) MS (EI) for $C_{24}H_{27}F_3IN_3O_7$: 652 (M-H).

EXAMPLE 3(cz). 3-({[3-(diethylamino)propyl]amino}methyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.38-7.33 (d, 1H), 7.32-7.26 (m, 1H), 7.09-7.00 (q, 1H), 6.66-6.58 (t, 1H), 4.24-4.16 (d, 1H), 4.11-3.99 (t, 2H), 3.92-3.85 (d, 1H), 3.10-3.02 (m, 8H), 2.99-2.96 (s, 2H), 2.92-2.87 (t, 2H), 1.93-1.87 (s, 3H), 1.27-1.20 (t, 6H); MS (EI) for $C_{24}H_{30}F_3IN_4O_2$: 591 (MH^+).

EXAMPLE 4

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(2-hydroxyethyl)azetidine-3-carboxamide



[00274] To a solution of 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidine-3-carboxylic acid (15 mg, 0.03 mmol), prepared using procedures similar to those in Example 1, in *N,N*-dimethylformamide (2.00 mL) was added HBTU (38 mg, 0.10 mmol). The mixture was stirred for 15 minutes at room temperature followed by the addition of 2-aminoethanol (3.6 µL, 0.06 mmol) and *N*-methylmorpholine (110 µL, 1.00 mmol). The mixture was allowed to stir at room temperature for 3 d, then diluted the mixture with chloroform (20 mL), and washed with water (30 mL). The aqueous phase was back extracted with chloroform (10 mL). The combined organic phases were dried over sodium sulfate, filtered and the filtrate concentrated *in vacuo*. The residue was purified by high pressure liquid chromatography to afford the title compound (9.20 mg, 58%) as the trifluoroacetic acid salt: ^{1}H NMR (400MHz, $CDCl_3$): 8.54 (s, 1H), 7.41-7.37 (m, 1H), 7.34-7.31 (m, 1H), 7.18-7.14 (m, 1H), 6.85-6.77 (m, 1H), 6.64-6.58 (m, 1H), 4.66 (br, 1H), 4.40-4.24 (br, 3H), 3.83-3.23 (br m, 7H), 1.18 (t, 3H); MS (EI) for $C_{19}H_{17}F_3IN_3O_3$: 542 (MNa^+).

[00275] Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, the following compounds of the invention were prepared:

EXAMPLE 4(a): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(3,4-dihydroxybutyl)azetidine-3-carboxamide: ^{1}H NMR (400 MHz, $CDCl_3$): 8.55 (s, 1H), 7.40 (dd, 1H), 7.31-7.35 (m, 1H), 7.14-7.18 (m, 1H), 6.78-6.84 (m, 1H), 6.59-6.65 (m, 1H), 6.14 (br s, 1H), 4.50-4.60 (m, 1H), 4.20-4.40 (m, 3H), 3.60-3.80 (m, 3H), 3.40-3.52 (m, 2H), 3.20-3.32 (m, 2H), 1.96 (br s, 1H), 1.18-1.28 (m, 2H). MS (EI) for $C_{21}H_{21}F_3IN_3O_4$: 562 (M-H).

EXAMPLE 4(b): *N*-butyl-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidine-3-carboxamide: ^{1}H NMR (400MHz, $CDCl_3$): 8.53 (s, 1H), 7.39 (dd, 1H), 7.33-7.31 (m, 1H), 7.17-7.13 (m, 1H), 6.83-6.77 (m, 1H), 6.64-6.58 (m, 1H), 5.50 (m, 1H), 4.57 (br, 1H), 4.29 (br m, 3H), 3.27 (m, 3H), 1.49 (m, 1H), 1.33 (m, 2H), 0.92 (t, 3H); MS (EI) for $C_{21}H_{21}F_3IN_3O_2$: 532 (MH^+), 554 (MNa^+).

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-prop-2-en-1-ylazetidine-3-carboxamide: ^{1}H NMR (400MHz, $CDCl_3$): 8.54 (s, 1H), 7.39 (dd, 1H), 7.34-7.31 (m, 1H), 7.17.7.12 (m, 1H), 6.83-6.77 (m, 1H), 6.64-6.58 (m, 1H), 5.88-5.77 (m, 1H), 5.57 (br, 1H), 5.21-5.16 (m, 2H), 4.59 (br, 1H), 4.30 (br m, 3H), 3.9 (tt, 2H), 3.32-3.25 (m, 1H)); MS (EI) for $C_{20}H_{17}F_3IN_3O_2$: 516 (MH^+), 538 (MNa^+).

EXAMPLE 4(c): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-ethylazetidine-3-carboxamide: ^{1}H NMR (400MHz, $CDCl_3$): 8.54 (s, 1H), 7.38 (dd, 1H),

7.33-7.30 (m, 1H),7.17-7.12 (m, 1H), 6.83-6.77 (m, 1H), 6.63-6.57 (m, 1H), 5.55 (br s, 1H), 4.57 (br s, 1H), 4.28 (br m, 1H), 3..36-3.29 (m, 2H), 3.27- 3..20 (m, 1H), 1.15 (t, 3H); MS (EI) for $C_{19}H_{17}F_3IN_3O_2$: 504 (MH^+), 526 (MNa^+).

EXAMPLE 4(d): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(2-hydroxyethyl)azetidine-3-carboxamide: ^{1}H NMR (400MHz, $CDCl_3$): 8.50 (s, 1H), 7.39 (dd, 1H), 7.33-7.30 (m, 1H),7.16-7.12 (m, 1H), 6.84-6.77 (m, 1H), 6.63-6.57 (m, 1H), 4.57 (br, 1H), 4.28 (br, 3H), 3.73 (t, 2H), 3.49-3.44 (m, 2H), 3.33-3.27 (m, 1H), 2.18 (br, 1H); MS (EI) for $C_{19}H_{17}F_3IN_3O_3$: 542 (MNa^+).

EXAMPLE 4(e): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(2-piperidin-1-ylethyl)azetidine-3-carboxamide: ^{1}H NMR (400MHz, $CDCl_3$): 11.28 (s, 1H), 8.55 (s, 1H), 7.38 (dd, 1H), 7.33-7.30 (m, 1H), 7.15-7.10 (m, 1H), 6.82-6.76 (m, 1H), 6.63-6.58 (m, 1H), 4.42 (b, 1H), 4.26 (br m, 3H), 3.68 (br s, 2H), 3.58 (br d, 2H), 3.36 (br m, 1H)3.17 (br s, 1H), 2.63 (m, 4H), 1.92 (m, 5 H); MS (EI) for $C_{24}H_{26}F_3IN_4O_2$: 587 (MH^+).

EXAMPLE 4(f): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-phenylazetidine-3-carboxamide: ^{1}H NMR (400MHz, $CDCl_3$): 8.52 (s, 1H), 7.50 (d, 1H), 7.41-7.27 (m, 4H), 7.16 (m, 2H), 6.85-6.78 (m, 1H), 6.65-6.59 (m, 1H), 4.37 (br, 3H), 3.43 (m, 1H); MS (EI) for $C_{23}H_{17}F_3IN_3O_2$: 574 (MNa^+).

EXAMPLE 4(g): *N*-[2-(diethylamino)ethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidine-3-carboxamide: ^{1}H NMR (400MHz, $CDCl_3$): 11.43 (s, 1H), 8.90 (s, 1H), 8.55 (s, 1H), 7.39 (dd, 1H), 7.33-7.30 (m, 1H), 7.15-7.10 (m, 1H), 6.87-6.77 (m, 1H), 6.63-6.58 (m, 1H), 4.44-4.22 (m, 4H), 3.65 (m, 2H), 3.38 (m, 1H), 3.19-3.13 (m, 5H), 1.33(t, 6H); MS (EI) for $C_{21}H_{21}F_3IN_3O_2$: 575 (MH^+).

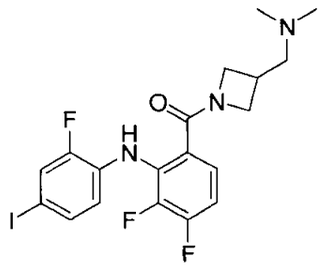
EXAMPLE 4(h): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-[(2,3-dihydroxypropyl)oxy]azetidine-3-carboxamide: MS (EI) for $C_{20}H_{19}F_3IN_3O_5$: 566 (MH^+).

EXAMPLE 4(i): 1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(2,3-dihydroxypropyl)azetidine-3-carboxamide: ^{1}H NMR (400 MHz, $CDCl_3$): 8.40 (br s, 1H), 7.35 (dd, 1H), 7.30 (br d, 1H), 7.16-7.09 (m, 1H), 6.89-6.76 (m, 2H), 6.58 (ddd, 1H), 4.58-4.40 (br, 1H), 4.27 (br t, 2H), 4.22-4.14 (br, 1H), 4.08-3.12 (m, 5H), 2.18-1.82 (br, 2H); MS (EI) for $C_{20}H_{19}F_3IN_3O_4$: 550 (MH^+).

EXAMPLE 4(j): 1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-hydroxyazetidine-3-carboxamide: ^{1}H NMR (400 MHz, $CDCl_3$): 8.23-8.10 (b, 1H), 7.35-7.28 (m, 2H), 7.14-7.07 (m, 1H), 6.86-6.80 (m, 1H), 6.60-6.54 (m, 1H), 4.52-4.38 (b, 1H), 4.32-4.08 (m, 3H), 3.30-3.21 (m, 1H); MS (EI) for $C_{17}H_{13}F_3IN_3O_3$: 492 (MH^+).

EXAMPLE 5

6-({3-[(dimethylamino)methyl]azetidin-1-yl}carbonyl)-2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)aniline



[00276] A mixture of 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidine-3-carboxylic acid (196 mg, 0.41 mmol), prepared using procedures similar to those in Example 1, triethylamine (58 μL, 0.41 mmol), PyBOP (213 mg, 0.41 mmol) and sodium borohydride (48 mg, 1.24 mmol) in tetrahydrofuran (2 mL) was stirred at room temperature for 15 hours. The reaction mixture was concentrated *in vacuo* and the resultant residue was partitioned between 20% aqueous citric acid and ethyl acetate. The organic portion was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a colorless residue that was purified by column chromatography. Eluting with 60% ethyl acetate in hexanes, isolated product was concentrated *in vacuo* to afford 48 mg, 0.11 mmol (25%) of [1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]methanol as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): 7.44 (d, 1H), 7.34 (d, 1H), 7.28-7.23 (m, 1H), 7.04-6.97 (m, 1H), 4.26-4.18 (m, 1H), 4.02-3.94 (m, 2H), 3.78-3.72 (m, 1H), 3.03 (d, 2H), 3.34 (s, 1H), 2.80-2.71 (m, 1H). MS (EI) for $C_{17}H_{14}F_3IN_2O$: 463 (MH^+).

[00277] A solution of 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]methanol (48 mg, 0.11 mmol), 1,4-diazabicyclo[2.2.2]octane (18 mg, 0.16 mmol) and methanesulfonyl chloride (10 μL, 0.13 mmol) in tetrahydrofuran (2 mL) was stirred at room temperature for 15 minutes. The mixture was then partitioned between water and ethyl acetate. The organic portion was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a colorless residue which was purified by column chromatography. Eluting with 70% ethyl acetate in hexanes, isolated product was concentrated *in vacuo* to afford 28 mg, 0.05 mmol (47%) of [1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]methyl methanesulfonate as a colorless residue which was immediately dissolved in

ethylene glycol dimethyl ether (2 mL). To the solution was added dimethylamine (excess) and the solution was stirred in a seal tube at 50 °C for 15 hours. The reaction mixture was concentrated *in vacuo*, and the resultant residue was purified by preparative reverse phase HPLC. Isolated product was concentrated *in vacuo* to afford 12 mg, 0.02 mmol (40%) of 6-({3-[dimethylamino)methyl]azetidin-1-yl}carbonyl)-2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)aniline acetate salt as a white solid. ^{1}H NMR (400 MHz, DMSO): 8.54 (br s, 1H), 7.58 (d, 1H), 7.37 (d, 1H), 7.33-7.28 (m, 1H), 7.18-7.12 (m, 1H), 6.70-6.64 (m, 1H), 4.18-4.12 (m, 1H), 3.99-3.76 (m, 1H), 3.52-3.47 (m, 1H), 2.52-2.48 (m, 1H), 2.39 (d, 2H), 1.85 (s, 6H); MS (EI) for $C_{19}H_{19}F_3IN_3O$: 490 (MH^+).

[00278] Using the same or analogous synthetic techniques and/or substituting with alternative reagents, the following compounds of the invention were prepared:

EXAMPLE 5(a): 2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)-6-[(3-{[(1-methylethyl)amino]methyl}azetidin-1-yl)carbonyl]aniline: ^{1}H NMR (400 MHz, $CDCl_3$): 8.54 (s, 1H), 7.40 (dd, 1H), 7.31-7.33 (m, 1H), 7.11-7.15 (m, 1H), 6.76-6.82 (m, 1H), 6.58-6.64 (m, 1H), 4.23-4.30 (m, 2H), 3.90-4.00 (m, 1H), 3.76-3.84 (m, 1H), 2.69-2.85 (m, 4H), 1.05 (d, 6H). MS (EI) for $C_{20}H_{21}F_3IN_3O$: 502 (M-H).

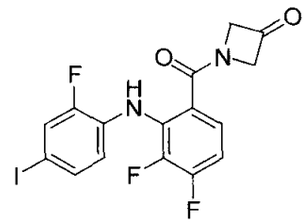
EXAMPLE 5(b): 2-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-2-yl]methyl}amino)ethanol: MS (EI) for $C_{19}H_{19}F_3IN_3O_2$: 506 (MH^+).

EXAMPLE 5(c): *N*-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-2-yl]methyl}ethane-1,2-diamine: MS (EI) for $C_{19}H_{20}F_3IN_4O$: 505 (MH^+).

EXAMPLE 5(d): 6-({3-[dimethylamino)methyl]azetidin-1-yl}carbonyl)-2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)aniline acetate salt: ^{1}H NMR (400 MHz, DMSO): 8.54 (br s, 1H), 7.58 (d, 1H), 7.37 (d, 1H), 7.33-7.28 (m, 1H), 7.18-7.12 (m, 1H), 6.70-6.64 (m, 1H), 4.18-4.12 (m, 1H), 3.99-3.76 (m, 1H), 3.52-3.47 (m, 1H), 2.52-2.48 (m, 1H), 2.39 (d, 2H), 1.85 (s, 6H); MS (EI) for $C_{19}H_{19}F_3IN_3O$: 490 (MH^+).

EXAMPLE 6

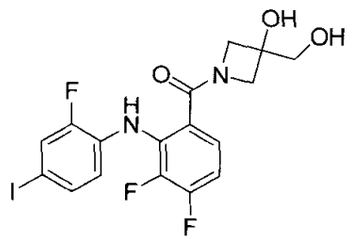
1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-one



[00279] 1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol (132 mg, 0.295 mmol)ures similar to those in Example 1, was dissolved in dichloromethane (8 mL) and cooled to 0 °C. Dess-Martin periodinane (187 mg, 0.441 mmol) was added and the mixture was stirred at ambient for 2 h. The mixture was quenched with saturated sodium bicarbonate solution: 10% sodium thiosulfate solution (1:1; 6 mL) and diluted with ethyl acetate. The organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, 40-50% ethyl acetate in hexanes) gave 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-one (122 mg, 0.273 mmol, 93% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 8.43 (br s, 1H), 7.44-7.38 (m, 1H), 7.36-7.32 (m, 1H), 7.27-7.20 (m, 1H), 6.86 (ddd, 1H), 6.64 (ddd, 1H), 4.94-4.93 (m, 4H); MS (EI) for $C_{16}H_{10}F_3IN_2O_2$: 447 (MH^+).

EXAMPLE 7

1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(hydroxymethyl)azetidin-3-ol



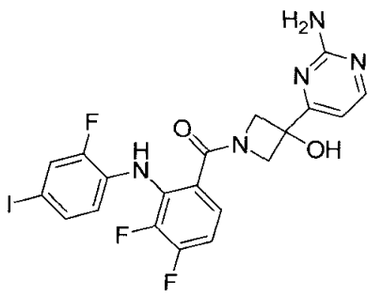
[00280] Methyl triphenylphosphonium bromide (508 mg, 1.42 mmol) was treated with potassium *tert*-butoxide (159 mg, 1.42mmol) in tetrahydrofuran (5 mL) at 0 °C for 10 minutes. 1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-one (270 mg, 0.605 mmol), prepared using procedures similar to those described in Example 6, was dissolved in tetrahydrofuran (2 mL) and was added to the mixture. The mixture was stirred at ambient for 15 h and then the mixture was filtered and the filtrate was partitioned

between ethyl acetate and water. The aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, 20% ethyl acetate in hexanes) gave 2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)-6-[(3-methylideneazetidin-1-yl)carbonyl]aniline (57 mg, 0.128 mmol, 21% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 8.56 (br s, 1H), 7.39 (dd, 1H), 7.35-7.30 (m, 1H), 7.18-7.12 (m, 1H), 6.86-6.76 (m, 1H), 6.62 (ddd, 1H), 5.14-5.00 (br, 2H), 4.74 (br d, 4H); MS (EI) for $C_{17}H_{12}F_3IN_2O$: 445 (MH^+).

[00281] 2,3-Difluoro-*N*-(2-fluoro-4-iodophenyl)-6-[(3-methylideneazetidin-1-yl)carbonyl]aniline (56 mg, 0.126 mmol) and 4-methylmorpholine *N*-oxide (44 mg, 0.376 mmol) were dissolved in acetone / water (4:1; 10 mL) and osmium tetroxide (4 wt.% in water; 0.7 mL) was added. The solution was stirred at ambient for 4 h, then was quenched with saturated sodium bisulfite (2 mL) and concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water. The organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, 80% ethyl acetate in hexanes) and then reverse phase HPLC gave 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(hydroxymethyl)azetidin-3-ol (17 mg, 0.036 mmol, 28% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 8.43 (br s, 1H), 7.40 (dd, 1H), 7.35-7.31 (m, 1H), 7.16-7.10 (m, 1H), 6.81 (ddd, 1H), 6.61 (ddd, 1H), 4.25-4.00 (m, 4H), 3.78 (s, 2H); MS (EI) for $C_{17}H_{14}F_3IN_2O_3$: 479 (MH^+).

EXAMPLE 8

3-(2-aminopyrimidin-4-yl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol



[00282] To a solution of 4-iodo-2-(methylthio)pyrimidine (2.00 g, 7.92 mmol) in tetrahydrofuran (4.00 ml) was added isopropylmagnesium chloride (815 mg, 7.92 mmol). The mixture was allowed to stir for 1 h at 0 °C, followed by the addition of 1,1-dimethylethyl 3-oxoazetidiene-1-carboxylate (1.64 g, 9.60 mmol), prepared using procedures similar to

those described in Example 3. The reaction mixture was then allowed to warm to room temperature and stirred for 6h. The mixture was quenched with 1 N hydrochloric acid (10 mL) and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate) to afford 1,1-dimethylethyl 3-hydroxy-3-[2-(methylthio)pyrimidin-4-yl]azetidine-1-carboxylate (380 mg, 16%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): 8.62-8.59 (d, 1H), 7.36-7.33 (d, 1H), 5.14-5.11 (s, 1H), 4.29-4.24 (d, 2H), 4.13-4.08 (d, 2H), 2.61-2.58 (s, 3H), 1.50-1.47 (s, 9H); MS (EI) for $C_{13}H_{19}N_3O_3S$: 298 (MH^+).

[00283] A solution of 1,1-dimethylethyl 3-hydroxy-3-[2-(methylthio)pyrimidin-4-yl]azetidine-1-carboxylate (480 mg, 1.62 mmol), and 3-chloroperoxybenzoic (558 mg, 3.23 mmol) acid in dichloromethane (25 mL) was stirred at room temperature for 22 h. The reaction mixture was quenched with a saturated solution of sodium thiosulfate and the pH adjusted to 7 with sodium carbonate. The organic layer was separated, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated *in vacuo*. The resulting crude 1,1-dimethylethyl 3-hydroxy-3-[2-(methylsulfonyl)pyrimidin-4-yl]azetidine-1-carboxylate (524 mg, 98%) was used without further purification. ^1H NMR (400 MHz, $CDCl_3$): 9.01-8.97 (d, 1H), 7.96-7.93 (d, 1H), 4.57-4.53 (s, 1H), 4.31-4.27 (d, 2H), 4.23-4.18 (d, 2H), 3.42-3.39 (s, 3H), 1.50-1.47 (s, 9H); MS (EI) for $C_{13}H_{19}N_3O_5S$: 330 (MH^+).

[00284] A solution of 1,1-dimethylethyl 3-hydroxy-3-[2-(methylsulfonyl)pyrimidin-4-yl]azetidine-1-carboxylate (215 mg, 0.652 mmol), and aqueous ammonia (7 mL, 28% solution) in dioxane (15 mL) within a sealed steel bomb cylinder was heated at 80°C for 4h. The mixture was cooled to room temperature and the solvent was evaporated. The residue was dissolved in dichloromethane and a solution of saturated sodium carbonate. The organic layer was separated, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated *in vacuo*. The resulting crude 1,1-dimethylethyl 3-(2-aminopyrimidin-4-yl)-3-hydroxyazetidine-1-carboxylate (140 mg, 100%) was used without further purification. ^1H NMR (400 MHz, $CDCl_3$): 8.38-8.35 (d, 1H), 6.97-6.94 (d, 1H), 5.30-5.28 (s, 2H), 4.23-4.18 (d, 2H), 4.08-4.04 (d, 2H), 1.48-1.45 (s, 9H).

[00285] To a solution of 1,1-dimethylethyl 3-(2-aminopyrimidin-4-yl)-3-hydroxyazetidine-1-carboxylate (140 mg, 0.524 mmol) in dichloromethane (10 ml) was added trifluoroacetic acid (3 ml). The reaction mixture was stirred for 2h at room temperature. The mixture was concentrated *in vacuo*. The resulting crude 3-(2-aminopyrimidin-4-yl)azetidin-3-ol (87 mg, 100%) was used without further purification.

[00286] A solution of 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid (201 mg, 0.512 mmol), prepared using procedures similar to those described in US 7,019,033, 3-(2-aminopyrimidin-4-yl)azetidin-3-ol (87 mg, 0.52 mmol), benzotriazol-1-yl-oxy-tris(pyrrolidino)phosphonium hexafluorophosphate (293 mg, 0.563 mmol) and *N,N*-diisopropylethylamine (270 uL, 2.82 mmol) in *N,N*-dimethylformamide (2 mL) was stirred at room temperature for 20h. The mixture was partitioned between ethyl acetate and saturated sodium bicarbonate. The organic layer was separated and washed with brine, dried over sodium sulfate, filtered and the filtrate concentrated *in vacuo*. The residue was purified by reverse phase HPLC to afford the title compound 3-(2-aminopyrimidin-4-yl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol (22 mg, 7%). ^{1}H NMR (400 MHz, CD_3OD): 8.23-8.20 (d, 1H), 7.48-7.43 (d, 1H), 7.35-7.32 (m, 2H), 7.09-7.00 (m, 1H), 6.88-6.84 (d, 1H), 6.70-6.63 (t, 1H), 4.59-4.54 (d, 1H), 4.45-4.40 (d, 1H), 4.23-4.18 (d, 1H), 3.04-3.99 (t, 1H); MS (EI) for $C_{20}H_{15}F_3IN_5O_2$: 542 (MH^+).

[00287] Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, the following compounds of the invention were prepared:

EXAMPLE 8(a): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-pyridin-2-ylazetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 8.47 (m, 1H), 7.80 (m, 1H), 7.65 (d, 1H), 7.44 (m, 1H), 7.33 (m, 3H), 7.04 (m, 1H), 6.65 (m, 1H), 4.61 (d, 1H), 4.44 (d, 1H), 4.29 (d, 1H), 4.12 (d, 1H). MS (EI) for $C_{21}H_{15}F_3IN_3O_2$: 526 (MH^+).

EXAMPLE 8(b): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1*H*-imidazol-2-yl)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7.42 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H), 7.02 (m, 3H), 6.63 (m, 1H), 4.65 (d, 1H), 4.42 (d, 1H), 4.33 (d, 1H), 4.16 (d, 1H). MS (EI) for $C_{19}H_{14}F_3IN_4O_2$: 515 (MH^+).

EXAMPLE 8(c): 3-(1*H*-benzimidazol-2-yl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7.55 (br s, 2H), 7.42 (m, 2H), 7.33 (m, 1H), 7.23 (m, 2H), 7.04 (m, 1H), 6.65 (m, 1H), 4.76 (d, 1H), 4.57 (d, 1H), 4.43 (d, 1H), 4.25 (d, 1H). MS (EI) for $C_{23}H_{16}F_3IN_4O_2$: 565 (MH^+).

EXAMPLE 8(d): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(5-methyl-1*H*-imidazol-2-yl)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7.41 (m, 1H), 7.36 (m, 1H), 7.31 (m, 1H), 7.02 (m, 1H), 6.67 (br s, 1H), 6.63 (m, 1H), 4.63 (d, 1H), 4.39 (d, 1H), 4.30 (d, 1H), 4.13 (d, 1H), 2.18 (s, 3H). MS (EI) for $C_{20}H_{16}F_3IN_4O_2$: 529 (MH^+).

EXAMPLE 8(e): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-prop-2-en-1-ylazetidin-3-ol: ^{1}H NMR (400 MHz, $CDCl_3$): 8.47 (br s, 1H), 7.40 (dd, 1H), 7.35-7.31 (m, 1H), 7.15-7.10 (m, 1H), 6.81 (ddd, 1H), 6.62 (ddd, 1H), 5.84-5.72 (m, 1H),

5.27-5.20 (m, 2H), 4.22-3.94 (m, 4H), 2.52 (d, 2H), 2.25 (s, 1H); MS (EI) for $C_{19}H_{16}F_3IN_2O_2$: 489 (MH^+).

EXAMPLE 8(f): 3-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]propane-1,2-diol: ^{1}H NMR (400 MHz, $CDCl_3$): 8.43 (br s, 1H), 7.39 (dd, 1H), 7.35-7.30 (m, 1H), 7.16-7.10 (m, 1H), 6.82 (ddd, 1H), 6.61 (ddd, 1H), 4.31-3.91 (m, 5H), 3.68 (br d, 1H), 3.54-3.49 (m, 1H), 2.01-1.80 (m, 2H); MS (EI) for $C_{19}H_{18}F_3IN_2O_4$: 523 (MH^+).

EXAMPLE 8(g): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-ethenylazetidin-3-ol: ^{1}H NMR (400 MHz, $CDCl_3$): 8.48 (br s, 1H), 7.40 (dd, 1H), 7.35-7.31 (m, 1H), 7.17-7.11 (m, 1H), 6.81 (ddd, 1H), 6.62 (ddd, 1H), 6.15 (dd, 1H), 5.39 (d, 1H), 5.28 (d, 1H), 4.30-4.10 (m, 4H); MS (EI) for $C_{18}H_{14}F_3IN_2O_2$: 475 (MH^+).

EXAMPLE 8(h): 1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethane-1,2-diol hydrochloride: ^{1}H NMR (400 MHz, d_6-DMSO): 8.66 (d, 1H), 7.58 (dd, 1H), 7.38 (d, 1H), 7.33-7.27 (m, 1H), 7.17 (q, 1H), 6.74-6.65 (m, 1H), 4.50-3.58 (br, 3H), 4.29 (dd, 1H), 4.14 (dd, 1H), 3.87 (t, 1H), 3.66 (t, 1H), 3.56-3.32 (m, 3H); MS (EI) for $C_{18}H_{16}F_3IN_2O_4$: 509 (MH^+).

EXAMPLE 8(i): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-ethylazetidin-3-ol: ^{1}H NMR (400 MHz, $CDCl_3$): 8.23 (br s, 1H), 7.40 (d, 1H), 7.33 (d, 1H), 7.15-7.10 (m, 1H), 6.85-6.79 (m, 1H), 6.64-6.58 (m, 1H), 4.14-3.94 (m, 4H), 1.78 (q, 2H), 0.96 (t, 3H); MS (EI) for $C_{18}H_{16}F_3IN_2O_2$: 477 (MH^+).

EXAMPLE 8(j): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-methylazetidin-3-ol: ^{1}H NMR (400 MHz, $CDCl_3$): 8.31 (br s, 1H), 7.40 (d, 1H), 7.33 (d, 1H), 7.15-7.11 (m, 1H), 6.85-6.78 (m, 1H), 6.65-6.59 (m, 1H), 4.24-4.04 (m, 4H), 1.55 (s, 3H); MS (EI) for $C_{17}H_{14}F_3IN_2O_2$: 463 (MH^+).

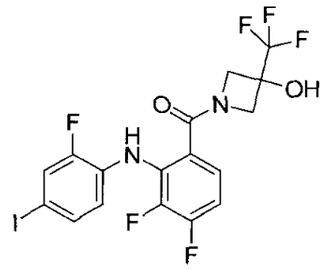
EXAMPLE 8(k): 3-(2-aminopyrimidin-4-yl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 8.22-8.20 (d, 1H), 7.48-7.43 (d, 1H), 7.38-7.30 (m, 1H), 7.09-7.01 (q, 1H), 6.88-6.84 (d, 1H), 6.70-6.61 (t, 1H), 4.59-4.54 (d, 1H), 4.44-4.39 (d, 1H), 4.23-4.19 (d, 1H), 4.05-3.99 (d, 1H), 3.90-3.81 (d, 1H), 1.99-1.97 (s, 3H); MS (EI) for $C_{20}H_{15}F_3I\ N_5O_2$: 542 (MH^+).

EXAMPLE 8(m): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1*H*-pyrrol-2-yl)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7.37 (dd, 1H), 7.31-7.23 (m, 2H), 7.07-6.97 (m, 1H), 6.73-6.68 (m, 1H), 6.65-6.56 (m, 1H), 6.06-5.98 (m, 2H), 4.49-4.40 (m,1H), 4.32-4.18 (m, 2H), 4.15-88-4.07 (m, 1H). MS (EI) for $C_{20}H_{15}F_3IN_3O_2$: 514 (MH^+)

EXAMPLE 8(n): 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-methyl-1*H*-imidazol-2-yl)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7.34 (dd, 1H), 7.31-7.25 (m, 1H), 7.23-7.18 (m, 1H), 7.11-7.09 (m, 1H), 7.06-6.97 (m, 1H), 6.89-6.86 (m, 1H), 6.62-6.55 (m, 1H), 4.88-4.80 (m, 1H), 4.52-4.44 (m,1H), 4.38-4.30 (m, 1H), 4.21-4.12 (m, 1H), 3.68 (s, 3H). MS (EI) for $C_{20}H_{16}F_3IN_4O_2$: 529 (MH^+).

EXAMPLE 9

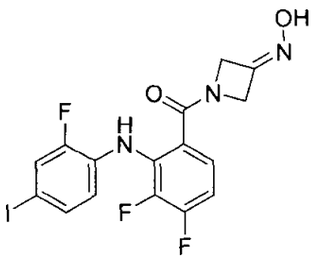
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(trifluoromethyl)azetidin-3-ol



[00288] 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-one (25 mg, 0.056 mmol), prepared using procedures described in Example 6, was taken into DMF (0.5 mL) followed by addition of (trifluoromethyl)trimethylsilane (40 μL, 0.28 mmol) and cesium carbonate (22 mg, 0.067mmol) and the mixture was stirred for one hour at room temperature. The mixture was partitioned with ethyl ether and water and the organic phase washed three times with additional water then brine and dried over anhydrous sodium sulfate. Filtration and concentration followed by silica gel flash chromatography of the residue using hexanes:ethyl acetate 3:2 as eluent afforded 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(trifluoromethyl)azetidin-3-ol (19.8 mg, 69% yield) as a colorless crystalline solid. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.31-8.26 (br, 1H), 7.40 (d, 1H), 7.33 (d, 1H), 7.13-7.10 (m, 1H), 6.86-6.80 (m, 1H), 6.65-6.60 (m, 1H), 4.42 (br s, 2H), 4.18 (br s, 2H). MS (EI) for $C_{17}H_{11}F_6IN_2O_2$: 517 (MH^+).

EXAMPLE 10

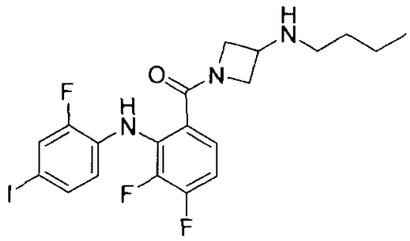
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-one oxime



[00289] To a solution of 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-one (100 mg, 0.22 mmol), prepared using procedures similar to those described in Example 6, in dioxane (1.0 mL) was added hydroxylamine (0.10 mL, 50% solution in water, 1.5 mmol), and the resulting solution was heated at 60 °C for 18 h. The mixture was cooled to room temperature and the crude product was purified by reverse phase HPLC to afford 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-one oxime (56 mg, 54% yield): ^{1}HNMR (400MHz, $CDCl_3$), 8.43 (br s), 7.43-7.39 (m, 2H), 7.35-7.32 (dd,1H), 7.19-7.15 (m, 1H), 6.87-6.81 (m,1H), 6.65-6.59 (m, 1H), 4.89 (br s, 2H), 4.85 (br s, 2H); MS (EI) for $C_{16}H_{11}F_3IN_3O_2$: 462 (MH^+).

Example 11

***N*-butyl-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine**

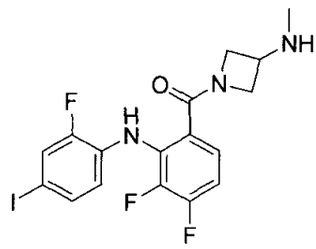


[00290] To a solution of 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine (0.09 M in acetonitrile, 500 μL, 0.045 mmol), prepared using procedures similar to those described in Example 2, was added triethylamine (20 μL, 0.135 mmol) and *n*-butylbromide (6.14 μL, 0.054 mmol) followed by additional acetonitrile (1.0 mL). The reaction mixture was stirred at room temperature for 16 h, at which time it was purified directly by reverse phase HPLC to afford the title compound (8.4 mg). ^{1}H NMR (400 MHz, $CDCl_3$): 8.50 (s, 1H), 7.39 (dd, 1H), 7.32 (dd, 1H), 7.13-7.09

(m, 1H), 6.84-6.77 (m, 1H), 6.63-6.57 (m, 1H), 4.35 (br s, 2H), 4.00 (br s, 1H), 3.87 (br s, 1H), 3.74-3.68 (m, 1H), 3.20 (br s, 3.5H), 2.56 (t, 2H), 2.03 (s, 2H), 1.50-1.42 (m, 2H), 1.39-1.29 (m, 2H), 0.91 (t, 3H). MS (EI) for $C_{20}H_{21}F_3IN_3O$: 504 (MH^+).

EXAMPLE 12

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-methylazetidin-3-amine



[00291] To a solution of 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine (0.10 M in acetonitrile, 1.0 mL, 0.09 mmol), prepared using procedures similar to those described in Example 2, in 1:1 ratio of methanol and tetrahydrofuran (2.0 mL) was added formaldehyde (37%wt, 6.7 μL, 0.09 mmol) followed by sodium cyanoborohydride (11.0 mg, 0.18 mmol). The reaction mixture was stirred at room temperature for 16 h, at which time it was quenched with saturated aqueous ammonium chloride. The solution was then purified directly by reverse phase HPLC to afford the title compound (14.9 mg). ^{1}H NMR (400 MHz, $CDCl_3$): 8.13 (br s, 1H), 7.35 (d, 1H), 7.30 (d, 1H), 7.09-7.04 (m, 1H), 6.84-6.78 (m, 1H), 6.60-6.54 (m, 1H), 4.46-4.33 (br m, 4H), 3.93 (br m, 1H), 2.64 (s, 3H). MS (EI) for $C_{17}H_{15}F_3IN_3O$: 462 (MH^+).

[00292] Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, the following compounds of the invention were prepared:

EXAMPLE 12(a). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-methylazetidin-3-amine: ^{1}H NMR (400 MHz, $CDCl_3$): 8.13 (br s, 1H), 7.35 (d, 1H), 7.30 (d, 1H), 7.09-7.04 (m, 1H), 6.84-6.78 (m, 1H), 6.60-6.54 (m, 1H), 4.46-4.33 (br m, 4H), 3.93 (br m, 1H), 2.64 (s, 3H). MS (EI) for $C_{17}H_{15}F_3IN_3O$: 462 (MH^+).

EXAMPLE 12(b). 2-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]amino}ethanol: ^{1}H NMR (400 MHz, $CDCl_3$): 8.20 (s, 1H), 7.36 (d, 1H), 7.30 (d, 1H), 7.13-7.09 (m, 1H), 6.85-6.79 (m, 1H), 6.61-6.55 (m, 1H), 4.43 (br m, 3H), 3.98 (br m, 1H), 3.87 (br m, 1H), 3.02 (br m, 1H), 1.24-1.20 (m, 1H). MS (EI) for $C_{18}H_{17}F_3IN_3O_2$: 492 (MH^+).

EXAMPLE 12(c). *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]propane-1,3-diamine: ^{1}H NMR (400 MHz, $CDCl_3$): 8.51 (s, 1H), 7.39 (d, 1H), 7.32 (d, 1H), 7.14-7.10 (m, 1H), 6.84-6.77 (m, 1H), 6.63-6.57 (m, 1H), 4.33 (br s, 2H), 3.99 (br s, 1H), 3.84 (br s, 1H), 3.71-3.64 (m, 1H), 2.91 (t, 2H), 2.70-2.66 (m, 2H), 2.01 (s, 4H), 1.76-1.69 (m, 2H). MS (EI) for $C_{19}H_{20}F_3IN_4O$: 505 (MH^+).

EXAMPLE 12(d). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-ethylazetidin-3-amine: ^{1}H NMR (400 MHz, $CDCl_3$): 8.47 (s, 1H), 7.38 (d, 1H), 7.31 (d, 1H), 7.13-7.09 (m, 1H), 6.83-6.77 (m, 1H), 6.62-6.57 (m, 1H), 4.49 (br s, 3H), 4.36 (br s, 2H), 4.08 (br s, 1H), 3.94 (br s, 1H), 3.77-3.72 (m, 1H), 2.69-2.63 (m, 2H), 1.99 (s, 2H), 1.14 (t, 3H). MS (EI) for $C_{18}H_{17}F_3IN_3O$: 476 (MH^+).

EXAMPLE 12(e). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(2-methylpropyl)azetidin-3-amine: ^{1}H NMR (400 MHz, $CDCl_3$): 8.50 (s, 1H), 7.38 (d, 1H), 7.31 (d, 1H), 7.14-7.09 (m, 1H), 6.83-6.76 (m, 1H), 6.63-6.57 (m, 1H), 4.34 (br s, 2H), 4.00 (br s, 1H), 3.86 (br s, 1H), 3.71-3.66 (m, 1H), 3.42 (br s, 2H), 2.36 (d, 2H), 2.00 (s, 1H), 1.75-1.65 (m, 1H), 0.91 (d, 6H). MS (EI) for $C_{20}H_{21}F_3IN_3O$: 504 (MH^+).

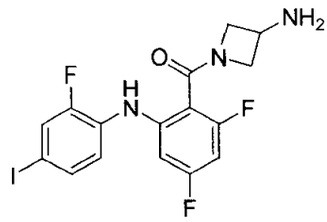
EXAMPLE 12(f). *N*-(cyclopropylmethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine: ^{1}H NMR (400 MHz, $CDCl_3$): 8.48 (s, 1H), 7.39 (d, 1H), 7.32 (d, 1H), 7.13-7.09 (m, 1H), 6.84-6.77 (m, 1H), 6.63-6.57 (m, 1H), 5.78 (s, 3H), 4.36 (br s, 2H), 4.10 (br s, 1H), 3.94 (br s, 1H), 3.81-3.75 (m, 1H), 2.49 (d, 2H), 2.01 (s, 4H), 0.94-0.86 (m, 1H), 0.53 (d, 2H), 0.13 (d, 2H). MS (EI) for $C_{20}H_{19}F_3IN_3O$: 502 (MH^+).

EXAMPLE 12(g). *N*-(cyclohexylmethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine: ^{1}H NMR (400 MHz, $CDCl_3$): 8.48 (s, 1H), 7.38 (dd, 1H), 7.31 (d, 1H), 7.13-7.08 (m, 1H), 6.83-6.77 (m, 1H), 6.63-6.57 (m, 1H), 4.55 (br s, 2H), 4.33 (br m, 2H), 4.02 (br s, 1H) 3.87 (br s, 1H), 3.71-3.65 (m, 1H), 2.38 (d, 2H), 1.74-1.68 (m, 4H), 1.46-1.36 (m, 1H), 1.27-1.12 (m, 3H), 0.94-0.84 (m, 2H). MS (EI) for $C_{23}H_{25}F_3IN_3O$: 544 (MH^+).

EXAMPLE 12(h). *N*-(cyclopentylmethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine: ^{1}H NMR (400 MHz, $CDCl_3$): 8.32 (s, 1H), 7.37 (d, 1H), 7.31 (d, 1H), 7.11-7.07 (m, 1H), 6.84-6.77 (m, 1H), 6.63-6.57 (m, 1H), 4.44-4.37 (m, 3H), 4.02-3.96 (m, 1H), 2.84 (d, 2H), 2.54 (br s, 5H), 2.20-2.12 (m, 1H), 1.88-1.81 (m, 2H), 1.68-1.54 (m, 4H), 1.24-1.15 (m, 2H). MS (EI) for $C_{22}H_{23}F_3IN_3O$: 530 (MH^+).

EXAMPLE 13

1-({2,4-difluoro-6-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine



[00293] 2,4,6-Trifluorobenzoic acid (643 mg, 3.65 mmol) and 2-fluoro-4-iodoaniline (1.0 g, 4.22 mmol) were taken into acetonitrile (30 mL) followed by addition of lithium amide (290 mg, 12.7 mmol) and the mixture was heated to 60 °C under a nitrogen atmosphere for one hour. On cooling to room temperature the mixture was added to 1 N aqueous hydrochloric acid (100 mL) and the precipitate formed was collected by filtration and washed once with water then hexanes and dried *in vacuo* to give 2,4-difluoro-6-[(2-fluoro-4-iodophenyl)amino]benzoic acid (849 mg, 59% yield) as a tan solid. ^{1}H-NMR (400 MHz, D_6-DMSO): 13.72 (br s, 1H), 9.46 (s, 1H), 7.75 (d, 1H), 7.56 (d, 1H) 7.28 (tr, 1H), 6.73-6.67 (m, 1H), 6.53 (d, 1H).

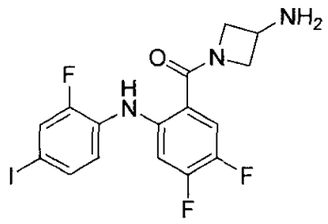
[00294] 2,4-Difluoro-6-[(2-fluoro-4-iodophenyl)amino]benzoic acid (100 mg, 0.25 mmol) was taken into DMF (1 mL) followed by addition of PyBOP (137 mg, 0.26 mmol) and the mixture was stirred for 15 minutes then NMM (60 μL, 0.5 mmol) and commercially available 1,1-dimethylethyl azetidin-3-ylcarbamate (43 mg, 0.25 mmol) were subsequently added. The mixture was allowed to stir for 12 hours at room temperature then partitioned with ethyl acetate and water. The organic phase was washed three times with additional water then brine and dried over anhydrous sodium sulfate. Filtration and concentration followed by silica gel flash chromatography of the residue using hexanes:ethyl acetate 3:1 as eluent afforded 1,1-dimethylethyl [1-({2,4-difluoro-6-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]carbamate (125 mg) as a colorless oil.

[00295] The oil was taken into trifluoroacetic acid (1 mL) and allowed to stand at room temperature for 5 minutes then concentrated *in vacuo*. The residue was portioned with ethyl acetate and saturated aqueous sodium bicarbonate and the organic phase washed with brine then dried over anhydrous sodium sulfate. The organic solution was filtered and concentrated then the residue taken into methanol (1 mL) followed by addition of 4 N HCl in dioxane until the solution was acidic. The solution was concentrated and the residue triturated with ethyl ether to give a thick precipitate. The solid was collected by filtration and dried *in vacuo* to give 1-({2,4-difluoro-6-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine

hydrochloride (58 mg, 48% overall yield). ^{1}H-NMR (400 MHz, D_6-DMSO): 8.67 (br s, 3H), 8.45 (s, 1H), 7.71 (d, 1H), 7.54 (d, 1H), 7.25 (tr, 1H), 6.77 (tr, 1H), 6.48 (d, 1H), 4.28-4.23 (m, 2H), 4.13-4.06 (m, 3H). MS (EI) for $C_{16}H_{13}F_3IN_3O$: 448 (MH^+).

EXAMPLE 14

1-({4,5-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine



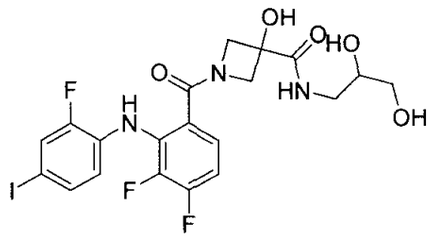
[00296] 2,4,5-Trifluorobenzoic acid (643 mg, 3.65 mmol) and 2-fluoro-4-iodoaniline (1.0 g, 4.22 mmol) were taken into acetonitrile (30 mL) followed by addition of lithium amide (290 mg, 12.7 mmol) and the mixture was heated to 60 °C under a nitrogen atmosphere for one hour. On cooling to room temperature the mixture was added to 1 N aqueous hydrochloric acid (100 mL) and the precipitate formed was collected by filtration and washed once with water then hexanes and dried *in vacuo* to give 4,5-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid (624 mg, 43% yield) as a tan solid. ^{1}H-NMR (400 MHz, D_6-DMSO): 13.65 (br s, 1H), 9.63 (s, 1H), 7.84 (tr, 1H), 7.71 (d, 1H), 7.52 (d, 1H), 7.32 (tr, 1H), 7.03-6.98 (dd, 1H).

[00297] 4,5-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid (100 mg, 0.25 mmol) was taken into DMF (1 mL) followed by addition of PyBOP (137 mg, 0.26 mmol) and the mixture was stirred for 15 minutes then NMM (60 μL, 0.5 mmol) and commercially available 1,1-dimethylethyl azetidin-3-ylcarbamate (43 mg, 0.25 mmol) were subsequently added. The mixture was allowed to stir for 12 hours at room temperature then partitioned with ethyl acetate and water. The organic phase was washed three times with additional water then brine and dried over anhydrous sodium sulfate. Filtration and concentration followed by silica gel flash chromatography of the residue using hexanes:ethyl acetate 3:1 as eluent afforded 1,1-dimethylethyl [1-({4,5-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]carbamate (131 mg) as a colorless oil. The oil was taken into trifluoroacetic acid (1 mL) and allowed to stand at room temperature for 5 minutes then concentrated *in vacuo*. The residue was portioned with ethyl acetate and saturated aqueous sodium bicarbonate and the organic phase washed with brine then dried over anhydrous sodium sulfate. The organic solution was filtered and concentrated then the

residue taken into methanol (1 mL) followed by addition of 4 N HCl in dioxane until the solution was acidic. The solution was concentrated and the residue triturated with ethyl ether to give a thick precipitate. The solid was collected by filtration and dried *in vacuo* to give 1-({4,5-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine hydrochloride (67 mg, 55% overall yield). ^{1}H-NMR (400 MHz, D_6-DMSO): 9.02 (s, 1H), 8.54 (br s, 3H), 7.68 (dd, 1H), 7.53-7.47 (m, 2H), 7.22 (tr, 1H), 7.16 (dd, 1H), 4.60 (br s, 1H), 4.23 (br s, 2H), 4.03 (br m, 2H). MS (EI) for $C_{16}H_{13}F_3IN_3O$: 448 (MH^+).

EXAMPLE 15

1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(2,3-dihydroxypropyl)-3-hydroxyazetidine-3-carboxamide



[00298] 1-(Diphenylmethyl)azetidin-3-ol hydrochloride (2.75 g, 9.98 mmol), prepared using procedures similar to those described for **Scheme 1** of the General Synthetic Section, 3Å molecular sieves and 4-methylmorpholine (1.1 mL, 10.0 mmol) were suspended in dichloromethane (20 mL) at 0 °C. 4-Methylmorpholine N-oxide (2.93 g, 25.0 mmol) and tetrapropylammonium perruthenate (140 mg, 0.399 mmol) were added and the mixture was stirred at ambient for 24 h. The mixture was filtered through a plug of silica using 5% triethylamine in ethyl acetate as eluent. The filtrate was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, 8:1 hexanes:ethyl acetate) gave 1-(diphenylmethyl)azetidin-3-one (871 mg, 3.68 mmol, 37% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 7.50-7.46 (m, 4H), 7.33-7.27 (m, 4H), 7.27-7.19 (m, 2H), 4.59 (s, 1H), 4.01 (s, 4H); MS (EI) for $C_{16}H_{15}NO$: 238 (MH^+).

[00299] 1-(Diphenylmethyl)azetidin-3-one (600 mg, 2.53 mmol), was dissolved in dichloromethane (1 mL) and treated with triethylamine (0.5 mL, 3.59 mmol) and trimethylsilylcyanide (0.8 mL, 6.01 mmol) at ambient for 2 h and then the mixture was concentrated *in vacuo* to afford 1-(diphenylmethyl)-3-[(trimethylsilyl)oxy]azetidine-3-carbonitrile (774 mg, 2.30 mmol, 91% yield) as a yellow solid. 1-(diphenylmethyl)-3-

[(trimethylsilyl)oxy]azetidine-3-carbonitrile (250 mg, 0.744 mmol) was dissolved in dichloromethane (2 mL) at 0 °C and concentrated sulfuric acid (0.2 mL) was added dropwise. The mixture was stirred at ambient for 2 h and then was cooled to 0 °C and 25% ammonium hydroxide solution was added carefully dropwise to pH ~10-11. The mixture was extracted twice with dichloromethane. The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford a residue which was triturated with hexanes/ether to afford 1-(diphenylmethyl)-3-hydroxyazetidine-3-carboxamide (160 mg, 0.567 mmol, 76% yield) as an off-white solid: ^{1}H NMR (400 MHz, $CDCl_3$): 7.92 (br s, 1H), 7.39-7.34 (m, 4H), 7.33-7.27 (m, 4H), 7.27-7.19 (m, 2H), 5.61 (br s, 1H), 4.45 (s, 1H), 4.34 (s, 1H), 3.50 (dd, 2H), 3.20 (dd, 2H); MS (EI) for $C_{17}H_{18}N_2O_2$: 283 (MH^+).

[00300] 1-(Diphenylmethyl)-3-hydroxyazetidine-3-carboxamide (1.1 g, 3.90 mmol) was treated with 10% sodium hydroxide in ethanol (15 mL) and water (2 mL) at reflux for 2 h and then was concentrated *in vacuo*. The resiude was neutralized with 1 N hydrochloric acid (pH ~7) and the precipitate was collected by filtration and lyophilized to afford 1-(diphenylmethyl)-3-hydroxyazetidine-3-carboxylic acid (assume 3.90 mmol) which was used without further purification: ^{1}H NMR (400 MHz, d_6-DMSO): 7.45-7.40 (m, 4H), 7.31-7.25 (m, 4H), 7.21-7.15 (m, 2H), 4.52 (s, 1H), 3.46 (dd, 2H), 3.02 (dd, 2H); MS (EI) for $C_{17}H_{17}NO_3$: 284 (MH^+).

[00301] 1-(Diphenylmethyl)-3-hydroxyazetidine-3-carboxylic acid (assume 3.90 mmol) was suspended in methanol (40 mL) and 4 N hydrochloric acid in dioxane (1 mL, 4 mmol) was added. 20 wt% Palladium hydroxide on carbon (100 mg) was added to the solution and the mixture was treated with hydrogen at 40 psi for 2 h. The mixture was filtered and the filtrate was concentrated *in vacuo* to afford 3-hydroxyazetidine-3-carboxylic acid hydrochloride which was dissolved in tetrahydrofuran (5 mL) and water (5 mL) and treated with potassium carbonate (1.615 g, 11.7 mmol) and di-*tert*-butyl dicarbonate (935 mg, 4.29 mmol) were added. The mixture was stirred at ambient for 17 h and then the mixture was partitioned between ethyl acetate and water. The aqueous portion was extracted with ethyl acetate and then was acidified to pH ~3-4 and extracted twice more with ethyl acetate. The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford 1-{[(1,1-dimethylethyl)oxy]carbonyl}-3-hydroxyazetidine-3-carboxylic acid which was dissolved in DMF (3 mL). Benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (2.028 g, 3.90 mmol) and *N,N*-diisopropylethylamine (0.7 mL, 4.03 mmol) were added. The mixture was stirred at ambient

for 5 minutes and then allylamine (0.6 mL, 8.03 mmol) was added and the mixture was stirred for 17 h. The mixture was partitioned between ethyl acetate and 5% lithium chloride. The organic portion was washed with 20% citric acid, saturated sodium bicarbonate and brine, then was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, ethyl acetate) gave 1,1-dimethylethyl 3-hydroxy-3-[(prop-2-en-1-ylamino)carbonyl]azetidine-1-carboxylate (782 mg, 3.05 mmol, 78% yield from 1-(diphenylmethyl)-3-hydroxyazetidine-3-carboxamide). 1,1-Dimethylethyl 3-hydroxy-3-[(prop-2-en-1-ylamino)carbonyl]azetidine-1-carboxylate (782 mg, 3.05 mmol) was dissolved in methanol (10 mL) and 4 N hydrochloric acid in dioxane (2 mL, 8 mmol) was added. The mixture was refluxed for 15 minutes and then was concentrated *in vacuo* to afford 3-hydroxy-*N*-prop-2-en-1-ylazetidine-3-carboxamide hydrochloride (3.05 mmol).

[00302] 3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid (1.20 g, 3.05 mmol), prepared using procedures similar to those described in US 7,019,033, 4-(dimethylamino)pyridine (1.20 g, 9.86 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (701 mg, 3.66 mmol) were dissolved in DMF (10 mL). The mixture was stirred at ambient for 5 minutes and then 3-hydroxy-*N*-prop-2-en-1-ylazetidine-3-carboxamide hydrochloride (3.05 mmol) in DMF (5 mL) was added and the mixture was stirred for 15 h. The mixture was partitioned between ethyl acetate and 5% lithium chloride. The organic portion was washed with 20% citric acid, saturated sodium bicarbonate and brine, then was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, 60-85% ethyl acetate in hexanes) and then reverse phase HPLC gave 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxy-*N*-prop-2-en-1-ylazetidine-3-carboxamide (150 mg, 0.282 mmol, 9% yield): ^{1}H NMR (400 MHz, d_6-DMSO): 8.64 (br s, 1H), 8.13 (t, 1H), 7.58 (dd, 1H), 7.38 (dd, 1H), 7.34-7.28 (m, 1H), 7.21-7.12 (m, 1H), 6.84 (br s, 1H), 6.72 (ddd, 1H), 5.83-5.72 (m, 1H), 5.10-4.99 (m, 2H), 4.38 (d, 1H), 4.20 (d, 1H), 4.02 (d, 1H), 3.86 (d, 1H), 3.73-3.68 (m, 2H); MS (EI) for $C_{20}H_{17}F_3IN_3O_3$: 532 (MH^+).

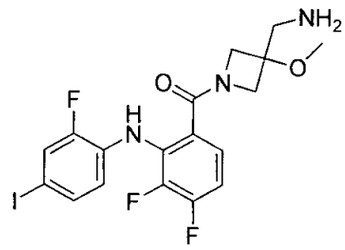
[00303] 1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxy-*N*-prop-2-en-1-ylazetidine-3-carboxamide (88 mg, 0.166 mmol) and 4-methylmorpholine *N*-oxide (58 mg, 0.496 mmol) were dissolved in acetone / water (4:1; 10 mL) and osmium tetroxide (2.5 wt.% in water; 0.1 mL) was added. The solution was stirred at ambient for 15 h, then was quenched with saturated sodium bisulfite (2 mL) and concentrated *in vacuo*. The residue was partitioned between ethyl acetate and brine. The aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with brine, dried over

anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by reverse phase HPLC gave 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(2,3-dihydroxypropyl)-3-hydroxyazetidine-3-carboxamide (68 mg, 0.120 mmol, 72% yield): ^{1}H NMR (400 MHz, d_6-DMSO): 8.65 (br s, 1H), 7.72 (t, 1H), 7.58 (dd, 1H), 7.41-7.36 (m, 1H), 7.34-7.28 (m, 1H), 7.21-7.12 (m, 1H), 6.92 (br s, 1H), 6.72 (ddd, 1H), 5.00-4.10 (br, 2H), 5.10-4.99 (m, 2H), 4.39 (d, 1H), 4.20 (d, 1H), 4.02 (d, 1H), 3.54-3.45 (m, 1H), 3.34-3.21 (m, 2H), 3.06-2.96 (m, 1H); MS (EI) for $C_{20}H_{19}F_3IN_3O_5$: 566 (MH^+).

[00304] EXAMPLE 15(a). Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, the following compounds of the invention were prepared: 1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidine-3-carboxamide: ^{1}H NMR (400 MHz, d_6-DMSO): 8.63 (br s, 1H), 7.58 (dd, 1H), 7.42-7.36 (m, 3H), 7.34-7.28 (m, 1H), 7.22-7.12 (m, 1H), 6.76-6.68 (m, 2H), 4.39 (d, 1H), 4.19 (d, 1H), 4.00 (d, 1H), 3.83 (d, 1H); MS (EI) for $C_{17}H_{13}F_3IN_3O_3$: 492 (MH^+).

EXAMPLE 16

6-{[3-(aminomethyl)-3-(methyloxy)azetidin-1-yl]carbonyl}-2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)aniline



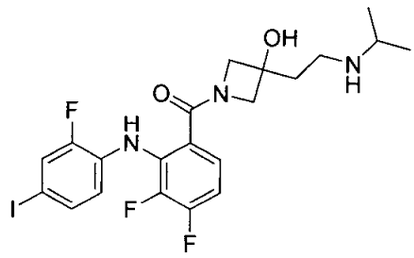
[00305] Phenylmethyl 1-oxa-5-azaspiro[2.3]hexane-5-carboxylate (165 mg, 0.75 mmol), prepared using procedures similar to those described in Reference 3, in THF (1 mL) was added to anhydrous ammonia saturated in THF (10 mL) and the mixture was allowed to stir in a sealed vessel at room temperature over 24 hours. The solution was then concentrated and taken back into THF (1 mL) followed by addition of di-*tert*-butyldicarbonate (164 mg, 0.75 mmol) and stirred for one hour at room temperature. The mixture was then concentrated and the residue purified by silica gel flash chromatography using hexanes:ethyl acetate (1:1) as eluent to give phenylmethyl 3-[({[(1,1-dimethylethyl)oxy]carbonyl}amino)methyl]-3-hydroxyazetidine-1-carboxylate (16.5 mg, 7% yield) and unreacted epoxide (120 mg, 73% recovery). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.34 (m, 5H), 5.10 (br, 1H), 5.09 (s, 2H), 4.68 (s, 1H), 3.90 (dd AB, 4H), 3.41 (d, 2H), 1.44 (s, 9H).

[00306] Phenylmethyl 3-[({[(1,1-dimethylethyl)oxy]carbonyl}amino)methyl]-3-hydroxyazetidine-1-carboxylate (16.5 mg, 0.05 mmol) and 10% Pd/C (8 mg) were taken into methanol (2 mL) and hydrogenated at ambient pressure over 12 hours. The catalyst was removed by filtration and the filtrate concentrated and dried *in vacuo*. The residue was taken into THF (1 mL) followed by addition of DIPEA (10 µL, 0.06 mmol) and 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoyl fluoride (19.8 mg, 0.05 mmol), prepared using procedures similar to those described in Reference 1, and the solution was stirred at room temperature for 30 minutes. Concentration and purification of the residue by silica gel flash chromatography using hexanes:ethyl acetate (1:1.5) afforded 1,1-dimethylethyl {[1-({3,4-difluoro-2[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidine-3-yl]methyl}carbamate (19 mg, 66% yield).

[00307] 1,1-Dimethylethyl {[1-({3,4-difluoro-2[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidine-3-yl]methyl}carbamate (8.0 mg, 0.014 mmol) and silver (I) oxide (12 mg, 0.05 mmol) were taken into methyl iodide (0.5 mL) and the mixture was brought to reflux for 4 hours. The suspension was then cooled to room temperature and diluted with an excess of ethyl ether then filtered. The filtrate was concentrated and purified by silica gel flash chromatography using hexanes:ethyl acetate (1:1) as eluent to give 1,1-dimethylethyl {[1-({3,4-difluoro-2[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(methyloxy)azetidine-3-yl]methyl}carbamate (2 mg). The material was taken into TFA (0.5 mL) and allowed to stand for 5 minutes then concentrated *in vacuo*. The residue was azetroped twice from methanol (2 mL) and the residue dried *in vacuo* to afford 6-{[3-(aminomethyl)-3-(methyloxy)azetidin-1-yl]carbonyl}-2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)aniline trifluoroacetate salt (2.3 mg, 27% yield) as an amorphous solid. MS (EI) for $C_{18}H_{17}F_3IN_3O$: 492 (MH^+).

EXAMPLE 17

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{2-[(1-methylethyl)amino]ethyl}azetidin-3-ol



[00308] A solution of *tert*-butyl acetate (566 μL, 4.2 mmol) in THF (10 mL) was cooled to -78 °C. To the solution was added LHMDS (5.25 mL of a 1.0 M solution in hexanes, 5.25 mmol), and the resulting mixture was stirred for 20 min at -78 °C. To the solution was added 1-(diphenylmethyl)azetidin-3-one (500 mg, 2.1 mmol), prepared using procedures similar to those described in Example 15. After stirring for 1 h, saturated aqueous ammonium chloride was added, and the mixture was warmed to rt. Water and ether were added, and the resulting biphasic mixture was partitioned. The aqueous phase was extracted once with ether. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (80% hexanes: 20% ethyl acetate) to provide 1,1-dimethylethyl [1-(diphenylmethyl)-3-hydroxyazetidin-3-yl]acetate as a pale yellow solid (644 mg, 1.8 mmol, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (m, 4H), 7.26 (m, 4H), 7.19 (m, 2H), 4.40 (s, 1H), 4.02 (s, 1H), 3.15 (m, 2H), 3.05 (m, 2H), 2.83 (s, 2H), 1.45 (s, 9H).

[00309] To a solution of 1,1-dimethylethyl [1-(diphenylmethyl)-3-hydroxyazetidin-3-yl]acetate (333 mg, 0.94 mmol) in THF (3 mL) at 0 °C was added lithium aluminum hydride (940 μL of a 1.0 M solution in THF, 0.94 mmol). The mixture was stirred for 3 h 20 min while warming to rt. Water (36 μL) was added carefully to the solution, followed by 15% sodium hydroxide (36 μL) and more water (108 μL). The resulting precipitate was removed by filtration through celite, and the filtrate was concentrated to dryness yielding 1-(diphenylmethyl)-3-(2-hydroxyethyl)azetidin-3-ol (228 mg, 0.80 mmol, 85% yield) as a colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (m, 4H), 7.26 (m, 4H), 7.19 (m, 2H), 4.37 (s, 1H), 3.92 (m, 2H), 3.32 (m, 2H), 2.96 (m, 2H), 2.07 (m, 2H).

[00310] Palladium hydroxide (100 mg) was suspended in a solution of 1-(diphenylmethyl)-3-(2-hydroxyethyl)azetidin-3-ol (228 mg, 0.80 mmol) in methanol (15 mL), and the mixture was subjected to an atmosphere of hydrogen at 50 psi for 4 h. The catalyst was then removed by filtration through celite, and the filtrate was concentrated *in vacuo* to provide 3-(2-hydroxyethyl)azetidin-3-ol. This material was used in the subsequent reaction without purification. To a solution of 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid (314 mg, 0.80 mmol), prepared using procedures similar to those described in US 7,019,033, in DMF (4 mL) was added PyBOP (416 mg, 0.80 mmol) and triethylamine (223 μL, 1.6 mmol). Finally, the unpurified 3-(2-hydroxyethyl)azetidin-3-ol was added, and the resulting mixture was stirred at rt for 16 h. Water and ethyl acetate were added, and the layers were separated. The aqueous phase was extracted with once more

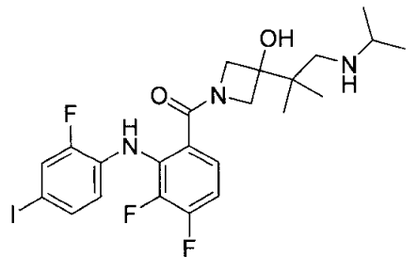
with ethyl acetate. The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography, eluting with ethyl acetate, to provide 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(2-hydroxyethyl)azetidin-3-ol as a colorless oil (303 mg, 0.62 mmol, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (s, 1H), 7.39 (dd, 1H), 7.32 (m, 1H), 7.13 (m, 1H), 6.81 (m, 1H), 6.60 (m, 1H), 4.37 (br s, 1H), 4.28 (br m, 4H), 3.94 (br s, 2H), 2.19 (br s, 1H), 2.02 (m, 2H); MS (EI) for $C_{18}H_{16}F_3IN_2O_3$: 491 (M-H).

[00311] A solution of oxalyl chloride (13 μL, 0.15 mmol) in dichloromethane (1 mL) was cooled to -78 °C, and DMSO (22 μL, 0.31 mmol) was then added. To this mixture was added 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(2-hydroxyethyl)azetidin-3-ol (67.8 mg, 0.14 mmol) as a suspension in dichloromethane (1 mL). After stirring at -78 °C for 10 min, triethylamine (78 μL, 0.56 mmol) was added and the mixture was allowed to warm to rt. The solution was diluted with dichloromethane, and washed with 0.5 N HCl. The aqueous phase wash then extracted with dichloromethane. The organic extracts were combined, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by flash chromatography to provide [1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]acetaldehyde as a white solid (22.1 mg, 0.045 mmol, 32% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.82 (s, 1H), 8.46 (s, 1H), 7.39 (m, 1H), 7.33 (m, 1H), 7.11 (m, 1H), 6.81 (m, 1H), 6.61 (m, 1H), 4.32-3.96 (br m, 4H), 3.41 (t, 2H), 3.07 (s, 1H); MS (EI) for $C_{18}H_{14}F_3IN_2O_3$: 491 (MH^+).

[00312] To a solution of [1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]acetaldehyde (38.0 mg, 0.078 mmol) in 1,2-dichloroethane (1 mL) was added isopropylamine (27 μL, 0.31 mmol) followed by sodium triacetoxyborohydride (26 mg, 0.12 mmol). The mixture was stirred for 3 h before quenching with 1 drop of concentrated HCl. The quenched mixture was concentrated to dryness, and then purified by preparative HPLC to provide 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{2-[(1-methylethyl)amino]ethyl}azetidin-3-ol (21.5 mg) as a pale yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.54 (s, 1H), 7.57 (dd, 1H), 7.38 (dd, 1H), 7.31 (m, 1H), 7.17 (m, 1H), 6.67 (m, 1H), 4.02 (m, 1H), 3.89 (m, 2H), 3.71 (m, 1H), 2.70 (m, 1H), 2.63 (m, 2H), 1.86 (s, 3H), 1.75 (m, 2H), 0.97 (d, 6H); MS (EI) for $C_{21}H_{23}F_3IN_3O_2$: 534 (MH^+).

EXAMPLE 18

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{1,1-dimethyl-2-[(1-methylethyl)amino]ethyl}azetidin-3-ol



[00313] To a solution of 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-one (500 mg, 1.12 mmol), prepared using procedures similar to those described in Example 6, in dichloromethane (5 mL) cooled to 0 °C was added titanium tetrachloride (125 μL, 1.12 mmol). The dark brown solution was stirred at 0 °C for 45 minutes, followed by the addition of methyltrimethylsilyl dimethylketene acetal (550 μL, 2.24 mmol) at 0 °C. Upon addition the solution was allowed to warm to room temperature, and was stirred for 1 hour. The reaction mixture was then partitioned between saturated aqueous sodium bicarbonate and ethyl acetate. The aqueous portion was extracted twice using ethyl acetate. The combined organic portion was washed with water, brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a brown oil which was purified by column chromatography. Eluting with 10% diethyl ether in dichloromethane, the isolated product was concentrated *in vacuo* to afford 520 mg, 0.95 mmol (85%) of methyl 2-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]-2-methylpropanoate as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$): 8.34 (s, 1H), 7.38 (d, 1H), 7.31 (d, 1H), 7.13-7.08 (m, 1H), 6.85-6.77 (m, 1H), 6.63-6.56 (m, 1H), 4.26-4.20 (m, 2H), 4.13-4.09 (m, 1H), 4.00-3.93 (m, 1H), 3.70 (s, 3H), 1.23 (s, 6H). MS (EI) for $C_{21}H_{20}F_3IN_2O_4$: 547 (MH^+).

[00314] A solution of methyl 2-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]-2-methylpropanoate (520 mg, 0.95 mmol) in 4N aqueous potassium hydroxide (5 mL) was stirred at 50°C for 1 hour. Using concentrated aqueous hydrochloric acid, the reaction mixture was acidified to pH 5, and then partitioned with ethyl acetate. The aqueous portion was extracted twice using ethyl acetate, and the combined organic portion was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 300 mg, 0.56 mmol (59%) of 2-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]-2-methylpropanoic acid as a white solid. ^{1}H NMR (400 MHz, DMSO): 8.49 (s, 1H), 7.57-7.52

(m, 1H), 7.37-7.25 (m, 2H), 7.17-7.13 (m, 1H), 6.68-6.58 (m, 1H), 3.98-3.94 (m, 2H), 3.80-3.77 (m, 1H), 3.55-3.52 (m, 1H), 0.88 (s, 6H). MS (EI) for $C_{20}H_{18}F_3IN_2O_4$: 535 (MH^+).

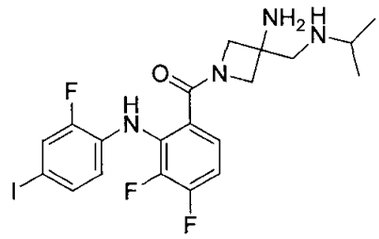
[00315] To solution of 2-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]-2-methylpropanoic acid (300 mg, 0.56 mmol) in tetrahydrofuran (5 mL) was added triethylamine (80 μL, 0.56 mmol), followed by PyBOP (295 mg, 0.56 mmol) and finally sodium borohydride (64 mg, 1.68 mmol). The mixture was stirred at room temperature for 1 hour. The reaction mixture was quenched by adding 20% aqueous citric acid, and then partitioned with ethyl acetate. The organic portion was washed with saturated aqueous sodium bicarbonate, brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a white solid which was purified by column chromatography. Eluting with 60% ethyl acetate in hexanes, the isolated product was concentrated *in vacuo* to afford 238 mg, 0.46 mmol (82%) of 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(2-hydroxy-1,1-dimethylethyl)azetidin-3-ol as a white solid. ^{1}H NMR (400 MHz, DMSO): 8.53 (s, 1H), 7.57 (d, 1H), 7.38-7.28 (m, 2H), 7.22-7.15 (m, 1H), 6.70-6.64 (m, 1H), 5.61 (s, 1H), 4.57 (br s, 1H), 4.30-4.27 (m, 1H), 4.18-4.15 (m, 1H), 3.80-3.77 (m, 1H), 3.68-3.64 (m, 1H), 3.25 (s, 2H), 0.76 (d, 6H); MS (EI) for $C_{20}H_{20}F_3IN_2O_3$: 521 (MH^+).

[00316] A mixture of 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(2-hydroxy-1,1-dimethylethyl)azetidin-3-ol (200 mg, 0.38 mmol) and Dess-Martin periodinane (240 mg, 0.57 mmol) in dichloromethane (2 mL) was stirred at room temperature for 2 hours. 10% aqueous sodium thiosulfate (2 mL), and saturated aqueous sodium bicarbonate (2 mL) was added and the mixture was stirred at room temperature for 15 minute. The mixture was partitioned and the aqueous layer was extracted twice using dichloromethane. The combined organic portion was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*, to afford a white solid which was purified by column chromatography. Eluting with 30% ethyl acetate in hexanes, the isolated product was concentrated *in vacuo* to afford 100 mg, 0.20 mmol (53%) of 2-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]-2-methylpropanal as a white solid, which was immediately dissolved in tetrahydrofuran (2 mL). To the solution was added isopropylamine (34 μL, 0.40 mmol), followed by triacetoxyborohydride (212 mg, 1.0 mmol). The solution was stirred at room temperature for 15 hours. The reaction mixture was concentrated *in vacuo* and partitioned between 20% aqueous citric acid and ethyl acetate. The aqueous portion was extracted twice using ethyl acetate, and the combined organic portion was washed with saturated aqueous sodium

bicarbonate, brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a yellow oil which was purified by preparative reverse phase HPLC. The isolated product was concentrated *in vacuo* to afford 50 mg, 0.07 mmol (36%) of 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{1,1-dimethyl-2-[(1-methylethyl)amino]ethyl}azetidin-3-ol acetate salt as a white solid. ^{1}H NMR (400 MHz, DMSO): 8.47 (br s, 1H), 7.55 (d, 1H), 7.36-7.29 (m, 2H), 7.22-7.15 (m, 1H), 6.68-6.63 (m, 1H), 4.17-4.08 (m, 2H), 3.76-3.73 (m, 1H), 3.56-3.52 (m, 1H), 2.58-2.51 (m, 1H), 2.45-2.37 (m, 2H), 0.92 (t, 6H), 0.78 (d, 6H); MS (EI) for $C_{23}H_{27}F_3IN_3O_2$: 562 (MH^+).

EXAMPLE 19

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1-methylethyl)amino]methyl}azetidin-3-amine



[00317] To a solution of the 1-(diphenylmethyl)-3-[(phenylmethyl)amino]azetidine-3-carbonitrile (0.80 g, 2.2 mmol), prepared using procedures similar to those described in Kozikowski and Fauq *Synlett* **1991,** *11,* 783-4, in ethanol (30 mL) was added solid sodium hydroxide (7.5 mmol), and the resulting mixture was stirred at room temperature for 3 days. Water (6 mL) was added to the reaction mixture and stirring was continued at 90 °C for 2 h. The pH of the reaction mixture was adjusted to 5 with concentrated hydrochloric acid and a white solid precipitated. The mixture was cooled , diluted with water (50 mL) and the solid was collected, washed with water then dried *in vacuo* to give the 1-(diphenylmethyl)-3-[(phenylmethyl)amino]azetidine-3-carboxylic acid (0.75g, 88% yield), MS (EI) for $C_{24}H_{24}N_2O_2$: 373 (MH^+).

[00318] To a mixture of 1-(diphenylmethyl)-3-[(phenylmethyl)amino]azetidine-3-carboxylic acid (0.50 g, 1.34 mmol), *N,N*-diisopropylethylamine (0.47 mL, 2.68 mmol) in DMF (3 mL) was added 1-benzotriazolyloxytripyrrolidinylphosphonium hexafluorophosphate (1.34g, 2.68 mol) and the resulting mixture was stirred at room temperature for 10 minutes. To this mixture was added 2-propylamine (0.22 mL, 2.68 mmol) and stirring was continued for 18 h. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with 2% aqueous citric acid, 5% lithium chloride, and brine solutions (50

mL each), dried over sodium sulfate, filtered and concentrated to give an oily residue which was purified by flash chromatography (silica gel, eluting with 15-25% ethyl acetate-hexane) to give 1-(diphenylmethyl)-*N*-(1-methylethyl)-3-[(phenylmethyl)amino]azetidine-3-carboxamide (0.51 g, 92% yield), MS (EI) for $C_{27}H_{31}N_3O$: 414 (MH^+).

[00319] To a solution of the 1-(diphenylmethyl)-*N*-(1-methylethyl)-3-[(phenylmethyl)amino]azetidine-3-carboxamide (0.40 g, 0.97 mmol) in tetrahydrofuran (10 mL) at room was added a solution of lithium aluminum hydride in tetrahydrofuran (1M, 2.90 mL, 2.90 mmol), and the resulting mixture was stirred at 50 °C for 3h. The reaction mixture was cooled to room temperature, quenched with 20% aqueous hydroxide solution (1 mL), diluted with ether (50 mL) and filtered. The filtrate was washed with brine solution (20 mL each), dried over sodium sulfate, filtered and concentrated to give an oily residue which was purified by flash chromatography (silica gel, eluting with 5% methanol-dichloromethane) to give 1-(diphenylmethyl)-3-{[(1-methylethyl)amino]methyl}-*N*-(phenylmethyl)azetidin-3-amine (0.35g, 90% yield), ^{1}H NMR (400 MHz, $CDCl_3$): 7.42-7.14 (m, 15H), 4.34 (s, 1H), 3.66 (s, 2H), 3.22-3.18 (d, 2H), 2.97 (s, 2H), 2.90-2.86(d, 2H), 2.68-2.62 (p, 1H), 1.09-1.07 (d, 6H); MS (EI) for $C_{27}H_{33}N_3$: 400 (MH^+).

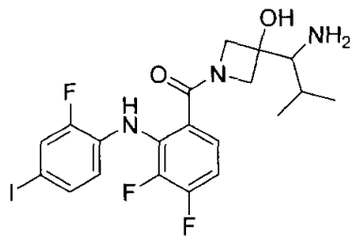
[00320] To a solution of the 1-(diphenylmethyl)-3-{[(1-methylethyl)amino]methyl}-*N*-(phenylmethyl)azetidin-3-amine (0.35 g , 0.88 mmol) in methanol was added a solution of hydrogen chloride in dioxane (4 molar solution, 0.96 mL, 4.40 mmol) and the resulting mixture was concentrated to give a white solid which was taken back into methanol. To this solution were added palladium hydroxide (20% on carbon, 0.50 g, 0.19 mmol) and the resulting mixture shaken at 50 psi in a Parr apparatus for 3h. The reaction mixture was filtered and concentrated to give a solid, which was washed with ether and dried *in vacuo* to give 3-{[(1-methylethyl)amino]methyl}azetidin-3-amine hydrochloride as a white solid (0.18 g, 81% yield). MS (EI) for $C_7H_{17}N_3$: 144 (MH^+).

[00321] To a mixture of the 3-{[(1-methylethyl)amino]methyl}azetidin-3-amine hydrochloride (20 mg, 0.079 mmol) in saturated sodium bicarbonate solution (1.0 mL) and dioxane (1.0 mL) was added 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoyl fluoride (31 mg, 0.079 mmol), prepared using procedures similar to those described in Reference 1, and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 x 5 mL). The combined extract was washed with water then brine solution (5 mL each), dried over sodium sulfate, filtered and concentrated to give an oily residue which was purified by reverse phase HPLC to afford 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1-

methylethyl)amino]methyl}azetidin-3-amine (15 mg, 37% yield). ^{1}H NMR (400 MHz, d_4-Methanol): 7.46-7.43 (dd, 1H), 7.35-7.33 (dd, 1H), 7.31-7.27 (m, 1H), 7.08-7.01 (dd, 1H), 6.63, 6.58 (td, 1H), 4.09-4.07 (d, 1H), 3.91-3.85 (dd, 2H), 3.76-3.73 (d, 1H). 2.80-2.74 (m, 1H), 2.73 (s, 2H), 1.07-1.05 (d, 6H); MS (EI) for $C_{20}H_{22}F_3IN_4O$: 519 (MH^+).

EXAMPLE 20

3-(1-amino-2-methylpropyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol



[00322] 1,1-Dimethylethyl 3-oxoazetidine-1-carboxylate (677.2 mg, 3.96 mmol), prepared using procedures similar to those described in Example 3, was taken into 2-methyl-1-ntropropane (5 mL) then cooled to 0 °C followed by addition of potassium *tert*-butoxide (444 mg, 3.96 mmol) and the resulting mixture was allowed to warm to room temperature over 30 minutes. The mixture was partitioned with ethyl acetate and 0.5 N aqueous hydrochloric acid then once with water and brine then dried over anhydrous magnesium sulfate. Filtration and concentration afforded a residue (1.5 g) that was further purified by silica gel flash chromatography using 3:1 hexanes:ethyl acetate as eluent to give 1,1-dimethylethyl 3-hydroxy-3-(2-methyl-1-nitropropyl)azetidine-1-carboxylate (730 mg, 67% yield) as a colorless crystalline solid. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.50 (d, 1H), 3.93 (dd AB, 2H), 3.85 (s, 2H), 3.58 (s, 1H), 2.54-2.48 (m, 1H), 1.44 (s, 9H), 1.04 (d, 6H).

[00323] 1,1-Dimethylethyl 3-hydroxy-3-(2-methyl-1-nitropropyl)azetidine-1-carboxylate (105 mg, 0.38 mmol) was taken into methanol (1 mL) followed by addition of 4 N anhydrous hydrogen chloride in dioxane (1 mL) and the acidic solution was allowed to stand for 15 minutes at room temperature then concentrated and dried *in vacuo* to an amorphous residue. 3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid (150 mg, 0.38 mmol), prepared using procedures similar to those described in US 7,019,033, was taken into DMF (0.7 mL) followed by addition of PyBOP (198 mg, 0.38 mmol) and the solution was allowed to stir for 10 minutes at room temperature. The above amine hydrochloride salt and DIPEA (190 μL, 1.1 mmol) in DMF solution (0.7 mL) was added and the mixture was allowed to stir for one hour at room temperature. The mixture was partitioned with ethyl acetate and 0.5 N aqueous

hydrochloric acid and the organic phase washed three times with water then brine and dried over anhydrous magnesium sulfate. Filtration and concentration afforded a residue that was further purified by silica gel flash chromatography using 1.5:1 hexanes:ethyl acetate as eluent to give 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(2-methyl-1-nitropropyl)azetidin-3-ol (189 mg, 90% yield) as an amorphous solid. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.41 (br s, 1H), 7.41 (dd, 1H), 7.34 (d, 1H), 7.09 (br m, 1H), 6.81 (q, 1H), 6.65-6.60 (m, 1H), 4.49 (d, 1H), 4.15-4.09 (m, 4H), 3.66 (s, 1H), 2.56-2.46 (m, 1H) 1.03 (d, 6H).

[00324] 1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(2-methyl-1-nitropropyl)azetidin-3-ol (189 mg, 0.34 mmol) was taken into 4:1 THF:water (5 mL) followed by addition of iron powder (192 mg, 3.4 mmol) and ammonium formate (429 mg, 6.8 mmol) and the mixture was heated to reflux. After four hours additional aliquots of iron powder (192 mg, 3.4 mmol) and ammonium formate (429 mg, 6.8 mmol) were added and the mixture was allowed to reflux an additional 12 hours. The mixture was cooled to room temperature and diluted with ethyl acetate then filtered. The filtrate was partitioned with ethyl acetate and saturated aqueous sodium bicarbonate then the organic layer washed with brine and dried over anhydrous sodium sulfate. Filtration and concentration afforded a residue that was further purified by silica gel flash chromatography using ethyl acetate to 10% methanol in dichloromethane as eluents to give a residue (36.5 mg) that was further purified by preparative reverse phase HPLC to give 3-(1-amino-2-methylpropyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol trifluoroacetate salt (7.9 mg) as a colorless amorphous solid after lyophillization of the combined pure fractions. ^{1}H-NMR (400 MHz, D_6-DMSO): 8.63 (s, 1H), 7.58 (dd, 1H), 7.37 (d, 1H), 7.35-7.31 (m, 1H), 7.17 (q, 1H), 6.71-6.66 (m, 1H), 4.23 (dd, 1H), 4.03 (dd, 1H), 3.80 (dd, 1H), 3.66 (dd, 1H), 2.34 (dd, 1H), 1.79-1.70 (m, 1H), 0.84-0.77 (m, 6H). MS (EI) for $C_{20}H_{21}F_3IN_3O_2$: 520 (MH^+).

[00325] Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, the following compounds of the invention were prepared:

EXAMPLE 20(a). 3-(1-aminoethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8.56 (s, 1H), 7.91 (br s, 2H), 7.58 (d, 1H), 7.39 (d, 1H), 7.36-7.32 (m, 1H), 7.24-7.17 (m, 1H), 6.72-6.65 (m, 2H), 4.33-4.29 (m, 1H), 4.23-4.19 (m, 1H), 4.16-4.14 (m, 1H), 4.07-3.94 (m, 1H), 3.82-3.77 (m, 1H), 3.51-3.45 (m, 1H), 1.15-1.12 (m, 1H), 1.10-1.08 (m, 1H). MS (EI) for $C_{18}H_{17}F_3IN_3O_2$: 492 (MH^+).

EXAMPLE 20(b). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[1-(ethylamino)ethyl]azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8.61 (d, 1H), 8.50 (s, 1H), 8.20 (s, 1H), 7.59 (d, 1H), 7.39 (d, 1H), 7.36-7.32 (m, 1H), 7.24-7.17 (m, 1H), 6.82 (s, 1H), 6.74-6.67 (m, 1H), 4.38 (d, 1H), 4.27 (d, 1H), 4.18 (d, 1H), 4.06 (d, 2H), 3.99 (d, 1H), 3.89 (d, 1H), 3.82 (d, 1H), 3.49-3.43 (m, 1H), 3.04-2.80 (m, 4H), 1.21-1.12 (m, 6H). MS (EI) for $C_{20}H_{21}F_3IN_3O_2$: 520 (MH^+).

EXAMPLE 20(c). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-nitroethyl)azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8.57 (d, 1H), 7.58 (d, 1H), 7.38 (d, 1H), 7.37-7.33 (m, 1H), 7.22-7.17 (m, 1H), 6.73-6.66 (m, 1H), 6.57 (s, 1H), 5.06-4.97 (m, 1H), 4.54 (d, 0.5H), 4.37 (d, 0.5 H), 4.29 (d, 0.5H), 4.14 (d, 0.5 H), 4.05 (d, 0.5 H), 3.95 (d, 0.5H), 3.86 (d, 0.5H), 3.80 (d, 0.5H), 1.44-1.38 (m, 3H). MS (EI) for $C_{18}H_{16}F_3IN_3O_4$: 523 (MH^+).

EXAMPLE 20(d). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[1-(methylamino)ethyl]azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8.63-8.55 (m, 1H), 8.44-8.23 (m, 1H), 7.79 (br s, 1H), 7.60 (d, 1H), 7.39 (d, 1H), 7.36-7.31 (m, 1H), 7.24-7.17 (m, 1H), 6.82 (br s, 0.5H), 6.73-6.65 (m, 1H), 4.38-3.77 (m, 4H), 1.18-1.07 (m, 3H). MS (EI) for $C_{19}H_{19}F_3IN_3O_2$: 505 (M^+).

EXAMPLE 20(e). methyl {1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}carbamate: ^{1}H NMR (400 MHz, d_6-DMSO): 8.59 (d, 1H), 7.58 (d, 1H), 7.41-7.05 (m, 4H), 6.72-6.64 (m, 1H), 5.84 (d, 1H), 4.20 (d, 0.5H), 4.08-4.04 (m, 1H), 3.92-3.85 (m, 1.5H), 3.76-3.71 (m, 1H), 3.69-3.63 (m, 1H), 3.46 (d, 2H), 0.99-0.95 (m, 3H). MS (EI) for $C_{20}H_{19}F_3IN_3O_4$: 550 (MH^+).

EXAMPLE 20(f). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[1-(dimethylamino)ethyl]azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 9.45 (s, 1H), 8.61 (d, 1H), 7.60 (d, 1H), 7.39 (d, 1H), 7.38-7.33 (m, 1H), 7.24-7.18 (m, 1H), 7.05 (s, 1H), 6.73-6.66 (m, 1H), 4.48 (d, 0.5H), 4.36 (d, 0.5 H), 4.26 (d, 0.5H), 4.16-4.11 (m, 1H), 4.00-3.94 (m, 1H), 3.86 (d, 0.5H), 3.60-3.54 (m, 1H), 2.75-2.70 (m, 3H), 2.66-2.62 (br s, 3H), 1.22 (dd, 3H). MS (EI) for $C_{20}H_{21}F_3IN_3O_2$: 520 (MH^+).

EXAMPLE 20(g). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-nitropropyl)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7.46 (m, 1H), 7.35 (m, 1H), 7.28 (m, 1H), 7.07 (m, 1H), 6.61 (m, 1H), 4.65 (m, 1H), 4.44 (m, 1H), 4.25 (m, 1H), 4.02 (m, 1H), 3.86 (m, 1H), 2.04 (m, 1H), 1.76 (m, 1H), 0.94 (m, 3H). MS (EI) for $C_{19}H_{17}F_3IN_3O_4$: 536 (MH^+).

EXAMPLE 20(h). 3-(1-aminopropyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7.45 (m, 1H), 7.34 (m, 1H), 7.28 (m, 1H), 7.05 (m, 1H), 6.61 (m, 1H), 4.21 (m, 1H), 4.09-3.86 (m, 2H), 3.78 (m, 1H), 2.63 (m, 1H), 1.50 (m, 1H), 1.24 (m, 1H), 0.98 (m, 3H). MS (EI) for $C_{19}H_{19}F_3IN_3O_2$: 506 (MH^+).

EXAMPLE 20(i). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[1-(ethylamino)propyl]azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7.45 (m, 1H), 7.34 (m, 1H), 7.28 (m, 1H), 7.05 (m, 1H), 6.61 (m, 1H), 4.23 (m, 1H), 4.02 (m, 1H), 3.90 (m, 1H), 3.79 (m, 1H), 2.70 (m, 1H), 2.54 (m, 1H), 1.53 (m, 1H), 1.40 (m, 1H), 1.05 (m, 3H), 0.95 (m, 3H). MS (EI) for $C_{21}H_{23}F_3IN_3O_2$: 534 (MH^+).

EXAMPLE 20(j). 3-[1-(diethylamino)propyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7.44 (m, 1H), 7.33 (m, 1H), 7.27 (m, 1H), 7.07 (m, 1H), 6.60 (m, 1H), 4.21 (m, 1H), 4.10 (m, 1H), 4.03-3.70 (m, 2H), 2.71-2.45 (m, 5H), 1.67 (m, 1H), 1.49 (m, 1H), 0.94 (m, 9H). MS (EI) for $C_{23}H_{27}F_3IN_3O_2$: 562 (MH^+).

EXAMPLE 20(k). 3-[amino(phenyl)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol): MS (EI) for $C_{23}H_{19}F_3IN_3O_2$: 554 (MH^+).

EXAMPLE 20(m). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(3-methyl-1-nitrobutyl)azetidin-3-ol): ^{1}H NMR (400MHz, $CDCl_3$): 8.38 (s, 1H), 7.39 (dd, 1H), 7.34-7.31 (m, 1H), 7.14-7.10 (m, 1H), 6.84-6.77 (m, 1H), 6.63-6.58 (m, 1H), 4.68 (dd, 1H), 4.23-4.04 (br m, 4H), 2.13 (t, 2H), 1.64-1.44 (br m, 3H), 0.93 (d, 6H); MS (EI) for $C_{21}H_{21}F_3IN_3O_4$: 564 (MH^+).

EXAMPLE 20(n). 3-(1-aminobutyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.48-7.43 (d, 1H), 7.38-7.33 (d, 1H), 7.32-7.26 (m, 1H), 7.09-7.00 (q, 1H), 6.66-6.58 (t, 1H), 4.33-4.22 (d, 1H), 4.13-3.81 (m, 3H), 3.17-3.09 (t, 1H), 1.93-1.89 (s, 3H), 1.89-1.82 (t, 3H), 1.56-1.24 (m, 4H), 0.97-0.88 (t, 3H); MS (EI) for $C_{20}H_{21}F_3IN_3O_2$: 520 (MH^+).

EXAMPLE 20(o). 3-(1-aminocyclopentyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, $CDCl_3$): 8.27-8.21 (s, 1H), 7.42-7.36 (d, 1H), 7.34-7.29 (d, 1H), 7.15-7.09 (t, 1H), 7.09-7.01 (q, 1H), 6.88-6.79 (q, 1H), 6.63-6.53 (m, 1H), 4.18-3.92 (m, 4H), 2.12-2.08 (s, 3H), 2.06-1.70 (m, 7H), 0.92-0.68 (m, 4H); MS (EI) for $C_{21}H_{21}F_3IN_3O_2$: 532 (MH^+).

EXAMPLE 20(p). *N*-{1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}acetamide: ^{1}H NMR (400

MHz, CDCl3): 8.42 (s, 1H), 7.41-7.38 (dd, 1H), 7.34-7.32 (dt, 1H), 7.12-7.09 (m, 1H), 6.85-6.78 (m, 1H), 6.63-6.57 (m, 1H), 5.76 (b, 1H), 4.28-3.98 (m, 5H), 2.00 (s, 3H), 1.20-1.19 (d, 3H); MS (EI) for $C_{20}H_{19}F_3IN_3O_3$: 534 (MH^+).

EXAMPLE 20(q). (2R)-*N*-{1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanamide: ^{1}H NMR (400 MHz, CDCl3): 8.47 (s, 1H), 7.45-7.40 (m, 5H), 7.33-7.31 (m, 1H), 7.21-7.19 (m, 1H), 7.12-7.05 (m, 1H), 6.85-6.76 (m, 1H), 6.63-6.58 (m, 1H), 4.20-3.99 (m, 5H), 3.36 (s, 1.5H), 3.34 (s,1.5H), 1.27-1.25 (d, 1.5H), 1.24-1.22 (d, 1.5H); MS (EI) for $C_{28}H_{24}F_6IN_3O_4$: 708 (MH^+).

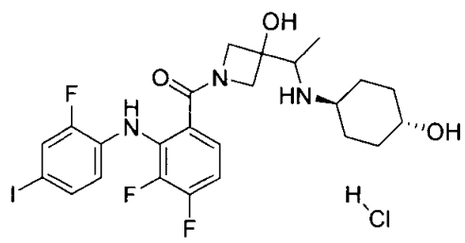
EXAMPLE 20(r). (2R)-*N*-{(1R)-1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanamide: ^{1}H NMR (400 MHz, CDCl3): 8.49 (s, 1H), 7.46-7.391 (m, 5H), 7.33-7.31 (m, 1H), 7.21-7.16 (m, 1H), 7.14-7.10 (m, 1H), 6.85-6.79 (m, 1H), 6.64-6.58 (m, 1H), 4.24-4.00 (m, 5H), 3.35 (s, 3H), 1.25-1.23 (d, 3H); MS (EI) for $C_{28}H_{24}F_6IN_3O_4$: 708 (MH^+).

EXAMPLE 20(s). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-methyl-1-nitroethyl)azetidin-3-ol: ^{1}H NMR (400 MHz, CDCl3): 8.28 (s, 1H), 7.41-7.38 (dd, 1H), 7.34-7.32 (dt, 1H), 7.14-7.10 (m, 1H), 6.87-6.81 (m, 1H), 6.64-6.59 (m, 1H), 4.33-4.15 (m, 4H), 1.64 (s, 6H); MS (EI) for $C_{19}H_{17}F_3IN_3O_4$: 536 (MH^+).

EXAMPLE 20(t). 3-(1-amino-1-methylethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol: ^{1}H NMR (400 MHz, CDCl3): 8.30 (s, 1H), 7.39-7.36 (dd, 1H), 7.32-7.30 (dt, 1H), 7.13-7.09 (m, 1H), 6.85-6.79 (m, 1H), 6.62-6.56 (m, 1H), 4.25-3.97 (m, 4H), 1.14 (s, 6H); MS (EI) for $C_{19}H_{19}F_3IN_3O_2$: 506 (MH^+).

EXAMPLE 21

1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{1-[(*trans*-4-hydroxycyclohexyl)amino]ethyl}azetidin-3-ol hydrochloride



[00326] Potassium *tert*-butoxide (1.672 g, 14.9 mmol) and ethyltriphenylphosphonium bromide (5.538 g, 14.9 mmol) were stirred in ether (30 mL) at amibient for 1 h.

1,1-Dimethylethyl 3-oxoazetidine-1-carboxylate (954 mg, 6.0 mmol), prepared using procedures similar to those described in Example 3, was added and the mixture was 35 °C for 4.5 h. Mixture was filtered through celite and the solid was washed with ether. The filtrate was washed with water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, 20% ether in hexanes) gave 1,1-dimethylethyl 3-ethylideneazetidine-1-carboxylate (506 mg, 2.76 mmol, 49% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 5.37-5.28 (m, 1H), 4.47-4.39 (m, 4H), 1.56-1.51 (m, 3H), 1.45 (s, 9H).

[00327] 1,1-Dimethylethyl 3-ethylideneazetidine-1-carboxylate (506 mg, 2.76 mmol), and 4-methylmorpholine *N*-oxide (1.04 g, 8.89 mmol) were dissolved in acetone / water (4:1; 30 mL) and osmium tetroxide (2.5 wt.% in *t*-butanol; 0.2 mL) was added. The solution was stirred at ambient for 5 days, then was quenched with saturated sodium bisulfite (2 mL) and concentrated *in vacuo*. The residue was partitioned between ethyl acetate and brine. The aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, ethyl acetate) gave 1,1-dimethylethyl 3-hydroxy-3-(1-hydroxyethyl)azetidine-1-carboxylate (375 mg, 1.73 mmol, 63% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 4.00-3.77 (m, 5H), 2.65 (br s, 1H), 1.86, (br s, 1H), 1.44 (s, 9H), 1.25 (d, 3H).

[00328] 1,1-Dimethylethyl 3-hydroxy-3-(1-hydroxyethyl)azetidine-1-carboxylate (200 mg, 0.922 mmol) was dissolved in methanol (5 mL) and 4 N hydrochloric acid in dioxane (1 mL, 4 mmol) was added. The mixture was refluxed for 15 minutes and then was concentrated *in vacuo* to afford 3-(1-hydroxyethyl)azetidin-3-ol hydrochloride (0.922 mmol).

[00329] 3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid (362 mg, 0.921 mmol), prepared using procedures similar to those described in US 7,019,033, 4-(dimethylamino)pyridine (337 mg, 2.76 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (212 mg, 1.11 mmol) were dissolved in DMF (3 mL). The mixture was stirred at ambient for 5 minutes and then 3-(1-hydroxyethyl)azetidin-3-ol hydrochloride (0.922 mmol) in DMF (2 mL) was added and the mixture was stirred for 15 h. The mixture was partitioned between ethyl acetate and 5% lithium chloride. The organic portion was washed with 20% citric acid, saturated sodium bicarbonate and brine, then was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, 80% ethyl acetate in hexanes) gave 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-hydroxyethyl)azetidin-3-ol (296 mg, 0.602 mmol, 65% yield): MS (EI) for $C_{18}H_{16}F_3IN_2O_3$: 493 (MH^+).

[00330] 1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-hydroxyethyl)azetidin-3-ol (267 mg, 0.543 mmol), was dissolved in dichloromethane (10 mL) and treated with 4-(dimethylamino)pyridine (80 mg, 0.661 mmol) and 2,4,6-triisopropylbenzenesulfonyl chloride (183 mg, 0.604 mmol) at ambient for 15 h. Triethylamine (0.076 mL, 0.545 mmol) was added and the mixture was stirred at ambient for 3 h and then at 35 °C for 4 h and then at ambient for a furhter 15 h. 2,4,6-Triisopropylbenzenesulfonyl chloride (110 mg, 0.363 mmol) was added and the mixture was stirred at 35 °C for 3 h and then 4-(dimethylamino)pyridine (80 mg, 0.661 mmol) was added and the mixture was stirred at 35 °C for 2 h. 2,4,6-Triisopropylbenzenesulfonyl chloride (303 mg, 1.0 mmol) was added and the mixture was stirred at 35 °C for a furhter 18 h. The mixture was adsorbed on to silica and purified by column chromatography (silica gel, 30-50% ethyl acetate in hexanes) to give 1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl 2,4,6-tris(1-methylethyl)benzenesulfonate (201 mg, 0.265 mmol, 49% yield): MS (EI) for $C_{33}H_{38}F_3IN_2O_5S$: 759 (MH^+).

[00331] 1-[1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl 2,4,6-tris(1-methylethyl)benzenesulfonate (194 mg, 0.256 mmol) was dissolved in tetrahydrofuran (2 mL) and was cooled to 0 °C. Sodium hydride (60 wt% dispersion in oil; 31 mg, 0.775 mmol) was added and the mixture was stirred at 0 °C for 15 minutes. The mixture was quenched with saturated sodium bicarbonate solution and partitioned with ethyl acetate. The aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, 50% ethyl acetate in hexanes) gave 2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)-6-[(2-methyl-1-oxa-5-azaspiro[2.3]hex-5-yl)carbonyl]aniline (120 mg, 0.253 mmol, 99% yield): MS (EI) for $C_{18}H_{14}F_3IN_2O_2$: 475 (MH^+).

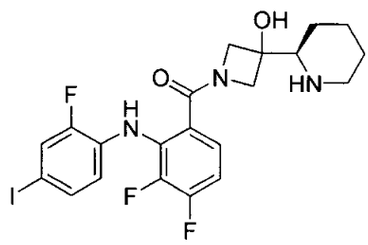
[00332] 2,3-Difluoro-*N*-(2-fluoro-4-iodophenyl)-6-[(2-methyl-1-oxa-5-azaspiro[2.3]hex-5-yl)carbonyl]aniline (50 mg, 0.105 mmol) was dissolved in dimethylsulfoxide (0.8 mL) and treated with *trans*-4-cyclohexanolamine (70 mg, 0.609 mmol) with 100 W microwave power at 100 °C for 45 minutes. The mixture was purified by reverse phase HPLC and the clean fractions were combined, neutralized with saturated sodium bicarbonate solution and the organic solvent was removed *in vacuo*. The remaining aqueous residue was extracted twice with ethyl acetate. The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give a residue which was

treated with aqueous hydrochloric acid and then was lyophilized to afford 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{1-[(*trans*-4-hydroxycyclohexyl)amino]ethyl}azetidin-3-ol hydrochloride (36 mg, 0.058 mmol, 55% yield): ^{1}H NMR (400 MHz, d_6-DMSO): 8.61 (br s, 0.5H), 8.55 (br s, 0.5H), 8.49-8.33 (m, 1H), 8.08-7.90 (m, 1H), 7.59 (dd, 1H), 7.39 (br d, 1H), 7.37-7.30 (m, 1H), 7.21 (br q, 1H), 6.81 (br d, 1H), 6.77-6.65 (m, 1H), 4.20 (br d, 1H), 4.09-4.02 (m, 1H), 3.97 (br d, 1H), 3.93-3.80 (m, 1H), 3.62-3.47 (m, 1H), 3.03-2.90 (m, 1H), 2.07-1.93 (m, 2H), 1.93-1.77 (m, 2H), 1.54-1.06 (m, 8H); MS (EI) for $C_{24}H_{27}F_3IN_3O_3$: 590 (MH^+).

[00333] EXAMPLE 21(a). Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, the following compound of the invention was prepared: 1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{1-[(1,1-dimethylethyl)amino]ethyl}azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8.63 (br s, 0.4H), 8.53 (br s, 0.6H), 7.56 (dt, 1H), 7.40-7.34 (m, 1H), 7.32-7.26 (m, 1H), 7.25-7.13 (m, 1H), 6.72-6.62 (m, 1H), 5.43 (br s, 1H), 4.14-3.56 (m, 4H), 2.69-2.53 (m, 1H), 1.00-0.85 (br, 12H); MS (EI) for $C_{22}H_{25}F_3IN_3O_2$: 548 (MH^+).

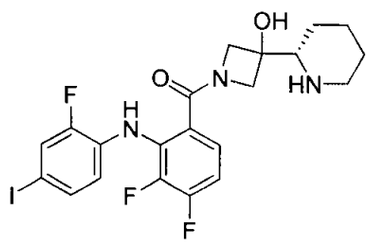
EXAMPLE 22(a) and 22(b)

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2R)-piperidin-2-yl]azetidin-3-ol



and

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2S)-piperidin-2-yl]azetidin-3-ol



[00334] To a solution of 1,1-dimethylethyl 2-(3-hydroxy-1-{[(phenylmethyl)oxy]carbonyl}azetidin-3-yl)piperidine-1-carboxylate (368 mg, 0.94 mmol), prepared using procedures similar to those described in Reference 5, in dichloromethane (5 mL) was added DMAP (115 mg, 0.94 mmol) and the resulting solution was cooled to 0°C. (*R*)-(-)-α-Methoxy-α-trifluoromethylphenylacetyl chloride (105 μL, 0.56 mmol) was added to the solution by syringe and the mixture was allowed to warm to room temperature then stirred an additional 12 hours. The solution was then partitioned with saturated aqueous soldium bicarbonate and the organic phase dried over anhydrous magnesium sulfate then filtered and concentrated to an oily residue. Silica gel flash chromatography using hexanes:ethyl acetate 3:1 as eluent afforded the less polar 1,1-dimethylethyl (2*R*)-2-(1-{[(phenylmethyl)oxy]carbonyl}-3-{[(2*R*)-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanoyl]oxy}azetidin-3-yl)piperidine-1-carboxylate (27.5 mg, 5% yield), the more polar 1,1-dimethylethyl (2*S*)-2-(1-{[(phenylmethyl)oxy]carbonyl}-3-{[(2*R*)-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanoyl]oxy}azetidin-3-yl)piperidine-1-carboxylate (105 mg, 19% yield) and starting material (253 mg, 69% recovery).

[00335] The starting material thus recovered was taken into dichloromethane (3 mL) followed by addition of DMAP (115 mg, 0.94 mmol) and (*R*)-(-)-α-methoxy-α-trifluoromethylphenylacetyl chloride (105 μL, 0.56 mmol) and the mixture was allowed to stir at room temperature over 12 hours. Proceeding as before afforded combined 1,1-dimethylethyl (2R)-2-(1-{[(phenylmethyl)oxy]carbonyl}-3-{[(2*R*)-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanoyl]oxy}azetidin-3-yl)piperidine-1-carboxylate (46.6 mg, 8% yield), the more polar 1,1-dimethylethyl (2*S*)-2-(1-{[(phenylmethyl)oxy]carbonyl}-3-{[(2*R*)-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanoyl]oxy}azetidin-3-yl)piperidine-1-carboxylate (228 mg, 41% yield) and starting material (100.8 mg, 27% recovery).

[00336] The starting material thus recovered was taken into tetrahydrofuran:dichloromethane (1:1, 2 mL) followed by addition of DMAP (47 mg, 0.39 mmol) and (R)-(-)-α-methoxy-α-trifluoromethylphenylacetyl chloride (80 μL, 0.43 mmol) and the mixture was heated to 60 °C over 12 hours. Proceeding as before afforded combined less polar 1,1-dimethylethyl (2*R*)-2-(1-{[(phenylmethyl)oxy]carbonyl}-3-{[(2*R*)-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanoyl]oxy}azetidin-3-yl)piperidine-1-carboxylate (144 mg, 26 % yield). The chiral ester derivatives thus obtained were again subject to silica gel flash chromatography using hexanes:ethyl acetate 3:1 as eluent to give the pure less polar 1,1-dimethylethyl (2*R*)-2-(1-{[(phenylmethyl)oxy]carbonyl}-3-{[(2*R*)-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanoyl]oxy}azetidin-3-yl)piperidine-1-carboxylate (122.8 mg, 22%

yield) and the more polar 1,1-dimethylethyl (2*S*)-2-(1-{[(phenylmethyl)oxy]carbonyl}-3-{[(2*R*)-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanoyl]oxy}azetidin-3-yl)piperidine-1-carboxylate (177.6 mg, 32% yield) both as colorless amorphous residues.

[00337] 1,1-Dimethylethyl (2*R*)-2-(1-{[(phenylmethyl)oxy]carbonyl}-3-{[(2*R*)-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanoyl]oxy}azetidin-3-yl)piperidine-1-carboxylate (122.8 mg, 0.21 mmol) was taken into methanol (4 mL) followed by addition of 1M aqueous sodium hydroxide (1 mL) and the resulting solution was stirred for one hour at room temperature. The solution was then partitioned with ethyl acetate and 1N aqueous hydrochloric acid. The organic layer was washed with brine, dried over anhydrous magnesium sulfate then filtered and concentrated. The residue was purified by silica gel flash chromatography using hexanes:ethyl acetate 2:1 to give 1,1-dimethylethyl (2*R*)-2-(3-hydroxy-1-{[(phenylmethyl)oxy]carbonyl}azetidin-3-yl)piperidine-1-carboxylate (60.8 mg, 81% yield) a colorless amorphous solid. 1,1-dimethylethyl (2*S*)-2-(3-hydroxy-1-{[(phenylmethyl)oxy]carbonyl}azetidin-3-yl)piperidine-1-carboxylate (87.4 mg, 75% yield) was prepared analogously.

[00338] 1,1-Dimethylethyl (2*R*)-2-(3-hydroxy-1-{[(phenylmethyl)oxy]carbonyl}azetidin-3-yl)piperidine-1-carboxylate (60.8 mg, 0.16 mmol) and 10% Pd/C (30 mg) were taken into methanol (2 mL) and the mixture hydrogenated at ambient pressure for one hour. The suspension was then filtered through a celite pad and concentrated then dried *in vacuo* to a colorless solid. The solid amine was taken into THF (1 mL) followed by addition of DIPEA (42 μL, 0.24 mmol) and 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoyl fluoride (63 mg, 0.16 mmol), prepared using procedures similar to those described in Reference 1, and the mixture stirred at room temperature for 30 minutes. The reaction mixture was partitioned with ethyl acetate and 1 N aqueous hydrochloric acid and the organic layer washed with brine, dried over anhydrous magnesium sulfate then filtered and concentrated. Purification of the residue by silica gel flash chromatography using hexanes:ethyl acetate 3:2 as eluent afforded 1,1-dimethylethyl (2*R*)-2-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]piperidine-1-carboxylate (74.9 mg, 74% yield) as an amorphous solid. 1,1-Dimethylethyl (2*R*)-2-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]piperidine-1-carboxylate ^{1}H NMR (400 MHz, $CDCl_3$): 8.53 (br s, 0.5H), 8.40 (br s, 0.5H), 7.41-7.38 (dd, 1H), 7.34-7.31(dt, 1H), 7.17-7.14 (m, 1H), 6.86-6.79 (m, 1H), 6.63-6.587 (m, 1H), 4.24-3.90 (m, 4H), 3.37-3.23 (m, 1H), 2.90-2.80 (m, 1H), 1.85-1.54 (m, 7H), 1.43 (s, 9H); MS (EI) for $C_{26}H_{29}F_3IN_3O_4$: 576 ($M-C_4H_9^+$).

[00339] 1,1-dimethylethyl (2*R*)-2-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]piperidine-1-carboxylate (74.9 mg, 0.12 mmol) was taken into methanol (1 mL) followed by addition of 4 N HCl in dioxane (1 mL) and the solution was stirred at room temperature for one hour. The solution was then concentrated and the residue partitioned with chloroform and saturated aqueous sodium bicarbonate. The organic layer was washed with brine, dried over anhydrous sodium sulfate then filtered and concentrated. Purification of the residue by silica gel flash chromatography using ethyl acetate then concentrated aqueous ammonia in chloroform and methanol (0.1:10:1) as eluents afforded 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2*R*)-piperidin-2-yl]azetidin-3-ol (57.3 mg) as a colorless amorphous solid. The free base was taken into methanol (1 mL) then brought to about pH 1 by addition of 4 N HCl in dioxane and the solution concentrated. The residue was triturated with ethyl ether to afford a suspension. The solid was collected by filtration to afford 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2*R*)-piperidin-2-yl]azetidin-3-ol hydrochloride salt (49 mg, 72% yield) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): 8.43-8.39 (d, 1H), 7.41-7.38 (dd, 1H), 7.33-7.31(dt, 1H), 7.14-7.10 (m, 1H), 6.84-6.80 (m, 1H), 6.63-6.57 (m, 1H), 4.12-3.99 (m, 4H), 3.10-3.08 (d, 1H), 2.72-2.69 (d, 1H), 2.64-2.62 (m, 1H), 1.61-1.58 (m, 2H), 1.36-1.16 (m, 4H); MS (EI) for $C_{21}H_{21}F_3IN_3O_2$: 532 (MH^+).

[00340] Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, the following compounds of the invention were prepared:

EXAMPLE 22(c). 1,1-dimethylethyl (2S)-2-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]piperidine-1-carboxylate: ^{1}H NMR (400 MHz, $CDCl_3$): 8.52 (br s, 0.5H), 8.39 (br s, 0.5H), 7.41-7.38 (dd, 1H), 7.34-7.31(dt, 1H), 7.17-7.12 (m, 1H), 6.85-6.79 (m, 1H), 6.63-6.57 (m, 1H), 4.25-3.88 (m, 4H), 3.34-3.26 (m, 1H), 2.80-2.90 (m, 1H), 1.85-1.54 (m, 7H), 1.43 (s, 9H); MS (EI) for $C_{26}H_{29}F_3IN_3O_4$: 576 ($M-C_4H_9^+$).

EXAMPLE 22(d). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2S)-piperidin-2-yl]azetidin-3-ol hydrochloride: ^{1}H NMR (400 MHz, d_4-Methanol): 7.49-7.46 (dd, 1H), 7.37-7.35(dt, 1H), 7.35-7.30 (m, 1H), 7.10-7.04 (m, 1H), 6.64-6.59 (m, 1H), 4.39-4.32 (dd, 1H), 4.21-4.18 (dd, 1H), 4.13-4.07 (m, 1H), 3.97-3.88 (dd, 1H), 3.57-3.32 (m, 1H), 3.02-2.96 (dd,1H), 1.90-1.50 (m, 7H); MS (EI) for $C_{21}H_{21}F_3IN_3O_2$: 532 (MH^+).

EXAMPLE 22(e). 1-({2-[(4-bromo-2-chlorophenyl)amino]-3,4-difluorophenyl}carbonyl)-3-piperidin-2-ylazetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.56 (d, 1H), 7.29-

7.38 (m, 2H), 7.08-7.16 (m, 1H), 6.64-6.70 (m, 1H), 4.30-4.40 (m, 1H), 4.18-4.26 (m, 1H), 4.04-4.14 (m, 1H), 3.90-4.00 (m, 1H), 3.16-3.26 (m, 2H), 2.86-2.96 (m, 1H), 1.91 (s, 3H), 1.76-1.88 (m, 3H), 1.44-1.64 (m, 3H). MS (EI) for $C_{21}H_{21}BrClF_2N_3O_2$: 500 (M-H).

EXAMPLE 22(f). 1-({2-[(4-bromo-2-fluorophenyl)amino]-3,4-difluorophenyl}carbonyl)-3-piperidin-2-ylazetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, DMSO): 8.52 (br s, 1H), 7.50 (d, 1H), 7.35-7.15 (m, 3H), 6.88-6.79 (m, 1H), 4.15-3.96 (m, 1H), 3.84-3.78 (m, 1H), 3.68-3.63 (m, 1H), 2.95-2.88 (m, 1H), 2.48-2.40 (m, 2H), 1.71-1.42 (m, 3H), 1.25-1.14 (m, 2H), 1.03-0.90 (m, 1H); MS (EI) for $C_{21}H_{21}BrF_3N_3O_2$: 485 (MH^+).

EXAMPLE 22(g). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-pyrrolidin-2-ylazetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7.45 (dd, 1H), 7.37-7.31 (m, 1H), 7.30-7.25 (m, 1H), 7.13-6.99 (m, 1H), 6.67-6.54 (m, 1H), 4.20-4.09 (m,1H), 4.08-3.91 (m, 2H), 3.88-3.79 (m, 1H), 3.27 (t, 1H), 2.99-2.89 (m, 1H), 2.88-2.81 (m, 1H), 1.93-1.67 (m, 3H), 1.55-1.42 (m, 1H). MS (EI) for $C_{20}H_{19}F_3IN_3O_2$: 518 (MH^+)

EXAMPLE 22(h). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-methylpyrrolidin-2-yl)azetidin-3-ol acetate (salt): ^{1}H NMR (400 MHz, CD_3OD): 7.46 (dd, 1H), 7.38-7.26 (m, 2H), 7.12-6.99 (m, 1H), 6.66-6.56 (m, 1H), 4.37-3.87 (m,4H), 2.94-2.82 (m, 1H), 2.75-2.63 (m, 3H), 2.20-2.06 (m, 1H), 2.00-1.67 (m, 8H). MS (EI) for $C_{21}H_{21}F_3IN_3O_2$: 532 (MH^+).

EXAMPLE 22(i). 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-ethylpyrrolidin-2-yl)azetidin-3-ol acetate (salt): ^{1}H NMR (400 MHz, CD_3OD): 7.46 (d, 1H), 7.38-7.33 (m, 1H), 7.32-7.27 (m, 1H), 7.12-7.01 (m, 1H), 6.66-6.57 (m, 1H), 4.34-3.89 (m,4H), 3.57 (t, 1H), 3.51-3.40 (m, 1H), 3.28-2.81(m, 3H), 2.25-1.72 (m, 8H), 1.31-1.18 (m, 3H). MS (EI) for $C_{22}H_{23}F_3IN_3O_2$: 546 (MH^+).

EXAMPLE 22(j). 1-({4-fluoro-5-[(2-fluoro-4-iodophenyl)amino]-1-methyl-1*H*-benzimidazol-6-yl}carbonyl)-3-[(2S)-piperidin-2-yl]azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, d_4-MeOH): 8.30 (s, 1H), 7.56 (s, 1H), 7.42 (d, 1H), 7.24 (d, 1H), 6.34 (m, 1H), 4.20 (d, 2H), 3.92 (s, 3H), 3.38-3.24 (m, 3H), 3.08 (bs, 1H), 2.88 (bs (1*H*), 1.90-1.70 (m, 3H), 1.66-1.32 (m, 3H); MS (EI) for $C_{23}H_{24}F_2IN_5O_2$: 568 (MH^+).

EXAMPLE 22(k). 1-({7-fluoro-6-[(2-fluoro-4-iodophenyl)amino]-1-methyl-1*H*-benzimidazol-5-yl}carbonyl)-3-[(2S)-piperidin-2-yl]azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, d_4-MeOH): 8.22 (s, 1H), 7.60 (s, 1H), 7.42 (d, 1H), 7.26 (d, 1H), 6.46 (m, 1H), 4.21 (d, 2H), 4.06 (s, 3H), 3.88 (m, 1H), 3.38-3.24 (m, 3H), 3.10 (bs, 1H), 2.88 (bs (1*H*), 1.88-1.70 (m, 3H), 1.64-1.28 (m, 3H); MS (EI) for $C_{23}H_{24}F_2IN_5O_2$: 568 (MH^+).

EXAMPLE 22(m). 4-[(4-bromo-2-fluorophenyl)amino]-3-fluoro-5-({3-hydroxy-3-[(2S)-piperidin-2-yl]azetidin-1-yl}carbonyl)-1-methylpyridin-2(1*H*)-one: MS (EI) for $C_{21}H_{23}BrF_2N_4O_3$: 498 (MH^+).

EXAMPLE 22(n). 1-({8-chloro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-a]pyridin-6-yl}carbonyl)-3-[(2S)-piperidin-2-yl]azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8.79 (s, 1H), 8.04 (d, 1H), 7.91 (d, 1H), 7.64 (dd, 1H), 7.55 (d, 1H), 6.95-7.02 (m, 1H), 4.38 (d, 1H), 4.15 (dd, 1H), 3.99 (dd, 1H), 3.72 (q, 1H), 3.32-3.39 (m, 1H), 3.00-3.12 (m, 1H), 1.93 (t, 3H), 1.51-1.70 (m, 3H); MS (EI) for $C_{22}H_{22}ClFIN_5O_2$: 532 (MH^+).

EXAMPLE 22(o). 1-({7-[(4-bromo-2-chlorophenyl)amino]-8-chloroimidazo[1,2-a]pyridin-6-yl}carbonyl)-3-[(2S)-piperidin-2-yl]azetidin-3-ol: ^{1}H NMR (400MHz, d_4-MeOH): 8.85 (s, 1H), 8.06 (d, 1H), 7.91 (d, 1H), 7.71 (d, 1H), 7.45 (d, 1H), 7.01 (d, 1H), 4.48 (d, 1H), 4.10-4.27 (m, 2H), 3.87 (q, 1H), 3.37 (d, 2H), 3.02 (s, 1H), 1.88-1.94 (m, 3H), 1.58-1.69 (m, 3H); $C_{22}H_{22}BrCl_2N_5O_2$: 540 (MH^+).

EXAMPLE 22(p). 1-({6-[(4-bromo-2-chlorophenyl)amino]-7-fluoro-3-methyl-1,2-benzisoxazol-5-yl}carbonyl)-3-[(2S)-piperidin-2-yl]azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8.50 (m, 1H), 7.51 (d, 1H), 7.42 (s, 1H), 7.26 (dd, 1H), 6.79 (dd, 1H), 4.20-3.98 (br m, 4H), 3.11 (d , 1H), 2.77-2.50 (br m, 5H), 1.80-1.15 (br m, 6H); MS (EI) for $C_{23}H_{23}BrClFN_4O_3$: 537 (MH^+).

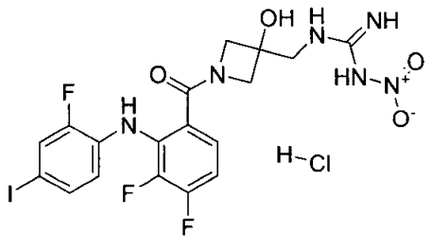
EXAMPLE 22(q). 1-({3-fluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2S)-piperidin-2-yl]azetidin-3-ol: ^{1}H NMR (400 MHz, d_4-MeOH): 7.53 (2d, 1H), 7.46 (m, 2H), 7.16 (t, 1H), 6.86 (m, 1H), 6.63 (m, 1H), 4.36 (m, 1H), 4.22 (m, 1H), 4.02 (m, 1H), 3.88 (m, 1H), 3.08 (d, 1H), 2.66 (dd, 1H), 2.56 (m, 1H), 1.82 (bs, 1H), 1.66 (d, 1H), 1.58 (d, 1H), 1.38 (m, 2H), 1.22 (m, 1H); MS (EI) for $C_{21}H_{22}F_2IN_3O_2$: 514 (MH^+).

EXAMPLE 22(r). 1-({4-fluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2S)-piperidin-2-yl]azetidin-3-ol: ^{1}H NMR (400 MHz, d_4-MeOH): 7.42 (2d, 1H), 7.34-7.18 (m, 4H), 6.46 (m, 1H), 4.10 (m, 2H), 3.84 (m, 2H), 3.04 (d, 1H), 2.52 (dd, 2H), 1.76 (bs, 0.5H), 1.58 (m, 2.5H), 1.32 (m, 2H), 1.18 (m, 0.5H), 1.04 (m, 0.5H); MS (EI) for $C_{21}H_{22}F_2IN_3O_2$: 514 (MH^+).

EXAMPLE 22(s). 5-[(2-fluoro-4-iodophenyl)amino]-6-({3-hydroxy-3-[(2S)-piperidin-2-yl]azetidin-1-yl}carbonyl)-2-methylpyridazin-3(2*H*)-one: ^{1}H NMR (400MHz, d_6-DMSO): 10.19 (s, 1H), 7.78 (dd, 1H), 7.59 (d, 1H), 7.32 (t, 1H), 5.95 (s, 1H), 4.59 (q, 1H), 4.13-4.27 (m, 2H), 3.77 (d, 1H), 3.62 (s, 3H), 3.02 (d, 2H), 2.71 (d, 1H), 1.78 (s, 1H), 1.68 (d, 1H), 1.53 (d, 1H), 1.32 (s, 2H), 1.17 (t, 1H); MS (EI) for $C_{20}H_{23}FIN_5O_3$: 528 (MH+).

Example 23

1-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}-3-nitroguanidine hydrochloride

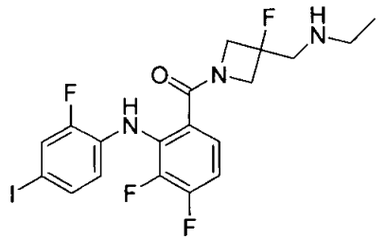


[00341] To a mixture of 2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)-6-(1-oxa-5-azaspiro[2,3]hex-5-ylcarbonyl)aniline (0.15g, 0.33 mmol), prepared using procedures similar to those described in Example 21, and nitroguanidine (0.1 g, 1.00 mmol) in tetrahydrofuran (3.00 mL) an aqueous solution of sodium hydroxide (1.0 mL, 2.0 mmol) was added and the reaction mixture was stirred at 70 °C for 16 hours. The reaction mixture was concentrated *in vacuo*. The crude product was purified by reverse phase preparative HPLC. The fractions were collected, and the solvent was concentrated. The residue was partitioned with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate, brine and dried over anhydrous sodium sulfate. Filtration and concentration resulted in an amorphous residue, which was dissolved in methanol, and 4 N HCl in dioxane (80 µL, 0.33 mmol) was added to the solution. A white precipitate formed and was collected by filtration. The solid was washed with hexane, and dried to afford 76 mg (38%) 1-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}-3-nitroguanidine hydrochloride. ^{1}H NMR (400 MHz, d_4-MeOH): 7.46 (2d, 1H), 7.36 (m, 1H), 7.29 (m, 1H), 7.02 (m, 1H), 6.63 (m, 1H), 4.22 (m, 1H), 4.01 (m, 2H), 3.86 (m, 1H), 3.51 (d, 2H); MS (EI) for $C_{18}H_{16}F_3IN_6O_4$: 565 (MH^+).

[00342] **EXAMPLE 23(a).** Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, the following compounds of the invention were prepared: 1-cyano-3-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}guanidine hydrochloride. ^{1}H NMR (400 MHz, d_4-MeOH): 7.47 (2d, 1H), 7.36 (m, 1H), 7.27 (m, 1H), 7.03 (m, 1H), 6.63 (m, 1H), 4.18 (m, 1H), 3.98 (m, 2H), 3.80 (m, 1H), 3.43 (s, 2H); MS (EI) for $C_{19}H_{16}F_3IN_6O_2$: 545 (MH^+).

EXAMPLE 24

6-({3-[(ethylamino)methyl]-3-fluoroazetidin-1-yl}carbonyl)-2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)aniline

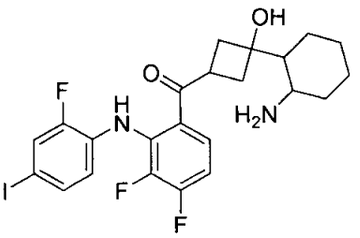


[00343] To 1,1-dimethylethyl [{1-({3,4-difuoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}ethylcarbamate (27 mg, 0.044 mmol), prepared using procedures similar to those in Example 3 and followed by Boc-protection, in chloroform (2.5 mL) added DAST (11.8 μL, 0.089 mmol) and stirred for 3.5 hr at room temperature. Quenched with water (15 mL), partitioned phases and extracted aqueous phase with chloroform (2 X 15mL). The combined chloroform extracts were dried over sodium sulfate, filtered and the filtrate concentrated *in vacuo*. The residue was purified on a silica gel column to afford 1,1-dimethylethyl [{1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-fluoroazetidin-3-yl]methyl}ethylcarbamate (19.0 mg, 70%).

[00344] To the 1,1-dimethylethyl [{1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-fluoroazetidin-3-yl]methyl}ethylcarbamate (19.0 mg, 0.031 mmol) in acetonitrile (1.0 mL) added a solution 4.0N hydrogen chloride in dioxane (1.0 mL). After 1.5hr the solution was concentrated *in vacuo*. The residue was purified by preparative reverse phase HPLC to afford the title compound (4.30 mg, 27%). ^{1}H NMR (400MHz, $CDCl_3$): 8.25 (s, 1H), 7.33 (dd, 1H), 7.33-7.25 (m, 1H), 7.18-7.14 (m, 1H), 6.84-6.77 (m, 1H), 6.63-6.58 (m, 1H), 4.33-4.05 (br m, 4H), 3.07-2.95 (br m, 2H), 2.65 (q, 2H), 1.08 (t, 3H); MS (EI) for $C_{19}H_{18}F_4IN_3O$: 508 (MH^+).

EXAMPLE 25

3-(2-aminocyclohexyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol



[00345] A solution of 1-(trimethylsiloxy)cyclohexene (200 mg, 1.17 mmol) and benzyl 3-oxoazetidine-1-carboxylate (289 mg, 1.41 mmol), prepared using procedures similar to those described in Reference 3, in tetrahydrofuran (3.90 mL) was cooled to -78 °C for 10 minutes followed by the addition of titanium tetrachloride (0.13 mL, 1.17 mmol). The reaction mixture stirred for an additional 5 hours at -78 °C. The mixture was quenched with aqueous sodium bicarbonate and the aqueous layer was extracted with ether (2x). The organic layer was separated, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated *in vacuo*. The residue was purified on silica gel chromatography column (3:2 hexanes/ethyl acetate) to afford benzyl 3-hydroxy-3-(2-oxocyclohexyl)azetidine-1-carboxylate (328 mg, 37%) . ^{1}H NMR ($CDCl_3$): 7.28-7.34 (m, 5H), 5.08 (s, 2H), 4.02 (d, 1H), 3.89 (d, 1H), 3.87 (s, 1H), 3.55 (s, 1H), 2.71 (q, 1H), 2.29-2.43 (m, 2H), 2.11 (s, 2H), 1.95 (s, 1H), 1.66 (d, 3H); MS (EI) for $C_{17}H_{21}NO_4$: 303 (MH+).

[00346] A solution of benzyl 3-hydroxy-3-(2-oxocyclohexyl)azetidine-1-carboxylate (100 mg, 330 mmol) in methanol (1.60 mL) in the presence of ammonium acetate (191 mg, 2.48 mmol was cooled to 0 °C for 1 hour. Sodium cyanoborohydride (81.5 mg, 1.30 mmol) was added and the mixture was stirred at room temperature for 16 hours. To the reaction mixture was added 6 N hydrogen chloride (800 µL) and extracted with ethyl acetate. The aqueous layer was basified with aqueous sodium bicarbonate (pH 9) and extracted with dichloromethane. The combined organic portion was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford benzyl-3-(2-aminocyclohexyl)-3-hydroxyazetidine-1-carboxylate (73.7 mg, 73%) . MS (EI) for $C_{17}H_{24}N_2O_3$: 305 (MH+).

[00347] To a solution of benzyl-3-(2-aminocyclohexyl)-3-hydroxyazetidine-1-carboxylate (202 mg, 0.663 mmol) in dioxane-water (1:1, 2.5 mL) was added di-*tert*-butyl dicarbonate (138 mg, 0.630 mmol) and solid sodium bicarbonate (112 mg, 1.33 mmol). The reaction mixture was stirred at room temperature for 2 hours and evaporated. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried

over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford benzyl 3-(2-*tert*-butoxycarbonylamino)cyclohexyl)-3-hydroxyazetidine-1-carboxylate (237 mg, 100%). ^{1}H NMR (CH_3OH): 7.15-7.21 (m, 5H), 5.45 (s, 0.5H), 5.20 (d, 0.5H), 4.95 (s, 2H), 4.81 (s, 1H), 3.81 (d, 2H), 1.43-1.74 (m, 5H), 1.39 (s, 1H), 1.31 (s, 11H), 1.20 (s, 1H). MS (EI) for $C_{22}H_{32}N_2O_5$: 405 (MH+).

[00348] A solution of benzyl 3-(2-tert-butoxycarbonylamino)cyclohexyl)-3-hydroxyazetidine-1-carboxylate (237 mg, 0.586 mmol) in ethyl acetate (2 mL) was hydrogenated over 10% palladium-carbon (200 mg, 0.586 mmol) at 40 psi for 16 hours. The reaction mixture was filtered and concentrated *in vacuo* to provide *tert*-butyl 2-(3-hydroxyazetidin-3-yl)cyclohexylcarbamate (181 mg, 100%). ^{1}H NMR ($CDCl_3$): 5.10 (s, 1H), 4.80 ((s, 1H), 3.78-3.86 (m, 1H), 3.61 (d, 1H), 3.57 (s, 1H), 3.36 (d, 1H), 1.77 (s, 2H). 1.40-1.53 (m, 1H), 1.36 (d, 9H), 1.25 (s, 2H). MS (EI) for $C_{14}H_{26}N_2O_3$: 271 (MH+).

[00349] To a solution of *tert*-butyl 2-(3-hydroxyazetidin-3-yl)cyclohexylcarbamate (181 mg, 0.669 mmol) and 3,4-difluoro-2-(2-fluoro-4-iodophenylamino)benzoyl fluoride (265 mg, 0.669 mmol), prepared using procedures similar to those described in Reference 1, in tetrahydrofuran (2.2 mL) was added *N,N*-diisopropylethylamine (110 μL) at room temperature. After an hour, the reaction mixture was heated to 50 °C and stirred for 45 minutes, at which time it was cooled to room temperature and evaporated. The residue was partitioned between ethyl acetate and 10% citric acid. The organic layer was washed with aqueous sodium chloride, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford *tert*-butyl-2-(1-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)benzoyl)-3-hydroxyazetidin-3-yl)cyclohexylcarbamate. This crude material was taken into the next step without further purification.

[00350] *Tert*-butyl-2-(1-(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)benzoyl)-3-hydroxyazetidin-3-yl)cyclohexylcarbamate was dissolved in a mixture of methanol (4 mL) and hydrogen chloride (4 M in dioxane) (3 mL). The solution was heated to reflux then cooled to room temperature and stirred for 16 hours. The reaction mixture was concentrated and purified by reverse phase HPLC. The purified fractions were evaporated to dryness and partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to afford an oil. The residue was taken up in methanol (2 mL) and was added hydrogen chloride (4M in dioxane) (700 μL) and evaporated to dryness to afford the title compound 3-(2-aminocyclohexyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol hydrochloride (44.7 mg, 12%).

^{1}H NMR (400MHz, d_6-DMSO): 8.58 (d, 1H), 7.59 (dd, 1H), 7.54 (s, 2H), 7.38 (d, 1H), 7.33 (t, 1H), 7.16-7.25 (m, 1H), 6.69 (dt, 1H), 6.41 (s, 1H), 4.26 (d, 0.5H), 4.17 (d, 0.5H), 4.04 (t, 1H), 3.90 (t, 1H), 3.79 (d, 0.5H), 3.65-3.73 (m, 0.5H), 3.45-3.51 (m, 1H), 1.88 (s, 1H), 1.65-1.88 (m, 2H), 1.47 (s, 4H), 1.16-1.37 (m, 2H); MS (EI) for $C_{22}H_{23}F_3IN_3O_2$: 546 (MH^+).

[00351] Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, the following compounds of the invention were prepared:

EXAMPLE 25(c).3-(2-aminocyclopentyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol; ^{1}H NMR (400MHz, d_6-DMSO): 8.56 (d, 1H), 7.82 (d, 1H), 7.59 (td, 1H), 7.45 (s, 1H), 7.38 (d, 1H), 7.30-7.35 (m, 1H), 7.18-7.24 (m, 1H), 6.68-6.72 (m, 1H0, 6.41 (s, 0.5H), 6.17 (s, 0.5H), 3.91-4.27 (m, 2.5H), 3.78-3.86 (m, 1H), 3.65-3.73 (m, 1H), 3.44-3.52 (m, 0.5H), 2.19-2.26 (m, 1H), 1.54-1.94 (m, 5H), 1.30-1.39 (m, 1H); MS (EI) for $C_{21}H_{21}F_3IN_3O_2$: 532 (MH^+).

EXAMPLE 25(a) and **EXAMPLE 25(b)**

(±)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(trans)-2-hydroxycyclohexyl]azetidin-3-ol

and

(±)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(cis)-2-hydroxycyclohexyl]azetidin-3-ol

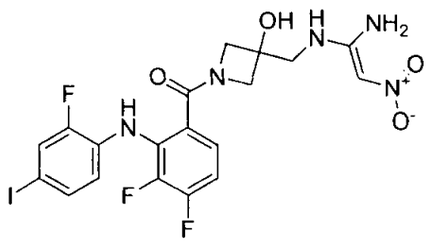
[00352] The compounds of examples 25a and 25b were synthesized starting from benzyl 3-hydroxy-3-(2-oxycyclohenyl)azetidine-1-carboxylate prepared according to the procedure given in example 25. The ketone was reduced to give benzyl 3-hydroxy-3-(2-hydroxycyclohexyl)azetidine-1-carboxylate as a mixture of racemic diastereomers which were subjected to hydrogenation to afford 3-(2-hydroxycyclohexyl)azetidin-3-ol. 3-(2-hydroxycyclohexyl)azetidin-3-ol was then carried forward in a coupling step with 3,4-difluoro-2-(2-fluoro-4-iodophenylamino)benzoyl fluoride in the usual manner. The coupled material thus obtained was purified by preparative reverse phase HPLC where fraction 1 was tentatively assigned as (±)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(trans)-2-hydroxycyclohexyl]azetidin-3-ol (Example 25a) and fraction 2 was tentatively assigned as (±)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(cis)-2-hydroxycyclohexyl]azetidin-3-ol.

EXAMPLE 25(a). First eluting fraction: ^{1}H NMR (400 MHz, d_4-MeOH): 7.44 (2d, 1H), 7.34 (t, 1H), 7.25 (m, 1H), 7.03 (m, 1H), 6.60 (m, 1H), 4.46 (d, 0.5H), 4.28 (d, 0.5H), 4.22 (d, 0.5H), 3.98 (dd, 1H), 3.89 (d, 0.5H), 3.85 (s, 0.5H), 3.77 (d, 0.5H), 3.56 (m, 1H), 1.90 (m, 1H), 1.46-1.74 (m, 4H), 0.98-1.32 (m, 4H); MS (EI) for $C_{22}H_{22}F_3IN_2O_3$: 547 (MH^+).

EXAMPLE 25(b). Second eluting fraction: ^{1}H NMR (400 MHz, d_4-MeOH): 7.44 (2d, 1H), 7.33 (d, 1H), 7.26 (m, 1H), 7.04 (m, 1H), 6.59 (dd, 1H), 4.20 (m, 1.5H), 4.19 (s, 0.5H), 4.00 (m, 1.5H), 3.86 (dd, 1H), 3.74 (d, 0.5H), 1.76 (m, 2H), 1.50-1.68 (m, 5H), 1.18-1.46 (m, 4H); MS (EI) for $C_{22}H_{22}F_3IN_2O_3$: 547 (MH^+).

Example 26

3-({[(E)-1-amino-2-nitroethenyl]amino}methyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol



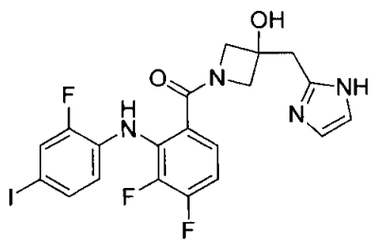
[00353] A solution of 3-(aminomethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol (0.24 g, 0.5 mmol), prepared using procedures similar to those described in Example 3, and commercially available 1,1-bis(methylthio)-2-nitroethylene (0.083 g, 0.5 mmol) in ethanol (5 mL) was stirred at 70 °C for 16 hours. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated to afford 0.10 g, (39%) 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(Z)-1-(methylthio)-2-nitroethenyl]amino}methyl)azetidin-3-ol. MS (EI) for $C_{20}H_{18}F_3IN_4O_4S$: 595 (MH^+).

[00354] To a solution of (0.05 g 0.08 mmol) 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(Z)-1-(methylthio)-2-nitroethenyl]amino}methyl)azetidin-3-ol in ethanol (2 mL) was added ammonium hydroxide (0.1 mL, 0.8 mmol) and the reaction mixture was stirred at 70 °C for 16 hours. The reaction mixture was concentrated *in vacuo*. The crude product was purified by reverse phase preparative HPLC. The fractions were collected and the solvent was concentrated. The residue was partitioned with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate, brine and dried over anhydrous sodium sulfate. Filtration and concentration resulted in an amorphous residue, which was dissolved in methanol, and 4 N HCl in dioxane (40 µL, 0.16 mmol) was added to the solution. A white precipitate formed and was collected by vacuum filtration. The solid was washed with hexane, and dried to afford 42 mg (87%) 3-({[(E)-1-amino-2-nitroethenyl]amino}methyl)-1-({3,4-difluoro-2-[(2-

fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol hydrochloride. ^{1}H NMR (400 MHz, d_4-MeOH): 7.58 (t, 0.5H), 7.44 (t, 0.5H), 7.36 (m, 1H), 7.31 (m, 1H), 7.04 (m, 1H), 6.63 (m, 1H), 3.90-4.30 (m, 4H) 3.72 (s, 2H); MS (EI) for $C_{19}H_{17}F_3IN_5O_4$: 564 (MH^+).

EXAMPLE 27

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1*H*-imidazol-2-ylmethyl)azetidin-3-ol



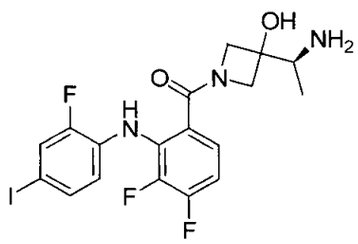
[00355] A solution of 2-methyl-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-imidazole (0.5 g, 2.3 mmol) (prepared using procedures similar to those described in Clader *et. al. J. of Med. Chem.* **1995,** *38(10),* 1600-7) in tetrahydrofuran (5 mL) was cooled to –78 °C, and *n*-butyllithium was added (2.5 M in hexanes, 0.990 mL, 2.5 mmol). After 2 hours, 1,1-dimethylethyl 3-oxoazetidine-1-carboxylate (0.60 g, 3.5 mmol), prepared using procedures similar to those described in Example 3, in 2.0 mL tetrahydrofuran was added and the solution was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched with an excess of saturated aqueous ammonium chloride solution and partitioned between water and ethyl acetate. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, 3:1 hexanes/ethyl acetate) gave 0.37 g (41%) of 3-{[1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-imidazol-2-yl]methyl}azetidin-3-ol: ^{1}H NMR (400 MHz, $CDCl_3$): 6.96-6.92 (m, 1H), 5.23 (s, 2H), 3.98 (d, 2H), 3.79 (d, 2H), 3.52-3.47 (m, 2H), 3.13 (s, 2H), 1.43 (s, 9H), 0.94-0.88 (m, 2H), 0.00 (s, 9H).

[00356] 3-{[1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-imidazol-2-yl]methyl}azetidin-3-ol (0.19 g, 0.49 mmol) was dissolved in dichloromethane (1.5 mL) and trifluroacetic acid (1.5 mL) was added. The reaction mixture was stirred at room temperature overnight and the solvent was removed under vacuum to give 0.16 g of 3-(1*H*-imidazol-2-ylmethyl)azetidin-3-ol trifluoroacetate salt (87%). The crude residue was used without further purification for the next step.

[00357] To a solution of 3-(1*H*-imidazol-2-ylmethyl)azetidin-3-ol trifluoroacetate salt (0.16 g, 0.42 mmol) and *N,N*-diisopropylethylamine (0.370 mL, 2.13 mmol) in tetrahydrofuran (2.0 mL) 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoyl fluoride (0.17 g, 0.42 mmol), prepared using procedures similar to those described in Reference 1, was added and the reaction mixture was stirred for 3 hours at room temperature. The solution was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate and the organic layer was dried over sodium sulfate and concentrated *in vacuo*. Purification by reverse-phase HPLC followed by lyophilization of the pure fractions gave 0.032 g (13%) of 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1*H*-imidazol-2-ylmethyl)azetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, CD_3OD): 7.45 (dd, 1H), 7.38-7.33 (m, 1H), 7.25-7.18 (m, 1H), 7.08-6.96 (m, 1H), 6.89 (s, 2H), 6.65-6.56 (m, 1H), 4.33-4.22 (m, 1H), 4.17-4.00 (m, 2H), 3.91-3.80 (m, 1H), 3.08 (s, 2H), 1.96 (s, 3H). MS (EI) for $C_{20}H_{16}F_3IN_4O_2$: 529 (MH^+).

EXAMPLE 28

3-[(1*R*)-1-aminoethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol



[00358] To a solution of diisopropylamine (6.5 mL, 46.3 mmol) in THF (200 mL) at -78 °C was added butyllithium (17 mL of a 2.5 M solution in hexanes, 42.5 mmol) over 5 min. The solution of lithium diisopropylamide was stirred for 15 min at -78 °C. A solution of (*S*)-4-benzyl-3-propionyl-2-oxazolidinone (9.0 g, 38.6 mmol) in THF (100 mL) was added to the lithium diisopropylamide by addition funnel over 26 min. The reaction temperature was kept below -70 °C during the course of the addition. After the addition, the mixture was stirred for a further 30 min at -78 °C. Then phenylmethyl 3-oxoazetidine-1-carboxylate (9.5 g, 46.3 mmol) was added by addition funnel over 25 minutes as a solution in THF (100 mL). Again, the reaction mixture was kept below -70 °C during the reagent addition. After stirring for an additional 1 hour at -78 °C, the reaction mixture was quenched with saturated ammonium chloride solution and was then allowed to warm to rt. Water was added to dissolve any precipitated ammonium chloride, and ethyl acetate was added. The layers were partitioned,

and the aqueous phase was extracted twice with ethyl acetate. The combined organic extracts were washed with 5% aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography (50% ethyl acetate: 50% hexanes) to provide phenylmethyl 3-hydroxy-3-{(1*R*)-1-methyl-2-oxo-2-[(4*S*)-2-oxo-4-(phenylmethyl)-1,3-oxazolidin-3-yl]ethyl}azetidine-1-carboxylate as a white crystalline solid (6.03 g, 13.8 mmol, 36% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 8H), 7.20 (d, 2H), 5.12 (s, 2H), 4.66 (m, 1H), 4.27-4.20 (m, 2H), 4.10 (q, 1H), 4.03-3.93 (m, 3H), 3.28 (dd, 1H), 2.77 (dd, 1H), 1.29 (d, 3H).

[00359] A solution of lithium hydroxide monohydrate (1.16 g, 27.6 mmol) in 30% hydrogen peroxide (13.2 mL, 138 mmol) was prepared and was subsequently added slowly to a solution of phenylmethyl 3-hydroxy-3-{(1*R*)-1-methyl-2-oxo-2-[(4*S*)-2-oxo-4-(phenylmethyl)-1,3-oxazolidin-3-yl]ethyl}azetidine-1-carboxylate (6.03 g, 13.8 mmol) in THF (80 mL) and water (20 mL) at 0 °C. After the mixture was stirred for 1 h at rt, the hydrogen peroxide was quenched carefully with 1 M sodium sulfite (150 mL, 150 mmol). The THF was removed *in vacuo*, and the mixture was then acidified to pH=2 with concentrated hydrochloric acid. The aqueous mixture was extracted twice with ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (gradient, 5% methanol: 95% dichloromethane to 10% methanol: 90% dichloromethane) to provide (2*R*)-2-(3-hydroxy-1-{[(phenylmethyl)oxy]carbonyl}azetidin-3-yl)propanoic acid as a colorless oil (2.77 g, 9.9 mmol, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.31 (m, 5H), 5.10 (s, 2H), 3.99 (s, 2H), 3.93 (s, 2H), 2.88 (q, 1H), 1.28 (d, 3H); MS (EI) for $C_{14}H_{17}NO_5$: 280 (MH^+).

[00360] To a solution of (2*R*)-2-(3-hydroxy-1-{[(phenylmethyl)oxy]carbonyl}azetidin-3-yl)propanoic acid (2.77 g, 9.9 mmol) in toluene (100 mL) was added triethylamine (1.52 mL, 10.9 mmol) followed by diphenyl phosphoryl azide (2.24 mL, 10.4 mmol). The mixture was heated to 80 °C for 2 h and was then cooled to rt. The volatile materials were removed *in vacuo*, and the residue was purified by column chromatography (gradient: 50% hexanes: 50% ethyl acetate up to 100% ethyl acetate). The desired product, (8*R*)-8-methyl-6-oxo-5-oxa-2,7-diazaspiro[3.4]octane-2-carboxylic acid phenylmethyl ester, was isolated as a viscous, colorless syrup (1.84 g, 6.6 mmol, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.32 (m, 5H), 5.66 (br s, 1H), 5.12 (s, 2H), 4.34 (dd, 1H), 4.30 (dd, 1H), 4.17 (dd, 1H), 4.05 (dd, 1H), 3.98 (q, 1H), 1.34 (d, 3H).

[00361] To a solution of (8*R*)-8-methyl-6-oxo-5-oxa-2,7-diazaspiro[3.4]octane-2-carboxylic acid phenylmethyl ester (1.84 g, 6.6 mmol) in methanol (66 mL) was added wet 10% palladium on carbon (50% by mass, 500 mg). The resulting suspension was stirred under 1 atm of hydrogen for 1 h. The catalyst was then removed by filtration through celite. The filtrate was concentrated *in vacuo* to provide (8*R*)-8-methyl-5-oxa-2,7-diazaspiro[3.4]octan-6-one as a white solid (0.99 g, quantitative yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (br s, 1H), 4.07 (d, 1H), 4.02 (d, 1H), 3.92 (d, 1H), 3.79 (d, 1H), 3.58 (d, 1H), 1.38 (d, 3H); MS (EI) for $C_6H_{10}N_2O_2$: 143 (MH^+).

[00362] A solution of (8*R*)-8-methyl-5-oxa-2,7-diazaspiro[3.4]octan-6-one (937 mg, 6.6 mmol), acetic acid (0.756 mL, 13.2 mmol), and benzaldehyde (1.0 mL, 9.9 mmol) in methanol (65 mL) was treated with sodium cyanoborohydride (829 mg, 13.2 mmol) at rt for 30 min. The mixture was then cooled to 0 °C, and 3 N hydrochloric acid (100 mL) was added. The methanol was then removed *in vacuo*. The resulting aqueous solution was washed with ethyl acetate. The ethyl acetate wash was back extracted with 1 N hydrochloric acid, and the aqueous acidic phases were combined and basified with potassium carbonate. The organic phase was discarded. The aqueous mixture was then extracted three times with ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The desired (8*R*)-8-methyl-2-(phenylmethyl)-5-oxa-2,7-diazaspiro[3.4]octan-6-one was obtained in 93% purity as a milky colorless liquid (1.33 g, 5.73 mmol, 87% yield). MS (EI) for $C_{13}H_{16}N_2O_2$: 233 (MH^+).

[00363] To a solution of (8*R*)-8-methyl-2-(phenylmethyl)-5-oxa-2,7-diazaspiro[3.4]octan-6-one (1.33 g, 5.7 mmol) in dioxane (40 mL) and water (20 mL) was added barium hydroxide octahydrate (9.0 g, 28.5 mmol), and the mixture was heated to reflux for 2 h. After cooling to rt, the mixture was acidified with 3 N hydrochloric acid (10 mL) and dichloromethane (50 mL) was added. The biphasic mixture was treated with potassium carbonate (1.6 g, 11.4 mmol) and di-*tert*-butyl dicarbonate (2.11 g, 9.7 mmol). After stirring vigorously at rt for 17 h, solids were removed by filtration, and the layers were partitioned. The aqueous phase was extracted with dichloromethane, and the organic extracts were combined and dried over magnesium sulfate, filtered, and concentrated. The residue was taken up in methanol (60 mL) and was treated with potassium carbonate (3.0 g, 22 mmol) added in two portions over 4 h at reflux. After cooling, the methanol was removed *in vacuo*, and the residual solids were loaded directly on to a silica column. After purification (5% methanol: 95% dichloromethane), 1,1-dimethylethyl {(1*R*)-1-[3-hydroxy-1-(phenylmethyl)azetidin-3-

yl]ethyl}carbamate was obtained as a colorless syrup (1.07 g, 3.5 mmol, 62% yield). MS (EI) for $C_{17}H_{26}N_2O_3$: 307 (MH^+).

[00364] To a solution of 1,1-dimethylethyl {(1*R*)-1-[3-hydroxy-1-(phenylmethyl)azetidin-3-yl]ethyl}carbamate (1.07 g, 3.5 mmol) in methanol was added wet 10% palladium on carbon (50% by mass, 250 mg). The resulting suspension was subjected to 1 atmosphere of hydrogen for 7 h, and an additional 250 mg of catalyst was added over the course of the reaction. The catalyst was then removed by filtration through celite. The filtrate was then concentrated *in vacuo* to provide 1,1-dimethylethyl [(1*R*)-1-(3-hydroxyazetidin-3-yl)ethyl]carbamate as a colorless syrup (800 mg, quantitative yield). MS (EI) for $C_{10}H_{20}N_2O_3$: 161 (M - *tert*-butyl + H).

[00365] To a solution of 1,1-dimethylethyl [(1*R*)-1-(3-hydroxyazetidin-3-yl)ethyl]carbamate (200 mg, 0.92 mmol) in dichloromethane (5 mL) was added diisopropylethylamine (228 µL, 1.38 mmol) and 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoyl fluoride (prepared according to the procedures described in Reference 1) (363 mg, 0.92 mmol). The mixture was stirred at rt for 16 h, after which the volatile materials were removed *in vacuo*. The residue was purified by column chromatography (50% hexanes : 50% ethyl acetate) to provide 1,1-dimethylethyl {(1*R*)-1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}carbamate as a colorless film (333 mg, 0.56 mmol, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (br s, 1H), 7.40 (dd, 1H), 7.32 (d, 1H), 7.12 (m, 1H), 6.81 (m, 1H), 6.61 (m, 1H), 4.74 (br d, 1H), 4.22 (d, 1H), 4.15-4.07 (m, 2H), 3.96 (br s, 1H), 3.77 (m, 1H), 1.43 (s, 9H), 1.18 (d, 3H); MS (EI) for $C_{23}H_{25}F_3IN_3O_4$: 536 (M - *tert*-butyl + H).

[00366] A solution of 1,1-dimethylethyl {(1*R*)-1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}carbamate (333 mg, 0.56 mmol) in methanol (10 mL) was treated with hydrochloric acid (4 N in dioxane, 1.4 mL, 5.6 mmol) at 60 °C for 30 min. After cooling, the volatile materials were removed *in vacuo* to provide 3-[(1*R*)-1-aminoethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol hydrochloride as a white solid (285 mg, 0.54 mmol, 97% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 1H), 7.83 (br s, 3H), 7.59 (dd, 1H), 7.39 (d, 1H), 7.34 (m, 1H), 7.21 (q, 1H), 6.69 (m, 1H), 6.65 (s, 1H), 4.25 (dd, 1H), 4.10 (dd, 1H), 3.98 (dd, 1H), 3.80 (m, 1H), 3.48 (m, 1H), 1.11 (dd, 3H); MS (EI) for $C_{18}H_{17}F_3IN_3O_2$: 492 (MH^+)

[00367] To establish the enantiomeric excess (ee) of this material, 3-[(1*R*)-1-aminoethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol

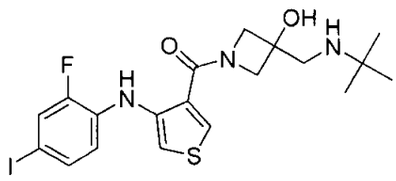
hydrochloride (21 mg, 0.040 mmol) was dissolved in dichloromethane (400 μL) and was treated with diisopropylethylamine (20 μL, 0.12 mmol) and (*R*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride at rt for 15 min. An aliquot was removed and was analyzed by chiral HPLC. The diastereomeric excess of (2*S*)-N-{(1*R*)-1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanamide was found to be 91%, and by extrapolation the ee of 3-[(1*R*)-1-aminoethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol was also assigned to be 91%.

[00368] Example 28a. Using the sequence described above, beginning with (*R*)-4-benzyl-3-propionyl-2-oxazolidinone, 3-[(1*S*)-1-aminoethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol was prepared using similar procedures except that the phenylmethyl 3-hydroxy-3-{(1*S*)-1-methyl-2-oxo-2-[(4*R*)-2-oxo-4-(phenylmethyl)-1,3-oxazolidin-3-yl]ethyl}azetidine-1-carboxylate required additional recrystallizations from isopropanol. Using the same method described above in Example 28, 3-[(1*S*)-1-aminoethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol was determined to have 98.4% ee. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 1H), 7.84 (br s, 3H), 7.59 (dd, 1H), 7.39 (d, 1H), 7.34 (m, 1H), 7.21 (q, 1H), 6.69 (m, 1H), 6.65 (s, 1H), 4.25 (dd, 1H), 4.10 (dd, 1H), 3.98 (dd, 1H), 3.80 (m, 1H), 3.48 (m, 1H), 1.11 (dd, 3H); MS (EI) for $C_{18}H_{17}F_3IN_3O_2$: 492 (MH^+).

[00369] Example 28b. To 3-[(1*S*)-1-aminoethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol (87.4 mg, 0.18 mmol), prepared using procedures similar to those described in Example 28, was added formaldehyde (37% aqueous, 14 mg, 0.18 mmol) in methanol (2 mL) and sodium borohydride (7 mg, 0.18 mmol). The mixture was stirred for 3 h at rt, after which sodium borohydride (16 mg, 0.42 mmol) was added. Upon stirring an additional 1.25 h, more formaldehyde (37% aqueous, 1 drop) was added, and the mixture was stirred 3 days at rt. A further small spatula (~50 mg) of sodium borohydride was then added, and the mixture was stirred at rt for 30 min. After quenching with 1 N HCl, the reaction mixture was purified directly by preparative HPLC. The clean material was converted to its hydrochloride salt to provide 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(1*S*)-1-(methylamino)ethyl]azetidin-3-ol as a yellow solid (21.7 mg, 0.040 mmol, 22% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.47 (dd, 1H), 7.36 (d, 1H), 7.31 (m, 1H), 7.06 (q, 1H), 6.62 (dt, 1H), 4.36 (dd, 1H), 4.21-3.91 (m, 3H), 3.44 (q, 1H), 2.66 (s, 3H), 1.29 (br m, 3H); MS (EI) for $C_{19}H_{19}F_3IN_3O_2$: 506 (MH^+).

EXAMPLE 29

3-{[(1,1-Dimethylethyl)amino]methyl}-1-({4-[(2-fluoro-4-iodophenyl)amino]-3-thienyl}carbonyl)azetidin-3-ol



[00370] To a mixture of methyl 4-oxotetrahydrothiophene-3-carboxylate (1.75 g, 11 mmol) (commercially available or prepared using procedures similar to those described in Rossy *et. al. J. Org. Chem.* **1980,** *45(4),* 617-2) in 15 mL of ethanol was added 2-fluoro-4-iodoaniline (2.6 g, 11 mmol) followed by addition of several drops of acetic acid . The mixture was refluxed for 3 hrs. The mixture was cooled to room temperature and the product precipitated. This product was filtered off, washed with ethyl acetate, ether, dried *in vacuo* to afford the methyl 4-[(2-fluoro-4-iodophenyl)amino]-2,5-dihydrothiophene-3-carboxylate (1.7 g, 42%). ^{1}HNMR(d_6-DMSO):9.80 (s,1H), 7.71 (d, 1H), 7.49 (dd, 1H), 7.24 (t, 1H), 4.10 (t, 2H), 3.79 (t, 2H), 3.69 (s, 3H); MS(EI) for $C_{12}H_{11}FINO_2S$: 380 (MH^+).

[00371] To a mixture of methyl 4-[(2-fluoro-4-iodophenyl)amino]-2,5-dihydrothiophene-3-carboxylate (1.2 g, 3.16 mmol) in 10 ml of anhydrous toluene was added 2,3,5,6-tetrachlorocyclohexa-2,5-diene-1,4-dione (0.78 g, 3.16 mmol). The mixture was refluxed for 2 h. The mixture was cooled to 50 °C and concentrated *in vacuo* to dryness and cooled to room temperature. To the residue was added ethanol and the mixture was refluxed for several minutes, cooled to room temperature and light blue crystalline product was filtered off and dried *in vacuo* to afford methyl 4-[(2-fluoro-4-iodophenyl)amino]thiophene-3-carboxylate (0.74 g, 62%). ^{1}HNMR(d_6-DMSO): 8.78 (s, 1H), 8.42(d, 1H), 7.64 (d, 1H), 7.46 (d, 1H), 7.37(t, 1H), 7.14 (s, 1H), 3.85(s, 3H); MS(EI) for $C_{12}H_9FINO_2S$: 378 (MH^+).

[00372] A mixture of methyl 4-[(2-fluoro-4-iodophenyl)amino]thiophene-3-carboxylate (0.74g, 1.96 mmol) in the solution of potassium hydroxide (0.3g) in ethanol / water (4ml/4ml) was heated up to 60 °C and stirred at this temperature for 30 min. The mixture was cooled to room temperature, diluted with 4 ml of water and extracted with ether. The water layer was acidified with 1 N HCl to pH 2, the product precipitated and was filtered off, washed several times with water and dried *in vacuo* to afford 4-[(2-fluoro-4-iodophenyl)amino]thiophene-3-carboxylic acid (0.59 g, 83%). ^{1}H NMR (d_6-DMSO): 13.20(s, 1H), 9.13 (s, 1H), 8.35 (d, 1H), 7.62 (dd, 1H), 7.48-7.38 (m, 2H), 7.11 (s, 1H); MS(EI) for $C_{11}H_7FINO_2S$: 362 (MH^-).

[00373] 4-[(2-fluoro-4-iodophenyl)amino]thiophene-3-carboxylic acid (200 mg, 0.551 mmol), 4-(dimethylamino)pyridine (202 mg, 1.65 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (127 mg, 0.662 mmol) were dissolved in DMF (3 mL). The mixture was stirred at ambient for 5 minutes and then 3-(hydroxymethyl)azetidin-3-ol hydrochloride (72 mg, 0.516 mmol) was added and the mixture was stirred for 15 h. The mixture was partitioned between ethyl acetate and 20% citric acid. The aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with 5% lithium chloride, saturated sodium bicarbonate and brine, then was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was crystallized from dichloromethane to afford 1-({4-[(2-fluoro-4-iodophenyl)amino]-3-thienyl}carbonyl)-3-(hydroxymethyl)azetidin-3-ol (247 mg, 0.551 mmol, quantitative yield) as off-white crystals: MS (EI) for $C_{15}H_{14}FIN_2O_3S$: 449 (MH^+).

[00374] 1-({4-[(2-Fluoro-4-iodophenyl)amino]-3-thienyl}carbonyl)-3-(hydroxymethyl)azetidin-3-ol (247 mg, 0.551 mmol), was suspended in dichloromethane (10 mL) and treated with 4-(dimethylamino)pyridine (80 mg, 0.661 mmol), and 2,4,6-triisopropylbenzenesulfonyl chloride (183 mg, 0.604 mmol) at ambient for 15 h. The mixture was adsorbed on to silica and purified by column chromatography (silica gel, 30% ethyl acetate in hexanes) to give [1-({4-[(2-fluoro-4-iodophenyl)amino]-3-thienyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl 2,4,6-tris(1-methylethyl)benzenesulfonate (101 mg, 0.141 mmol, 26% yield): MS (EI) for $C_{30}H_{36}FIN_2O_5S_2$: 715 (MH^+).

[00375] [1-({4-[(2-Fluoro-4-iodophenyl)amino]-3-thienyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl 2,4,6-tris(1-methylethyl)benzenesulfonate (101 mg, 0.141 mmol) was dissolved in tetrahydrofuran (2 mL) and was treated with sodium hydride (60 wt% dispersion in oil; 17 mg, 0.425 mmol) at ambient for 20 minutes. Tetrahydrofuran (2 mL) and *tert*-butylamine (0.1 mL) were added and the mixture was stirred at ambient for 16 h. The mixture was concentrated *in vacuo* and partitioned between ethyl acetate and water. The organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by reverse phase HPLC and the clean fractions were combined, neutralized with saturated sodium bicarbonate solution and the organic solvent was removed *in vacuo*. The remaining aqueous residue was extracted twice with ethyl acetate. The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford 3-{[(1,1-dimethylethyl)amino]methyl}-1-({4-[(2-fluoro-4-iodophenyl)amino]-3-thienyl}carbonyl)azetidin-3-ol (8 mg, 0.016 mmol, 11% yield): ^{1}H NMR (400 MHz, d_6-DMSO): 9.64 (br, 1H), 8.08 (d, 1H), 7.59 (dd, 1H), 7.44

(dd, 1H), 7.36 (t, 1H), 7.12 (d, 1H), 4.39 (d, 1H), 4.22 (d, 1H), 4.03 (d, 1H), 3.80 (d, 1H), 2.68 (br, 2H) 1.04 (s, 9H); MS (EI) for $C_{19}H_{23}FIN_3O_2S$: 504 (MH^+).

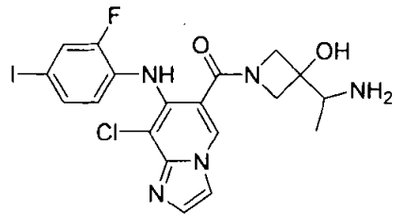
[00376] Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, the following compounds of the invention were prepared:

EXAMPLE 29(a). 3-[(dimethylamino)methyl]-1-({4-[(2-fluoro-4-iodophenyl)amino]-3-thienyl}carbonyl)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7.91 (d, 1H), 7.46- 7.41 (m, 2H), 7.33 (t, 1H), 7.00 (d, 1H), 4.66 (s, 1H), 4.49 (s, 1H), 4.30 (s, 1H), 4.15 (s, 1H), 3.54 (s, 1H), 3.17- 3.13 (m, 3H), 2.90 (s, 2H), 1.87- 1.83 (m, 3H); MS(EI) for $C_{17}H_{19}FIN_3O_2S$: 476 (MH^+).

EXAMPLE 29(b). 1-({4-[(2-fluoro-4-iodophenyl)amino]-3-thienyl}carbonyl)azetidin-3-amine: ^{1}H NMR (400 MHz, CD_3OD): 7.90 (d, 1H), 7.46-7.41 (m, 2H), 7.31 (t, 1H), 6.99 (d, 1H), 4.47 (br.s, 2H), 4.22-4.16 (m, 2H); MS(EI) for $C_{14}H_{13}FIN_3OS$: 418 (MH^+).

EXAMPLE 30

3-(1-aminoethyl)-1-({8-chloro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-a]pyridin-6-yl}carbonyl)azetidin-3-ol



[00377] To a suspension of sodium hydride (72 mg, 1.75 mmol, 60% wt) in tetrahydrofuran (1 mL) cooled to 0 °C was added nitroethane (125 μL, 1.75 mmol). The suspension was allowed to warm to room temperature and was stirred for 15 minutes, then cooled back to 0 °C. To the suspension was added dropwise a solution of 1,1-dimethylethyl 3-oxoazetidine-1-carboxylate (300 mg, 1.75 mmol, in 2 mL of tetrahydrofuran), prepared using procedures similar to those described in Reference 3. The suspension was stirred at room temperature for 1 hour. The reaction mixture was quenched by adding 20% aqueous citric acid, and then was partitioned with ethyl acetate. The aqueous portion was extracted twice using ethyl acetate and the combined organic portion was washed with saturated sodium bicarbonate, brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a colorless oil that was purified by column chromatography. Eluting with 30% ethyl acetate in hexanes, the isolated product was concentrated *in vacuo* to afford 250 mg, 1.02 mmol (58%) of 1,1-dimethylethyl 3-hydroxy-3-(1-nitroethyl)azetidine-1-carboxylate as a

colorless oil. ^{1}H NMR (400 MHz, DMSO): 6.46 (s, 1H), 5.01 (q, 1H), 4.24-3.97 (m, 2H), 3.77-3.60 (m, 2H), 1.41 (d, 3H), 1.39 (s, 9H).

[00378] 1,1-Dimethylethyl 3-hydroxy-3-(1-nitroethyl)azetidine-1-carboxylate was dissolved in methanol (5 mL) and treated with 4 N HCl in dioxane. The solution was briefly heated to reflux and then was concentrated *in vacuo* to afford 178 mg, 0.98 mmol (96%) of 3-(1-nitroethyl)azetidin-3-ol hydrochloride as a white solid. ^{1}H NMR (400 MHz, DMSO): 9.30 (br s, 1H), 8.96 (br s, 1H), 5.12 (q, 1H), 4.44-4.38 (m, 1H), 4.22-4.17 (m, 1H), 3.94-3.87 (m, 1H), 3.85-3.77 (m, 1H), 1.44 (d, 3H).

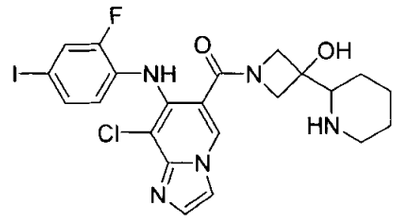
[00379] A solution of 8-chloro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-*a*]pyridine-6-carboxylic acid (150 mg, 0.35 mmol) (prepared using procedures similar to those described in US 2006030610 and US 2005054701), *N,N*-diisopropylethylamine (300 µL, 1.74 mmol), PyBOP (180 mg, 0.35 mmol) and 3-(1-nitroethyl)azetidin-3-ol hydrochloride (76 mg, 0.42 mmol) in dimethylformamide (3 mL) was stirred at room temperature for 15 hours. The reaction mixture was then partitioned between 5% aqueous lithium chloride, and ethyl acetate. The aqueous portion was extracted twice using ethyl acetate. The combined organic portion was washed with 20% aqueous citric acid, brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a brown residue which was purified by column chromatography. Eluting with 5% methanol in dichloromethane, the isolated product was concentrated *in vacuo* to afford 195 mg, 0.35 mmol (100%) of 1-({8-chloro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-*a*]pyridin-6-yl}carbonyl)-3-(1-nitroethyl)azetidin-3-ol as a yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$): 8.28 (s, 1H), 7.68 (s, 1H), 7.59 (s, 1H), 7.43 (d, 1H), 7.31 (d, 1H), 7.23 (br s, 1H), 6.55-6.51 (m, 1H), 6.02 (br s, 1H), 4.79 (q, 1H), 4.45-3.96 (4H), 1.56 (d, 3H). MS (EI) for $C_{20}H_{19}ClFIN_6O_4$: 560 (MH^+).

[00380] To a solution of 1-({8-chloro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-*a*]pyridin-6-yl}carbonyl)-3-(1-nitroethyl)azetidin-3-ol (195 mg 0.35 mmol) in tetrahydrofuran/water (5 mL, 4:1) was added iron powder (193 mg, 3.5 mmol) and ammonium formate (438 mg, 7.0 mmol). The mixture was stirred at 80°C for 1 hour, then cooled to room temperature and filtered through a pad of celite. The celite was washed three times with boiling ethanol (20 mL). The filtrate was concentrated *in vacuo* and the residue was diluted with ethyl acetate. The precipitate which formed was filtered through a pad a celite and the filtrate was partitioned with water. The aqueous portion was extracted twice with ethyl acetate. The combined organic portion was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a yellow residue which was purified by preparative reverse phase HPLC. The isolated product was concentrated *in vacuo* to afford

35 mg, 0.05 mmol (15%) of 3-(1-aminoethyl)-1-({8-chloro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-a]pyridin-6-yl}carbonyl)azetidin-3-ol acetate salt as a white solid. ^{1}H NMR (400 MHz, DMSO): 8.79 (s, 1H), 8.00 (s, 1H), 7.61 (s, 1H), 7.54 (d, 1H), 7.32 (d, 1H), 6.54-6.48 (m, 1H), 4.24-4.13 (m, 1H), 3.98-3.84 (m, 2H), 3.61-3.56 (m, 1H), 2.83 (q, 1H), 0.92-0.88 (m, 3H); MS (EI) for $C_{19}H_{18}ClFIN_5O_2$: 530 (MH^+).

EXAMPLE 31

1-({8-chloro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-a]pyridin-6-yl}carbonyl)-3-piperidin-2-ylazetidin-3-ol



[00381] To a solution of 1,1-dimethylethyl 2-(3-hydroxy-1-{[(phenylmethyl)oxy]carbonyl}azetidin-3-yl)piperidine-1-carboxylate (595 mg, 1.52 mmol), prepared using procedures similar to those described in Reference 5, in methanol (5 mL) was added catalytic palladium on carbon (5% wt). The heterogeneous mixture was stirred under a hydrogen gas atmosphere for 15 hours at ambient pressure and then was filtered. The filtrate was concentrated *in vacuo* to afford 385 mg, 1.50 mmol (98%) of 1,1-dimethylethyl 2-(3-hydroxyazetidin-3-yl)piperidine-1-carboxylate as a colorless film without further purification.

[00382] A solution of 8-chloro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-*a*]pyridine-6-carboxylic acid (78 mg, 0.18 mmol) (prepared using procedures similar to those described in US 2006030610 and US 2005054701), 1,1-dimethylethyl 2-(3-hydroxyazetidin-3-yl)piperidine-1-carboxylate (46.7 mg, 0.18 mmol), 4-(dimethylamino)pyridine (66 mg, 0.55 mmol), and finally 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (42 mg, 0.21 mmol) in dimethylformamide (2 mL) was stirred at room temperature for 15 hours. The reaction mixture was partition between 5% aqueous lithium chloride and ethyl acetate and the aqueous portion was extracted twice using ethyl acetate. The combined organic portion was washed with 1 N HCl, brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a brown residue which was purified by column chromatography. Eluting with ethyl acetate, the isolated product was concentrated *in vacuo* to afford 101 mg, 0.15 mmol (83%) of 1,1-dimethylethyl 2-[1-({8-chloro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-a]pyridin-6-yl}carbonyl)-3-hydroxyazetidin-3-yl]piperidine-1-carboxylate as a white solid.

The solid was immediately dissolved in methanol (5 mL) and 4 N HCl in dioxane was added. The solution was briefly heated to reflux and then was concentrated *in vacuo*. The resultant residue was purified by preparative reverse phase HPLC. Isolated product was concentrated *in vacuo* to afford 36 mg, 0.06 mmol (40%) of 1-({8-chloro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-a]pyridin-6-yl}carbonyl)-3-piperidin-2-ylazetidin-3-ol acetate as a white solid. ^{1}H NMR (400 MHz, DMSO): 8.78 (s, 1H), 8.19 (s, 0.5H), 8.15 (s, 0.5H), 8.00 (s, 1H), 7.62 (s, 1H), 7.55 (d, 1H), 7.31 (d, 1H), 6.54-6.49 (m, 1H), 4.24-4.12 (m, 1H), 3.97-3.86 (m, 2H), 3.63-3.56 (m, 1H), 2.98-2.90 (m, 1H), 2.50-2.40 (m, 1H), 1.72-1.61 (m, 1H), 1.56-1.43 (m, 2H), 1.32-1.14 (m, 2H), 1.07-0.94 (m, 1H); MS (EI) for $C_{22}H_{22}ClFIN_5O_2$: 570 (MH^+).

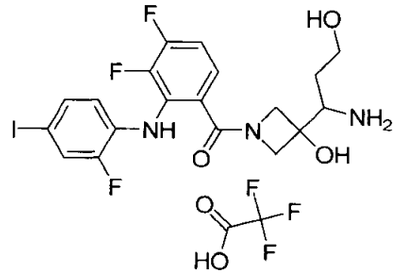
[00383] Using the same or analogous synthetic techniques and/or substituting with alternative reagents, the following compounds of the invention were prepared:

EXAMPLE 31(a). 1-({4-fluoro-5-[(2-fluoro-4-iodophenyl)amino]-1-methyl-1*H*-benzimidazol-6-yl}carbonyl)-3-piperidin-2-ylazetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, DMSO): 8.35 (s, 1H), 7.84-7.77 (m, 1H), 7.54-7.49 (m, 2H), 7.25 (d, 1H), 6.31-6.25 (m, 1H), 4.04-3.92 (m, 2H), 3.90 (s, 3H), 3.86-3.78 (m, 1H), 3.70-3.62 (m, 1H), 2.94-2.85 (m, 1H), 2.45-2.32 (m, 2H), 1.66-1.36 (m, 3H), 1.26-1.08 (m, 2H), 1.01-0.80 (m, 1H); MS (EI) for $C_{23}H_{24}F_2IN_5O_2$: 568 (MH^+).

EXAMPLE 31(a). 1-({7-[(4-bromo-2-chlorophenyl)amino]-8-chloroimidazo[1,2-a]pyridin-6-yl}carbonyl)-3-piperidin-2-ylazetidin-3-ol acetate salt: ^{1}H NMR (400 MHz, DMSO): 8.87 (s, 1H), 8.29 (s, 0.5H), 8.21 (s, 0.5H), 8.04 (s, 1H), 7.67-7.63 (m, 2H), 7.32 (d, 1H), 6.59 (d, 1H), 4.35-4.22 (m, 1H), 4.08-3.98 (m, 2H), 3.72-3.67 (m, 1H), 2.96-2.88 (m, 1H), 2.50-2.44 (m, 2H), 1.66-1.42 (m, 3H), 1.26-1.17 (m, 2H), 1.04-0.94 (m, 1H); MS (EI) for $C_{22}H_{22}BrCl_2N_5O_2$: 540 (MH^+).

EXAMPLE 32

3-(1-Amino-3-hydroxypropyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol trifluoroacetate salt



[00384] Potassium *tert*-butoxide (1.393 g, 12.4 mmol) and [2-(1,3-dioxolan-2-yl)ethyl]-triphenylphosphonium bromide (5.51 g, 12.4 mmol) were stirred in ether (30 mL) at amibient for 1 h. Phenylmethyl 3-oxoazetidine-1-carboxylate (1.025 g, 5.0 mmol), prepared using procedures similar to those described in Reference 3, was added and the mixture was stirred at 35 °C for 6 h and then at ambient for 4 days. Mixture was filtered through celite and the solid was washed with ether. The filtrate was washed with water, brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, 20% ether in hexanes) gave phenylmethyl 3-[2-(1,3-dioxolan-2-yl)ethylidene]azetidine-1-carboxylate (220 mg, 0.761 mmol, 15% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 7.39-7.28 (m, 5H), 5.43-5.35 (m, 1H), 5.11 (s, 2H), 4.89 (t, 1H), 4.56 (br d, 4H), 4.00-3.92 (m, 2H), 3.91-3.83 (m, 2H), 2.27 (br t, 2H).

[00385] Phenylmethyl 3-[2-(1,3-dioxolan-2-yl)ethylidene]azetidine-1-carboxylate (220 mg, 0.761 mmol), and 4-methylmorpholine N-oxide (287 mg, 2.45 mmol) were dissolved in acetone / water (4:1; 10 mL) and osmium tetroxide (4 wt.% in water; 0.05 mL) was added. The solution was stirred at ambient for 20 h, then was quenched with saturated sodium bisulfite (2 mL) and concentrated *in vacuo*. The residue was partitioned between ethyl acetate and brine. The aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, ethyl acetate) gave phenylmethyl 3-[2-(1,3-dioxolan-2-yl)-1-hydroxyethyl]-3-hydroxyazetidine-1-carboxylate (244 mg, 0.755 mmol, 99% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 7.38-7.28 (m, 5H), 5.11-5.07 (m, 3H), 4.14-4.01 (m, 4H), 3.96-3.86 (m, 5H), 3.47 (d, 1H), 2.97-2.94 (m, 1H), 1.98-1.84 (m, 2H).

[00386] Phenylmethyl 3-[2-(1,3-dioxolan-2-yl)-1-hydroxyethyl]-3-hydroxyazetidine-1-carboxylate (235 mg, 0.728 mmol) was dissolved in methanol (5 mL) and treated with 5 wt% palladium on carbon (50 mg) under hydrogen at ambient for 1.5 h. The mixture was filtered and the filtrate was concentrated *in vacuo* to afford 3-[2-(1,3-dioxolan-2-yl)-1-hydroxyethyl]azetidin-3-ol (0.729 mmol): MS (EI) for $C_8H_{15}NO_4$: 190 (MH^+).

[00387] 3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoic acid (287 mg, 0.730 mmol), prepared using procedures similar to those described in US 7,019,033, 4-(dimethylamino)pyridine (178 mg, 1.46 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (168 mg, 0.88 mmol) were dissolved in DMF (3 mL). The mixture was stirred at ambient for 10 minutes and then 3-[2-(1,3-dioxolan-2-yl)-1-hydroxyethyl]azetidin-3-ol (0.729 mmol) in DMF (2 mL) was added and the mixture was stirred for 15 h. The mixture was partitioned between ethyl acetate and 5% lithium chloride.

The organic portion was washed with 20% citric acid, saturated sodium bicarbonate and brine, then was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, gradient 90% ethyl acetate in hexanes to 100% ethyl acetate) gave 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[2-(1,3-dioxolan-2-yl)-1-hydroxyethyl]azetidin-3-ol (148 mg, 0.262 mmol, 36% yield): MS (EI) for $C_{21}H_{20}F_3IN_2O_5$: 565 (MH^+).

[00388] 1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[2-(1,3-dioxolan-2-yl)-1-hydroxyethyl]azetidin-3-ol (148 mg, 0.262 mmol), was dissolved in dichloromethane (10 mL) and treated with 4-(dimethylamino)pyridine (38 mg, 0.31 mmol), triethylamine (0.036 mL, 0.262 mmol) and 2,4,6-triisopropylbenzenesulfonyl chloride (303 mg, 1.0 mmol) at 35 °C for 15 h. 2,4,6-Triisopropylbenzenesulfonyl chloride (100 mg, 0.33 mmol) was added and the mixture was stirred at 35 °C for 3.5 h. The mixture was adsorbed on to silica and purified by column chromatography (silica gel, 40-50% ethyl acetate in hexanes and then 100% ethyl acetate) to give 1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]-2-(1,3-dioxolan-2-yl)ethyl 2,4,6-tris(1-methylethyl)benzenesulfonate (30 mg, 0.0361 mmol, 14% yield): MS (EI) for $C_{36}H_{42}F_3IN_2O_7S$: 831 (MH^+).

[00389] 1-[1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]-2-(1,3-dioxolan-2-yl)ethyl 2,4,6-tris(1-methylethyl)benzenesulfonate (50 mg, 0.060 mmol) was dissolved in tetrahydrofuran (1 mL) and was cooled to 0 °C. Sodium hydride (60 wt% dispersion in oil; 7 mg, 0.18 mmol) was added and the mixture was stirred at 0 °C for 45 minutes. The mixture was quenched with saturated sodium bicarbonate solution and partitioned with ethyl acetate. The aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, 50% ethyl acetate in hexanes) gave 6-{[2-(1,3-dioxolan-2-ylmethyl)-1-oxa-5-azaspiro[2.3]hex-5-yl]carbonyl}-2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)aniline (31 mg, 0.057 mmol, 94% yield): MS (EI) for $C_{21}H_{18}F_3IN_2O_4$: 547 (MH^+).

[00390] 6-{[2-(1,3-Dioxolan-2-ylmethyl)-1-oxa-5-azaspiro[2.3]hex-5-yl]carbonyl}-2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)aniline (31 mg, 0.057 mmol) was dissolved in dimethylformamide (0.5 mL) and sodium azide (20 mg, 0.308 mmol) was added. The mixture was stirred at ambient for 22 h. The mixture was partitioned between ethyl acetate and 5% lithium chloride. The aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with water, brine, then was dried over anhydrous

sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, 50% ethyl acetate in hexanes) gave 3-[1-azido-2-(1,3-dioxolan-2-yl)ethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol (25 mg, 0.042 mmol, 74% yield): MS (EI) for $C_{21}H_{19}F_3IN_5O_4$: 590 (MH^+).

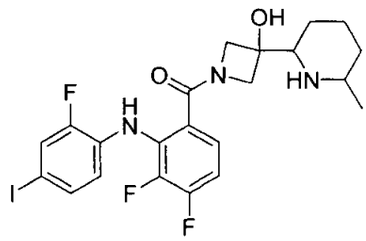
[00391] 3-[1-Azido-2-(1,3-dioxolan-2-yl)ethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol (24 mg, 0.041 mmol) was dissolved in tetrahydrofuran (0.5 mL) and treated with 5% aqueous hydrochloric acid (0.5 mL) at ambient for 15 h. The misture was neutralised with saturated sodium bicarbonate solution and was extracted twice with ethyl acetate. The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford 3-azido-3-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]propanal (21 mg, 0.0385 mmol) which was suspended in ethanol (2 mL) and treated with sodium borohydride (5 mg, 0.132 mmol) at ambient for 2 h. The mixture was quenched with acetic acid (4 drops) and concentrated *in vacuo*. The residue was partitioned between saturated sodium bicarbonate solution and ethyl acetate. The aqueous portion was extracted with ethyl acetate. The combined organic portion was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Column chromatography (silica gel, 70-80% ethyl acetate in hexanes) gave 3-(1-azido-3-hydroxypropyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol (14 mg, 0.0255 mmol, 62% yield from 3-[1-azido-2-(1,3-dioxolan-2-yl)ethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol): ^{1}H NMR (400 MHz, $CDCl_3$): 8.33 (br s, 1H), 7.40 (dd, 1H), 7.32 (br d, 1H), 7.13 (br t, 1H), 6.83 (br q, 1H), 6.61 (ddd, 1H), 4.32-3.94 (m, 4H), 3.92-3.84 (m, 1H), 3.82-3.71 (m, 2H), 2.56 (br, 1H), 1.94 (br, 2H), 1.26 (br, 1H); MS (EI) for $C_{19}H_{17}F_3IN_5O_3$: 548 (MH^+).

[00392] 3-(1-Azido-3-hydroxypropyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol (14 mg, 0.0255 mmol) was dissolved in tetrahydrofuran and water (1:1, 0.5 mL) and polymer supported triphenylphosphine (~3 mmol/g; 20 mg, 0.06 mmol) was added. The mixture was stirred at 55 °C for 1 h. Triphenylphosphine (10 mg, 0.038 mmol) was added and the mixture was stirred at 55 °C for 1.5 h. The mixture was filtered and the filtrate was purified by reverse phase HPLC to afford 3-(1-amino-3-hydroxypropyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol trifluoroacetate salt (1.7 mg, 0.003 mmol, 10% yield): ^{1}H NMR (400 MHz, CD_3OD): 7.47 (dd, 1H), 7.36 (br d, 1H), 7.33-7.28 (m, 1H), 7.05 (br q, 1H), 6.62 (ddd, 1H), 4.38-4.26 (m, 1H), 4.18-4.00 (m, 2H), 3.98-3.88 (m,

1H), 3.78-3.67 (m, 2H), 3.61-3.56 (m, 1H), 1.87-1.70 (m, 2H); MS (EI) for $C_{19}H_{19}F_3IN_3O_3$: 522 (MH^+).

EXAMPLE 33

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(6-methylpiperidin-2-yl)azetidin-3-ol



[00393] To a solution of *N,N*-diisopropylamine (1.6 mL, 11.2 mmol) cooled to -78 °C in THF (15 mL) was added a 2.5 M solution of n-BuLi in hexane (4.5 mL, 11.2 mmol) dropwise over 5 minutes and the mixture was stirred at this temperature for an addition 15 minutes. 6-methyl-1-(phenylmethyl)piperidine-2-carbonitrile (2.4 g, 11.2 mmol) (prepared using procedures similar to those in Bonin *et. al. Tet. Lett.* **1982,** *23(33),* 3369-72) in THF (10 mL) was then added dropwise over 20 minutes and the reaction mixture was stirred for a further 30 minutes. Next a solution of 1,1-dimethylethyl 3-oxoazetidine-1-carboxylate (1.3 g, 7.5 mmoL), prepared using procedures similar to those in Example 3, in THF (10 mL) was added dropwise over 30 minutes. The reaction mixture was gradually warmed to room temperature and allowed to stir overnight. The reaction mixture was quenched with 10% citric acid and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water, brine, dried over anhydrous sodium sulfate then filtered and concentrated *in vacuo* to give crude product as yellow oil. Further purification by flash chromatography (30% ethyl acetate in hexanes) afforded 1,1-dimethylethyl 3-[2-cyano-6-methyl-1-(phenylmethyl)piperidin-2-yl]-3-hydroxyazetidine-1-carboxylate as a pale yellow oil (0.2 g, 7% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 7.17-7.40 (m, 5H), 4.42 (d, 1H), 4.04-4.18 (m, 1H), 3.83-4.00 (m, 1H), 3.70-3.75 (m, 2H), 1.70-1.87 (m, 4H), 1.45 (s, 3H), 1.41 (s, 9H), 1.22-1.26 (m,1H), 1.13-1.18 (m, 2H); MS (EI) for $C_{22}H_{31}N_3O_3$: 386 (MH^+).

[00394] To a stirred solution of 1,1-dimethylethyl 3-[2-cyano-6-methyl-1-(phenylmethyl)piperidin-2-yl]-3-hydroxyazetidine-1-carboxylate (180 mg, 0.47 mmol) in ethanol (1 mL) was added acetic acid (53.5 µL, 0.94 mmol) followed by sodium cyanoborohydride (58.7 mg, 0.94 mmol) and the reaction mixture stirred at 70 °C overnight. After cooling to room temperature the suspension was filtered through celite and the solid

washed with additional ethanol. The filtrate was concentrated *in vacuo* and taken up in ethyl acetate (30 mL). The organic layer was washed with 2 M sodium hydroxide solution. The sodium hydroxide layer was separated and washed with ethyl acetate (10 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give crude1,1-dimethylethyl 3-hydroxy-3-[6-methyl-1-(phenylmethyl)piperidin-2-yl]azetidine-1-carboxylate as yellow oil (60 mg, 36% yield). Crude product was used further without purification. ^{1}H NMR (400 MHz, $CDCl_3$): 7.22-7.35 (m, 5H), 4.08 (d, 1H), 3.85-3.96 (m, 3H), 3.57 (d, 1H), 3.33-3.36 (m, 1H), 2.91-3.06 (m, 2H), 1.63-1.70 (m, 4H), 1.44 (s, 9H), 1.23 (d,3H), 1.05 (d, 2H); MS (EI) for $C_{21}H_{32}N_2O_3$: 361 (MH^+).

[00395] To a solution of 1,1-dimethylethyl 3-hydroxy-3-[6-methyl-1-(phenylmethyl)piperidin-2-yl]azetidine-1-carboxylate (60 mg, 0.16 mmol) in methanol (0.5 mL) was added hydrogen chloride (4N in dioxane, 0.5 mL) and the reaction mixture stirred at 60 °C for one hour. The reaction mixture was cooled to room temperature and concentrated *in vacuo* and aezotroped 3 times from methanol and diethyl ether. On drying the hydrochloride salt of 3-[6-methyl-1-(phenylmethyl)piperidin-2-yl]azetidin-3-ol was obtained as a dark brown residue (40 mg, 81% yield), which was used further without purification. ^{1}H NMR (400MHz, CD_3OD): 7.58-7.63 (m, 2H), 7.47-7.49 (m, 3H), 4.78 (d, 1H), 4.44-4.62 (m, 2H), 4.29 (s, 2H), 4.22-4.26 (m, 1H), 4.12-4.18 (m, 1H), 4.08 (s, 1H), 1.60-2.00 (m, 8H), 1.48 (d, 3H); MS (EI) for $C_{16}H_{25}ClN_2O$: 261 (MH^+).

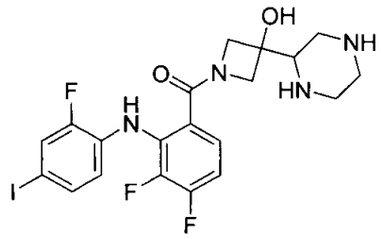
[00396] To a solution of 3-[6-methyl-1-(phenylmethyl)piperidin-2-yl]azetidin-3-ol hydrochloride (40 mg, 0.13 mmol) in ethyl acetate (3 mL) was added acetic acid (0.5 mL) and Pd/C (50 mg) and the mixture was hydrogenated at 35 psi for 3 hours. The reaction mixture was filtered through celite. The filtrate was concentrated *in vacuo*. The obtained residue was dissolved in a small amount of ethyl acetate and concentrated hydrochloric acid was added and the mixture was concentrated *in vacuo* to give the crude dihydrochloride salt of 3-[6-methylpiperidin-2-yl]azetidin-3-ol (20 mg, 54%). The crude product was used further without purification. ^{1}H NMR (400MHz, CD_3OD): 4.20-4.40 (m, 1H), 4.00-4.10 (m, 1H), 3.60-3.90 (m, 2H), 1.50-2.00 (m, 6H), 1.45 (d, 3H), 1.26-1.30 (m, 1H); MS (EI) for $C_9H_{20}Cl_2N_2O$: 171 (MH^+).

[00397] To a 0 °C solution of 3-[6-methylpiperidin-2-yl]azetidin-3-ol dihydrochloride (20 mg, 0.08 mmol) in DMF (1 mL) was added *N,N*-diisopropylethylamine (42 µL, 0.26 mmol) followed by 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino] benzoyl fluoride (32 mg, 0.08 mmol), prepared using procedures similar to those described in Reference 1, and the reaction

mixture stirred at 0 °C for 30 min. The mixture was diluted with acetonitrile and purified by preparative reverse phase HPLC (CH_3CN/H_2O with 0.1% TFA). Fractions were collected and lyophilized to give 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(6-methylpiperidin-2-yl)azetidin-3-ol acetate salt (7 mg, 16% yield) as a white solid. ^{1}H NMR (400MHz, CD_3OD): 7.44-7.50 (m, 1H), 7.34-7.37 (m, 1H), 7.28-7.32 (m, 1H), 7.02-7.12 (m, 1H), 6.60-6.63 (m, 1H), 4.10-4.30 (m, 2H), 3.95-4.09 (m, 2H), 3.80-3.95 (m, 1H), 3.55-3.65 (m, 1H), 3.34-3.36 (m, 1H), 1.90 (s, 3H), 1.62-1.84 (m, 6H), 1.40-1.52 (m, 1H), 1.33 (d, 3H); MS (EI) for $C_{22}H_{23}F_3IN_3O_2$: 546 (MH^+).

EXAMPLE 34

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-piperazin-2-ylazetidin-3-ol



[00398] To a solution of commercially available 1,4-bis(phenylmethyl)piperazine-2,5-dione (2.0 g, 6.8 mmol) in dry THF (50 mL) at -78 °C was added lithium diisopropylamide (2.0 M solution in heptane/THF/ethylbenzene, 3.4 mL, 6.8 mmol). The resulting reddish brown suspension was stirred for 23 min at -78 °C, and then a solution of 1,1-dimethylethyl 3-oxoazetidine-1-carboxylate (770 mg, 4.5 mmol) in THF (10 mL) was added over 30 min by syringe pump. The mixture became a bright yellow solution as it was allowed to warm to room temperature over 3 hours. The mixture was quenched with saturated aqueous ammonium chloride. Water was added to dissolve precipitated salts, and the resulting mixture was extracted twice with ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography (60% ethyl acetate: 40% hexanes) to provide 1,1-dimethylethyl 3-[3,6-dioxo-1,4-bis(phenylmethyl)piperazin-2-yl]-3-hydroxyazetidine-1-carboxylate as a colorless foam (1.04 g, 2.23 mmol, 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 7.39-7.29 (m, 7H), 7.23-7.19 (m, 3H), 5.34 (d, 1H), 4.82 (d, 1H), 4.58 (d, 1H), 4.37 (d, 1H), 4.37 (d, 1H), 4.22 (d, 1H), 4.15 (s, 1H), 4.08 (d, 1H), 3.97 (d, 1H), 3.75 (d, 1H), 3.74 (d, 1H), 3.67 (d, 1H), 3.64 (br s, 1H), 1.43 (s, 9H).

[00399] A solution of 1,1-dimethylethyl 3-[3,6-dioxo-1,4-bis(phenylmethyl)piperazin-2-yl]-3-hydroxyazetidine-1-carboxylate (1.04 g, 2.2 mmol) in methanol (10 mL) was treated with hydrogen chloride in dioxane (4 N, 5.5 mL, 22 mmol) at 60 °C for 25 min. After cooling to room temperature the solution was concentrated. Ethyl acetate and 2 N hydrochloric acid were added to the residue and the phases were separated. The organic phase was discarded. The aqueous phase was basified with 5 M sodium hydroxide and the resulting solution was extracted 4 times with ethyl acetate. The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography (85% dichloromethane: 14% methanol: 1% aqueous ammonium hydroxide) to provide 3-(3-hydroxyazetidin-3-yl)-1,4-bis(phenylmethyl)piperazine-2,5-dione as a colorless film (493 mg, 1.35 mmol, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 7.39-7.28 (m, 6H), 7.25-7.20 (m, 4H), 5.39 (d, 1H), 4.80 (d, 1H), 4.44 (d, 1H), 4.36 (d, 1H), 4.26 (d, 1H), 4.11 (s, 1H), 3.97 (d, 1H), 3.83 (d, 1H), 3.71 (d, 1H), 3.27 (m, 2H); MS (EI) for $C_{21}H_{23}N_3O_3$: 366 (MH^+).

[00400] A solution 3-(3-hydroxyazetidin-3-yl)-1,4-bis(phenylmethyl)piperazine-2,5-dione (493 mg, 1.35 mmol) in ethyleneglycol dimethylether (12 mL) was treated with sodium borohydride (511 mg, 13.5 mmol) followed by slow addition of boron trifluoride-diethyl etherate. The reaction mixture was then heated to reflux for 3 hours. After cooling to 0 °C, methanol (17 mL) was added followed by careful addition of concentrated hydrochloric acid (7 mL). The resulting mixture was heated to reflux for 70 minutes. After cooling to room temperature, insoluble residue was removed by filtration. The filtrate was concentrated to an aqueous mixture of about 10 mL in volume. This mixture was cooled to 0 °C and was then basified to pH 10 with 5 M sodium hydroxide (approximately 17 mL). Dichloromethane (10 mL) was then added followed by di-*tert*-butyl dicarbonate (442 mg, 2.03 mmol). The mixture was warmed to room temperature and stirred for 15 minutes. The layers were separated and the aqueous phase was extracted twice with dichloromethane. The organic extracts were combined, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography (70% hexanes: 30% ethyl acetate) to provide 1,1-dimethylethyl 3-[1,4-bis(phenylmethyl)piperazin-2-yl]-3-hydroxyazetidine-1-carboxylate as a white foam (408 mg, 0.93 mmol, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 7.35-7.24 (m, 10H), 4.12 (br s, 1H), 3.88 (d, 1H), 3.78-3.65 (m, 4H), 3.53 (d, 1H), 3.43 (d, 1H), 3.21 (m, 1H), 2.80 (br s, 1H), 2.66 (m, 1H), 2.57-2.37 (m, 4H), 1.41 (s, 9H); MS (EI) for $C_{26}H_{35}N_3O_3$: 438 (MH^+).

[00401] To a solution of 1,1-dimethylethyl 3-[1,4-bis(phenylmethyl)piperazin-2-yl]-3-hydroxyazetidine-1-carboxylate (408 mg, 0.93 mmol) in methanol (15 mL) was added 10% palladium on carbon (wet), and the resulting suspension was subjected to an atmosphere of hydrogen for 21 hours. The catalyst was removed by filtration through celite, and the filter cake was rinsed with methanol. The combined filtrate was concentrated to provide 1,1-dimethylethyl 3-hydroxy-3-piperazin-2-ylazetidine-1-carboxylate as a brown syrup (227 mg, 0.88 mmol, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 3.94-3.76 (m, 5H), 3.12 (m, 1H), 3.01 (m, 1H), 2.94-2.81 (m, 3H), 2.78-2.70 (m, 2H); MS (EI) for $C_{12}H_{23}N_3O_3$: 258 (MH^+).

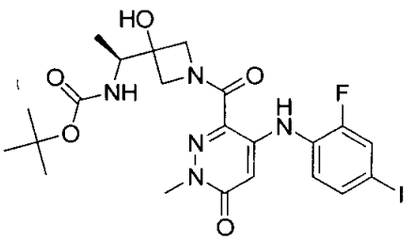
[00402] To a solution of 1,1-dimethylethyl 3-hydroxy-3-piperazin-2-ylazetidine-1-carboxylate (227 mg, 0.88 mmol) and *N,N*-diisopropylethylamine (436 µL, 2.64 mmol) in THF (5 mL) was added 2-nitrobenzenesulfonyl chloride (195 mg, 0.88 mmol). The mixture was stirred at room temperature for 2 hours. The solution was concentrated and the residue was purified by column chromatography (95% dichloromethane: 5% methanol) to provide 1,1-dimethylethyl 3-hydroxy-3-{4-[(2-nitrophenyl)sulfonyl]piperazin-2-yl}azetidine-1-carboxylate as a white foam (308 mg, 0.70 mmol, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 7.98 (m, 1H), 7.72 (m, 2H), 7.64 (m, 1H), 3.96 (d, 1H), 3.94 (d, 1H), 3.85 (d, 1H), 3.79 (d, 1H), 3.79-3.73 (m, 2H), 3.11 (m, 1H), 3.05 (dd, 1H), 3.00 (br s, 1H), 2.94 (dt, 1H), 2.78 (dt, 1H), 2.68 (dd, 1H), 1.45 (s, 9H).

[00403] To a solution of 1,1-dimethylethyl 3-hydroxy-3-{4-[(2-nitrophenyl)sulfonyl]piperazin-2-yl}azetidine-1-carboxylate (308 mg, 0.70 mmol) in methanol (10 mL) was added HCl in dioxane (4 N, 1.75 mL, 7.0 mmol), and the mixture was heated to 60 °C for 30 minutes. The solution was concentrated to provide 3-{4-[(2-nitrophenyl)sulfonyl]piperazin-2-yl}azetidin-3-ol as a sticky white solid. This material was dissolved in dichloromethane (7 mL). To the solution was added *N,N*-diisopropylethylamine (1.16 mL, 7.0 mmol) followed by 3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]benzoyl fluoride (277 mg, 0.7 mmol), prepared using procedures similar to those described in Reference 1, and the resulting mixture was stirred at room temperature for 16 hours. The solution was concentrated and the residue was purified by column chromatography (95% dichloromethane: 5% methanol) to provide 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{4-[(2-nitrophenyl)sulfonyl]piperazin-2-yl}azetidin-3-ol as a pale yellow foam (453 mg, 0.63 mmol, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 8.49 (s, 1H), 7.96 (dd, 1H), 7.71 (m, 2H), 7.53 (dd, 1H), 7.39 (dd, 1H), 7.33 (d, 1H), 7.15 (m, 1H), 6.84 (br s, 1H), 6.62 (m, 1H), 4.29-3.97 (br m, 4H), 3.79-3.62 (m, 3H), 3.26-2.99 (br m, 3H), 2.92-2.62 (br m, 3H); MS (EI) for $C_{26}H_{23}F_3IN_5O_6S$: 718 (MH^+).

[00404] To a solution of 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{4-[(2-nitrophenyl)sulfonyl]piperazin-2-yl}azetidin-3-ol (139.4 mg, 0.19 mmol) in DMF (1 mL) was added potassium carbonate (79 mg, 0.57 mmol) and thiophenol (21 μL, 0.21 mmol). The mixture was stirred for 45 min at room temperature then quenched with water. The aqueous mixture was extracted twice with ethyl acetate, and the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated. The residue was purified by preparative reverse phase HPLC to provide 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-piperazin-2-ylazetidin-3-ol as a white solid (26.8 mg, 0.05 mmol). ^{1}H NMR (400 MHz, CD_3OD): 7.45 (dd, 1H), 7.36 (m, 1H), 7.32 (m, 1H), 7.03 (m, 1H), 6.62 (ddd, 1H), 4.51 (br dd, 1H), 4.31 (br dd, 1H), 4.17-3.92 (m, 4H), 3.73-3.56 (m, 3H), 3.46 (br m, 1H), 3.26 (m, 1H); MS (EI) for $C_{20}H_{20}F_3IN_4O_2$: 533 (MH^+).

EXAMPLE 36

1,1-Dimethylethyl {(1*S*)-1-[1-({4-[(2-fluoro-4-iodophenyl)amino]-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}carbamate



[00405] To a suspension of 4-[(2-fluoro-4-iodophenyl)amino]-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid (50 mg, 0.13 mmol) in DMF (2 mL), prepared using similar procedures to those described in Reference 4, at room temperature was added 1-hydroxybenzotriazole (36.3 mg, 0.27 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (52 mg, 0.27 mmol) and the reaction was stirred for 2 hours. 1,1-Dimethylethyl [(1*S*)-1-(3-hydroxyazetidin-3-yl)ethyl]carbamate (30 mg, 0.13 mmol), prepared using procedures similar to those in Example 28, and triethylamine (0.04 mL) were added and the mixture was stirred for 15 hours. The reaction mixture was partitioned between saturated sodium chloride and ethyl acetate. The organic layer was washed with 5% lithium chloride solution, saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give crude product as yellow oil. The oil was purified by column chromatography (silica gel, ethyl acetate) to afford 1,1-dimethylethyl {(1*S*)-1-[1-({4-[(2-fluoro-4-iodophenyl)amino]-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl}carbonyl)-3-

hydroxyazetidin-3-yl]ethyl}carbamate as a yellow oil (55 mg, 73% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 10.24-10.23 (m, 1H), 7.52-7.50 (m, 2H), 7.12-7.07 (m, 1H), 6.10-6.09 (m, 1H), 5.13-5.09 (m, 1H), 4.91-4.82 (m, 1H), 4.60-4.39 (m, 2H), 4.10-4.08 (m, 1H), 4.00-3.87 (m, 2H), 3.70 (d, 3H), 1.43 (s, 9H), 1.24-1.20 (m, 3H); MS (EI) for $C_{22}H_{27}FIN_5O_5$: 588 (MH^+).

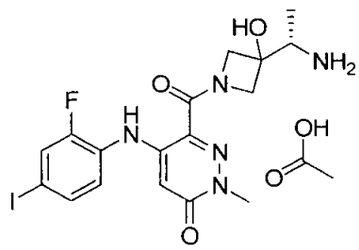
[00406] Using the same or analogous synthetic techniques and substituting, as necessary, with alternative reagents, the following compounds of the invention were prepared:

EXAMPLE 36(a). 1,1-Dimethylethyl {(1*S*)-1-[1-({5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-1-methyl-1*H*-benzimidazol-6-yl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}carbamate: ^{1}H NMR (400 MHz, $CDCl_3$): 7.95 (s, 1H), 7.45-7.44 (m, 1H), 7.33-7.27 (m, 2H), 7.15-7.12 (m, 1H), 6.50-6.47 (m, 1H), 4.82-4.74 (m, 1H), 4.17-3.92 (m, 4H), 3.86 (s, 3H), 3.74-3.60 (m, 1H), 1.40 (s, 9H), 1.11-1.06 (m, 3H). MS (EI) for $C_{25}H_{28}BrClFN_5O_4$: 598 (MH^+) with a chloro, bromo isotope pattern.

EXAMPLE 36(b). 1,1-Dimethylethyl (2*S*)-2-[1-({5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-1-methyl-1*H*-benzimidazol-6-yl}carbonyl)-3-hydroxyazetidin-3-yl]piperidine-1-carboxylate: MS (EI) for $C_{28}H_{32}BrClFN_5O_4$: 638 (MH^+) with a chloro, bromo isotope pattern.

Example 37

6-({3-[(1*S*)-1-aminoethyl]-3-hydroxyazetidin-1-yl}carbonyl)-5-[(2-fluoro-4-iodophenyl)amino]-2-methylpyridazin-3(2*H*)-one acetate salt



[00407] 1,1-Dimethylethyl {(1*S*)-1-[1-({4-[(2-fluoro-4-iodophenyl)amino]-1-methyl-6-oxo-1,6-dihydropyridazin-3-yl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}carbamate (55 mg, 0.09 mmol), prepared using procedures similar to those described in Example 36, was taken up in methanol (2 mL) and hydrochloric acid (4N in dioxane, 1 mL, 4 mmol) was added and the reaction was stirred at 60 °C for 2 hours. The reaction mixture was concentrated *in vacuo* and was purified by reverse-phase HPLC followed by lyophilization of the pure fractions to afford 6-({3-[(1*S*)-1-aminoethyl]-3-hydroxyazetidin-1-yl}carbonyl)-5-[(2-fluoro-4-

iodophenyl)amino]-2-methylpyridazin-3(2*H*)-one acetate as yellow solid (40 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): 10.17 (d, 1H), 7.52-7.46 (m, 2H), 7.09 (t, 1H), 6.13-6.12 (m, 1H), 4.51-4.48 (m, 2H), 4.18-4.03 (m, 2H), 3.73 (d, 3H), 3.35-3.28 (m, 1H), 3.22-2.80 (br, 3H), 1.21-1.19 (m, 3H); MS (EI) for $C_{17}H_{19}FIN_5O_3$: 488 (MH^+).

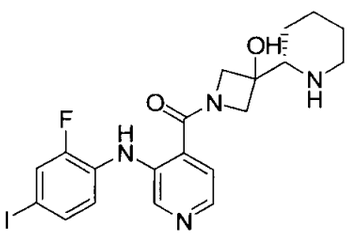
[00408] Using the same or analogous synthetic techniques and/or substituting with alternative reagents, the following compounds of the invention were prepared:

Example 37(a). 3-[(1*S*)-1-Aminoethyl]-1-({5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-1-methyl-1*H*-benzimidazol-6-yl}carbonyl)azetidin-3-ol hydrochloride. MS (EI) for $C_{20}H_{20}BrClFN_5O_2$: 498 (MH^+) with a chloro, bromo isotope pattern

Example 37(b). 1-({5-[(4-Bromo-2-chlorophenyl)amino]-4-fluoro-1-methyl-1*H*-benzimidazol-6-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol hydrochloride. ^{1}H NMR (400 MHz, CD_3OD): 9.42 (s, 1H), 7.97-7.96 (m, 1H), 7.57 (s, 1H), 7.30-7.27 (m, 1H), 6.70-6.66 (m, 1H), 4.60-4.55 (m, 1H), 4.28 (t, 1H), 4.19 (s, 3H), 4.13-3.98 (m, 2H), 3.38-3.32 (m, 2H), 3.00 (t, 1H), 1.86-1.30 (m, 6H). MS (EI) for $C_{23}H_{24}BrClFN_5O_2$. HCl: 538 (MH^+) with a chloro, bromo isotope pattern

EXAMPLE 38

1-({3-[(2-fluoro-4-iodophenyl)amino]pyridin-4-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol



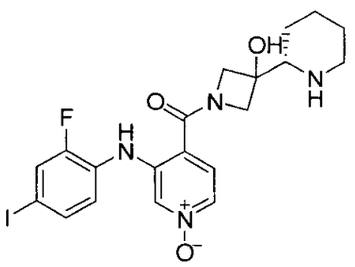
[00409] 3-[(2-Fluoro-4-iodophenyl)amino]pyridine-4-carboxylic acid (200 mg, 0.559 mmol), prepared using procedures similar to those described in WO 2006/045514, was suspended in DMF (7 mL) and 1-hydroxybenzotriazole (151 mg, 1.12 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (214 mg, 1.12 mmol) were added. The mixture was stirred at ambient for 10 minutes and then triethylamine (0.078 mL, 0.559 mmol) was added. After a further 20 minutes, 1,1-dimethylethyl (2*S*)-2-(3-hydroxyazetidin-3-yl)piperidine-1-carboxylate (143 mg, 0.559 mmol), prepared using similar procedures to those described in Example 22(a) and 22(b), and triethylamine (0.16 mL, 1.15 mmol) were added and the mixture was stirred for 15 hours. The mixture was partitioned between ethyl acetate and saturated ammonium chloride. The organic portion was washed with 5% lithium

chloride and twice with saturated sodium bicarbonate, then was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 60-80% ethyl acetate in hexanes) to give 1,1-dimethylethyl (2*S*)-2-[1-({3-[(2-fluoro-4-iodophenyl)amino]pyridin-4-yl}carbonyl)-3-hydroxyazetidin-3-yl]piperidine-1-carboxylate (368 mg, 0.587 mmol, 74% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 8.73 (br m, 1H), 8.62 (br s, 1H), 8.14 (d, 1H), 7.47 (dd, 1H), 7.43-7.39 (m, 1H), 7.20-7.12 (m, 2H), 4.38-4.21 (m, 2H), 4.16-4.01 (m, 2H), 4.01-3.88 (m, 1H), 3.44-3.30 (m, 1H), 2.98-2.83 (m, 1H), 2.00-1.88 (m, 1H), 1.71-1.50 (m, 6H), 1.44 (s, 9H); MS (EI) for $C_{25}H_{30}FIN_4O_4$: 597 (MH^+).

[00410] 1,1-Dimethylethyl (2*S*)-2-[1-({3-[(2-fluoro-4-iodophenyl)amino]pyridin-4-yl}carbonyl)-3-hydroxyazetidin-3-yl]piperidine-1-carboxylate (24 mg, 0.040 mmol) was dissolved in methanol (2 mL) and treated with 4 N hydrochloric acid in dioxane (0.25 mL, 1 mmol) at reflux for 20 minutes. The mixture was concentrated *in vacuo* and was purified by reverse-phase HPLC followed by lyophilization of the pure fractions to afford 1-({3-[(2-fluoro-4-iodophenyl)amino]pyridin-4-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol acetate (14 mg, 0.025 mmol, 63% yield): ^{1}H NMR (400 MHz, d_6-DMSO): 8.62 (br s, 1H), 8.46 (s, 1H), 8.18 (dd, 1H), 7.65 (dd, 1H), 7.45 (d, 1H), 7.37 (t, 1H), 7.16-7.08 (m, 1H), 4.25 (dd, 1H), 4.04 (dd, 1H), 3.90 (t, 1H), 3.70 (d, 1H), 2.95 (br d, 1H), 2.52-2.42 (m, 2H), 1.78-1.68 (m, 1H), 1.57 (br t, 1H), 1.47 (br d, 1H), 1.35-1.13 (m, 2H), 1.10-0.96 (m, 1H); MS (EI) for $C_{20}H_{22}FIN_4O_2$: 497 (MH^+).

EXAMPLE 39

1-({3-[(2-fluoro-4-iodophenyl)amino]-1-oxidopyridin-4-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol



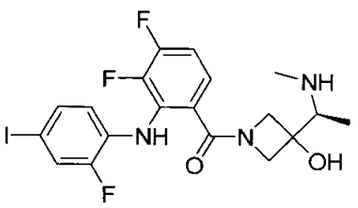
[00411] 1,1-Dimethylethyl (2*S*)-2-[1-({3-[(2-fluoro-4-iodophenyl)amino]pyridin-4-yl}carbonyl)-3-hydroxyazetidin-3-yl]piperidine-1-carboxylate (80 mg, 0.134 mmol), prepared using procedures similar to those described in Example 38, was dissolved in dichloromethane (3 mL) and treated with 3-chloroperoxybenzoic acid (73% pure; 32 mg,

0.135 mmol) at ambient for 7 hours. 3-chloroperoxybenzoic acid (73% pure; 32 mg, 0.135 mmol) was added and the mixture was stirred for 15 hours. The mixture was purified by column chromatography (silica gel, 0-10% ethanol in ethyl acetate) to give 1,1-dimethylethyl (2*S*)-2-[1-({3-[(2-fluoro-4-iodophenyl)amino]-1-oxidopyridin-4-yl}carbonyl)-3-hydroxyazetidin-3-yl]piperidine-1-carboxylate (57 mg, 0.093 mmol, 69% yield): ^{1}H NMR (400 MHz, $CDCl_3$): 9.38 (s, 1H), 8.00 (s, 1H), 7.68 (dd, 1H), 7.51 (dd, 1H), 7.46 (d, 1H), 7.19 (br d, 1H), 7.09 (t, 1H), 5.78 (br, 1H), 4.44-3.98 (m, 3H), 3.98-3.87 (m, 1H), 3.49-3.39 (m, 1H), 3.07-2.88 (m, 1H), 2.01-1.91 (m, 1H), 1.70-1.47 (m, 6H), 1.45 (s, 9H); MS (EI) for $C_{25}H_{30}FIN_4O_5$: 613 (MH^+).

[00412] 1,1-Dimethylethyl (2*S*)-2-[1-({3-[(2-fluoro-4-iodophenyl)amino]-1-oxidopyridin-4-yl}carbonyl)-3-hydroxyazetidin-3-yl]piperidine-1-carboxylate (57 mg, 0.093 mmol) was dissolved in methanol (2 mL) and treated with 4N hydrochloric acid in dioxane (0.25 mL, 1 mmol) at 50 °C for 2.25 hours. The mixture was concentrated *in vacuo* and was purified by reverse-phase HPLC followed by lyophilization of the pure fractions to afford 1-({3-[(2-fluoro-4-iodophenyl)amino]-1-oxidopyridin-4-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol acetate (35 mg, 0.061 mmol, 66% yield): ^{1}H NMR (400 MHz, d_6-DMSO): 7.83 (s, 1H), 7.72 (dt, 2H), 7.55-7.51 (m, 1H), 7.47-7.41 (m, 1H), 7.24 (t, 1H), 4.45-4.32 (m, 1H), 4.14-3.95 (m, 2H), 3.72 (d, 1H), 2.97 (d, 1H), 2.58-2.43 (m, 2H), 1.80-1.73 (m, 1H), 1.67-1.55 (m, 1H), 1.49 (br d, 1H), 1.38-1.16 (m, 2H), 1.16-1.01 (m, 1H); MS (EI) for $C_{20}H_{22}FIN_4O_3$: 513 (MH^+).

EXAMPLE 40

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(1*S*)-1-(methylamino)ethyl]azetidin-3-ol



[00413] To 3-[(1*S*)-1-aminoethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol (87.4 mg, 0.18 mmol), prepared using similar procedures to those described in Example 28, was added formaldehyde (37% aqueous, 14 mg, 0.18 mmol) in methanol (2 mL) and sodium borohydride (7 mg, 0.18 mmol). The mixture was stirred for 3 h at rt, after which sodium borohydride (16 mg, 0.42 mmol)

was added. Upon stirring an additional 1.25 h, more formaldehyde (37% aqueous, 1 drop) was added, and the mixture was stirred 3 days at rt. A further small spatula (~50 mg) of sodium borohydride was then added, and the mixture was stirred at rt for 30 min. After quenching with 1 N HCl, the reaction mixture was purified directly by preparative HPLC. The clean material was converted to its hydrochloride salt to provide 1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(1*S*)-1-(methylamino)ethyl]azetidin-3-ol as a yellow solid (21.7 mg, 0.040 mmol, 22% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.47 (dd, 1H), 7.36 (d, 1H), 7.31 (m, 1H), 7.06 (q, 1H), 6.62 (dt, 1H), 4.36 (dd, 1H), 4.21-3.91 (m, 3H), 3.44 (q, 1H), 2.66 (s, 3H), 1.29 (br m, 3H); MS (EI) for $C_{19}H_{19}F_3IN_3O_2$: 506 (MH^+).

Biological Example 1

Biochemical Assay

[00414] For a biochemical measurement of MEK1 inhibitory activity, compounds of the invention were screened in a triple coupled cRaf-MEK-ERK2 assay using ALPHASCREEN (Registered Trademark of Perkin Elmer) technology (Perkin Elmer). The compound of the invention, 0.5 μL of 100% DMSO stock solution, is diluted into an assay buffer composed of 20 mM Tris (pH = 7.5), 10 mM magnesium chloride, 0.03% CHAPS and 1 mM DTT. Subsequently, 10 μL of substrate mixture is added composed of unactive MEK1 (3 nM), ATP (50 μM), unactive ERK2 (4 nM), biotinylated MBP peptide (b-FFKNIVTPRTPPPSQGK, 1 μM) and antiphospho MBP peptide (0.5 nM). The mixture is then gently shaken for 30 minutes at room temperature followed by addition of active cRaf (5 μL at 0.5 nM) to initiate reaction. The mixture is then shaken for 100 minutes at room temperature then quenched by addition of 10 μL of a mixture of 5μg/mL streptavidin donor beads and 5μg/mL protein A acceptor beads in detection buffer (75 mM Hepes pH = 7.5, 300 mM sodium chloride, 120 mM EDTA, 0.3% BSA and 0.03% Tween), followed by incubation overnight and signal detection on an ALPHAQuest® (Registered Trademark of Perkin Elmer) plate reader (Perkin Elmer).

[00415] Compounds of the invention are inhibitors of MEK. The extent to which these compounds are MEK inhibitors can be determined by one of ordinary skill in the art. In particular, the compounds can be tested in the assay described in Biological Example 1. When tested in that assay, certain compounds of the invention demonstrated the ability to bind to MEK. In one embodiment of the invention, the MEK inhibitor is selected from the compounds in Table 1 having a MEK-binding affinity of about 4 μM or less. In another

embodiment, the MEK inhibitor is selected from the compounds in Table 1 having a MEK-binding affinity of about 3 μM or less. In another embodiment, the MEK inhibitor is selected from the compounds in Table 1 having a MEK-binding affinity of about 2 μM or less. In another embodiment, the MEK inhibitor is selected from the compounds in Table 1 having a MEK-binding affinity of about 1.6 μM or less. In another embodiment, the MEK inhibitor is selected from the compounds in Table 1 having a MEK-binding affinity of about 1 μM or less. In another embodiment, the MEK inhibitor is selected from the compounds in Table 1 having a MEK-binding affinity of about 0.7 μM or less. In another embodiment, the MEK inhibitor is selected from the compounds in Table 1 having a MEK-binding affinity of about 0.3 μM or less. In another embodiment, the MEK inhibitor is selected from the compounds in Table 1 having a MEK-binding affinity of about 0.2 μM or less. In another embodiment, the MEK inhibitor is selected from the compounds in Table 1 having a MEK-binding affinity of about 0.1 μM or less. In another embodiment, the MEK inhibitor is selected from the compounds in Table 1 having a MEK-binding affinity of about 0.05 μM or less.

Biological Example 2

Endogenous ERK Phosphorylation ELISA Assay

[00416] MDA-MB-231T (ATCC), Calu-6 (ATCC), HCT 116 (ATCC), A2058 (ATCC), and A375 (ATCC) cells were seeded at 20000, 30000, 30000, 20000, and 30000 cells/well, respectively, onto black 96-well microtiter plates (Costar 3904), in DMEM (Cellgro) containing 10% FBS (Heat-Inactivated, Cellgro), 1% NEAA (Cellgro), and 1% Pen/Strep (Cellgro). SK-MEL-28 (ATCC) cells were seeded at 20000 cells/well in MEM (ATCC) containing 10% FBS (Heat-Inactivated, Cellgro), and 1% Pen/Strep (Cellgro). The cells were then incubated at 37°C, 5% CO_2 for 24 h. Serum starvation was performed by replacing the medium with serum-free DMEM or MEM for an additional 24 h. Serial dilutions of test compounds in fresh serum-free medium in a final concentration of 0.3% DMSO (vehicle) were added to the cells and incubated for 1 h. Negative control wells were in serum-free medium + 0.3% DMSO only. After treatment, the medium was removed and cells were fixed with 4% formaldehyde, followed by quenching of endogenous peroxidases with 0.6% H_2O_2. Plates were then blocked (10% FBS, Cellgro) and incubated with mouse monoclonal anti-phospho-p44/42 MAPK, E10 (1:2000, Cell Signaling), followed by secondary antibody

(HRP-conjugated, goat anti-mouse IgG, 1:3000 from Jackson ImmunoResearch Laboratories, Inc). Washing of the plates was performed with PBS-T (0.1% Triton X-100) in between all incubation steps. A luminol-based substrate solution was then added and plates read using the Victor Wallac machine. IC_{50} values were determined based on total ERK phosphorylation with compound treatment versus total ERK phosphorylation with 0.3% DMSO treatment alone.

Biological Example 3
BrdU Cell Proliferation Assay

[00417] MDA-MB-231T (ATCC), Calu-6 (ATCC), HCT 116 (ATCC), A2058 (ATCC), A375 (ATCC), and Colo-205 (ATCC) cells were plated at densities of 2500, 3500, 3500, 2500, 3500, and 15000 cells/well onto 96-well microtiter plates (Cat# 3904, Costar), in DMEM (Cellgro) containing 10% FBS (Heat Inactivated, Cellgro), 1% Pen/Strep (Cellgro), and 1% NEAA (Cellgro). SK MEL-28 (ATCC) and WM-266-4 (ATCC) were plated at densities of 2000 and 6000 cells/well in MEM (ATCC) containing 10% FBS (Heat-Inactivated, Cellgro), and 1% Pen/Strep (Cellgro). The cells were incubated overnight at 37°C, 5% CO_2 for 18 h. The next day, cells were treated with a serial dilution of compound in medium (containing a final concentration of 0.3% DMSO). Triplicate wells were used for each compound concentration. The control wells received 0.3% DMSO media. The cultures were incubated at 37°C, 5% CO_2 for an additional 48 h. The cells were assayed for proliferation according to the "Cell Proliferation ELISA, Bromo Deoxyuridine (BrdU) (chemiluminescence) kit" from Roche. The cells were treated with the BrdU labeling solution and then fixed with FixDenat solution. Anti-BrdU-POD (PerOxiDase) conjugate was added to the cells, after which the plates were washed 3x with 1X PBS. Substrate solution was added, and the plates were read for luminescence using the Victor Wallac machine. IC_{50} values were calculated based on the cell proliferation with compound treatment compared to the vehicle control.

Biological Example 4
In vivo mouse models

[00418] Female athymic nude mice (NCr) 5-8 weeks of age and weighing approximately 20g were purchased from Taconic (Germantown, NY). Prior to initiation of a study, the animals were allowed to acclimate for a minimum of 48 h. During these studies, animals were provided food and water ad libitum and housed in a room conditioned at 70-75°F and

60% relative humidity. A 12 h light and 12 h dark cycle was maintained with automatic timers.

[00419] Colo-205 human colorectal carcinoma cells were cultured in vitro in DMEM (Mediatech) supplemented with 10% Fetal Bovine Serum (Hyclone), Penicillin-Streptomycin and non-essential amino acids at 37 °C in a humidified, 5% CO_2 atmosphere. On day 0, cells were harvested by trypsinization, and $3x10^6$ cells (passage #3, 92% viability) in 0.1 ml ice-cold Hank's balanced salt solution were implanted intradermally in the hind-flank of 5-8 week old female athymic nude mice.

[00420] A375 human melanoma cells were cultured in vitro in DMEM (Mediatech) supplemented with 10% Fetal Bovine Serum (Hyclone), Penicillin-Streptomycin and non-essential amino acids at 37 °C in a humidified, 5% CO_2 atmosphere. On day 0, cells were harvested by trypsinization, and $5x10^6$ cells (passage #8, >99% viability) in 0.1 mL ice-cold Hank's balanced salt solution were implanted intradermally in the hind-flank of 5-8 week old female athymic nude mice.

[00421] A2058 human melanoma cells were cultured in vitro in DMEM (Mediatech) supplemented with 10% Fetal Bovine Serum (Hyclone), Penicillin-Streptomycin and non-essential amino acids at 37 °C in a humidified, 5% CO_2 atmosphere. On day 0, cells were harvested by trypsinization, and $3x10^6$ cells (passage #5, 80% viability) in 0.1 mL ice-cold Hank's balanced salt solution were implanted intradermally in the hind-flank of 5-8 week old female athymic nude mice.

[00422] MDA-MB-231 human breast adenocarcinoma cells were cultured in vitro in DMEM (Mediatech) supplemented with 10% Fetal Bovine Serum (Hyclone), Penicillin-Streptomycin and non-essential amino acids at 37 °C in a humidified, 5% CO_2 atmosphere. On day 0, cells were harvested by trypsinization, and $1x10^6$ cells (passage #6, >99% viability) in 0.1 mL ice-cold Hank's balanced salt solution were implanted subcutaneously into the mammary fat pad of 5-8 week old female athymic nude mice.

[00423] Calu-6 human lung anaplastic carcinoma cells were cultured in vitro in DMEM (Mediatech) supplemented with 10% Fetal Bovine Serum (Hyclone), Penicillin-Streptomycin and non-essential amino acids at 37 °C in a humidified, 5% CO_2 atmosphere. On day 0, cells were harvested by trypsinization, and $5x10^6$ cells (passage #8, 96% viability) in 0.1 mL ice-cold Hank's balanced salt solution were implanted intradermally in the hind-flank of 5-8 week old female athymic nude mice.

[00424] For subcutaneous or intradermal tumors, the mean tumor weight of each animal in the respective control and treatment groups was determined twice weekly during the study.

Tumor weight (TW) was determined by measuring perpendicular diameters with a caliper, using the following formula: tumor weight (mg) = [tumor volume = length (mm) x width^2 (mm^2)]/2.

[00425] Percent inhibition of tumor growth (TGI) is determined with the following formula:

$$\left[1 - \left[\frac{(X_f - X_0)}{(Y_f - X_0)}\right]\right] * 100$$

where X_0 = average TW of all tumors on group day; X_f = TW of treated group on Day f; Y_f = TW of vehicle control group on Day f

[00426] If tumors regress below their starting sizes, then the percent tumor regression is determined with the following formula:

$$\left[\frac{(X_0 - Xf)}{X_0}\right] * 100$$

TGI is calculated individually for each tumor to obtain a mean ± SEM value for each experimental group. Statistical significance is determined using the 2-tailed Student's t-test (significance defined as $P<0.05$).

Pharmaceutical Composition Examples

[00427] The following are representative pharmaceutical formulations containing a compound of Formula I.

Tablet Formulation

The following ingredients are mixed intimately and pressed into single scored tablets.

Ingredient	Quantity per tablet, mg
compound of this invention	400
Cornstarch	50
croscarmellose sodium	25
Lactose	120
magnesium stearate	5

Capsule Formulation

The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

Ingredient	Quantity per tablet, mg
compound of this invention	200
lactose, spray-dried	148
magnesium stearate	2

Suspension Formulation

The following ingredients are mixed to form a suspension for oral administration.

Ingredient	Amount
compound of this invention	1.0 g
fumaric acid	0.5 g
sodium chloride	2.0 g
methyl paraben	0.15 g
propyl paraben	0.05 g
granulated sugar	25.5 g
sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
Flavoring	0.035 mL
Colorings	0.5 mg
distilled water	q.s. to 100 mL

Injectable Formulation

The following ingredients are mixed to form an injectable formulation.

Ingredient	Amount
compound of this invention	1.2 g
sodium acetate buffer solution	0.4 M 2.0 mL
HCl (1 N) or NaOH (1 M)	q.s. to suitable pH
water (distilled, sterile)	q.s.to 20 mL

[00428] All of the above ingredients, except water, are combined and heated to 60-70.degree. C. with stirring. A sufficient quantity of water at 60.degree. C. is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. to 100 g.

Suppository Formulation

[00429] A suppository of total weight 2.5 g is prepared by mixing the compound of the invention with Witepsol.RTM. H-15 (triglycerides of saturated vegetable fatty acid; Riches-Nelson, Inc., New York), and has the following composition:

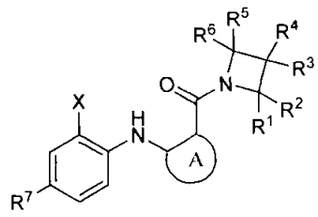
Ingredient	Quantity per tablet, mg

Ingredient	Quantity per tablet, mg
compound of this invention	500
Witepsol® H-15	balance

[00430] The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. The invention has been described with reference to various specific embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. All patents, patent applications and publications cited in this application are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual patent, patent application or publication were so individually denoted.

We claim:

1. A compound of formula I:



I

or a pharmaceutically acceptable salt or solvate, thereof, wherein A, X, R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are as defined in Group A, Group B, Group C, or Group D:

Group A:

A is arylene optionally substituted with one, two, three or four groups selected from R^{10}, R^{12}, R^{14}, R^{16}, and R^{19} where R^{10}, R^{12}, R^{14} and R^{16} are independently hydrogen, alkyl, alkenyl, alkynyl, halo, haloalkoxy, hydroxy, alkoxy, amino, alkylamino, dialkylamino, haloalkyl, $-NHS(O)_2R^8$, -CN, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$ and $-NR^8C(O)R^{8'}$ and where R^{19} is hydrogen, alkyl, or alkenyl;

X is alkyl, halo, haloalkyl, or haloalkoxy;

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl; where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; or one of R^1 and R^2 together with the carbon to which they are attached, R^3 and R^4 together with the carbon to which they are attached, and R^5 and R^6 together with the carbon to which they are attached form C(O) or C(=NOH);

m is 0, 1, or 2;

R^7 is hydrogen, halo or alkyl;

R^8, $R^{8'}$ and $R^{8''}$ are independently selected from hydrogen, hydroxy, optionally substituted alkoxy, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl; where the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two three, four, or five groups independently selected from alkyl, halo, hydroxy, hydroxyalkyl, optionally substituted alkoxy, alkoxyalkyl, haloalkyl, carboxy, alkoxycarbonyl, alkenyloxycarbonyl, optionally substituted cycloalkyl, optionally substituted cycloalkyloxycarbonyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted aryloxycarbonyl, optionally substituted arylalkyl, optionally substituted arylalkyloxy, optionally substituted arylalkyloxycarbonyl, nitro, cyano, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, $-S(O)_nR^{31}$ (where n is 0, 1, or 2 and R^{31} is optionally substituted alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), $-NR^{34}SO_2R^{34a}$ (where R^{34} is hydrogen or alkyl and R^{34a} is alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl), $-SO_2NR^{35}R^{35a}$ (where R^{35} is hydrogen or alkyl and R^{35a} is alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl), $-NR^{32}C(O)R^{32a}$ (where R^{32} is hydrogen or alkyl and R^{32a} is alkyl, alkenyl, alkoxy, or cycloalkyl), $-NR^{30}R^{30'}$ (where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl), and $-C(O)NR^{33}R^{33a}$ (where R^{33} is hydrogen or alkyl and R^{33a} is alkyl, alkenyl, alkynyl, or cycloalkyl); and

R^9 is alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl; where the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally susbstituted with one, two, three, four, or five groups selected from halo, hydroxy, alkyl, haloalkyl, haloalkoxy, amino, alkylamino, and dialkylamino;

Group B:

A is heteroarylene optionally substituted with one, two, three, or four groups selected from R^{10}, R^{12}, R^{14}, R^{16} and R^{19} where R^{10}, R^{12}, R^{14} and R^{16} are independently hydrogen, alkyl, alkenyl, alkynyl, halo, haloalkoxy, hydroxy, alkoxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkylsulfonylamino, alkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, alkenyloxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, or alkylcarbonylamino; where R^{19} is hydrogen, alkyl, or alkenyl; and where each alkyl and alkenyl, either alone or as part of another group

within R^{10}, R^{12}, R^{14}, R^{16}, and R^{19}, is independently optionally substituted with halo, hydroxy, or alkoxy;

X is alkyl, halo, haloalkyl, or haloalkoxy;

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl, where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; or one of R^1 and R^2 together with the carbon to which they are attached, R^3 and R^4 together with the carbon to which they are attached, and R^5 and R^6 together with the carbon to which they are attached form C(O) or C(=NOH);

m is 1 or 2;

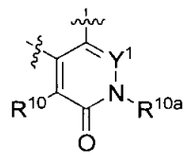
R^7 is hydrogen, halo or alkyl; and

R^8, $R^{8'}$ and $R^{8''}$ are independently selected from hydrogen, hydroxy, optionally substituted alkoxy, alkyl, haloalkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, where the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two three, four, or five groups independently selected from alkyl, halo, hydroxy, hydroxyalkyl, optionally substituted alkoxy, alkoxyalkyl, haloalkyl, carboxy, carboxy ester, nitro, cyano, $-S(O)_nR^{31}$ (where n is 0, 1, or 2 and R^{31} is optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), $-NR^{36}S(O)_2R^{36a}$ (where R^{36} is hydrogen, alkyl, or alkenyl and R^{36a} is alkyl, alkenyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), $-S(O)_2NR^{37}R^{37a}$ (where R^{37} is hydrogen, alkyl, or alkenyl and R^{37a} is alkyl, alkenyl, optionally substituted aryl, optionally substituted

cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted aryloxy, optionally substituted arylalkyloxy, optionally substituted heteroaryl, -NHC(O)R^{32} (where R^{32} is alkyl, alkenyl, alkoxy, or cycloalkyl) and -$NR^{30}R^{30'}$ (where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl), and -C(O)NHR^{33} (where R^{33} is alkyl, alkenyl, alkynyl, or cycloalkyl);

Group C:

A is



where R^{10} is hydrogen, alkyl, alkenyl, alkynyl, halo, haloalkoxy, hydroxy, alkoxy, amino, alkylamino, dialkylamino, haloalkyl, -NHS(O)$_2R^8$, -CN, -C(O)R^8, -C(O)OR^8, -C(O)$NR^8R^{8'}$ and –NR^8C(O)$R^{8'}$;

R^{10a} is hydrogen, alkyl, or alkenyl;

Y^1 is =CH- or =N-;

X is alkyl, halo, haloalkyl, or haloalkoxy;

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, halo, nitro, -$NR^8R^{8'}$, -OR^8, -NHS(O)$_2R^8$, -CN, -S(O)$_mR^8$, -S(O)$_2NR^8R^{8'}$, -C(O)R^8, -C(O)OR^8, -C(O)$NR^8R^{8'}$, -NR^8C(O)$OR^{8'}$, -NR^8C(O)$NR^{8'}R^{8''}$, -NR^8C(O)$OR^{8'}$, -NR^8C(O)$R^{8'}$, -$CH_2N(R^{25})(NR^{25a}R^{25b})$, -$CH_2NR^{25}$C(=NH)$(NR^{25a}R^{25b})$, -$CH_2NR^{25}$C(=NH)(N($R^{25a}$)($NO_2$)), -$CH_2NR^{25}$C(=NH)(N($R^{25a}$)(CN)), -$CH_2NR^{25}$C(=NH)($R^{25}$), -$CH_2NR^{25}$C($NR^{25a}R^{25b}$)=CH($NO_2$), alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl, where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, -OR^8, -$NR^8R^{8'}$, -NR^8S(O)$_2R^9$, -CN, -S(O)$_mR^9$, -C(O)R^8, -C(O)OR^8, -C(O)$NR^8R^{8'}$, -NR^8C(O)$NR^{8'}R^{8''}$, -NR^8C(O)$OR^{8'}$ and -NR^8C(O)$R^{8'}$; or one of R^1 and R^2 together with the carbon to which they are

attached, R^3 and R^4 together with the carbon to which they are attached, and R^5 and R^6 together with the carbon to which they are attached form C(O) or C(=NOH);

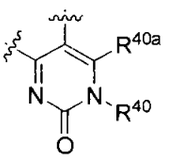
m is 1 or 2;

R^7 is hydrogen, halo or alkyl; and

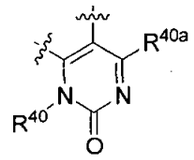
R^8, $R^{8'}$ and $R_{8''}$ are independently selected from hydrogen, hydroxy, optionally substituted alkoxy, alkyl, haloalkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, where the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two three, four, or five groups independently selected from alkyl, halo, hydroxy, hydroxyalkyl, optionally substituted alkoxy, alkoxyalkyl, haloalkyl, carboxy, carboxy ester, nitro, cyano, $-S(O)_nR^{31}$ (where n is 0, 1, or 2 and R^{31} is optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), $-NR^{36}S(O)_2R^{36a}$ (where R^{36} is hydrogen, alkyl, or alkenyl and R^{36a} is alkyl, alkenyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), $-S(O)_2NR^{37}R^{37a}$ (where R^{37} is hydrogen, alkyl, or alkenyl and R^{37a} is alkyl, alkenyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted aryloxy, optionally substituted arylalkyloxy, optionally substituted heteroaryl, $-NHC(O)R^{32}$ (where R^{32} is alkyl, alkenyl, alkoxy, or cycloalkyl) and $-NR^{30}R^{30'}$ (where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl), and $-C(O)NHR^{33}$ (where R^{33} is alkyl, alkenyl, alkynyl, or cycloalkyl); or

Group D:

A is



(b) or



(c)

R^{40} and R^{40a} are independently hydrogen or alkyl;

X is alkyl, halo, haloalkyl, or haloalkoxy;

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl, where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; or one of R^1 and R^2 together with the carbon to which they are attached, R^3 and R^4 together with the carbon to which they are attached, and R^5 and R^6 together with the carbon to which they are attached form C(O) or C(=NOH);

m is 1 or 2;

R^7 is hydrogen, halo or alkyl; and

R^8, $R^{8'}$ and $R_{8''}$ are independently selected from hydrogen, hydroxy, optionally substituted alkoxy, alkyl, haloalkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, where the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two three, four, or five groups independently selected from alkyl, halo, hydroxy, hydroxyalkyl, optionally substituted alkoxy, alkoxyalkyl, haloalkyl, carboxy, carboxy ester, nitro, cyano, $-S(O)_nR^{31}$ (where n is 0, 1, or 2 and R^{31} is optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), $-NR^{36}S(O)_2R^{36a}$ (where R^{36} is

hydrogen, alkyl, or alkenyl and R^{36a} is alkyl, alkenyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), $-S(O)_2NR^{37}R^{37a}$ (where R^{37} is hydrogen, alkyl, or alkenyl and R^{37a} is alkyl, alkenyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted aryloxy, optionally substituted arylalkyloxy, optionally substituted heteroaryl, $-NHC(O)R^{32}$ (where R^{32} is alkyl, alkenyl, alkoxy, or cycloalkyl) and $-NR^{30}R^{30'}$ (where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl), and $-C(O)NHR^{33}$ (where R^{33} is alkyl, alkenyl, alkynyl, or cycloalkyl).

2. The Compound of Claim 1 selected from Group A, Group B, and Group C where

Group A

A is phenylene optionally substituted with one or two groups selected from R^{10}, R^{12}, R^{14}, and R^{16} where R^{10}, R^{12}, R^{14} and R^{16} are independently hydrogen or halo;

X is halo;

R^1, R^2, R^5 and R^6 are hydrogen;

R^3 is hydrogen, halo, hydroxy, alkoxy, or amino;

R^4 is hydrogen, $-NR^8R^{8'}$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, or heteroaryl; where the alkyl is optionally substituted with one, two, or three groups independently selected from $-OR^8$, halo, nitro, $-S(O)_mR^9$, optionally substituted heterocycloalkyl, $-NR^8R^{8'}$, $-NR^8C(O)R^{8'}$, $-NR^8S(O)_2R^9$, $-NR^8C(O)OR^{8'}$, and aryl; where the cycloalkyl is optionally substituted with one or two groups selected from $-OR^8$ and $-NR^8R^{8'}$; where the heterocycloalkyl is optionally substituted with one or two groups independently selected from alkyl and $-C(O)OR^8$; and where the heteroaryl is optionally substituted with $-NR^8R^{8'}$; or

R^3 and R^4 together with the carbon to which they are attached form C(O) or C(=NOH);

m is 0;

R^7 is halo;

R^8 and $R^{8'}$ are independently selected from hydrogen, hydroxy, alkyl, alkenyl, alkynyl, aryl, heterocycloalkyl, heteroaryl, and cycloalkyl;

where the R^8 and $R^{8'}$ alkyl are independently optionally substituted with one, two, or three groups indendently selected from hydroxy, $-NR^{30}R^{30'}$ (where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl), optionally substituted heteroaryl, optionally substituted cycloalkyl), optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, $-C(O)NR^{33}R^{33a}$ (where R^{33} is hydrogen or alkyl and R^{33a} is alkyl, alkenyl, alkynyl, or cycloalkyl), optionally substituted aryloxy, $-S(O)_nR^{31}$ (where n is 0 and R^{31} is alkyl), carboxy, alkoxycarbonyl, and $-NR^{32}C(O)R^{32a}$ (where R^{32} is hydrogen or alkyl and R^{32a} is alkyl, alkenyl, alkoxy, or cycloalkyl); or where the alkyl is optionally substituted with one, two, three, four, or five halo;

where the R^8 and $R^{8'}$ heteroaryl are independently optionally substituted with one or two groups indendently selected from amino and alkyl;

where the R^8 and $R^{8'}$ heterocycloalkyl are independently optionally substituted with one, two, or three groups indendently selected from alkyl, alkoxycarbonyl, optionally substituted arylalkyl, hydroxy, alkoxy, and hydroxyalkyl;

where the R^8 and $R^{8'}$ aryl are independently optionally substituted with one or two groups indendently selected from hydroxy, alkoxy, halo, $-NR^{32}C(O)R^{32a}$ (where R^{32} is hydrogen or alkyl and R^{32a} is alkyl, alkenyl, alkoxy, or cycloalkyl), and $-NR^{34}SO_2R^{34a}$ (where R^{34} is hydrogen or alkyl and R^{34a} is alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl); and

where the R^8 and $R^{8'}$ cycloalkyl are independently optionally substituted with one, two, or three groups indendently selected from hydroxy, hydroxyalkyl, alkoxy, carboxy, $-C(O)NR^{33}R^{33a}$ (where R^{33} is hydrogen or alkyl and R^{33a} is alkyl, alkenyl, alkynyl, or cycloalkyl), and optionally substituted cycloalkyl; and

R^9 is alkyl or aryl;

Group B

A is thien-3,4-diyl, benzo[*d*]isoxazol-5,6-diyl, 1*H*-indazol-5,6-diyl (optionally substituted at the N1 position with R^{19} where R^{19} is alkyl or alkenyl), benzo[*d*]oxazol-5,6-diyl, 1*H*-benzo[d]imidazol-5,6-diyl (optionally substituted at the N1 position with R^{19} where R^{19} is alkyl or alkenyl), 1*H*-benzo[*d*][1,2,3]triazol-5,6-diyl (optionally substituted at the N1 position with R^{19} where R^{19} is alkyl or alkenyl), imidazo[1,2-*a*]pyridin-6,7-diyl, cinnolin-6,7-diyl, quinolin-6,7-diyl, pyridin-3,4-diyl, 1-oxido-pyridin-3,4-diyl, [1,2,4]triazolo[4,3-a]pyridin-6,7-diyl, or 2,3-dihydroimidazo[1,2-a]pyridin-6,7-diyl;

where A is optionally substituted with one, two, or three groups independently selected from R^{10}, R^{12}, R^{14}, R^{16} and R^{19} where R^{10}, R^{12}, R^{14} and R^{16} are independently hydrogen, alkyl, halo, or amino; and R^{19} is hydrogen or alkyl;

X is halo;

R^1, R^2, R^5 and R^6 are hydrogen;

R^3 is hydrogen or hydroxy;

R^4 is $-NR^8R^{8'}$, heterocycloalkyl, heteroaryl, or alkyl; where the alkyl is optionally substituted with $-NR^8R^{8'}$ and where the heteroaryl is optionaly substituted with alkyl;

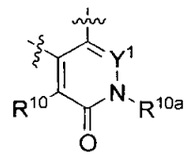
R^7 is halo;

R^8 is hydrogen or alkyl; and

$R^{8'}$ is hydrogen, alkyl, or cycloalkyl; where the cycloalkyl is optionally substituted with one or two groups independently selected from hydroxy and alkyl;

Group C

A is



(a)

R^{10} is hydrogen or halo;

R^{10a} is hydrogen or alkyl;

Y^1 is =CH- or =N-;

X is halo;

R^1, R^2, R^5 and R^6 are hydrogen;

R^3 is hydrogen or hydroxy;

R^4 is $-NR^8R^{8'}$, heterocycloalkyl, heteroaryl, or alkyl; where the alkyl is optionally substituted with $-NR^8R^{8'}$ and where the heteroaryl is optionaly substituted with alkyl;

R^7 is halo;

R^8 is hydrogen or alkyl; and

$R^{8'}$ is hydrogen, alkyl, or cycloalkyl; where the cycloalkyl is optionally substituted with one or two groups independently selected from hydroxy and alkyl.

3. The compound of Claim 1 where R^3 is halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$,

$-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl; where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; and R^4 is as defined in Claim 1; or R^3 and R^4 together with the carbon to which they are attached form C(O) or C(=NOH).

4. The compound of Claim 1 where R^3 and R^4 are independently halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl; where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; or R^3 and R^4 together with the carbon to which they are attached form C(O) or C(=NOH).

5. The compound according to claim 1 wherein R^7 is halo.

6. The compound according to claim 1 wherein X is halo.

7. The compound according to claim 1 wherein R^1, R^2, R^5, and R^6 are hydrogen.

8. The compound of Claim 1 selected from Group A where A is phenylene; and R^4 is $-NR^8R^{8'}$ (where R^8 is hydrogen, hydroxy, alkyl, alkoxy, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl and $R^{8'}$ is hydroxy, alkoxy, aryl, cycloalkyl, heteroaryl, or heterocycloalkyl), $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$,

$-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkenyl, or alkynyl; where the alkenyl and alkynyl are optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; or R^3 and R^4 together with the carbon to which they are attached form C(O) or C(=NOH).

9. The compound of Claim 1 where R^3 is hydrogen, halo, hydroxy, amino, or alkoxy.

10. The compound of Claim 1 where R^4 is hydrogen, $-NR^8R^{8'}$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, or heteroaryl; where the alkyl is optionally substituted with one, two, or three $-OR^8$, halo, nitro, $-S(O)_mR^9$, optionally substituted heterocycloalkyl, $-NR^8R^{8'}$, $-NR^8C(O)R^{8'}$, $-NR^8S(O)_2R^9$, $-NR^8C(O)OR^{8'}$, aryl; where the cycloalkyl is optionally substituted with one or two $-NR^8R^{8'}$; where the heterocycloalkyl is optionally substituted with one or two groups independently selected from alkyl and $-C(O)OR^8$; and where the heteroaryl is optionally substituted with $-NR^8R^{8'}$.

11. The compound of Claim 1 selected from Group A where A is phenylene optionally substituted with one or two groups independently selected from R^{10}, R^{12}, R^{14}, and R^{16} where R^{10}, R^{12}, R^{14} and R^{16} are independently hydrogen or halo.

12. The compound of Claim 1 selected from Group A where A is phenylene; R^3 is hydrogen; and R^4 is hydrogen, $-NR^8R^{8'}$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, alkyl, or heterocycloalkyl; where the alkyl is optionally substituted with one or two groups independently selected from $-OR^8$ and $-NR^8R^{8'}$; and where the heterocycloalkyl is optionally substituted with $-NR^8R^{8'}$.

13. The compound of Claim 1 selected from Group A where A is phenylene; R^3 is alkoxy; and R^4 is alkyl or heterocycloalkyl where the alkyl is substituted with $-NR^8R^{8'}$.

14. The compound of Claim 1 selected from Group A where A is phenylene; R^3 is halo; and R^4 is alkyl or heterocycloalkyl where the alkyl is substituted with $-NR^8R^{8'}$.

15. The compound of Claim 1 selected from Group A where A is phenylene and R^3 and R^4 together with the carbon to which they are attached form C(O) or C(=NOH).

16. The compound of Claim 1 selected from Group A where A is phenylene; R^3 is hydroxy; and R^4 is hydrogen, $-C(O)NR^8R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, heterocycloalkyl, cycloalkyl, heterocycloalkyl, or heteroaryl; where the alkyl is optionally substituted with one, two, or three groups selected from $-OR^8$, halo, nitro, $-S(O)_mR^9$, optionally substituted heterocycloalkyl, $-NR^8R^{8'}$, $-NR^8C(O)R^{8'}$, optionally substituted heteroaryl, $-NR^8S(O)_2R^9$, $-NR^8C(O)OR^{8'}$, and aryl; where the cycloalkyl is optionally substituted with one or two groups indeopendently selected from $-NR^8R^{8'}$ and $-C(O)NR^{33}R^{33a}$; where the heterocycloalkyl is optionally substituted with one, two or three groups independently selected from alkyl and $-C(O)OR^8$; and where the heteroaryl is optionally substituted with $-NR^8R^{8'}$.

17. The compound of Claim 1 selected from Group A where A is phenylene; R^7 is iodo or bromo; X is fluoro or chloro; and R^1, R^2, R^5, and R^6 are hydrogen; and R^{10}, R^{12}, R^{14}, and R^{16} are independently hydrogen or fluoro.

18. The compound of Claim 17 where R^{10} is 3-fluoro and R^{12}, R^{14}, and R^{16} are hydrogen or halo; R^{10} is 3-fluoro, R^{12} is 4-fluoro, and R^{14} and R^{16} are hydrogen; R^{10} is 4-fluoro, R^{12} is 5-fluoro, and R^{14} and R^{16} are hydrogen; R^{10} is 4-fluoro, R^{12} is 6-fluoro, and R^{14} and R^{16} are hydrogen; or R^{12} is 4-fluoro and R^{10}, R^{14}, and R^{16} are hydrogen.

19. The Compound of Claim 1 selected from Group A where A is phenylene and R^3 is hydroxy.

20. The Compound of Claim 19 where R^4 is $-C(O)NR^8R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, cycloalkyl, heterocycloalkyl, or heteroaryl; where the alkyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, or four groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$,

$-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$; or where the alkyl is optionally substituted with one, two, three, four, five, six or seven halo.

21. The Compound of Claim 20 where R^4 is alkyl, heterocycloalkyl, or heteroaryl; where the alkyl is optionally substituted with $-NR^8R^{8'}$; where the heterocycloalkyl is optionally substituted with alkyl or $-C(O)OR^8$; and where the heteroaryl is optionally substituted with alkyl.

22. The Compound of Claim 1 where

R^1 is halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, or $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl; where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, -CN, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ and $-NR^8C(O)R^{8'}$;

R^3 is hydroxy; and R^4 is heterocycloalkyl, alkyl, or heteroaryl, where the alkyl is optionally substituted with $-NR^8R^{8'}$ and where the heteroaryl is optionally substituted with alkyl.

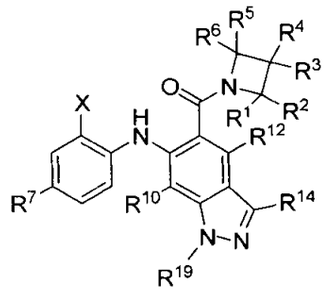
23. The Compound of Claim 1 selected from Group B where A is thien-3,4-diyl, benzo[*d*]isoxazol-5,6-diyl, 1*H*-indazol-5,6-diyl (optionally substituted at the N1 position with R^{19} where R^{19} is alkyl or alkenyl), benzo[*d*]oxazol-5,6-diyl, 1*H*-benzo[d]imidazol-5,6-diyl (optionally substituted at the N1 position with R^{19} where R^{19} is alkyl or alkenyl), 1*H*-benzo[*d*][1,2,3]triazol-5,6-diyl (optionally substituted at the N1 position with R^{19} where R^{19} is alkyl or alkenyl), imidazo[1,2-*a*]pyridin-6,7-diyl, cinnolin-6,7-diyl, quinolin-6,7-diyl, pyridin-3,4-diyl, 1-oxido-pyridin-3,4-diyl, [1,2,4]triazolo[4,3-a]pyridin-6,7-diyl, or 2,3-dihydroimidazo[1,2-a]pyridin-6,7-diyl.

24. The Compound of Claim 1 where A is thien-3,4-diyl; R^{10} and R^{12} are hydrogen; X and R^7 are halo; and R^1, R^2, R^5, and R^6 are hydrogen.

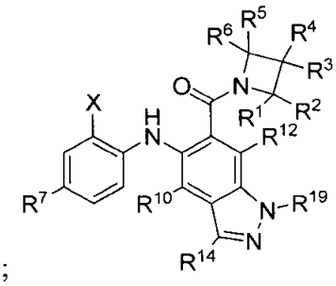
25. The Compound of Claim 24 where R^3 is hydrogen or hydroxy; and R^4 is $-NR^8R^{8'}$, heterocycloalkyl, heteroaryl, or alkyl, where the alkyl is optionally substituted with $-NR^8R^{8'}$.

26. The Compound of Claim 1 selected from Group B where A is benzo[*d*]isoxazol-5,6-diyl; R^{10}, R^{12}, and R^{14} are independently hydrogen, halo, or alkyl; R^1, R^2, R^5, and R^6 are hydrogen; X and R^7 are halo; R^3 is hydroxy; and R^4 is heterocycloalkyl, alkyl, or heteroaryl, where the alkyl is optionally substituted with $-NR^8R^{8'}$ and where the heteroaryl is optionally substituted with alkyl.

27. The Compound of Claim 23 according to Formula I(g) or I(h):



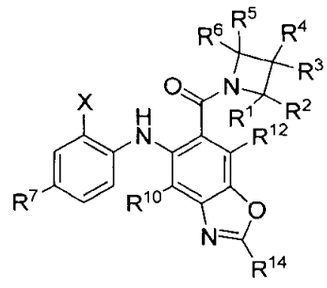
I(g);



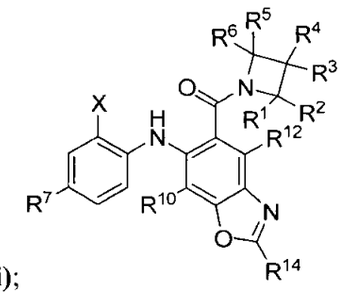
I(h);

where R^{10}, R^{12}, and R^{14} are independently hydrogen, halo, or alkyl; R^{19} is alkyl or alkenyl; R^1, R^2, R^5, and R^6 are hydrogen; X and R^7 are halo; R^3 is hydroxy; and R^4 is heterocycloalkyl, alkyl, or heteroaryl, where the alkyl is optionally substituted with $-NR^8R^{8'}$ and where the heteroaryl is optionally substituted with alkyl.

28. The Compound of Claim 23 according to Formula I(i) or I(j):



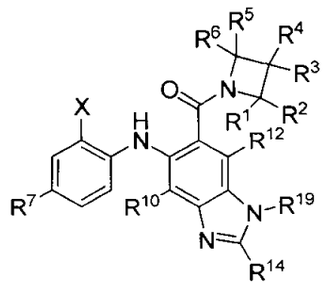
I(i);



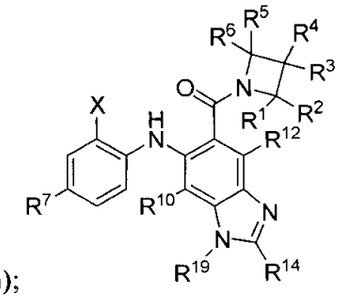
I(j);

where R^{10}, R^{12}, and R^{14} are independently hydrogen, halo, or alkyl; R^1, R^2, R^5, and R^6 are hydrogen; X and R^7 are halo; R^3 is hydroxy; and R^4 is heterocycloalkyl, alkyl, or heteroaryl, where the alkyl is optionally substituted with $-NR^8R^{8'}$ and where the heteroaryl is optionally substituted with alkyl.

29. The Compound of 23 according to Formula I(n) or I(o):



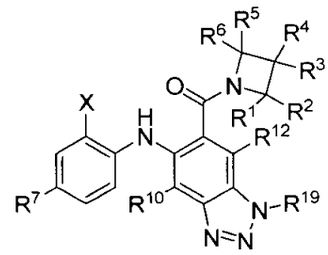
I(n);



Io);

where R^7 is halo or alkyl; X is halo; R^{19} is alkyl; R^1, R^2, R^5, and R^6 are hydrogen; R^{10}, R^{12}, and R^{14} are independently hydrogen or halo; R^3 is hydroxy; and R^4 is heterocycloalkyl, alkyl, or heteroaryl, where the alkyl is optionally substituted with $-NR^8R^{8'}$ and where the heteroaryl is optionally substituted with alkyl.

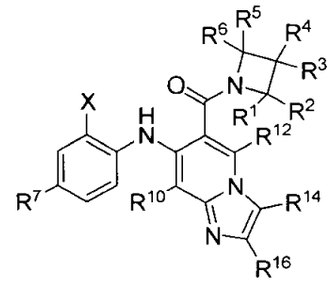
30. The Compound of 23 according to Formula I(p):



I(p)

where R^1, R^2, R^5, and R^6 are hydrogen; X and R^7 are halo; R^{10} and R^{12} are independently hydrogen, halo, or alkyl; R^{19} is hydrogen or alkyl; R^3 is hydroxy; and R^4 is heterocycloalkyl, alkyl, or heteroaryl, where the alkyl is optionally substituted with $-NR^8R^{8'}$ and where the heteroaryl is optionally substituted with alkyl.

31. The Compound of 23 according to Formula I(q):

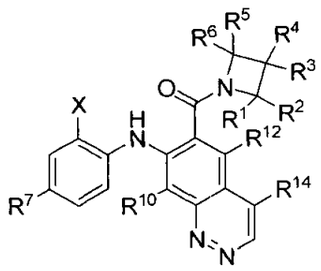


I(q)

where R^1, R^2, R^5, and R^6 are hydrogen; X and R^7 are halo; R^{10}, R^{12}, R^{14}, and R^{16} are independently hydrogen or halo; R^3 is hydroxy; and R^4 is heterocycloalkyl, alkyl, or

heteroaryl, where the alkyl is optionally substituted with -$NR^8R^{8'}$ and where the heteroaryl is optionally substituted with alkyl.

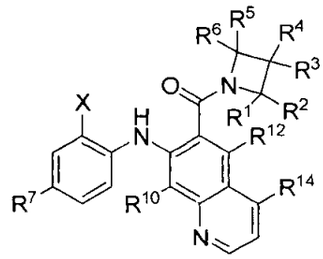
32. The Compound of 23 according to Formula I(r):



I(r)

where R^1, R^2, R^5, and R^6 are hydrogen; X and R^7 are halo; R^{10} and R^{12} are independently hydrogen, halo, or alkyl; R^{14} is hydrogen, halo, alkyl, or amino; R^3 is hydroxy; and R^4 is heterocycloalkyl, alkyl, or heteroaryl, where the alkyl is optionally substituted with -$NR^8R^{8'}$ and where the heteroaryl is optionally substituted with alkyl.

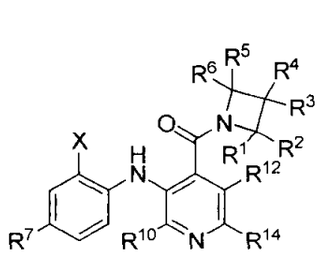
33. The Compound of 23 according to Formula I(s):



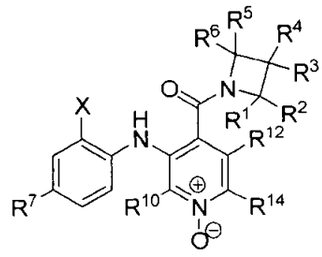
I(s)

R^1, R^2, R^5, and R^6 are hydrogen; X and R^7 are halo; R^{10} and R^{12} are independently hydrogen, halo, or alkyl; R^{14} is hydrogen, halo, alkyl, or amino; R^3 is hydroxy; and R^4 is heterocycloalkyl, alkyl, or heteroaryl, where the alkyl is optionally substituted with -$NR^8R^{8'}$ and where the heteroaryl is optionally substituted with alkyl.

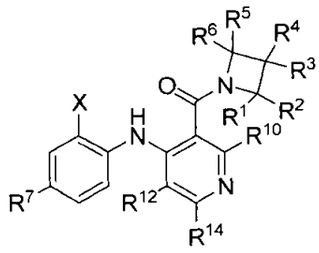
34. The Compound of 23 according to Formula I(u), I(v), I(w), or I(x):



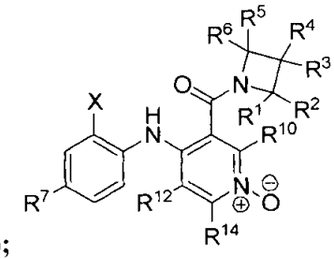
I(u);



I(v);



I(w);



I(x);

where R^1, R^2, R^5, and R^6 are hydrogen; X and R^7 are halo; R^{10}, R^{12}, and R^{14} are independently hydrogen, halo, or alkyl; R^3 is hydroxy; and R^4 is heterocycloalkyl, alkyl, or heteroaryl, where the alkyl is optionally substituted with $-NR^8R^{8'}$ and where the heteroaryl is optionally substituted with alkyl.

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-methylazetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-ethenylazetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-one; oxime;
[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]methanol;
1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethane-1,2-diol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-hydroxyazetidine-3-carboxamide;
1,1-dimethylethyl [1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]carbamate;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(pyrrolidin-1-ylmethyl)azetidin-3-ol;
3-[(diethylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(dimethylamino)methyl]azetidin-3-ol;
N-butyl-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidine-3-carboxamide;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-prop-2-en-1-ylazetidine-3-carboxamide;
N-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-2-methylpropanamide;
N-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]formamide;
N-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-3,4-dihydroxybutanamide;
methyl [1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]carbamate;
N-butyl-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine;
1-({4-[(2-fluoro-4-iodophenyl)amino]-3-thienyl}carbonyl)azetidin-3-amine;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2*R*)-piperidin-2-yl]azetidin-3-ol;
(*R*)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-pyrrolidin-2-ylazetidin-3-ol;
(*S*)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-pyrrolidin-2-ylazetidin-3-ol;
3-(aminomethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
3-[(1*S*)-1-aminoethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
3-[(1*R*)-1-aminoethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;

(*R*)-(3-(1-aminopropyl)-3-hydroxyazetidin-1-yl)(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)methanone;
(*S*)-(3-(1-aminopropyl)-3-hydroxyazetidin-1-yl)(3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl)methanone;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-ethylazetidine-3-carboxamide;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(2-hydroxyethyl)azetidine-3-carboxamide;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(2-piperidin-1-ylethyl)azetidine-3-carboxamide;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-phenylazetidine-3-carboxamide;
N-[2-(diethylamino)ethyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidine-3-carboxamide;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(morpholin-4-ylmethyl)azetidin-3-ol;
1-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}piperidin-4-ol;
3-{[bis(2-hydroxyethyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
N-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-2-(4-methylpiperazin-1-yl)acetamide;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(4-methylpiperazin-1-yl)methyl]azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(4-methyl-1,4-diazepan-1-yl)methyl]azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[methyl(1-methylpyrrolidin-3-yl)amino]methyl}azetidin-3-ol;
3-(1,4'-bipiperidin-1'-ylmethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
N-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-*N*,*N*-bis(2-hydroxyethyl)glycinamide;
3-({4-[2-(diethylamino)ethyl]piperazin-1-yl}methyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxyethyl)(methyl)amino]methyl}azetidin-3-ol;
N-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-2-piperidin-1-ylacetamide;
N-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-*N*3-(2-hydroxyethyl)-*N*3-methyl-beta-alaninamide;

N-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-*N*3,*N*3-bis(2-hydroxyethyl)-beta-alaninamide;
N-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-*N*2,*N*2-diethylglycinamide;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-methylazetidin-3-amine;
1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-*N*,*N*-dimethylpyrrolidin-3-amine;
2-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]amino}ethanol;
N-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]propane-1,3-diamine;
3-[(dimethylamino)methyl]-1-({4-[(2-fluoro-4-iodophenyl)amino]-3-thienyl}carbonyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-methyl-*N*-(2-pyridin-2-ylethyl)azetidin-3-amine;
N-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]-*N*2-methylglycinamide;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-ethylazetidin-3-amine;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(2-methylpropyl)azetidin-3-amine;
N-(cyclopropylmethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine;
N-(cyclohexylmethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine;
N-(cyclopentylmethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine;
3-(azetidin-1-ylmethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-[(2,3-dihydroxypropyl)oxy]azetidine-3-carboxamide;
2-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-2-yl]methyl}amino)ethanol;
N-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-2-yl]methyl}ethane-1,2-diamine;
N-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-yl]glycinamide;
6-({3-[(dimethylamino)methyl]azetidin-1-yl}carbonyl)-2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)aniline;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1-methylethyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(3,4-dihydroxybutyl)azetidine-3-carboxamide;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(2,3-dihydroxypropyl)azetidine-3-carboxamide;

1-({2,4-difluoro-6-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine;
1-({4,5-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-amine;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidine-3-carboxamide;
6-{[3-(aminomethyl)-3-(methyloxy)azetidin-1-yl]carbonyl}-2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)aniline;
N-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}acetamide;
2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)-6-[(3-{[(1-methylethyl)amino]methyl}azetidin-1-yl)carbonyl]aniline;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(ethylamino)methyl]azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{2-[(1-methylethyl)amino]ethyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(2-hydroxy-1,1-dimethylethyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{1,1-dimethyl-2-[(1-methylethyl)amino]ethyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1-methylethyl)amino]methyl}azetidin-3-amine;
3-[(cyclopropylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2,2,2-trifluoroethyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1*H*-imidazol-1-ylmethyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1,1-dimethylethyl)amino]methyl}azetidin-3-ol;
3-[(cyclopentylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxy-*N*-prop-2-en-1-ylazetidine-3-carboxamide;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-*N*-(2,3-dihydroxypropyl)-3-hydroxyazetidine-3-carboxamide;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1*H*-1,2,3-triazol-1-ylmethyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2,2-dimethylpropyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(propylamino)methyl]azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-methylpropyl)amino]methyl}azetidin-3-ol;

3-{[(cyclopropylmethyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(phenylmethyl)amino]methyl}azetidin-3-ol;
3-{[(cyclohexylmethyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
3-[(butylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(1-ethylpyrrolidin-2-yl)methyl]amino}methyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxyethyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(dimethylamino)ethyl]amino}methyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxy-1,1-dimethylethyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(4-methylphenyl)ethyl]amino}methyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(prop-2-en-1-ylamino)methyl]azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(1-methylpyrrolidin-2-yl)ethyl]amino}methyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2,3-dihydro-1*H*-inden-2-ylamino)methyl]azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(tetrahydrofuran-2-ylmethyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(tetrahydro-2*H*-pyran-4-yl)ethyl]amino}methyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(1*S*,2*S*)-2-hydroxycyclopentyl]amino}methyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1,1-dimethylprop-2-yn-1-yl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(3-pyrrolidin-1-ylpropyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1,2-dimethylpropyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(1*H*-imidazol-4-

yl)ethyl]amino}methyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[1-methyl-2-(methyloxy)ethyl]amino}methyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[3-(ethyloxy)propyl]amino}methyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1-ethylpropyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(3,3-dimethylbutyl)amino]methyl}azetidin-3-ol;
ethyl 4-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)piperidine-1-carboxylate;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(3-methylbutyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(ethyloxy)ethyl]amino}methyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[3-(dimethylamino)propyl]amino}methyl)azetidin-3-ol;
3-[(cyclobutylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
3-({[3-(diethylamino)propyl]amino}methyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[3-(1*H*-imidazol-1-yl)propyl]amino}methyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(methylthio)ethyl]amino}methyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[1-(phenylmethyl)piperidin-4-yl]amino}methyl)azetidin-3-ol;
3-({[2,2-bis(methyloxy)ethyl]amino}methyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1,1,3,3-tetramethylbutyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1,1-dimethylpropyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2,3-dihydro-1*H*-inden-1-ylamino)methyl]azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[({2-[(phenylmethyl)oxy]cyclopentyl}amino)methyl]azetidin-3-ol;

3-{[(3-amino-2-hydroxypropyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-hydroxy-1-(phenylmethyl)ethyl]amino}methyl)azetidin-3-ol;
3-[(cyclooctylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
3-{[(1-cyclohexylethyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
3-[(cycloheptylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-pyridin-3-ylethyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[3-(methylthio)propyl]amino}methyl)azetidin-3-ol;
N-cyclohexyl-*N*~2~-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}-2-methylalaninamide;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(3-hydroxypropyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-pyridin-4-ylethyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[1-(phenylmethyl)pyrrolidin-3-yl]amino}methyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(2-thienyl)ethyl]amino}methyl)azetidin-3-ol;
3-[({2-[bis(1-methylethyl)amino]ethyl}amino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(phenyloxy)ethyl]amino}methyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(phenylamino)methyl]azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxypropyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[({2-[(1-methylethyl)oxy]ethyl}amino)methyl]azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1-ethylpiperidin-3-yl)amino]methyl}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(methyloxy)ethyl]amino}methyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-nitropropyl)azetidin-3-ol;
3-(1-aminoethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(1-methylpiperidin-4-yl)methyl]amino}methyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[4-(dimethylamino)butyl]amino}methyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-furan-2-ylethyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{1-[(1,1-dimethylethyl)amino]ethyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-ethylbutyl)amino]methyl}azetidin-3-ol;
1-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}pyrrolidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({(2*S*)-2-[(methyloxy)methyl]pyrrolidin-1-yl}methyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxyphenyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(4-hydroxyphenyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(3-hydroxyphenyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(phenyloxy)methyl]azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1r,3r,5*R*,7*R*)-tricyclo[3.3.1.1~3,7~]dec-2-ylamino]methyl}azetidin-3-ol;
3-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)propane-1,2-diol;
N-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}-L-alanine;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(phenylthio)methyl]azetidin-3-ol;
N-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}-D-alanine;
methyl *N*-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-

yl]methyl}alaninate;
3-[({1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)oxy]propane-1,2-diol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]amino}methyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1-methylbutyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1-methylpropyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-methylbutyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(pentylamino)methyl]azetidin-3-ol;
3-[(1*S*)-1-aminoethyl]-1-({8-fluoro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-*a*]pyridin-6-yl}carbonyl)azetidin-3-ol;
1-({8-fluoro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-*a*]pyridin-6-yl}carbonyl)-3-[(1*S*)-1-(methylamino)ethyl]azetidin-3-ol;
3-[(cyclohexylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[1-(ethylamino)ethyl]azetidin-3-ol;
3-[(azepan-3-ylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(dimethylamino)-1-methylethyl]amino}methyl)azetidin-3-ol;
N-cyclopropyl-1-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)cyclopentanecarboxamide;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[2-(2,3-dihydro-1*H*-indol-3-yl)ethyl]amino}methyl)azetidin-3-ol;
N~2~-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}-*N*-ethyl-2-methylalaninamide;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2-methylhydrazino)methyl]azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(hydroxyamino)methyl]azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(methyloxy)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(ethyloxy)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[1-(ethylamino)propyl]azetidin-3-ol;
3-[(azetidin-3-ylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(1,3-thiazol-2-ylamino)methyl]azetidin-3-ol;
3-(1*H*-benzimidazol-2-yl)-1-({8-fluoro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-*a*]pyridin-6-yl}carbonyl)azetidin-3-ol;
3-(1*H*-benzimidazol-2-yl)-1-({7-[(4-bromo-2-fluorophenyl)amino]-8-fluoroimidazo[1,2-*a*]pyridin-6-yl}carbonyl)azetidin-3-ol;
1,1-dimethylethyl [3-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)propyl]carbamate;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(pyrrolidin-2-ylmethyl)amino]methyl}azetidin-3-ol;
1,1-dimethylethyl 4-[({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)methyl]piperidine-1-carboxylate;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(2-hydroxyphenyl)methyl]amino}methyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(3-hydroxyphenyl)methyl]amino}methyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(4-hydroxyphenyl)methyl]amino}methyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(4-hydroxybutyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxyethyl)oxy]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(1*S*,2*S*)-2-hydroxycyclohexyl]amino}methyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(1,1-dimethyl-2-pyrrolidin-1-ylethyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(1-methyl-1*H*-imidazol-4-yl)methyl]amino}methyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(1-methyl-1*H*-imidazol-5-yl)methyl]amino}methyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[(2*S*)-2-(methyloxy)cyclopentyl]amino}methyl)azetidin-3-ol;
3-{[1,1'-bi(cyclohexyl)-2-ylamino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[3-(methyloxy)phenyl]amino}methyl)azetidin-3-ol;
1-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-

yl]methyl}amino)cyclopentanecarboxylic acid;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(4-fluorophenyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(1,3,5-triazin-2-ylamino)methyl]azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(*trans*-4-hydroxycyclohexyl)amino]methyl}azetidin-3-ol;
3-[(cyclopent-3-en-1-ylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
N-[4-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)phenyl]acetamide;
N-[3-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)phenyl]acetamide;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-methylpyrrolidin-2-yl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(1*H*-1,2,4-triazol-3-ylamino)methyl]azetidin-3-ol;
3-[1-(diethylamino)propyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
3-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)-5-(hydroxymethyl)cyclopentane-1,2-diol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-piperidin-2-ylazetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(3-fluorophenyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-methylpiperidin-2-yl)azetidin-3-ol;
1-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}guanidine;
1-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}-3-nitroguanidine;
N-{1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}acetamide;
(2*R*)-*N*-{1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanamide;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(piperidin-4-ylmethyl)amino]methyl}azetidin-3-ol;
3-{[(3-aminopropyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[({[2-(4-methylpiperazin-1-yl)phenyl]methyl}amino)methyl]azetidin-3-ol;
3-{[(1,1-dimethylethyl)amino]methyl}-1-({4-[(2-fluoro-4-iodophenyl)amino]-3-thienyl}carbonyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxycyclohexyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2,2,3,3,3-pentafluoropropyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(3,3,3-trifluoropropyl)amino]methyl}azetidin-3-ol;
N-{3-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)phenyl]methanesulfonamide;
N-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}methanesulfonamide;
3-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)-1*H*-pyrazol-5-ol;
(1*R*,2*S*)-4-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)cyclopentane-1,2-diol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[1-(hydroxymethyl)cyclohexyl]amino}methyl)azetidin-3-ol;
3-{[(3-chlorophenyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
3-{[(4-chlorophenyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
3-[(5-amino-3-methyl-1*H*-pyrazol-1-yl)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(5-methyl-1*H*-pyrazol-3-yl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-ethylpyrrolidin-2-yl)azetidin-3-ol;
(2*R*)-*N*-{(1*S*)-1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}-3,3,3-trifluoro-2-(methyloxy)-2-phenylpropanamide;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[4-(methyloxy)phenyl]amino}methyl)azetidin-3-ol;
3-(1-amino-2-methylpropyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
3-{[(4-aminophenyl)amino]methyl}-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-hydroxy-2-methylcyclopentyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{1-[(4-hydroxycyclohexyl)amino]ethyl}azetidin-3-ol;
methyl (2xi)-2-deoxy-2-({[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}amino)-beta-D-arabino-hexopyranoside;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-pyridin-2-ylazetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-({[1-(hydroxymethyl)cyclopentyl]amino}methyl)azetidin-3-ol;
1-cyano-3-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}guanidine;
6-({3-[(ethylamino)methyl]-3-fluoroazetidin-1-yl}carbonyl)-2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)aniline;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-nitroethyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(3-fluoro-4-hydroxyphenyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-{[(2-fluoro-4-hydroxyphenyl)amino]methyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[1-(methylamino)ethyl]azetidin-3-ol;
3-(1-aminoethyl)-1-({8-chloro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-a]pyridin-6-yl}carbonyl)azetidin-3-ol;
1-({8-fluoro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-*a*]pyridin-6-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol;
1-({8-fluoro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-*a*]pyridin-6-yl}carbonyl)-3-{(1*S*)-1-[(2-hydroxy-2-methylcyclopentyl)amino]ethyl}azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1*H*-imidazol-2-yl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1*H*-pyrrol-2-yl)azetidin-3-ol;
N-{[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]methyl}benzenecarboximidamide;
3-({[(E)-1-amino-2-nitroethenyl]amino}methyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-methyl-1-nitroethyl)azetidin-3-ol;
3-(1-amino-1-methylethyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
3-[(1*H*-benzimidazol-2-ylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(1*H*-imidazol-2-ylamino)methyl]azetidin-3-ol;
methyl {1-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]ethyl}carbamate;

3-(1*H*-benzimidazol-2-yl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[1-(dimethylamino)ethyl]azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(pyrimidin-2-ylamino)methyl]azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(pyridin-2-ylamino)methyl]azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1-methyl-1*H*-imidazol-2-yl)azetidin-3-ol;
3-(1-aminobutyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
1-({2-fluoro-3-[(2-fluoro-4-iodophenyl)amino]pyridin-4-yl}carbonyl)-3-[(2*S*)-pyrrolidin-2-yl]azetidin-3-ol;
1-({8-fluoro-7-[(2-fluoro-4-iodophenyl)amino]-4-methylcinnolin-6-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol;
3-[amino(phenyl)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(5-methyl-1*H*-imidazol-2-yl)azetidin-3-ol;
1,1-dimethylethyl (2*S*)-2-[1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-hydroxyazetidin-3-yl]piperidine-1-carboxylate;
1-({2-[(4-bromo-2-chlorophenyl)amino]-3,4-difluorophenyl}carbonyl)-3-piperidin-2-ylazetidin-3-ol;
3-(1-amino-3-hydroxypropyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(1*H*-imidazol-2-ylmethyl)azetidin-3-ol;
3-(1-aminocyclopentyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
3-(2-aminocyclohexyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
3-(2-aminocyclopentyl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-azetidin-3-ol;
1-({4-fluoro-5-[(2-fluoro-4-iodophenyl)amino}-1-methyl-1*H*-benzimidazol-6-yl}carbonyl)-3-piperidin-2-ylazetidin-3-ol;
1-({5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-1-methyl-1*H*-benzimidazol-6-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol;
1-({8-chloro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-a]pyridin-6-yl}carbonyl)-3-piperidin-2-ylazetidin-3-ol;
1-({2-[(4-bromo-2-fluorophenyl)amino]-3,4-difluorophenyl}carbonyl)-3-piperidin-2-ylazetidin-3-ol;
1-({7-[(4-bromo-2-fluorophenyl)amino]-8-fluoroimidazo[1,2-*a*]pyridin-6-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(3-methyl-1-nitrobutyl)azetidin-3-ol;
3-(2-aminopyrimidin-4-yl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol;
1-({7-[(4-bromo-2-chlorophenyl)amino]-8-chloroimidazo[1,2-a]pyridin-6-yl}carbonyl)-3-piperidin-2-ylazetidin-3-ol;
1-({8-chloro-7-[(2-fluoro-4-iodophenyl)amino]imidazo[1,2-a]pyridin-6-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol;
1-({7-[(4-bromo-2-chlorophenyl)amino]-8-chloroimidazo[1,2-a]pyridin-6-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol;
1--({4-fluoro-5-[(2-fluoro-4-iodophenyl)amino]-1-methyl-1*H*-benzimidazol-6-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol;
3-[(1*S*)-1-aminoethyl]-1-({5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-1-methyl-1*H*-benzimidazol-6-yl}carbonyl)azetidin-3-ol;
1-({5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-1-methyl-1*H*-benzimidazol-6-yl}carbonyl)-3-[(1*S*)-1-

(methylamino)ethyl]azetidin-3-ol;
4-[(4-bromo-2-fluorophenyl)amino]-3-fluoro-5-({3-hydroxy-3-[(2*S*)-piperidin-2-yl]azetidin-1-yl}carbonyl)pyridin-2(1*H*)-one;
4-[(2-fluoro-4-iodophenyl)amino]-5-({3-hydroxy-3-[(2*S*)-piperidin-2-yl]azetidin-1-yl}carbonyl)-1-methylpyridin-2(1*H*)-one;
4-[(2-fluoro-4-iodophenyl)amino]-5-({3-hydroxy-3-[(2*S*)-piperidin-2-yl]azetidin-1-yl}carbonyl)-1-methylpyridin-2(1*H*)-one;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(1*S*,2*S*)-2-hydroxycyclohexyl]azetidin-3-ol;
4-[(2-fluoro-4-iodophenyl)amino]-5-({3-hydroxy-3-[(1*S*)-1-(methylamino)propyl]azetidin-1-yl}carbonyl)-1-methylpyridin-2(1*H*)-one;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(1*S*,2*R*)-2-hydroxycyclohexyl]azetidin-3-ol;
5-({3-[(1*S*)-1-(dimethylamino)ethyl]-3-hydroxyazetidin-1-yl}carbonyl)-4-[(2-fluoro-4-iodophenyl)amino]-1-methylpyridin-2(1*H*)-one;
4-[(2-fluoro-4-iodophenyl)amino]-5-({3-hydroxy-3-[(methylamino)methyl]azetidin-1-yl}carbonyl)-1-methylpyridin-2(1*H*)-one;
5-{[3-(1*H*-benzimidazol-2-yl)-3-hydroxyazetidin-1-yl]carbonyl}-4-[(4-bromo-2-fluorophenyl)amino]-1-methylpyridin-2(1*H*)-one;
4-[(4-bromo-2-fluorophenyl)amino]-5-{[3-hydroxy-3-(1-methyl-1*H*-benzimidazol-2-yl)azetidin-1-yl]carbonyl}-1-methylpyridin-2(1*H*)-one;
4-[(4-bromo-2-fluorophenyl)amino]-5-({3-hydroxy-3-[(2*S*)-pyrrolidin-2-yl]azetidin-1-yl}carbonyl)-1-methylpyridin-2(1*H*)-one;
1-({3-fluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol;
1-({4-fluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol;
1-({6-[(4-bromo-2-chlorophenyl)amino]-7-fluoro-3-methyl-1,2-benzisoxazol-5-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-(6-methylpiperidin-2-yl)azetidin-3-ol;
1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)-3-piperazin-2-ylazetidin-3-ol;
5-[(2-fluoro-4-iodophenyl)amino]-6-({3-hydroxy-3-[(2*S*)-piperidin-2-yl]azetidin-1-yl}carbonyl)-2-methylpyridazin-3(2*H*)-one;
5-[(4-bromo-2-chlorophenyl)amino]-6-({3-hydroxy-3-[(2*S*)-piperidin-2-yl]azetidin-1-yl}carbonyl)-2-methylpyridazin-3(2*H*)-one;
5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-6-({3-hydroxy-3-[(2*S*)-pyrrolidin-2-yl]azetidin-1-yl}carbonyl)-2-methylpyridazin-3(2*H*)-one;
5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-6-({3-hydroxy-3-[(2*R*)-pyrrolidin-2-yl]azetidin-1-yl}carbonyl)-2-methylpyridazin-3(2*H*)-one;
6-({3-[(1*S*)-1-aminoethyl]-3-hydroxyazetidin-1-yl}carbonyl)-5-[(2-fluoro-4-iodophenyl)amino]-2-methylpyridazin-3(2*H*)-one;
6-({3-[(1*S*)-1-aminoethyl]-3-hydroxyazetidin-1-yl}carbonyl)-5-[(4-bromo-2-chlorophenyl)amino]-2-methylpyridazin-3(2*H*)-one;
5-[(4-bromo-2-chlorophenyl)amino]-6-{[3-((1*S*)-1-{[(3*R*,4*S*)-3,4-dihydroxycyclopentyl]amino}ethyl)-3-hydroxyazetidin-1-yl]carbonyl}-2-methylpyridazin-3(2*H*)-one;
5-[(4-bromo-2-fluorophenyl)amino]-6-[(3-hydroxy-3-{(1*S*)-1-[(2-hydroxy-2-methylcyclopentyl)amino]propyl}azetidin-1-yl)carbonyl]-2-methylpyridazin-3(2*H*)-one;

6-({3-[(1*S*)-1-aminopropyl]-3-hydroxyazetidin-1-yl}carbonyl)-5-[(4-bromo-2-fluorophenyl)amino]-2-methylpyridazin-3(2*H*)-one;
6-{[3-(1*H*-benzimidazol-2-yl)-3-hydroxyazetidin-1-yl]carbonyl}-5-[(2-fluoro-4-iodophenyl)amino]-2-methylpyridazin-3(2*H*)-one;
5-[(2-fluoro-4-iodophenyl)amino]-6-{[3-hydroxy-3-(1-methyl-1*H*-benzimidazol-2-yl)azetidin-1-yl]carbonyl}-2-methylpyridazin-3(2*H*)-one;
1-({2-fluoro-3-[(2-fluoro-4-iodophenyl)amino]pyridin-4-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol;
1-({3-[(2-fluoro-4-iodophenyl)amino]pyridin-4-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol;
1-({3-[(2-fluoro-4-iodophenyl)amino]-1-oxidopyridin-4-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol;
1-({2-fluoro-3-[(2-fluoro-4-bromophenyl)amino]pyridin-4-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol;
3-[(1*S*)-1-aminopropyl]-1-({3-[(2-fluoro-4-iodophenyl)amino]pyridin-4-yl}carbonyl)azetidin-3-ol;
1-({3-[(2-fluoro-4-iodophenyl)amino]pyridin-4-yl}carbonyl)-3-[(1*S*)-1-(methylamino)propyl]azetidin-3-ol;
(1*R*,2*S*)-4-({(1*S*)-1-[1-({2-fluoro-3-[(2-fluoro-4-iodophenyl)amino]pyridin-4-yl}carbonyl)-3-hydroxyazetidin-3-yl]propyl}amino)cyclopentane-1,2-diol;
1-({7-[(4-bromo-2-chlorophenyl)amino]-8-fluoro-4-methylcinnolin-6-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol;
1-({7-[(4-bromo-2-fluorophenyl)amino]-8-fluoro-4-methylcinnolin-6-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol;
3-[(1*S*)-1-aminoethyl]-1-({7-[(4-bromo-2-fluorophenyl)amino]cinnolin-6-yl}carbonyl)azetidin-3-ol;
1-({7-[(4-bromo-2-fluorophenyl)amino]cinnolin-6-yl}carbonyl)-3-{(1*S*)-1-[(2-hydroxy-2-methylcyclopentyl)amino]ethyl}azetidin-3-ol;
1-({7-[(4-bromo-2-fluorophenyl)amino]cinnolin-6-yl}carbonyl)-3-[(1*S*)-1-(dimethylamino)ethyl]azetidin-3-ol;
3-[(1*S*)-1-aminoethyl]-1-({5-[(2-fluoro-4-iodophenyl)amino]-1*H*-1,2,3-benzotriazol-6-yl}carbonyl)azetidin-3-ol;
3-[(1*S*)-1-(dimethylamino)ethyl]-1-({5-[(2-fluoro-4-iodophenyl)amino]-1-methyl-1*H*-1,2,3-benzotriazol-6-yl}carbonyl)azetidin-3-ol;
1-({5-[(2-fluoro-4-iodophenyl)amino]-1*H*-1,2,3-benzotriazol-6-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol;
1-({5-[(2-fluoro-4-iodophenyl)amino]-1-methyl-1*H*-1,2,3-benzotriazol-6-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol;
1-({5-[(2-fluoro-4-iodophenyl)amino]-1*H*-1,2,3-benzotriazol-6-yl}carbonyl)-3-{(1*S*)-1-[(2-hydroxy-2-methylcyclopentyl)amino]ethyl}azetidin-3-ol;
3-[(1*S*)-1-aminoethyl]-1-({4-fluoro-5-[(2-fluoro-4-iodophenyl)amino]-1*H*-1,2,3-benzotriazol-6-yl}carbonyl)azetidin-3-ol;
1-({4-fluoro-5-[(2-fluoro-4-iodophenyl)amino]-1*H*-1,2,3-benzotriazol-6-yl}carbonyl)-3-[(2*S*)-piperidin-2-yl]azetidin-3-ol;
5-({3-[(1*S*)-1-aminoethyl]-3-hydroxyazetidin-1-yl}carbonyl)-6-[(2-fluoro-4-iodophenyl)amino]pyrimidin-2(1*H*)-one;
6-[(2-fluoro-4-iodophenyl)amino]-5-({3-hydroxy-3-[(2*S*)-piperidin-2-yl]azetidin-1-yl}carbonyl)pyrimidin-2(1*H*)-one;
4-[(2-fluoro-4-iodophenyl)amino]-5-({3-hydroxy-3-[(2*S*)-piperidin-2-yl]azetidin-1-yl}carbonyl)pyrimidin-2(1*H*)-one; and
5-({3-[(1*S*)-1-aminoethyl]-3-hydroxyazetidin-1-yl}carbonyl)-4-[(2-fluoro-4-iodophenyl)amino]pyrimidin-2(1*H*)-one.

38. A pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt or solvate therof, and a pharmaceutically acceptable carrier, excipient, or diluent.

39. A method of inhibiting MEK comprising administering to a patient a therapeutically effective amount of a compound of Formula I, or a pharm,aceutically acceptable salt or solvate thereof, and optionally a pharmaceutically acceptable carrier, excipient, or diluent.

40. A method of treating a disease, disorder, or syndrome which method comprises administering to a patient a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable carrier, excipient, or diluent.

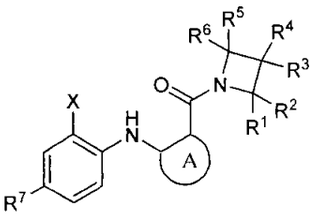
41. The method of Claim 40 where the disease is a proliferative disease.

42. A method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable carrier, excipient, or diluent.

43. The method of claim 42 where the cancer is melanoma, colon cancer, rectal cancer, pancreatic cancer, breast cancer, non-small cell lung cancer, small cell lung cancer, papillary and anaplastic thyroid cancer, endometrial cancer, or ovarian cancer.

ABSTRACT OF THE DISCLOSURE

Disclosed are compounds of Formula I:



I

and pharmaceutically acceptable salts and solvates thereof. Such compounds are MEK inhibitors and are useful in the treatment of proliferative diseases, such as cancer. Also disclosed are pharmaceutical compositions containing such compounds as well as methods of using the compounds and compositions of the invention in the treatment of cancer.

INHIBIDORES DE MEK Y MÉTODOS PARA SU USO

Campo de la Invención

Esta invención se relaciona con ciertos inhibidores de MEK que son útiles en el tratamiento de enfermedades hiperproliferativas, tales como el cáncer, en mamíferos. Esta invención también se relaciona con un método para usar dichos compuestos en el tratamiento de enfermedades proliferativas en mamíferos, especialmente humanos, y con composiciones farmacéuticas, que contienen dichos compuestos.

Referencia Cruzada a Solicitudes de Patente Relacionadas

Los solicitantes reivindican prioridad conforme al Título 35, artículo 119(e) del Código de Estados Unidos de las Solicitudes Provisorias de Patentes en trámite N° 60/724.578, presentada el 7 de octubre de 2005 y N° 60/802.840, presentada el 23 de mayo de 2006, cuyas invenciones se incorporan en la presente como referencia en su totalidad.

Estado del Arte

Las mejoras en la especificidad de los agentes usados para tratar el cáncer son de considerable interés debido a los

beneficios terapéuticos que se notarían si se pudieran reducir los efectos colaterales asociados con la administración de estos agentes. Tradicionalmente, las mejoras dramáticas en el tratamiento del cáncer están asociadas con la identificación de agentes terapéuticos que actúan a través de mecanismos novedosos.

Las proteína cinasas son enzimas que catalizan la fosforilación de proteínas, en particular, los grupos hidroxi en los residuos de tirosina, serina y treonina de las proteínas. Las consecuencias de esta actividad aparentemente simple son asombrosas; la diferenciación y la proliferación celular; es decir, virtualmente todos los aspectos de la vida celular de un modo u otro dependen de la actividad de la proteína cinasa. Además, se ha relacionado la actividad anormal de la proteína cinasa con un sinnúmero de trastornos, que van desde enfermedades que relativamente no ponen en riesgo la vida tales como la soriasis hasta enfermedades muy virulentas tales como el glioblastoma (cáncer de cerebro).

Las proteína cinasas se pueden clasificar en categorías como de tipo receptor o de tipo no receptor. Las tirosina cinasas de tipo receptor tienen una parte extracelular, una transmembrana, y una parte intracelular, mientras que las tirosina cinasas de tipo no receptor son enteramente

intracelulares. Están compuestas por una gran cantidad de receptores de transmembrana con actividad biológica diversa. De hecho, se han identificado alrededor de 20 subfamilias diferentes de tirosina cinasas de tipo receptor. Una de las subfamilias de la tirosina cinasa, denominada subfamilia HER, está compuesta de EGFR (HER1), HER2, HER3 y HER4. Los ligandos de esta subfamilia de receptores identificados hasta ahora incluyen el factor de crecimiento epitelial, TGF-alfa, anfiregulina, HB-EGF, betacelulina y heregulina. Otra sufamilia de estas tirosina cinasas de tipo receptor es la subfamilia insulina, que incluye INS-R, IGF-R, e IR-R. La subfamilia PDGF incluye el PDGF-alfa y beta receptores, CSFIR, c-kit y FLK-II. Además, hay una familia FLK, que está compuesta por el receptor de dominio de inserción de cinasa (KDR), cinasa-1 de hígado fetal (FLK-1), cinasa-4 de hígado fetal (FLK-4), y la tirosina cinasa-1 similar a fms (flt-1). Las familias PDGF y FLK generalmente se consideran juntas debido a las similitudes de los dos grupos. Para un análisis detallado de las tirosina cinasas de tipo receptor, véase Plowman et al, *DN&P* 7(6): 334-339, 1994, que se incorpora por la presente como referencia.

El tipo no receptor de tirosina cinasas también está compuesto de numerosas subfamilias, que incluyen Src, Frk, Btk, Csk, Abl, Zap70, Fes/Fps, Fak, Jak, Ack, y LIMK. Cada una de estas

subfamilias además se subdivide en receptores variados. Por ejemplo, la subfamilia Src es una de las más grandes e incluye Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr, y Yrk. La subfamilia Src de enzimas ha sido vinculada a la oncogénesis. Para un análisis más detallado del tipo no receptor de tirosina cinasas, véase Bolen, *Oncogene*, **8**:2025-2031 (1993), que se incorpora en la presente como referencia.

Dado que las proteína cinasas y sus ligandos cumplen funciones críticas en diferentes actividades celulares, la desregulación de la actividad enzimática de las proteína cinasas puede derivar en propiedades celulares alteradas, tales como el crecimiento celular incontrolado asociado con el cáncer. Además de las indicaciones oncológicas, la señalización de cinasa alterada está implicada en otras numerosas enfermedades. Éstas incluyen, en forma no taxativa, trastornos inmunológicos, enfermedades cardiovasculares, enfermedades inflamatorias, y enfermedades degenerativas. En consecuencia, tanto las tirosina cinasas receptoras como no receptoras son blancos atractivos para el descubrimiento de fármacos de moléculas pequeñas.

Una meta particularmente atractiva para el uso terapéutico de la modulación de las cinasas se relaciona con las indicaciones oncológicas. Por ejemplo, la modulación de la actividad de las

proteínas cinasas para el tratamiento del cáncer se ha demostrado exitosamente con la aprobación por la FDA (Administración de Alimentos y Medicamentos) de Gleevec® (mesilato de imatinib, producido por Novartis Pharmaceutical Corporation de East Hanover, NJ) para el tratamiento de la Leucemia Mieloide Crónica (CML) y los cánceres de estroma gastrointestinal. Gleevec es un inhibidor de Abl cinasa selectivo.

La modulación (particularmente la inhibición) de la proliferación y la angiogénesis celular, dos procesos celulares claves necesarios para el crecimiento y la supervivencia del tumor (Matter A. *Drug Disc Technol* **2001** *6*, 1005-1024), es una meta atractiva para el desarrollo de fármacos de molécula pequeña. La terapia anti-angiogénica representa un enfoque potencialmente importante para el tratamiento de los tumores sólidos y otras enfermedades asociadas con la vascularización disregulada, que incluye la enfermedad isquémica de las arterias coronarias, la retinopatía diabética, la soriasis y la artritis reumatoide. Asimismo, los agentes antiproliferativos celulares son deseables para hacer lento o detener el crecimiento de los tumores.

Un blanco particularmente atractivo para la modulación de molécula pequeña, con respecto a la actividad antiangiogénica y antiproliferativa es MEK. La inhibición de MEK1 (MAPK/ERK Kinase [MAPK/ERK Cinasa) es una estrategia prometedora para controlar el crecimiento de los tumores que dependen de la señalización de la vía de ERK/MAPK aberrante Solit et al., 2006; Wellbrock et al., 2004). La cascada de transducción de señales de MEK-ERK es una vía conservada que regula el crecimiento, la proliferación, la diferenciación y la apóptosis celular en respuesta a factores de crecimiento, citocinas y hormonas. La vía opera corriente abajo de Ras que suele regularse en forma ascendente o mutarse en los tumores humanos. Se ha demostrado que MEK es un efector crítico de la función de Ras. La vía de ERK/MAPK se regula en forma ascendente en un 30% de la totalidad de los tumores y se han identificado mutaciones de activación oncogénica en K-Ras y B-Raf en el 22% y en el 18% de la totalidad de los cánceres respectivamente (Allen et al., 2003; Bamford S, 2004; Davies et al., 2002; Malumbres and Barbacid, 2003). Una gran parte de los cánceres humanos, que incluyen el 65% (B-Raf) de los malanomas malignos, el 60% (K-Ras) y el 4% (B-Raf) de los cánceres pancreáticos, el 50& de los cánceres colorectales (colon, en particular, K-Ras: 30%, B-Raf: 15%), el 20% (K-Ras) de los cánceres de pulmón, el 27% (B-Raf) del cáncer de tiroides papilar y anaplástico y el 10%-20% (B-Raf) de los

cánceres ováricos endometriales, alojan mutaciones de Ras y Raf activadoras. Se ha mostrado que la inhibición de la vía de ERK, y en particular la inhibición de la actividad de MEK cinasa, deriva en efectos antimetastásicos y antiangiogénicos principalmente debido a una reducción del contacto célula-célula y la motilidad así como la regulación descendente de la expresión del factor de crecimiento endotelial vascular (VEGF). Además, la expresión de MEK o ERK negativa dominante redujo la capacidad transformadora de Ras mutante como se observa en el cultivo celular y en el crecimiento primario y metastásico de xenoinjertos de tumores humanos in vivo. En consecuencia, la vía de transducción de señales de MEK-ERK es una vía apropiada para que sea el objetivo de la intervención terapéutica.

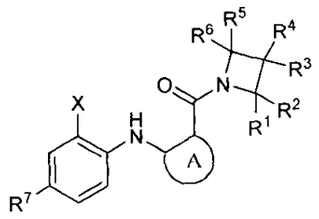
Por consiguiente, la identificación de compuestos de molécula pequeña que inhiben, regulan y/o modulan específicamente la transducción de señales de cinasas, particularmente MEK, es deseable como un medio para tratar o prevenir estados de enfermedad asociados con el cáncer y es un objetivo de esta invención.

Resumen de la Invención

El siguiente es solamente un resumen de ciertos aspectos de la invención y no se desea que tenga carácter taxativo. Éstos y otros aspectos se describen en forma más completa a continuación. Todas las referencias citadas en esta memoria descriptiva por la presente se incorporan como referencia en su totalidad. En caso de discrepancia entre la invención expresa de esta memoria descriptiva y las referencias incorporadas como referencia, regirá la invención expresa de esta memoria descriptiva.

Esta invención proporciona compuestos que inhiben, regulan y/o modulan la transducción de señales de las cinasas, particularmente MEK. Los compuestos de la invención son ciertos derivados de azetidin-1-il(2-(2-fluorofenilamino)ciclico)metanonas que son útiles en el tratamiento de enfermedades hiperproliferativas, tales como el cáncer, en humanos. Esta invención también proporciona métodos para fabricar el compuesto, métodos para usar dichos compuestos en el tratamiento de enfermedades hiperproliferativas en humanos y composiciones farmacéuticas que contienen dichos compuestos.

En un aspecto, la invención proporciona un compuesto de la Fórmula I



I

o una sal o solvato farmacéuticamente aceptable de él, en donde A, X, R^1, R^2, R^3, R^4, R^5, R^6, y R^7 son lo definido en el Grupo A, el Grupo B, el Grupo C, o el Grupo D:

Grupo A:

A es arileno optativamente sustituido con uno, dos, tres o cuatro grupos seleccionados de R^{10}, R^{12}, R^{14}, y R^{16} donde R^{10}, R^{12}, R^{14} y R^{16} son independientemente hidrógeno, alquilo, alquenilo, alquinilo, halo, haloalcoxi, hidroxi, alcoxi, amino, alquilamino, dialquilamino, haloalquilo, $-NHS(O)_2R^8$, $-CN$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$ y $-NR^8C(O)R^{8'}$;

X es alquilo, halo, haloalquilo, o haloalcoxi;

R^1, R^2, R^3, R^4, R^5 y R^6 son independientemente hidrógeno, halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, $-CN$, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, o heterocicloalquilo, donde el alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, y

heterocicloalquilo se sustituyen optativamente con uno, dos, tres, cuatro, cinco, seis, o siete grupos seleccionados independientemente de halo, alquilo, haloalquilo, nitro, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, heteroarilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ y $-NR^8C(O)R^{8'}$; o uno de R^1 y R^2 junto con el carbono al cual están unidos, R^3 y R^4 junto con el carbono al cual están unidos, y R^5 y R^6 junto con el carbono al cual están unidos, forman C(O) o C(=NOH);

m es 0, 1, o 2;

R^7 es hidrógeno, halo o alquilo;

R^8, $R^{8'}$ y $R^{8''}$ se seleccionan independientemente de hidrógeno, hidroxi, alcoxi optativamente sustituido, alquilo, alquenilo, alquinilo, arilo, cicloalquilo, heteroarilo, y heterocicloalquilo; donde el alquilo, alquenilo, alquinilo, arilo, cicloalquilo, heteroarilo, y heterocicloalquilo se sustituyen optativamente con uno, dos, tres, cuatro o cinco grupos seleccionados independientemente de alquilo, halo, hidroxi, hidroxialquilo, alcoxi optativamente sustituido, alcoxialquilo, haloalquilo, carboxi, alcoxicarbonilo, alqueniloxicarbonilo, cicloalquilo optativamente sustituido, cicloalquiloxicarbonilo optativamente sustituido, arilo

optativamente sustituido, ariloxi optativamente sustituido, ariloxicarbonilo optativamente sustituido, arilalquilo optativamente sustituido, arilalquiloxi optativamente sustituido, arilalquiloxicarbonilo optativamente sustituido, nitro, ciano, heterocicloalquilo optativamente sustituido, heteroarilo optativamente sustituido, $-S(O)_nR^{31}$ (donde n es 0, 1, o 2 y R^{31} es alquilo optativamente sustituido, arilo optativamente sustituido, heterocicloalquilo optativamente sustituido, o heteroarilo optativamente sustituido), $-NR^{34}SO_2R^{34a}$ (donde R^{34} es hidrógeno o alquilo y R^{34a} es alquilo, alquenilo, cicloalquilo, arilo, heteroarilo, o heterocicloalquilo), $-SO_2NR^{35}R^{35a}$ (donde R^{35} es hidrógeno o alquilo y R^{35a} es alquilo, alquenilo, cicloalquilo, arilo, heteroarilo, o heterocicloalquilo), $-NR^{32}C(O)R^{32a}$ (donde R^{32} es hidrógeno o alquilo y R^{32a} es alquilo, alquenilo, alcoxi, o cicloalquilo), $-NR^{30}R^{30'}$ (donde R^{30} y $R^{30'}$ son independientemente hidrógeno, alquilo, o hidroxialquilo), y $-C(O)NR^{33}R^{33a}$ (donde R^{33} es hidrógeno o alquilo y R^{33a} es alquilo, alquenilo, alquinilo, o cicloalquilo);

R^9 es alquilo, alquenilo, alquinilo, arilo, cicloalquilo, heteroarilo, y heterocicloalquilo; donde el alquilo, alquenilo, alquinilo, arilo, cicloalquilo, heteroarilo, y heterocicloalquilo se sustituyen independiente y optativamente con uno, dos, tres, cuatro o cinco grupos seleccionados de

halo, hidroxi, alquilo, haloalquilo, haloalcoxi, amino, alquilamino, y dialquilamino;

R^{25} y R^{25b} son independientemente hidrógeno, alquilo, alquenilo, cicloalquilo optativamente sustituido, o arilo optativamente sustituido; y

R^{25a} es hidrógeno, alquilo, o alquenilo;

Grupo B:

A es heteroarileno optativamente con uno, dos, tres o cuatro grupos seleccionados de R^{10}, R^{12}, R^{14}, R^{16} y R^{19} donde R^{10}, R^{12}, R^{14} y R^{16} son independientemente hidrógeno, alquilo, alquenilo, alquinilo, halo, haloalcoxi, hidroxi, alcoxi, ciano, amino, alquilamino, dialquilamino, haloalquilo, alquilsulfonilamino, alquilcarbonilo, alquenilcarbonilo, alcoxicarbonilo, alqueniloxicarbonilo, aminocarbonilo, alquilaminocarbonilo, dialquilaminocarbonilo, o alquilcarbonilamino; donde R^{19} es hidrógeno, alquilo, o alquenilo; y donde cada alquilo y alquenilo, solo o como parte de otro grupo dentro de R^{10}, R^{12}, R^{14}, R^{16}, y R^{19} se sustituye independiente y optativamente con halo, hidroxi, o alcoxi;

X es alquilo, halo, haloalquilo, o haloalcoxi;

R^1, R^2, R^3, R^4, R^5 y R^6 son independientemente hidrógeno, halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, $-CN$, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$,

$-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, o heterocicloalquilo, en donde el alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, y heterocicloalquilo se sustituyen optativamente con uno, dos, tres, cuatro, cinco, seis o siete grupos seleccionados independientemente de halo, alquilo, haloalquilo, nitro, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, heteroarilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ y $-NR^8C(O)R^{8'}$; o uno de R^1 y R^2 junto con el carbono al cual están unidos, R^3 y R^4 junto con el carbono al cual están unidos, y R^5 y R^6 junto con el carbono al cual están unidos forman C(O) o C(=NOH);

m es 1 o 2;

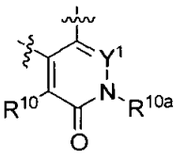
R^7 es hidrógeno, halo o alquilo; y

R^8, $R^{8'}$ y $R^{8''}$ se seleccionan independientemente de hidrógeno, hidroxi, alcoxi optativamente sustituido, alquilo, haloalquilo, alquenilo, alquinilo, arilo, cicloalquilo, heteroarilo, y heterocicloalquilo, donde el alquilo, alquenilo, alquinilo, arilo, cicloalquilo, heteroarilo, y heterocicloalquilo se sustituyen independiente y optativamente con uno, dos, tres, cuatro o cinco grupos alquilo, halo,

hidroxi, hidroxialquilo, alcoxi optativamente sustituido, alcoxialquilo, haloalquilo, carboxi, carboxi éster, nitro, ciano, $-S(O)_nR^{31}$ (donde n es 0, 1, o 2 y R^{31} es alquilo optativamente sustituido, arilo optativamente sustituido, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, o heteroarilo optativamente sustituido), $-NR^{36}S(O)_2R^{36a}$ (donde R^{36} es hidrógeno, alquilo, o alquenilo y R^{36a} es alquilo, alquenilo, arilo optativamente sustituido, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, o heteroarilo optativamente sustituido), $-S(O)_2NR^{37}R^{37a}$ (donde R^{37} es hidrógeno, alquilo, o alquenilo y R^{37a} es alquilo, alquenilo, arilo optativamente sustituido, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, o heteroarilo optativamente sustituido), cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, ariloxi optativamente sustituido, arilalquiloxi optativamente sustituido, heteroarilo optativamente sustituido, $-NHC(O)R^{32}$ (donde R^{32} es alquilo, alquenilo, alcoxi, o cicloalquilo) y $-NR^{30}R^{30'}$ (donde R^{30} y $R^{30'}$ son independientemente hidrógeno, alquilo, o hidroxialquilo), y $-C(O)NHR^{33}$ (donde R^{33} es alquilo, alquenilo, alquinilo, o cicloalquilo);

Grupo C:

A es



(a)

donde R^{10} es hidrógeno, alquilo, alquenilo, alquinilo, halo, haloalcoxi, hidroxi, alcoxi, amino, alquilamino, dialquilamino, haloalquilo, $-NHS(O)_2R^8$, -CN, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$ y $-NR^8C(O)R^{8'}$;

R^{10a} es hidrógeno, alquilo, o alquenilo;

Y^1 es =CH- o =N-;

X es alquilo, halo, haloalquilo, o haloalcoxi;

R^1, R^2, R^3, R^4, R^5 y R^6 son independientemente hidrógeno, halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, o heterocicloalquilo, donde el alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, y heterocicloalquilo se sustituyen independiente y optativamente con uno, dos, tres, cuatro, cinco, seis o siete grupos seleccionados independientemente de halo, alquilo,

haloalquilo, nitro, cicloalquilo optativamente sutituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, heteroarilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ y $-NR^8C(O)R^{8'}$; o uno de R^1 y R^2 junto con el carbono al cual están unidos, R^3 y R^4 junto con el carbono al cual están unidos, y R^5 y R^6 junto con el carbono al cual están unidos forman C(O) o C(=NOH);

m es 1 o 2;

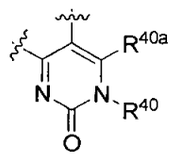
R^7 es hidrógeno, halo o alquilo; y

R^8, $R^{8'}$ y $R^{8''}$ se seleccionan independientemente de hidrógeno, hidroxi, alcoxi optativamente sustituido, alquilo, haloalquilo, alquenilo, alquinilo, arilo, cicloalquilo, heteroarilo, y heterocicloalquilo, donde el alquilo, alquenilo, alquinilo, arilo, cicloalquilo, heteroarilo, y heterocicloalquilo se sustituyen independiente y optativamente con uno, dos, tres, cuatro o cinco grupos seleccionados independientemente de alquilo, halo, hidroxi, hidroxialquilo, alcoxi optativamente sustituido, alcoxialquilo, haloalquilo, carboxi, carboxi éster, nitro, ciano, $-S(O)_nR^{31}$ (donde n es 0, 1, o 2 y R^{31} es alquilo optativamente sustituido, arilo optativamente sustituido, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, o heteroarilo optativamente sustituido), $-NR^{36}S(O)_2R^{36a}$ (donde R^{36}

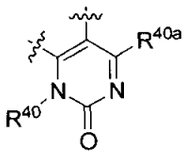
es hidrógeno, alquilo, o alquenilo y R^{36a} es alquilo, alquenilo, arilo optativamente sustituido, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, o heteroarilo optativamente sustituido), $-S(O)_2NR^{37}R^{37a}$ (donde R^{37} es hidrógeno, alquilo, o alquenilo y R^{37a} es alquilo, alquenilo, arilo optativamente sustituido, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sutituido, o heteroarilo optativamente sustituido), cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, ariloxi optativamente sustituido, arilalquiloxi optativamente sustituido, heteroarilo optativamente sustituido, $-NHC(O)R^{32}$ (donde R^{32} es alquilo, alquenilo, alcoxi, o cicloalquilo) y $-NR^{30}R^{30'}$ (donde R^{30} y $R^{30'}$ son independientemente hidrógeno, alquilo, o hidroxialquilo), y $-C(O)NHR^{33}$ (donde R^{33} es alquilo, alquenilo, alquinilo, o cicloalquilo); o

Grupo D:

A es



(b) o



(c)

R^{40} y R^{40a} son independientemente hidrógeno o alquilo;

X es alquilo, halo, haloalquilo, o haloalcoxi;

R^1, R^2, R^3, R^4, R^5 y R^6 son independientemente hidrógeno, halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, $-CN$, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, o heterocicloalquilo, donde el alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, y heterocicloalquilo se sustituyen independiente y optativamente con uno, dos, tres, cuatro, cinco, seis o siete grupos halo, alquilo, haloalquilo, nitro, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, heteroarilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ y $-NR^8C(O)R^{8'}$; o uno de R^1 y R^2 junto con el carbono al cual están unidos, R^3 y R^4 junto con el

carbono al cual están unidos, y R^5 y R^6 junto con el carbono al cual están unidos forman C(O) o C(=NOH);

m es 1 o 2;

R^7 es hidrógeno, halo o alquilo; y

R^8, $R^{8'}$ y $R_{8''}$ se seleccionan indpendientemente de hidrógeno, hidroxi, alcoxi optativamente sustituido, alquilo, haloalquilo, alquenilo, alquinilo, arilo, cicloalquilo, heteroarilo, y heterocicloalquilo, donde el alquilo, alquenilo, alquinilo, arilo, cicloalquilo, heteroarilo, y heterocicloalquilo se sustituyen independiente y optativamente con uno, dos, tres, cuatro o cinco grupos seleccionados independientemente de alquilo, halo, hidroxi, hidroxialquilo, alcoxi optativamente sustituido, alcoxialquilo, haloalquilo, carboxi, carboxi éster, nitro, ciano, $-S(O)_nR^{31}$ (donde n es 0, 1, o 2 y R^{31} es alquilo optativamente sustituido, arilo optativamente sustituido, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, o heteroarilo optativamente sustituido), $-NR^{36}S(O)_2R^{36a}$ (donde R^{36} es hidrógeno, alquilo, o alquenilo y R^{36a} es alquilo, alquenilo, arilo optativamente sustituido, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, o heteroarilo optativamente sustituido), $-S(O)_2NR^{37}R^{37a}$ (donde R^{37} es hidrógeno, alquilo, o alquenilo y R^{37a} es alquilo, alquenilo, arilo optativamente sustituido, cicloalquilo optativamente sustituido, heterocicloalquilo

optativamente sustituido, o heteroarilo optativamente sustituido), cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, ariloxi optativamente sustituido, arilalquiloxi optativamente sustituido, heteroarilo optativamente sutituido, $-NHC(O)R^{32}$ (donde R^{32} es alquilo, alquenilo, alcoxi, o cicloalquilo) y $-NR^{30}R^{30'}$ (donde R^{30} y $R^{30'}$ son independientemente hidrógeno, alquilo, o hidroxialquilo), y $-C(O)NHR^{33}$ (donde R^{33} es alquilo, alquenilo, alquinilo, o cicloalquilo).

Un segundo aspecto de la invención proporciona una composición farmacéutica que comprende un compuesto de la Fórmula I, o una sal o solvato farmacéuticamente aceptable de él, y un portador, excipiente o diluyente farmacéuticamente aceptable.

En un tercer aspecto, la invención se refiere a un método de inhibir MEK que comprende administrar a un paciente una cantidad terapéuticamente eficaz de un compuesto de la Fórmula I, o una sal o solvato farmacéuticamente aceptable de él, y optativamente un portador, excipiente o diluyente.

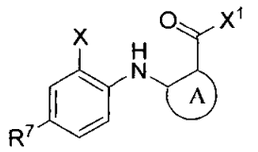
En un cuarto aspecto, la invención comprende un método para inhibir MEK en una célula, que comprende poner a la célula en contacto con un compuesto de la Fórmula I o una sal o solvato

farmacéuticamente aceptable de él, o con una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de un compuesto de la Fórmula I y un portador, excipiente o diluyente farmacéuticamente aceptable.

Un quinto aspecto de la invención proporciona un método para tratar una enfermedad, un trastorno o un síndrome cuyo método comprende administrar a un paciente un compuesto de la Fórmula I o una sal o un solvato farmacéuticamente aceptable de él, o una composición que comprende una cantidad terapéuticamente eficaz de un compuesto de la Fórmula I y un portador, excipiente o diluyente farmacéuticamente aceptable.

Un sexto aspecto de la invención se refiere a un proceso para preparar un compuesto de la Fórmula I, que comprende:

(a) hacer reaccionar un compuesto intermedio de la Fórmula 19:



19

donde X^1 es OH o halo, específicamente cloro o fluoro, y todos los demás grupos son los definidos en el Resumen de la Invención para un compuesto seleccionado del Grupo A, el Grupo B, el Grupo C, y el Grupo D; con un compuesto intermedio de la fórmula 17:



17

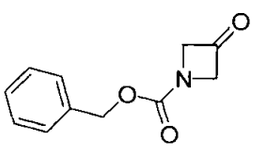
donde R^1, R^2, R^3, R^4, R^5, y R^6 son los definidos en el Resumen de la Invención para un compuesto seleccionado del Grupo A, el Grupo B, el Grupo C, y el Grupo D; y

(b) optativamente separar isómeros individuales; y

(c) optativamente modificar cualquiera de los grupos R^1, R^2, R^3, R^4, R^5, y R^6.

Un séptimo aspecto de la invención se refiere a un proceso para preparar compuestos intermedios de las fórmulas 3, 4, 5, 6, 10 y 11, que comprende:

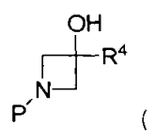
(a) hacer reaccionar un compuesto intermedio de la fórmula 2(a):



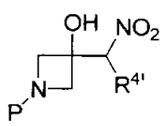
2(a)

con R^4M (donde R^4M es un reactivo de Grignard o una especie organometálica y R^4 es lo definido en el Resumen de la Invención para un compuesto del Grupo A, el Grupo B, el Grupo C, o el Grupo D); con $R^{4'}CH_2NO_2$ (donde $R^{4'}$ es hidrógeno o alquilo optativamente sustituido como se describió para R^4 en

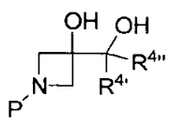
el Resumen de la Invención para un compuesto del Grupo A, el Grupo B, el Grupo C, o el Grupo D); con $R^{4'}R^{4''}C(O)$ ($R^{4'}$ es alquilo optativamente sustituido como se desribió para R^4 en el Resumen de la Invención para el Grupo A, el Grupo B, el Grupo C, o el Grupo D y $R^{4''}$ es hidrógeno o $R^{4'}$); con $R'R''CHP(Ph)_3$ (donde R' y R'' son independientemente hidrógeno, alquilo, alquenilo, arilo, o heteroarilo y el alquilo, alquenilo, arilo, y heteroarilo son optativamente sustituidos como se describió para R^4 en el Resumen de la Invención para un compuesto del Grupo A, el Grupo B, el Grupo C, o el Grupo D); con un auxiliar de oxazolidinona quiral y el posterior tratamiento con una base, tal como hidróxido de litio, en peróxido de hidrógeno acuoso; o con un grupo herocicloalquilo protegido con N donde P^1 es Boc y P^2 es CBz o P^1 es CBz y P^2 es Boc; para dar los compuestos intermedios de las fórmulas 3, 4, 5, 6, 12, y 13, respectivamente:



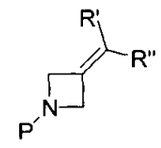
(**3**);



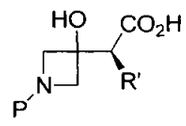
(**4**);



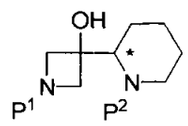
(**5**);



(**6**);

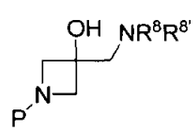


(**10**); y



(**13**);

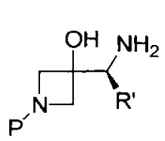
(b) optativamente también hacer reaccionar **6** con *m*-CPBA y formar un epóxido y también abrir el epóxido con una amina de la fórmula $NHR^8R^{8'}$ y dar un compuesto intermedio de la fórmula **8**:



8

donde P es un grupo protector de N y R^8 y $R^{8'}$ son los definidos en el Resumen de la Invención para un compuesto del Grupo A, el Grupo B, el Grupo C, o el Grupo D;

(c) optativamente también someter a **10** a un reordenamiento de Curtius y un posterior tratamiento para dar un compuesto intermedio de la fórmula 12:



12

donde P es un grupo protector de N y R' es un grupo alquilo tal como metilo o etilo;

(d) optativamente también resolver isómeros individuales; y

(e) optativamente modificar cualquiera de los grupos R^1, R^2, R^3, R^4, R^5, y R^6.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Abreviaturas y Definiciones

Las siguientes abreviaturas y términos tienen las definiciones indicadas en toda la descripción:

Ac	Acetilo
br	Ancho
°C	Grados Celsius
CBZ	CarboBenZoxi = benciloxicarbonilo
d	Doblete
dd	Doblete de doblete
dt	Doblete de triplete
DAST	Trifluoruro de (dietilamino)azufre
DCM	Diclorometano

DIPEA	N,N-diisopropiletilamina
DMAP	4-dimetilaminopiridina
DMF	N,N-dimetilformamida
DMSO	Sulfóxido de dimetilo
DPPA	Difenilfosforil azida
EDCI	1-(3-dimetilaminopropil)-3-etilcarbodiimida
EI	Ionización de Impacto de Electrones
Et	Etilo
g	Gramo(s)
GC	Cromatografía de gas
h o hr	Hora(s)
HBTU	Hexafluorofosfato de 2-(1H-benzotriaol-1-il)-1,1,3,3-tetrametiluronio
HOAc	Ácido acético
HOBt	Hidroxibenzotriazol
HPLC	Cromatografía de líquidos de alta presión
L	Litro(s)
LDA	Diisopropilamidade litio
LHMDS	Hexametildisilazidade litio
M	Molar o molaridad

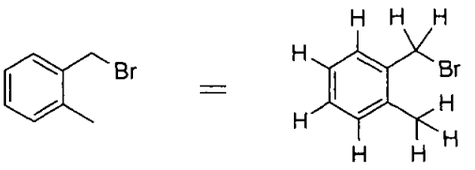
m	Multiplete
MCPBA	Ácido meta-cloroperbenzoico
Me	Metilo
mg	Miligramo(s)
MHz	Megahertz (frecuencia)
min	Minuto(s)
mL	Mililitro(s)
mM	Milimolar
mmol	Milimol(es)
mol	Mol(es)
MS	Análisis de espectro de masa
N	Normal o normalidad
nM	Nanomolar
NMM	N-metilmorfolina
NMR	Espectroscopio de resonancia magnética nuclear
PyBOP	Hexafluorofosfato de benzotriazol-1-il-oxi-tris-pirrolidin-fosfonio
q	Cuarteto
RT	Temperatura ambiente
s	Singulete
s-	Secundario
t-	Terciario

t o tr	Triplete
THF	Tetrahidrofurano
µL	Microlitro
µM	Micromol(es) o micromolar

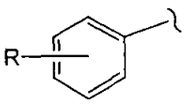
El símbolo "-" significa un enlace simple, "=" significa un enlace doble, "≡" significa un enlace triple y "---" significa un enlace simple y optativamente un enlace doble. Cuando se ilustran o se describen estructuras químicas, a menos que se diga explícitamente de otro modo, se asume que todos los carbonos tienen una sustitución del hidrógeno para adaptarse a una valencia del flúor.

Cuando se ilustran o describen estructuras químicas, a menos que se diga explícitamente de otro modo, se asume que todos los carbonos tienen una sustitución del hidrógeno para adaptarse a una valencia del flúor. Por ejemplo, en la estructura del lado izquierdo del esquema siguiente hay nueve hidrógenos implícitos. Los nueve hidrógenos se ilustran en la estructura del lado derecho. En algunas ocasiones un átomo particular de una estructura se describe en la fórmula textual que tiene un hidrógeno o hidrógenos como sustitución (hidrógeno definido expresamente), por ejemplo, $-CH_2CH_2-$. Un experto en el arte entiende que las técnicas descriptivas

mencionadas son comunes en el arte químico para hacer breve y simple la descripción de estructuras que de otro modo son complejas.

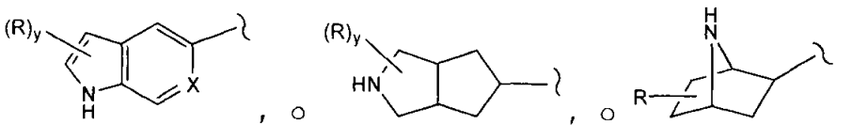


Si un grupo "R" se ilustra como "flotando" sobre un sistema de anillo, como por ejemplo, en la fórmula:



entonces, a menos que se defina de otro modo, un sustituyente "R" puede residir sobre cualquier átomo del sistema de anillo, asumiendo el reemplazo de un hidrógeno ilustrado, implícito o definido expresamente de uno de los átomos del anillo, siempre que se forme una estructura estable.

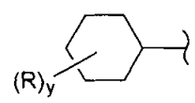
Si un grupo "R" se ilustra "flotando" sobre un sistema de anillo fusionado, como por ejemplo en las fórmulas:



entonces, a menos se defina de otro modo, un sustituyente "R" puede residir sobre cualquier átomo del sistema de anillo fusionado, asumiendo el reemplazo de un hidrógeno ilustrado

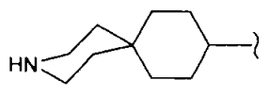
(por ejemplo el -NH- en la fórmula precedente), hidrógeno implícito (por ejemplo como en la fórmula precedente, donde los hidrógenos no se muestran pero se entiende que están presentes), o hidrógeno definido expresamente (por ejemplo donde en la fórmula precedente, "X" equivale a =CH-) de uno de los átomos del anillo, siempre que se forme una estructura estable. En el ejemplo ilustrado, el grupo "R" puede residir sobre el anillo de 5 miembros o de 6 miembros del sistema de anillo fusionado. En la fórmula ilustrada anteriormente, cuando y es 2 por ejemplo, entonces las dos "R" pueden residir sobre dos átomos cualquiera del sistema de anillo, nuevamente asumiendo que cada uno reemplaza a un hidrógeno ilustrado, implícito o definido expresamente sobre el anillo.

Cuando un grupo "R" se ilustra que existe sobre un sistema de anillo que contiene carbonos saturados, como por ejemplo en la fórmula:



donde, en este ejemplo, "y" puede ser más de uno, suponiendo que cada uno reemplaza a un hidrógeno ilustrado, implícito o definido expresamente sobre el anillo; entonces, a menos que se diga de otro modo, donde la estructura resultante es estable, dos "R" pueden residir sobre el mismo carbono. Un

ejemplo simple es cuando R es un grupo metilo, puede existir un dimetilo geminal sobre un carbono del anillo ilustrado (un carbono "anular"). En otro ejemplo, dos R sobre el mismo carbono, que incluyen ese carbono, pueden formar un anillo, creando así una estructura de anillo espirocíclico (un grupo "espirociclilo") con el anillo ilustrado como por ejemplo en la fórmula:



"Acilo" significa un radical -C(O)R donde R es alquilo optativamente sustituido, alquenilo optativamente sustituido, haloalquilo, cicloalquilo, cicloalquilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, heterocicloalquilo, o heterocicloalquilalquilo, como se definen en la presente, por ejemplo, acetilo, benzoilo, trifluorometilcarbonilo, o 2-metoxietilcarbonilo.

"Acilamino" significa un grupo -NRR' donde R es acilo, definido en la presente, y R' es hidrógeno o alquilo.

"Administración" y variantes de ella (por ejemplo, "administrando" un compuesto) con referencia a un compuesto de la invención significa introducir el compuesto o un profármaco del compuesto en el sistema del animal que necesita el

tratamiento. Cuando un compuesto de la invención o un profármaco de él se proporciona en combinación con uno o más agentes activos adicionales (por ejemplo, cirugía, radiación, y quimioterapia, etc), la "administración" y sus variantes se entienden cada una que incluyen la introducción concurrente o secuencial del compuesto o el profármaco de él y otros agentes.

"Alquenilo" significa un radical de hidrocarburo monovalente lineal de uno a seis átomos de carbono o un radical de hidrocarburo monovalente ramificado de tres a 6 átomos de carbono cuyo radical contiene por lo menos un enlace doble, por ejemplo, etenilo, propenilo, 1-but-3-enilo, 1-pent-3-enilo, 1-hex-5-enilo y similares.

"Alquenilcarbonilo" significa un grupo -C(O)R donde R es alquenilo, definido en la presente.

"Alqueniloxicarbonilo" significa un grupo -C(O)OR donde R es alquenilo, definido en la presente.

"Alcoxi" significa un grupo -OR donde R es un grupo alquilo definido en la presente. Ejemplos incluyen metoxi, etoxi, propoxi, isopropoxi y similares. Alcoxi inferior se refiere a grupos que contienen de uno a seis carbonos.

"Alcoxialquilo" significa un grupo alquilo, definido en la presente, sustituido con por lo menos uno, preferentemente uno, dos, o tres grupos alcoxi definidos en la presente. Ejemplos representativos incluyen metoximetilo y similares.

"Alcoxicarbonilo" significa un grupo -C(O)OR donde R es un alquilo definido en la presente.

"Alcoxicarbonilamino" significa un grupo -NR'R" donde R' es hidrógeno, alquilo, hidroxi, o alcoxi y R" es alcoxicarobnilo, definido en la presente.

"Alquilo" significa un radical de hidrocarburo monovalente saturado lineal de uno a ocho átoos de carbono o un radical de hidrocarburo monovalente saturado ramificado de tres a ocho átomos de carbono, por ejemplo, metilo, etilo, propilo, 2-propilo, butilo (que incluye todas las formas isoméricas), o pentilo (que incluye todas las formas isoméricas), y similares.

"Alquilamino" significa un radical de -NHR donde R es alquilo definido en la presente, o un derivado de N-óxido, o un derivado protegido de él, por ejemplo, metilamino, etilamino, *n*-propilamino, *iso*-propilamino, *n*-butilamino, *iso*-butilamino, *terc*-butilamino, o metilamino-N-óxido y similares.

"Alquilaminoalquilo" significa un grupo alquilo sustituido con uno o dos grupos alquilamino, definidos en la presente.

"Alquilaminocarbonilo" significa un grupo -C(O)R donde R es alquilamino, definido en la presente.

"Alquilcarbonilo" significa un grupo -C(O)R donde R es alquilo, definido en la presente.

"Alquilcarbonilamino" significa un grupo -NRR' donde R es hidrógeno o alquilo como se define en la presente y R' es alquilcarbonilo, definido en la presente.

"Alquilcarboniloxi" significa un grupo -OC(O)R donde R es alquilo, definido en la presente.

"Alquilsulfonilamino" significa un grupo $-NRS(O)_2R'$ donde R es hidrógeno o alquilo definido en la presente, y R' es alquilo, definido en la presente.

"Alquinilo" significa un radical de hidrocarburo recto o ramificado que tiene de 2 a 8 átomos de carbono y por lo menos un enlace triple e incluye etinilo, propinilo, butinilo, pentin-2-ilo y similares.

"Aminoalquilo" significa un grupo alquilo sustituido con por lo menos uno, preferentemente uno, dos o tres, grupos amino.

"Aminocarbonilo" significa un grupo $-C(O)NH_2$.

"Arilo" significa un anillo monocarbocíclico o bicarbocíclico de seis a catorce miembros monovalente, en donde el anillo monocíclico es aromático y por lo menos uno de los anillos en el anillo bicíclico es aromático. A menos que se diga de otro modo, la valencia del grupo puede estar ubicada en cualquier átomo de cualquier anillo dentro del radical, si lo permiten las normas de las valencias. Ejemplos representativos incluyen fenilo, naftilo e indanilo y similares.

"Arileno" significa un anillo monocarbocíclico o bicarbocíclico de seis a catorce miembros divalente, en donde el anillo monocíclico es aromático y por lo menos uno de los anillos del anillo bicíclico es aromático. Ejemplos representativos incluyen fenileno, naftileno, e indanileno y similares.

"Arilalquilo" significa un grupo alquilo, definido en la presente, sustituido con uno o dos grupos arilo, definido en la presente. Ejemplos incluyen bencilo, fenetilo y similares.

"Carboxi éster" significa un grupo -C(O)OR donde R es alquilo inferior, alquenilo inferior, alquinilo inferior, cicloalquilo, arilo o arilalquilo, cada uno de los cuales se define en la presente. Ejemplos representativos incluyen metoxicarbonilo, etoxicarbonilo, y benciloxicarbonilo y similares.

"Cicloalquilo" significa un radical de hidrocarburo monovalente, saturado o parcialmente insaturado, monocíclico o bicíclico fusionado (pero no aromático) de tres a diez átomos de carbono del anillo. Los radicales de hidrocarburo bicíclicos fusionados incluyen sistemas de anillo en puente. A menos que se diga de otro modo, la valencia del grupo puede estar ubicada sobre cualquier átomo de cualquier anillo dentro del radical, si lo permiten las normas de las valencias. Uno o dos átomos de carbono del anillo se pueden reemplazar por un grupo -C(O)-, -C(S)-, o -C(=NH)-. Más específicamente, el término cicloalquilo incluye, en forma no taxativa, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, o ciclo-3-enilo y similares.

"Dialquilamino" significa un radical -NRR' donde R y R' son alquilo definido en la presente, o un derivado de N-óxido, o un derivado protegido de él, por ejemplo dimetilamino,

dietilamino, N,N-metilpropilamino o N,N-metiletilamino, y similares.

"Dialquilaminoalquilo" significa un grupo alquilo sustituido con uno o dos grupos dialquilamino, definido en la presente.

"Dialquilaminocarbonilo" significa un grupo -C(O)R donde R es dialquilamino, definido en la presente.

"Policíclico fusionado" o "sistema de anillo fusionado" significa un sistema de anillo policíclico que contiene anillos fusionados y, a menos que se indique de otro modo, puede contener anillos en puente; es decir, donde dos anillos tienen más de un átomo compartido en sus estructuras. En esta solicitud de patente, los policíclicos fusionados y los sistemas de anillos fusionados no son necesariamente todos sistemas de anillos aromáticos. Normalmente, pero no necesariamente, los policíclicos fusionados comparten un grupo de átomos vecinos, por ejemplo naftaleno o 1,2,3,4-tetrahidro-naftaleno. Un sistema de anillo espiro no es un policíclico fusionado por esta definición, sin que los sistemas de anillos policíclicos fusionados de la invención pueden ellos mismos tener anillos espiro unidos a ellos a través de un solo átomo del anillo del policíclico fusionado. En algunos ejemplos, como lo apreciará un experto en el arte, dos grupos adyacentes

sobre un sistema aromático pueden contener heteroátomos y pueden ser optativamente sustituidos con uno o más grupos. Además se debe señalar que los carbonos saturados de dichos grupos fusionados (es decir las estructuras de anillos saturados) pueden contener dos grupos de sustitución.

"Haloalcoxi" significa un grupo -OR' donde R' es haloalquilo definido en la presente, por ejemplo, trifluorometoxi, o 2,2,2-trifluoroetoxi y similares.

"Halógeno" o "halo" significa fluoro, cloro, bromo o yodo.

"Haloalquilo" significa un grupo alquilo, definido en la presente, que se sustituye con uno o más halógenos, preferentemente de uno a cinco átomos de halo. Ejemplos representativos incluyen trifluorometilo, difluorometilo, 1-cloro-2-fluoro-etilo y similares.

"Heteroarilo" significa un radical monovalente, monocíclico, bicíclico fusionado o tricíclico fusionado, de 5 a 14 átomos del anillo que contiene uno o más, preferentemente uno, dos, tres o cuatro heteroátomos del anillo seleccionados independientemente de -O-, $-S(O)_n-$ (n es 0, 1, o 2), -N-, $-N(R^x)-$ y los átomos del anillo restantes son carbono, en donde el anillo que comprende un anillo monocíclico es aromático y

en donde por lo menos uno de los anillos fusionados que comprenden un radical bicíclico o tricíclico es aromático. Uno o dos átomos de carbono del anillo de cualquier anillo no aromático que comprende un radical bicíclico o tricíclico se puede reemplazar por un grupo -C(O)-, -C(S)- o -C(=NH)-. R^x es hidrógeno, alquilo, hidroxi, alcoxi, acilo, o alquilsulfonilo. A menos que se diga de otro modo, la valencia puede estar ubicada sobre cualquier átomo de cualquier anillo del grupo heteroarilo, si lo permiten las normas de las valencias. En particular, cuando el punto de la valencia está ubicado sobre el nitrógeno, R^x está ausente. Más específicamente, el término heteroarilo incluye, en forma no taxativa, 1,2,4-triazolilo, 1,3,5-triazolilo, ftalimidilo, piridinilo, pirrolilo, imidazolilo, tienilo, furanilo, indolilo, 2,3-dihidro-1H-indolilo (que incluye, por ejemplo, 2,3-dihidro-1H-indol-2-ilo o 2,3-dihidro-1H-indol-5-ilo, y similares), isoindolilo, indolinilo, isoindolinilo, bencimidazolilo, benzodioxol-4-ilo, benzofuranilo, cinolinilo, indolizinilo, naftiridin-3-ilo, ftalazin-3-ilo, ftalazin-4-ilo, pteridinilo, purinilo, quinazolinilo, quinoxalinilo, tetrazoilo, pirazolilo, pirazinilo, pirimidinilo, piridazinilo, oxazolilo, isooxazolilo, oxadiazolilo, benzoxazolilo, quinolinilo, isoquinolinilo, tetrahidroisoquinolinilo (que incluye por ejemplo, tetrahidroisoquinolin-4-ilo o tetrahidroisoquinolin-6-ilo, y similares), pirrolo[3,2-c]piridinilo (que incluye,

por ejemplo, pirrolo[3,2-c]piridin-2-ilo o pirrolo[3,2-c]piridin-7-ilo, y similares), benzopiranilo, tiazolilo, isotiazolilo, tiadiazolilo, benzotiazoilo, benzotienilo, y sus derivados, o N-óxido o un derivado protegido de él.

"Heteroarileno" significa un radical divalente monocíclico, bicíclico fusionado o tricíclico fusionado de 5 a 14 átomos del anillo que contiene uno o más, preferentemente uno, dos, tres, o cuatro heteroátomos del anillo seleccionados independientemente de -O-, $-S(O)_n-$ (n es 0, 1 o 2), -N-, $-N(R^{19})-$, y los átomos del anillo restantes son carbono, en donde el anillo comprende un radical monocíclico es aromático y en donde por lo menos uno de los anillos fusionados que comprenden un radical bicíclico o tricíclico es aromático. Uno o dos átomos de carbono del anillo de cualquier anillo no aromático que comprende un radical bicíclico o tricíclico se puede reemplazar por un grupo -C(O)-, -C(S)-, o -C(=NH)-. R^{19} es hidrógeno, alquilo o alquenilo. A menos que se diga de otro modo, las valencias pueden estar ubicadas sobre cualquier átomo de cualquier anillo del grupo heteroarileno, si lo permiten las normas de las valencias. En particular, cuando el punto de la valencia está ubicado sobre el nitrógeno, R^x está ausente. Más específicamente, el término heteroarilo incluye, en forma no taxativa, tien-diilo, benzo[d]isoxazol-diilo, benzo[d]isotiazol-diilo, 1H-indazol-diilo (optativamente

sustituido en la posición de N1 con R^{19}), benzo[d]oxazol-diilo, benzo[d]tiazol-diilo, 1H-benzo[d]imidazol-diilo (optativamente sustituido en la posición de N1 con R^{19}), 1H-benzo[d][1,2,3]triazol-diilo (optativamente sustituido en la posición N1 con R^{19}), imidazol[1,2-a]piridin-diilo, cinolin-diilo, quinolin-diilo, piridin-diilo, 1-óxido-piridin-diilo, [1,2,4]triazolo[4,3-a]piridin-diilo y 2,3-dihidroimidazo[1,2-a]piridin-diilo, y similares.

"Heterocicloalquilo" significa un grupo monocíclico monovalente saturado o parcialmente insaturado (pero no aromático) de 3 a 8 átomos del anillo o un grupo bicíclico fusionado monovalente saturado o parcialmente insaturado (pero no aromático) de 5 a 12 átomos del anillo en donde uno o más, específicamente uno, dos, tres o cuatro heteroátomos del anillo independientemente seleccionados de O, $S(O)_n$ (n es 0, 1 o 2), N, $N(R^y)$ (donde R^y es hidrógeno, alquilo, hidroxi, alcoxi, acilo o alquilsulfonilo), los átomos del anillo restantes son carbono. Uno o dos átomos del anillo se pueden reemplazar por un grupo -C(O)-, -C(S)-, -C(=NH)-. El radical bicíclico fusionado incluye sistemas de anillo en puente. A menos que se diga de otro modo, la valencia del grupo puede estar ubicada sobre cualquier átomo de cualquier anillo dentro del radical, si lo permiten las normas de las valencias. Cuando el punto de la valencia está ubicado sobre un átomo de

nitrógeno, R^y está ausente. Más específicamente, el término heterocicloalquilo incluye, en forma no taxativa, azetidinilo, pirrolidinilo, 2-oxopirrolidinilo, 2,5-dihidro-1*H*-pirrolilo, piperidinilo, 4-piperidonilo, morfolinilo, piperazinilo, 2-oxopiperazinilo, tetrahidropiranilo, 2-oxopiperidinilo, tiomorfolinilo, tiamorfolinilo, perhidroazepinilo, pirazolidinilo, imidazolinilo, imidazolidinilo, dihidropiridinilo, tetrahodropiridinilo, oxazolinilo, oxazolidinilo, isoxazolidinilo, tiazolinilo, tiazolidinilo, quinuclidinilo, isotiazolidinilo, octahidroindolilo, octahidroisoindolilo, decahidroisoquinolilo, tetrahidrofurilo, y tetrahidropiranilo, y los derivados de ellos y N-óxido o un derivado protegido de él.

"Hidroxialquilo" significa un alquilo, definido en la presente, sustituido con por lo menos uno, preferentemente uno, dos o tres grupo(s) hidroxi, siempre que si dos grupos hidroxi están presentes no son ambos el mismo átomo de carbono. Ejemplos representativos incluyen, en forma no taxativa, hidroximetilo, 2-hidroxietilo, 2-hidroxipropilo, 3-hidroxipropilo, 1-(hidroximetil)-2-metilpropilo, 2-hidroxibutilo, 3-hidroxibutilo, 4-hidroxibutilo, 2,3-dihidroxipropilo, 1-(hidroximetil)-2-hidroxietilo, 2,3-dihidroxibutilo, 3,4-dihidroxibutilo y 2-(hidroximetil)-3-hidroxipropilo, preferentemente 2-hidroxietilo,

2,3-dihidroxipropilo, y 1-(hidroximetil)-2-hidroxietilo, y similares.

"Hidroxiamino" significa un grupo -NH(OH).

"Optativo" u "optativamente" signitica que el evento o la circunstancia descrito posteriormente puede o no ocurrir y que la descripción incluye instancias en las cuales dicho evento o circunstancia e instancias en las cuales no ocurre. Un experto en el arte entenderá que con respecto a cualquier molécula descrita como que contiene uno o más sustituyentes optativos, se entiende que sólo los compuestos estéricamente prácticos y/o sintéticamente viables están incluidos. "Optativamente sustituido" se refiere a todos los modificadores posteriores en un término. Por lo tanto, por ejemplo, en el término "aril-alquilo de C_{1-8} optativamente sustituido", tanto la parte de "alquilo de C_{1-8}" y la parte de "arilo" de la molécula puede o no ser sustituido. Una lista de ejemplos de sustituciones optativas se presenta a continuación en la definición de "sustituido".

"Alcoxi optativamente sustituido" significa un radical de -OR donde R es alquilo optativamente sustituido definido en la presente. Ejemplos representativos incluyen $-OCH_2CH_2OCH_3$, $-OCH_2CH_2OH$, $-OCH_2CH(NH_2)CH_3$ y similares.

"Alquilo optativamente sustituido" significa un radical de alquilo, definido en la presente, optativamente sustituido con uno o más grupo(s), específicamente uno, dos, tres, cuatro o cinco grupos, seleccionados independientemente de alquilcarbonilo, alquenilcarbonilo, cicloalquilcarbonilo, alquilcarboniloxi, alquenilcarboniloxi, amino, alquilamino, dialquilamino, aminocarbonilo, alquilaminocarbonilo, dialquilaminocarbonilo, ciano, cianoalquilaminocarbonilo, alcoxi, alqueniloxyi, halo, hidroxi, hidroxialcoxi, carboxi, alquilcarbonilamino, alquilcarboniloxi, $-S(O)_{0-2}$-alquilo, $-S(O)_{0-2}$-alquenilo, aminosulfonilo, alquilaminosulfonilo, dialquilaminosulfonilo, $-NR^cS(O)_2$-alquilo (donde R^c es hidrógeno, alquilo, alquenilo optativamente sustituido, alquinilo optativamente sustituido, hidroxi, alcoxi, alqueniloxi, o cianoalquilo), alquilaminocarboniloxi, dialquilaminocarboniloxi, alquilaminoalquiloxi, dialquilaminoalquiloxi, alcoxicarbonilo, alqueniloxicarbonilo, alcoxicarbonilamino, alquilaminocarbonilamino, dialquilaminocarbonilamino, alcoxialquiloxi, y $-C(O)NR^aR^b$ (donde R^a y R^b son independientemente hidrógeno, alquilo, alquenilo optativamente sustituido, alquinilo optativamente sustituido, hidroxi, alcoxi, alqueniloxi, o cianoalquilo).

"Arilo optativamente sustituido" significa un grupo arilo, definido en la presente, que optativamente se sustituye con

uno, dos, tres, cuatro o cinco grupos seleccionados de halo, haloalquilo, haloalcoxi, hidroxi, alquilo, alquenilo, alquinilo, alcoxi, carboxi, carboxi éster, amino, alquilamino, dialquilamino, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, heteroarilo optativamente sustituido, -C(O)NR'R" (donde R' es hidrógeno o alquilo y R" es hidrógeno, alquilo, arilo, heteroarilo, o heterocicloalquilo), -NR'C(O)R" (donde R' es hidrógeno o alquilo y R" es alquilo, arilo, heteroarilo, o heterocicloalquilo), y $-NHS(O)_2R'$ (donde R' es alquilo, arilo, o heteroarilo).

"Arilalquilo optativamente sustituido" significa un grupo alquilo sustituido con uno o dos grupo(s) arilo optativamente sustituido como se define en la presente.

"Arilalquiloxi optativamente sustituido" significa un grupo -OR donde R es arilalquilo optativamente sustituido, como se define en la presente.

"Arilalquiloxicarbonilo optativamente sustituido" significa un grupo -C(O)R donde R es arilalquiloxi optativamente sustituido, definido en la presente.

"Ariloxi optativamente sustituido" significa un grupo -OR donde R es arilo optativamente sustituido, definido en la presente.

"Ariloxicarbonilo optativamente sustituido" significa un grupo -C(O)R donde R es ariloxi optativamente sustituido definido en la presente.

"Cicloalquilo optativamente sustituido" significa un radical de cicloalquilo, definido en la presente, que se sustituye optativamente con uno, dos, tres o cuatro grupo seleccionado independientemente de alquilo, alquenilo, alquinilo, halo, haloalquilo, haloalcoxi, oxo, hidroxi, ciano, nitro, amino, monoalquil(de C_1-C_6)amino, dialquilamino, haloalquilo, haloalcoxi, aminoalquilo, alquilaminoalquilo, dialquilaminoalquilo, carboxi, carboxi éster, cicloalquilo, hidroxialquilo, -C(O)NR'R" (donde R' es hidrógeno, alquilo, hidroxi, o alcoxi, y R" es hidrógeno, alquilo, arilo, heteroarilo, o heterocicloalquilo), heterocicloalquilo optativamente sustituido, heteroarilo optativamente sustituido, -NR'C(O)R" (donde R' es hidrógeno o alquilo y R" es alquilo, arilo, heteroarilo, o heterocicloalquilo), y -$NHS(O)_2R'$ (donde R' es alquilo, arilo, o heterociclilo).

"Cicloalquiloxicarbonilo optativamente sustituido" significa un grupo -C(O)OR donde R es cicloaquilo optativamente sustituido definido en la presente.

"Heteroarilo optativamente sustituido" significa un grupo heteroarilo, definido en la presente, optativamente sustituido con uno, dos, tres, cuatro o cinco grupos seleccionados de halo, haloalquilo, haloalcoxi, alquilo, alquenilo, alquinilo, alcoxi, hidroxi, oxo (si lo permiten las normas de las valencias), carboxi, carboxi éster, amino, alquilamino, dialquilamino, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, heteroarilo, arilo optativamente sustituido, -C(O)NR'R" (donde R' es hidrógeno o alquilo y R" es hidrógeno, alquilo, arilo, heteroarilo, o heterocicloalquilo), -NR'C(O)R" (donde R' es hidrógeno o alquilo y R" es alquilo, arilo, heteroarilo o heterocicloalquilo), y $-NHS(O)_2R'$ (donde R' es alquilo, arilo o heteroarilo).

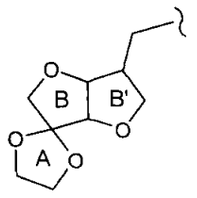
"Heterocicloalquilo optativamente sustituido" significa un anillo de heterocicloalquilo, definido en la presente, optativamente sustituido con uno, dos, tres, cuatro o cinco grupos seleccionados de halo, haloalquilo, haloalcoxi, hidroxi, oxo, alquilo, alquenilo, alquinilo, alcoxi, cicloalquilo optativamente sustituido, heterocicloalquilo,

arilo optativamente sustituido, heteroarilo optativamente sustituido, alquilaminoalquilo, dialquilaminoalquilo, carboxi, alcoxicarbonilo, ariloxicarbonilo, arilalquiloxicarbonilo, cicloalquiloxicarbonilo, cicloalquilalquiloxicarbonilo, -C(O)NR'R" (donde R' es hidrógeno o alquilo y R" es hidrógeno, alquilo, arilo, heteroarilo, o heterocicloalquilo), -NR'C(O)R" (donde R' es hidrógeno o alquilo y R" es alquilo, arilo, heteroarilo, o heterocicloalquilo), amino, alquilamino, dialquilamino, y $-NHS(O)_2R'$ (donde R' es alquilo, arilo, o heteroarilo).

"Sistema de anillo en puente saturado" se refiere a un sistema de anillo bicíclico o policíclico que no es aromático. Dicho sistema puede contener una insaturación aislada o conjugada, pero no anillos aromáticos heteroaromáticos en su estructura de núcleo (pero puede tener sustitución sobre él). Por ejemplo, hexahidro-furo[3,2-b]furano, 2,3,3a,4,7,7a-hexahidro-1H-indeno, 7-aza-biciclo[2.2.1]heptano, y 1,2,3,4,4a,5,8,8a-octahidro-naftaleno están incluidos en la clase "sistema de anillo en puente saturado".

"Espiro", "espirociclilo" o "anillo espiro" se refiere a un anillo originado en un carbono anular de otro anillo. Por ejemplo, como se ilustra a continuación, un átomo del anillo del sistema de anillo en puente saturado (anillos B y B'),

pero no un átomo de cabeza de puente, puede ser un átomo compartido entre el sistema de anillo en puente y un espirociclilo (anillo A) unido a él.



"Rendimiento" para cada una de las reacciones descritas en la presente se expresa como un porcentaje del rendimiento teórico.

"Paciente" para los propósitos de la presente invención incluye humanos y otros animales, particularmente mamíferos, y otros organismos. Por lo tanto los métodos son aplicables tanto para aplicaciones de terapia humana como veterinaria. En una realización específica el paciente es mamífero, y en una realización más específica el paciente es humano.

"Enfermedades o condiciones dependientes de cinasa" se refieren a las condiciones patológicas que dependen de la actividad de una o más proteína cinasas. Las cinasas participan directa o indirectamente en las vías de transducción de señales de una variedad de actividades

celulares que incluyen la proliferación, adhesión, migración, diferenciación e invasión. Las enfermedades asociadas con las actividades de las cinasas incluyen el crecimiento de tumores, la neovascularización patológica que soporta el crecimiento de tumores sólidos, y asociadas con otras enfermedades donde está involucrada la vascularización local excesiva tales como enfermedades oculares (retinopatía diabética, degeneración macular relacionada con la edad, y similares) e inflamación (soriasis, artritis reumatoide, y similares).

Si bien no deseamos ligarnos a la teoría, las fosfatasas también pueden cumplir una función en las "enfermedades o condiciones que dependen de las cianasas", como análogos de cinasas; es decir, las cinasas fosforiladas y fosfatasas desfosforiladas, por ejemplo los sustratos de proteína. En consecuencia los compuestos de la invención, mientras modulan la actividad de cinasa como se describe en la presente, también pueden modular, directa o indirectamente, la actividad de las fosfatasas. Esta modulación adicional, si está presente, puede ser sinergística (o no) para la actividad de los compuestos de la invención hacia una cinasa o familia de cinasas relacionada o interdependiente de otro modo. En cualquier caso, como se dijo previamente, los compuestos de la invención son útiles para tratar enfermedades caracterizadas en parte por niveles anormales de la proliferación celular (es

decir, el crecimiento de los tumores), la muerte celular programada (apóptosis), la migración celular y la invasión y la angiogénesis asociada con el crecimiento de tumores.

"Cantidad terapéuticamente eficaz" es una cantidad de un compuesto de la invención, que cuando se administra a un paciente, mejora un síntoma de la enfermedad. La cantidad de un compuesto de la invención que constituye una "cantidad terapéuticamente eficaz" varía según el compuesto, el estado de enfermedad y su severidad, la edad del paciente a quien se debe tratar y similares. La cantidad terapéuticamente eficaz puede ser determinada habitualmente por un experto en el arte que tiene consideración por sus conocimientos y por esta invención.

"Cáncer" se refiere a estados de enfermedad proliferativa celular, que incluyen en forma no taxativa: Cardiaca: sarcoma (angiosarcoma, fibrosarcoma, rabdomiosarcoma, liposarcoma), mixoma, rabdomioma, fibroma, lipoma y teratoma; Pulmonar: carcinoma broncogénico (célula escamosa, célula pequeña indiferenciada, célula grande indiferenciada, adenocarcinoma), carcinoma alveolar (bronquiolar), adenoma bronquial, sarcoma, linfoma, hanlartoma condromatoso, inesotelioma; Gastrointestinal: de esófago (carcinoma de células escamosas, adenocarcinoma, leiomiosarcoma, linfoma), de estómago

(carcinoma, linfoma, leiomiosarcoma), de páncreas (adenocarcinoma ductal, insulinoma, glucagonoma, gastrinoma, tumores carcinoides, vipoma), de intestino delgado (adenocarcinoma, linfoma, tumores carcinoides, sarcoma de Kaposi, leiomioma, hemangioma, lipoma, neurofibroma, fibroma), de intestino grueso (adenocarcinoma, adenoma tubular, adenoma velloso, hamartoma, leiomioma); de tracto genitourinario: de riñón (adenocarcinoma, tumor de Wilm [nefroblastoma], linfoma, leucemia), de vejiga y uretra (carcinoma de células escamosas, carcinoma de células transicionales, adenocarcinoma), de próstata (adenocarcinoma, sarcoma), de testículos (seminoma, teratoma, carcinoma embrional, teratocarcinoma, coriocarcinoma, sarcoma, carcinoma de células intersticiales, fibroma, fibroadenoma, tumores adenomatoides, lipoma); de hígado: hepatoma (carcinoma hepatocelular), colangiocarcinoma, hepatoblastoma, angiosarcoma, adenoma hepatocelular, hemangioma; de huesos: sarcoma osteogénico (osteosarcoma), fibrosarcoma, histiocitoma fibroso maligno, condrosarcoma, sarcoma de Ewing, linfoma maligno (sarcoma de células reticuladas), mieloma múltiple, cordoma de tumor de células giganates malignas, osteocronfroma (exostosis osteocartilaginosas), condroma benigno, condroblastoma, condromixofibroma, osteoma osteoide y tumores de células gigantes; del sistema nervioso: de cráneo (osteoma, hemangioma, granuloma, xantoma, osteítis deformante), de

meninges (meningioma, meningiosarcoma, gliomatosis), de cerebro (astrocitoma, meduloblastoma, glioma, ependimoma, germinoma [pinealoma], glioblastoma multiforme, oligodendroglioma, Schwannoma, retinoblastoma, tumores congénitos), neurofibroma de médula espinal, meningioma, glioma, sarcoma); Ginecológica: de útero (carcinoma de endometrio), de cuello (carcinoma de cuello, displasia de cuello pretumor), de ovarios (carcinoma ovárico [cistadenocarcinoma seroso, cistadenocarcinoma mucinoso, carcinoma no clasificado], tumores de células granulosa-tecales, tumores de células de Sertoli-Leydig, disgerminoma, teratoma maligno), de vulva (carcinoma de células escamosas, carcinoma intraepitelial, adenocarcinoma, fibrosarcoma, melanoma), de vagina (carcinoma de células transparentes, carcinoma de células escamosas, sarcoma botrioide (rabdomiosarcoma embrional], de las trompas de Falopio (carcinoma); Hematológico: de sangre (leucemia mieloide [aguda y crónica], leucemia linfoblástica aguda, leucemia linfocítica crónica, enfermedades mieloproliferativas, mieloma múltiple, síndrome mielodisplásica), enfermedad de Hodgkin, linfoma que no es de Hodgkin [linfoma maligno]; de piel: melanoma maligno, carcinoma de células basales, carcinoma de células escamosas, sarcoma de Kaposi, nevos displásticos de moles, lipoma, angioma, dermatofibroma, queloides, soriasis; y de las Glándulas Adrenales: neuroblastoma.

Una "sal farmacéuticamente aceptable" de un compuesto significa una sal que es farmacéuticamente aceptable y que posee la actividad farmacológica deseada del compuesto parental. Se entiende que las sales farmacéuticamente aceptables son no tóxicas. Se puede halla información adicional sobre sales farmacéuticamente aceptables en *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, que se incorpora en la presente como referencia, o S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977; 66:1-19, que se incorpora en la presente como referencia.

Ejemplos de sales de adición ácidas farmacéuticamente aceptables incluyen aquellas formadas con ácidos inorgánicos tales como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico, ácido fosfórico, y similares; así como ácidos orgánicos tales como ácido acético, ácido trifluoroacético, ácido propiónico, ácido hexanoico, ácido ciclopentanopropiónico, ácido glicólico, ácido pirúvico, ácido láctico, ácido oxálico, ácido maleico, ácido malónico, ácido succínico, ácido fumárico, ácido tartárico, ácido cítrico, ácido benzoico, ácido cinámico, ácido 3-(4-hidroxibenzoil)benzoico, ácido mandélico, ácido tanosulfónico, ácido etanosulfónico, ácido 1,2-etanodisulfónico, ácido 2-hidroxietanosulfónico, ácido bencenosulfónico, ácido 4-

clorobencenosulfónico, ácido 2-naftalenosulfónico, ácido 4-toluenosulfónico, ácido alcanforsulfónico, ácido glucoheptonico, ácido 4,4'-metilenbis-(3-hidroxi-2-en-1-carboxílico), ácido 3-fenilpropiónico, ácido trimetilacético, ácido butilacético terciario, ácido lauril sulfúrico, ácido glucónico, ácido glutámico, ácido hidroxinaftoico, ácido salicílico, ácido steárico, ácido mucónico, ácido p-toluenosulfónico, y ácido salicílico.

Ejemplos de sales de adición de base farmacéuticamente aceptables incluyen aquellas que se forman cuando un protón ácido presente en el compuesto parental se reemplaza por un ion metal, tal como sales de sodio, potasio, litio, amonio, calcio, magnesio, hierro, zinc, cobre, manganeso, aluminio y similares. Las sales preferibles son las sales de amonio, potasio, sodio, calcio, y magnesio. Las sales derivadas de bases no tóxicas orgánicas farmacéuticamente aceptables incluyen, en forma no taxativa, sales aminas primarias, secundarias y terciarias, aminas sustituidas que incluyen aminas sustituidas naturales, aminas cíclicas y resinas de intercambio de iones básicos. Ejemplos de bases orgánicas incluyen incluyen isopropilamina, trimetolamina, dietilamina, trietilamina, tripropilamina, etanolamina, 2-dimetilaminoetanol, 2-dietilaminoetanol, diciclohexilamina, lisina, arginina, histidina, cafeina, procaína, hidrabamina,

colina, betaína, etlendiamina, glucosamina, metilglucamina, teobromina, purinas, piperazina, piperidina, N-etilpiperidina, trometamina, *N*-metilglucamina, resinas de poliamina, y similares. Los ejemplos de bases orgánicas incluyen isopropilamina, dietilamina, etanolamina, trimetilamina, diciclohexilamina, coline, y cafeína.

"Profármaco" se refiere a compuestos que se transforman (normalmente en forma rápida) *in vivo* para dar el compuesto parental de las fórmulas precedentes, por ejemplo mediante hidrólisis en sangre. Ejemplos comunes incluyen, en forma no taxativa, formas de éster y de amida de un compuesto que tiene una forma activa que lleva un grupo ácido carboxílico. Ejemplos de ésteres farmacéuticamente aceptables de los compuestos de esta invención incluyen, en forma no taxativa, ésteres de alquilo (por ejemplo, con entre uno y seis carbonos) el grupo alquilo es una cadena recta o ramificada. Los ésteres aceptables incluyen ésteres de cicloalquilo y ésteres de arilalquilo tales como, en forma no taxativa, bencilo. Ejemplos de amidas farmacéuticamente aceptables de los compuestos de esta invención incluyen, en forma no taxativa, amidas primarias, y alquil amidas secundarias y terciarias (por ejemplo, con entre uno y seis carbonos). Las amidas y ésteres de los compuestos de la presente invención se pueden preparar de acuerdo con métodos convencionales. Se

proporciona un análisis completo de profármacos en T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 of the A.C.S. Symposium Series, y en Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, ambos incorporados en la presente como referencia para todos los propósitos.

"Metabolito" se refiere al producto de ruptura o de extremo de un compuesto o su sal producido mediante el metabolismo o de la biotransformación en el cuerpo de un animal o humano; por ejemplo, la biotransformación en una molécula más polar por ejemplo mediante la oxidación, reducción, o hidrólisis, o en su conjugado (véase Goodman and Gilman, "The Pharmacological Basis of Therapeutics" 8.sup.th Ed., Pergamon Press, Gilman et al. (eds), 1990 para un análisis de la biotransformación(es). Como se usa en la presente, el metabolito de un compuestode la invención o su sal puede ser la forma biológicamente activa del compuesto en el cuerpo. En un ejemplo, se puede usar un profármaco de manera tal que la forma biológicamente activa, un metabolito, se libera *in vivo*. En otro ejemplo, un metabolito biológicamente activo se descubre por casualidad, es decir no se realizó ningún diseño de profármaco *per se*. Un experto en el arte conoce un ensayo de la actividad de un metabolito de un compuesto de la presente invención a la luz de la presente invención.

"Tratar" o "tratamiento" de una enfermedad, trastorno o síndrome, como se utiliza en la presente, incluye (i) prevenir que la enfermedad, el trastorno o el síndrome ocurra en un humano, es decir hacer que los síntomas clínicos de la enfermedad, el trastorno o el síndrome no se se desarrollen en un animal que puede estar expuesto o predispuesto a la enfermedad, al trastorno o al síndrome pero que aún no experimenta o presenta síntomas de la enfermedad, el trastorno o el síndrome; (ii) inhibir la enfermedad, el trastorno o el síndrome, es decir detener su desarrollo, y (iii) aliviar la enfermedad, el trastorno o el síndrome, es decir provocar el retroceso de la enfermedad, el trastorno o el síndrome. Como se sabe en el arte, pueden ser necesarios ajustes para la síntesis en función de la administración localizada, la edad, el peso corporal, la salud general, el sexo, la dieta, el tiempo de administración, la interacción de fármacos y la severidad de la condición y los podrá determinar un experto en el arte con la experimentación habitual.

Realizaciones de la invención

En una realización de la invención, R^7 es halo y todos los demás grupos son lo definido en el Resumen de la Invención para el Grupo A, el Grupo B, el Grupo C o el Grupo D. En una realización más específica, R^7 es yodo o bromo. En una

realización aún más específica, R^7 es yodo. Aún más específicamente, el compuesto es aquel donde R^7 es yodo o bromo y todos los demás grupos son lo definido en el Resumen de la Invención para el Grupo A.

En otra realización de la invención, X es halo y todos los demás grupos son lo definido en el Resumen de la Invención para el Grupo A, el Grupo B, el Grupo C o el Grupo D. En una realización más específica, X es fluoro o cloro. En una realización aún más específica, X es fluoro. Aún más específicamente, el compuesto es aquel donde X es fluoro o cloro y todos los demás grupos son lo definido en el Resumen de la Invención para el Grupo A.

En otra realización de la Invención, R^7 y X son halo y todos los demás grupos son lo definido en el Resumen de la Invención para el Grupo A, el Grupo B, el Grupo C o el Grupo D. Más específicamente, R^7 es yodo y X es fluoro. Aún más específicamente, el compuesto es aquel donde R^7 es yodo y X es fluoro y todos los demás grupos son lo definido en el Resumen de la Invención para el Grupo A.

En otra realización de la invención, R^1, R^2, R^5 y R^6 son hidrógeno y todos los demás grupos son lo definido en el Resumen de la Invención para el Grupo A, el Grupo B, el Grupo

C o el Grupo D. Más específicamente, R^1, R^2, R^5 y R^6 son hidrógeno y todos los demás grupos son lo definido en el Resumen de la Invención para el Grupo A.

En otra realización de la invención, el compuesto de la Fórmula I se selecciona del Grupo A donde todos los grupos son lo definido en el Resumen de la Invención.

En otra realización de la invención, (A1), X y R^7 son halo y todos los demás grupos son lo definido en el Resumen de la invención para un compuesto del Grupo A.

En otra realización (A2), el compuesto de la Fórmula I se selecciona del Grupo A donde R^{10} y R^{12} son independientemente hidrógeno o halo. En una realización más específica, R^{10} y R^{12} son independientemente hidrógeno o fluoro. Más específicamente, R^{10} es 3-fluoro y R^{12} es hidrógeno. En otra realización más específica, R^{10} y R^{12} son fluoro, más específicamente, 3-fluoro y 4-fluoro, 4-fluoro y 5-fluoro, o 4-fluoro y 6-fluoro.

En otra realización de la invención, (A3), el compuesto es aquel donde R^1, R^2, R^5 y R^6 son hidrógeno y todos los demás grupos son lo definido en el Resumen de la Invención para el Grupo A.

En otra realización (A4), el compuesto de la Fórmula I se selecciona del Grupo A donde X, R^7 y A son lo definido en el Resumen de la Invención; y

uno de R^1, R^2, R^3, R^4, R^5, y R^6 es halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, $-CN$, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, o heterocicloalquilo; donde el alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, y heterocicloalquilo se sustituyen independiente y optativamente con uno, dos, tres, cuatro, cinco, seis o siete grupos seleccionados independientemente de halo, alquilo, haloalquilo, nitro, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, heteroarilo optativamente sustituido, heteroarilalquilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$; y $-NR^8C(O)R^{8'}$; y los demás de R^1, R^2, R^3, R^4, R^5, y R^6 son los definidos en el Resumen de la Invención; o

uno de R^1 y R^2 junto con el carbono al cual están unidos, R^3 y R^4 junto con el carbono al cual están unidos, y R^5 y R^6 junto

con el carbono al cual están unidos forman C(O) o C(=NOH); y los demás de R^1, R^2, R^3, R^4, R^5, y R^6 son los definidosen el Resumen de la Invención.

En otra realización de la Invención (A5), el compuesto de la Fórmula I se selecciona del Grupo A donde X, R^7 y A son los definidos en el Resumen de la Invención; y

R^3 es halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, $-CN$, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, o heterocicloalquilo; donde el alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, y heterocicloalquilo se sustituyen independiente y optativamente con uno, dos, tres, cuatro, cinco, seis o siete grupos seleccionados independientemente de halo, alquilo, haloalquilo, nitro, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, heteroarilo optativamente sustituido, heteroarilalquilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-$

$NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ y $-NR^8C(O)R^{8'}$; y R^4 es lo definido en el Resumen de la Invención; o

R^3 y R^4 junto con el carbono al cual están unidos forman C(O) o C(=NOH); y

R^1, R^2, R^5 y R^6 son lo definido en el Resumen de la Invención.

Una realización más específica de la realización A5 es aquella donde R^1, R^2, R^5 y R^6 son hidrógeno.

En otra realización de la invención (A6), el compuesto de la Fórmula I se selecciona del Grupo A donde X, R^7 y A son lo definido en el Resumen de la Invención; y

R^3 y R^4 son independientemente halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, o heterocicloalquilo; donde el alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, y heterociclilo se sustituyen independiente y optativamente con uno, dos, tres, cuatro, cinco, seis o siete grupos seleccionados independientemente de halo, alquilo, haloalquilo, nitro, cicloalquilo optativamente sustituido,

heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, heteroarilo optativamente sustituido, heteroarilalquilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ y $-NR^8C(O)R^{8'}$; o

R^3 y R^4 junto con el carbono al cual están unidos forman C(O) o C(=NOH);

R^1, R^2, R^5 y R^6 son lo definido en el Resumen de la Invención.

Una ralización más específica de la realización A6 es aquella donde R^1, R^2, R^5 y R^6 son hidrógeno.

En otra realización de la Invención (A7), el compuesto de la Fórmula I se selecciona del Grupo A donde X y R^7 son halo, A es fenileno optativamente sustituido con R^{10} y R^{12} son independientemente hidrógeno o halo; R^1, R^2, R^5 y R^6 son hidrógeno;

R^3 es hidrógeno, y R^4 es $-NR^8R^{8'}$ (donde R^8 es hidrógeno, hidroxi, alquilo, alcoxi, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y $R^{8'}$ es hidroxi, alcoxi, arilo, cicloalquilo, heteroarilo, o heterocicloalquilo), $-NHS(O)_2R^8$, $-CN$, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, alquenilo y alquinilo; donde el alquenilo y alquinilo se sustituyen

optativamente con uno, dos, tres, cuatro, cinco, seis o siete grupos seleccionados independientemente de halo, alquilo, haloalquilo, nitro, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, heteroarilo optativamente sustituido, heteroarilalquilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^8$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ y $-NR^8C(O)R^{8'}$; o

R^3 y R^4 junto con el carbono al cual están unidos forman C(O) o C(=NOH);

m, $R^{8''}$ y R^9 son lo definido en el Resumen de la Invención para el compuesto del Grupo A; y a menos que se especifique en esta realización, R^8 y $R^{8'}$ son lo definido en el Resumen de la Invención para un compuesto del Grupo A.

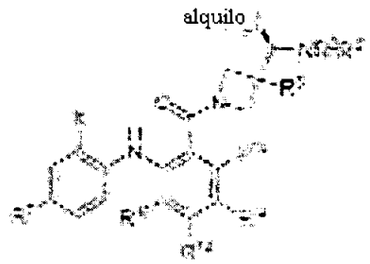
En otra realización de la invención (A8), el compuesto de la Fórmula I se selecciona del Grupo A donde R^3 es hidrógeno, halo, hidroxi, alcoxi, o amino. Más específicamente, R^3 es hidrógeno, halo, alcoxi, o amino. Más específicamente, R^3 es hidrógeno, fluoro, hidroxi, metoxi, o amino. Aún más específicamente, R^3 es hidroxi.

En una realización más específica de la realización A8, X y R^7 son halo, A es fenileno optativamente sustituido con R^{10} y R^{12}

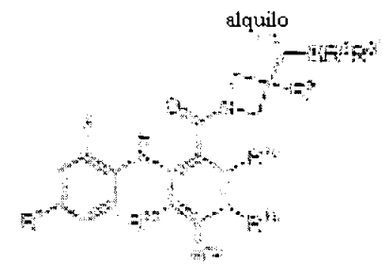
cuando R^{10} y R^{12} son independientemente hidrógeno o halo; R^1, R^2, R^5 y R^6 son hidrógeno, y R^4 es lo definido en el Resumen de la Invención para un compuesto del Grupo A.

Otra realización específica de la invención (A9) es aquella donde el compuesto de la Fórmula I se selecciona del Grupo A donde R^1, R^2, R^5 y R^6 son hidrógeno; R^3 es hidrógeno, halo, hidroxi, alcoxi, o amino; y R^4 es heterocicloalquilo, heteroarilo, o alquilo sustituido con $-NR^8R^{8'}$ donde R^8 y $R^{8'}$ y todos los demás grupos son lo definido en el Resumen de la Invención para un compuesto del Grupo A.

Otra realización especifica de la realización A9 es aquella donde R^4 es alquilo sustituido con $-NR^8R^{8'}$ donde R^8 y $R^{8'}$ y todos los demás grupos son lo definido en el Resumen de la Invención para un compuesto del Grupo A. Específicamente, el compuesto es un compuesto de las Fórmulas I(a) o I(b):



I(a);



I(b)

donde R^3 es lo definido en A9; X, R^7, R^8, $R^{8'}$, R^{10}, R^{12}, R^{14} y R^{16} son lo definido en el Resumen de la Invención para un compuesto del Grupo A.

Otra realización específica de la realización A9 es aquella donde R^4 es heterocicloalquilo.

En una realización específica de la realización A9, el compuesto es aquel donde X y R^7 son halo; A es fenileno optativamente sustituido con R^{10} y R^{12} donde R^{10} y R^{12} son independientemente hidrógeno o halo; R^3 es hidroxi; y R^4 es alquilo sustituido con $-NR^8R^{8'}$ o R^4 es heterocicloalquilo optativamente sustituido con uno, dos, o tres grupos seleccionados independientemente de halo, alquilo, haloalquilo, nitro, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilaquilo optativamente sustituido, heteroarilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^{8'}$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)R^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ y $-NR^8C(O)R^{8'}$; y donde m, R^3, R^8, $R^{8'}$, $R^{8''}$ y R^9 son lo definido en el Resumen de la Invención para un compuesto del Grupo A.

En otra realización de la invención (A10), el compuesto de la Fórmula I se selecciona del Grupo A donde

R^4 es

a) hidrógeno;

b) $-CH_2N(R^{25})(NR^{25a}R^{25b})$;

c) $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$;

d) $-CH_2NR^{25}C(=NH)(N(R^{25a}R^{25b})(NO_2))$;

e) $-CH_2NR^{25}C(=NH)(N(R^{25a}R^{25b})(CN))$;

f) $-CH_2NR^{25}C(=NH)(R^{25})$;

g) $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$;

h) Alquilo;

i) Alquilo sustituido con uno o dos $-OR^8$ donde R^8 es hidrógeno, arilo, o alquilo donde el alquilo se sustituye con uno o dos hidroxi;

j) Alquilo sustituido con uno, dos o tres halo;

k) Alquilo sustituido con nitro;

l) Alquilo sustituido con $-S(O)_mR^9$ (donde m es 0 y R^9 es arilo);

m) Alquilo sustituido con heterocicloalquilo optativamente sustituido;

n) Alquenilo;

o) $-NR^8R^{8'}$ (donde R^8 y $R^{8'}$ son independientemente hidrógeno; alquilo, alquenilo; alquilo sustituido con uno o dos hidroxi; alquilo sustituido con uno o dos $-NR^{30}R^{30'}$ donde R^{30} y $R^{30'}$ son independientemente hidrógeno, alquilo, o hidroxialquilo; alquilo sustituido con heteroarilo

optativamente sustituido; o alquilo sustituido con cicloalquilo optativamente sustituido);

p) $-C(O)NR^{8}R^{8'}$ (donde R^{8} es hidrógeno, alquilo o alquenilo; y $R^{8'}$ es hidrógeno, hidroxi, alquilo, alquenilo, alquilo sustituido con uno o dos hidroxi; alquilo sustituido con heterocicloalquilo optativamente sustituido; alquilo sustituido con $-NR^{30}R^{30'}$ donde R^{30} y $R^{39'}$ son independientemente hidrógeno, alquilo o hidroxialquilo; alcoxi optativamente sustituido);

q) $-NR^{8}C(O)OR^{8'}$ (donde R^{8} y $R^{8'}$ son independientemente hidrógeno, alquilo, alquenilo);

r) Alquilo sustituido con $-NR^{8}R^{8'}$ (donde R^{8} es hidrógeno, alquilo, alquenilo, alquinilo, o alquilo sustituido con uno o dos hidroxi; y $R^{8'}$ es hidrógeno; hidroxi, alcoxi, alquilo, alquenilo, alquinilo, alcoxi optativamente sustituido, alquilo sustituido con uno o dos hidroxi; alquilo sustituido con uno o dos alcoxi; alquilo sustituido con $-NR^{30}R^{30'}$ donde R^{30} y $R^{30'}$ son independientemente hidrógeno, alquilo o hidroxialquilo; alquilo sustituido con uno o dos hidroxi y uno o dos $-NR^{30}R^{30'}$ donde R^{30} y $R^{30'}$ son independientemente hidrógeno, alquilo, o hidroxialquilo; alquilo sustituido con uno, dos, tres, cuatro o cinco halo; alquilo sustituido con ciclolquilo optativamente sustituido; alquilo sustituido con arilo optativamente sustituido; alquilo sustituido

con uno o dos hidroxi y un arilo optativamente sustituido, alquilo sustituido con heterocicloalquilo optativamente sustituido; alquilo sustituido con heteroarilo optativamente sustituido; heteroarilo; arilo; arilo sustituido con uno o dos hidroxi; arilo sustituido con uno o dos alcoxi; arilo sustituido con uno o dos halo; arilo sustituido con uno o dos $-NR^{32}R^{32a}$ donde R^{32} es hidrógeno o alquilo y R^{32a} es alquilo, alquenilo, alcoxi o cicloalquilo; arilo sustituido cno $-NR^{34}SO_2R^{34a}$ donde R^{34} es hidrógeno o alquilo y R^{34a} es alquilo, alquenilo, cicloalquilo, arilo, heteroarilo, o heterocicloalquio; cicloalquilo; cicloalquilo sustituido con uno o dos hidroxi; cicloalquilo sustituido con uno o dos hidroxi y uno o dos hidroxialquilo; cicloalquilo sustituido con uno dos alcoxi; cicloalquilo sustituido con carboxi; cicloalquilo sustituido con $-C(O)NR^{33}R^{33a}$ donde R^{33} es hidrógeno o alquilo y R^{33a} es alquilo, alquenilo, alquinilo o cicloalquilo; alquilo sustituido con $-C(O)NR^{33}R^{33a}$ donde R^{33} es hidrógeno o alquilo y R^{33a} es alquilo, alquenilo, alquinilo o cicloalquilo; cicloalquilo sustituido con cicloalquilo optativamente sustituido; heterocicloalquilo; heterocicloalquilo sustituido con alquilo; heterocicloalquilo sustituido con alcoxicarbonilo; heterocicloalquilo sustituido con arilalquilo optativamente sustituido; heterocicloalquilo

sustituido con uno o dos hidroxi; heterocicloalquilo optativamente sustituido con uno o dos alcoxi; heterocicloalquilo sustituido con uno o dos hidroxialquilo; heterocicloalquilo sustituido con uno o dos hidroxi, uno o dos alcoxi y uno o dos hidroxialquilo; alquilo sustituido con ariloxi optativamente sustituido; alquilo sustituido con $-S(O)_mR^{31}$ donde m es 0 y R^{31} es alquilo; alquilo sustituido con carboxi; alquilo sustituido con alcoxicarbonilo; o alquilo sustituido con $-NR^{32}C(O)OR^{32a}$ donde R^{32} es hidrógeno o alquilo y R^{32a} es alquilo, alquenilo, alcoxi o cicloalquilo);

s) $-NR^8C(O)R^{8'}$ donde R^8 es hidrógeno, alquilo, o alquenilo; y $R^{8'}$ es hidrógeno; alquilo; alquilo sustituido con uno o dos hidroxi; alquilo sustituido con heterocicloalquilo optativamente sustituido; alquilo sustituido con $-NR^{30}R^{30'}$ donde R^{30} y $R^{30'}$ son independientemente hidrógeno, alquilo, hidroxialquilo o alquenilo);

t) Cicloalquilo;

u) Cicloalquilo sustituido con $-NR^8R^{8'}$ donde R^8 y $R^{8'}$ son independientemente hidrógeno, alquilo o alquenilo;

v) Heterocicloalquilo;

w) Heterocicloalquilo sustituido con $-NR^8R^{8'}$ donde R^8 y $R^{8'}$ son independientemente hidrógeno, alquilo o alquenilo;

x) Heterocicloalquilo sustituido con uno o dos alquilo;

y) Heterocicloalquilo sustituido con $-C(O)OR^8$ donde R^8 es alquilo o alquenilo;

z) Alquilo sustituido con $-NR^8C(O)R^{8'}$ (donde R^8 es hidrógeno, alquilo, o alquenilo y $R^{9'}$ es alquilo; alquenilo; o alquilo sustituido con alcoxi, arilo, y uno, dos o tres halo);

aa) Heteroarilo;

bb) Heteroarilo sustituido con $-NR^8R^{8'}$ donde R^8 y $R^{8'}$ son independientemente hidrógeno, alquilo o alquenilo; alquilo sustituido con heteroarilo optativamente sustituido;

cc) Alquilo sustituido con $-NR^8S(O)_2R^{8'}$ donde R^8 es hidrógeno, alquilo o alquenilo y $R^{8'}$ es alquilo o alquenilo;

dd) Alquilo sustituido con $-NR^8C(O)OR^{8'}$ donde R^8 y $R^{8'}$ son independientemente hidrógeno, alquilo o alquenilo;

ee) Alquilo sustituido con un arilo y un $-NR^8R^{8'}$ donde R^8 y $R^{8'}$ son independientemente hidrógeno, alquilo, o alquenilo; y

ff) Alquilo sustituido con uno o dos $-OR^8$ (donde R^8 es hidrógeno) y uno o dos $-NR^8R^{8'}$ donde R^8 y $R^{8'}$ son independientemente hidrógeno, alquilo o alquenilo.

Aún más específicamente, R^4 es hidrógeno, $-CH_2N(H)(NHCH_3)$, $-CH_2NHC(=NH)(NH_2)$, $-CH_2NHC(=NH)(NHNO_2)$, $-CH_2NHC(=NH)(NHCN)$, $-CH_2NHC(=NH)$(fenilo), $-CH_2NHC(NH_2)=CH(NO_2)$, metilo, etilo,

hidroximetilo, 2,3-dihidroxipropilo, 3-hidroxi-2-metil-prop-2-ilo, N-(1-metoxi-prop-2-il)-aminometilo, N-(etoxipropil)-aminometilo, N-(etoxietil)-aminometilo, N-(2,2-dimetoxietil)-aminometilo, N-(metoxietil)-aminometilo, N-(isopropoxietil)-aminometilo, trifluorometilo, 1-nitro-etilo, 1-metil-1-nitro-etilo, 1-nitro-propilo, 3-metil-1-nitro-butilo, feniltiometilo, alilo, etenilo, 2-metiltio-etilaminometilo, 3-metiltio-propilaminometilo, N-(terc-butoxicarbonilaminopropil)-aminometilo, N-(1-carboxietil)-aminometilo, N-(1R-carboxietil)-aminometilo, N-(1S-carboxietil)-aminometilo, N-(1-metoxicarboniletil)-aminometilo, $-NH_2$, $-NH(CH_2)_3CH_3$, $-NHCH_3$, $-NH(CH_2CH_3)$, $-NHCH_2CH(CH_3)_2$, $-NHCH_2CH_2OH$, $-NHCH_2CH_2NH_2$, $-N(CH_3)CH_2CH_2$(heteroarilo), $-NHCH_2$(cicloalquilo), $-C(O)NH_2$, $-C(O)NHOH$, $-C(O)NH(OCH_2CH(OH)CH_2OH)$, $-C(O)NH(CH_2)_3CH_3$, $-C(O)NHCH_2CH=CH_2$, $-C(O)NHCH_2CH_3$, $-C(O)NHCH_2CH_2OH$, $C(O)NHCH_2CH(OH)CH_2OH$, $-C(O)NHCH_2CH_2CH(OH)CH_2OH$, $-C(O)NHCH_2CH_2$(piperidin-1-ilo), $-C(O)NH$(fenilo), $-C(O)NHCH_2CH_2N(CH_2CH_3)_2$, $-NHC(O)OC(CH_3)_2$, $-NHC(O)OCH_3$, azetidinilmetilo, pirrolidinilmetilo, 3-hidroxi-pirrolidinilmetilo, 2-(metoximetil)-pirrolidinilmetilo, 2S-(metoximetil)-pirrolidinilmetilo, 2R-(metoximetil)-pirrolidinilmetilo, morfolinilmetilo, hidroxipiperidinilmetilo, 4-alquil-piperazinilmetilo, 4-alquil-homopiperazinilmetilo, 4-(heterocicloalquil)-

piperidinilmetilo, 4-(dialquilaminoalquil)-piperazinilmetilo, N-hidroxiaminometilo, N-metoxiaminometilo, N-etoxiaminometilo, N-etilaminometilo, 1-(N-etil-amino)-etilo, N,N-dietilaminometilo, N,N-dimetilaminometilo, aminometilo, 1-amino-etilo, 1R-amino-etilo, 1S-amino-etilo, 1-(metilamino)-etilo, 1-(N,N-dimetilamino)-etilo, 1-amino-1-metil-etilo, 1-aminopropilo, 1S-aminopropilo, 1R-aminopropilo, N-(n-propil)-aminometilo, N-(isopropil)-aminometilo, 2-(N-isopropilamino)-etilo, 3-(N-isopropilamino)-2-metil-prop-2-ilo, 1-(N-amino)-propilo, 1-(N,N-dietil-amino)-propilo, 1-aminobutilo, 1-amino-isobutilo, N-(2-aminoetil)-aminoetilo, N-(n-butil)-aminoetilo, N-isobutilaminometilo, terc-butilaminometilo, 1-(terc-butilamino)-etilo, sec-butilaminometilo, N-(2-metil-but-3-il)-aminometilo, N-(3,3-dimetil-butil)-aminoetilo, N-(3-metil)but-3-il)-aminometilo, N-(2-metilbutil)-aminometilo, N-(pent-3-il)-aminometilo, n-pentilaminometilo, isopentilaminometilo, sec-pentilaminometilo, neopentilaminometilo, N-(2,2,4-trimetil-pent-4-il)-aminometilo, N-(2-etil-butil)-aminometilo, N-alil-amino-metilo, 3-metil-but-1-in-3-ilaminometilo, N-(2,3-dihidroxipropiloxi)-aminometilo, N-ciclopropilaminometilo, N-ciclobutilaminometilo, N-ciclopentilaminometilo, N-ciclopenten-4-ilaminometilo, N-(1(R,S)-hidroxi-ciclopent-2-il)-aminometilo, N-(1S-hidroxi-ciclopent-2-il)-aminometilo, N-(1R-hidroxi-ciclopent-2-il)-aminometilo, N-(1(R,S)-hidroxi-1-metil-ciclopent-2-il)-aminometilo, N-(1S-hidroxi-1-metil-

ciclopent-2-il)-aminometilo, N-(1R-hidroxi-1-metil-ciclopent-2-il)-aminometilo, N-(3,4-dihidroxi-ciclopentil)-aminometilo, N-(1-hidroximetil-ciclopent-1-il)-aminometilo, N-(2,3-dihidroxi-4-hidroximetil-ciclopentil)-aminometilo, N-(1(R,S)-metoxi-ciclopent-2-il)-aminometilo, N-(1S-metoxi-ciclopent-2-il)-aminometilo, N-(1R-metoxi-ciclopent-2-il)-aminometilo, N-(1-carboxi-ciclopentil)-aminometilo, N-ciclohexilaminometilo, N-(1(R,S)-hidroxi-ciclohex-2-il)-aminometilo, N-(cis-4-hidroxi-ciclohexil)-aminometilo, N-(trans-4-hidroxi-ciclohexil)-aminometilo, 1-[N-(cis-4-hidroxi-ciclohexil)-amino]-etilo, 1-[N-(trans-4-hidroxi-ciclohexil)-amino]-etilo, N-(1(R)-hidroxi-ciclohex-2-il)-aminometilo, N-(1(S)-hidroxi-ciclohex-2-il)-aminometilo, N-(1-hidroximetil-ciclohexil)-aminometilo, N-(2-ciclohexil-ciclohexil)-aminometilo, N-{(2R,3S,4R,6R)-2-(hidroximetil)-3,4-dihidroxi-6-metoxi-tetrahidro-2H-piran-5-il}-aminometilo, N-(cicloheptil)-aminometilo, N-(ciclooctil)-aminometilo, [(1r,3r,5R,7R)-triciclo[3.3.1.$1^{3,7}$]dec-2-ilamino]metil,N-[1-(ciclopropilaminocarbonil)-ciclopentil]-aminometilo, -$CH_2NHC(CH_3)_2C(O)NH$(ciclohexilo), -$CH_2NHC(CH_3)_2C(O)NH(CH_2CH_3)$, N-(1-benciloxi-ciclopent-2-il)-aminometilo, N-(ciclopropilmetil)-aminometilo, N-(ciclohexilmetil)-aminometilo, N-(1-ciclohexiletil)-aminometilo, N-(imidazolil)-aminometilo, N-(1,3,3-triazinil)-aminometilo, N-(5-hidroxi-pirazol-3-il)-aminometilo, N-(3-metil-pirazol-3-il)-

aminometilo, N-(bencimidazolil)-aminometilo, N-(pirimidin-2-il)-aminometilo, N-(piridin-2-il)-aminometilo, N-(piridin-3-il)-aminometilo, N-(piridin-4-il)-aminometilo, N-indan-1-il-aminometilo, N-indan-2-il-aminometilo, fenilaminometilo, N-(2-hidroxifenil)-aminometilo, N-(3-hidroxifenil)-aminometilo, N-(4-hidroxifenil)-aminometilo, N-(2-metoxifenil)-aminometilo, N-(3-metoxifenil)-aminometilo, N-(4-metoxifenil)-aminometilo, N-(2-fluorofenil)-aminometilo, N-(3-fluorofenil)-aminometilo, N-(4-fluorofenil)-aminometilo, N-(2-clorofenil)-aminometilo, N-(3-clorofenil)-aminometilo, N-(4-clorofenil)-aminometilo, N-(3-metilcarbonilamino-fenil)-aminometilo, N-(4-metilcarbonilamino-fenil)-aminometilo, N-(2-aminofenil)-aminometilo, N-(3-aminofenil)-aminometilo, N-(4-aminofenil)-aminometilo, N-(2-metilsulfonilaminofenil)-aminometilo, N-(3-metilsulfonilaminofenil)-aminometilo, N-(3-metisulfonilaminofenil)-aminometilo, N-(4-metilsulfonilaminofenil)-aminometilo, N-(2-fluoro-4-hidroxi-fenil)-aminometilo, N-(3-fluoro-4-hidroxi-fenil)-aminometilo, N-(bencil)-aminometilo, N-(2-hidroxifenilmetil)-aminometilo, N-(3-idroxifenilmetil)-aminometilo, N-(4-hidroxifenilmetil)-aminometilo, N-(2-(N-metilpiperazin-1-il)-fenilmetil)-aminometilo, N-(4-alquil-fenetil)-aminometilo, N-(1-hidroxi-3-fneil-prop-2-il)-aminometilo, N-(pirrolidin-2-ilmetil)-aminometilo, N-(N-alquil-pirrolidinilmetil)-aminometilo, N-(N-alquilo-pirrolidiniletil)-aminometilo, N-(pirrolidinilpropil)-

aminometilo, N-(1,1-metil-2-pirrolidin-1-il-etil)-aminometilo, N-(tetrahidrofuranilmetil)-aminometilo, N-(tetrahidro-2H-piran-4-ilmetil)-aminometilo, N-(tetrahidro-2H-piraniletil)-aminometilo, N-(piperidin-4-ilmetil)-aminometilo, N-(N-metilpiperidin-4-ilmetil)-aminometilo, N-(N-terc-butoxicarbonilpiperidin-4-ilmetil)-aminometilo, N-(N-metilimidazol-4-ilmetil)-aminometilo, N-(N-metilimidazol-5-ilmetil)-aminometilo, N-[2-(imidazol-4-il)-etil]-aminometilo, N-[3-(imidazolil)-propil]-aminometilo, N-(piridin-3-iletil)-aminometilo, N-(piridin-4-iletil)-aminometilo, N-(tien-2-iletil)-aminometilo, N-(furan-2-iletili)-aminometilo, N-(5-metil-1,3,4-oxadiazol-2-ilmetil)-aminometilo, N-(2-indolin-3-iletil)-aminometilo, 2-(N,N-dimetilamino)-etilaminometilo, 2-(N,N-dimetilamino)-1-metil-etilaminometilo, 3-aminopropilaminometilo, 3-(N,N-dimetilamino)-propilaminometilo, 3-(N,N-dietilamino)-propilaminometilo, N-(N,N-diisopropilaminoetil)-aminoetilo, N-(N,N-dimetilaminobutil)-aminometilo, N-(3-hidroxipropil)-aminometilo, N-(2-hidroxipropil)-aminometilo, N-(1,2-dihidroxipropil)-aminometilo, N-(1-amino-2-hidroxi-prop-3-il)-aminometilo, N-(N-etoxicarbonil-piperidin-4-il)-aminometilo, N-(N-benzopiperidin-4-il)-aminometilo, N-(homopiperidin-3-il)-aminometilo, N-(N-bencilpirrolidin-3-il)-aminometilo, N-(N-etilpieperidin-3-il)aminometilo, 2,2,2-trifluoroetilaminometilo, 3,3,3-trifluoropropilaminometilo,

2,2,3,3,3-pentafluoropropilaminometilo, $-CH_2N(CH_2CH_2OH)_2$, $-CH_2N(CH_3)(CH_2CH_2OH)$, $-CH_2NH(CH_2CH_2OH)$, $-CH_2NH(CH_2CH_2CH_2CH_2OH)$, $-CH_2N(CH_3)$(N-metil-pirrolidin-3-ilo), $-CH_2NH(C(CH_3)_2CH_2OH)$, $-NHC(O)CH(CH_3)_2$, $-NHC(O)CH_2N(CH_2CH_3)_2$, $-NHC(O)CH_2NH(CH_3)$, $-NHC(O)CH_2CH(OH)CH_2OH$, $-NHC(O)CH_2NH_2$, $-NHC(O)CH_2N(CH_2CH_2OH)_2$, $-NHC(O)CH_2CH_2N(CH_2CH_2OH)_2$, $-NHC(O)CH_2$(4-alquil-piperazinilo), $-NHC(O)CH_2$(piperidinilo), N-(feniloxietil)-aminometilo, ciclopentilo, 1-amino-ciclopentilo, (cis,trans)-2-amino-ciclopentilo, (cis,trans)-2-amino-ciclopentilo, cis-2-amino-ciclopentilo, trans-2-amino-ciclopentilo, (cis,trans)-2-hidroxi-ciclohexilo, cis-2-hidroxi-ciclohexilo, trans-2-hidroxi-ciclohexilo, (cis,trans)-2-amino-ciclohexilo, cis-2-amino-ciclohexilo, trans-2-amino-ciclohexilo, azetidin-3-ilo, pirrolidinilo, N-alquil-pirrolidinilo, 3-(dialquilamino)-pirrolidinilo, piperidinilo, 2-metil-piperidin-6-ilo, N-terc-butoxicarbonilpiperidin-2-ilo, piperazinilo, $-CH_2NHC(O)CH_3$, $-CH(CH_3)NHC(O)CH_3$, $-CH(CH_3)NHC(O)C(OCH_3)(CF_3)$fenilo, pirrol-1-ilo, pirrol-2-ilo, pirrol-3-ilo, imidazol-1-ilo, imidazol-2-ilo, imidazol-4-ilo, imidazol-3-ilo, N-metil-imidazol-2-ilo, 5-metil-imidazol-2-ilo, 1,2,4-triazol-3-ilo, tiazol-2-ilo, 2-aminopirimidin-2-ilo, piridinilo, bencimidazolilo, imidazol-1-ilmetilo, imidazol-2-ilmetilo, triazolilmetilo, (5-amino-3-metilpirazol-1-il)-metilo, fenoximetilo, metilsulfonilaminometilo, 1-(metoxicarbonilamino)-etilo, 1-amino-1-fenilmetilo, o 1-amino-3-ihdroxi-propilo.

Una realización más específica de la realización A10 es aquella donde X y R^7 son halo; A es fenileno optativamente sustituido con R^{10} y R^{12} donde R^{10} y R^{12} son independientemente hidrógeno o halo; R^1, R^2, R^5 y R^6 son hidrógeno; y R^3 es hidrógeno, halo, hidroxi, alcoxi o amino.

Una realización más específica de la realización A10 es aquella donde R^3 es hidrógeno y R^4 es

a) hidrógeno;

b) $-NR^8R^{8'}$ donde R^8 y $R^{8'}$ son independientemente hidrógeno; alquilo; alquenilo; alquilo sustituido con uno o dos hidroxi; alquilo sustituido con uno o dos $-NR^{30}R^{30'}$ donde R^{30} y $R^{30'}$ son independientemente hidrógeno, alquilo, o hidroxialquilo; alquilo sustituido con heteroarilo optativamente sustituido; o alquilo sustituido con cicloalquilo optativamente sustituido;

c) $-C(O)NR^8R^{8'}$ (donde R^8 es hidrógeno, alquilo, o alquenilo; y $R^{8'}$ es hidrógeno; hidroxi; alquilo; alquenilo; alquilo sustituido con uno o dos hidroxi; alquilo sustituido con heterocicloalquilo; alquilo sustituido con $-NR^{30}R^{30'}$ donde R^{30} y $R^{30'}$ son independientemente hidrógeno, alquilo, o hidroxialquilo; o alcoxi optativamente sustituido);

d) $-NR^8C(O)OR^{8'}$ (donde R^8 y $R^{8'}$ son independientemente hidrógeno, alquilo o alquenilo);

e) $-NR^8C(O)R^{8'}$ (donde R^8 es hidrógeno, alquilo o alquenilo; y $R^{8'}$ es hidrógeno; alquilo; alquilo sustituido con uno o dos hidroxi; alquilo sustituido con heterocicloalquilo optativamente sustituido; alquilo sustituido con $-NR^{30}R^{30'}$ donde R^{30} y $R^{30'}$ son independientemente hidrógeno, alquilo, hidroxialquilo o alquenilo);

f) Alquilo;

g) Alquilo sustituido con uno o dos $-OR^8$ (donde R^8 es hidrógeno);

h) Alquilo sustituido con $-NR^8R^{8'}$ (donde R^8 es hidrógeno, alquilo, alquenilo o alquilo sustituido con uno o dos hidroxi; y $R^{8'}$ es hidrógeno, alquilo, alquenilo, alquinilo, alquilo sustituido con uno o dos hidroxi; heterocicloalquilo sustituido con alquilo; o alquilo sustituido con $-NR^{30}R^{30'}$ donde R^{30} y $R^{30'}$ son independientemente hidrógeno, alquilo o hidroxialquilo);

i) Heterocicloalquilo; o

j) Heterocicloalquilo sustituido con $-NR^8R^{8'}$ (donde R^8 y $R^{8'}$ son independientemente hidrógeno, alquilo o alquenilo).

Aún más específicamente, R^3 es hidrógeno y R^4 es hidrógeno, hidroximetilo, $-NH_2$, $-NH(CH_2)_3CH_3$, $-NH(CH_2CH_3)$, $-NHCH_2CH(CH_3)_2$, $-NHCH_2CH_2OH$, $-NHCH_2CH_2CH_2NH_2$, $-NH(CH_3)CH_2CH_2$(piridin-2-ilo), $-NHCH_2$(ciclopropilo), $-NHCH_2$(ciclopentilo), $-NHCH_2$(ciclohexilo), $-C(O)NHOH$, $-C(O)NH(OCH_2CH(OH)CH_2OH)$, $-C(O)NH(CH_2)_3CH_3$, -

$C(O)NHCH_2CH=CH_2$, $-C(O)NHCH_2CH_3$, $-C(O)NHCH_2CH_2OH$, $-C(O)NHCH_2CH(OH)CH_2OH$, $-C(O)NHCH_2CH_2CH(OH)CH_2OH$, $-C(O)NHCH_2CH_2$(piperidin-1-ilo), $-C(O)NH$(fenilo), $-C(O)NHCH_2CH_2N(CH_2CH_3)_2$, N-(isopropil)-aminometilo, N,N-dimetilaminometilo, N-(2-aminometil)-aminometilo, $-NHC(O)OC(CH_3)_3$, $-NHC(O)OCH_3$, $-NHC(O)CH(CH_3)_2$, $-NHC(O)CH_2NH_2$, $-NHC(O)CH_2N(CH_2CH_3)_2$, $-NHC(O)CH_2NH(CH_3)$, $-NHC(O)H$, $-NHC(O)CH_2CH(OH)CH_2OH$, $-NHC(O)CH_2N(CH_2CH_2OH)_2$, $-NHC(O)CH_2CH_2N(CH_2CH_2OH)$, $-NHC(O)CH_2$(4-alquil-piperazinilo), $-NHC(O)CH_2$(piperidinilo), pirrolidinilo, 3-(dialquilamino)-pirrolidinilo, piperidinilo, 2-metilpiperidin-6-ilo, N-metilpiperidin-2-ilo, o piperazin-2-ilo.

Una realización más específica de la realización A10 es aquella donde R^3 es alcoxi y R^4 es alquilo sustituido con $-NR^8R^{8'}$ (donde R^8 y $R^{8'}$ son independientemente hidrógeno, alquilo, o alquenilo). Más específicamente, R^3 es metoxi y R^4 es alquilo sustituido con $-NR^8R^{8'}$ (donde R^8 y $R^{8'}$ son independientemente hidrógeno, alquilo o alquenilo).

Una realización más específica de la realización A10 es aquella donde R^3 es halo y R^4 es alquilo sustituido con $-NR^8R^{8'}$ son independientemente hidrógeno, alquilo o alquenilo). Más específicamente, R^3 es fluoro y R^4 es alquilo sustituido con -

$NR^8R^{8'}$ (donde R^8 y $R^{8'}$son independientemente hidrógeno, alquilo y alquenilo).

Una realización más específica de la realización A10 es aquella donde R^3 es amino y R^4 es alquilo sustituido con $-NR^8R^{8'}$ (donde R^8 y $R^{8'}$ son independientemente hidrógeno, alquilo o alquenilo).

Una realización más específica de la realización A10 es aquella donde R^3 es hidroxi y R^4 es

a) hidrógeno;

b) $-CH_2N(R^{25})(NR^{25a}R^{25b})$;

c) $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$;

d) $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$;

e) $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$;

f) $-CH_2NR^{25}C(=NH)(R^{25})$;

g) $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO)$;

h) Alquilo;

i) Alquenilo;

j) Alquilo sustituido con uno o dos $-OR^8$ donde R^8 es hidrógeno, arilo, o alquilo donde el alquilo se sustituye con uno o dos hidroxi;

k) Alquilo sustituido con uno, dos o tres halo;

l) Alquilo sustituido con nitro;

m) Alquilo sustituido con $-S(O)_mR^9$ (donde m es 0 y R^9 es arilo);

n) Alquilo sustituido con heterocicloalquilo optativamente sustituido;

o) Alquilo sustituido con $-NR^8R^{8'}$ (donde R^8 es hidrógeno, alquilo, alquenilo, alquinilo, o alquilo sustituido con uno o dos hidroxi; y $R^{8'}$ es hidrógeno; hidroxi, alcoxi, alquilo, alquenilo, alquinilo, alcoxi optativamente sustituido, alquilo sustituido con uno o dos hidroxi, alquilo sustituido con $-NR^{30}R^{30'}$ donde R^{30} y $R^{30'}$ son independientemente hidrógeno, alquilo, o hidroxialquilo; alquilo sustituido con uno o dos hidroxi y uno o dos $-NR^{30}R^{30'}$ donde R^{30} y $R^{30'}$ don independientemente hidrógeno, alquilo o hidroxialquilo; heterocicloalquilo sustituido con alquilo, alcoxicarbonilo o arilalquilo optativamente sustituido; alquilo sustituido con uno, dos, tres, cuatro o cinco halo; alquilo sustituido con cicloalquilo optativamente sustituido; alquilo sustituido con arilo optativamente sustituido; alquilo sustituido con uno o dos hidroxi y un arilo optativamente sustituido; alquilo sustituido con heterocicloalquilo optativamente sustituido; alquilo sustituido con heteroarilo optativamente sustituido; heteroarilo, arilo, arilo sustituido con uno o dos hdiroxi; alquilo sustituido con uno o dos alcoxi; arilo sustituido con uno o dos halo;

arilo sustituido con uno o dos $-NR^{32}C(O)R^{32a}$ donde R^{32} es hidrógeno o alquilo y R^{32a} es alquilo, alquenilo, alcoxi, o cicloalquilo; arilo sustituido con $-NR^{34}SO_2R^{34a}$ donde R^{34} es hidrógeno o alquilo y R^{34a} es alquilo, alquenilo, cicloalquilo, arilo, heteroarilo, o heterocicloalquilo; cicloalquilo; cicloalquilo sustituido con uno o dos hidroxi; cicloalquilo sustituido con uno o dos hidroxi y uno o dos hidroxialquilo; cicloalquilo sustituido con uno o dos alcoxi; cicloalquilo sustituido con carboxi; cicloalquilo sustituido con $-C(O)NR^{33}R^{33a}$ donde R^{33} es hidrógeno y R^{33a} es hidrógeno o alquilo y R^{33a} es alquilo, alquenilo, alquinilo o cicloalquilo; cicloalquilo sustituido con cicloalquilo optativamente sustituido; heterocicloalquilo; heterocicloalquilo susituido con uno o dos hidroxi; heterocicloalquilo sustituido con uno o dos alcoxi; heterocicloalquilo sustituido con uno o dos hidroxialquilo; heterocicloalquilo sustituido con uno o dos hidroxi y uno o dos hidroxialquilo; alquilo sustituido con $-C(O)NR^{33}R^{33a}$ donde R^{33} es hidrógeno o alquilo y R^{33a} es alquilo, alquenilo, alquinilo, o cicloalquilo; alquilo sustituido con ariloxi optativamente sustituido; alquilo sustituido con $-S(O)_nR^{31}$ donde n es 0 y R^{31} es alquilo; alquilo sustituido con carboxi; alquilo sustituido con alcoxicarbonilo; o alquilo sustituido con $-NR^{32}C(O)NR^{32a}$ donde R^{32} es

hidrógeno o alquilo y R^{32a} es alquilo, alquenilo, alcoxi o cicloalquilo);

p) Heterocicloalquilo;

q) $-C(O)NR^{8}R^{8'}$ (donde R^{8} es hidrógeno, alquilo, o alquenilo; y $R^{8'}$ es hidrógeno, alquilo, alquenilo o sustituido con uno o dos hidroxi);

r) Alquilo sustituido con $-NR^{8}C(O)R^{8'}$ (donde R^{8} es hidrógeno, alquilo, o alquenilo y $R^{8'}$ es alquilo, alquenilo o alquilo sustituido con alcoxi, arilo y uno, dos o tres halo);

s) Cicloalquilo;

t) Cicloalquilo sustituido con $-NR^{8}R^{8'}$ donde R^{8} y $R^{8'}$ son independientemente hidrógeno, alquilo o alquenilo;

u) Cicloalquilo sustituido con $-C(O)NR^{33}R^{33a}$ donde R^{33} es hidrógeno o alquilo y R^{33a} es alquilo, alquenilo, alquinilo o cicloalquilo;

v) Heterocicloalquilo;

w) Heterocicloalqulo sustituido con uno o dos alquilo;

x) Heterocicloalquilo sustituido con $-C(O)NR^{8}$ donde R^{8} es alquilo o alquenilo;

y) Heteroarilo;

z) Heteroarilo optativamente sustituido con $-NR^{8}R^{8'}$ donde R^{8} y $R^{8'}$ son independientemente hidrógeno, alquilo o alquenilo;

aa) Alquilo sustituido con heteroarilo optativamente sustituido;

bb) Alquilo sustituido con $-NR^8S(O)R^9$ donde R^8 es hidrógeno, alquilo o alquenilo y R^9 es alquilo o alquenilo;

cc) Alquilo sustituido con $-NR^8C(O)OR^{8'}$ donde R^8 y $R^{8'}$ son independientemente hidrógeno, alquilo o alquenilo;

dd) Alquilo sustituido con un arilo y un $-NR^8R^{8'}$ donde R^8 y $R^{8'}$ son independientemente hidrógeno, alquilo o alquenilo; o

ee) Alquilo sustituido con uno o dos $-OR^8$ (donde R^8 es hidrógeno) y uno o dos $-NR^8R^{8'}$ donde R^8 y $R^{8'}$ son independientemente hidrógeno, alquilo o alquenilo.

Aún más específicamente, R^3 es hidroxi y R^4 es hidrógeno, $-CH_2N(H)(NHCH_3)$, $-CH_2NHC(=NH)(NH_2)$, $-CH_2NHC(=NH)(NHNO_2)$, $-CH_2NHC(=NH)(NHCN)$, $-CH_2NHC(=NH)$(fenilo), $-CH_2NHC(NH_2)=CH(NO_2)$, metilo, etilo, hidroximetilo, 2,3-dihidroxipropilo, 3-hidroxi-2-metil-prop-2-enilo, N-(1-metoxi-prop-2-il)-aminometilo, N-(etoxipropil)-aminometilo, N-(etoxietil)-aminometilo, N-(2,2-dimetoxietil)-aminometilo, N-(metiletil)-aminometilo, N-(isopropiletil)-aminometilo, trifluorometilo, 1-nitro-etilo, 1-metil-1-nitro-etilo, 1-nitro-propilo, 3-metil-1-nitro-butilo, feniltiometilo, alilo, etenilo, 2-metiltio-etilaminometilo, 3-metiltio-propilaminometilo, N-(terc-butoxicarbonilaminopropil)-aminometilo, N-(1-carboxietil)-aminometilo, N-(1R-carboxietil)-aminometilo, N-(1S-carboxietil)-aminometilo, N-(1-metoxicarboniletil)-

aminometilo, azetidinilmetilo, pirrolidinilmetilo, 3-hidroxi-pirrolidinilmtilo, 2-(metoximetil)-pirrolidinilmetilo, 2S-(metoximetil)-pirrolidinilmetilo, 2R-(metoximetil)-pirrolidinilmetilo, morfolinilmetilo, 4-hidroxipiperidinilmetilo, 4-metil-piperaizinilmetilo, 4-metil-homopiperazinilmetilo, 4-(piperidinil)-piperidinilmetilo, 4-[2-(N,N-dietilamino)-etil]-piperaizinilmetilo, N-hidroxiaminometilo, N-metoxiaminometilo, N-etoxiaminometilo, N-etilaminometilo, 1-(N-etil-amino)-etilo, N,N-dietilaminometilo, N,N-dimetilaminometilo, aminometilo, 1-amino-etilo, 1R-amino-etilo, 1S-amino-etilo, 1-(metilamino)-etilo, 1-(N,N-dimetilamino)-etilo, 1-amino-1-metil-etilo, 1-aminopropilo, 1S-aminopropilo, 1R-aminometilo, N-(s-propil)-aminometilo, N-(isopropil)-aminometilo, 2-(N-isopropilamino)-etilo, 3-(N-isopropilamino)-2-metil-prop-2-ilo, 1-(N-etil-amino)-propilo, 1-(N,N-dietil-amino)-propilo, 1-aminobutilo, 1-amino-isobutilo, N-(n-butil)-aminometilo, N-isobutilaminometilo, terc-butilaminometilo, 1-(terc-butilamino)-etilo, sec-butilaminometilo, N-(2-metil-but-3-il)-aminometilo, N-(3,3-dimetil-butil)-aminometilo, N-(3-metilbut-3-il)-aminometilo, N-(2-metilbutil)-aminometilo, N-(pent-3-il)-aminometilo, n-pentilaminometilo, isopentilaminometilo, sec-pentilaminometilo, neopentilaminometilo, N-(2,2,4-trimetil-pent-4-il)-aminometilo, N-(2-etil-butil)-aminometilo, N-alil-aminometilo, 3-metil-but-1-in-3-ilaminometilo, N-(2,3-

dihidroxipropiloxi)-aminometilo, N-ciclopropilaminometilo, N-ciclopentilaminometilo, N-ciclpenten-4-ilaminometilo, N-(1(R,S)-hidroxi-ciclopent-2-il)-aminometilo, N-(1S-hidroxi-ciclopent-2-il)-aminometilo, N-(1R-hidroxi-ciclopent-2-il)-aminometilo, N-(1(R,S)-hidroxi-1-metil-ciclopent-2-il)-aminometilo, N-(1S-hidroxi-1-metil-ciclopent-2-il)-aminometilo, N-(1R-hidroxi-1-metil-ciclopent-2-il)-aminometilo, N-(3,4-dihidroxi-ciclopentil)-aminometilo, N-(1-hidroximetil-ciclopent-1-il)-aminometilo, N-(2,3-dihidroxi-4-dihidroximetil-ciclopentil)-aminometilo, N-(1(R,S)-metoxi-ciclopent-2-il)-aminometilo, N-(1S-metoxi-ciclopent-2-il)-aminometilo, N-(1R-metoxi-ciclopent-2-il)-aminometilo, N-(1-carboxi-ciclopentil)-aminometilo, N-ciclohexilaminometilo, N-(1(R,S)-hidroxi-ciclohex-2-il-)-aminometilo, N-(1(R)-hidroxi-ciclohex-2-il)-aminometilo, N-(1(S)-hidroxi-ciclohex-2-il)-aminometilo, N-(cis-4-hidroxi-ciclohexil)-aminometilo, N-(trans-4-hidroxi-ciclohexil)-aminometilo, 1-[N-(cis-4-hidroxi-ciclohexil)-amino]-etilo, 1-[N-(trans-4-hidroxi-ciclohexil)-amino]-etilo, N-(1-hidroximeti-ciclohexil)-aminometilo, N-(2-ciclohexil-ciclohexil)-aminometilo, N-{(2R,3S,4R,6R)-2-(hidroximetil)-3,4-dihidroxi-6-metoxi-tetrahidro-2H-piran-5-il)-aminometilo, N-(cicloheptil)-aminometilo, N-(ciclopentil)-aminometilo, [(1r,3r,5R,7R)-triciclo[3.3.1.$1^{3,7}$]dec-2-ilamino]metilo, N-(1-benciloxi-ciclopent-2-il)-aminometilo, N-[1-(ciclopropilaminocarbonil)-ciclopentil]-aminometilo, -

$CH_2NHC(CH_3)_2C(O)NH$(ciclohexilo), $-CH_2NHC(CH_3)_2C(O)NH(CH_2CH_3)$, N-(ciclopropilmetil)-aminometilo, N-(ciclohexilmetil)-aminometilo, N-(1-ciclohexiletil)-aminometilo, N-(imidazolil)-aminometilo, N-(1,3,5-triazinil)-aminometilo, N-(3-hidroxi-pirazol-3-il)-aminometilo, N-(5-metil-pirazol-3-il)-aminometilo, N-(bencimidazolil)-aminometilo, N-(pirimidin-2-il)-aminometilo, N-(piridin-2-il)-aminometilo, N-(piridin-3-il)-aminometilo, N-(piridin-4-il)-aminometilo, N-indan-2-il-aminometilo, N-indan-2-il-aminometilo, fenilaminometilo, N-(2-hidroxifenil)-aminometilo, N-(3-hidroxifenil)-aminometilo, N-(4-hidroxifenil)-aminometilo, N-(2-metoxifenil)-aminometilo, N-(3-metoxifenil)-aminometilo, N-(4-metoxifenil)-aminometilo, N-(2-fluorofenil)-aminomtilo, N-(3-fluorofenil)-aminometilo, N-(4-fluorofenil)-aminometilo, N-(2-clorofenil)-aminometilo, N-(3-clorofenil)-aminometilo, N-(4-clorofenil)-aminometilo, N-(3-metilcarbonilamino-fenil)-aminofenilo, N-(4-metilcarbonilamino-fenil)-aminometilo, N-(2-aminofenil)-aminometilo, N-(3-aminofenil)-aminometilo, N-(4-aminofenil)-aminometilo, N-(2-metilsulfonilaminofenil)-aminometilo, N-(3-metilsulfonilaminofenil)-aminometilo, N-(4-metilsulfonilaminofenil)-aminometilo, N-(2-fluoro-4-hidroxi-fenil)-aminometilo, N-(3-fluoro-4-hidroxi-fenil)-ainometilo, N-(bencil)-aminometilo, N-(2-hidroxifenilmetil)-aminometilo, N-(3-hidroxifenilmetil)-aminometilo, N-(4-hidroxifenilmetil)-aminometilo, N-(2-(N-metilpiperazin-1-il)-fenilmetil)-

aminometilo, N-(4-metil-fenetil)-aminometilo, N-(1-hidroxi-3-fenil-prop-2-il)-aminometilo, N-(pirrolidin-2-ilmetil)-aminometilo, N-(N-etil-pirrolidinilmetil)-aminometilo, N-(N-metil-pirrolidin-2-iletil)-aminometilo, N-(pirrolidinilpropil)-aminometilo, N-(1,1-dimetil-2-pirrolidin-1-il-etil)-aminometilo, N-(tetrahidrofuranilmetil)-aminometilo, N-(tetrahidro-2H-piran-4-ilmetil)-aminometilo, N-(tetrahidro-2H-piraniletil)-aminometilo, N-(piperidin-4-ilmetil)-aminometilo, N-(N-metilpiperidin-4-ilmetil)-aminometilo, N-(N-terc-butoxicarbonilpiperidin-4-ilmetil)-aminometilo, N-(N-metilimidazol-5-ilmetil)-aminometilo, N-(N-metilimidazol-4-ilmetil)-aminometilo, N-[2-(imidazol-4-il)-etil]-aminometilo, N-[3-(imidazolil)-propil]-aminometilo, N-(piridin-3-iletil)-aminometilo, N-(piridin-4-iletil)-aminometilo, N-(tien-2-iletil)-aminometilo, N-(furan-2-iletil)-aminometilo, N-(5-metil-1,3,4-oxadiazol-2-ilmetil)-aminometilo, N-(2-indolin-3-iletil)-aminometilo, 2-(N,N-dimetilamino)-etilaminometilo, 2-(N,N-dimetilamino)-1-metil-etilaminometilo, 3-aminopropilaminometilo, 3-(N,N-dimetilamino)-propilaminometilo, 3-(N,N-dietilamino)-propilaminometilo, N-(N,N-diisopropilaminoetil)-aminometilo, N-(N,N-dimetilaminobutil)-aminometilo, 3-hidroxipropilaminometilo, N-(1,2-dihidroxipropil)-aminometilo, N-(1-amino-2-hidroxi-prop-3-il)-aminometilo, N-(N-etoxicarbonil-piperidin-4-il)-aminometilo, N-(N-

bencilpiperidin-4-il)-aminometilo, N-(homopiperidin-3-il)-aminometilo, N-(N-bencilpirrolidin-aminometilo, N-(N-etilpiperidin-3-il)aminometilo, 2,2,2-trifluorometilaminometilo, 3,3,3-trifluoropropilaminometilo, 2,2,3,3,3-pentafluoropropilaminometilo, $-CH_2N(CH_2CH_2OH)_2$, $-CH_2N(CH_3)(CH_2CH_2OH)$, $-CH_2NH(CH_2CH_2OH)$, $-CH_2NH(CH_2CH_2CH_2OH)$, $-CH_2NH(C(CH_3)_2CH_2OH)$, $-CH_2N(CH_3)$(N-metil-pirrolidin-3-ilo), $-C(O)NH_2$, $-C(O)NHCH_2CH=CH_2$, $-C(O)NHCH_2CH(OH)CH_2OH$, N-(feniloxietil)-aminometilo, $-CH_2NHC(O)CH_3$, $-CH(CH_3)NHC(O)CH_3$, $-CH(CH_3)NHC(O)C(OCH_3)(CF_3)$fenilo, ciclopentilo, 1-amino-ciclopentilo, (cis,trans)-2-amino-ciclopentilo, (cis,trans)-2-amino-ciclopentilo, cis-2-amino-ciclopentilo, trans-2-amino-ciclopentilo, (cis,trans)-2-hidroxi-ciclohexilo, cis-2-hidroxi-ciclohexilo, trans-2-hidroxi-ciclohexilo, (cis,trans)-2-amino-ciclohexilo, cis-2-amino-ciclohexilo, trans-2-amino-ciclohexilo, azetidin-3-ilo, pirrolidinilo, N-metil-pirrolidin-2-ilo, N-etil-pirrolidin-2-ilo, 3-(dimetilamino)-pirrolidinilo, piperidinilo, 2-metil-piperidin-6-ilo, N-metilpiperiidin-2-ilo, N-terc-butoxicarbonilpiperidin-2-ilo, piperazin-2-ilo, pirrol-1-ilo, pirrol-2-ilo, pirrol-3-ilo, imidazol-1-ilo, imidazol-2-ilo, imidazol-4-ilo, imidazol-5-ilo, N-metil-imidazol-2-ilo, 5-metil-imidazol-2-ilo, 1,2,4-triazol-3-ilo, tiazol-2-ilo, 2-aminopirimidin-3-ilo, piridin-3-ilo, piridin-4-ilo, bencimidazolilo, imidazol-1-ilmetilo, imidazol-2-ilmetilo, triazol-1-ilmetilo, (5-amino-3-metil-

pirazol-3-il)-metilo, fenoximetilo, 2-hidroxietiloximetilo, metilsulfonilaminometilo, 1-(metoxicarbonilamino)-etilo, 1-amino-1-pentil-metilo, o 1-amino-3-hidroxi-propilo.

Otra realización específica de la invención (A11) es aquella donde el compuesto de la Fórmula I se selecciona del Grupo A donde R^3 y R^4 junto con el carbono al cual están unidos forman C(O) o C(=NOH). Más específicamente, X y R^7 son halo; A es fenileno optativamente sustituido con R^{10} y R^{12} donde R^{10} y R^{12} son independientemente hidrógeno o halo; R^1, R^2, R^5 y R^6 son hidrógeno; y R^3 y R^4 junto con el carbono al cual están unidos forman C(O) o C(=NOH).

Otra realización específica de la invención (A12) es aquella donde el compuesto de la Fórmula I se selecciona del Grupo A donde X y R^7 son halo; A es fenileno optativamente sustituido con R^{10} y R^{12} donde R^{10} y R^{12} son independientemente hidrógeno o halo; y R^1, R^2, R^5 y R^6 son hidrógeno.

Otra realización específica de la invención (A13) es aquella donde el compuesto de la Fórmula I se selecciona del Grupo A donde A es fenileno.

Otra realización específica de la invención (A14) es aquella donde el compuesto de la Fórmula I se selecciona del Grupo A

donde R^1 es hidrógeno y R^2 es alquilo sustituido con $-NR^8R^{8'}$ donde R^8 y $R^{8'}$ y todos los demás grupos son lo definido en el Resumen de la Invención para un compuesto del Grupo A.

Otra realización especifica de la invención (A15) es aquella donde el compuesto de la Fórmula I se selecciona del Grupo A donde A es fenileno; R^7 es yodo o bromo; X es fluoro o cloro; y R^1, R^2, R^5 y R^6 son hidrógeno, y R^{10}, R^{12}, R^{14} y R^{16} son independientemente hidrógeno o fluoro. Más específicamente, R^{10} es 3-fluoro y R^{12}, R^{14} y R^{16} son hidrógeno o halo; R^{10} es 3-fluoro, R^{12} es 4-fluoro,, y R^{14} y R^{16} son hidrógeno; R^{10} es 4-fluoro, R^{12} es 5-fluoro y R^{14} y R^{16} son hidrógeno; R^{10} es 4-fluoro, R^{12} es 6-fluoro y R^{14} y R^{16} son hidrógeno; o R^{12} es 4-fluoro y R^{10}, R^{14} y R^{16} son hidrógeno.

En otra realización de la invención es un compuesto de la Fórmula seleccionada del Grupo A donde R^3 es hidroxi y R^4 es heterocicloalquilo, alquilo o heteroarilo, donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ (donde R^8 es hidrógeno o alquilo y $R^{8'}$ es hidrógeno, alquilo o cicloalquilo donde el cicloalquilo se sustituye optativamente con grupos seleccionados independientemente de hidroxi y alquilo) y el heteroarilo se sustituye optativamente con alquilo. Específicamente, R^3 es hidroxi y R^4 es heterocicloalqulo o alquilo, donde el alquilo se sustituye optativamente con -

$NR^8R^{8'}$ (donde R^8 es hidrógeno o alquilo y $R^{8'}$ es hidrógeno, alquilo o cicloalquilo donde el cicloalquilo se sustituye optativamente con grupos seleccionados independientemente de hidroxi y alquilo).

En otra realización de la invención (B1) el compuesto de la Fórmula I se selecciona del Grupo B donde todos los grupos son lo definido en el Resumen de la Invención.

En otra realización de la invención (B2), X y R^7 son halo y todos los demás grupos son lo definido en el Resumen de la Invención para un compuesto del Grupo B. Específicamente, X es fluoro o cloro y R^7 es yodo o bromo.

En otra realización de la invención (B3), el compuesto se selecciona del Grupo B donde R^3 es halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, $-CN$, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(NR^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, o heterociclilo; donde el alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, y heterocicloalquilo son independiente y optativamente sustituidos con uno, dos, tres,

cuatro, cinco, seis o siete grupos independientemente seleccionados de halo, alquilo, haloalquilo, nitro, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, heteroarilo optativamente sustituido, heteroarilalquilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ y $-NR^8C(O)R^{8'}$, y R^4 es lo definido en el Resumen de la Invención; o R^3 y R^4 junto con el carbono al cual están unidos forman C(O) o C(=NOH); y todos los demás grupos son lo definido en el Resumen de la Invención para un compuesto del Grupo B. Más específicamente, R^1, R^2, R^5 y R^6 son hidrógeno; y X y R^7 son halo.

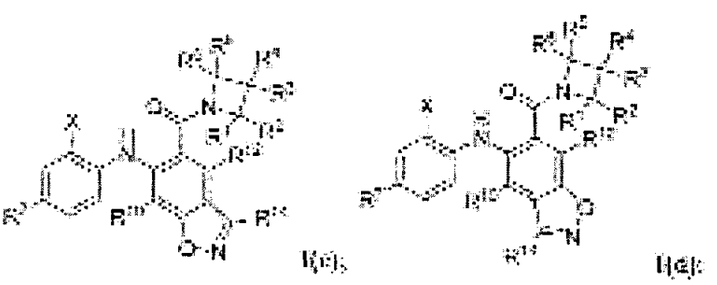
En otra realización de la invención (B4), el compuesto se selecciona del Grupo B donde R^3 y R^4 son independientemente halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, $-CN$, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2R^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, o heterocicloalquilo; donde el alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, y

posición de N1 con R^{19} donde R^{19} es lo definido en el resumen de la invención para un compuesto del Grupo B), imidazo[1,2-a]piridin-diilo, cinolin-diilo, quinolin-diilo, piridin-diilo, 1-óxido-piridin-diilo, [1,2,4]triazolo[3,4-apiridin-diilo, y 2,3-dihidroimidazo[1,2-a]piridin-diilo; y A está también optativamente sustituido con uno, dos, tres, o cuatro grupos seleccionados de R^{10}, R^{12}, R^{14} y R^{16} donde R^{10}, R^{12}, R^{14} y R^{16} y todos los demás grupos son lo definido en el resumen de la invención para un compuesto del Grupo B. Más específicamente, A se selecciona de tien-3,4-diilo, benzo[d]isoxazol-5,6-diilo, benzo[d]isotiazol-5,6-diilo, 1H-indazol-5,6-diilo (optativamente sustituido en la posición de N1 con R^{19} donde R^{19} es alquilo o alquenilo), benzo[d]oxazol-5,6-diilo, benzo[d]tiazol-5,6-diilo, 1H-benzo[d]imidazol-5,6-diilo (optativamente sustituido en la posición de N1 con R^{19} donde R^{19} es alquilo o alquenilo), 1H-benzo[d][1,2,3]triazol-5,6-diilo (optativamente sustituido en la posición de N1 con R^{19} donde R^{19} es alquilo o alquenilo), imidazolo[1,2-a]piridin-5,6-diilo, cinolin-6,7-diilo, quinolin-6,7-diilo, piridin-3,4-diilo, 1-óxido-piridin-3,4-diilo, [1,2,4]triazolo[4,3-a]piridin-6,7-diilo, y 2,3-dihidroimidazo[1,2-a]piridin-6,7-diilo.

En otra realización de la invención (B6), el compuesto de la Fórmula I se selecciona del Grupo B donde A es tien-diilo y X, R^1, R^2, R^3, R^4 R^5, R^6, R^7, R^{10} y R^{12} son lo definido en el resumen

de la invención para un compuesto del Grupo B. Más específicamente, A es tien-3,4-diilo, R^{10} y R^{12} son hidrógeno, X y R^7 son halo; y R^1, R^2, R^5 y R^6 son hidrógeno. Aún más específicamente, X es fluoro o cloro; R^7 es yodo o bromo; R^3 es hidrógeno o hidroxi; y R^4 es $-NR^8R^{8'}$ (donde R^8 y $R^{8'}$ son independientemente hidrógeno o alquilo), heterocicloalquilo, heteroarilo (optativamente sustituido con alquilo), o alquilo donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ (donde R^8 es hidrógeno o alquilo y $R^{8'}$ es hidrógeno, alquilo, o cicloalquilo donde el cicloalquilo se sustituye optativamente con uno o dos grupos seleccionados independientemente de hidroxi y alquilo).

En otra realización (B7), el compuesto es de la Fórmula I(c) o I(d):



donde X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{12} y R^{14} son lo definido en el Resumen de la Invención para un compuesto del Grupo B. Más específicamente, R^1, R^2, R^5 y R^6 son hidrógeno, X y R^7 son halo; R^3 y R^4 son lo definido en el resumen de la invención para el Grupo B; y R^{10}, R^{14} y R^{16} son independientemente

hidrógeno, halo o alquilo. Aún más específicamente, X es fluoro o cloro y R^7 es yodo o bromo; R^{10} es hidrógeno o halo, más específicamente hidrógeno o fluoro; R^{12} es hidrógeno; R^{14} es hidrógeno o alquilo; y R^3 es hidroxi. Aún más específicamente, R^4 es heterocicloalquilo, alquilo, o heteroarilo, donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ (donde R^8 es hidrógeno o alquilo y $R^{8'}$ es hidrógeno, alquilo o cicloalquilo donde el cicloalquilo se sustituye optativamente con grupos seleccionados independientemente de hidroxi y alquilo y el heteroarilo se sustituye optativamente con alquilo. Aún más específicamente, R^4 es piperidinilo, pirrolidinilo, 1(R,S)-amino-etilo, 1(R)-amino-etilo, 1(S)-amino-etilo, 1(R,S)-(metilamino)-etilo, 1(R)-(metilamino)-etilo, 1(S)-(metilamino)-etilo, 1(R,S)-(dimetilamino)-etilo, 1(R)-(dimetilamino)-etilo, 1(S)-(dimetilamino)-etilo, 1(R,S)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo, 1(R)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo o 1(S)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo.

En otra realización de la invención (B8), el compuesto es de la Fórmula I(e) o I(f):

optativamente sustituido, heteroarilalquilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ y $-NR^8C(O)R^{8'}$; y R^4 es lo definido en el resumen de la invención; o R^3 y R^4 junto con el carbono al cual están unidos forman C(O) o C(=NOH); y

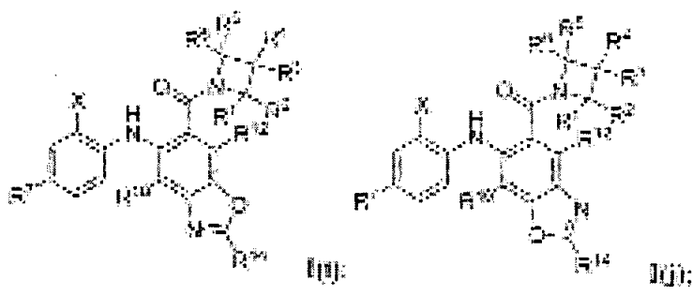
todos los demás grupos son lo definido en el resumen de la invención para un compuesto del Grupo B.

En una realización más específica de la realización B9, el compuesto es de la fórmula I(g) o I(h) donde R^3 es hidroxi y todos los demás grupos son lo definido en el resumen de la invención para un compuesto del Grupo B.

En una realización más específica de la realización B9, el compuesto es de la fórmula I(g) o I(h) donde R^1, R^2, R^5 y R^6 son hidrógeno, X y R^7 son halo; R^3 y R^4 son lo definido en el resumen de la invención para el Grupo B; R^{10}, R^{12} y R^{14} son independientemente hidrógeno, halo, o alquilo; y R^{19} es hidrógeno o metilo. Aún más específicamente, X es fluoro o cloro y R^7 es yodo o bromo; R^{10} es hidrógeno o halo, más específicamente hidrógeno o fluoro; R^{12} y R^{14} son hidrógeno; R^3 es hidroxi; y R^{14} es heterocicloalquilo, alquilo o hetaroarilo, donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ (donde R^8 es hidrógeno o alquilo y $R^{8'}$ es hidrógeno, alquilo o

cicloalquilo donde el cicloalquilo se sustituye optativamente con uno o dos grupos seleccionados independientemente de hidroxi y alquilo) y el heteroarilo se sustituye optativamente con alquilo.

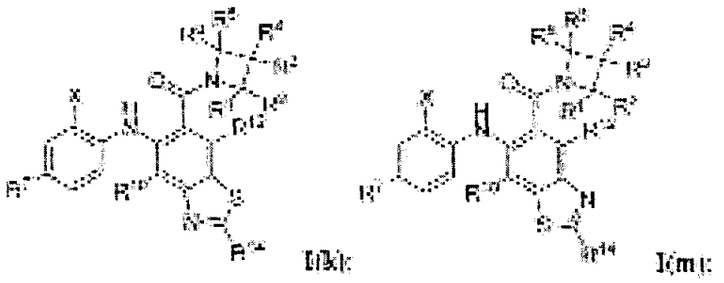
En otra realización de la invención (B10), el compuesto es de la Fórmula I(i) o I(j):



donde X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{12} y R^{14} son lo definido en el resumen de la invención para un compuesto del Grupo B. Más específicamente, R^1, R^2, R^5 y R^6 son hidrógeno, X y R^7 son halo; R^3 y R^4 son lo definido en el resumen de la invención para el Grupo B; y R^{10}, R^1 y R^{14} son independientemente hidrógeno, halo, o alquilo. Aún más específicamente, X es fluoro o cloro; y R^7 es yodo o halo, más específicamente hidrógeno o fluoro; R^{12} y R^{14} son hidrógeno; R^3 es hidroxi; y R^4 es heterocicloalquilo, alquilo o heteroarilo, donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ (donde R^8 es hidrógeno o alquilo y $R^{8'}$ es hidrógeno, alquilo o cicloalquilo donde el cicloalquilo se sustituye optativamente con uno o dos grupos

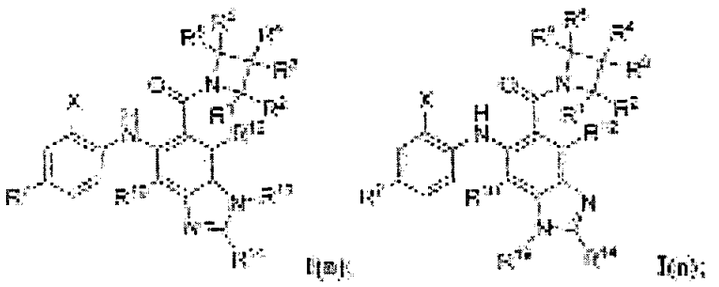
seleccionados independientemente de hidroxi y alquilo) y el heteroarilo se sustituye optativamente con alquilo.

En otra realización de la invención (B11), el compuesto es de la Fórmula I(k) o I(m):



donde X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{12} y R^{14} son lo definido en el resumen de la invención para un compuesto del Grupo B. Más específicamente, R^1, R^2, R^5 y R^6 son hidrógeno, X y R^7 son halo; R^3 y R^4 son lo definido en el resumen de la invención para el Grupo B; y R^{10}, R^{12} y R^{14} son independientemente hidrógeno, halo, o alquilo. Aún más específicamente, X es fluoro o cloro y R^7 es yodo o bromo, más específicamente hidrógeno o fluoro; R^{12} y R^{14} son hidrógeno; R^3 es hidroxi; y R^4 es heterocicloalquilo, alquilo o heteroarilo, donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ (donde R^8 es hidrógeno o alquilo y $R^{8'}$ es hidrógeno, alquilo o cicloalquilo donde el cicloalquilo se sustituye optativamente con uno o dos grupos seleccionados independientemente de hidroxi y alquilo) y el heteroarilo se sustituye optativamente con alquilo.

En otra realización de la invención (B12), el compuesto es de la Fórmula I(n) o I(o):



donde X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{12}, R^{14} y R^{19} son lo definido en el resumen de la invención para un compuesto del Grupo B.

En una realización más específica de la realización B12, el compuesto es de la Fórmula I(n) o I(o), donde R^7 es halo o alquilo; y todos los demás grupos son lo definido en el resumen de la invención para el Grupo B. Más específicamente, R^7 es yodo o bromo.

En una realización más específica de la realización B12, el compuesto es de la fórmula I(n) o I(o) donde X es halo, haloalquilo o haloalcoxi; y todos los demás grupos son lo definido en el resumen de la invención para un compuesto del Grupo B. Más específicamente, X es halo. Aún más específicamente X es fluoro o cloro.

En una realización más específica de la realización B12, el compuesto es de la fórmula I(n) o I(o) donde

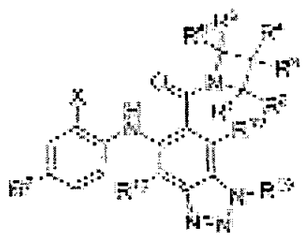
R^3 es halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, $-CN$, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO))$, $-CH_2NR^{25}C(=N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, o heterocicloalquilo; donde el alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, y heterocicloalquilo se sustituyen independiente y optativamente con uno, dos, tres, cuatro, cinco, seis o siete grupos seleccionados independientemente de halo, alquilo, haloalquilo, nitro, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, heteroarilo optativamente sustituido, heteroarilalquilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-R^8C(O)OR^{8'}$ y $-NR^8C(O)R^{8'}$; y R^4 es lo definido en el resumen de la invención; o

R^3 y R^4 junto con el carbono al cual están unidos forman C(O) o C(=NOH); y a menos que se indique de otro modo; R^8 y $R^{8'}$ son lo definido en el resumen de la invención; y todos los demás

grupos son lo definido en el resumen de la invención para un compuesto del Grupo B.

En una realización más específica de la realización B12, el compuesto es de la fórmula I(n) I(o) donde R^{19} es alquilo; R^1, R^2, R^5 y R^6 son hidrógeno; X y R^7 son halo; R^3 y R^4 son lo definido en el Resumen de la Invención para el Grupo B; y R^{10}, R^{12} y R^{14} son independientemente hidrógeno o halo. Aún más específicamente, R^{19} es metilo; X es fluoro o cloro y R es yodo o bromo; R^{10} es hidrógeno o fluoro; R^{12} y R^{14} son hidrógeno; y R^3 es hidroxi. Aún más específicamente, R^4 es heterocicloalquilo, alquilo o heteroarilo, donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ (donde R^8 es hidrógeno o alquilo y $R^{8'}$ es hidrógeno, alquilo o cicloalquilo donde el cicloalquilo se sustituye optativamente con uno o dos grupos seleccionados independientemente de hidroxi y alquilo) y el heteroarilo se sustituye optativamente con alquilo. Aún más específicamente, R^4 es piperidinilo, pirrolidinilo, 1(R,S)-amino-etilo, 1(R)-amino-etilo, 1(S)-amino-etilo, 1(R,S)-(metilamino)-etilo, 1(R)-(metilamino)-etilo, 1(S)-(metilamino)-etilo, 1(R,S)-(dimetilamino)-etilo, 1(R)-(dimetilamino)-etilo, 1(S)-(dimetilamino)-etilo, 1(R,S)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo, 1(R)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo, o 1(S)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo.

En otra realización de la invención (B13), el compuesto es de la Fórmula I(p):

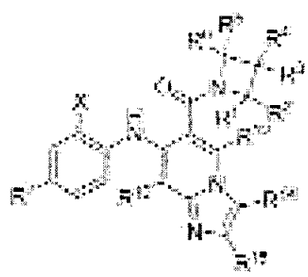


I(p)

donde X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{12}, R^{14} y R^{19} son lo definido en el resumen de la invención para un compuesto del Grupo B. Más específicamente, R^1, R^2, R^5 y R^6 son hidrógeno, X y R^7 son halo; R^3 y R^4 son lo definido en el resumen de la invención para el Grupo B; y R^{10} y R^{12} son independientemente hidrógeno, halo, o alquilo. Aún más específicamente, X es fluoro o cloro; R^7 es yodo o bromo; R^{19} es hidrógeno o halo, más específicamente hidrógeno o fluoro; R^{12} es hidrógeno; R^{19} es hidrógeno o alquilo, más específicamente hidrógeno o metilo; R^3 es hidroxi. Aún más específicamente, R^4 es heterocicloalquilo, alquilo o heteroarilo, donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ (donde R^8 es hidrógeno o alquilo y $R^{8'}$ es hidrógeno, alquilo o cicloalquilo donde el cicloalquilo se sustituye optativamente con uno o dos grupos seleccionados independientemente de hidroxi y alquilo) y el heteroarilo se sustituye optativamente con alquilo. Aún más específicamente, R^4 es piperidinilo, pirrolidinilo, 1(R,S)-amino-etilo, 1(R)-

amino-etilo, 1(S)-amino-etilo, 1(R,S)-(metilamino)-etilo, 1(R)-(metilamino)-etilo, 1(S)-(metilamino)-etilo, 1(R,S)-(dimetilamino)-etilo, 1(R)-(dimetilamino)-etilo, 1(S)-(dimetilamino)-etilo, 1(R,S)-(3,4-cis-dihidroxiciclopentilamino)-etilo, 1(R)-(3,4-cis-dihidroxiciclopentilamino)-etilo, o 1(S)-(3,4-cis-dihidroxiciclopentilamino)-etilo.

En otra realización de la invención (B14), el compuesto es de la Fórmula I(q):



I(q)

donde X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{12}, R^{14} y R^{16} son lo definido en el resumen de la invención para un compuesto del Grupo B.

En una realización más específica de la realización B14, el compuesto es de la fórmula I(q) donde

R^3 es halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, $-CN$, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^8$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, -

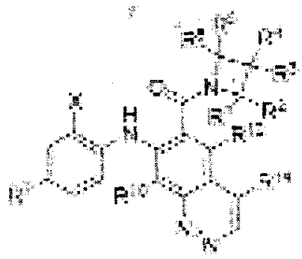
$CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, o heterocicloalquilo; donde el alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo o heterocicloalquilo se sustituyen independiente y optativamente con uno, dos, tres, cutro, cinco, seis o siete grupos seleccionados independientemente de halo, alquilo, haloalquilo, nitro, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, heteroarilo optativamente sustituido, heterocicloalquilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)OR^8$, $C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ y $-NR^8C(O)OR^{8'}$; y R^4 es lo definido en el resumen de la invención; o

R^3 y R^4 junto con el carbono al cual están unidos forman C(O) o C(=NOH); y todos los demás grupos son lo definido en el resumen de la invención para un compuesto del Grupo B.

En una realización más específica de la realización B14, el compuesto es de la fórmula I(q) donde R^1, R^2, R^5 y R^6 son hidrógeno; X y R^7 son halo; R^3 y R^4 son lo definido en el resumen de la invención para el Grupo B; y R^{10}, R^{12}, R^{14} y R^{16}

son independientemente hidrógeno o halo. Aún más especificmaente, R^{10} es halo y R^{12}, R^{14} y R^{16} son hidrógeno. Aún más específicamente, X es fluoro o cloro; R^7 es yodo o bromo; R^{10} es cloro; y R^3 es hidroxi. Aún más específicamente, R^4 es heterocicloalquilo, alquilo, o heteroarilo, donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ (donde R^8 es hidrógeno o alquilo y $R^{8'}$es hidrógeno, alquilo, o cicloalquilo donde el cicloalquilo se sustituye optativamente con uno o dos grupos independientemente seleccionados de hidroxi y alquilo) y el heteroarilo se sustituye optativamente con alquilo. Aún más específicamente, R^4 es piperidinilo, pirrolidinilo, bencimidazolilo, 1(R,S)-amino-etilo, 1(R)-amino-etilo, 1(S)-amino-etilo, 1(R,S)-(metilamino)-etilo, 1(R)-(metilamino)-etilo, 1(S)-(metilaimino)-etilo, 1(R,S)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo, 1(R)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo, o 1(S)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo.

En otra realización de la invención (B15), el compuesto es de la Fórmula I(r):

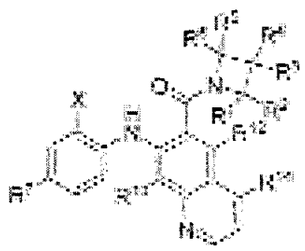


Ic-1

donde X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{12} y R^{14} son lo defindio en el resumen de la invención para un compuesto del Grupo B. Más específicamente, R^1, R^2, R^5 y R^6 son hidrógeno, X y R^7 son halo; R^3 y R^4 son lo definido en el resumen de la invención para el Grupo B; R^{10} y R^{12} son independientemente hidrógeno, halo, o alquilo; y R^{14} es hidrógeno, halo, alquilo o amino. Aún más específicamente, X es fluoro o cloro; R^7 es yodo o bromo; R^{10} es hidrógeno o halo, más específicamente hidrógeno o fluoro; R^{12} es hidrógeno; R^{14} es hidrógeno, alquilo, o amino, más específicamente hidrógeno, metilo o amino; R^3 es hidroxi. Aún más específicamente, R^4 es heterocicloalquilo, alquilo, o heteroarilo, donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ (donde R^8 es hidrógeno o alquilo y $R^{8'}$ es hidrógeno, alquilo o cicloalquilo donde el cicloalquilo se sustituye optativamente con uno o dos grupos seleccionados independientemente de hidroxi y alquilo) y el heteroarilo se sustituye optativamente con alquilo. Aún más específicamente, R^4 es piperidinilo, pirrolidinilo, 1(R,S)-amino-etilo, 1(R)-amino-etilo, 1(S)-amino-etilo, 1(R,S)-(metilamino)-etilo,

1(R)-(metilamino)-etilo, 1(S)-(metilamino)-etilo, 1(R,S)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo, 1(R)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo, o 1(S)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo.

En otra realización de la invención (B16), el compuesto es de la Fórmula I(s):

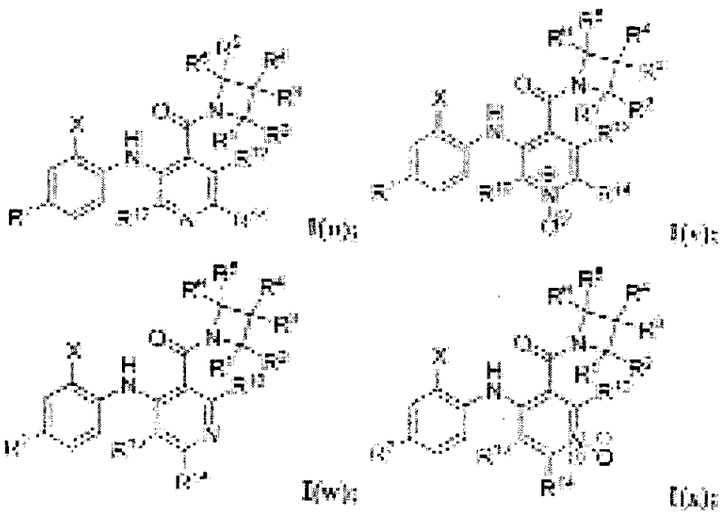


I(s)

donde X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{12} y R^{14} son lo definido en el resumen de la invención para un compuesto del Grupo B. Más específicamente, R^1, R^2, R^5 y R^6 son hidrógeno, X y R^7 son halo; R^3 y R^4 son lo definido en el resumen de la invención para el Grupo B; y R^{10} y R^{12} son independientemente hidrógeno, halo o alquilo; y R^{14} es hidrógeno, halo, alquilo o amino. Aún más específicamente, X es fluoro o cloro y R^7 es yodo o bromo; R^{10} es hidrógeno o halo, más específicamente hidrógeno o fluoro; R^{12} es hidrógeno; R^{14} es hidrógeno, metilo, o amino; R^3 es hidroxi, y R^4 es heterocicloalquilo, alquilo o heteroarilo, donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ (donde R^8 es hidrógeno o alquilo y $R^{8'}$ es hidrógeno, alquilo o

cicloalquilo donde el cicloalquilo se sustituye optativamente con uno o dos grupos seleccionados independientemente de hidroxi y alquilo) y el heteroarilo se sustituye optativamente con alquilo.

En otra realización de la invención (B18), el compuesto es de la Fórmula I(u), I(v), I(w) o I(x):



donde X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{12} y R^{14} son lo definido en el resumen de la invención para un compuesto del Grupo B.

En una realización más específica de la realización B18, el compuesto es de la fórmula I(u), I(v), I(w), o I(x) donde R^3 es halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, $-CN$, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, -

$CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, o heterocicloalquilo; donde el alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, o heterocicloalquilo se sustituyen independiente y optativamente con uno, dos, tres, cuatro, cinco, seis o siete grupos seleccionados independientemente de halo, alquilo, haloalquilo, nitro, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, heteroarilo optativamente sustituido, heteroarilalquilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ y $-NR^8C(O)R^{8'}$; y R^4 es lo definido en el resumen de la invención para un compuesto del Grupo B; o R^3 y R^4 junto con el carbono al cual están unidos forman C(O) o C(=NOH); y todos los demás grupos son lo definido en el resumen de la invención para un compuesto del Grupo B.

En una realización más específica de la realización B18, el compuesto es de la fórmula I(t), I(u), I(v) o I(w) donde R^3 y R^4 son independientemente halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NRS(O)_2R^8$, $-CN$, $-S(O)_mR^9$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-$

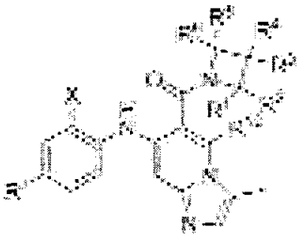
$CH_2N(R^{25})(N^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, o heterocicloalquilo; donde el alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, y heterocicloalquilo se sustituyen independientemente con uno, dos, tres, cuatro, cinco, seis o siete grupos seleccionados independientemente de halo, alquilo, haloalquilo, nitro, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, heteroarilo optativamente sustituido, heteroarilalquilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ y $-NR^8C(O)R^{8'}$; o R^3 y R^4 junto con el carbono al cual están unidos forman C(O) o C(=NOH); y todos los demás grupos son lo definido en el resumen de la invención para un compuesto del Grupo B.

En una realización más específica la realización B18, el compuesto es de la fórmula I(u), I(v), I(w), o I(x) donde R^4 es heterocicloalquilo, heteroarilo (optativamente sustituido con alquilo), alilo donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ (donde R^8 es hidrógeno o alquilo y $R^{8'}$ es hidrógeno, alquilo, o cicloalquilo donde el cicloalquilo se sustituye

optativamente con uno o dos grupos seleccionados independientemente de hidroxi y alquilo). Más específicamente, R^4 es piperidinilo, pirrolidinilo, 1(R,S)-amino-pentilo, 1(R)-amino-propilo, 1(S)-amino-propilo, 1(R,S)-(metilamino)-propilo, 1(R)-(metilamino)-propilo, 1(S)-(metilamino)-propilo, 1(R,S)-(3,4-cis-dihidroxi-ciclopentilamino)-propilo, 1(R)-(3,4-cis-dihidroxi-ciclopentilamino)-propilo, o 1(S)-(3,4-cis-dihidroxi-ciclopentilamino)-propilo.

En una realización más específica de la realización B18, el compuesto es de la fórmula I(u), I(v), I(w) o I(x), donde R^1, R^2, R^5 y R^6 son hidrógeno, X y R^7 son halo; R^3 y R^4 son lo definido en el resumen de la invención para el Grupo B; y R^{10}, R^{12} y R^{14} son independientemente hidrógeno, halo, o alquilo. Aún más específicamente, X es fluoro o cloro; R^7 es yodo o bromo; R^{10} es hidrógeno o halo, más específicamente hidrógeno o fluoro; R^{12} y R^{14} son hidrógeno; y R^3 es hidroxi. Aún más específicamente, R^4 es heterocicloalquilo, alquilo o heteroarilo, donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ (donde R es hidrógeno o alquilo y $R^{8'}$ es hidrógeno, alquilo, o cicloalquilo donde el cicloalquilo se sustituye optativamente con uno o dos grupos seleccionados independientemente de hidroxi y alquilo) y el heteroarilo se sustituye optativamente con alquilo.

En otra realización de la invención (B19), el compuesto es de la fórmula I(cc)



I(cc)

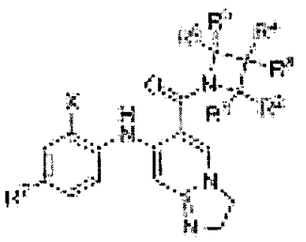
donde X, R^1, R^2, R^3, R^4, R^5, R^6 y R^7 son lo definido en el resumen de la invención para el compuesto del Grupo B. Específicamente, R^1, R^2, R^5 y R^6 son hidrógeno, y X y R^7 son halo. Más específicamente, X es fluoro o cloro; y R^3 es hidrógeno o hidroxi; R^7 es yodo o bromo. Aún más específicamente, R^4 es heterocicloalquilo, alquilo, o heteroarilo, donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ (donde R^8 es hidrógeno o alquilo y $R^{8'}$ es hidrógeno, alquilo o cicloalquilo donde el cicloalquilo se sustituye optativamente con uno o dos grupos seleccionados independientemente de hidroxi y alquilo) y el heteroarilo se sustituye optativamente con alquilo. Aún más específicamente, R^4 es piridinilo, pirrolidinilo, bencimidazolilo, N-metil-bencimidazolilo, metilaminometilo, 1(R,S)-amino-etilo, 1(R)-amino-etilo, 1(S)-amino-etilo, 1(R,S)-(metilamino)-etilo, 1(R)-metilamino)-etilo, 1(S)-(metilamino)-etilo, 1(R,S)-(dimetilamino)-etilo, 1(R)-(dimetilamino)-etilo, 1(S)-(dimetilamino)-etilo, 1(R,S)-amino-propilo, 1(R)-amino-

propilo, 1(S)-amino-propilo, 1(R,S)-(metilamino)-propilo, 1(R)-(metilamino)-propilo, 1(S)-(metilamino)-propilo, 1(R,S)-(dimetilamino)-propilo, 1(R)-(dimetilamino)-propilo, 1(S)-(dimetilamino)-propilo, 1(R,S)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo, 1(R)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo, o 1(S)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo.

Una realización específica (B19a) de la realización B19 es aquella donde R^4 es heterocicloalquilo o alquilo donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ (donde R^8 es hidrógeno o alquilo y $R^{8'}$ es hidrógeno, alquilo o cicloalquilo donde el cicloalquilo se sustituye optativamente con uno o dos grupos seleccionados independientemente de hidroxi y alquilo). Específicamente, R^4 es piperidinilo, pirrolidinilo, metilaminometilo, 1(R,S)-amino-etilo, 1(R)-amino-etilo, 1(S)-amino-etilo, 1(R,S)-(metilamino)-etilo, 1(R)-(metilamino)-etilo, 1(S)-(metilamino)-etilo, 1(R,S)-(dimetilamino)-etilo, 1(R)-(dimetilmino)-etilo, 1(S)-(dimetilamino)-etilo, 1(R,S)-amino-propilo, 1(R)-amino-propilo, 1(S)-amino-propilo, 1(R,S)-(metilamino)-propilo, 1(R)-(metilamino)-propilo, 1(S)-(metilamino)-propilo, 1(R,S)-(dimetilamino)-propilo, 1(R)-(dimetilamino)-propilo, 1(S)-(dimetilamino)-propilo, 1(R,S)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo, 1(R)-(3,4-cis-

dihidroxi-ciclopentilamino)-etilo, o 1(S)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo.

En otra realización de la invención (B20), el compuesto es de la fórmula I(dd):



I(dd)

donde X, R^1, R^2, R^3, R^4, R^5, R^6 y R^7 son lo definido en el resumen de la invención para el compuesto del Grupo B. Específicamente, R^1, R^2, R^5 y R^6 son hidrógeno, y X y R^7 son halo. Más específicamente, X es fluoro o cloro; y R^3 es hidrógeno o hidroxi; R^7 es yodo o bromo. Aún más específicamente, R^4 es heterocicloalquilo, alquilo, o heteroarilo, donde el alquilo se sustituye optativamente con -$NR^8R^{8'}$ (donde R^8 es hidrógeno o alquilo y $R^{8'}$ es hidrógeno, alquilo o cicloalquilo donde el cicloalquilo se sustituye optativamente con uno o dos grupos seleccionados independientemente de hidroxi y alquilo) y el heteroarilo se sustituye optativamente con alquilo. Aún más específicamente, R^4 es piridinilo, pirrolidinilo, bencimidazolilo, N-metil-bencimidazolilo, metilaminometilo, 1(R,S)-amino-etilo, 1(R)-

amino-etilo, 1(S)-amino-etilo, 1(R,S)-(metilamino)-etilo, 1(R)-metilamino)-etilo, 1(S)-(metilamino)-etilo, 1(R,S)-(dimetilamino)-etilo, 1(R)-(dimetilamino)-etilo, 1(S)-(dimetilamino)-etilo, 1(R,S)-amino-propilo, 1(R)-amino-propilo, 1(S)-amino-propilo, 1(R,S)-(metilamino)-propilo, 1(R)-(metilamino)-propilo, 1(S)-(metilamino)-propilo, 1(R,S)-(dimetilamino)-propilo, 1(R)-(dimetilamino)-propilo, 1(S)-(dimetilamino)-propilo, 1(R,S)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo, 1(R)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo, o 1(S)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo.

Una realización específica (B20a) de la realización B20 es aquella donde R^4 es heterocicloalquilo o alquilo donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ (donde R^8 es hidrógeno o alquilo y $R^{8'}$ es hidrógeno, alquilo o cicloalquilo donde el cicloalquilo se sustituye optativamente con uno o dos grupos seleccionados independientemente de hidroxi y alquilo). Específicamente, R^4 es piperidinilo, pirrolidinilo, metilaminometilo, 1(R,S)-amino-etilo, 1(R)-amino-etilo, 1(S)-amino-etilo, 1(R,S)-(metilamino)-etilo, 1(R)-(metilamino)-etilo, 1(S)-(metilamino)-etilo, 1(R,S)-(dimetilamino)-etilo, 1(R)-(dimetilmino)-etilo, 1(S)-(dimetilamino)-etilo, 1(R,S)-amino-propilo, 1(R)-amino-propilo, 1(S)-amino-propilo, 1(R,S)-(metilamino)-propilo, 1(R)-(metilamino)-propilo, 1(S)-

(metilamino)-propilo, 1(R,S)-(dimetilamino)-propilo, 1(R)-(dimetilamino)-propilo, 1(S)-(dimetilamino)-propilo, 1(R,S)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo, 1(R)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo, o 1(S)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo.

En una realización de la invención (C1), el compuesto de la Fórmula I se selecciona del Grupo C donde todos los grupos son lo definido en el resumen de la invención.

En otra realización de la invención (C2), X y R^7 son halo y todos los demás grupos son lo definido para el compuesto seleccionado del grupo C.

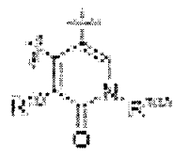
En otra realización de la invenión (C3), el compuesto se selecciona del Grupo C donde R^3 es halo, nitro, $-NR^8R^{9'}$, $-OR^8$, $-HS(O)R^8$, -CN, $-S(O)_mR^8$, $S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^8$, $-NR^8C(O)NR^{9'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, o heterociclolquilo; donde el alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo o heterocicloalquilo se sustituyen independiente y optativamente con uno, dos, tres, cuatro,

cinco, seis, o siete grupos seleccionados independientemente de halo, alquilo, haloalquilo, nitro, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, heteroarilo optativamente sustituido, heteroarilalquilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ y $-NR^8C(O)R^{8'}$; y R^4 es lo definido en el resumen de la invención; o R^3 y R^4 junto con el carbono al cual están unidos forman C(O) o C(=NOH); y todos los demás grupos son lo definido en el resumen de la invención para un compuesto del Grupo C. Más específicamente, R^1, R^2, R^3 y R^4 son hidrógeno; y X y R^7 son halo.

En otra realización de la invención (C4), el compuesto se selecciona del Grupo C donde R^3 y R^4 son independientemente halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, $-CN$, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2R^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, o heterocicloalquilo; donde el alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, y heterocicloalquilo se sustituyen independiente y optativamente

con uno, dos, tres, cuatro, cinco, seis o siete grupos seleccionados independientemente de halo, alquilo, haloalquilo, nitro, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, heteroarilo optativamente sustituido, heteroarilalquilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, y $-NR^8C(O)R^{8'}$; o R^3 y R^4 junto con el carbono al cual están unidos forman C(O) o C(=NOH); y todos los demás grupos son lo definido en el Resumen de la invención para un compuesto del Grupo C. Más específicamente, R^1, R^2, R^5 y R^6 son hidrógeno y X y R^7 son halo.

En otra realización de la invención (C5), A es



y X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10} y R^{10a} son lo definido en el resumen de la invención para un compuesto del Grupo C. Más específicamente, R^1, R^2, R^5 y R^6 son hidrógeno, X y R^7 son un halo; R^{10} es hidrógeno o halo; y R^{10a} es alquilo. Aún más específicamente, X es fluoro o cloro; R^3 es hidroxi; R^7 es yodo o bromo; R^{10} es hidrógeno o fluoro; y R^{10a} es metilo. Aún más específicamente, R^4 es heterocicloalquilo, alquilo o

heteroarilo, donde el alquilo se sustituye optativamente con -$NR^8R^{8'}$ (donde R^8 es hidrógeno y $R^{8'}$ es hidrógeno, alquilo, o cicloalquilo donde el cicloalquilo se sustituye optativamente con uno o dos grupos seleccionados independientemente de hidroxi y alquilo) y el heteroarilo se sustituye optativamente con alquilo. Aún más específicamente, R^4 es piperidinilo, pirrolidinilo, bencimidazolilo, N-metil-bencimidazolilo, metilaminometilo, 1(R,S)-amino-etilo, 1(R)-amino-etilo, 1(S)-amino-etilo, 1(R,S)-(metilamino)-etilo, 1(R)-(metilamino)-etilo, 1(S)-(metilamino)-etilo, 1(R,S)-(dimetilamino)-etilo, 1(R)-(dimetilmino)-etilo, 1(S)-(dimetilamino)-etilo, 1(R,S)-amino-propilo, 1(R)-amino-propilo, 1(S)-amino-propilo, 1(R,S)-(metilamino)-propilo, 1(R)-(metilamino)-propilo, 1(S)-(metilamino)-propilo, 1(R,S)-(dimetilamino)-propilo, 1(R)-(dimetilamino)-propilo, 1(S)-(dimetilamino)-propilo, 1(R,S)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo, 1(R)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo, o 1(S)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo.

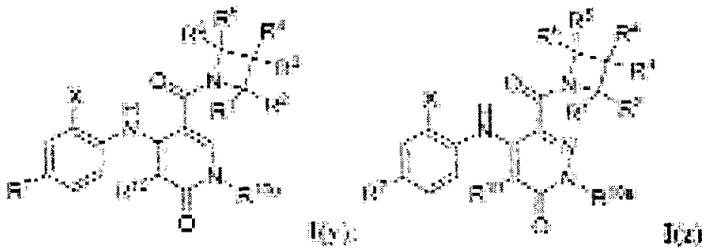
En otra realización de la invención (C6), A es



y X, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10} y R^{10a} son lo definido en el resumen de la invención para un compuesto del Grupo C. Más

específicamente, R^1, R^2, R^5 y R^6 son hidrógeno, X y R^7 son un halo; R^{10} es hidrógeno o halo; y R^{10a} es alquilo. Aún más específicamente, X es fluoro o cloro; R^3 es hidroxi; R^7 es yodo o bromo; R^{10} es hidrógeno o fluoro; y R^{10a} es metilo. Aún más específicamente, R^4 es heterocicloalquilo, alquilo o heteroarilo, donde el alquilo se sustituye optativamente con -$NR^8R^{8'}$ (donde R^8 es hidrógeno y $R^{8'}$ es hidrógeno, alquilo, o cicloalquilo donde el cicloalquilo se sustituye optativamente con uno o dos grupos seleccionados independientemente de hidroxi y alquilo) y el heteroarilo se sustituye optativamente con alquilo. Aún más específicamente, R^4 es piperidinilo, pirrolidinilo, bencimidazolilo, N-metil-bencimidazolilo, metilaminometilo, 1(R,S)-amino-etilo, 1(R)-amino-etilo, 1(S)-amino-etilo, 1(R,S)-(metilamino)-etilo, 1(R)-(metilamino)-etilo, 1(S)-(metilamino)-etilo, 1(R,S)-(dimetilamino)-etilo, 1(R)-(dimetilmino)-etilo, 1(S)-(dimetilamino)-etilo, 1(R,S)-amino-propilo, 1(R)-amino-propilo, 1(S)-amino-propilo, 1(R,S)-(metilamino)-propilo, 1(R)-(metilamino)-propilo, 1(S)-(metilamino)-propilo, 1(R,S)-(dimetilamino)-propilo, 1(R)-(dimetilamino)-propilo, 1(S)-(dimetilamino)-propilo, 1(R,S)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo, 1(R)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo, o 1(S)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo.

En otra realización de la invención (C7), el compuesto es de la fórmula I(y) o I(z):



Donde R^1, R^2, R^5 y R^6 son hidrógeno; X y R^7 son halo; R^3, R^4, R^{10} y R^{10a} son lo definido en el resumen de la invención para un compuesto del Grup C. En una realización más específica, X es fluoro o cloro; R^7 es yodo o bromo; R^{10} es hidrógeno, halo o alquilo, más específicamente hidrógeno o halo; y R^{10a} es alquilo, más específicamente metilo. Aún más específicamente, R^{10} es hidrógeno o fluoro; R^3 es hidroxi; y R^4 es heterocicloalquilo, alquilo o heteroarilo, donde el alquilo se sutituye optativamente con $-NR^8R^{9'}$ (donde R^8 es hidrógeno o alquilo y $R^{8'}$ es hidrógeno, alquilo o cicloalquilo, donde el cicloalquilo se sustituye optativamente con uno o dos grupos seleccionados independientemente de hidroxi y alquilo) y el heteroarilo se sustituye optativamente con alquilo.

En una realización de la invención (D), el compuesto de la Fórmula I se selecciona del Grupo D donde todos los grupos son lo definido en el resumen de la invención.

En otra realización de la invención (D1), X y R^7 son halo y todos los demás grupos son lo definido para el compuesto seleccionado del grupo D.

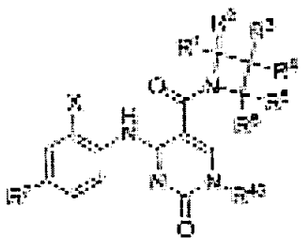
En otra realización de la invenión (D2), el compuesto se selecciona del Grupo D donde R^3 es halo, nitro, $-NR^8R^{9'}$, $-OR^8$, $-HS(O)R^8$, $-CN$, $-S(O)_mR^8$, $S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^8$, $-NR^8C(O)NR^{9'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, o heterociclolquilo; donde el alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo o heterocicloalquilo se sustituyen independiente y optativamente con uno, dos, tres, cuatro, cinco, seis, o siete grupos seleccionados independientemente de halo, alquilo, haloalquilo, nitro, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, heteroarilo optativamente sustituido, heteroarilalquilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ y $-NR^8C(O)R^{8'}$; y R^4 es lo definido en el resumen de la invención; o R^3 y R^4 junto con el carbono al cual están unidos forman C(O) o C(=NOH); y todos los demás

grupos son lo definido en el resumen de la invención para un compuesto del Grupo C. Más específicamente, R^1, R^2, R^3 y R^4 son hidrógeno; y X y R^7 son halo.

En otra realización de la invención (D3), el compuesto se selecciona del Grupo D donde R^3 y R^4 son independientemente halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, $-CN$, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2R^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, o heterocicloalquilo; donde el alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, y heterocicloalquilo se sustituyen independiente y optativamente con uno, dos, tres, cuatro, cinco, seis o siete grupos seleccionados independientemente de halo, alquilo, haloalquilo, nitro, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, heteroarilo optativamente sustituido, heteroarilalquilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, y $-NR^8C(O)R^{8'}$; o R^3 y R^4 junto con el carbono al cual están unidos forman C(O) o C(=NOH); y todos

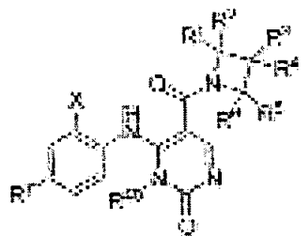
los demás grupos son lo definido en el Resumen de la invención para un compuesto del Grupo C. Más específicamente, R^1, R^2, R^5 y R^6 son hidrógeno y X y R^7 son halo.

En otra realización de la invención (D4), A es



Ia1

o



Ib1

Donde R^{40} es hidrógeno o metilo (específicamente, R^{40} es hidrógeno) y todos los demás grupos son lo definido en el resumen de la invención. Específicamente, R^1, R^2, R^5 y R^6 son hidrógeno; X y R^7 son halo; y R^{40} es hidrógeno o metilo. Más específicamente, X es fluoro o cloro; y R^3 es hidrógeno o hidroxi; R^7 es yodo o bromo. Aún más específicamente, R^4 es heterocicloalquilo, alquilo o heteroarilo, donde el alquilo se sutituye optativamente con $-NR^8R^{9'}$ (donde R^8 es hidrógeno o alquilo y $R^{8'}$ es hidrógeno, alquilo o cicloalquilo, donde el cicloalquilo se sustituye optativamente con uno o dos grupos seleccionados independientemente de hidroxi y alquilo) y el heteroarilo se sustituye optativamente con alquilo. Aún más específicamente, R^4 es piperidinilo, pirrolidinilo, bencimidazolilo, N-metil-bencimidazolilo, metilaminometilo, 1(R,S)-amino-etilo, 1(R)-amino-etilo, 1(S)-amino-etilo,

1(R,S)-(metilamino)-etilo, 1(R)-(metilamino)-etilo, 1(S)-(metilamino)-etilo, 1(R,S)-(dimetilamino)-etilo, 1(R)-(dimetilmino)-etilo, 1(S)-(dimetilamino)-etilo, 1(R,S)-amino-propilo, 1(R)-amino-propilo, 1(S)-amino-propilo, 1(R,S)-(metilamino)-propilo, 1(R)-(metilamino)-propilo, 1(S)-(metilamino)-propilo, 1(R,S)-(dimetilamino)-propilo, 1(R)-(dimetilamino)-propilo, 1(S)-(dimetilamino)-propilo, 1(R,S)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo, 1(R)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo, o 1(S)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo.

Una realización más específica (D4a) de la invención de D4 es aquella donde R^4 es heterocicloalaquilo o alquilo donde el alquilo se sustituye optativamente con $-NR^8R^{9'}$ (donde R^8 es hidrógeno o alquilo y $R^{8'}$ es hidrógeno, alquilo o cicloalquilo, donde el cicloalquilo se sustituye optativamente con uno o dos grupos seleccionados independientemente de hidroxi y alquilo). Específicamente, R^4 es piperidinilo, pirrolidinilo, bencimidazolilo, N-metil-bencimidazolilo, metilaminometilo, 1(R,S)-amino-etilo, 1(R)-amino-etilo, 1(S)-amino-etilo, 1(R,S)-(metilamino)-etilo, 1(R)-(metilamino)-etilo, 1(S)-(metilamino)-etilo, 1(R,S)-(dimetilamino)-etilo, 1(R)-(dimetilmino)-etilo, 1(S)-(dimetilamino)-etilo, 1(R,S)-amino-propilo, 1(R)-amino-propilo, 1(S)-amino-propilo, 1(R,S)-(metilamino)-propilo, 1(R)-(metilamino)-propilo, 1(S)-

(metilamino)-propilo, 1(R,S)-(dimetilamino)-propilo, 1(R)-(dimetilamino)-propilo, 1(S)-(dimetilamino)-propilo, 1(R,S)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo, 1(R)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo, o 1(S)-(3,4-cis-dihidroxi-ciclopentilamino)-etilo.

Otra realización de la invención (E) se refiere a un compuesto seleccionado del Grupo A, el Grupo B y el Grupo C donde:

Grupo A

A es fenileno optativamente sustituido con uno o dos grupos seleccionados de R^{10}, R^{12}, R^{14} y R^{16} donde R^{10}, R^{12}, R^{14} y R^{16} son independientemente hidrógeno o halo;

X es halo;

R^1, R^2, R^5 y R son hidrógeno;

R^3 es hidrógeno, halo, hidroxi, alcoxi o amino;

R^4 es hidrógeno, $-NR^8R^{8'}$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2NR(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a}R^{25b})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a}R^{25b})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}(NR^{25a}R^{25b})=CH(NO_2)$, alquilo, alquenilo, cicloalquilo, heterocicloalquilo, o heteroarilo; en donde el alquilo de R^4 se sustituye optativamente con uno, dos, o tres grupos seleccionados independientemente de $-OR^8$, halo, nitro, $-S(O)_mR^9$, heterocicloalquilo optativamente sustituido, $-NR^8R^{8'}$, $-NR^8C(O)R^{8'}$, $-NR^8S(O)_2R^{8'}$, $-NR^8C(O)OR^{8'}$, y arilo; donde el cicloalquilo de R^4 se sustituye optativamente con uno o dos

grupos seleccionados de $-OR^8$ y $-NR^8R^{8'}$; donde el heterocicloalquilo de R^4 se sustituye optativamente con uno o dos grupos seleccionados independientemente de alquilo y $-C(O)OR^8$; y donde el heteroarilo de R^4 se sustituye optativamente con $-NR^8R^{8'}$; o

R^3 y R^4 junto con el carbono al cual están unidos forman C(O) o C(=NOH);

m es 0;

R^7 es halo;

R^8 y $R^{8'}$ se seleccionan independientemente de hidrógeno, hidroxi, alquilo, alquenilo, alquinilo, arilo, heterocicloalquilo, heteroarilo y cicloalquilo;

Donde R^8 y $R^{8'}$ se sustituyen independiente y optativamente con uno, dos, o tres grupos seleccionados independientemente de hidroxi, $-NR^8R^{8'}$ (donde R^8 y $R^{8'}$ son independientenente hidrógeno, alquilo o hidroxialquilo), heteroarilo optativamente sustituido, cicloalquilo optativamente sustituido), alcoxi optativamente sustitudo, cicloalquilo optativamente sustituido, arilo optativamente sustituido, heterocicloaquilo optativamente sustituido, heteroarilo optativamente sustituido, $-C(O)NR^{33}R^{33a}$ (donde R^{33} es hidrógeno o alquilo y R^{33a} es alquilo, alquenilo, alquinilo, o cicloalquilo), ariloxi optativamente sustituido, $-S(O)_mR^{31}$ (donde m es 0 y R^{31} es alquilo, carboxi, alcoxicarobonilo, y $-NR^{32}C(O)R^{32a}$ (donde R^{32} es hidrógeno o alquilo y R^{32a} es alquilo,

alquenilo, alcoxi, o cicloalquilo); o donde el alquilo se sustituye optativamente con uno, dos, tres, cuatro o cinco halo;

Donde los heteroarilos de R^8 y $R^{8'}$ se sustituyen independiente y optativamente con uno o dos grupos seleccionados independientemente de amino y alquilo;

Donde los heterocicloalquilos de R^8 y $R^{8'}$ se sustituyen independiente y optativamente con uno, dos, o tres grupos seleccionados independientemente de alquilo, alcoxicarbonilo, arilalquilo optativamente sustituido, hidroxi, alcoxi, e hidroxialquilo;

Donde los arilos de R^8 y $R^{8'}$ se sustituyen independiente y optativamente con uno o dos grupos seleccionados independientemente de hidroxi, alcoxi, halo, $-NR^{32}C(O)R^{32a}$ (donde R^{32} es hidrógeno o alquilo y R^{32a} es alquilo, alquenilo, alcoxi, o cicloalquilo) y $-NR^{34}SO_2R^{34a}$ (donde R^{34} es hidrógeno o alquilo y R^{34a} es alquilo, alquenilo, cicloalquilo, arilo, heteroarilo o heterocicloalquilo); y

Donde R^8 y $R^{8'}$ se sustituyen independiente y optativamente con uno, dos o tres grupos seleccionados independientemente de hdiroxi, hidroxialquilo, alcoxi, carboxi, $-C(O)NR^{33}R^{33a}$ (donde R^{33} es hidrógeno o alquilo y R^{33a} es alquilo, alquenilo, alquinilo o cicloalquilo) y cicloalquilo optativamente sustituido; y

R^9 es alquilo o arilo;

Grupo B

A es tien-3,4-diilo, benzo[d]isoxazol-5,6-diilo, 1H-imidazol-5,6-diilo (optativamente sustituido en la posición de N1 con R^{19} donde R^{19} es alquilo o alquenilo), benzo[d]oxazol-5,6-diilo, benzo[d]tiazol-5,6-diilo, 1H-benzo[d]-5,6-diilo (optativamente sustituido en la posición de N1 con R^{19} donde R^{19} es alquilo o alquenilo), 1H-benzo[d][1,2,3]triazol-5,6-diilo (optativamente sustituido en la posición de N1 con R^{19} donde R^{19} es alquilo o alquenilo), imidazo[1,2-a]piridin-6,7-diilo, quinolin-6,7-diilo, piridin-3,4-diilo, o 1-óxido-piridin-3,4-diilo, donde A se sustituye optativamente con uno, dos, o tres, grupos seleccionados independientemente de R^{10}, R^{12}, R^{14}, R^{16} y R^{19} donde R^{10}, R^{12}, R^{14} y R^{16} son independientemente hidrógeno, alquilo, halo o amino; y R^{19} es hidrógeno o alquilo;

X es halo;

R^1, R^2, R^5 y R^6 son hidrógeno;

R^3 es hidrógeno o hidroxi;

R^4 es $-NR^8R^{8'}$, heterocicloalquilo, heteroarilo, o alquilo, donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ y donde el heteroarilo se sustituye optativamente con alquilo;

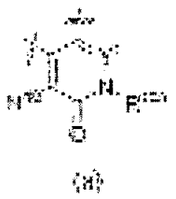
R^7 es halo;

R^8 es hidrógeno o alquilo; y

$R^{8'}$ es hidrógeno, alquilo, o cicloalquilo, donde el cicloalquilo se sustituye optativamente con uno o dos grupos seleccionados independientemente de hidroxi y alquilo;

Grupo C

A es



(a)

Donde R^{10} es hidrógeno o alquilo;

R^{10a} es hidrógeno o alquilo;

Y es =CH o =N-;

X es halo;

R^1, R^2, R^5 y R^6 son hidrógeno;

R^3 es hidrógeno o hidroxi;

R^4 es $-NR^8R^{8'}$, heterocicloalquilo, heteroarilo, o alquilo, donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ y donde el heteroarilo se sustituye optativamente con alquilo;

R^7 es halo;

R^8 es hidrógeno o alquilo; y

$R^{8'}$ es hidrógeno, alquilo, o cicloalquilo, donde el cicloalquilo se sustituye optativamente con uno o dos grupos seleccionados independientemente de hidroxi y alquilo

Una realización de la invención proporciona una composición farmacéutica que comprende un compuesto de la Fórmula I seleccionada del Grupo A, o una sal o solvato

farmacéuticamente aceptable de él y un portador, excipiente o diluyente farmacéuticamente aceptable.

Otra realización de la invención proporciona una composición farmacéutica que comprende un compuesto de la fórmula I seleccionado del grupo B, o una sal o solvato farmacéuticamente aceptable de él y un portador, excipiente o diluyente farmacéuticamente aceptable. Específicamente, el compuesto es de la Fórmula I(c), I(d), I(e), I(f), I(g), I(h), I(i), I(j), I(k), I(m), I(n), I(o), I(p), I(q), I(r), I(s), I(t), I(u), I(v), I(w), I(x), I(cc) o I(dd).

Otra realización de la invención proporciona una composición farmacéutica que comprende un compuesto de la fórmula I seleccionado del grupo C o una sal o solvato farmacéuticamente aceptable de él, y un portador, excipiente o diluyente farmacéuticamente aceptable.

Otra realización de la invención proporciona una composición farmacéutica que comprende un compuesto de la fórmula I seleccionado del grupo D, o una sal o solvato farmacéuticamente aceptable de él, y un portador, excipiente o diluyente farmacéuticamente aceptable.

En otra realización, la invención comprende un método para inhibir MEK en una célula, que comprende poner una célula en contacto con un compuesto de la fórmula I seleccionado del grupo A o una sal o solvato farmacéuticamente aceptable de él, o con una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de un compuesto de la fórmula I seleccionado del grupo A y un portador, excipiente o diluyente farmacéuticamente aceptable.

En otra realización, la invención comprende un método para inhibir MEK en una célula, que comprende poner una célula en contacto con un compuesto de la fórmula I seleccionado del grupo B o una sal o solvato farmacéuticamente aceptable de él, o con una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de un compuesto de la fórmula I seleccionado del grupo B y un portador, excipiente o diluyente farmacéuticamente aceptable.

En otra realización, la invención comprende un método para inhibir MEK en una célula, que comprende poner una célula en contacto con un compuesto de la fórmula I seleccionado del grupo C o una sal o solvato farmacéuticamente aceptable de él, o con una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de un compuesto de la fórmula I

seleccionado del grupo C y un portador, excipiente o diluyente farmacéuticamente aceptable.

En otra realización, la invención comprende un método para inhibir MEK en una célula, que comprende poner una célula en contacto con un compuesto de la fórmula I seleccionado del grupo D o una sal o solvato farmacéuticamente aceptable de él, o con una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de un compuesto de la fórmula I seleccionado del grupo D y un portador, excipiente o diluyente farmacéuticamente aceptable.

Otra realización de la invención proporciona un método para tratar una enfermedad proliferativa cuyo método comprende administrar a un paciente un compuesto de la Fórmula I o una sal o solvato farmacéuticamente aceptable de él, o administrar una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de un compuesto de la fórmula I y un portador, excipiente o diluyente farmacéuticamente aceptable. En una realización específica, la enfermedad es cáncer. Más específicamente, el cáncer se selecciona de melanoma maligno, cáncer colorectal, cáncer pancreático, cáncer de mamas, cáncer de pulmón de células no pequeñas, cáncer de pulmón de células pequeñas, cáncer papilar y de tiroides neoplástico, y cáncer de ovario endometrial.

Un experto en el arte entenderá que ciertos complejos de proteína-ligando cristalizados y sus coordinados de estructura de rayos X correspondientes se pueden usar para revelar nueva información estructural útil para entender la actividad biológica de las cinasas que se describe en la presente. Asimismo, las características estructurales claves de la proteasa mencionada, particularmente la forma del sitio de unión al ligando, son útiles en métodos para designar o identificar moduladores selectivos de cinasa y para resolver las estructuras de otras proteínas con características similares. Dichos complejos de proteína-ligando, que tienen compuestos de la invención como su componente de ligando, son un aspecto de la invención.

Asimismo, un experto en el arte apreciará que dichos cristales de calidad de rayos X adecuados se pueden usar como parte de un método para identificar un agente candidado capaz de unirse y modular la actividad de las cinasas. Dichos métodos pueden caracterizarse por los siguientes aspectos: a) introduciren un programa de computación adecuado, información que define un dominio de unión al ligando de una cinasa en una conformación (por ejemplo, definida por coordinados de estructura de rayos X obtenidos de cristales de calidad de rayos X adecuados descritos anteriormente) en donde el programa de computación crea un modelo de las estructuras tridimensionales del dominio

de unión al ligando; b) introducir un modelo de la estructura tridimensional de un agente candidato en el programa de computación, c) superponer el modelo del agente candidato sobre el modelo del dominio de unión al ligando y d) evaluar si el modelo de agente candidato se ajusta espacialmente dentro del dominio de unión al ligando. Los aspectos a-d no necesariamente se llevan a cabo en el orden mencionado. Dichos métodos también pueden implicar: realizar un diseño racional de fármaco con el modelo de la estructura tridimensional, y seleccionar un agente candidato potencial en conjunto con el modelo de computación.

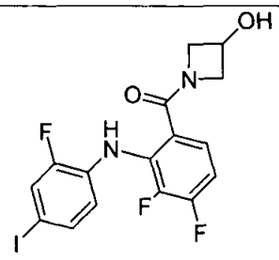
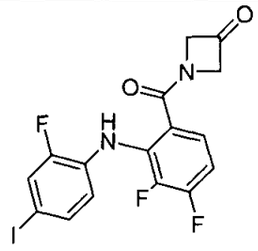
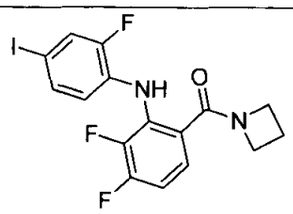
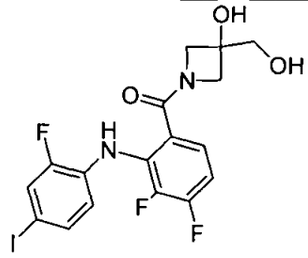
Además, un experto en el arte apreciará que dichos métodos también pueden implicar: emplear un agente candidato, que se determinó de este modo que se ajusta espacialmente en el dominio de unión al ligando, en un ensayo de actividad biológica para modulación de cinasa y determinar si el agente candidado modula la actividad de cinasa en el ensayo. Dichos métodos también pueden incluir administrar el agente candidato, que se determinó que modula la actividad de cinasa, a un mamífero que sufre una condición que se puede tratar mediante la modulación de cinasa, tal como los descritos anteriormente.

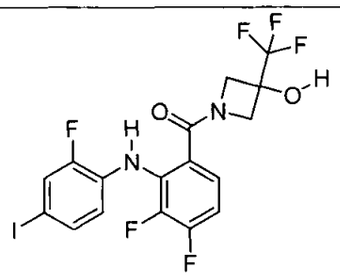
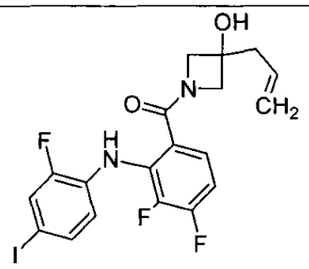
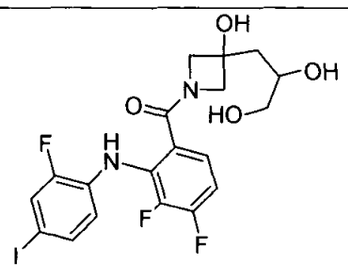
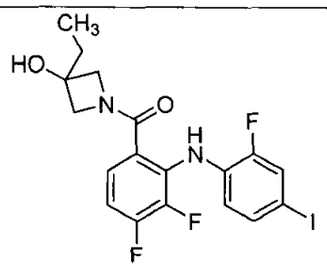
Asimismo, un experto en el arte apreciará que los compuestos de la invención se pueden usar en un método para evaluar la

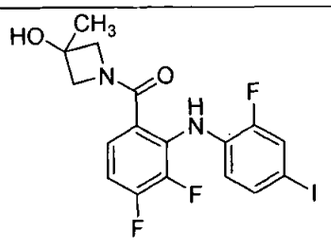
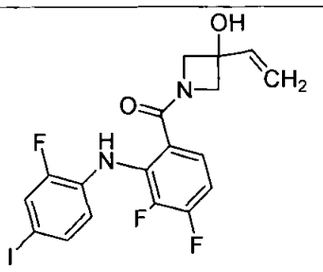
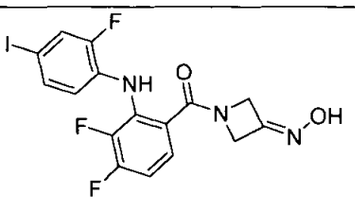
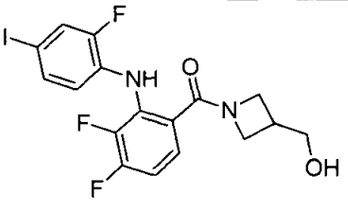
actividad de un agente de ensayo para asociarse con una molécula o complejo molecular que comprende un dominio de unión al ligando de una cinasa. Dicho método se puede caracterizar por los siguientes aspectos: a) crear un modelo de computación de un receptáculo de unión a cinasa usando coordinados de estructuras obtenidos de cristales de calidad de rayos X adecuados de la cinasa; b) emplear algoritmos de computación para realizar una operación de ajuste entre el agente de ensayo y el modelo de computación del receptáculo de unión, y c) analizar los resultados de la operación de ajuste para cuantificar la asociación entre el agente de ensayo y el modelo de computación del receptáculo de unión.

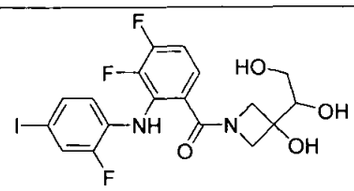
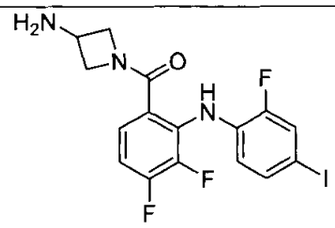
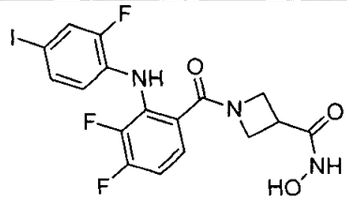
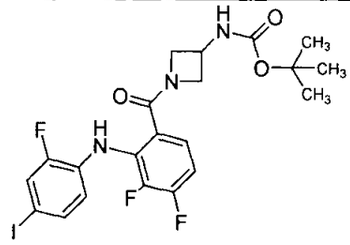
Compuestos Representativos

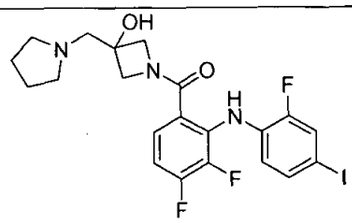
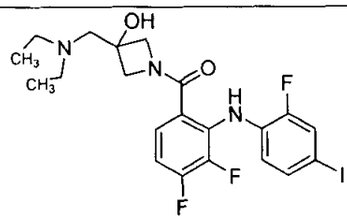
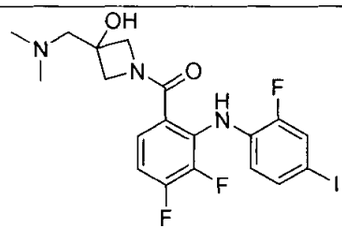
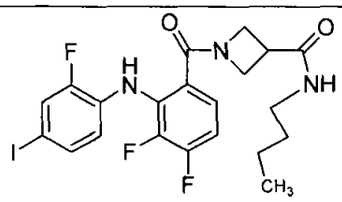
Los compuestos representativos de la Fórmula I se ilustran a continuación. Los ejemplos son solamente ilustrativos y no limitan el alcance de la invención de ninguna manera. Los compuestos de la invención tienen nombres de acuerdo con la aplicación sistemática de las normas de nomenclaturas acordadas por la Unión Internacional de Química Pura y Aplicada (IUPAC), la Unión Internacional de Bioquímica y Biología Molecular (IUBMB) y el Servicio de Resúmenes Químicos (CAS). Los nombres se generaron usando el software de denominación de ACD/Labs, edición 8.00, versión de producto 8.08.

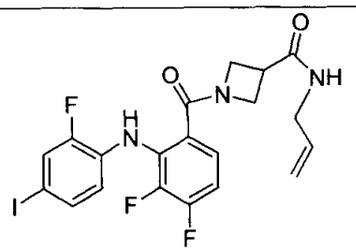
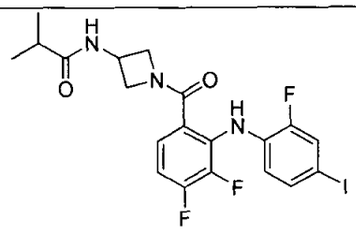
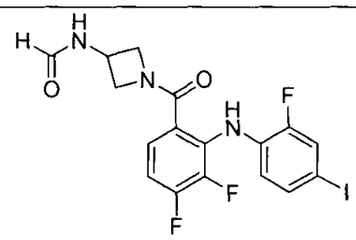
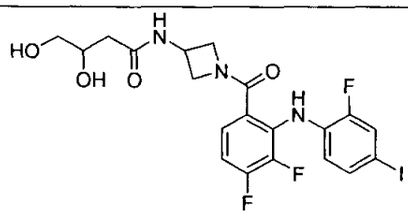
Compuesto N°	Estructura	Nombre
1.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}-carbonil)azetidin-3-ol
2.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ona
3.		6-(azetidin-1-ilcarbonil)-2,3-difluoro-*N*-(2-fluoro-4-yodofenil)anilina
4.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(hidroximetil)azetidin-3-ol

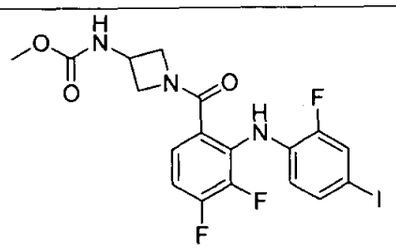
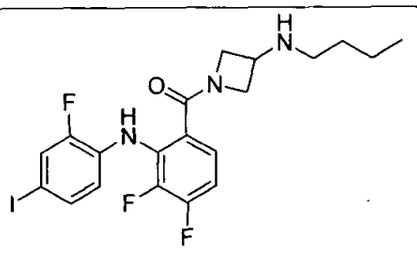
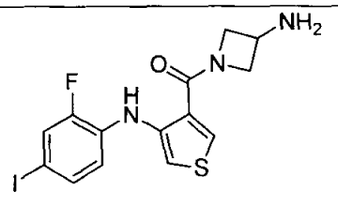
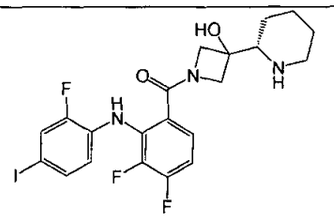
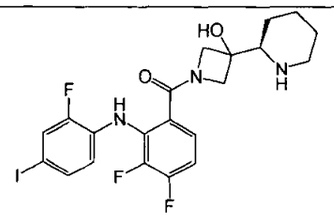
5.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(trifluorometil)azetidin-3-ol
6.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-prop-2-en-1-ilazetidin-3-ol
7.		3-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]propano-1,2-diol
8.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-etilazetidin-3-ol

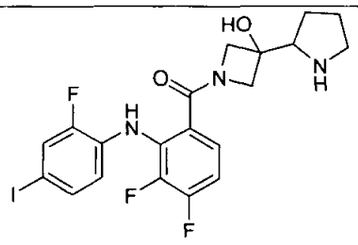
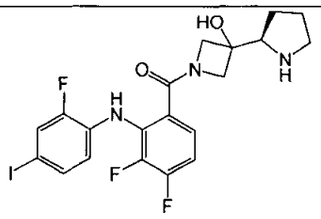
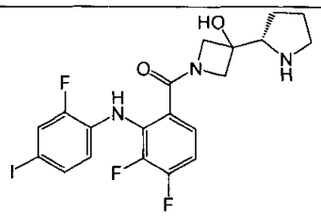
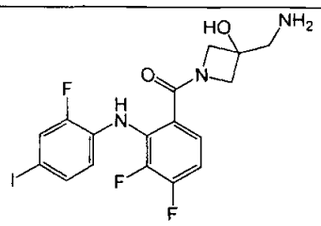
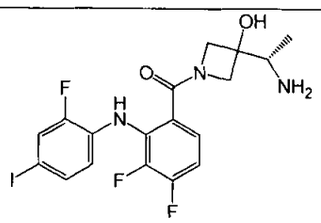
9.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-metilazetidin-3-ol
10.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-etenilazetidin-3-ol
11.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ona oxima
12.		[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]metanol

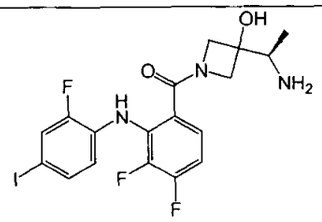
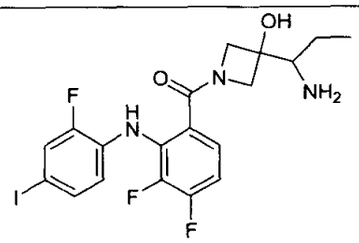
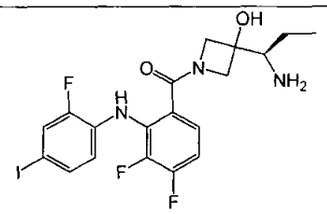
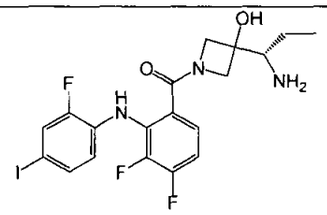
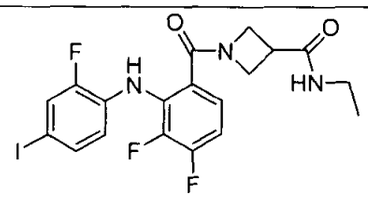
13.		1-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]etano-1,2-diol
14.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-amina
15.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-hidroxiazetidina-3-carboxamida
16.		[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]carbamato de 1,1-dimetiletilo

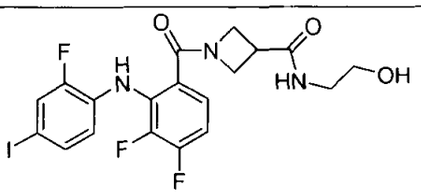
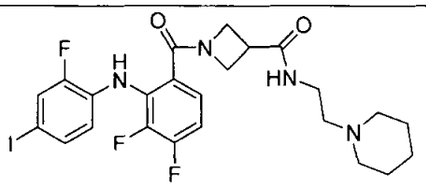
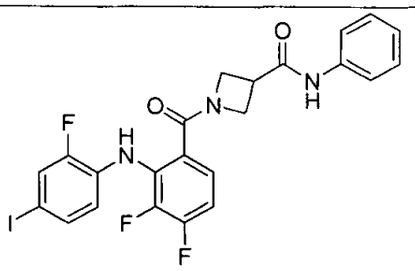
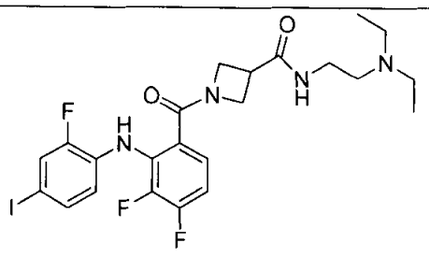
17.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(pirrolidin-1-ilmetil)azetidin-3-ol
18.		3-[(dietilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol
19.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonyl)-3-[(dimetilamino)metil]azetidin-3-ol
20.		*N*-butil-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidina-3-carboxamida

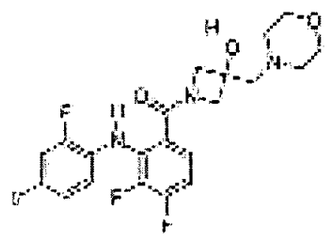
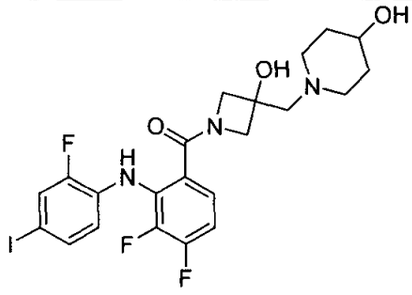
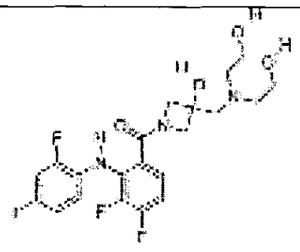
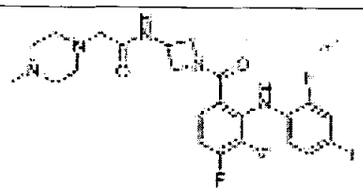
21.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-prop-2-en-1-ilazetidina-3-carboxamida
22.		*N*-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]-2-metilpropanamida
23.		*N*-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]formamida
24.		*N*-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]-3,4-dihidroxibutanamida

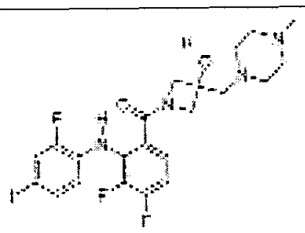
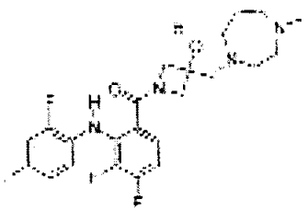
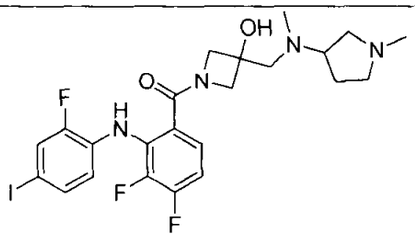
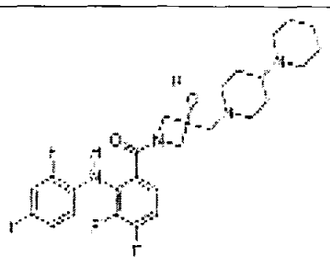
25.		metil [1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]carbamato
26.		*N*-butil-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-amina
27.		1-({4-[(2-fluoro-4-yodofenul)amino]-3-tienil}carbonil)azetidin-3-amina
28.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol
29.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(2*R*)-piperidin-2-il]azetidin-3-ol

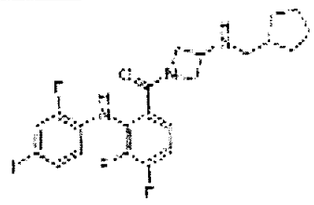
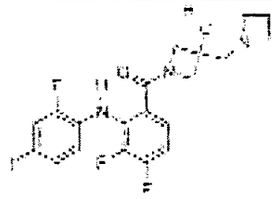
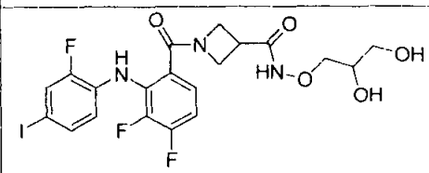
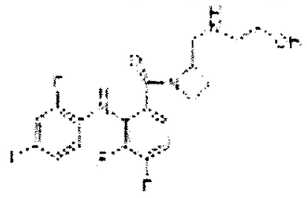
30.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-pirrolidin-2-ilazetidin-3-ol
31.		(*R*)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-pirrolidin-2-ilazetidin-3-ol
32.		(*S*)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-pirrolidin-2-ilazetidin-3-ol
33.		3-(aminometil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil} carbonil)azetidin-3-ol
34.		3-[(1*S*)-1-aminoetil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil} carbonil)azetidin-3-ol

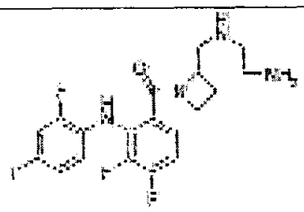
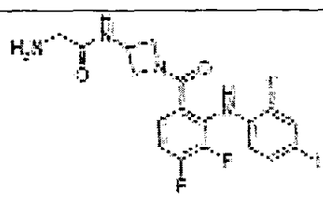
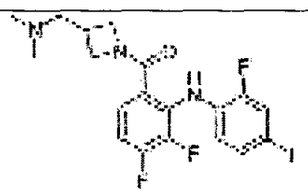
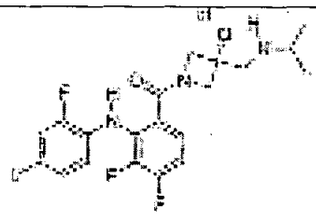
35.		3-[(1R)-1-aminoetil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol
36.		(3-(1-aminopropil)-3-hidroxiazetidin-1-il)(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)metanona
37.		(*R*)-(3-(1-aminopropil)-3-hidroxiazetidin-1-il)(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)metanona
38.		(*S*)-(3-(1-aminopropil)-3-hidroxiazetidin-1-il)(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)metanona
39.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-etilazetidina-3-carboxamida

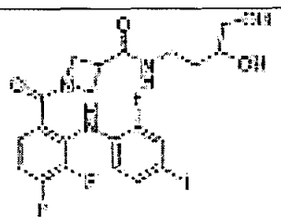
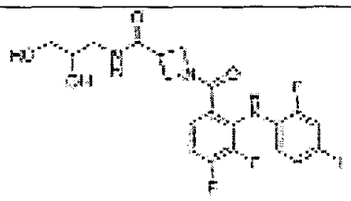
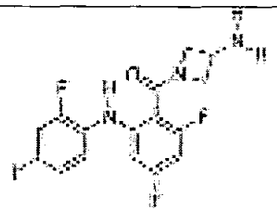
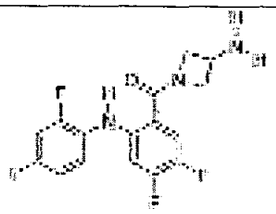
40.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-(2-hidroxietil)azetidina-3-carboxamida
41.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-(2-piperidin-1-iletil)azetidina-3-carboxamida
42.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-fenilazetidina-3-carboxamida
43.		*N*-[2-(dietilamino)etil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidina-3-carboxamida

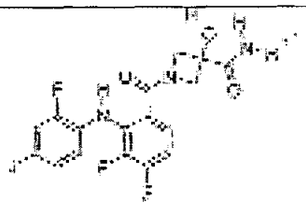
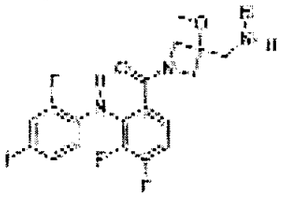
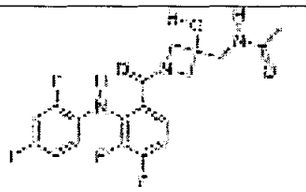
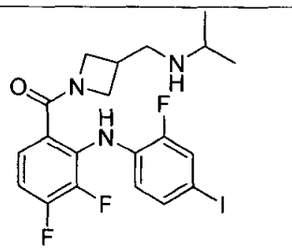
44.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-(morfolin-4-ilmetil)azetidin-3-ol
45.		1-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil} carbonil)-3-hidroxiazetidin-3-il]metil}piperidin-4-ol
46.		3-{[bis(2-hidroxietil)amino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil} carbonil)azetidin-3-ol
47.		N-[1-({3,4-difluroro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)azetidin-3-il] -2-(4-metilpiperazin-2-il) acetamida

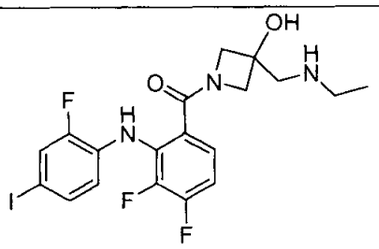
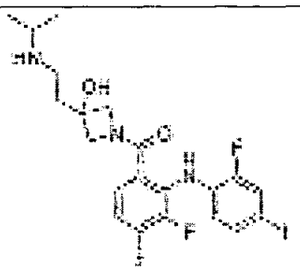
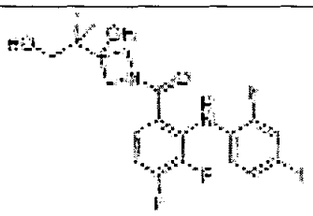
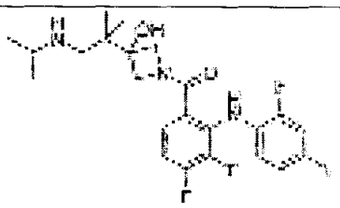
48.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-[(4-metilpiperazin-1-il)metil] azetidin-3-ol
49.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-[(4-metil-1,4-diazepan-1-il)metil]azetidin-3-ol
50.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil} carbonil)-3-{[metil(1-metilpirrolidin-3-il)amino]metil}azetidin-3-ol
51.		3-(1,4'-bipiperidin-1'-ilmetil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil} carbonil)azetidin-3-ol

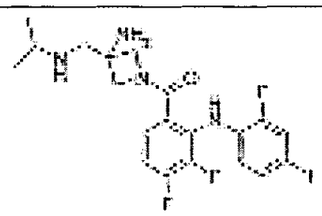
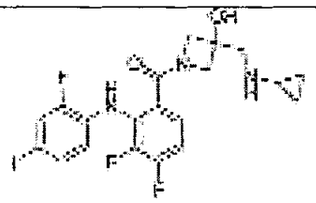
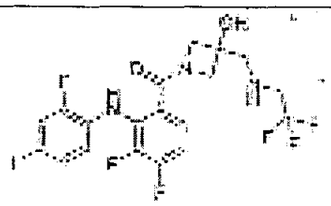
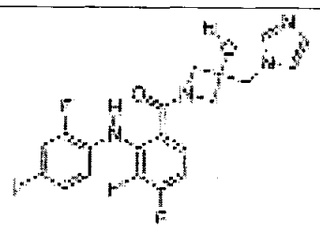
70.		*N*-(ciclopentilmetil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-amina
71.		3-(azetidin-1-ilmetil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol
72.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-[(2,3-dihidroxipropil)oxi]azetidina-3-carboxamida
73.		2-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-2-il]metil}amino)etanol

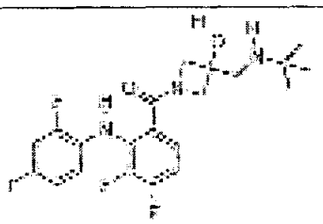
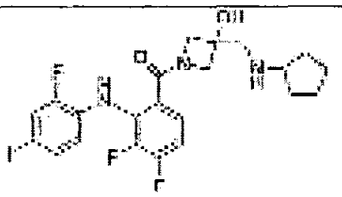
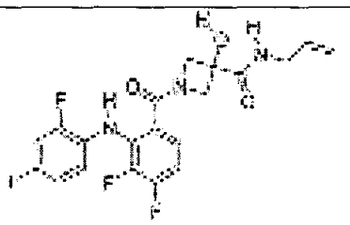
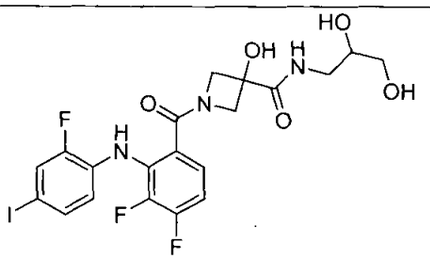
74.		*N*-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-2-il]metil}etano-1,2-diamina
75.		*N*-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]glycinamida
76.		6-({3-[(dimetilamino)metil]azetidin-1-il}carbonil)-2,3-difluoro-*N*-(2-fluoro-4-yodofenil)anilina
77.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1-metiletil)amino]metil}azetidin-3-ol

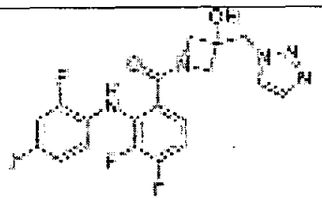
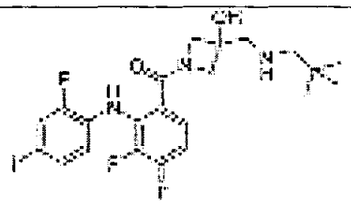
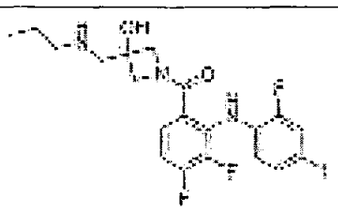
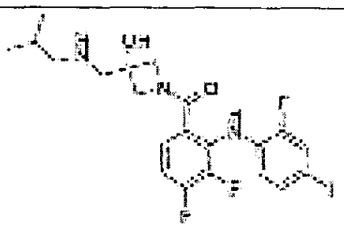
78.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-(3,4-dihidroxibutil)azetidine-3-carboxamida
79.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-(2,3-dihidroxipropil)azetidina-3-carboxamida
80.		1-({2,4-difluoro-6-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-amina
81.		1-({4,5-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-amina

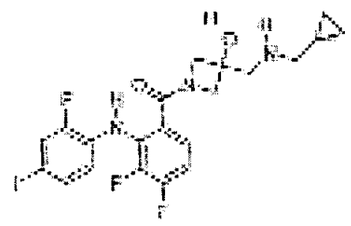
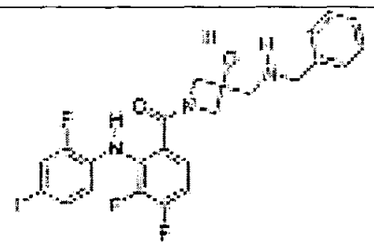
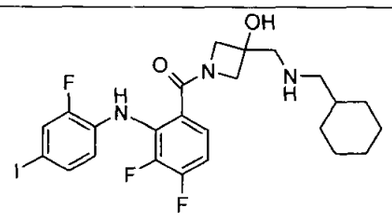
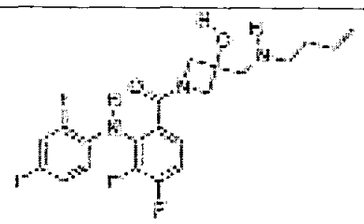
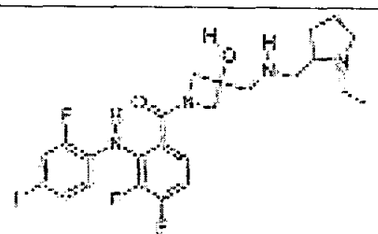
82.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidina-3-carboxamida
83.		6-{[3-(aminometil)-3-(metiloxi)azetidin-1-il]carbonil}-2,3-difluoro-*N*-(2-fluoro-4-yodofenil)anilina
84.		*N*-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}acetamida
85.		2,3-difluoro-*N*-(2-fluoro-4-yodofenil)-6-[(3-{[(1-metiletil)amino]metil}azetidin-1-il)carbonil]anilina

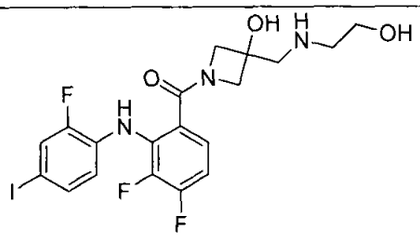
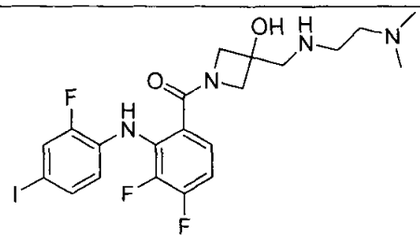
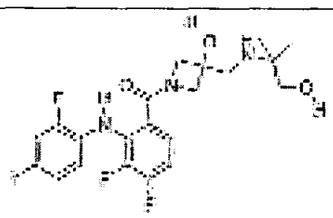
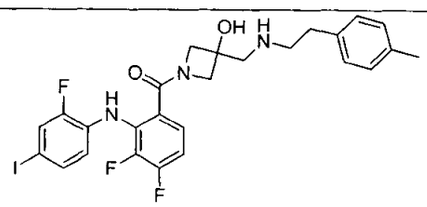
86.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(etilamino)metil]azetidin-3-ol
87.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{2-[(1-metiletil)amino]etil}azetidin-3-ol
88.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(2-hidroxi-1,1-dimetiletil)azetidin-3-ol
89.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{1,1-dimetil-2-[(1-metiletil)amino]etil}azetidin-3-ol

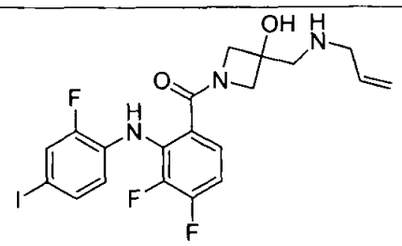
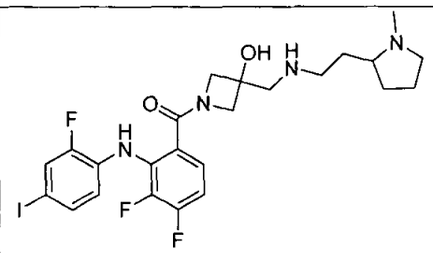
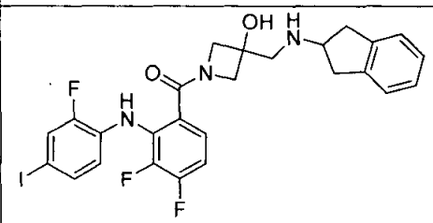
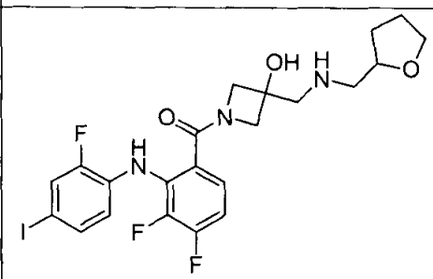
90.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1-metiletil)amino]metil}azetidin-3-amina
91.		3-[(ciclopropilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol
92.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2,2,2-trifluoroetil)amino]metil}azetidin-3-ol
93.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1*H*-imidazol-1-ilmetil)azetidin-3-ol

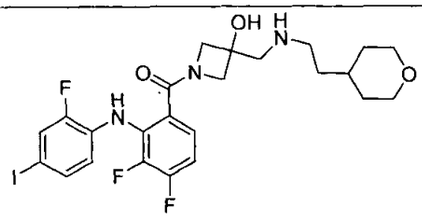
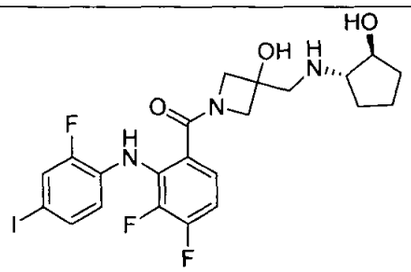
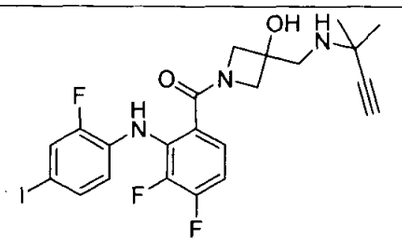
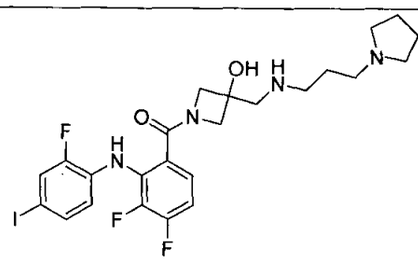
94.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1,1-dimetiletil)amino]metil}azetidin-3-ol
95.		3-[(ciclopentilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol
96.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxi-*N*-prop-2-en-1-ilazetidina-3-carboxamida
97.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-(2,3-dihidroxipropil)-3-hidroxiazetidina-3-carboxamida

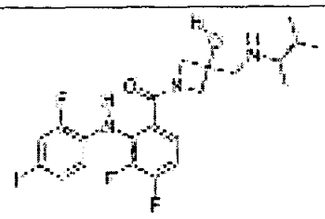
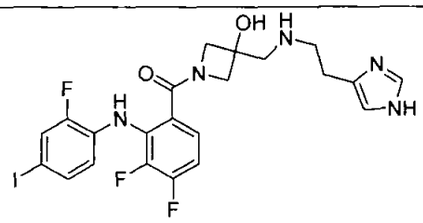
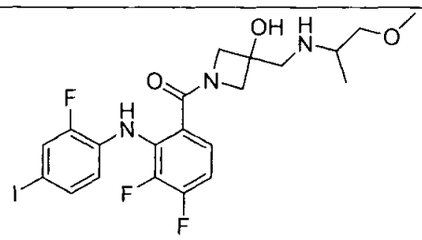
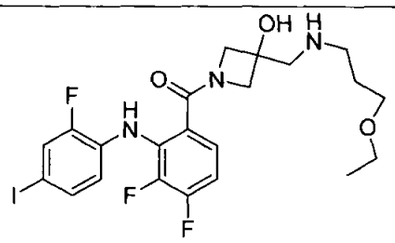
98.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1*H*-1,2,3-triazol-1-ilmetil)azetidin-3-ol
99.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2,2-dimetilpropil)amino]metil}azetidin-3-ol
100.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(propilamino)metil]azetidin-3-ol
101.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-metilpropil)amino]metil}azetidin-3-ol

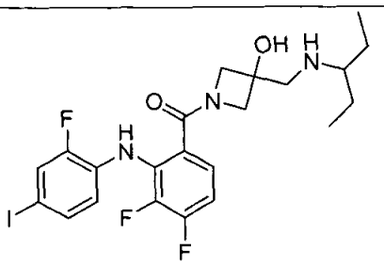
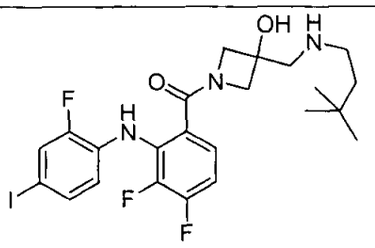
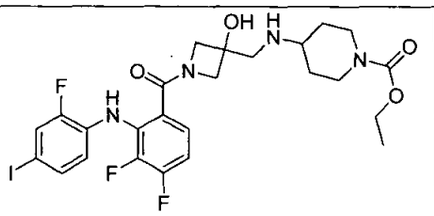
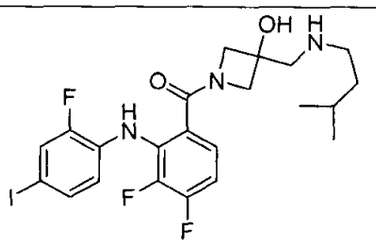
102.		3-{[(ciclopropilmetil)amino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol
103.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(fenilmetil)amino]metil}azetidin-3-ol
104.		3-{[(ciclohexilmetil)amino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol
105.		3-[(butilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol
106.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(1-

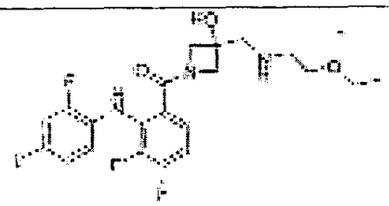
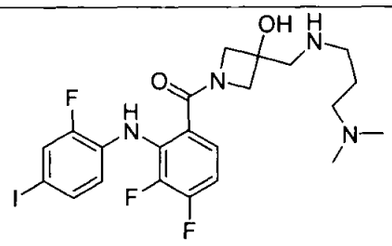
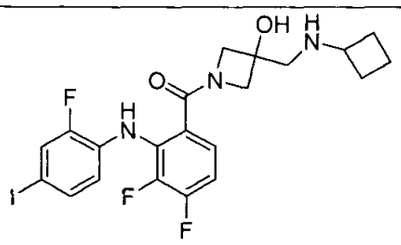
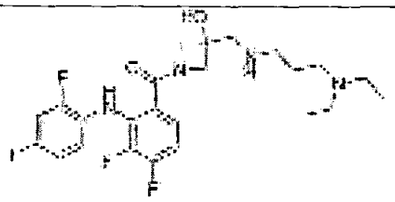
		etilpirrolidin-2-il)metil] amino}metil)azetidin-3-ol
107.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-{[(2-hidroxietil)amino]metil} azetidin-3-ol
108.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-({[2-(dimetilamino)etil]amino} metil)azetidin-3-ol
109.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-{[(2-hidroxi-1,1-dimetiletil)amino]metil} azetidin-3-ol
110.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-({[2-(4-metilfenil)etil]amino}metil)

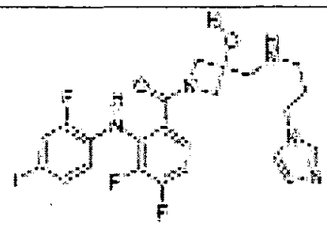
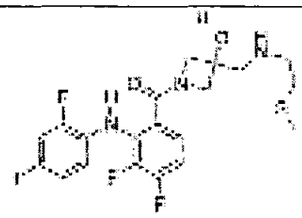
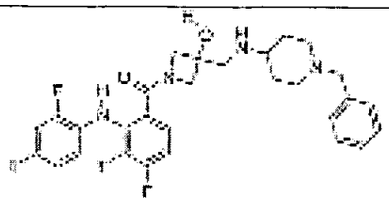
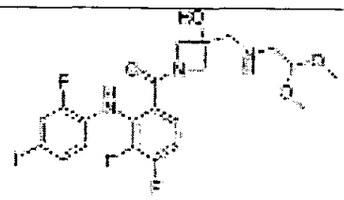
		azetidin-3-ol
111.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(prop-2-en-1-ilamino)metil]azetidin-3-ol
112.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(1-metilpirrolidin-2-il)etil]amino}metil)azetidin-3-ol
113.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(2,3-dihidro-1*H*-inden-2-ilamino)metil]azetidin-3-ol
114.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(tetrahidrofuran-2-ilmetil)amino]metil}azetidin-3-ol

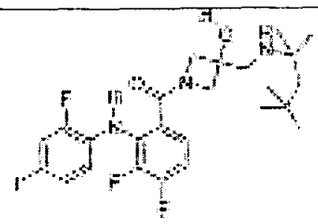
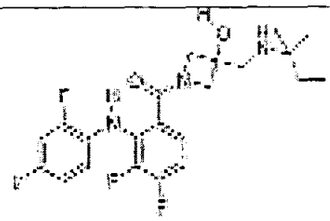
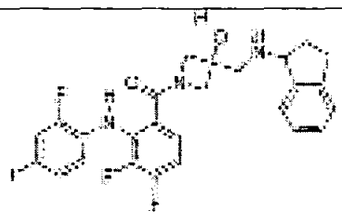
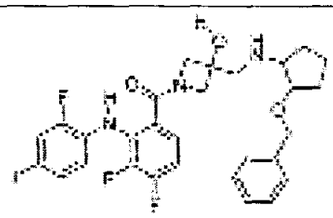
115.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-({[2-(tetrahidro-2*H*-pyran-4-il)etil]amino}metil)azetidin-3-ol
116.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-({[(1*S*,2*S*)-2-hidroxiciclopentil]amino} metil)azetidin-3-ol
117.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-{[(1,1-dimetilprop-2-in-1-il)amino]metil}azetidin-3-ol
118.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-{[(3-pirrolidin-1-ilpropil)amino]metil} azetidin-3-ol

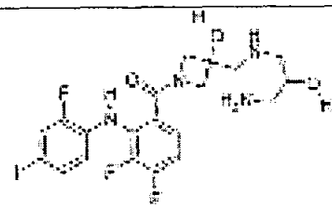
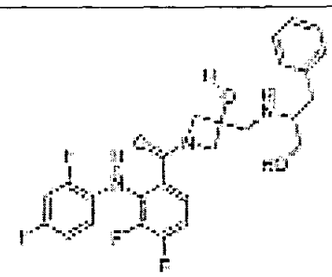
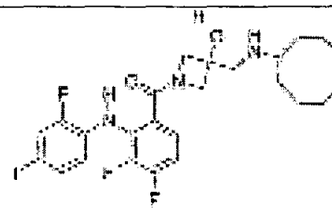
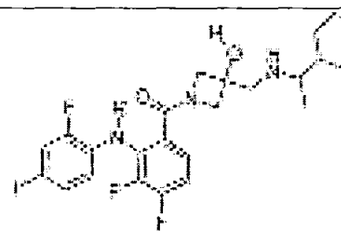
119.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-{[(1,2-dimetilpropil)amino]metil} azetidin-3-ol
120.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-({[2-(1*H*-imidazol-4-il)etil]amino}metil)azetidin-3-ol
121.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-({[1-metil-2-(metiloxi)etil]amino}metil) azetidin-3-ol
122.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-({[3-(etiloxi)propil]amino}metil) azetidin-3-ol

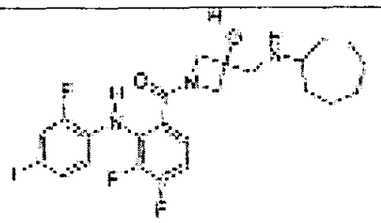
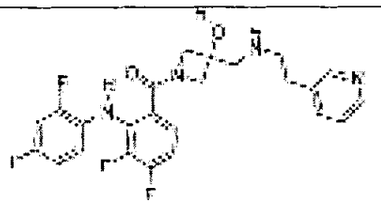
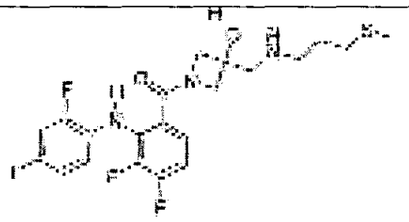
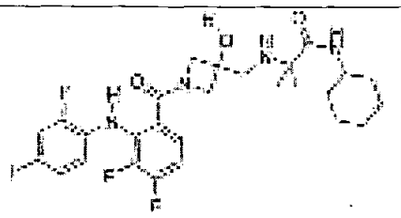
123.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1-etilpropil)amino]metil}azetidin-3-ol
124.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(3,3-dimetilbutil)amino]metil}azetidin-3-ol
125.		etil 4-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]ienil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)piperidina-1-carboxilato
126.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(3-metilbutil)amino]metil}azetidin-3-ol

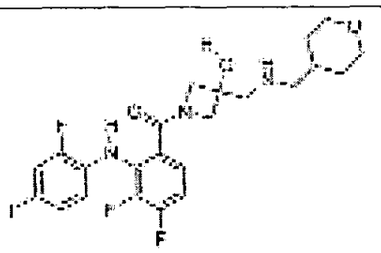
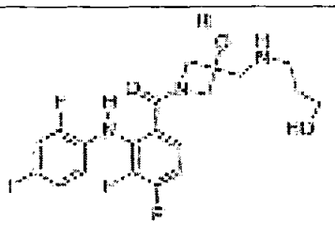
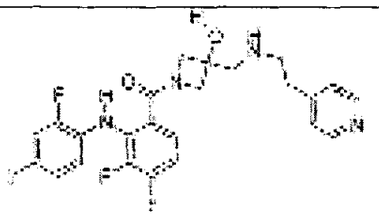
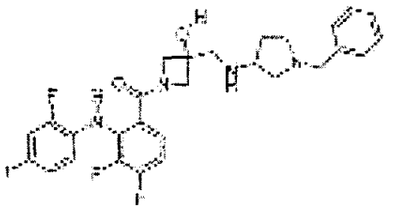
127.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(etiloxi)etil]amino}metil)azetidin-3-ol
128.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[3-(dimetilamino)propil]amino}metil)azetidin-3-ol
129.		3-[(ciclobutilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenyl)amino]fenil}carbonil)azetidin-3-ol
130.		3-({[3-(dietilamino)propil]amino}metil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol

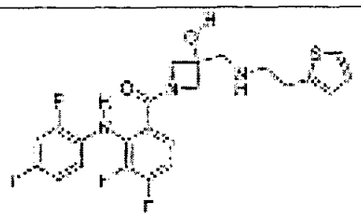
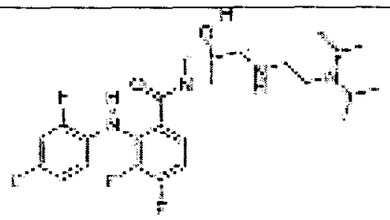
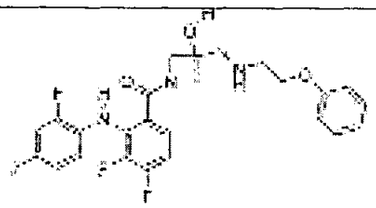
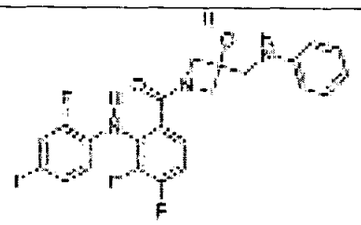
131.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[3-(1*H*-imidazol-1-il)propil]amino}metil)azetidin-3-ol
132.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(metiltio)etil]amino}metil)azetidin-3-ol
133.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[1-(fenilmetil)piperidin-4-il]amino}metil)azetidin-3-ol
134.		3-({[2,2-bis(metiloxi)etil]amino} metil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol

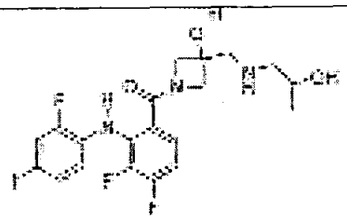
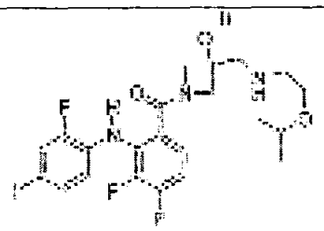
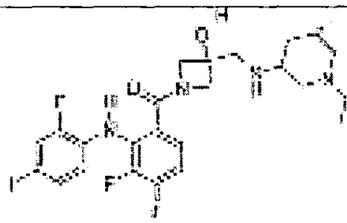
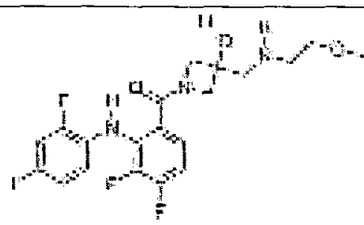
135.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-{[(1,1,3,3-tetrametilbutil)amino]metil} azetidin-3-ol
136.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-{[(1,1-dimetilpropil)amino]metil} azetidin-3-ol
137.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-[(2,3-dihidro-1*H*-inden-1-ilamino)metil]azetidin-3-ol
138.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-[({2-[(fenilmetil)oxi]ciclopentil} amino)metil]azetidin-3-ol

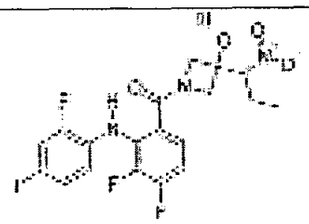
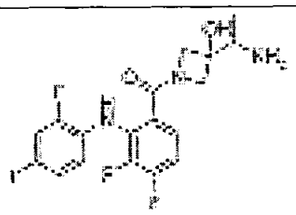
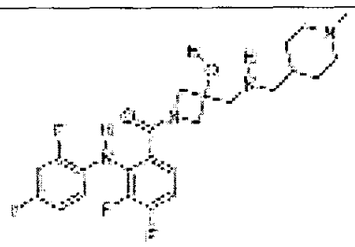
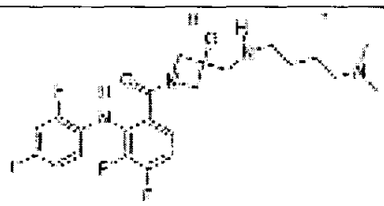
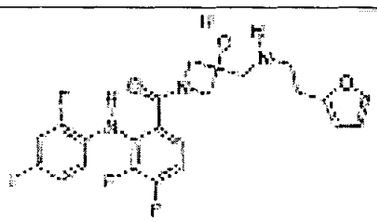
139.		3-{[(3-amino-2-hidroxipropil)amino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol
140.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-hidroxi-1-(fenilmetil)etil]amino}metil)azetidin-3-ol
141.		3-[(ciclooctilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol
142.		3-{[(1-ciclohexiletil)amino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol

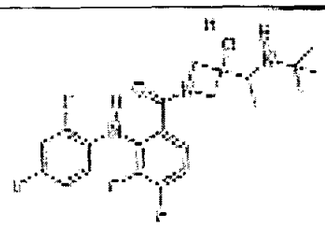
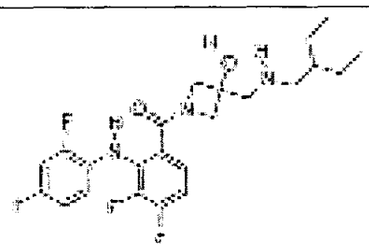
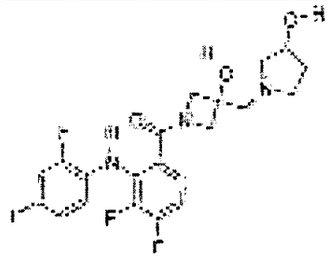
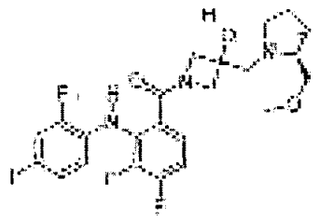
143.		3-[(cicloheptilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol
144.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-piridin-3-iletil)amino]metil}azetidin-3-ol
145.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[3-(metiltio)propil]amino}metil)azetidin-3-ol
146.		*N*-ciclohexil-N^2-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}-2-metilalaninamide

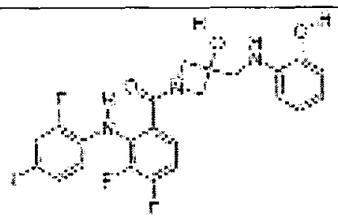
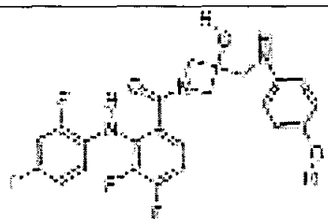
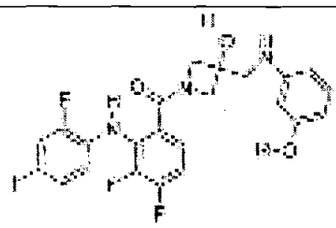
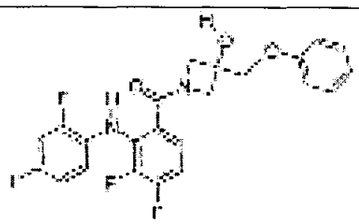
147.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(tetrahidro-2*H*-piran-4-ilmetil)amino]metil}azetidin-3-ol
148.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(3-hidroxipropil)amino]metil}azetidin-3-ol
149.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-piridin-4-iletil)amino]metil}azetidin-3-ol
150.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[1-(fenilmetil)pirrolidin-3-il]amino}metil)azetidin-3-ol

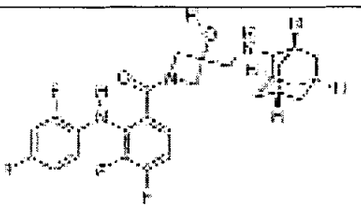
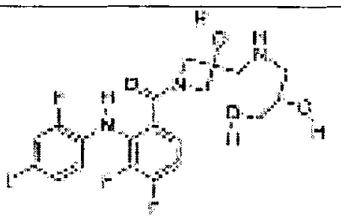
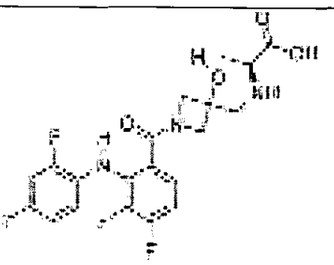
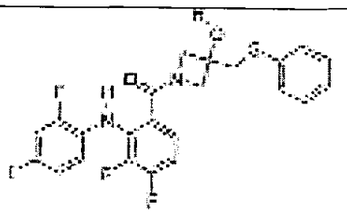
151.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-({[2-(2-tienil)etil]amino}metil) azetidin-3-ol
152.		3-[({2-[bis(1-metiletil)amino]etil}amino) metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil} carbonil)azetidin-3-ol
153.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-({[2-(feniloxi)etil]amino}metil) azetidin-3-ol
154.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-[(fenilamino)metil]azetidin-3-ol

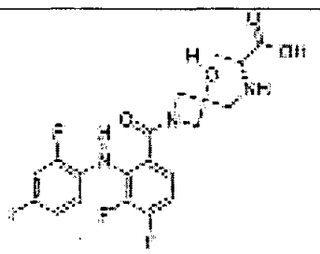
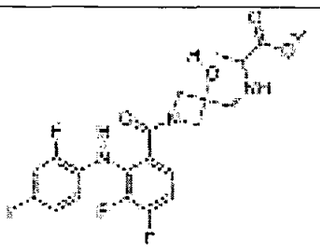
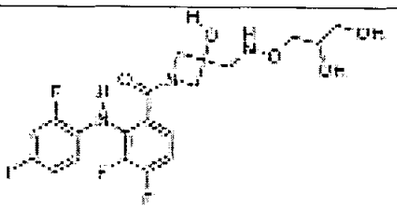
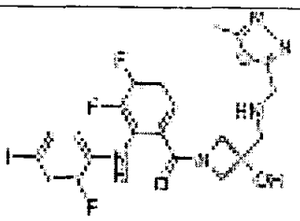
155.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-{[(2-hidroxipropil)amino]metil} azetidin-3-ol
156.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-[({2-[(1-metiletil)oxi]etil}amino) metil]azetidin-3-ol
157.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-{[(1-etilpiperidin-3-il)amino]metil}azetidin-3-ol
158.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-({[2-(metiloxi)etil]amino}metil) azetidin-3-ol

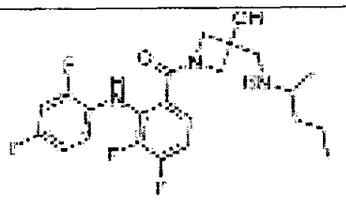
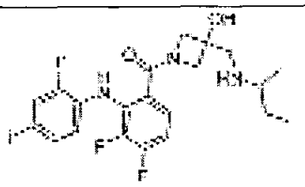
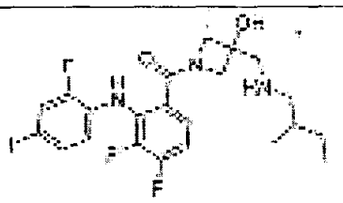
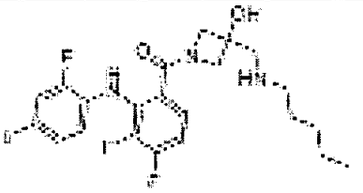
159.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1-nitropropil)azetidin-3-ol
160.		3-(1-aminoetiyl)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol
161.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(1-metilpiperidin-4-il)metil]amino}metil)azetidin-3-ol
162.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[4-(dimetilamino)butil]amino}metil)azetidin-3-ol
163.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-furan-2-iletil)amino]metil}

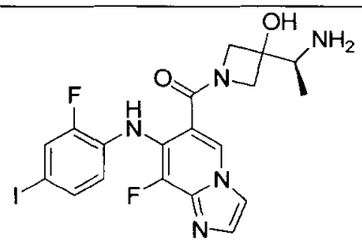
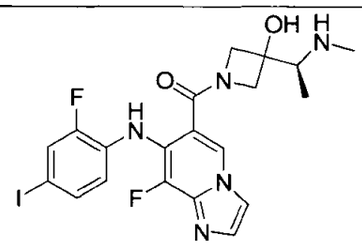
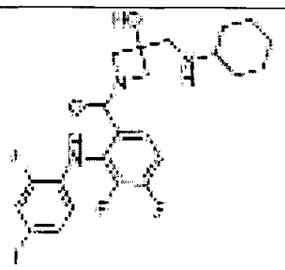
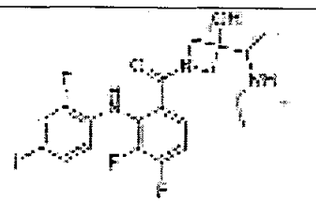
		azetidin-3-ol
164.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{1-[(1,1-dimetiletil)amino]etil}azetidin-3-ol
165.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-etilbutil)amino]metil}azetidin-3-ol
166.		1-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodogenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}pirrolidin-3-ol
167.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({(2*S*)-2-[(metiloxi)metil]pirrolidin-1-il}metil)azetidin-3-ol

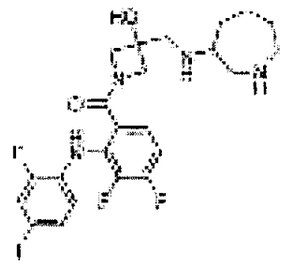
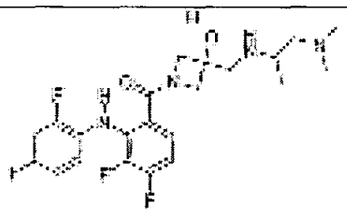
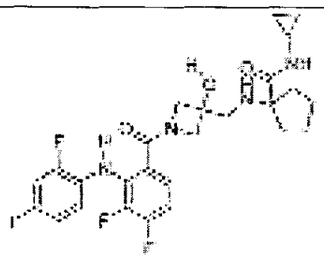
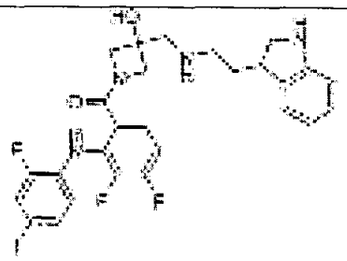
168.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-{[(2-hidroxifenil)amino]metil} azetidin-3-ol
169.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-{[(4-hidroxifenil)amino]metil} azetidin-3-ol
170.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-{[(3-hidroxifenil)amino]metil} azetidin-3-ol
171.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-[(feniloxi)metil]azetidin-3-ol

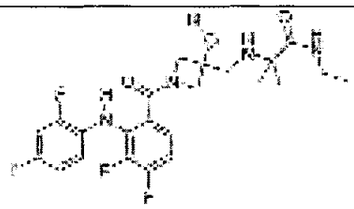
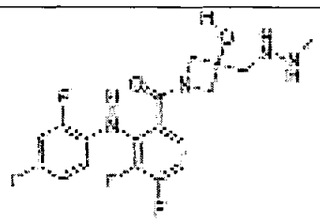
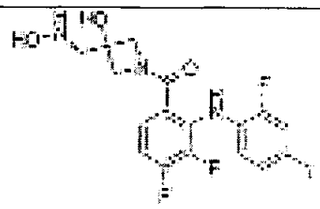
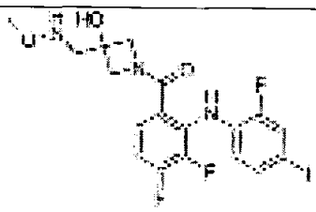
172.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1r,3r,5*R*,7*R*)-triciclo[3.3.1.1^{3,7}]dec-2-ilamino]metil}azetidin-3-ol
173.		3-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)propano-1,2-diol
174.		*N*-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}-L-alanina
175.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(feniltio)metil]azetidin-3-ol

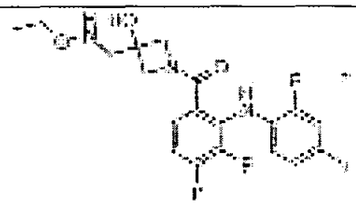
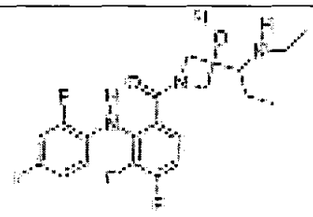
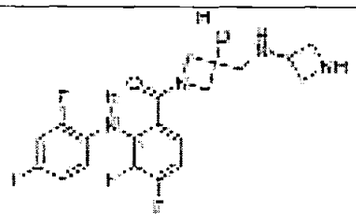
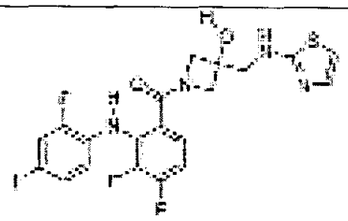
176.		*N*-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}-D-alanina
177.		metil *N*-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}alaninato
178.		3-[({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)oxi]propano-1,2-diol
179.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(5-metil-1,3,4-oxadiazol-2-il)metil]amino}metil)azetidin-3-ol

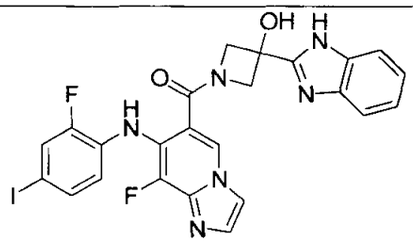
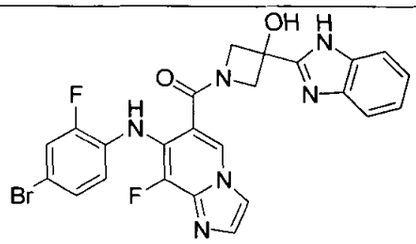
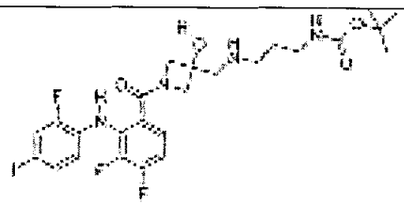
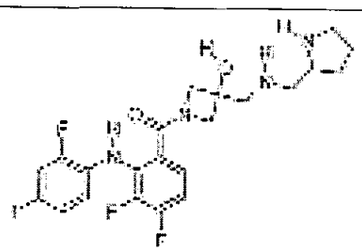
180.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1-metilbuti)amino]metil}azetidin-3-ol
181.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1-metilpropil)amino]metil}azetidin-3-ol
182.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-metilbutil)amino]metil}azetidin-3-ol
183.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(pentilamino)metil]azetidin-3-ol

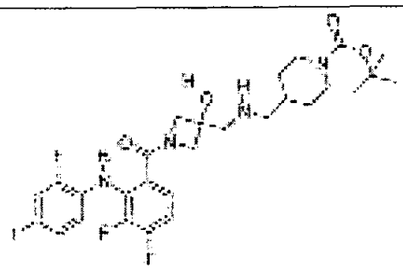
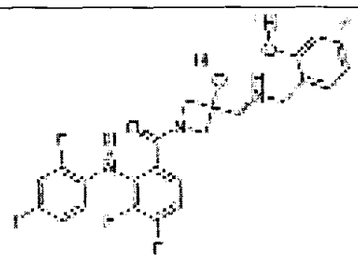
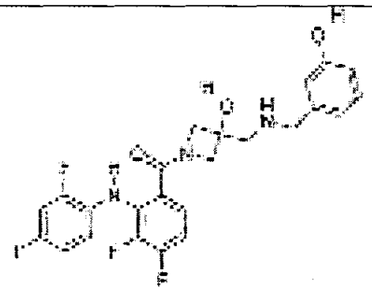
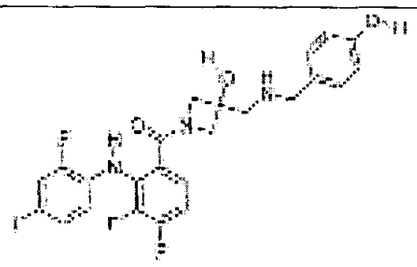
184.		3-[(1*S*)-1-aminoetil]-1-({8-fluoro-7-[(2-fluoro-4-yodofenil)amino]imidazo[1,2-*a*]piridin-6-il}carbonil)azetidin-3-ol
185.		1-({8-fluoro-7-[(2-fluoro-4-yodofenil)amino]imidazo[1,2-*a*]piridin-6-il}carbonil)-3-[(1*S*)-1-(metilamino)etil]azetidin-3-ol
186.		3-[(ciclohexilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol
187.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[1-(etilamino)etil]azetidin-3-ol

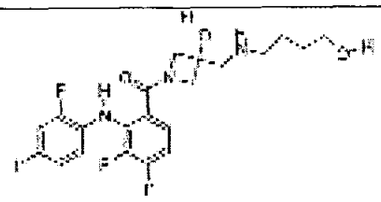
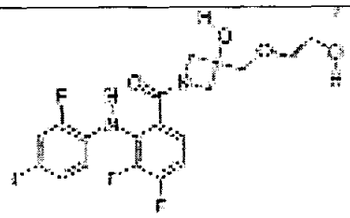
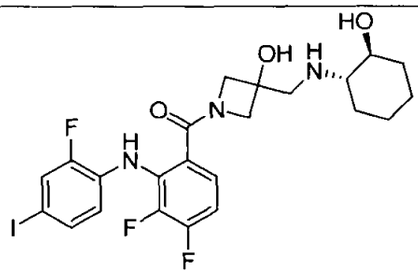
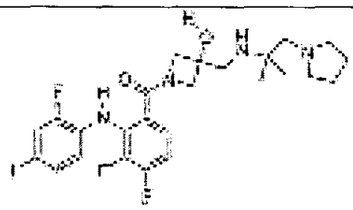
188.		3-[(azepan-3-ilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol
189.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(dimetilamino)-1-metiletil]amino}metil)azetidin-3-ol
190.		*N*-ciclopropil-1-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)ciclopentanocarboxamida
191.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(2,3-dihidro-1*H*-indol-3-il)etil]amino}metil)azetidin-3-ol

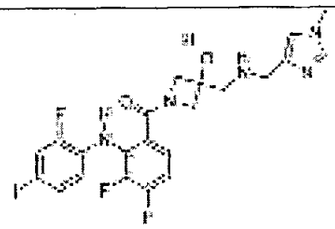
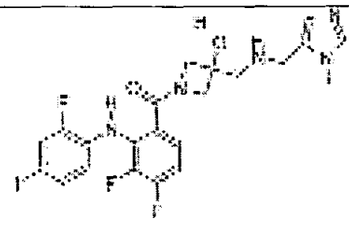
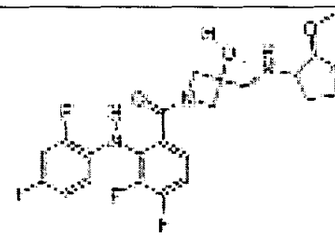
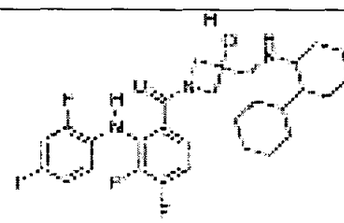
192.		N^2-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}-*N*-etil-2-metilalaninamida
193.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(2-metilhidrazino)metil]azetidin-3-ol
194.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(hidroxiamino)metil]azetidin-3-ol
195.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(metiloxi)amino]metil}azetidin-3-ol

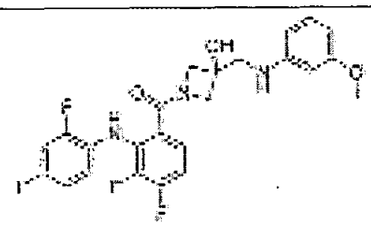
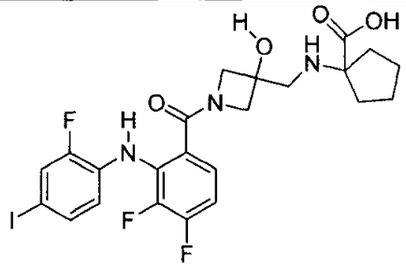
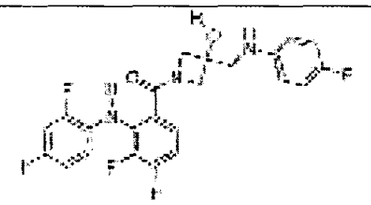
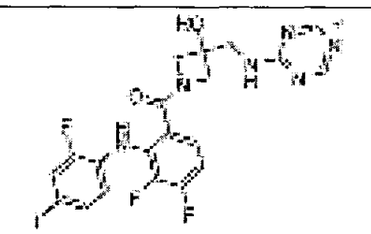
196.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-{[(etiloxi)amino]metil} azetidin-3-ol
197.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-[1-(etilamino)propil]azetidin-3-ol
198.		3-[(azetidin-3-ilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil} carbonil)azetidin-3-ol
199.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-[(1,3-tiazol-2-ilamino) metil]azetidin-3-ol

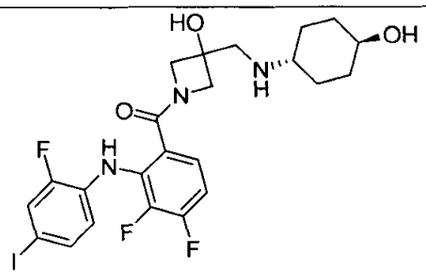
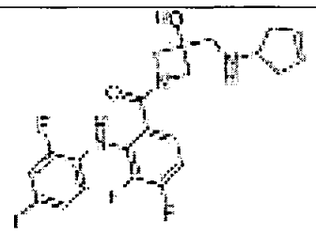
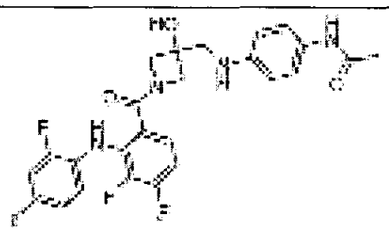
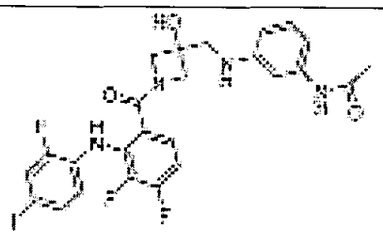
200.		3-(1*H*-benzimidazol-2-il)-1-({8-fluoro-7-[(2-fluoro-4-yodofenil)amino]imidazo[1,2-*a*]piridin-6-il}carbonil)azetidin-3-ol
201.		3-(1*H*-benzimidazol-2-il)-1-({7-[(4-bromo-2-fluorofenil)amino]-8-fluoroimidazo[1,2-*a*]piridin-6-il}carbonil)azetidin-3-ol
202.		1,1-dimetiletil [3-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)propil]carbamato
203.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(pirrolidin-2-ilmetil)amino]metil}azetidin-3-ol

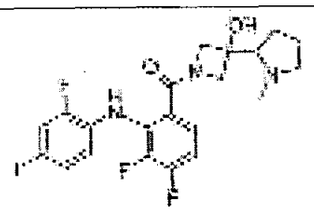
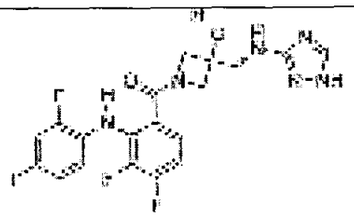
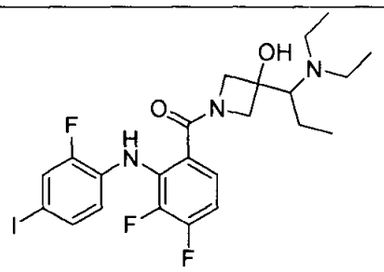
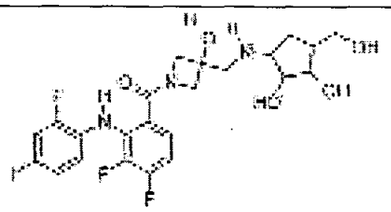
204.		1,1-dimetiletil 4-[({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)metil]piperidina-1-carboxilato
205.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(2-hidroxifenil)metil]amino}metil)azetidin-3-ol
206.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(3-hidroxifenil)metil]amino}metil)azetidin-3-ol
207.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(4-hidroxifenil)metil]amino}metil)azetidin-3-ol

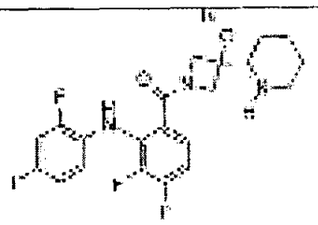
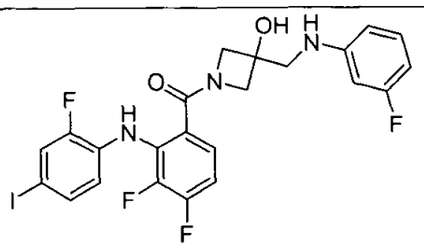
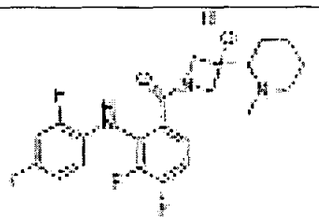
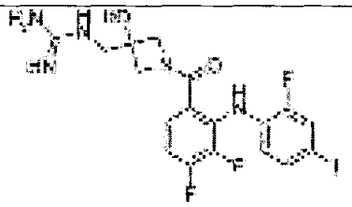
208.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(4-hidroxibutil)amino]metil}azetidin-3-ol
209.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-hidroxietil)oxi]metil}azetidin-3-ol
210.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(1*S*,2*S*)-2-hidroxiciclohexil]amino}metil)azetidin-3-ol
211.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1,1-dimetil-2-pirrolidin-1-iletil)amino]metil}azetidin-3-ol

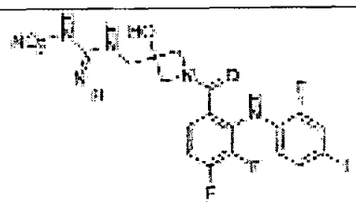
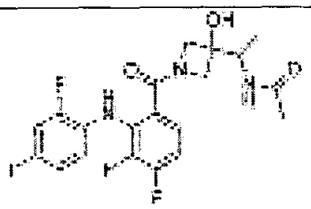
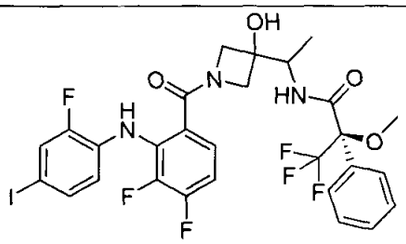
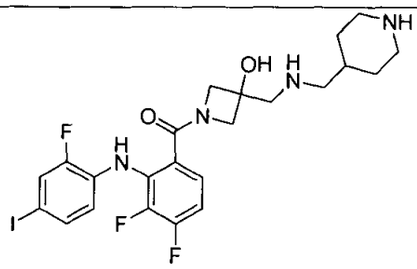
212.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(1-metil-1*H*-imidazol-4-il)metil]amino}metil)azetidin-3-ol
213.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(1-metil-1*H*-imidazol-5-il)metil]amino}metil)azetidin-3-ol
214.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(2*S*)-2-(metiloxi)ciclopentil]amino}metil)azetidin-3-ol
215.		3-{[1,1'-bi(ciclohexil)-2-ilamino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol

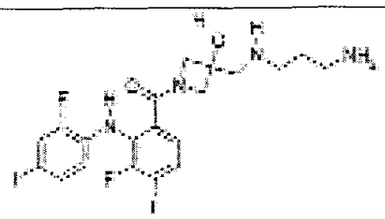
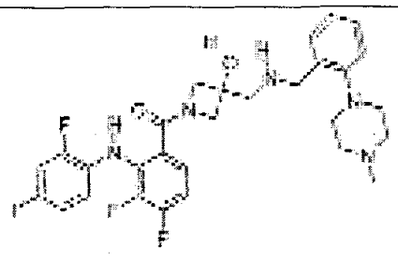
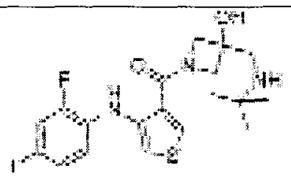
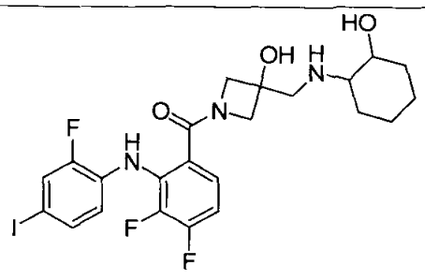
216.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-({[3-(metiloxi)fenil]amino}metil) azetidin-3-ol
217.		Ácido 1-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil} carbonil)-3-hidroxiazetidin-3-il]metil}amino) ciclopentanocarboxílico
218.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-{[(4-fluorofenil)amino]metil} azetidin-3-ol
219.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-[(1,3,5-triazin-2-ilamino)metil]azetidin-3-ol

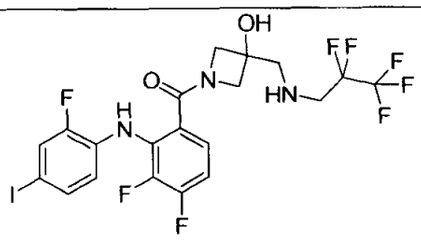
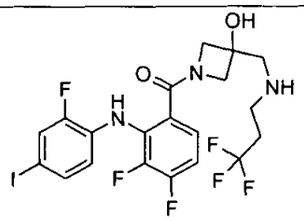
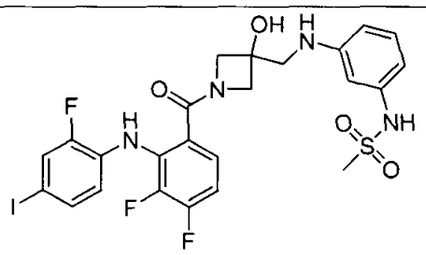
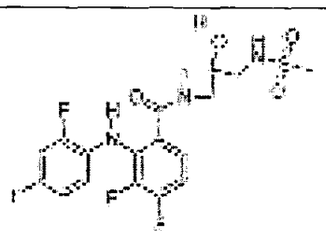
220.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-{[(*trans*-4-hidroxiciclohexil)amino] metil}azetidin-3-ol
221.		3-[(ciclopent-3-en-1-ilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil} carbonil)azetidin-3-ol
222.		*N*-[4-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-iidroxiazetidin-3-il]metil}amino)fenil] acetamida
223.		*N*-[3-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino) fenil]acetamida

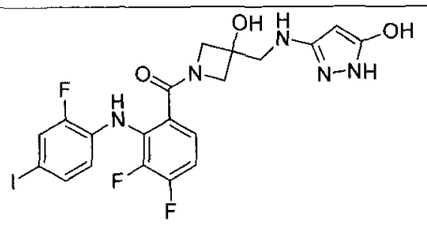
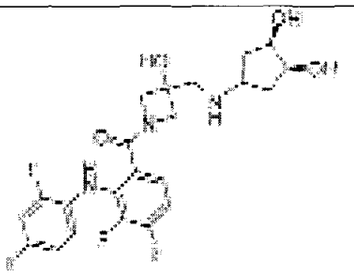
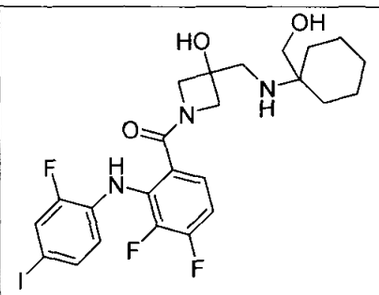
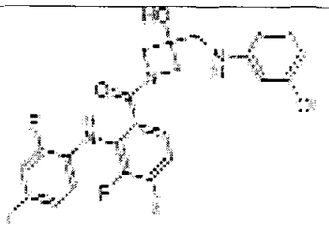
224.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1-metilpirrolidin-2-il)azetidin-3-ol
225.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(1*H*-1,2,4-triazol-3-ilamino)metil]azetidin-3-ol
226.		3-[1-(dietilamino)propil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol
227.		3-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)-5-(hidroximetil)ciclopentano-1,2-diol

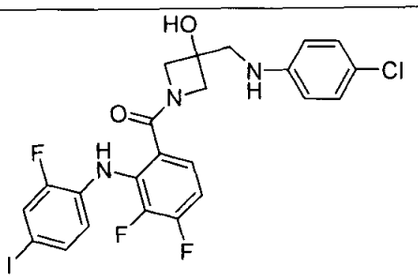
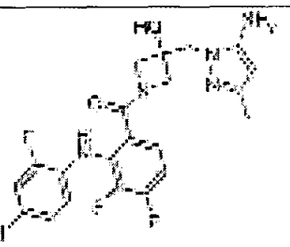
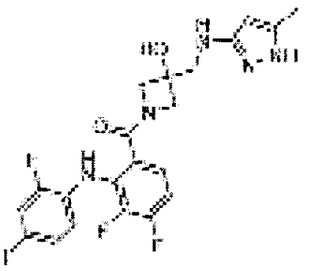
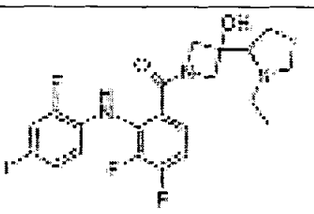
228.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-piperidin-2-ilazetidin-3-ol
229.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(3-fluorofenil)amino]metil}azetidin-3-ol
230.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1-metilpiperidin-2-il)azetidin-3-ol
231.		1-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}guanidina

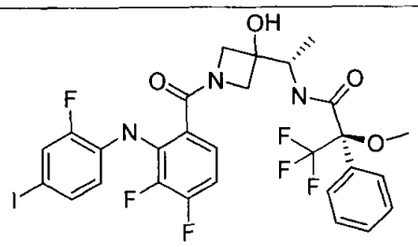
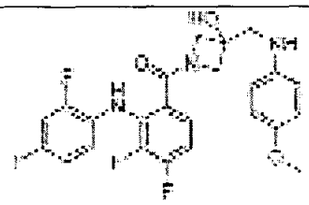
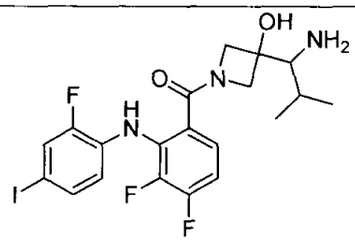
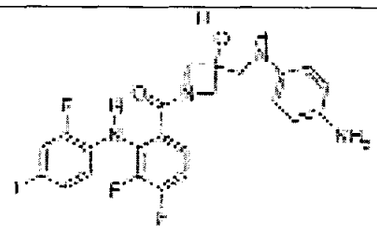
232.		1-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}-3-nitroguanidina
233.		*N*-{1-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]etil}acetamida
234.		(2*R*)-*N*-{1-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]etil}-3,3,3-trifluoro-2-(metiloxi)-2-fenilpropanamida
235.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(piperidin-4-ilmetil)amino]metil}azetidin-3-ol

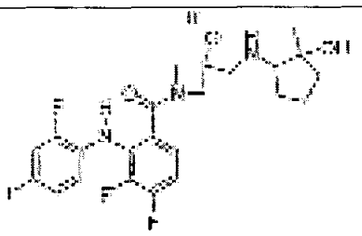
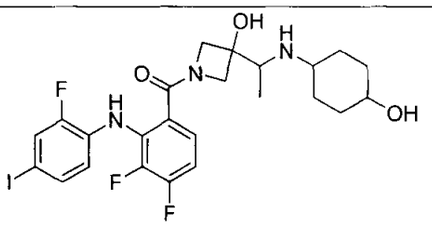
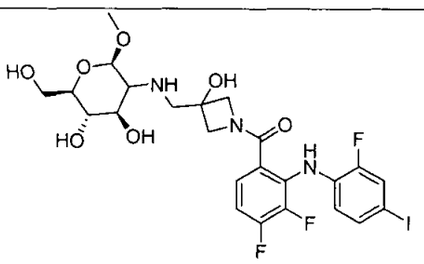
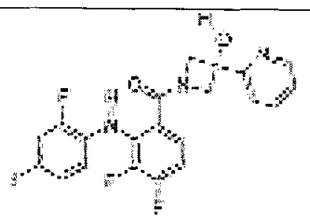
236.		3-{[(3-aminopropil)amino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol
237.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[({[2-(4-metilpiperazin-1-il)fenil]metil}amino)metil]azetidin-3-ol
238.		3-{[(1,1-dimetiletil)amino]metil}-1-({4-[(2-fluoro-4-yodofenil)amino]-3-tienil}carbonil)azetidin-3-ol
239.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-hidroxiciclohexil)amino]metil}azetidin-3-ol

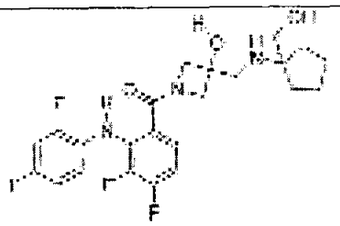
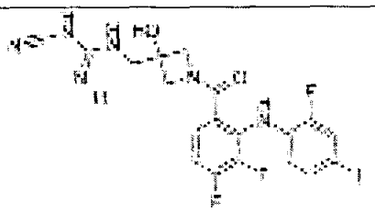
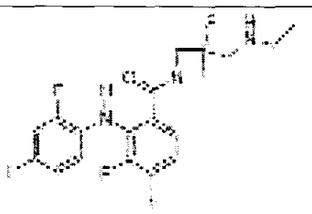
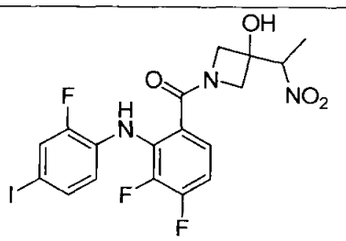
240.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2,2,3,3,3-pentafluoropropil)amino]metil}azetidin-3-ol
241.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(3,3,3-trifluoropropil)amino]metil}azetidin-3-ol
242.		*N*-[3-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)fenil]metanosulfonamida
243.		*N*-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}metanosulfonamida

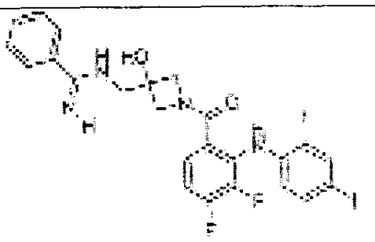
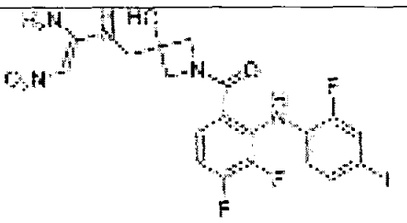
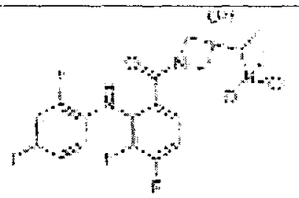
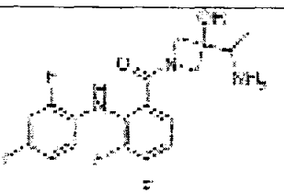
244.		3-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)-1*H*-pirazol-5-ol
245.		(1*R*,2*S*)-4-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)ciclopentano-1,2-diol
246.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[1-(hidroximetil)ciclohexil]amino}metil)azetidin-3-ol
247.		3-{[(3-clorofenil)amino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-

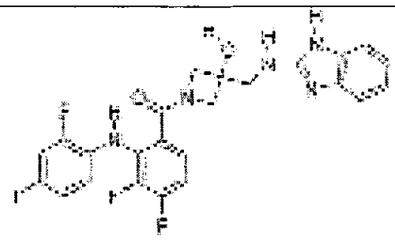
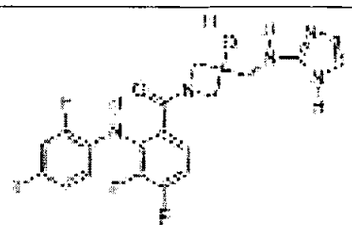
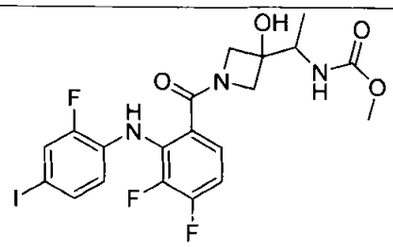
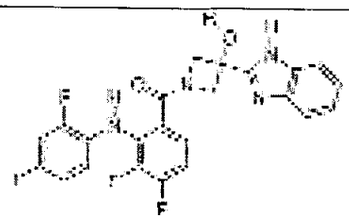
		yodofenil)amino]fenil} carbonil)azetidin-3-ol
248.		3-{[(4-clorofenil)amino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil} carbonil)azetidin-3-ol
249.		3-[(5-amino-3-metil-1*H*-pirazol-1-il)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil} carbonil)azetidin-3-ol
250.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil) amino]fenil} carbonil)-3-{[(5-metil-1*H*-pirazol-3-il)amino] metil}azetidin-3-ol
251.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil) amino]fenil} carbonil)-3-(1-etilpirrolidin-2-

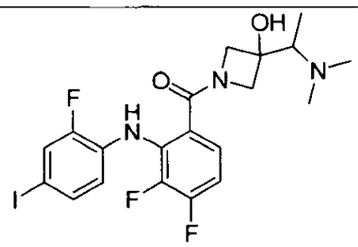
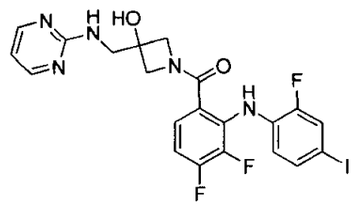
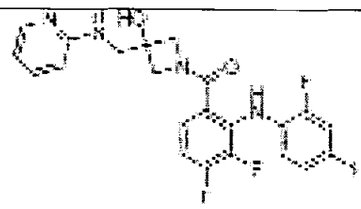
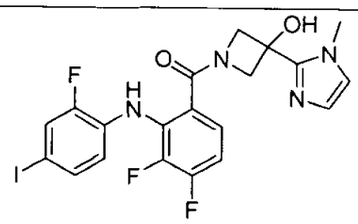
		il)azetidin-3-ol
252.		(2*R*)-*N*-{(1*S*)-1-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil) amino]fenil}carbonil)-3-hidroxiazetidin-3-il]etil}-3,3,3-trifluoro-2-(metiloxi)-2-fenilpropanamida
253.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil) amino]fenil}carbonil)-3-({[4-(metiloxi)fenil] amino}metil)azetidin-3-ol
254.		3-(1-amino-2-metilpropil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil) azetidin-3-ol
255.		3-{[(4-aminofenil)amino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}

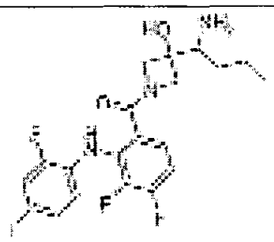
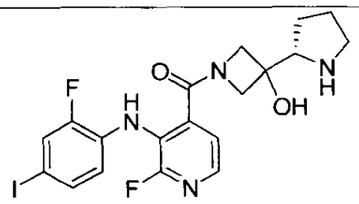
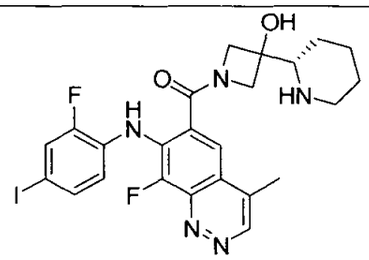
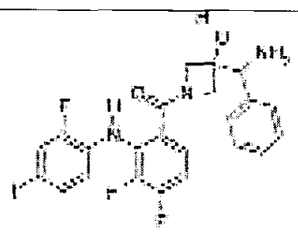
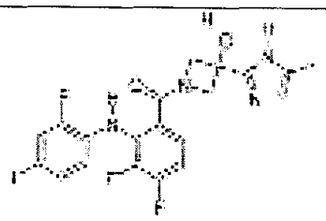
		carbonil)azetidin-3-ol
256.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil) amino]fenil}carbonil)-3-{[(2-hidroxi-2-metilciclopentil)amino]metil}azetidin-3-ol
257.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil) amino]fenil}carbonil)-3-{1-[(4-hidroxiciclohexil) amino]etil}azetidin-3-ol
258.		metil (2xi)-2-desoxi-2-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil) amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)-beta-D-arabino-hexopiranosida
259.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-piridin-2-ilazetidin-3-ol

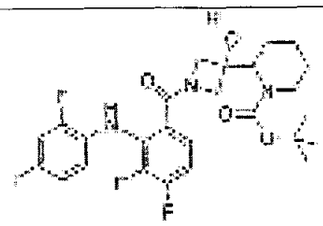
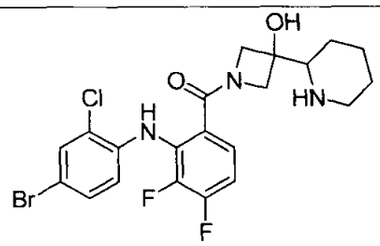
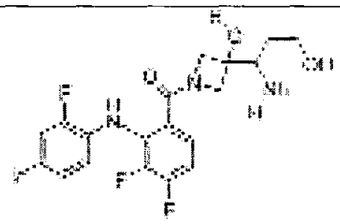
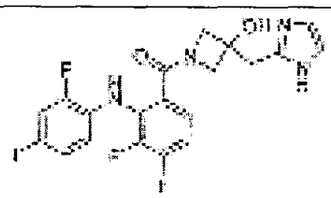
260.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[1-(hidroximetil)ciclopentil]amino}metil)azetidin-3-ol
261.		1-ciano-3-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}guanidina
262.		6-({3-[(etilamino)metil]-3-fluoroazetidin-1-il}carbonil)-2,3-difluoro-*N*-(2-fluoro-4-yodofenil)anilina
263.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1-nitroetil)azetidin-3-ol

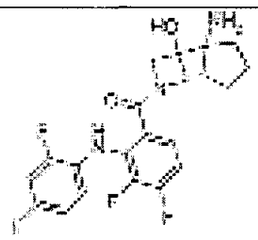
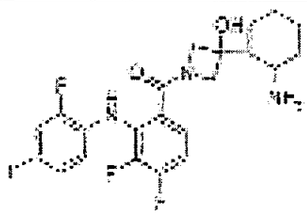
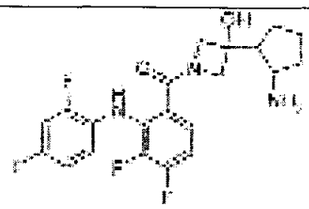
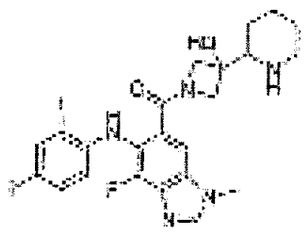
272.		*N*-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}bencencarboximidamida
273.		3-({[(E)-1-amino-2-nitroetenil]amino}metil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol
274.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1-metil-1-nitroetil)azetidin-3-ol
275.		3-(1-amino-1-metiletil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol

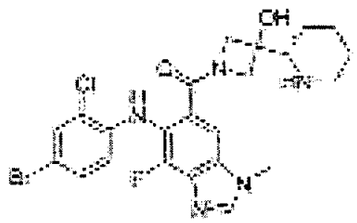
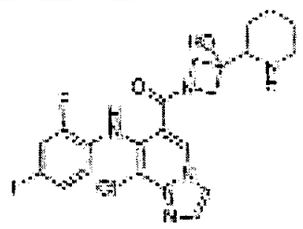
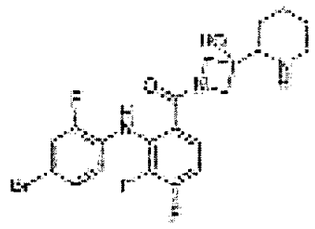
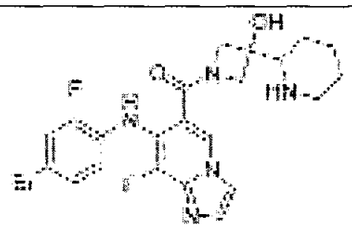
276.		3-[(1*H*-benzimidazol-2-ilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol
277.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(1*H*-imidazol-2-ilamino)metil]azetidin-3-ol
278.		metil {1-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]etil}carbamato
279.		3-(1*H*-bencimidazol-2-il)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol

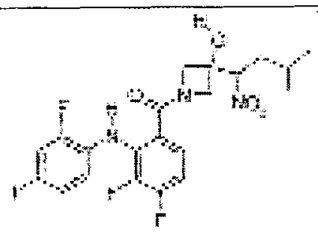
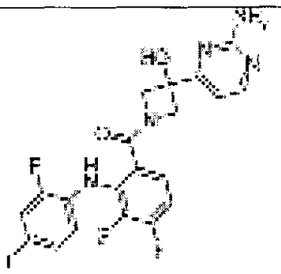
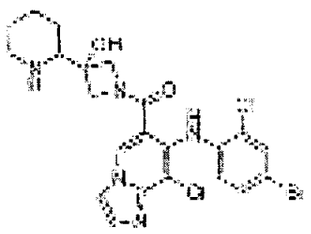
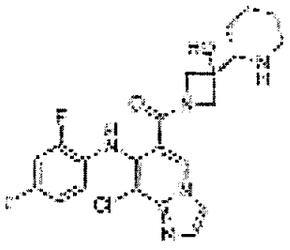
280.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-[1-(dimetilamino)etil] azetidin-3-ol
281.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-[(pirimidin-2-ilamino) metil]azetidin-3-ol
282.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-[(piridin-2-ilamino) metil]azetidin-3-ol
283.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-(1-metil-1*H*-imidazol-2-il)azetidin-3-ol

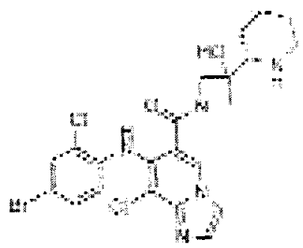
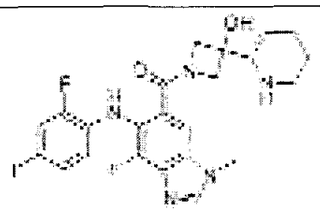
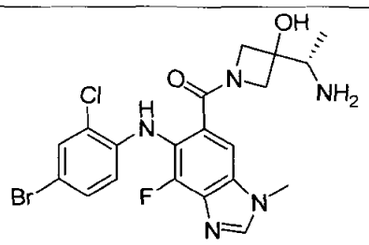
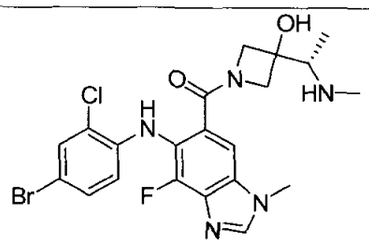
284.		3-(1-aminobutil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol
285.		1-({2-fluoro-3-[(2-fluoro-4-yodofenil)amino]piridin-4-il}carbonil)-3-[(2*S*)-pirrolidin-2-il]azetidin-3-ol
286.		1-({8-fluoro-7-[(2-fluoro-4-yodofenil)amino] -4-metilcinolin-6-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol
287.		3-[amino(fenil)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol
288.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(5-metil-1*H*-imidazol-2-

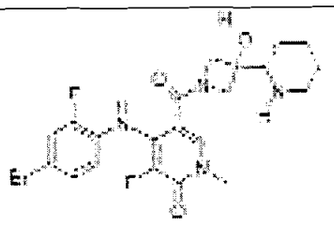
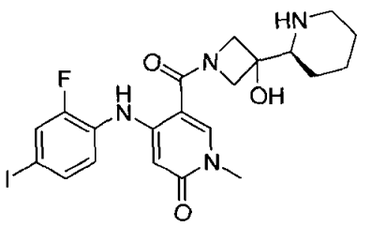
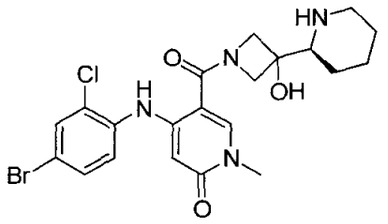
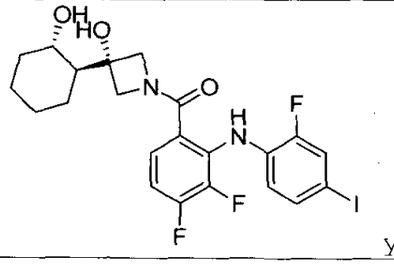
		il)azetidin-3-ol
289.		1,1-dimetiletil (2*S*)-2-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-hidroxiazetidin-3-il] piperidina-1-carboxilato
290.		1-({2-[(4-bromo-2-clorofenil)amino]-3,4-difluorofenil}carbonil)-3-piperidin-2-ilazetidin-3-ol
291.		3-(1-amino-3-hidroxipropil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil} carbonil)azetidin-3-ol
292.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-(1*H*-imidazol-2-ilmetil) azetidin-3-ol

293.		3-(1-aminociclopentil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol
294.		3-(2-aminociclohexil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol
295.		3-(2-aminociclopentil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-azetidin-3-ol
296.		1-({4-fluoro-5-[(2-fluoro-4-yodofenil)amino]-1-metil-1*H*-bencimidazol-6-il}carbonil)-3-piperidin-2-ilazetidin-3-ol

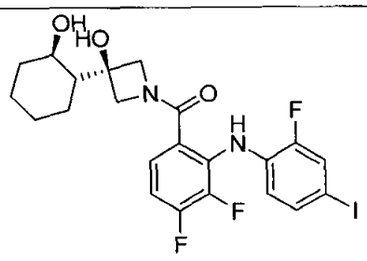
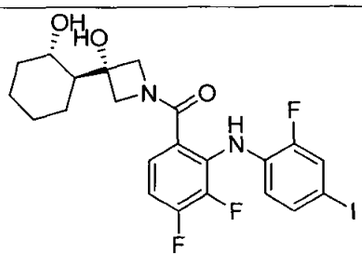
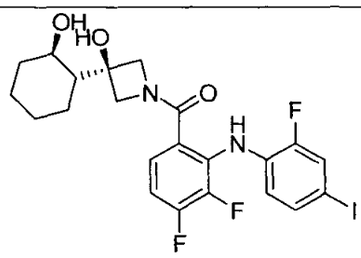
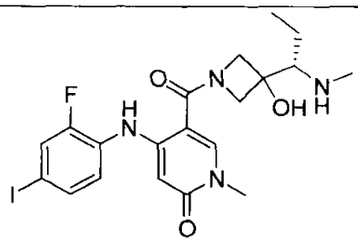
297.		1-({5-[(4-bromo-2-clorofenil)amino]-4-fluoro-1-metil-1*H*-bencimidazol-6-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol
298.		1-({8-cloro-7-[(2-fluoro-4-yodofenil)amino]imidazo[1,2-a]piridin-6-il}carbonil)-3-piperidin-2-ilazetidin-3-ol
299.		1-({2-[(4-bromo-2-fluorofenil)amino]-3,4-difluorofenil}carbonil)-3-piperidin-2-ilazetidin-3-ol
300.		1-({7-[(4-bromo-2-fluorofenil)amino]-8-fluoroimidazo[1,2-*a*]piridin-6-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol

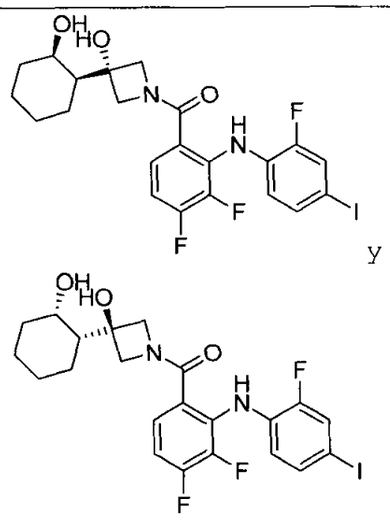
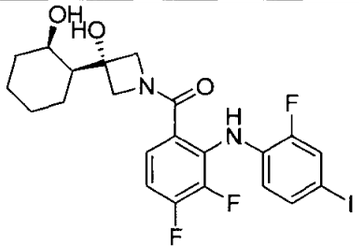
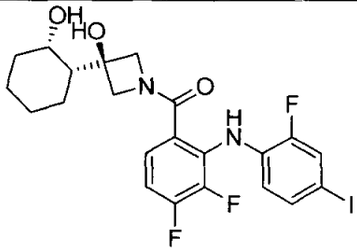
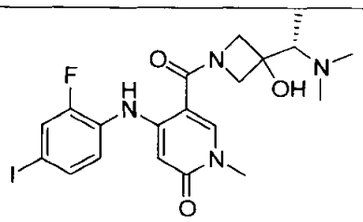
301.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-(3-metil-1-nitrobutil) azetidin-3-ol
302.		3-(2-aminopirimidin-4-il)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)azetidin-3-ol
303.		1-({7-[(4-bromo-2-clorofenil)amino]-8-cloroimidazo[1,2-a] piridin-6-il}carbonil)-3-piperidin-2-ilazetidin-3-ol
304.		1-({8-cloro-7-[(2-fluoro-4-yodofenil)amino] imidazo[1,2-a]piridin-6-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol

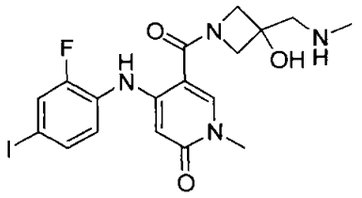
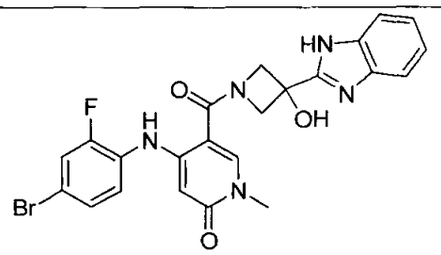
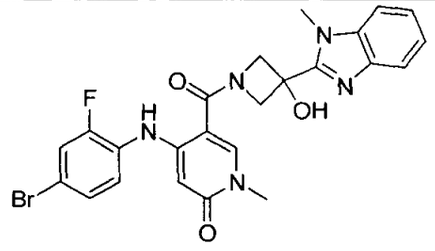
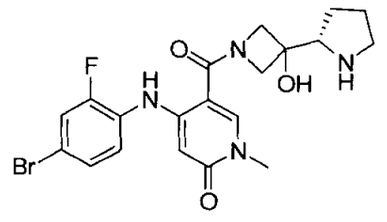
305.		1-({7-[(4-bromo-2-clorofenil)amino]-8-cloroimidazo[1,2-a]piridin-6-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol
306.		1-({4-fluoro-5-[(2-fluoro-4-yodofenil)amino]-1-metil-1*H*-bencimidazol-6-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol
307.		3-[(1*S*)-1-aminoetil]-1-({5-[(4-bromo-2-clorofenil)amino]-4-fluoro-1-metil-1*H*-bencimidazol-6-il}carbonil)azetidin-3-ol
308.		1-({5-[(4-bromo-2-clorofenil)amino]-4-fluoro-1-metil-1*H*-bencimidazol-6-il}carbonil)-3-[(1*S*)-1-(metilamino)etil]azetidin-

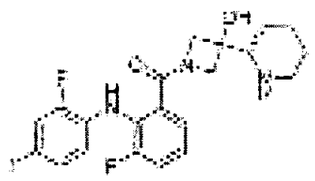
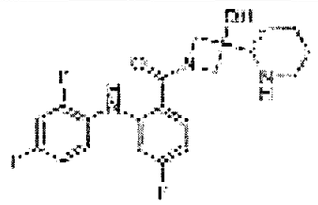
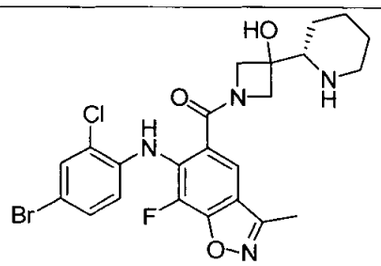
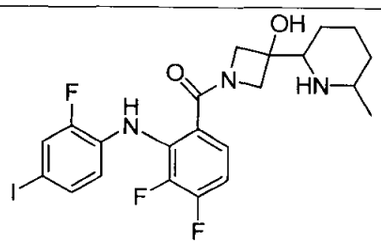
		3-ol
309.		4-[(4-bromo-2-fluorofenil)amino]-3-fluoro-5-({3-hidroxi-3-[(2*S*)-piperidin-2-il]azetidin-1-il}carbonil)piridin-2(1*H*)-ona
310.		4-[(2-fluoro-4-yodofenil)amino]-5-({3-hidroxi-3-[(2*S*)-piperidin-2-il]azetidin-1-il}carbonil)-1-metilpiridin-2(1*H*)-ona
311.		4-[(2-fluoro-4-yodofenil)amino]-5-({3-hidroxi-3-[(2*S*)-piperidin-2-il]azetidin-1-il}carbonil)-1-metilpiridin-2(1*H*)-ona
312.		(±)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(*trans*)-2-

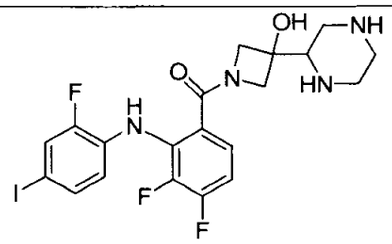
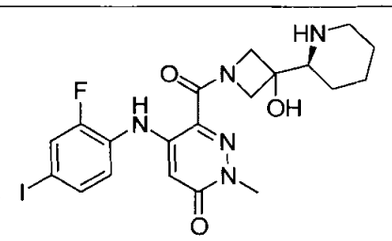
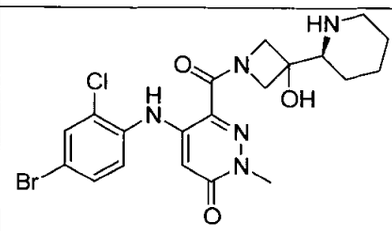
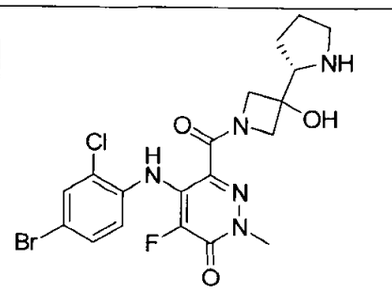
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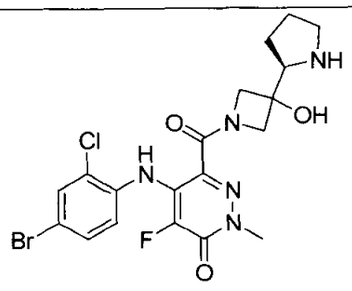
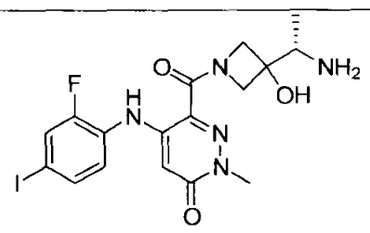
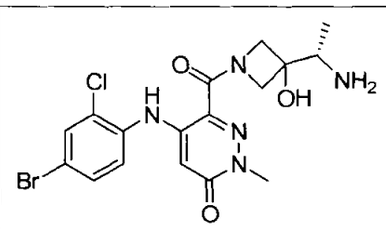
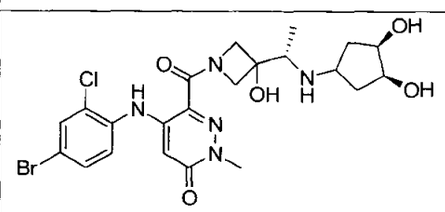
		hidroxiciclohexil] azetidin-3-ol
313.		(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)(3-hidroxi-3-((1*S*,2*S*)-2-hidroxiciclohexil) azetidin-1-il)metanona
314.		(3,4-difluoro-2-(2-fluoro-4-yodofenilamino) fenil)(3-hidroxi-3-((1*S*,2*R*)-2-hidroxiciclohexil) azetidin-1-il)metanona
315.		4-[(2-fluoro-4-yodofenil)amino]-5-({3-hidroxi-3-[(1*S*)-1-(metilamino)propil] azetidin-1-il}carbonil)-1-metilpiridin-2(1*H*)-ona

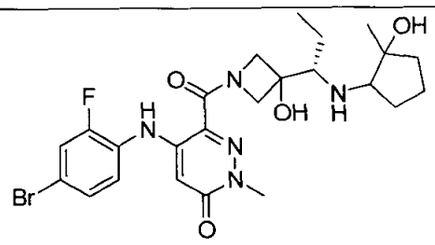
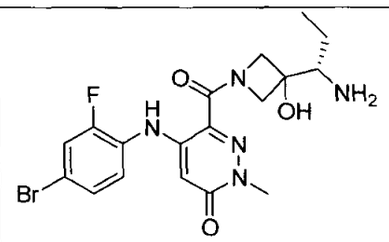
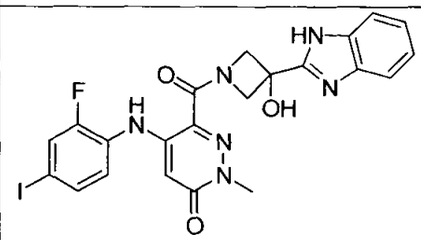
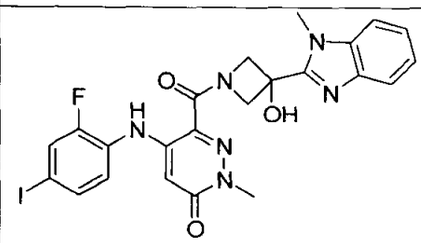
316.	 y	(±)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(*cis*)-2-hidroxiciclohexil]azetidin-3-ol
317.		(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)(3-hidroxi-3-((1*S*,2*R*)-2-hidroxiciclohexil)azetidin-1-il)metanona
318.		(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)(3-hidroxi-3-((1*R*,2*S*)-2-hidroxiciclohexil)azetidin-1-il)metanona
319.		5-({3-[(1*S*)-1-(dimetilamino)etil]-3-hidroxiazetidin-1-il}carbonil)-4-[(2-fluoro-4-yodofenil)amino]-1-metilpiridin-2(1*H*)-ona

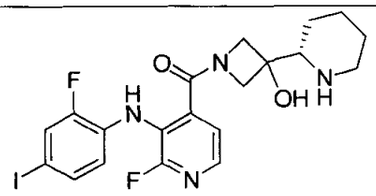
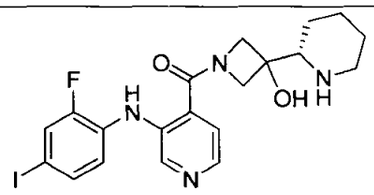
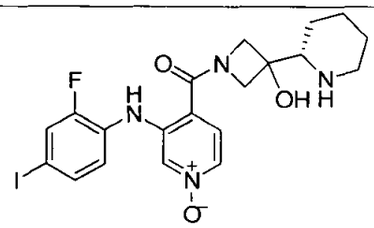
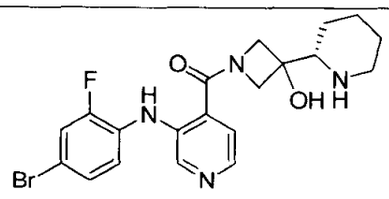
320.		4-[(2-fluoro-4-yodofenil)amino]-5-({3-hidroxi-3-[(metilamino)metil]azetidin-1-il}carbonil)-1-metilpiridin-2(1*H*)-ona
321.		5-{[3-(1*H*-bencimidazol-2-il)-3-hidroxiazetidin-1-il]carbonil}-4-[(4-bromo-2-fluorofenil)amino]-1-metilpiridin-2(1*H*)-ona
322.		4-[(4-bromo-2-fluorofenil)amino]-5-{[3-hidroxi-3-(1-metil-1*H*-bencimidazol-2-il)azetidin-1-il]carbonil}-1-metilpiridin-2(1*H*)-ona
323.		4-[(4-bromo-2-fluorofenil)amino]-5-({3-hidroxi-3-[(2*S*)-pirrolidin-2-il]azetidin-1-il}carbonil)-1-metilpiridin-2(1*H*)-ona

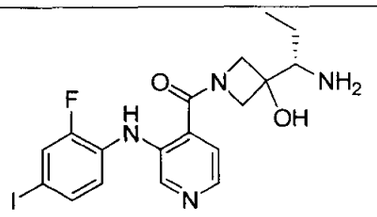
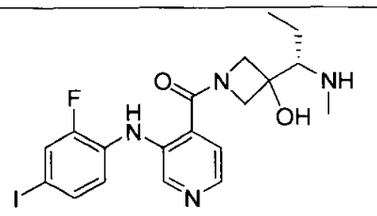
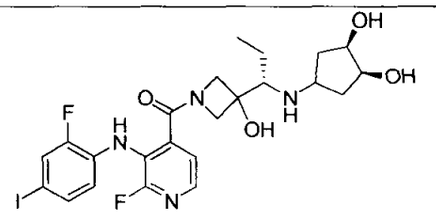
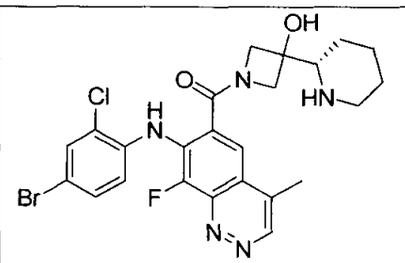
324.		1-({3-fluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol
325.		1-({4-fluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol
326.		1-({6-[(4-bromo-2-clorofenil)amino]-7-fluoro-3-metil-1,2-bencisoxazol-5-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol
327.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] fenil}carbonil)-3-(6-metilpiperidin-2-il)azetidin-3-ol

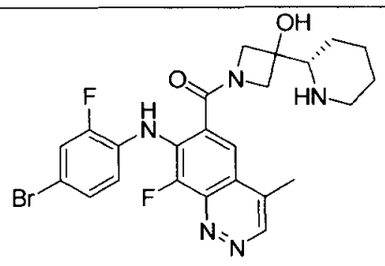
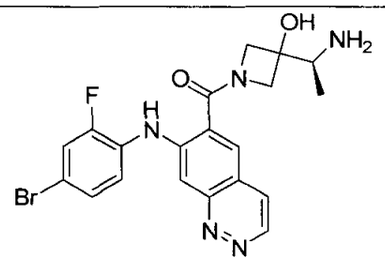
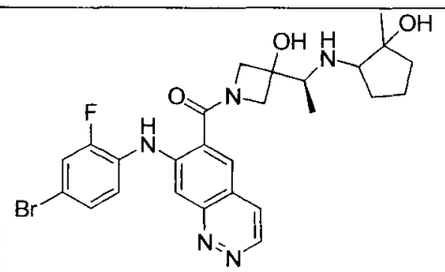
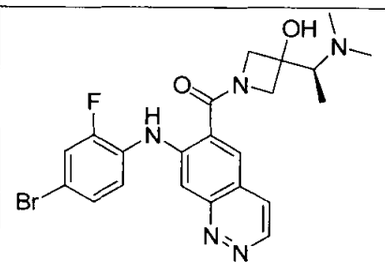
328.		1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-piperazin-2-ilazetidin-3-ol
329.		5-[(2-fluoro-4-yodofenil)amino]-6-({3-hidroxi-3-[(2*S*)-piperidin-2-il]azetidin-1-il}carbonil)-2-metilpiridazin-3(2*H*)-ona
330.		5-[(4-bromo-2-clorofenil)amino]-6-({3-hidroxi-3-[(2*S*)-piperidin-2-il]azetidin-1-il}carbonil)-2-metilpiridazin-3(2*H*)-ona
331.		5-[(4-bromo-2-clorofenil)amino]-4-fluoro-6-({3-hidroxi-3-[(2*S*)-pirrolidin-2-il]azetidin-1-il}carbonil)-2-metilpiridazin-3(2*H*)-ona

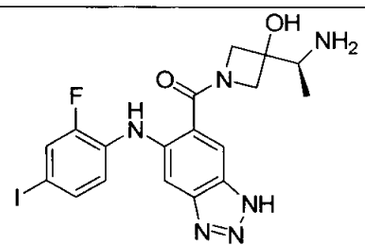
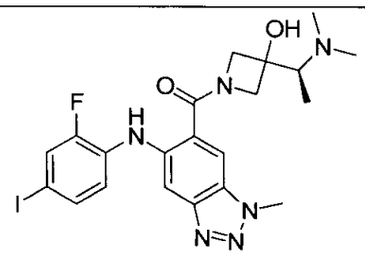
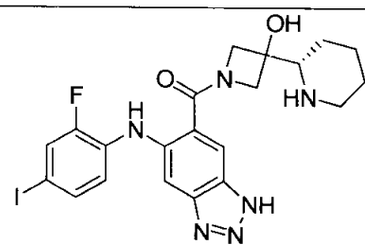
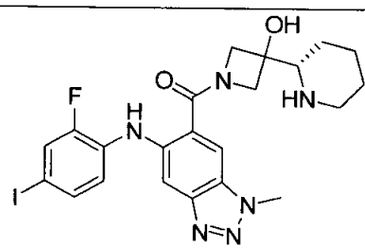
332.		5-[(4-bromo-2-clorofenil)amino]-4-fluoro-6-({3-hidroxi-3-[(2*R*)-pirrolidin-2-il]azetidin-1-il}carbonil)-2-metilpiridazin-3(2*H*)-ona
333.		6-({3-[(1*S*)-1-aminoetil]-3-hidroxiazetidin-1-il}carbonil)-5-[(2-fluoro-4-yodofenil)amino]-2-metilpiridazin-3(2*H*)-ona
334.		6-({3-[(1*S*)-1-aminoetil]-3-hidroxiazetidin-1-il}carbonil)-5-[(4-bromo-2-clorofenil)amino]-2-metilpiridazin-3(2*H*)-ona
335.		5-[(4-bromo-2-clorofenil)amino]-6-{[3-((1*S*)-1-{[(3*R*,4*S*)-3,4-dihidroxiciclopentil]amino}etil)-3-hidroxiazetidin-1-il]carbonil}-2-

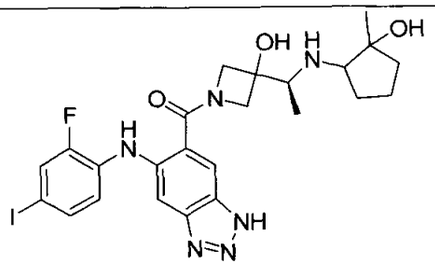
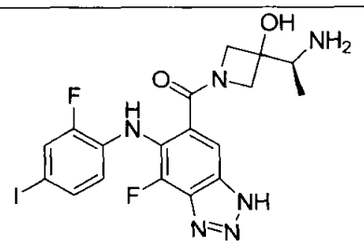
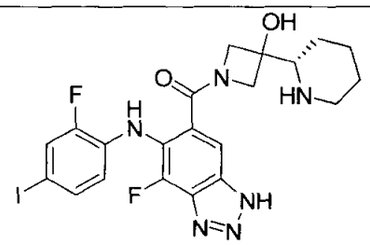
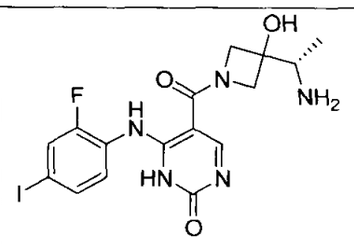
		metilpiridazin-3(2*H*)-ona
336.		5-[(4-bromo-2-fluorofenil)amino]-6-[(3-hidroxi-3-{(1*S*)-1-[(2-hidroxi-2-metilciclopentil)amino]propil}azetidin-1-il)carbonil]-2-metilpiridazin-3(2*H*)-ona
337.		6-({3-[(1*S*)-1-aminopropil]-3-hidroxiazetidin-1-il}carbonil)-5-[(4-bromo-2-fluorofenil)amino]-2-metilpiridazin-3(2*H*)-ona
338.		6-{[3-(1*H*-benzimidazol-2-il)-3-hidroxiazetidin-1-il]carbonil}-5-[(2-fluoro-4-yodofenil)amino]-2-metilpiridazin-3(2*H*)-ona
339.		5-[(2-fluoro-4-yodofenil)amino]-6-{[3-hidroxi-3-(1-metil-1*H*-bencimidazol-2-

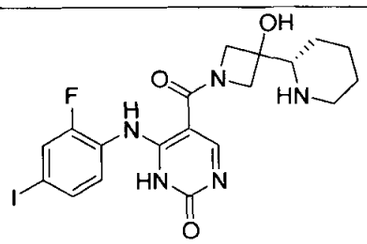
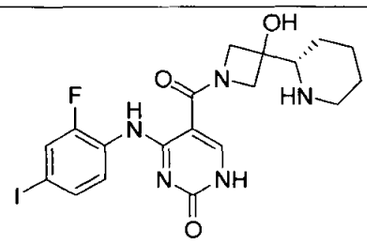
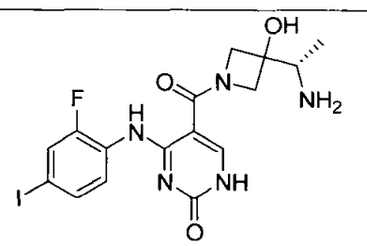
		il)azetidin-1-il]carbonil}-2-metilpiridazin-3(2*H*)-ona
340.		1-({2-fluoro-3-[(2-fluoro-4-yodofenil)amino]piridin-4-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol
341.		1-({3-[(2-fluoro-4-yodofenil)amino]piridin-4-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol
342.		1-({3-[(2-fluoro-4-yodofenil)amino]-1-oxidopiridin-4-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol
343.		1-({2-fluoro-3-[(2-fluoro-4-bromofenil)amino]piridin-4-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-

		ol
344.		3-[(1*S*)-1-aminopropil]-1-({3-[(2-fluoro-4-yodofenil)amino]piridin-4-il}carbonil)azetidin-3-ol
345.		1-({3-[(2-fluoro-4-yodofenil)amino]piridin-4-il}carbonil)-3-[(1*S*)-1-(metilamino)propil] azetidin-3-ol
346.		(1*R*,2*S*)-4-({(1*S*)-1-[1-({2-fluoro-3-[(2-fluoro-4-yodofenil)amino] piridin-4-il}carbonil)-3-hidroxiazetidin-3-il] propil}amino)ciclopentano-1,2-diol
347.		1-({7-[(4-bromo-2-clorofenil)amino]-8-fluoro-4-metilcinolin-6-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol

348.		1-({7-[(4-bromo-2-fluorofenil)amino]-8-fluoro-4-metilcinolin-6-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol
349.		3-[(1*S*)-1-aminoetil]-1-({7-[(4-bromo-2-fluorofenil)amino]cinolin-6-il}carbonil)azetidin-3-ol
350.		1-({7-[(4-bromo-2-fluorofenil)amino]cinolin-6-il}carbonil)-3-{(1*S*)-1-[(2-hidroxi-2-metilciclopentil)amino]etil}azetidin-3-ol
351.		1-({7-[(4-bromo-2-fluorofenil)amino]cinolin-6-il}carbonil)-3-[(1*S*)-1-(dimetilamino)etil]azetidin-3-ol

352.		3-[(1*S*)-1-aminoetil]-1-({5-[(2-fluoro-4-yodofenil)amino]-1*H*-1,2,3-benzotriazol-6-il}carbonil)azetidin-3-ol
353.		3-[(1*S*)-1-(dimetilamino)etil]-1-({5-[(2-fluoro-4-yodofenil)amino]-1-metil-1*H*-1,2,3-benzotriazol-6-il}carbonil)azetidin-3-ol
354.		1-({5-[(2-fluoro-4-yodofenil)amino]-1*H*-1,2,3-benzotriazol-6-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol
355.		1-({5-[(2-fluoro-4-yodofenil)amino]-1-metiyl-1*H*-1,2,3-benzotriazol-6-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol

356.		1-({5-[(2-fluoro-4-yodofenil)amino]-1*H*-1,2,3-benzotriazol-6-il}carbonil)-3-{(1*S*)-1-[(2-hidroxi-2-metilciclopentil)amino]etil}azetidin-3-ol
357.		3-[(1*S*)-1-aminoetil]-1-({4-fluoro-5-[(2-fluoro-4-yodofenil)amino]-1*H*-1,2,3-benzotriazol-6-il}carbonil)azetidin-3-ol
358.		1-({4-fluoro-5-[(2-fluoro-4-yodofenil) amino]-1*H*-1,2,3-benzotriazol-6-il} carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol
359.		5-({3-[(1*S*)-1-aminoetil]-3-hidroxiazetidin-1-il}carbonil)-6-[(2-fluoro-4-yodofenil)amino]pirimidin-2(1*H*)-ona

360.		6-[(2-fluoro-4-yodofenil)amino]-5-({3-hidroxi-3-[(2*S*)-piperidin-2-il]azetidin-1-il}carbonil)pirimidin-2(1*H*)-ona
361.		4-[(2-fluoro-4-yodofenil)amino]-5-({3-hidroxi-3-[(2*S*)-piperidin-2-il]azetidin-1-il}carbonil)pirimidin-2(1*H*)-ona
362.		5-({3-[(1*S*)-1-aminoetil]-3-hidroxiazetidin-1-il}carbonil)-4-[(2-fluoro-4-yodofenil)amino]pirimidin-2(1*H*)-ona

Administración General

En un aspecto, la invención proporciona composiciones farmacéuticas que comprenden un inhibidor de MEK de acuerdo con la invención y un portador, excipiente o diluyente farmacéuticamente aceptable. En otras ciertas realizaciones, la administración puede ser preferentemente por vía oral. La administración de los compuestos de la invención, o sus sales farmacéuticamente aceptables, en forma pura o en una composición farmacéutica apropiada, se puede llevar a cabo mediante cualquiera de las modalidades aceptadas de administración o agentes para cumplir funciones similares. Por lo tanto, la administración puede ser, por ejemplo, por vía oral, nasal, parenteral (intravenosa, intramuscular, o subcutánea), tópica, transdérmica, intravaginal, intravesical, intracisternal, o rectal, en la forma de formas de dosificación sólidas, semisólidas, polvo liofilizado, o líquidas, tales como por ejemplo, tabletas, supositorios, pastillas, cápsulas de gelatina elástica blanda y dura, polvos, soluciones, suspensiones, o aerosoles, o similares, preferentemente en formas de dosificación unitarias adecuadas para la administración simple de dosificaciones precisas.

Las composiciones incluyen un portador o excipiente farmacéutico convencional y un compuesto de la invención como

el agente activo, y, además, pueden incluir portadores y coadyuvantes, etc.

Los coadyuvantes incluyen agentes conservantes, de humedecimiento, de suspensión, edulcorantes, saborizantes, de perfume, emulsionantes, y de distribución. La prevención de la acción de microorganismos se puede asegurar mediante diferentes agentes antibacterianos y fungicidas, por ejemplo, parabenos, clorobutanol, fenol, ácido sórbico, y similares. También puede ser deseable incluir agentes isotónicos, por ejemplo azúcares, cloruro de sodio, y similares. La absorción prolongada de la forma farmacéutica inyectable se puede producir usando agentes que retardan la absorción, por ejemplo, monoestearato de aluminio y gelatina.

Si se desea, una composición farmacéutica de la invención puede contener también cantidades minoritarias de sustancias auxiliares tales como agentes de humedecimiento y emulsionantes, agentes reguladores del pH, antioxidantes, y similares, tales como, por ejemplo, ácido cítrico, monolaurato de sorbitan, oleato de trietanolamina, hidroxitolueno butilado, etc.

La elección de la formulación depende de diferentes factores tales como la modalidad de la administración de fármacos (por

ejemplo, para la administración oral, formulaciones en la forma de tabletas, pastillas o cápsulas son preferidas) y la biodisponibilidad de la sustancia farmacológica. Recientemente, se han desarrollado formulaciones farmacéuticas especialmente para fármacos que presentan poca biodisponibilidad basados en el principio de que la biodisponibilidad se puede aumentar aumentando el área superficial, es decir, disminuyendo el tamaño de las partículas. Por ejemplo, la Patente Estadounidense N° 4.107.288 describe una formulación farmacéutica que tiene partículas en la gama de tamaño de 10 a 1.000 nm en donde el material activo se apoya en una matriz entrecruzada de macromoléculas. La Patente Estadounidense N° 5.145.684 describe la producción de una formulación farmacéutica en donde la sustancia farmacológica se pulveriza a nanopartículas (tamaño promedio de las partículas de 400 nm) en la presencia de un modificador de la superficie y luego se dispersa en un medio líquido para dar una formulación farmacéutica que presenta notablemente alta biodisponibilidad.

Las composiciones adecuadas para la inyección parenteral pueden comprender soluciones, dispersiones, suspensiones o emulsiones acuosas o no acuosas estériles fisiológicamente aceptables, y polvos estériles para su reconstitución en soluciones o dispersiones inyectables estériles. Ejemplos de

portadores, diluyentes, solventes o vehículos acuosos o no acuosos adecuados incluyen agua, etanol, polioles (propilenglicol, polietilenglicol, glicerol, y similares), mezclas adecuadas de ellos, aceites vegetales (tales como aceite de oliva) y ésteres orgánicos inyectables tales como oleato de etilo. La fluidez correcta se puede mantener, por ejemplo, usando un recubrimiento tal como lecitina, manteniendo el tamaño de las partículas requerido en el caso de las dispersiones y usando surfactantes.

Una vía de administración específica es la oral, usando un régimen de dosificación diario conveniente que se puede ajustar de acuerdo con el grado de severidad del estado de enfermedad que se está tratando.

Las formas de dosificación sólidas para la administración oral incluyen cápsulas, tabletas, pastillas, polvos y gránulos. En dichas formas de dosificación sólidas, el compuesto activo se mezcla con por lo menos un excipiente (o portador) habitual inerte tal como citrato de sodio o fosfato dicálcico o (a) rellenos o extensores, como por ejemplo, almidones, lactosa, sucrosa, glucosa, manitol y ácido silícico, (b) ligantes, como por ejemplo, derivados de celulosa, almidón, alginatos, gelatina, polivinilpirrolidona, sucrosa, y goma de acacia, (c) humectantes, como por ejemplo, glicerol, (d) agentes

desintegradores, como por ejemplo, agar-agar, carbonato de calcio, almidón de papa o tapioca, ácido algínico, sodio de croscaramelosa, silicatos complejos, y carbonato de sodio, (e) retardadores de la solución, como por ejemplo, parafina, (f) aceleradores de la solución, como por ejemplo, compuestos de amonio cuaternario, (g) agentes de humedecimiento, como por ejemplo, alcohol cetílico, y monoestearato de glicerol, estearato de magnesio y similares, (h) adsorbentes, como por ejemplo, caolín y bentonita, y (i) lubricantes, como por ejemplo, talco, estearato de calcio, estearato de magnesio, polietilenglicoles sólidos, sulfato de laurilo de sodio, o mezclas de ellos. En el caso de las cápsulas, tabletas y pastillas, las formas de dosificación también pueden comprender agentes tampones.

Las formas de dosificación sólidas descritas anteriormente se pueden preparar con recubrimientos y cápsulas, tales como recubrimientos entéricos y otros conocidos en el arte. Pueden contener agentes opacadores y también pueden tener una composición tal que liberen el compuesto o compuestos activos cierta parte del tracto intestinal en forma retardada. Ejemplos de composiciones encapsuladas que usarse son las sustancias poliméricas y ceras. Los compuestos activos también pueden estar en forma microencapsulada, si es apropiada, con uno o más de los excipientes mencionados anteriormente.

Las formas de dosificación líquidas para la administración oral incluyen emulsiones, soluciones, suspensiones, jarabes y elixires farmacéuticamente aceptables. Dichas formas de dosificación se preparan, por ejemplo, disolviendo, dispersando, etc, un compuesto(s) de la invención, o una sal farmacéuticamente aceptable de él, y coadyuvantes farmacéuticos optativos en un portador, tal como, por ejemplo, agua, solución salina, dextrosa acuosa, glicerol, etanol y similares, agentes de solubilización y emulsionadores, como por ejemplo, alcohol etílico, alcohol isopropílico, carbonato de etilo, acetato de etilo, alcohol bencílico, benzoato de bencilo, propilenglicol, 1,3-butilenglicol, dimetilformamida; aceites, en particular, aceite de semilla de algodón, aceite de maní, aceite de germen de maíz, aceite de oliva, aceite de castor y aceite de sésamo, glicerol, alcohol tetrahidrofurfurílico, polietilenglicoles y ésteres de ácidos grasos de sorbitanl, o mezclas de estas sustancias, y similares, para formar así una solución o suspensión.

Las suspensiones, además de los compuestos activos, pueden contener agentes de suspensión, como por ejemplo, alcoholes isoestearílicos etoxilados, polioxietileno sorbitol y ésteres de sorbitan, celulosa microcristalina, metahidróxido de aluminio, agar-agar y tragacanto, o mezclas de estas sustancias y similares.

Las composiciones para la administración rectal son, por ejemplo, supositorios que se pueden preparar mezclando los compuestos de la presente invención con por ejemplo excipientes o portadores no irratantes adecuados tales como manteca de cacao, polietilenglicol o cera para supositorios, que son sólidos a temperaturas normales pero líquidos a la temperatura corporal y en consecuencia, se funden mientras están en una cavidad corporal adecuada y liberan el componente activo que está dentro de ellos.

Las formas de dosificación para la administración tópica de un compuesto de esta invención incluyen ungüentos, polvos, aspersiones e inhaladores. El componente activo se mezcla en condiciones estériles con un portador fisiológicamente aceptable y cualquier conservante, tampón o propelente que pueda ser necesario. Las formulaciones oftálmicas, ungüentos oculares, polvos y soluciones también están contempladas como que están dentro del alcance de esta invención.

Se pueden usar gases comprimidos para dispersar un compuesto de esta invención en forma de aerosol. Los gases inertes adecuados para este propósito son nitrógeno, dióxido de carbono, etc.

Generalmente, según la modalidad de administración deseada, las composiciones farmacéuticamente aceptables contienen del 1% al 99% en peso de un compuesto(s) de la invención, o una sal farmacéuticamente aceptable de él y un 99% a 1% en peso de un excipiente farmacéutico adecuado. En un ejemplo, la composición tiene del 5% al 75% en peso de un compuesto(s) de la invención, o una sal farmacéuticamente aceptable de él, y el resto son excipientes farmacéuticos adecuados.

Los métodos actuales para preparar dichas formas de dosificación son conocidos, o serán evidentes, para un experto en el arte, por ejemplo, véase Remington's Pharmaceutical Sciences, 18th Ed. (Mack Publishing Company, Easton, Pa., 1994). La composición que se debe administrar en cualquier caso contiene una cantidad terapéuticamente eficaz de un compuesto de la invención, o una sal farmacéuticamente aceptable de él, para el tratamiento de un estado de enfermedad de acuerdo con las enseñanzas de esta invención.

Los compuestos de la invención, o sus sales o hidratos farmacéuticamente aceptables, se administran en una cantidad terapéuticamente eficaz que varía según una variedad de factores que incluyen la actividad del compuesto específico empleado, la estabilidad metabólica y la duración de la acción del compuesto, la edad, el peso corporal, la salud general, el

sexo, la dieta, la forma y el tiempo de administración, la velocidad de excreción, la combinación de fármacos, la severidad de los estados de enfermedad particulares, y el huésped que se está sometiendo a la terapia. Los compuestos de la presente invención se pueden administrar a un paciente a niveles de dosificación en la gama de 0,1 a 1.000 mg por día. Para un adulto humano normal que tiene un peso corporal de 70 kilogramos, una dosificación en la gama de 0,01 a 100 mg por kilogramo de peso corporal por día es un ejemplo. La dosificación específica usada, sin embargo, puede variar. Por ejemplo, la dosificación puede depender de numerosos factores que incluyen los requisitos del paciente, la severidad de la condición que se está tratando, y la actividad farmacológica del compuesto que se está usando. La determinación de las dosificaciones óptimas para un paciente particular es conocida para un experto en el arte.

Si se formula como una dosis fija, dichos productos de combinación emplean los compuestos de esta invención dentro de la gama de dosificación descrita anteriormente y los demás agentes farmacéuticamente activos dentro de su gama de dosificación aprobada. Los compuestos de la presente invención pueden alternativamente usarse en secuencia con un agente(s) farmacéuticamente aceptable cuando la formulación de combinación es inapropiada.

Las formulaciones farmacéuticas representativas que contienen un compuesto de la Fórmula I se describen a continuación en los Ejemplos de Composiciones Farmacéuticas.

Utilidad

Ciertos compuestos de esta invención se han ensayado usando el ensayo descrito en el Ejemplo Biológico 1 y se han determinado que son inhibidores de MEK. Como tales compuestos de la Fórmula I son útiles para tratar enfermedades, particularmente el cáncer en donde la actividad de MEK contribuye a la patología y/o a la sintomatología de la enfermedad. Por ejemplo, el cáncer en donde la actividad de MEK contribuye a su patología y/o sintomatología incluye melanomas, cáncer colorectal, cáncer pancreático, cáncer de pulmón, cáncer papilar y de tiroides anaplástico y cánceres de ovarios endometriales, y similares.

Los ensayos in vitro adecuados para medir la actividad de MEK y la inhibición de ellos por compuestos son conocidos en el arte. Por ejemplo, véase WO 2006/061712 para medir MEK1 y MEK2 in vitro. Para más detalles de un ensayo in vitro para medir la actividad de MEK véase Ejemplos Biológicos, Ejemplo 1 a continuación. Siguiendo los ejemplos revelados en la presente, así como aquel revelado en el arte, un experto en el arte

puede determinar la actividad inhibitoria de un compuesto de esta invención.

Los ensayos para la medición de la eficacia in vitro en el tratamiento del cáncer son conocidos en el arte. Por ejemplo, véase WO 2006/061712, que se incorpora en la presente como referencia, para ensayos basados en células para el cáncer de colon. Además, los modelos de tumores basados en células se describen en Ejemplos Biológicos, Ejemplos 2 y 3 a continuación.

Los modelos in vivo adecuados para el cáncer son conocidos para los expertos en el arte (que incluye WO 2006/061712). Para ver más detalles de modelos in vivo para el cáncer colorectal, melanoma, adenocarcinoma de mamas, y carcinoma anaplástico de pulmón, véase Ejemplos Biológicos, Ejemplo 4, a continuación.

Síntesis General

Los compuestos de esta invención pueden prepararse mediante los procedimientos sintéticos descritos a continuación. Los materiales iniciales y los reactivos usados en la preparación de estos compuestos están disponibles de proveedores comerciales tales como Aldrich Chemical Co. (Milwaukee,

Wisconsin), o Bachem (Torrance, California) o se preparan mediante métodos conocidos para los expertos en el arte siguiendo procedimientos expuestos en las referencias tales como Fieser y Fieser's Reagents for Organic Synthesis, Vlumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 y Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry (John Wiley and Sons, 4th Edition) y Larock's Comprehensive Organic Transformations (VCF Publishers Inc., 1989). Estos esquemas son solamente ilustrativos de algunos métodos mediante los cuales los compuestos de esta invención se pueden sintetizar y se pueden hacer diferentes modificaciones de estos esquemas y les serán sugeridos a los expertos en el arte que hacen referencia a esta invención. Los materiales iniciales y los intermedios de la reacción se pueden aislar y purificar si se desea usando técnicas convencionales, que incluyen en forma no taxativa filtración, destilación, cristalización, cromatografía y similares. Dichos materiales se pueden caracterizar usando medios convencionales, que incluyen constantes físicas y datos espectrales.

A menos que se especifique lo contrario, las reacciones descritas en la presente tienen lugar a presión atmosférica y en una gama de temperaturas de -78°C a 150°C, más

preferentemente de 0°C a 125°C y más preferentemente a temperatura ambiente, por ejemplo a 20°C. A menos que se diga de otro modo (como en el caso de una hidrogenación) todas las reacciones se realizan bajo una atmósfera de nitrógeno.

Los profármacos se pueden preparar mediante técnicas conocidas para un experto en el arte. Estas técnicas generalmente modifican los grupos funcionales apropiados en un compuesto dado. Estos grupos funcionales modificados regeneran los grupos funcionales originales mediante la manipulación de rutina o in vivo. Se pueden preparar amidas y ésteres de los compuestos de la presente invención de acuerdo con métodos convencionales. Se proporciona un análisis completo de profármacos en T. Higuchi y V. Stella, "Pro-drugs as Novel Delivery Systems", Vol. 14 de la ACS Symposium Series, y en Bioreversible Carriers in Drug Design, ed. Edward Roche, American Pharmaceutical Association and Pergamon Press, 1987, ambas incorporadas en la presente como referencia con todos los propósitos.

Los compuestos de la invención, o sus sales farmacéuticamente aceptables, pueden tener átomos de carbono asimétricos o átomos de nitrógeno cuaternados en su estructura. Los compuestos de la Fórmula I que se pueden preparar mediante las síntesis descritas en la presente pueden existir como un solo

estereoisómero, racemato, y como mezclas de enantiómeros y diasterómeros. Los compuestos también pueden existir como isómeros geométricos. Todos estos estereoisómeros, racematos únicos y mezclas de ellos, y los isómeros geométricos están dentro del alcance de la invención. Algunos de los compuestos de la invención pueden existir como tautómeros. Por ejemplo, cuando una cetona o aldehído está presente, la molécula puede existir en la forma de enol; cuando una amida está presente, la molécula puede existir en la forma del ácido imídico y cuando una enamina está presente, la molécula puede existir como una imina. Todos esos tautómeros están dentro del alcance de la invención.

La presente invención también incluye derivados de N-óxido y derivados protegidos de compuestos de la Fórmula I. Por ejemplo, cuando los compuestos de la Fórmula I contienen un átomo de nitrógeno oxidable, el átomo de nitrógeno se puede convertir en N-óxido mediante métodos conocidos en el arte. Cuando los compuestos de la Fórmula I contienen grupos tales como hidroxi, carboxi, tiol o cualquier grupo que contiene un átomo(s) de nitrógeno, estos grupos se pueden proteger con un "grupo protector" adecuado. Una lista amplia de grupos protectores adecuados se puede encontrar en T.W. Greene, *Protective Groups in Organic Synthesis,* John Wiley & Sons, Inc., 1991, cuya invención se incorpora en la presente como

referencia en su totalidad. Los derivados protegidos de compuestos de la Fórmula I se pueden preparar mediante métodos conocidos en el arte.

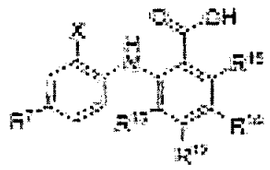
Los métodos para la preparación y/o separación y aislamiento de un solo estereoisómero de mezclas racémicas o mezclas no racémicas de estereoisómeros son conocidos en el arte. Por ejemplo, los isómeros (R) y (S) ópticamente activos se pueden preparar usando síntesis quirales o reactivos quirales, o se pueden resolver usando técnicas convencionales. Los enantiómeros (isómeros R y S) se pueden resolver mediante métodos conocidos para un experto en el arte, por ejemplo, mediante la formación de sales o complejos diastereoisómericos que se pueden separar, por ejemplo, mediante cristalización, mediante la formación de derivados diastereoisoméricos que se pueden separar, por ejemplo, mediante cristalización, reacción selectiva de un enantiómero con un reactivo específico del enantiómero, por ejemplo la oxidación o reducción enzimática, y luego la separación de los enantiómeros modificados y no modificados; o una cromatografía de gases y líquidos o de líquidos en un medio quiral, por ejemplo sobre un soporte quiral, tal como sílice con un ligando quiral unido o en la presencia de un solvente quiral. Se apreciará que cuando se convierte un enantiómero deseado en otra entidad química mediante uno de los procedimientos de separación descritos

anteriormente, puede ser necesario otro paso para liberar la forma enantiomérica deseada. Alternativamente, el enantiómero específico se puede sintetizar mediante síntesis asimétrica usando reactivos ópticamente activos, sustratos, catalizadores o solventes o convirtiendo un enantiómero en el otro mediante transformaciones asimétricas. Para una mezcla de enantiómeros, enriquecida en un enantiómero particular, el componente enantiomérico principal se puede enriquecer más (con la pérdida concomitante en el rendimiento) mediante recristalización.

Además, los compuestos de la presente invención pueden existir en formas no solvatadas así como solvatadas con solventes farmacéuticamente aceptables tales como agua, etanol y similares. En general, las formas solvatadas se consideran equivalentes a las formas no solvatadas para los propósitos de la presente invención.

La química para la preparación de los compuestos de esta invención es conocida para los expertos en el arte.

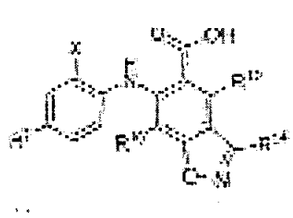
Un compuesto intermedio de la fórmula II



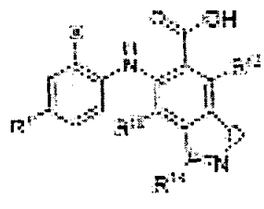
III

donde R^7, X, R^{10}, R^{12}, R^{14} y R^{16} son lo definido en el resumen de la invención para el grupo A, se puede preparar usando procedimientos conocidos para un experto en el arte. En particular véase (por ejemplo) US 7.019.033, WO 2002006213, WO 2003062191, WO 2003062189, WO 2002018319, WO 2001005592, WO 2000064856, WO 9901421, WO 2004065789, Davis, E.M. et al, *Org. Process Res. & Dev.* 2005, 9, 843-6 y Shapiro, N. et al, *Synthetic Commun.* 2005, 35, 2265-9 que se incorporan en la presente como referencia. Los siguientes compuestos intermedios se prepararon usando procedimientos similares a los descritos en las referencias precedentes: ácido 3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]benzoico; ácido 2-[(2-cloro-4-yodofenil)amino]-3,4-difluorobenzoico; ácido 4-fluoro-2-[(2-fluoro-4-yodofenil)amino]benzoico; ácido 4,5-difluoro-2-[(2-fluoro-4-yodofenil)amino]benzoico; y ácido 2-[(4-bromo-2-fluorofenil)amino]-3,4-difluorobenzoico.

Un compuesto intermedio de la Fórmula III(a) o III(b):



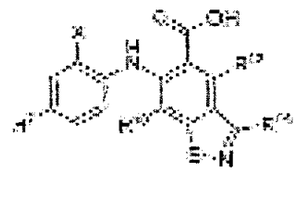
III(a)



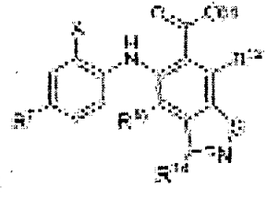
III(b)

donde R^7, X, R^{10}, R^{12} y R^{14} son lo definido en el resumen de la invención para el grupo B, se puede preparar usando procedimientos conocidos para un experto en el arte. En particular para la fórmula III(a), donde R^{14} es amino o alquilo (particularmente metilo); R^{10} es halo (particularmente fluoro); R^7 es hidrógeno o halo (particularmente bromo o cloro); X es halo (particularmente, cloro); y R^{12} es hidrógeno, véase por ejemplo WO 2006030610, US 2005049419, y US 2005/054701 que se incorporan en la presente como referencia. El ácido 6-[(4-bromo-2-clorofenil)amino]-7-fluoro-3-metil-1,2-bencisoxazol-5-carboxílico se preparó usando métodos similares a los descritos en WO 2006030610, US 2005049419, y US 2005/054701.

Un compuesto intermedio de la Fórmula IV(a) o IV(b):



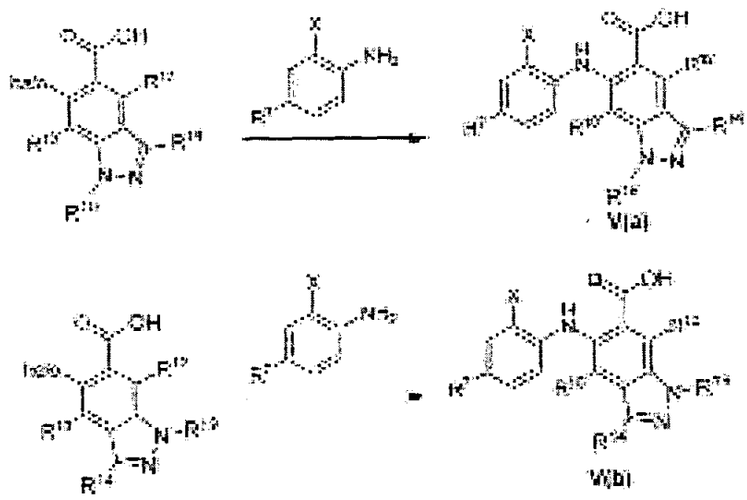
IV(a)



IV(b)

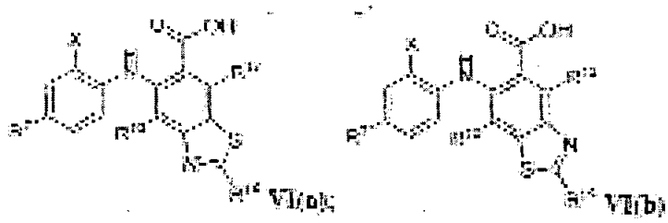
donde R^7, X, R^{10}, R^{12} y R^{14} son lo definido en el resumen de la invención para el grupo B, se puede preparar usando procedimientos conocidos para un experto en el arte.

Un compuesto intermedio de la Fórmula V(a) o V(b):



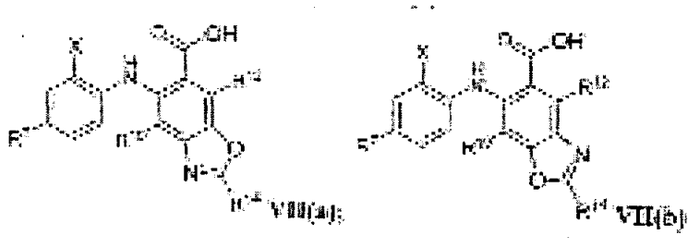
donde R^7, X, R^{10}, R^{12}, R^{14} y R^{19} son lo definido en el resumen de la invención para el grupo B, se puede preparar usando procedimientos conocidos para un experto en el arte. En particular el precursor de halo de V(a) se puede preparar usando, por ejemplo, WO 2003101968 y WO2002083648 que se incorporan en la presente como referencia. En particular el precursor de halo de V(b) se puede preparar usando, por ejemplo, US2004192653, US2004180896, US2004176325 que se incorporan en la presente como referencia. Los precursores de halo luego reaccionan con una anilina apropiada y dan los compuestos intermedios de la Fórmula V(a) y V(b).

Un compuesto intermedio de la Fórmula VI(a) o VI(b):



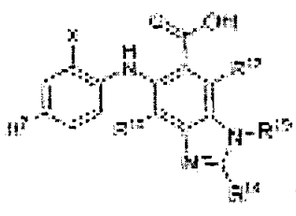
donde R^7, X, R^{10}, R^{12} y R^{14} son lo definido en el resumen de la invención para el grupo B, se puede preparar usando procedimientos conocidos para un experto en el arte. En particular para VI(b) véase por ejemplo WO2000042022 y WO2001005390 que se incorporan en la presente como referencia.

Un compuesto intermedio de la Fórmula VII(a) o VII(b):

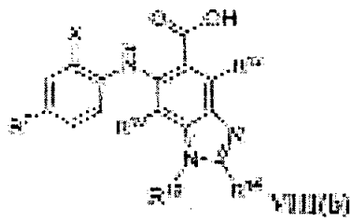


donde R^7, X, R^{10}, R^{12} y R^{14} son lo definido en el resumen de la invención para el grupo B, se puede preparar usando procedimientos conocidos para un experto en el arte. Para el compuesto intermedio VII(b) véase por ejemplo WO2001005390 y WO2000042022 que se incorporan en la presente como referencia.

Un compuesto intermedio de la Fórmula VIII(a) o VIII(b):



VIII(a);

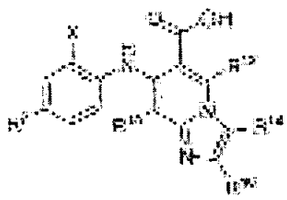


VIII(b)

donde R^7, X, R^{10}, R^{12}, R^{14} y R^{19} son lo definido en el resumen de la invención para el grupo B, se puede preparar usando procedimientos conocidos para un experto en el arte. En particular para la Fórmula VIII(b) donde R^{10} es halo (particularmente fluoro), R^{12} es hidrógeno, R^{14} es hidrógeno y R^{19} es hidrógeno o alquilo (particularmente metilo) o alquenilo (particularmente alilo), véase WO 05/023251, WO2005009975, y WO 2001005390 que se incorporan en la presente como referencia. En particular para VIII(a) donde X es halo (particularmente cloro o fluoro) o alquilo (particularmente metilo), R^7 es halo (particularmente yodo, bromo, o cloro) o haloalcoxi (particularmente trifluorometoxi), R^{10} es halo (particularmente fluoro o cloro), R^{14} es hidrógeno o alquilo (particularmente metilo) y R^{19} es hidrógeno o alquilo (particularmente metilo), véase por ejemplo US 2004/0116710, WO 03/077914, WO 03/077855, WO 00/42022, WO2005009975, y WO2001005390 que se incorporan en la presente como referencia. Los siguientes compuestos intermedios se prepararon usando procedimientos similares a los descritos en US 2004/0116710, WO 03/077914, WO 03/077855, WO 00/42022, WO2005009975, y WO2001005390: ácido 5-[(4-bromo-2-clorofenil)amino]-4-fluoro-

1-metil-1H-bencimidazol-6-carboxílico y ácido 4-fluoro-5-[(2-fluoro-4-yodofenil)amino]-1-metil-1H-bencimidazol-6-carboxílico.

Un compuesto intermedio de la fórmula IX:

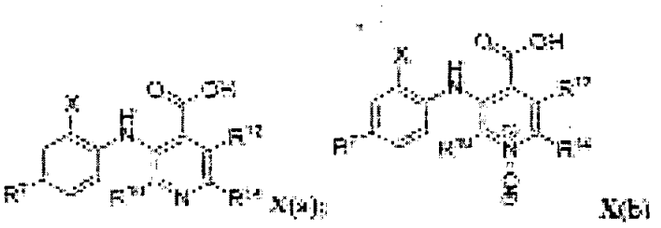


IX

donde R^7, X, R^{10}, R^{12}, R^{14} y R^{16} son lo definido en el resumen de la invención para el grupo B, se puede preparar usando procedimientos conocidos para un experto en el arte. En particular, R^{10} es hidrógeno o halo (particularmente cloro o fluoro); R^{12} es hidrógeno; R^{14} es hidrógeno, amino, alquilamino o dialquilamino; R^{16} es hidrógeno; X es halo (particularmente cloro); y R^7 es halo (particularmente bromo) véase por ejemplo WO 05/023759, US 2005/0054701, US 2006030610, US 2005049419 y US 2005049276 que se incorporan en la presente como referencia. Los siguientes compuestos intermedios se prepararon usando procedimientos similares a los descritos en WO 05/023759, así como en US 2006030610, así como en US 2005/0054701: ácido 7-[(4-bromo-2-clorofenil)amino]-8-cloroimidazo[1,2-a]piridina-6-carboxílico y ácido 8-cloro-7-[(2-fluoro-4-yodofenil)amino]imidazo[1,2-a]piridina-6-

carboxílico. Los siguientes compuestos intermedios se pueden preparar usando procedimientos similares a los descritos en las referencias que se dieron anteriormente: ácido 8-fluoro-7-[(2-fluoro-4-yodofenil)amino]imidazo[1,2-a]piridina-6-carboxílico y ácido 7-[(4-bromo-2-fluorofenil)amino]-8-fluoroimidazo[1,2-a]piridina-6-carboxílico.

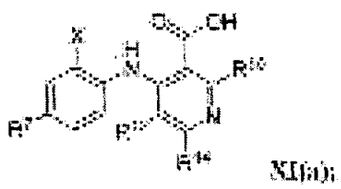
Un compuesto intermedio de la Fórmula X(a) y X(b):



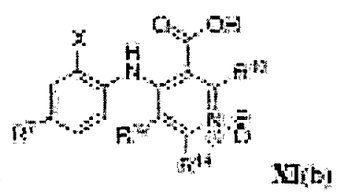
donde R^7, X, R^{10}, R^{12} y R^{14} son lo definido en el resumen de la invención para el grupo B, se puede preparar usando procedimientos conocidos para un experto en el arte. En particular, donde R^{10} es hidrógeno, halo (específicamente cloro), o alquilo (específicamente metilo), R^{12} es hidrógeno y R^{14} es hidrógeno, halo (específicamente bromo), véase por ejemplo WO 06/045514 que se incorpora en la presente como referencia. Para preparar el compuesto intermedio de la fórmula X(b), el nitrógeno del anillo de piridina de X(a) puede entonces oxidarse con un agente tal como MCPBA o H_2O_2. Los siguientes compuestos intermedios X(a) y X(b) se prepararon usando métodos similares a los descritos en WO 06/045514: ácido 3-[(2-fluoro-4-yodofenil)amino]piridin-4-

carboxílico y 1-óxido del ácido 3-[(2-fluoro-2-yodofenil)amino]piridina-4-carboxílico. Los siguientes compuestos intermedios de X(a) se pueden preparar usando métodos similares a los descritos en WO 06/045514: ácido 2-fluoro-3-[(2-fluoro-4-yodofenil)amino]piridina-4-carboxílico y ácido 3-[(4-bromo-2-fluorofenil)amino]piridina-4-carboxílico.

Un compuesto intermedio de la fórmula XI(a):



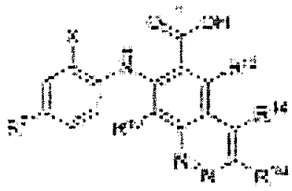
XI(a)



XI(b)

donde R^7, X, R^{10}, R^{12} y R^{14} son lo definido en el resumen de la invención para el grupo B, se puede preparar usando procedimientos conocidos para un experto en el arte. En particular, donde R^{10} es hidrógeno, R^{12} es hidrógeno o halo (particularmente cloro o fluoro), R^{14} es amina o halo (particularmente cloro), X es halo (particularmente cloro) y R^7 es halo (particularmente bromo), véase por ejemplo US 2005/0054701, US 200549419 y US 2006030610 que se incorporan en la presente como referencia. El compuesto intermedio de la fórmula XI(b) se puede preparar oxidando el nitrógeno del anillo de piridina de XI(a) con un agente tal como MCPBA o H_2O_2.

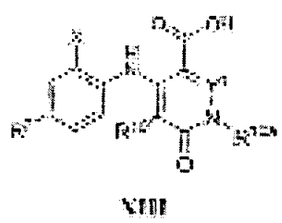
Un compuesto intermedio de la fórmula XII:



XII

donde R^7, X, R^{10}, R^{12}, R^{14} y R^{16} son lo definido en el resumen de la invención para el grupo B, se puede preparar usando procedimientos conocidos para un experto en el arte. En particular véase por ejemplo WO 05/051302 que se incorpora en la presente como referencia. Los siguientes compuestos intermedios se pueden preparar usando métodos similares a los descritos en WO 05/051301: ácido 8-fluoro-7-[(2-fluoro-4-yodofenil)amino]-4-metilcinolina-6-carboxílico; ácido 7-[(4-bromo-2-clorofenil)amino]-8-fluoro-4-metilcinolina-6-carboxílico; ácido 7-[(4-bromo-2-fluorofenil)amino]-8-fluoro-4-metilcinolina-6-carboxílico; y ácido 7-[(4-bromo-2-fluorofenil)-amino]cinolina-6-carboxílico.

Un compuesto intermedio de la fórmula XIII:



XIII

donde R^7, X, R^{10}, R^{10a}, y Y^1 son lo definido en el resumen de la invención para el grupo C, se puede preparar usando procedimientos conocidos para un experto en el arte, que incluyen por ejemplo los procedimientos de US 05/0256123, Wallace, E. M. et al J. Med. Chem. 2006, 49, 441-4, WO 2005000818 y WO 2005051301 (donde Y^1 es carbono) que se incorporan en la presente como referencia. El ácido 4-[(4-bromo-2-fluorofenil)amino]-5-fluoro-1-metil-6-oxo-1,6-dihidropiridina-3-carboxílico se preparó usando procedimientos similares a aquellos descritos en US 05/0256123 y en WO 2005051301. El ácido 4-cloro-1-metil-6-oxo-1,6-dihidropiridina-3-carboxílico se preparó usando procedimientos similares a aquellos descritos en US 2005256123. Los siguientes compuestos intermedios se pueden preparar usando los métodos revelados en las referencias precedentes:

ácido 4-[(2-fluoro-4-yodofenil)amino]-1-metil-6-oxo-1,6-dihidropiridina-3-carboxílico;

ácido 4-[(4-bromo-2-clorofenil)amino]-1-metil-6-oxo-1,6-dihidropiridina-3-carboxílico;

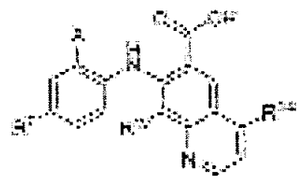
ácido 4-[(4-bromo-2-fluorofenil)amino]-1-metil-6-oxo-1,6-dihidropiridina-3-carboxílico;

ácido 4-[(4-bromo-2-clorofenil)amino]-1-metil-6-oxo-1,6-dihidropiridina-3-carboxílico;

ácido 4-[(4-bromo-2-clorofenil)amino]-5-fluoro-1-metil-6-oxo-1,6-dihidropiridina-3-carboxílico; y

ácido 4-[(4-bromo-2-fluorofenil)amino]-1-metil-6-oxo-1,6-dihidropiridina-3-carboxílico.

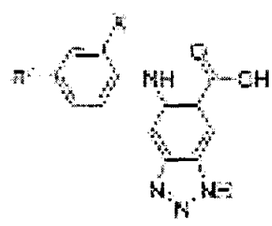
Un compuesto intermedio de la fórmula XIV:



XIV

donde R^7, X, R^{10}, y R^{14} son lo definido en el resumen de la invención para el grupo B, se puede preparar usando procedimientos conocidos para un experto en el arte. En particular, véase por ejemplo WO 05/051302 que se incorpora en la presente como referencia.

Un compuesto intermedio de la fórmula XVI

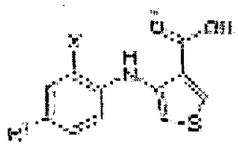


XVI

donde X y R^7 son lo definido en el resumen de la invención para un compuesto del grupo B, se puede preparar usando procedimientos conocidos para un experto en el arte. En particular, véase por ejemplo WO 2001005390 y WO 2000042022 para ver procedimientos que se pueden usar para preparar los

siguientes: ácido 5-[(2-fluoro-4-yodofenil)amino]-1H-benzotriazol-6-carboxílico; ácido 5-[(2-fluoro-4-yodofenil)amino]-1-metil-1H-benzotriazol-6-carboxílico; y ácido 4-fluoro-5-[(2-fluoro-4-yodofenil)amino]-1H-benzotriazol-6-carboxílico.

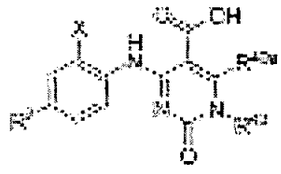
Un compuesto intermedio de la Fórmula XVII:



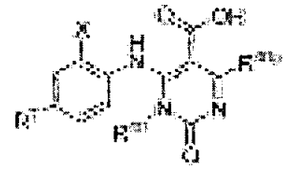
XVII

donde X y R^7 son lo definido en el resumen de la invención para un compuesto del grupo B, se puede preparar usando procedimientos conocidos para un experto en el arte. En particular, véase el Ejemplo 29.

Un compuesto intermedio de la fórmula XVIII(a) o XVIII(b)

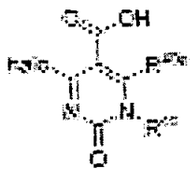
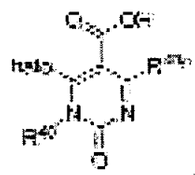


XVIII(a)

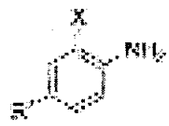


XVIII(b)

donde X, R^7, R^{40}, y R^{40a} son lo definido en el resumen de la invención para un compuesto del grupo D, se puede preparar usando procedimientos conocidos para un experto en el arte. En particular, los precursores de halo para XVIII(a) y XVIII(b)

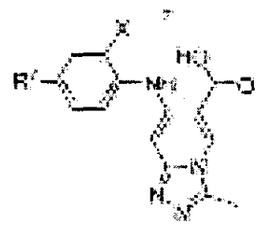

y

, respectivamente

se pueden preparar usando procedimientos similares a aquellos descritos en Machon y Dlugosz Acta Poloniae Pharmaceutica 1983, 40(1), 1-6 y en von Angerer, Sciences of Synthesis 2004, 16, 379-572 (Revisión General escrita en inglés). Los precursores de halo luego reaccionan con



usando procedimientos conocidos para un experto en el arte y los métodos sintéticos revelados allí. Los siguientes compuestos intermedios se pueden preparar como se describió anteriormente: ácido 6-[(2-fluoro-4-yodofenil)amino]-2-oxo-1,2-dihidropiridina-5-carboxílico y ácido 4-[(2-fluoro-4-yodofenil)amino]-2-oxo-1,2-dihidropiridina-5-carboxílico.

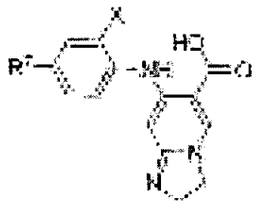
Un compuesto intermedio de la fórmula XIX:



XIX

donde X y R^7 son lo definido en el resumen de la invención para un compuesto del grupo C, se puede preparar usando procedimientos conocidos para un experto en el arte. En particular, véase US 2005049276.

Un compuesto intermedio de la fórmula XX

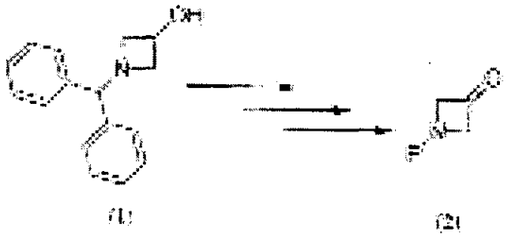


XX

donde X y R^7 son lo definido en el resumen de la invención para un compuesto del grupo C, se puede preparar usando procedimientos conocidos para un experto en el arte. En particular, véase US 2005049276.

La síntesis de las azetidinas sustituidas en la posición 3 se puede realizar en forma conveniente de acuerdo con el Esquema 1:

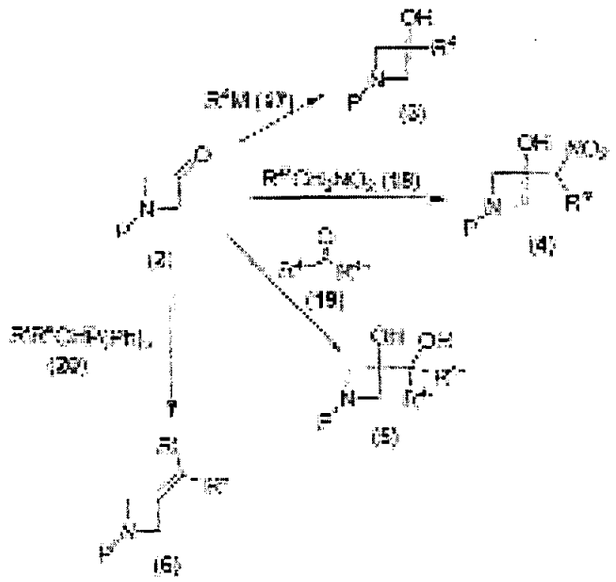
Esquema 1



partiendo desde la azetidina-3-ol (1) protegida con N-difenilmetilo, preparada rápidamente mediante la reacción de epiclorohidrina y difenilmetilamina (Chatterjee, Shym S.: Triggle, D.J. Chemical Communications (London) 1968, 2, 93). El intercambio del grupo protector, de Boc a CBz, sobre la azetidina se realiza de acuerdo con los protocolos de la bibliografía (Greene, T.W., Wuts, P.G. Protective Groups in Organic Synthesis, Wiley-Interscience) y la posterior oxidación hacia la azetidinona (2) donde P es CBz proporciona un compuesto intermedio para la preparación de compuestos de la invención.

Por ejemplo, los compuestos intermedios cetona de la fórmula 2 pueden tener funcionalidades amplias en la posición 3 de acuerdo con el Esquema 2:

Esquema 2



Un compuesto intermedio de la fórmula (3), donde R^4 es lo definido en el resumen de la invención para un compuesto del Grupo A, del Grupo B, del Grupo C o del Grupo D se puede preparar haciendo reaccionar el compuesto intermedio 2 con reactivos de Grignard u otras especies organometálicas de la fórmula 17, tales como organolitios. Alternativamente, el compuesto intermedio 2 puede reaccionar con aniones el nitroalcano de la fórmula 18 preparado in situ como en la reacción de Henry (La reacción de Henry, ejemplos recientes: Lazzio, F.A. Tetrahedron 2001, 57(6), 915-845) para dar (4) donde $R^{4'}$ es hidrógeno o alquilo optativamente sustituido como se describe para R^4 en el resumen de la invención para un compuesto del Grupo A, del Grupo B, del Grupo C o del Grupo D. Alternativamente, el compuesto intermedio 2 puede reaccionar

con aniones de cetona o aldehído de la fórmula 19 en una condensación del tipo de Claisen para dar (5) donde $R^{4'}$ es alquilo optativamente sustituido como se describe para R^4 en el Resumen de la Invención para un compuesto del Grupo A, del Grupo B, del Grupo C o del Grupo D y $R^{4''}$ es hidrógeno o $R^{4'}$. Además, 2 puede reaccionar con reactivos de Wittig de la fórmula 20 (donde R' y R" son independientemente hidrógeno, alquilo, alquenilo, arilo o heteroarilo y el alquilo, alquenilo, arilo y heteroarilo se sustituyen optativamente como se describe para R^4 en el Resumen de la Invención para un compuesto del Grupo A, del Grupo B, del Grupo C o del Grupo D) para preparar compuestos intermedios de la fórmula 6, que también son útiles como precursores para los compuestos de la invención.

De acuerdo con el Esquema 3, los compuestos intermedios de la fórmula (6) donde (R' y R" son hidrógeno y P es un grupo precursor de nitrógeno tal como CBz o Boc).

Esquema 3

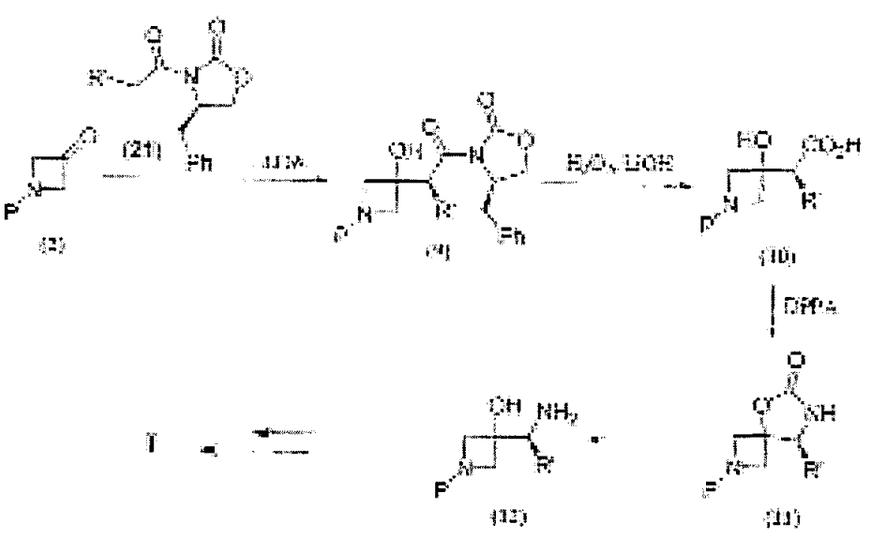


también se puede convertir en el epóxido correspondiente (7) y la reacción posterior con una base de nitrógeno adecuada u

otros nucleófilos se puede realizar para dar acceso a una amplia gama de derivados de azetidin-3-ol tales como (8), donde R^8 y $R^{8'}$ son lo definido en el Resumen de la Invención.

En algunos casos se desea la preparación de compuestos ópticamente puros donde la azetidina contiene uno o más estereocentros. Numerosas técnicas para la preparación de compuestos ópticamente puros a través tanto de técnicas de resolución como la síntesis asimétrica son conocidas en el arte. En uno de tales casos, se puede emplear una metodología de síntesis asimétrica donde un precursor de azetidina de la fórmula (2) reacciona con un compuesto intermedio de la fórmual 21 donde R' no es hidrógeno, como se ilustra en el Esquema 4.

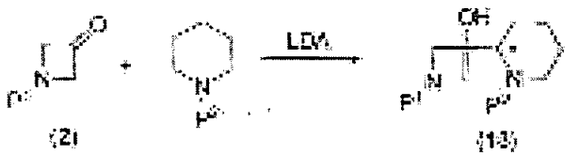
Esquema 4



Uno de tales enfoques útiles usa la metodología de oxazolidinona de Evans (condensación de aldol diastereoselectiva usando un auxiliar de oxazolidinona quiral. Gage, James R., Evans, David A., Organic Synthesis 1990, 68, 83-91). La condensación de la azetidinona (2) con la oxazolidinona quiral en la presencia de una base tal como LDA da la oxazolidinona intermedia (9), donde P es un grupo protector de nitrógeno tal como CBz o Boc con diastereoselectividad. El tratamiento con hidróxido de litio en peróxido de hidrógeno acuoso da el ácido carboxílico (10) que puede someterse al reordenamiento de Curtius para proporcionar la oxazolidinona quiral (11) que luego se transporta según sea necesario a un compuesto intermedio útil (12). Se puede emplear otra manipulación y derivación de grupos protectores según sea necesario para preparar compuestos de la Fórmula I.

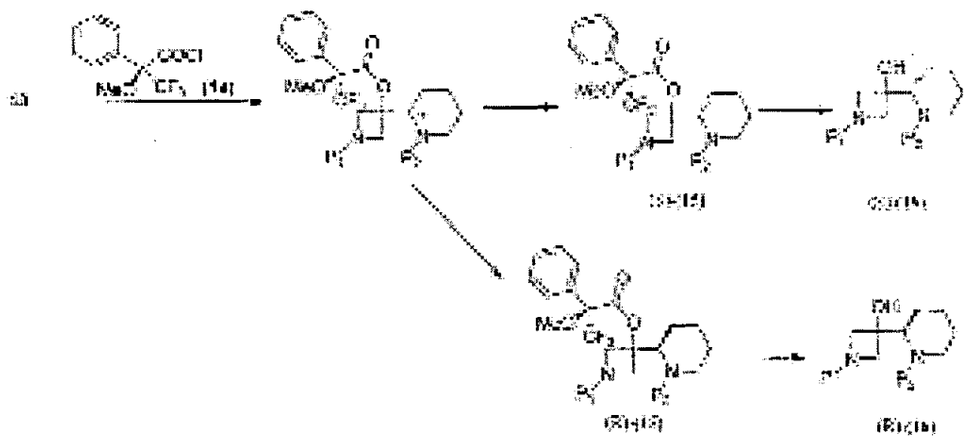
Alternativamente, una mezcla racémica de un compuesto intermedio de la fórmula (13), útil para preparar un compuesto de la Fórmula I donde R^3 es hidroxi y R^4 es heterocicloalquilo (en particular, donde R^4 es una piperidina protegida con N), se puede preparar de acuerdo con el Esquema 5.

Esquema 5



En los esquemas de la reacción P^1 y P^2 son grupos protectores de nitrógeno ortogonales. Por ejemplo, P^1 es Boc y P^2 es CBz o P^1 es CBz y P^2 es Boc. La reacción se realiza in situ ensayando 22 para generar la amina litiada y posteriormente tratándola con una cetona tal como (2) de acuerdo con el método de Peter Beak (Beak, Peter, Lee, Won Koo α-Lithioamine synthetic equivalents: syntheses of diastereoisomers from the Boc-piperidines. Journal of Organic Chemistry 1990, 55(9), 2578-80). El racemato (13) así preparado se puede resolver mediante funcionalización, como se describe en el Esquema 6, con un ácido quiral tal como el ácido de Mosher fácil de obtener (14).

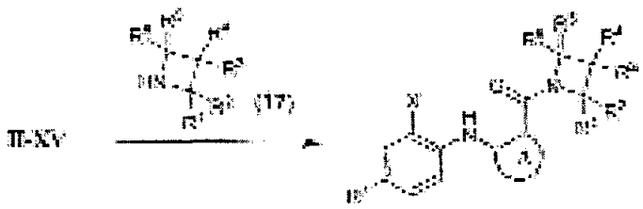
Esquema 6



Los éteres diastereoméricos (15) resultantes se pueden separar por medios cromatográficos y luego transportarse individualmente como los compuestos intermedios enantioméricamente puros (R)-(16) y (S)-(16).

Los compuestos de la invención se pueden preparar haciendo reaccionar un compuesto intermedio de la Fórmula II, III(a), III(b), IV(a), IV(b), V(a), V(b), VI(a), VI(b), VII(a), VII(b), VIII(a), VIII(b), IX, X(a), X(b), XI(a), XI(b), XII, XIII, XIV, XVI, XVII, XVIII(a), XVIII(b), XIX, o XX con el compuesto intermedio 17 de acuerdo con el Esquema 7.

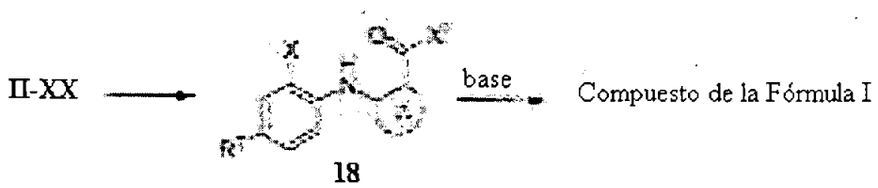
Esquema 7



La reacción se realiza en un solvente tal como DMF, THF, o DCM en la presencia de una base tal como DIPEA, N-metilmorfolina, DMAP, o trietilamina y optativamente en la presencia de un agente de acoplamiento tal como PyBOP, HBTU o EDCI.

Alternativamente un compuesto intermedio de la fórmula II, III(a), III(b), IV(a), IV(b), V(a), V(b), VI(a), VI(b), VII(a), VII(b), VIII(a), VIII(b), IX, X(a), X(b), XI(a), XI(b), XII, XIII, XIV, XVI, XVII, XVIII(a), XVIII(b), XIX, o XX se puede convertir en un haluro de ácido de acuerdo con el Esquema 8.

Esquema 8



18

donde X^2 es halo, tal como cloro o fluoro, y todos los demás grupos son lo definido en el Resumen de la Invención para un compuesto del Grupo A, del Grupo B, del Grupo C o del Grupo D. la reacción se realiza en un solvente tal como dioxano, THF o

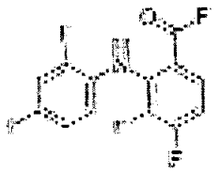
DCM en la presencia de una base tal como DIPEA, bicarbonato de sodio. El haluro de ácido de la fórmula 18 puede reaccionar entonces con un compuesto intermedio azetidina de la fórmula 17 para preparar un compuesto de la Fórmula I.

Ejemplos Sintéticos

En general, los compuestos que se enumeran a continuación se identificaron mediante LC-MS y/o se aislaron y se caracterizaron mediante ^{1}H-NMR (más generalmente 400 MHz). Se realizaron análisis de cromatografía de líquidos-espectro de masa (LC-MS) usando por lo menos uno de: un Hewlett-Packard Serie 1100 MSD, un Agilent 1100 Serie LC/MSD (disponible en Agilent Technologies Deutschland GmbH de Waldbronn (Alemania), o un Waters 8-Channel MUX System (disponible en Waters Corporation de Milford, Massachustts). Los compuestos se identificaron de acuerdo con su ion positivo [MH^+] o [MNa^+] (modalidad positiva) o ion negativo [MH^-] (modalidad negativa) de masa observada. Los datos de ^{1}H-NMR para compuestos se tomaron con un Espectrómetro Varian AS400 (400 MHz, disponible en Varian GmbH, Darmstadt, Alemania). Los materiales iniciales y los compuestos intermedios usados para preparar un compuesto de la invención están comercialmente disponibles o los puede preparar un experto en el arte.

Referencia 1

Fluoruro de 3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]benzoilo

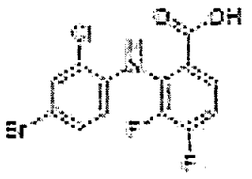


A una mezcla agitada de ácido 3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino] benzoico (12 g, 30,5 mmol), preparado usando procedimientos similares a aquellos descritos en US 7.019.033, en diclorometano (70 mL) a 0°C, se agregó piridina (2,5 mL, 30,8 mmol) y luego se agregó gota a gota fluoruro cianúrico (2,8 mL, 33,6 mmol). La mezcla de la reacción se agitó a 0°C durante 10 minutos y luego se calentó a temperatura ambiente y se agitó durante 2 horas. La mezcla de la reacción se diluyó con agua y se extruyó con diclorometano (100 mL). La capa acuosa se extrajo una vez con diclorometano (50 mL). Las capas orgánicas combinadas se lavaron con una solución de bicarbonato de sodio acuosa saturada, salmuera, se secaron sobre sulfato de sodio anhidro y se concentraron en vacío para dar el producto crudo como un sólido amarronado. El producto crudo se purificó mediante cromatografía rápida (tapón, 25% acetato de etilo en hexanos) para dar fluoruro de 3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]benzoilo como un sólido beige (11,8 g, rendimiento del 97%). ^{1}H NMR (400 MHz,

CD_3OD): 8,41 (s, 1H), 7,80-7,81 (m, 1H), 7,52 (dd, 1H), 7,43-7,47 (m, 1H), 6,96-7,03 (m, 1H), 6,85-6,92 (m, 1H).

Referencia 2

Ácido 2-[(4-bromo-2-clorofenil)amino]-3,4-difluorobenzoico



A una solución de ácido 2,3-trifluorobenzoico (1 g, 5,68 mmol) y 4-bromo-2-cloroanilina (1,2 g, 5,68 mmol) en acetonitrilo (10 mL) se agregó amida de litio (0,39 g, 17,04 mmol) y la reacción se agitó a 60°C durante 1,5 horas. La mezcla se enfrió a temperatura ambiente y luego a 0°C y se acidificó con ácido clorhídrico acuoso. El precipitado obtenido se recogió mediante filtración y se lavó con agua fría y se secó en vacío y dio ácido 2-[(4-bromo-2-clorofenil)amino]-3,4-difluorobenzoico (1,92 g, rendimiento del 94%) como un sólido beige. MS(EI) para $C_{13}H_7BrClF_2NO_2$: 363 (MH^+].

Usando las mismas técnicas u otras análogas y sustituyendo, según sea necesario, con otros reactivos, se preparó el ácido 2-[(4-yodo-2-fluorofenil)amino]-3-fluorobenzoico. MS (EI) para $C_{13}H_8F_2INO_2$: 376 (MH^+).

Referencia 3

Fenilmetil 1-oxa-5-azaespiro[2.3]hexano-5-carboxilato

A una solución de clorhidrato de azetidin-3-ol en tetrahidrofurano (90 mL) y agua (10 mL) se agregó trietilamina (15 mL) y luego se agregó lentamente cloroformato de bencilo (8,0 mL, 0,056 mol) a temperatura ambiente. La mezcla de la reacción se agitó a temperatura ambiente durante 16 horas y luego se repartió con agua y acetato de etilo. La capa orgánica se lavó con salmuera, se secó sobre sulfato de magnesio anhidro y se concentró. El residuo se purificó mediante cromatografía rápida (SiO_2, 25%-50% acetato de etilo en hexanos) para dar fenilmetil 3-hidroxiazetidina-1-carboxilato (3,56 g, rendimiento del 33%) como un aceite transparente e incoloro. ^1H NMR (400 MHz, $CDCl_3$): 7,36-7,31 (m, 5H), 5,09 (s, 2H), 4,64-4,57 (m, 1H), 4,22 (dd, 2H), 3,88 (dd, 2H), 2,61 (d, 1H, J=4,0 Hz). MS (EI) para $C_{11}H_{13}NO_3$: 208 (MH^+).

A una solución de fenilmetil 3-hiroxiazetidina-1-carboxilato (3,5 g, 0,0168 mol) en diclorometano (100 mL), se agregó peryodinano de Dess-Martin (10,7 g, 0,025 mol) a temperatura ambiente y se agitó durante 5 horas. La mezcla de la reacción se enfrió con una relación de 1:1 del bicarbonato de sodio acuoso saturado y 1M tiosulfato de sodio (200 mL) y luego se repartió con diclorometano. La capa orgánica se secó sobre

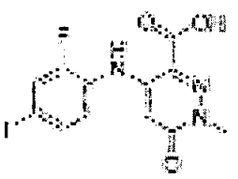
sulfato de magnesio anhidro y se concentró en vacío y dio fenilmetil 3-oxazetidina-1-carboxilato (3,43 g, rendimiento del 99%) como un aceite transparente e incoloro sin nueva purificación. ^{1}H NMR (400 MHz, $CDCl_3$): 7,39-7,31 (m, 5H), 5,17 (s, 2H), 4,77 (s, 4H). MS (EI) para $C_{11}H_{11}NO_3$: 205 (M^+).

Una suspensión de bromuro de metiltrifenilfosfonio (23,0 g, 0,0649 mol) y terc-butóxido de potasio (7,3 g, 0,0649 mol) en éter dietílico (140 mL) se agitó a temperatura ambiente durante 20 minutos, y luego se calentó a 35°C durante 1 hora. A esta mezcla de la reacción amarilla brillante se agregó lentamente una solución diluida de fenilmetil 3-oxazetidina-1-carboxilato (3,33 g, 0,0162 mol) en éter dietílico (50 mL). La mezcla de la reacción se agitó a 35°C durante 12 horas luego se filtró a través de un lecho de zeolita y se enjuagó con éter etílico. El filtrado se lavó con agua y salmuera, se secó sobre sulfato de magnesio anhidro y se concentró. El residuo se purificó mediante cromatografía rápida (SiO_3, 5%-10% acetato de etilo en hexanos) y dio fenilmetil 3-metilidenazetidina-1-carboxilato (2,46 g, rendimiento del 75%) como un aceite transparente e incoloro). ^{1}H NMR (400 MHz, $CDCl_3$): 7,27-7,22 (m, 5H), 5,02 (s, 2H), 4,93-4,90 (m, 2H), 4,48-4,47 (m, 4H). MS (EI) para $C_{12}H_{13}NO_2$: 203 (M^+).

A una solución de fenilmetil 3-metilidenazetidina-1-carboxilato (2,46 g, 0,012 mol) en cloroformo (100 mL) se agregó ácido 3-cloroperoxibenzoico (12,5 g, 0,0726 mol) a 0°C. La mezcla de la reacción se dejó calentar a temperatura ambiente durante un período de 12 horas, luego se enfrió con 1 M tiosulfato de sodio / bicarbonato de sodio acuoso saturado (1:1). Las capas se separaron y la capa orgánica se secó sobre sulfato de magnesio anhidro y luego se concentraron. El residuo se purificó mediante cromatografía rápida (5%-15% acetato de etilo en hexanos) y dio fenilmetil 1-oxa-5-azaespiro[2.3]hexano-5-carboxilato (2,2 g, rendimiento del 83%) como un aceite transparente e incoloro. ^{1}H NMR (400 MHz, $CDCl_3$): 7,37-7,29 (m, 5H), 5,12 (s, 2H), 4,35-4,26 (m, 4H), 2,85 (s, 2H). MS (EI) para $C_{12}H_{13}NO_3$: 220 (MH^+).

Referencia 4

Ácido 4-(2-fluoro-4-yodofenilamino)-1-metil-6-oxo-1,6-dihidropiridazina-3-carboxílico



El ácido 4-cloro-1-metil-6-oxo-1,6-dihidropiridazina-3-carboxílico se preparó usando procedimientos similares a aquellos descritos en US 2005256123.

A una solución del ácido 4-cloro-1-metil-6-oxo-1,6-dihidropiridazina-3-carboxílico (350 mg, 1,855 mmol) y 2-fluoro-4-yodoanilina (1,06 g, 4,453 mmol) en tetrahidrofurano (13,3 mL) se asperjó con nitrógeno durante 5 minutos y luego se agregó lentamente bis(trimetilsilil)amida de litio, 1,0 M en THF (7,4 mL). La mezcla de la reacción se agitó durante otras 4 horas a temperatura ambiente. La mezcla de la reacción se enfrió con 1 N HCl y se concentró en vacío. El residuo se repartió entre acetato de etilo y 1 N HCl acuoso. La capa acuosa se extrajo (3x con acetato de etilo. La capa orgánica combinada se lavó con salmuera, se secó sobre sulfato de sodio anhidro, se filtró y se evaporó y dio el ácido 4-(2-fluoro-4-yodofenilamino)-1-metil-6-oxo-1,6-dihidropiridazina-3-carboxílico (939 mg, rendimiento del 100%). ^{1}H NMR (400 MHz, $CDCl_3$): 7,27 (dd, 1H), 7,21 (d, 1H), 6,54 (d, 1H), 4,84 (s ancho, 3H), 2,09 (s, 1H), 1,26 (t, 3H); MS (EI) para $C_{12}H_9N_3O_3FI$ 389 (MH^+).

Una solución del ácido 4-(2-fluoro-4-yodofenilamino)-1-metil-6-oxo-1,6-dihidropiridazina-3-carboxílico (939 mg, 2,413 mmol) en diclorometano (60 mL) en la presencia de dimetilformamida (8,0 mL) se enfrió a 0°C. Se agregó cloruro de malonilo (1,26 mL, 14,48 mmol) y se agitó a temperatura ambiente durante 1 hora. La mezcla de la reacción se evaporó y se repartió entre acetato de etilo y 1 M cloruro de amonio acuoso. La capa acuosa se extrajo 1x con acetato de etilo. Las capas orgánicas

combinadas se lavaron con salmuera, se secaron sobre sulfato de sodio anhidro, se filtraron y se concentraron en vacío y dieron cloruro de 4-(2-fluoro-4-yodoenilamino)-1-metil-6-oxo-1,6-dihidropiridazina-3-carboxílico. Este material crudo se llevó al siguiente paso sin nueva purificación. MS (EI) para $C_{12}H_8N_3O_2ClFI$: 408 (MH^+).

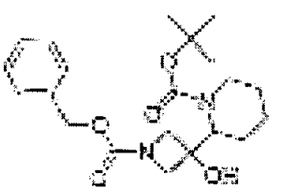
A una solución de cloruro de 4-(2-fluoro-4-yodoenilamino)-1-metil-6-oxo-1,6-dihidropiridazina-3-carboxílico en metanol (15 ml) y benceno (12 mL) se agregó gota a gota diazometano (1 mL) y se agitó a temperatura ambiente durante 15 minutos. La mezcla de la reacción se enfrió con ácido acético y se evaporó. El residuo se repartió entre acetato de etilo y salmuera. La capa orgánica se separó, se secó sobre sulfato de sodio anhidro, se filtró y se concentró en vacío. El residuo se purificó sobre una columna de cromatografía de gel de sílice (7:3 hexanos/acetato de etilo) y dio metil 4-(2-fluoro-4-yodofenilamino)-1-metil-6-oxo-1,6-dihidropiridazina-3-carboxilato (84,9 mg, rendimiento del 8,7%). ^1H NMR (400 MHz, $CDCl_3$): 7,49-7,56 (m, 3H), 7,12 (t, 1H), 6,13 (d, 1H), 4,00 (s, 3H), 3,83 (s, 3H); MS (EI) para $C_{13}H_{11}N_3O_3FI$: 404 (MH^+).

Metil 4-(2-fluoro-4-yodofenilamino)-1-metil-6-oxo-1,6-dihidropiridazina-3-carboxilato (84,9 mg, 0,211 mmol) se disolvió en tetrahidrofurano (5 mL), metanol (2,5 mL) y agua (2,5 mL). Se agregó hidróxido de litio 2M acuoso (200 µL) a temperatura ambiente. Después de 10 minutos, la mezcla de la

reacción se calentó a 50°C durante 30 minutos y se continuó agitando a temperatura ambiente durante 16 horas en cuyo momento los solventes se evaporaron. El residuo se hizo ácido con 2M ácido clorhídrico acuoso a pH 2 y se extrajo con acetato de etilo. La capa orgánica se separó, se secó sobre sulfato de sodio anhidro, se filtró y se concentró en vacío y proporcionó el Ácido 4-(2-fluoro-4-yodofenilamino)-1-metil-6-oxo-1,6-dihidropiridazina-3-carboxílico (54 mg, rendimiento del 66%). MS (EI) para $C_{12}H_9N_3O_3FI$: 390 (MH^+).

Referencia 5

1,1-dimetiletil 2-(3-hidroxi-1-{[(fenilmetil)oxi]carbonil}azetidina-3-il)piridina-1-carboxilato

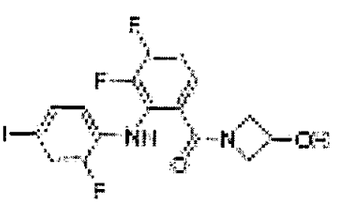


A una solución de 1,1-dimetiletil 1-piperidina-1-carboxilato (0,90 g, 2,7 mmol) en éter dietílico anhidro (9,0 mL) bajo gas nitrógeno anhidro se agregó N,N,N'N'-tetrametiletano-1,2-diamina (0,41 mL, 2,7 mmol) y la solución se enfrió a -78°C. A esta solución se agregó (2-metilpropil)litio (2, mL, 1,4 M en ciclohexano, 3,0 mmol) en porciones pequeñas. A esta solución de anión se agregó fenilmetil 3-oxoazetidina-1-carboxilato

(1,0 g, 5,4 mmol), preparada usando procedimientos descritos en la Referencia 3, en éter anhidro (2,0 mL), mientras se mantenía la temperatura interna por debajo de -60°C. La solución se dejó calntar a temperatura ambiente y se agitó toda la noche. La reacción se enfrió con agua y se repartió entre agua y éter dietílico. Las capas se separaron y la capa acuosa se extrajo con éter dietílico dos veces. Las capas orgánicas combinadas se secaron (sulfato de magnesio), se filtraron y se concentraron en vacío. La cromatografía (gel de sílice, 3:1 hexanos/acetato de etilo) dio 0,13 g (13%) de 1,1-dimetiletil 2-(3-hidroxi-1-{[(fenilmetil)oxi]carbonil}azetidina-3-il)piridina-1-carboxilato. ^{1}H NMR (400 MHz, $CDCl_3$): 7,31 (m, 5H), 5,08 (s, 2H), 4,05 (d, 1H), 4,00 (d, 1H), 3,84 (d, 2H), 3,80 (s ancho, 1H), 3,55 (s ancho, 1H), 3,10 (s ancho, 1H), 1,92 (m, 1H), 1,45-1,62 (m, 6H), 1,43 (s, 9H). MS (EI) para $C_{21}H_{30}N_2O_5$: 335 (M-tBu), 315 (M-OtBu).

EJEMPLO 1

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol



El ácido 3,4-difluoro-1-[(2-fluoro-4-yodofenil)amino]benzoico (2,1 g, 5,3 mmol), preparado usando procedimientos similares a aquellos de US 7.019.033, se llevó a DMF (10 mL) y luego se agregó PyBOP (2,6 g, 5,3 mmol) y la mezcla se dejó agitar a temperatura ambiente durante 15 minutos. Luego se agregaron clorhidrato de azetidin-3-ol (870 mg, 8,0 mmol) y DIPEA (1,85 mL, 11,2 mmol) y la mezcla se dejó agitar una hora adicional a temperatura ambiente. La mezcla luego se repartió con acetato de etilo y 0,5 M solución de hidróxido de sodio acuosa. La capa orgánica luego se lavó con agua (3x) y luego con salmuera y se secó sobre sulfato de sodio anhidro. La filtración y la concentración y luego la cromatografía rápida de gel de sílice usando un eluyente de acetato de etilo : hexanos (5:1) dio 1-({(3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}crbonil)azetidin-3-ol (2,09 g, rendimiento del 87%) como un sólido amorfo incoloro. ^{1}H NMR (400 MHz, $CDCl_3$): 8,47 (s, 1H), 7,39 (dd, 1H), 7,32 (d, 1H), 7,13-7,09 (m, 1H), 6,84-6,78 (m, 1H), 6,63-6,57 (m, 1H), 4,74-4,67 (m, 1H), 4,43-4,39 (m, 2H), 4,20-3,96 (br d, 2H), 2,50 (d, 1H).

Usando las mismas técnicas sintéticas o técnicas sintéticas análogas y sustituyendo según sea necesario con reactivos alternativos, se prepararon los compuestos de los Ejemplos 1(a)-(e).

EJEMPLO 1(a). 1-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]-*N*,*N*-dimetilpirrolidin-3-amina. El compuesto del título se preparó haciendo reaccionar ácido 3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]benzoico con *N*-metil-*N*-(2-(piridin-2-il)etil)azetidin-3-amina. El compuesto intermedio azetidina se preparó usando procedimientos similares a los descritos en Abdel-Magid, et.al., *Tetrahedron Letters* **1990**, *31(39)*, 5595 partiendo con *terc*-butil 3-oxoazetidina-1-carboxilato, que en sí se describe en el Ejemplo 3. El compuesto del título: ^{1}H NMR (400 MHz, d_6-DMSO): 8,56 (s, 1H), 7,58 (m, 1H), 7,38 (d, 1H), 7,31 (m, 1H), 7,16 (m, 1H), 6,67 (m, 1H), 4,16 (m, 1H), 3,97 (m, 2H), 3,77 (m, 1H), 3,26 (br s, 4H), 2,63 (m, 1H), 2,42 (br s, 6H), 1,99 (br s, 1H), 1,74 (br s, 1H). MS (EI) para $C_{22}H_{24}F_3IN_4O$: 545 (MH^+).

EJEMPLO 1(b). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-metil-*N*-(2-piridin-2-iletil)azetidin-3-amina. El compueto del título se preparó haciendo reaccionar ácido 3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]benzoico con 1-(azetidin-3-il)-N,N-dimetilpirrolidin-3-amina. El compuesto intermedio azetidina se preparó usando procedimientos similares a aquellos descritos en Abdel-Magid, et.al., *Tetrahedron Letters* **1990**, *31(39)*, 5595 partiendo de *terc*-butil 3-oxoazetidina-1-carboxilato, que en sí mismo se preparó como se describe en el

Ejemplo 3. El compuesto del título: ^{1}H NMR(400 MHz, CD_3OD): 8,50 (d, 1H), 7,94 (t, 1H), 7,50-7,30 (m, 5H), 7,07 (q, 1H), 6,66-6,61 (m, 1H), 4,52-4,48 (m, 2H), 4,31(s, 2H), 4,23-4,18 (m, 1H), 3,48-3,46 (m, 2H), 3,17-3,13 (m, 2H), 2,88 (s, 3H); MS(EI) para $C_{24}H_{22}F_3IN_4O$: 567 (MH^+).

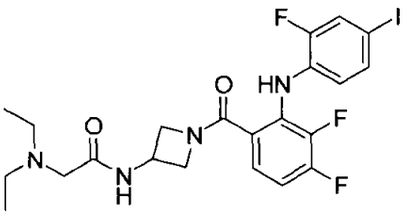
EJEMPLO 1(c). 6-(Azetidin-1-ilcarbonil)-2,3-difluoro-*N*-(2-fluoro-4-yodofenil)anilina: ^{1}H NMR (400 MHz, $CDCl_3$): 8,57 (s, 1H), 7,41-7,38 (dd, 1H), 7,34-7,31 (dt, 1H), 7,13-7,09 (m, 1H), 6,83-6,77 (m, 1H), 6,64-6,58 (m, 1H), 4,27 (b, 2H), 4,18 (b, 2H), 2,38-2,30 (p, 2H); MS (EI) para $C_{16}H_{12}F_3IN_3O$: 433 (MH^+).

EJEMPLO 1(d). [1-({3,4-Difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]metanol: ^{1}H NMR (400 MHz, $CDCl_3$): 8,52 (s, 1H), 7,41-7,38 (dd, 1H), 7,34-7,31 (dt, 1H), 7,15-7,11 (m, 1H), 6,83-6,77 (m, 1H), 6,64-6,58 (m, 1H), 4,29-4,20 (m, 2H), 4,09 (b, 1H), 3,93 (b, 1H), 3,82-3,81 (d, 2H), 2,89-2,75 (m, 1H); MS (EI) para $C_{17}H_{14}F_3IN_2O_2$: 463 (MH^+).

EJEMPLO 1(e). Ácido 1-({3,4-Difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidina-3-carboxílico: ^{1}H NMR (400 MHz, $CDCl_3$): 7,79 (b, 2H), 7,42-7,38 (dd, 1H), 7,34-7,32 (dt, 1H), 7,15-7,11 (m, 1H), 6,89-6,83 (m, 1H), 6,65-6,60 (m, 1H), 4,46-4,29 (m, 4H), 3,55-3,47 (m, 1H); MS (EI) para $C_{17}H_{12}F_3IN_2O_3$: 477 (MH^+).

EJEMPLO 2

***N*-[1-({3,4-Difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]-*N2,N2*-dietilglicinamida**



Una solución del ácido 3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]benzoico (200 mg, 0,51 mmol), preparado usando procedimientos similares a aquellos de US 7.019.033, PyBOP (256 mg, 0,51 mmol), terc-butil azetidin-3-ilcarbamato comercialmente disponible (131 mg, 0,77 mmol) y N,N-diisoprpiletilamina (180 µL, 1,02 mmol) en dimetilformamida (3 mL) se agitó a temperatura ambiente durante 15 horas. La mezcla se repartió entre 5% cloruro de litio acuoso y acetato de etilo. La parte orgánica se lavó con 20% ácido cítrico acuoso, bicarbonato de sodio acuoso saturado, salmuera, se secó sobre sulfato de sodio, se filtró y se concentró en vacío y dio un residuo marrón que se purificó mediante cromatografía de columna de gel de sílice eluyendo con 30% acetato de etilo en hexanos y dio 1,1-dimethylethyl [1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]carbamato (225 mg, rendimiento del 80%) como un aceite incoloro. ^{1}H NMR (400 MHz, DMSO): 8,56 (s, 1H), 7,60-7,55 (m,

2H), 7,38 (d, 1H), 7,30-7,26 (m, 1H), 7,20-7,13 (m, 1H), 6,71-6,66 (m, 1H), 4,37-4,20 (m, 2H), 4,18-4,06 (m, 1H), 3,98-3,93 (m, 1H), 3,82-3,75 (m, 1H), 1,37 (s, 9H). MS (EI) $C_{21}H_{21}N_3O_3F_3I$: 548 (MH^+).

Una solución de 1,1-dimetiletil [1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]carbamato (113 mg, 0,20 mmol) y ácido trifluoroacético (500 µL) en diclorometano (2 mL) se agregó y se agitó a temperatura ambiente durante una hora y luego se repartió entre bicarbonato de sodio acuoso saturado y diclorometano. La parte orgánica se lavó con salmuera, se secó sobre sulfato de sodio anhidro y se concentró y dio un residuo incoloro que se purificó mediante cromatografía de columna con 10% metanol en diclorometano y dio 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-amina (85 mg, rendimiento 95%) como una espuma blanca. ^1H NMR (400 MHz, $CDCl_3$): 8,53 (s, 1H), 7,39 (d, 1H), 7,32 (d, 1H), 7,13-7,09 (m, 1H), 6,84-6,77 (m, 1H), 6,63-6,57 (m, 1H), 4,46-4,39 (m, 2H), 3,98-3,75(br m, 4H); MS (EI) para $C_{16}H_{13}F_3IN_3O$: 448 (MH^+).

Una solución de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-amina (100 mg, 0,22 mmol), PyBOP (131 mg, 0,25 mmol), *N,N*-diisopropiletilamina (80 µL, 0,44 mol) y ácido bromoacético (35 mg, 0,25 mmol) en dimetilformamida (1 mL) se agitó a temperatura ambiente

durante 15 horas. La mezcla de la reacción se concentró en vacío y el residuo resultante se purificó mediante cromatografía de columna eluyendo con 80% acetato de etilo y dio 2-bromo-*N*-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]acetamida (102 mg, rendimiento 82%) como una espuma blanca. MS (EI) para $C_{18}H_{14}BrF_3IN_3O_2$: 568.

Una solución de 2-bromo-*N*-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]acetamida (30 mg, 0,05 mmol) y *N,N*-dietilamina (100 µL, exceso) en diclorometano (2 mL) se agitó a temperatura ambiente durante 15 horas. La mezcla de la reacción se concentró en vacío y se purificó mediante HPLC de fase invertida preparativa (CH_3CN/H_2O con 0,1% TFA). El producto aislado se concentró en vacío y dio sal de trifluoroacetato de *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]-*N2,N2*-dietilglicinamida (13,0 mg, rendimiento del 38%) como un sólido blanco. ^{1}H NMR (400 MHz, $CDCl_3$): 9,36 (br s, 1H), 9,25 (d, 1H), 8,60 (s, 1H), 7,60 (d, 1H), 7,40 (d, 1H), 7,33-7,27 (m, 1H), 7,22-7,15 (m, 1H), 6,73-6,66 (m, 1H), 4,54-4,40 (m, 2H), 4,25-4,20 (m, 1H), 4,04-3,82 (m, 4H), 3,17-3,12 (m, 4H), 1,18-1,15 (m, 6H); MS (EI) $C_{22}H_{24}F_3IN_4O_2$: 561 (MH^+).

Usando las mismas técnicas sintéticas o técnicas sintéticas análogas y/o sustituyendo con reactivos alternativos, se prepararon los compuestos de los Ejemplos 2(a)-(n).

EJEMPLO 2(a). 1,1-Dimetiletil [1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]carbamato: ^{1}H NMR (400 MHz, $CDCl_3$): 8,52 (br s, 1H), 7,40 (dd, 1H), 7,33 (dt, 1H), 7,13-7,07 (m, 1H), 6,80 (ddd, 1H), 6,61 (ddd, 1H), 5,01-4,88 (br, 1H), 4,55-4,37 (br, 4H), 4,05 (br d, 1H), 1,43 (s, 9H); MS (EI) para $C_{21}H_{21}F_3IN_3O_3S$: 548 (MH^+).

EJEMPLO 2(b). Sal de trifluoroacetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-amina: ^{1}H NMR (400 MHz, $CDCl_3$): 8,53 (s, 1H), 7,39 (d, 1H), 7,32 (d, 1H), 7,13-7,09 (m, 1H), 6,84-6,77 (m, 1H), 6,63-6,57 (m, 1H), 4,46-4,39 (m, 2H), 3,98-3,75(br m, 4H); MS (EI) para $C_{16}H_{13}F_3IN_3O$: 448 (MH^+).

EJUEMPLO 2(c). *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]-2-metilpropanamida: ^{1}H NMR (400 MHz, DMSO): 8,60 (s, 1H), 8,38 (d, 1H), 7,59 (d, 1H), 7,38 (d, 1H), 7,32-7,28 (m, 1H), 7,18-7,13 (m, 1H), 6,72-6,66 (m, 1H), 4,45-4,35 (m, 1H), 4,18-3,77 (m, 4H), 2,36-2,28 (m, 1H), 0,99 (d, 6H); MS (EI) $C_{20}H_{19}F_3IN_3O_2$: 518 (MH^+).

EJEMPLO 2(d). *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]formamida: ^{1}H NMR (400 MHz, DMSO): 8,69 (d, 1H), 8,58 (s, 1H), 8,02 (s, 1H), 7,59 (d, 1H), 7,39 (d, 1H), 7,31-7,27 (m, 1H), 7,19-7,13 (m, 1H), 6,70-6,66 (m, 1H), 4,55-4,46 (m, 1H), 4,42-4,36 (m, 1H),

4,20-4,16 (m, 1H), 4,01-3,97 (m, 1H), 3,82-3,79 (m, 1H); MS (EI) $C_{17}H_{13}F_3IN_3O_2$: 476 (MH^+).

EJEMPLO 2(e). *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]-3,4-dihidroxibutanamida: ^1H NMR (400 MHz, DMSO): 8,60 (s, 1H), 8,47 (d, 1H), 7,59 (d, 1H), 7,39 (d, 1H), 7,31-7,28 (m, 1H), 7,20-7,14 (m, 1H), 6,72-6,66 (m, 1H), 4,45-4,35 (m, 2H), 4,18-4,14 (m, 1H), 4,00-3,92 (m, 1H), 3,84-3,78 (m, 2H), 3,31-3,18 (m, 2H), 2,38-2,18 (m, 1H), 2,09-2,03 (m, 1H); MS (EI) $C_{20}H_{19}F_3IN_3O_4$: 550 (MH^+).

EJEMPLO 2(f). metil [1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]carbamato: ^1H NMR (400 MHz, DMSO): 8,58 (s, 1H), 7,84 (d, 1H), 7,59 (d, 1H), 7,39 (d, 1H), 7,35-7,27 (m, 1H), 7,20-7,13 (m, 1H), 6,71-6,66 (m, 1H), 4,38-4,25 (m, 2H), 4,17-4,12 (m, 1H), 4,00-3,97 (m, 1H), 3,83-3,78 (m, 1H), 3,53 (s, 3H); MS (EI) $C_{18}H_{15}F_3IN_3O_3$: 506 (MH^+).

EJEMPLO 2(g). Sal de trifluoroacetato de *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]-2-(4-metilpiperazin-1-il)acetamida: ^1H NMR (400 MHz, DMSO): 8,64 (s, 1H), 8,54 (d, 1H), 7,60 (d, 1H), 7,39 (d, 1H), 7,32-7,29 (m, 1H), 7,21-7,15 (m, 1H), 6,72-6,66 (m, 1H), 4,54-4,28 (m, 2H), 4,19-4,15 (m, 1H), 4,06-4,00 (m, 1H), 3,91-3,84 (m, 1H), 3,44-3,24 (m, 2H), 3,16-2,92 (m, 6H), 2,78 (s, 3H), 2,62-2,50 (m, 2H); MS (EI) $C_{23}H_{25}F_3IN_5O_2$: 588 (MH^+).

EJEMPLO 2(h). Sal de trifluoroacetato de *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]-*N*,*N*-bis(2-hidroxietil)glicinamidat: ^{1}H NMR (400 MHz, DMSO): 9,19 (d, 1H), 7,60 (d, 1H), 7,41 (d, 1H), 7,31-7,27 (m, 1H), 7,21-7,15 (m, 1H), 6,73-6,66 (m, 1H), 4,51-4,40 (m, 2H), 4,23-4,18 (m, 1H), 4,05-3,98 (m, 3H), 3,86-3,82 (m, 1H), 3,75-3,69 (m, 3H), 3,32 (br s, 4H) $C_{22}H_{24}F_3IN_4O_4$: 593 (MH^+).

EJEMPLO 2(i). Sal de trifluoroacetato de *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]-2-piperidin-1-ilacetamida: ^{1}H NMR (400 MHz, DMSO): 9,20 (d, 1H), 7,60 (d, 1H), 7,41 (d, 1H), 7,31-7,27 (m, 1H), 7,21-7,15 (m, 1H), 6,73-6,66 (m, 1H), 4,52-4,40 (m, 2H), 4,24-4,18 (m, 1H), 4,05-4,00 (m, 1H), 3,87-3,80 (m, 3H), 3,40-3,32 (m, 2H), 3,00-2,91 (m, 2H), 1,82-1,66 (m, 6H); MS (EI) $C_{23}H_{24}F_3IN_4O_2$: 573 (MH^+).

EJEMPLO 2(j). Clorhidrato de *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]-N3-(2-hidroxietil)-N3-metil-beta-alaninamida: ^{1}H NMR (400 MHz, DMSO): 9,36 (br s, 1H), 8,86 (d, 1H), 8,60 (s, 1H), 7,59 (d, 1H), 7,39 (d, 1H), 7,32-7,26 (m, 1H), 7,21-7,14 (m, 1H), 6,72-6,66 (m, 1H), 5,35-5,33 (m, 1H), 4,48-4,37 (m, 2H), 4,20-4,15 (m, 1H), 4,02-3,96 (m, 1H), 3,84-3,79 (m, 1H), 3,74-3,68 (m, 2H), 3,42-3,06 (m, 4H), 2,75 (s, 3H), 2,65-2,60 (m, 2H); MS (EI) $C_{22}H_{24}F_3IN_4O_3$: 577 (MH^+).

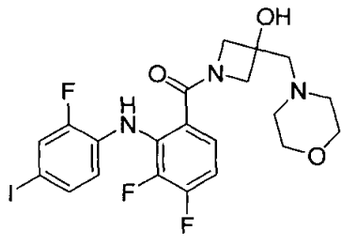
EJEMPLO 2(k). Clorhidrato de *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]-N3,N3-bis(2-hidroxietil)-beta-alaninamida: ^{1}H NMR (400 MHz, DMSO): 9,39 (br s, 1H), 8,91 (d, 1H), 8,61 (s, 1H), 7,59 (d, 1H), 7,39 (d, 1H), 7,31-7,27 (m, 1H), 7,21-7,14 (m, 1H), 6,72-6,66 (m, 1H), 5,31 (br s, 2H), 4,46-4,36 (m, 2H), 4,20-4,15 (m, 1H), 4,02-3,97 (m, 1H), 3,85-3,72 (m, 5H), 3,30-3,17 (m, 4H), 2,68-2,63 (m, 2H); MS (EI) $C_{23}H_{26}F_3IN_4O_4$: 607 (MH^+).

EJEMPLO 2(m). Sal de trifluoroacetato de *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]-N2-metilglicinamida: ^{1}H NMR (400 MHz, DMSO): 9,09 (d, 1H), 8,69 (br s, 2H), 8,60 (s, 1H), 7,60 (d, 1H), 7,39 (d, 1H), 7,31-7,27 (m, 1H), 7,22-7,15 (m, 1H), 6,73-6,66 (m, 1H), 4,54-4,41 (m, 2H), 4,25-4,19 (m, 1H), 3,99-3,96 (m, 1H), 3,84-3,78 (m, 1H), 3,72-3,67 (m, 2H), 2,58-2,54 (m, 3H); MS (EI) $C_{19}H_{18}F_3IN_4O_2$: 519 (MH^+).

EJEMPLO 2(n). Sal de trifluoroacetato de *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]glicinamida: ^{1}H NMR (400 MHz, DMSO): 8,59 (s, 1H), 8,46 (br s, 1H), 7,59 (d, 1H), 7,39 (d, 1H), 7,32-7,28 (m, 1H), 7,20-7,13 (m, 1H), 6,72-6,66 (m, 1H), 4,49 (br s, 1H), 4,40-4,35 (m, 1H), 4,18-4,13 (m, 1H), 4,05-4,01 (m, 1H), 3,86-3,81 (m, 1H), 3,07 (s, 2H); MS (EI) $C_{18}H_{16}F_3IN_4O_2$: 505 (MH^+).

EJEMPLO 3

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(morfolin-4-ilmetil)azetidin-3-ol



Una mezcla de clorhidrato de 3-azetidinol (10 g, 91 mmol), bicarbonato de di-terc-butilo (18,8 g, 86,3 mmol) y bicarbonato de sodio (15,3 g, 182 mmol) en dioxano:agua (400 mL, 1:1) se agitó a temperatura ambiente durante 15 horas. La parte orgánica se removió en vacío y la parte acuosa se extrajo con acetato de etilo tres veces. La parte orgánica combinada se lavó con 5% HCl acuoso, agua, salmuera, se secó sobre sulfato de sodio y se concentró en vacío y dio 12,8 g, 74 mmol (81%) de 1,1-dimetiletil 3-hidroxiazetidina-1-carboxilato como un aceite incoloro sin nueva purificación. ^{1}H NMR (400 MHz, DMSO): 5,62 (d, 1H), 4,40-4.33 (m, 1H), 4,02-3,95 (m, 2H), 3,62-3,54 (m, 2H), 1,37 (s, 9H). GC/MS para $C_8H_{15}NO_3$: 173.

Una solución de cloruro de oxalilo (545 µL, 6,36 mmol) en diclorometano (25 mL) se enfrió a -78 °C. Mientras se mantenía

una temperatura interna de -78°C, se agregó gota a gota DMSO (903 µL, 12,7 mmol), luego 1,1-dimetiletil 3-hidroxiazetidina-1-carboxilato (1 g, 5.78 mmol en 30 mL de diclorometano) y finalmente trietilamina (3,25 mL, 23,1 mmol en 20 mL de diclorometano). La mezcla se dejó calentar a temperatura ambiente y se agitó durante 15 horas. La mezcla de la reacción se diluyó con agua y se repartió y la parte orgánica se lavó dos veces con agua. La parte acuosa combinada se extrajo una vez con diclorometano. La parte orgánica combinada se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y se concentró en vacío y dio un aceite amarillo que se purificó mediante cromatografía de columna. Eluyendo con 30% acetato de etilo y hexanos, el producto aislado se concentró en vacío y dio 893 mg, 5,20 mmol (90%) de 1,1-dimetiletil 3-oxoazetidina-1-carboxiltato como un aceite incoloro, que se solidificó al estar en reposo. ^{1}H NMR (400 MHz, DMSO): 4,67 (s, 4H), 1,42 (s, 9H). GC/MS para $C_8H_{13}NO_3$: 171

Una mezcla de terc-butóxido de potasio (15,5 g, 137 mmol) y bromuro de metiltrifenilfosfina (49 g, 137 mmol) en éter dietílico (300 mL) se agitó a temperatura ambiente durante 1 hora, luego se agregó 1,1-dimetiletil 3-oxoazetidina-1-carboxilato (10 g, 58 mmol en 100 mL de éter dietílico). La mezcla se agitó a 35°C durante 2 horas y luego se dejó enfriar a temperatura ambiente. La mezcla se filtró a través de un

tampón de celita, lavando con éter dietílico. El filtrado se repartió con agua y se lavó dos veces con agua, salmuera, se secó sobre sulfato desodio, se filtró y se concentró en vacío y dio un aceite naranja que se purificó mediante cromatografía de columna. Eluyendo con 10% acetato de etilo en hexanos, el producto aislado se concentró en vacío y dio 9,80 g, 58 mmol (100%) de 1,1-dimetiletil 3-metilidenazetidina-1-carboxilato como un aceite incoloro. ^{1}H NMR (400 MHz, DMSO): 5,05-4,85 (m, 2H), 4,95-4,63 (m, 4H), 1,45 (s, 9H). GC-MS para $C_9H_{15}NO_2$: 169.

A una solución de 1,1-dimetiletil 3-metilidenazetidina-1-carboxilato (2,96 g, 17,5 mmol) en cloroformo (180 mL) se agregó ácido 3-cloroperoxibenzoico (77%, 13,9 g, 62,0 mmol) y la mezcla resultante se agitó a temperatura ambiente durante 2 días. La mezcla de la reacción se enfrió con una mezcla 1:1 (150 mL) de 10% soluciones de tiosulfato de sodio y bicarbonato de sodio saturado. La parte orgánica se aisló, se secó sobre sulfato de sodio, se filtró y se concentró y dio un residuo aceitoso que luego se purificó mediante cromatografía rápida (15%-50%, acetato de etilo-hexanos) y dio 1,1-dimetiletil 1-oxa-5-azaespiro[2.3]hexano-5-carboxilato (1,65 g, 51%), GC-MS para $C_9H_{15}NO_3$: 185.

1,1-Dimetiletil 1-oxa-5-azaespiro[2.3]hexano-5-carboxilato (51 g, 0,28 mmol) se llevó a THF (1 mL), luego se agregó morfolina

(123 µL, 1,4 mmol) y la mezcla se agitó durante una hora a temperatura ambiente. La solución luego se concentró y el residuo se repartió con acetato de etilo y agua. La capa orgánica se lavó una vez con agua luego con salmuera y la capa orgánica se secó sobre sulfato de sodio anhidro. La filtración y la concentración dieron un aceite incoloro que se purificó mediante cromatografía rápida de gel de sílice usando acetato de etilo a 10% de metanol en diclorometano como eluyentes. Las fracciones puras combinadas se conentraron y el residuo se trató con TFA puro (1 mL) durante 5 minutos y luego se concentraron. El residuo se llevó a metanol (2 mL) y se basificó a pH > 10 agregando Biorad AG-1X hidróxido en forma de resina. La filtración y la concentración dio 3-(morfolin-4-ilmetil)azetidin-3-ol (11,6 mg, rendimiento del 24%) como un aceite incoloro. ^{1}H NMR (400 MHz, CD_3OD): 3,69-3,66 (m, 4H), 3,55 (d, 2H), 3,49 (d, 2H), 2,66 (s, 2H), 2,57-2,55 (m, 4H).

3-(Morfolin-4-ilmetil)azetidin-3-ol (11,6 mg, 0,07 mmol) se llevó a DMF (1 mL) y luego se agregó DIPEA (35 µL, 0,21 mmol) y fluoruro de 3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]benzoilo (28 mg, 0,07 mmol), preparado usando procedimientos similares a aquellos descritos en la Referencia 1, y la mezcla se agitó durante 30 minutos a temperatura ambiente. La solución luego se concentró en vacío y el residuo

se purificó mediante HPLC de fase invertida preparativa. La liofilización de la fracción combinada dio sal de trifluoroacetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(morfolin-4-ilmetil)azetidin-3-ol (6,3 mg) como un sólido amorfo incoloro. ^{1}H NMR (400 MHz, CD_3OD): 7,48 (d, 1H), 7,36 (d, 1H), 7,33-7,29 (m, 1H), 7,08-7,02 (m, 1H), 6,65-6,60 (m, 1H), 4,39 (br d, 1H), 4,24-4,18 (br, 2H), 4,08-3,96 (br m, 3H), 3,80 (br s, 2H), 3,51 (d, 2H), 3,40 (br s, 2H), 3,24 (br s, 2H).

Usando las mismas técnicas sintéticas u otras análogas y sustituyendo según sea necesario, con otros reactivos, se prepararon los siguientes compuestos.

EJEMPLO 3(a). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(pirrolidin-1-ilmetil)azetidin-3-ol: MS (EI) para $C_{21}H_{21}F_3IN_3O_2$: 532 (MH^+).

EJEMPLO 3(b). 1-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}piperidin-4-ol: MS (EI) para $C_{22}H_{23}F_3IN_3O_3$: 562 (MH^+).

EJEMPLO 3(c). 3-{[bis(2-hidroxietil)amino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: MS (EI) para $C_{21}H_{23}F_3IN_3O_4$: 566 (MH^+).

EJEMPLO 3(d). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenyl)amino]fenil}carbonil)-3-[(4-metilpiperazin-1-il)metil]azetidin-3-ol: MS (EI) para $C_{22}H_{24}F_3IN_4O_2$: 561 (MH^+).

EJEMPLO 3(e). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(4-metil-1,4-diazepan-1-il)metil]azetidin-3-ol: MS (EI) para $C_{23}H_{26}F_3IN_4O_2$: 575 (MH^+).

EJEMPLO 3(f). 1-({3,4-difluoro-2-{(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[metil(1-metilpirrolidin-3-il)amino]metil}azetidin-3-ol: MS (EI) para $C_{23}H_{26}F_3IN_4O_2$: 575 (MH^+).

EJEMPLO 3(g). 3-(1,4'-bipiperidin-1'-ilmetil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: MS (EI) para $C_{27}H_{32}F_3IN_3O_2$: 629 (MH^+).

EJEMPLO 3(h). 3-({4-[2-(dietilamino)etil]piperazin-1-il}metil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: MS (EI) para $C_{27}H_{35}F_3IN_3O_2$: 647 (MH^+).

EJEMPLO 3(i). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-hidroxietil)(metil)amino]metil}azetidin-3-ol: MS (EI) para $C_{20}H_{21}F_3IN_3O_3$: 536 (MH^+).

EJEMPLO 3(j). 3-(azetidin-1-ilmetil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: MS (EI) para $C_{20}H_{19}F_3IN_3O_2$: 518 (MH^+).

EJEMPLO 3(k). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1-metiletil)amino]metil}azetidin-3-ol: MS (EI) para $C_{20}H_{21}F_3IN_3O_2$: 520 (MH^+).

EJEMPLO 3(m). 3-(aminometil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: MS (EI) para $C_{17}H_{15}F_3IN_3O_2$: 478 (MH^+).

EJEMPLO 3(n). *N*-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}acetamida: MS (EI) para $C_{19}H_{17}F_3IN_3O_3$: 520 (MH^+).

EJEMPLO 3(o). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1,1-dimetiletil)amino]metil}azetidin-3-ol: MS (EI) para $C_{21}H_{23}F_3IN_3O_4$: 534 (MH^+).

EJEMPLO 3(q). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(hidroxiamino)metil]azetidin-3-ol: ^1H NMR (400 MHz, d_4-MeOH): 7,45 (2d, 1H), 7,35 (m, 1H), 7,28 (m, 1H), 7,03 (m, 1H), 6,63 (m, 1H), 4,32 (d, 1H), 4,05 (dd, 2H), 3,85 (d, 1H), 3,00 (s, 2H); MS (EI) para $C_{17}H_{15}F_3IN_3O_3$: 494 (MH^+).

EJEMPLO 3(r). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(metiloxi)amino]metil}azetidin-3-ol: ^1H NMR (400 MHz, d_4-MeOH): 7,45 (2d, 1H), 7,35 (m, 1H), 7,27 (m, 1H), 7,04 (m, 1H), 6,62 (m, 1H), 4,26 (d, 1H), 4,08 (d, 1H), 4,00 (d, 1H),

3,84 (d, 1H), 3,30 (s, 3H), 3,00 (d, 2H); MS (EI) para $C_{18}H_{17}F_3IN_3O_3$: 508 (MH^+).

EJEMPLO 3(s). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(etiloxi)amino]metil}azetidin-3-ol: ^1H NMR (400 MHz, d_4-MeOH): 7,45 (2d, 1H), 7,34 (m, 1H), 7,26 (m, 1H), 7,03 (m, 1H), 6,63 (m, 1H), 4,26 (d, 1H), 4,12 (d, 1H), 4,00 (d, 1H), 3,84 (d, 1H), 3,61 (dd, 2H), 3,00 (s, 2H), 1,06 (t, 3H); MS (EI) para $C_{19}H_{19}F_3IN_3O_3$: 522 (MH^+).

EJEMPLO 3(t). Sal de acetato de 1-{[1-({3,4-difluoro-2-[(2-fluoro-4-ydofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}guanidina: ^1H NMR (400 MHz, d_4-MeOH): 7,46 (2d, 1H), 7,36 (m, 1H), 7,30 (m, 1H), 7,04 (m, 1H), 6,62 (m, 1H), 4,18 (d, 1H), 4,08 (d, 1H), 4,02 (d, 1H), 3,88 (1*H*), 3,40 (s, 2H); MS (EI) para $C_{18}H_{17}F_3IN_5O_2$: 520 (MH^+).

EJEMPLO 3(u). Clorhidrato de *N*-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}bencencarboximidamida: ^1H NMR (400 MHz, d_4-MeOH): 7,70 (d, 3H), 7,58 (m, 2H), 7,46 (dd, 1H), 7,36 (m, 1H), 7,31 (m, 1H), 7,04 (m, 1H), 6,62 (m, 1H), 4,28 (m, 1H), 4,15 (m, 2H), 3,96 (m, 1H), 3,78 (s, 2H); MS (EI) para $C_{24}H_{20}F_3IN_4O_2$: 581 (MH^+).

EJEMPLO 3(v). Clorhidrato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(pirimidin-2-ilamino)metil]azetidin-3-ol: ^1H NMR (400 MHz, d_4-MeOH): 8,48

(s, 2H), 7,46 (2d, 1H), 7,36 (m, 1H), 7,28 (m, 1H), 7,04 (m, 1H), 6,85 (t, 1H), 6,61 (m, 1H), 4,24 (d, 1H), 4,06 (t, 2H), 3,87 (d, 1H), 3,75 (d, 2H); MS (EI) para $C_{21}H_{17}F_3IN_5O_2$: 556 (MH^+).

EJEMPLO 3(w). Clorhidrato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(piridin-2-ilamino)metil]azetidin-3-ol: ^1H NMR (400 MHz, d_4-MeOH): 7,87 (dd, 1H), 7,85 (dd, 1H), 7,46 (2d, 1H), 7,36 (m, 2H), 7,06 (m, 2H), 6,89 (m, 1H), 6,61 (m, 1H), 4,53 (d, 2H), 4,46 (m, 1H), 4,28 (m, 1H), 4,16 (m, 1H), 3,96 (m, 1H); MS (EI) para $C_{22}H_{18}F_3IN_4O_2$: 555 (MH^+).

EJEMPLO 3(x). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(etilamino)metil]azetidin-3-ol: ^1H NMR (400 MHz, d_6-DMSO): 8,61 (s, 2H), 7,59 (d, 1H), 7,40 (d, 1H), 7,36-7,33 (m, 1H), 7,23-7,18 (m, 1H), 6,71 (s, 2H), 4,31-4,26 (m, 1H), 4,13-4,05 (m, 2H), 3,88-3,84 (m, 1H), 3,21 (br m, 2H), 2,97-2,90 (m, 2H), 1,19 (t, 3H). MS (EI) para $C_{19}H_{19}F_3IN_3O_2$: 506 (MH^+).

EJEMPLO 3(y). 3-[(ciclopropilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: ^1H NMR (400 MHz, d_6-DMSO): 8,99 (br s, 2H), 8,60 (s, 1H), 7,58 (d, 1H), 7,39 (d, 1H), 7,36-7,33 (m, 1H), 7,23-7,16 (m, 1H), 6,72 (s, 2H), 4,34-4,29 (m, 1H), 4,14-4,04 (m, 2H), 3,88-3,84 (m, 1H), 2,70-2,64 (m, 1H), 0,89 (br s, 2H), 0,74-0,69 (br s, 2H). MS (EI) para $C_{20}H_{19}F_3IN_3O_2$: 518 (MH^+).

EJEMPLO 3(z). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2,2,2-trifluoroetil)amino]metil}azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8,60 (s, 1H), 7,58 (d, 1H), 7,38 (d, 1H), 7,35-7,30 (m, 1H), 7,22-7,17 (m, 1H), 6,72-6,67 (m, 1H), 4,25-4,19 (m, 1H), 4,07-3,98 (m, 2H), 3,86-3,77 (m, 2H), 3,19-3,09 (m, 2H). MS (EI) para $C_{19}H_{16}F_6IN_3O_2$: 560 (MH^+).

EJEMPLO 3(aa). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1*H*-1,2,3-triazol-1-ilmetil)azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8,55 (s, 1H), 8,04 (s, 1H), 7,66 (s, 1H), 7,58 (d, 1H), 7,39 (d, 1H), 7,34-7,29 (m, 1H), 7,22-7,15 (m, 1H), 6,72-6,66 (m, 1H), 6,29 (s, 1H), 4,64 (s, 2H), 4,29-4,25 (m, 1H), 4,13-4,09 (m, 1H), 4,00-3,96 (m, 1H), 3,77-3,73 (m, 1H), 3,16 (d, 1H). MS (EI) para $C_{19}H_{15}F_3IN_5O_2$: 530 (MH^+).

EJEMPLO 3(bb). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2,2-dimetilpropil)amino]metil}azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8,61 (s, 1H), 8,30 (s, 2H), 7,59 (d, 1H), 7,39 (d, 1H), 7,36-7,17 (m, 4H), 6,77-6,66 (m, 4H), 4,35-4,30 (m, 1H), 4,16-4,08 (m, 2H), 3,92-3,87 (m, 1H), 3,31-3,27 (m, 2H), 2,78-2,74 (m, 2H), 1,76 (s, 4H), 0,99 (s, 9H). MS (EI) para $C_{22}H_{25}F_3IN_3O_2$: 548 (MH^+).

EJEMPLO 3(cc). Sal de acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(4-

metilfenil)etil]amino}metil)azetidin-3-ol: ^{1}H NMR (400 MHz, $CDCl_3$): 8,48 (s, 1H), 7,39 (dd, 1H), 7,31-7,34 (m, 1H), 7,08 (dd, 5H), 6,77-6,83 (m, 1H), 6,58-6,63 (m, 1H), 4,20 (br s, 1H), 4,01 (d, 1H), 2,87 (t, 4H), 2,75 (t, 4H), 2,5 (br s, 2H), 2,33 (s, 3H), 2,08 (s, 2H). MS (EI) para $C_{26}H_{25}F_3IN_3O_2$: 594 (M-H).

EJEMPLO 3(dd). Sal de acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(2,3-dihidro-1*H*-inden-2-ilamino)metil]azetidin-3-ol: ^{1}H NMR (400 MHz, $CDCl_3$): 8,48 (s, 1H), 7,40 (dd, 1H), 7,32-7,34 (m, 1H), 7,15-7,22 (m, 4H), 7,10-7,14 (m, 1H), 6,77-6,83 (m, 1H), 6,58-6,64 (m, 1H), 4,22 (br s, 1H), 4,04 (d, 1H), 3,57-3,63 (m, 1H), 3,17 (dd, 2H), 2,94 (s, 2H), 2,75 (dd, 2H), 2,48 (br s, 4H), 2,08 (s, 2H). MS (EI) para $C_{26}H_{23}F_3IN_3O_2$: 592 (M-H).

EJEMPLO 3(ee). Sal de acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(1S,2S)-2-hidroxiciclopentil]amino}metil)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7,46 (dd, 1H), 7,33-7,37 (m, 1H), 7,26-7,31 (m, 1H), 7,00-7,08 (m, 1H), 6,58-6,65 (m, 1H), 4,2 (t, 1H), 3,86-4,06 (m, 4H), 2,92-3,10 (m, 3H), 2,00-2,10 (m, 1H), 1,91-1,97 (m, 3H), 1,66-1,78 (m, 2H), 1,52-1,61 (m, 1H), 1,32-1,44 (m, 1H). MS (EI) para $C_{22}H_{23}F_3IN_3O_3$: 560 (M-H).

EJEMPLO 3(ff). Sal de acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1,2-dimetilpropil)amino]metil}azetidin-3-ol: ^{1}H NMR (400 MHz,

CD_3OD): 7,45 (dd, 1H), 7,33-7,37 (m, 1H), 7,26-7,31 (m, 1H), 7,01-7,08 (m, 1H), 6,59-6,64 (m, 1H), 4,14-4,22 (m, 1H), 3,98-4,06 (m, 2H), 3,84-3,90 (m, 1H), 2,86-3,20 (m, 2H), 2,65 (br s, 1H), 1,92 (s, 2H), 1,76-1,86 (m, 1H), 1,06 (d, 3H), 0,91 (dd, 6H). MS (EI) para $C_{22}H_{25}F_3I\ N_3O_2$: 546 (M-H).

EJEMPLO 3(gg). Sal de acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[1-metil-2-(metiloxi)etil]amino}metil)azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7,55 (dd, 1H), 7,33-7,36 (m, 1H), 7,26-7,31 (m, 1H), 7,01-7,09 (m, 1H), 6,59-6,65 (m, 1H), 4,14-4,22 (m, 1H), 3,96-4,06 (m, 2H), 3,85-3,92 (m, 1H), 3,40-3,48 (m, 1H), 3,34 (s, 3H), 2,90-3,15 (m, 3H), 1,94 (s, 3H), 1,11 (d, 3H). MS (EI) para $C_{21}H_{23}F_3IN_3O_3$: 548 (M-H).

EJEMPLO 3(hh). Sal de acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1-etilpropil)amino]metil}azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7,45 (dd, 1H), 7,33-7,36 (m, 1H), 7,26-7,31 (m, 1H), 7,01-7,09 (m, 1H), 6,58-6,65 (m, 1H), 4,15-4,20 (m, 1H), 3,99-4,06 (m, 2H), 3,86-3,91 (m, 1H), 2,94 (s, 2H), 2,55-2,63 (m, 1H), 1,92 (s, 2H), 1,48-1,58 (m, 4H), 0,92 (t, 6H). MS (EI) para $C_{22}H_{25}F_3IN_3O_2$: 546 (M-H).

EJEMPLO 3(ii). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1*H*-imidazol-1-ilmetil)azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7,67 (br s, 1H), 7,48 (m, 1H), 7,36 (m, 1H), 6,91 (br s, 1H), 6,63 (m,

1H), 4,25 (s, 2H), 4,22 (m, 1H), 4,02 (m, 2H), 3,82 (m, 1H). MS (EI) para $C_{20}H_{16}F_3IN_4O_2$: 529 (MH^+).

EJEMPLO 3(jj). 3-{[(ciclopropilmetil)amino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-iodofenil)amino]-fenil}carbonil)azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7,47 (m, 1H), 7,36 (m, 1H), 7,31 (m, 1H), 7,05 (m, 1H), 6,62 (m, 1H), 4,30 (m, 1H), 4,24 (m, 2H), 3,99 (m, 1H), 3,66 (m, 2H), 2,91 (d, 2H), 1,08 (m, 1H), 0,71 (m, 2H), 0,40 (m, 2H). MS (EI) para $C_{21}H_{21}F_3IN_3O_2$: 532 (MH^+).

EJEMPLO 3(kk). Clorhidrato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(fenilmetil)amino]metil}azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7,47 (m, 5H), 7,43 (m, 1H), 7,35 (m, 1H), 7,27 (m, 1H), 7,04 (m, 1H), 6,61 (m, 1H), 4,24 (m, 3H), 4,08 (m, 2H), 3,96 (m, 1H). MS (EI) para $C_{24}H_{21}F_3IN_3O_2$: 568 (MH^+).

EJEMPLO 3(mm). 3-[(butilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: ^1H NMR (400MHz, d_6-DMSO): 8,56 (s, 1H), 7,57 (dd, 1H), 7,36 (d, 1H), 7,31 (t, 1H), 7,17 (q, 1H), 6,67 (dt, 1H), 4,04 (d, 1H), 3,88 (q, 2H), 3,69 (d, 1H), 2,59 (s, 2H), 1,90 (s, 2H), 1,22-1,33 (m, 4H), 0,84 (t, 3H); MS (EI) para $C_{21}H_{23}F_3IN_3O_2$: 534 (MH^+).

EJEMPLO 3(nn). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(1-etilpirrolidin-2-il)metil]amino}metil)azetidin-3-ol: ^1H NMR (400MHz, d_6-DMSO): 8,59 (s, 1H), 7,57 (dd, 1H), 7,36 (d, 1H), 7,31 (t, 1H), 7,17

(q, 1H), 6,68 (dt, 1H), 4,02 (t, 1H), 3,89 (q, 2H), 3,69 (d, 1H), 2,98 (s, 1H), 2,67-2,76 (m, 1H), 2,62 (s, 1H), 2,39-2,45 (m, 1H), 2,29 (s, 1H), 1,97-2,13 (m, 2H), 1,69 (s, 1H), 1,54 (s, 3H), 0,97 (t, 3H); MS (EI) para $C_{24}H_{28}F_3IN_4O_2$: 589 (MH^+).

EJEMPLO 3(oo). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-hidroxietil)amino]metil}azetidin-3-ol: ^1H NMR (400MHz, d_6-DMSO): 8,57 (s, 1H), 7,57 (dd, 1H), 7,37 (d, 1H), 7,32 (t, 1H), 7,18 (q, 1H), 6,68 (dt, 1H), 4,06 (d, 1H), 3,87 (d, 2H), 3,70 (d, 1H), 3,42 (t, 2H), 2,65 (s, 2H), 2,56 (dt, 2H). 1,91 (s, 2H); MS (EI) para $C_{19}H_{19}F_3IN_3O_3$: 522 (MH^+).

EJEMPLO 3(pp). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(dimetilamino)etil]amino}metil)azetidin-3-ol: ^1H NMR (400MHz, d_6-DMSO): 8,58 (s, 1H), 7,57 (dd, 1H), 7,36 (d, 1H), 7,31 (t, 1H), 7,17 (q, 1H), 6,68 (dt, 1H), 4,02 (d, 1H), 3,87 (t, 2H), 3,70 (d, 1H), 2,62 (s, 1H), 2,54 (t, 1H), 2,23 (t, 1H), 2,09 (s, 4H), 7,85 (s, 6H); MS (EI) para $C_{21}H_{24}F_3IN_4O_2$: 549 (MH^+).

EJEMPLO 3(qq). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(1-metilpirrolidin-2-il)etil]amino}metil)azetidin-3-ol: ^1H NMR (400MHz, d_6-DMSO): 8,58 (s, 1H), 7,57 (dt, 1H), 7,36 (d, 1H), 7,31 (t, 1H), 7,17 (q, 1H), 6,68 (dt, 1H), 4,04 (d, 1H), 3,89 (d, 2H), 3,79 (d, 1H), 2,88-2,92 (m, 1H), 2,61 (s, 2H), 2,15 (s, 3H), 1,93-2,04

(m, 2H), 1,75-1,83 (m, 3H), 1,54-1,70 (m, 3H), 1,20-1,37 (m, 2H); MS (EI) para $C_{24}H_{28}F_3IN_4O_2$: 589 (MH^+).

EJEMPLO 3(rr). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(tetrahidrofuran-2-ilmetil)amino]metil}azetidin-3-ol: ^1H NMR (400MHz, d_6-DMSO): 8,58 (s, 1H), 7,57 (dd, 1H), 7,37 (d, 1H), 7,31 (t, 1H), 7,14 (q, 1H), 6,68 (dt, 1H), 5,75 (s, 1H), 4,03 (t, 1H), 3,87 (t, 2H), 3,76 (q, 1H), 3,68 (q, 2H), 3,54-3,58 (m, 1H), 2,63 (s, 2H), 1,91 (s, 2H), 1,71-1,87 (m, 3H), 1,40-1,48 (m, 1H); MS (EI) para $C_{22}H_{23}F_3IN_3O_3$: 562 (MH^+).

EJEMPLO 3(ss). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(3-pirrolidin-1-ilpropil)amino]metil}azetidin-3-ol: ^1H NMR (400MHz, d_6-DMSO): 8,58 (s, 1H), 7,57 (dd, 1H), 7,36 (d, 1H), 7,31 (t, 1H), 7,17 (q, 1H), 6,68 (dt, 1H), 4,04 (d, 1H), 3,89 (d, 2H), 3,69 (d, 1H), 2,60 (s, 1H), 2,34-2,37 (m, 4H), 1,86 (s, 8H), 1,64 (s, 2H), 1,46-1,53 (m, 1H); MS (EI) para $C_{24}H_{28}F_3IN_4O_2$: 589 (MH^+).

EJEMPLO 3(tt). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(metiloxi)etil]amino}metil)azetidin-3-ol: ^1H NMR (400MHz, d_6-DMSO): ^1H NMR (400MHz, d_6-DMSO): 8,57 (s, 1H), 7,57 (dd, 1H), 7,37 (d, 1H), 7,31 (t, 1H), 7,17 (q, 1H), 6,68 (dt, 1H), 4,03 (d, 1H), 3,86 (d, 2H), 3,70 (d, 1H), 3,21 (s, 3H), 2,63 (s, 4H), 1,88 (s, 2H); MS (EI) para $C_{20}H_{21}F_3IN_3O_3$: 536 (MH^+).

EJEMPLO 3(uu). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(1-metilpiperidin-4-il)metil]amino}metil)azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8,58 (s, 1H), 7,57 (d, 1H), 7,37 (d, 1H), 7,31 (t, 1H), 7,17 (q, 1H), 6,68 (t, 1H), 4,03 (d, 1H), 3,89 (t, 2H), 3,69 (d, 1H), 2,68 (d, 2H), 2,57 (s, 1H), 2,34 (d, 2H), 1,88 (s, 4H), 1,73 (t, 2H), 1,57 (d, 2H), 1,23 (s, 1H), 1,05 (q, 2H); MS (EI) para $C_{24}H_{28}F_3IN_4O_3$: 589 (MH^+).

EJEMPLO 3(vv). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[4-(dimetilamino)butil]amino}metil)azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 7,57 (dd, 1H), 7,36 (d, 1H), 7,31 (t, 1H), 7,18 (q, 1H), 6,68 (dt, 1H), 4,03 (t, 2H), 3,88 (t, 2H), 3,70 (d, 1H), 3,08 (s, 1H), 2,60 (s, 1H), 2,44-2,47 (m, 2H), 2,28-2,33 (m, 1H), 2,07-2,16 (m, 6H), 1,29-1,35 (m, 4H); MS (EI) para $C_{23}H_{28}F_3IN_4O_2$: 577 (MH^+).

EJEMPLO 3(ww). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-furan-2-iletil)amino]metil}azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8,58 (s, 1H), 7,57 (d, 1H), 7,49 (s, 1H), 7,36 (d, 1H), 7,31 (t, 1H), 7,17 (q, 1H), 6,68 (t, 1H), 6,33 (s, 1H), 6,08 (s, 1H), 5,72 (s, 1H), 4,04 (d, 1H), 3,87 (d, 2H), 3,70 (d, 1H), 2,74 (d, 2H), 2,69 (d, 2H), 2,64 (s, 2H); MS (EI) para $C_{23}H_{21}F_3IN_3O_3$: 572 (MH^+).

EJEMPLO 3(xx). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-etilbutil)amino]metil}azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8,58 (s, 1H), 7,56 (dd, 1H), 7,36 (d, 1H), 7,31 (t, 1H), 7,17 (q, 1H), 6,67 (dt, 1H), 4,03 (d, 1H), 3,90 (d, 2H), 3,69 (d, 1H), 2,58 (s, 2H), 2,37 (d, 2H), 1,17-1,27 (m, 5H), 0,78 (t, 6H); MS (EI) para $C_{23}H_{27}F_3IN_3O_2$: 562 (MH^+).

EJEMPLO 3(yy). 1,1-dimetletil [3-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)propil]carbamato: ^{1}H NMR (400MHz, d_6-DMSO): 8,58 (s, 1H), 7,57 (d, 1H), 7,30-7,38 (m, 3H), 7,17 (q, 1H), 6,82 (t, 1H), 6,68 (dt, 1H), 4,07 (d, 1H), 3,89 (d, 2H), 3,70 (d, 1H), 3,36 (s, 2H), 2,93 (q, 2H), 2,61 (s, 2H), 1,46 (t, 2H), 1,36 (s, 9H); MS (EI) para $C_{25}H_{30}F_3IN_4O_4$: 635 (MH^+).

EJEMPLO 3(zz). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(pirrolidin-2-ilmetil)amino]metil}azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8,53 (s, 1H), 7,58 (dd, 1H), 7,37 (d, 1H), 7,33 (d, 1H), 7,18 (q, 1H), 6,67 (dt, 1H), 6,25 (s, 1H), 4,07 (d, 1H), 3,96 (q, 2H), 3,78 (s, 3H), 3,34 (s, 6H), 1,73 (s, 1H), 1,35-1,39 (m, 1H); MS (EI) para $C_{22}H_{24}F_3IN_4O_2$: 561 (MH^+).

EJEMPLO 3(aaa). 1,1-dimetiletil 4-[({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)metil]piperidine-1-carboxilato: ^{1}H NMR (400MHz, d_6-DMSO): 8,56 (s, 1H), 7,56 (dd, 1H), 7,36 (d, 1H), 7,30 (t,

1H), 7,17 (q, 1H), 6,68 (dt, 1H), 4,03 (d, 1H), 3,88 (t, 4H), 3,69 (d, 1H), 2,58 (s, 2H), 2,35 (d, 2H), 1,60 (d, 2H), 1,47 (s, 1H), 1,39 (s, 10H), 0,90 (q, 2H); MS (EI) para $C_{28}H_{34}F_3IN_4O_4$: 675 (MH^+).

EJEMPLO 3(bbb). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(2-hidroxifenil)metil]amino}metil)azetidin-3-ol: ^1H NMR (400MHz, d_6-DMSO): 8,56 (s, 1H), 7,54 (dd, 1H), 7,35 (d, 1H), 7,30 (t, 1H), 7,17 (q, 1H), 7,05 (t, 2H), 6,64-6,72 (m, 3H), 4,07 (d, 1H), 3,90 (t, 2H), 3,78 (s, 2H), 3,72 (d, 1H), 2,65 (s, 2H); MS (EI) para $C_{24}H_{21}F_3IN_3O_3$: 584 (MH^+).

EJEMPLO 3(ccc). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(3-hidroxifenil)metil]amino}metil)azetidin-3-ol: ^1H NMR (400MHz, d_6-DMSO): 8,58 (s, 1H), 7,56 (d, 1H), 7,35 (d, 1H), 7,29 (t, 1H), 7,16 (q, 1H), 7,06 (t, 1H), 6,64-6,72 (m, 3H), 6,60 (dd, 1H), 4,07 (d, 1H), 3,88 (t, 2H), 3,69 (d, 1H), 3,60 (s, 2H), 2,58 (d, 2H); MS (EI) para $C_{24}H_{21}F_3IN_3O_3$: 584 (MH^+).

EJEMPLO 3(ddd). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(4-hidroxifenil)metil]amino}metil)azetidin-3-ol: ^1H NMR (400MHz, d_6-DMSO): 8,57 (s, 1H), 7,55 (dd, 1H), 7,35 (d, 1H), 7,27 (t, 1H), 7,16 (q, 1H), 7,06 (d, 2H), 6,64-6,70 (m, 3H), 4,04 (d, 1H), 3,85 (t, 2H), 3,68 (d, 1H), 3,55 (s, 2H), 2,56 (d, 2H); MS (EI) para $C_{24}H_{21}F_3IN_3O_3$: 584 (MH^+).

EJEMPLO 3(eee). 3-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)-5-(hidroximetil)ciclopentano-1,2-diol: ^{1}H NMR (400MHz, d_6-DMSO): 8,60 (s ancho, 1H), 7,57 (dd, 1H), 7,37 (d, 1H), 7,32 (t, 1H), 7,16 (q, 1H), 6,68 (t, 1H), 4,06 (q, 2H), 3,86 (t, 3H), 3,72 (dd, 1H), 3,60 (t, 1H), 3,36-3,43 (m, 2H), 3,30 (dd, 1H), 2,80 (q, 1H), 2,62-2.72 (m, 2H), 1,88-1,95 (m, 1H), 0,82-0,90 (m, 1H); MS (EI) para $C_{23}H_{25}F_3IN_3O_5$: 608 (MH^+).

EJEMPLO 3(fff). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(piperidin-4-ilmetil)amino]metil}azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8,59 (s ancho, 1H), 7,57 (dd, 1H), 7,37 (d, 1H), 7,30 (t, 1H), 7,17 (q, 1H), 6,68 (dt, 1H), 4,03 (d, 1H), 3,87 (d, 2H), 3,69 (d, 1H), 3,01 (d, 2H), 2,59 (s, 2H), 2,43-2,56 (m, 1H), 2,35 (d, 2H), 1,65 (d, 2H), 1,47 (s, 1H), 1,07 (q, 2H); MS (EI) para $C_{23}H_{26}F_3IN_4O_2$: 575 (MH^+).

EJEMPLO 3(ggg). 3-{[(3-aminopropil)amino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 7,57 (dd, 1H), 7,37 (d, 1H), 7,31 (t, 1H), 7,17 (q, 1H), 6,68 (dt, 1H), 4,05 (d, 1H), 3,88 (d, 2H), 3,69 (d, 1H), 2,61 (t, 3H), 2,53-2,56 (m, 1H), 1,49 (t, 1.49); MS (EI) para $C_{23}H_{26}F_3IN_4O_2$: 535 (MH^+).

EJEMPLO 3(hhh). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[({[2-(4-metilpiperazin-1-

il)fenil]metil}amino)metil]azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8,59 (s ancho, 1H), 7,55 (dd, 1H), 7,34 (t, 2H), 7,28 (d, 1H), 7,13-7,20 (m, 1H), 7,05 (d, 1H), 6,99 (t, 1H), 6,66 (dt, 1H), 4,03 (d, 1H), 3,90 (t, 2H), 3,71 (d, 3H), 2,83 (s, 5H), 2,60 (s, 2H), 2,42 (s, 3H), 2,20 (s, 3H); MS (EI) para $C_{29}H_{31}F_3IN_5O_2$: 666 (MH^+).

EJEMPLO 3(iii). 3-[(1*H*-bencimidazol-2-ilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8,04 (s, 2H), 7,28-7,35 (m, 2H), 7,23-7,26 (m, 2H), 7,09-7,12 (m, 2H), 6,80 (q, 1H), 6,57-6,63 (m, 1H), 5,28 (s ancho, 2H), 4,38 (s, 3H), 4,25 (s, 1H), 4,21 (d, 2H); MS (EI) para $C_{24}H_{19}F_3IN_5O_2$: 594 (MH^+).

EJEMPLO 3(jjj). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(1*H*-imidazol-2-ilamino)metil]azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 12,12 (s, 1H), 8,68 (s, 1H), 7,57-7,61 (m, 3H), 7,36-7,41 (m, 2H), 7,19 (q, 1H), 6,99 (s, 1H), 6,91 (s, 1H), 6,71 (dt, 1H), 6,45 (s, 1H), 4,28 (d, 1H), 4,06 (d, 1H), 4,03 (d, 1H), 3,82 (d, 2H); MS (EI) para $C_{24}H_{17}F_3IN_5O_2$: 544 (MH^+).

EJEMPLO 3(kkk). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{2-[(2,2,3,3,3-pentafluoropropil)amino]etil}azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8,58 (br s, 1H), 7,56 (dd, 1H), 7,37 (dd, 1H), 7,34-7,28 (m, 1H), 7,22-7,13 (m, 1H), 6,68 (ddd, 1H), 5,82 (br s,

1H), 4,06 (d, 1H), 3,91 (t, 2H), 3,70 (d, 1H), 3,40-3,25 (m, 2H), 2,76 (d, 2H), 2,40-2,31 (m, 1H); MS (EI) para $C_{20}H_{16}F_8IN_3O_2$: 610 (MH^+).

EJEMPLO 3(mmm). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{2-[(3,3,3-trifluoropropil)amino]etil}azetidin-3-ol: ^1H NMR (400 MHz, d_6-DMSO): 8,58 (br s, 1H), 7,57 (dd, 1H), 7,37 (dd, 1H), 7,34-7,28 (m, 1H), 7,22-7,13 (m, 1H), 6,68 (ddd, 1H), 5,76 (br s, 1H), 4,05 (d, 1H), 3,88 (d, 2H), 3,70 (d, 1H), 2,71 (t, 2H), 2,63 (s, 2H), 2,41-2,26 (m, 2H); MS (EI) para $C_{20}H_{18}F_6IN_3O_2$: 574 (MH^+).

EJEMPLO 3(nnn). Sal de acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(2,3-dihidro-1*H*-inden-1-ilamino)metil]azetidin-3-ol: ^1H NMR (400 MHz, DMSO): 8,1-8,56 (m, 1H), 7,55 (d, 1H), 7,37-7,07 (m, 8H), 6,71-6,64 (m, 1H), 4,16-4,05 (m, 2H), 3,98-3,85 (m, 2H), 3,72-3,68 (m, 1H), 2,90-2,82 (m, 1H), 2,74-2,64 (m, 2H), 1,91 (s, 3H), 1,73-1,63 (m, 1H); MS (EI) para $C_{26}H_{23}F_3IN_3O_2$: 594 (MH^+).

EJEMPLO 3(ooo). Sal de acetato de 3-[(ciclooctilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol acetate salt: ^1H NMR (400 MHz, DMSO): 8,56 (s, 1H), 7,55 (d, 1H), 7,20-7,14 (m, 2H), 6,70-6,66 (m, 1H), 4,03-3,98 (m, 1H), 3,92-3,86 (m, 2H), 3,72-3,67 (m, 1H), 2,60 (s, 2H), 1,90 (s, 3H), 1,64-1,22 (m, 15H); MS (EI) para $C_{25}H_{29}F_3IN_3O_2$: 588 (MH^+).

EJEMPLO 3(ppp). Sal de acetato de 3-[(cicloheptilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: ^{1}H NMR (400 MHz, DMSO): 8,55 (s, 1H), 7,55 (d, 1H), 7,36-7,28 (m, 2H), 7,21-7,14 (m, 1H), 6,70-6,66 (m, 1H), 4,04-4,00 (m, 1H), 3,92-3,85 (m, 2H), 3,71-3,66 (m, 1H), 2,60 (s, 2H), 1,90 (s, 3H), 1,70-1,13 (m, 13H); MS (EI) para $C_{24}H_{27}F_3IN_3O_2$: 574 (MH^+).

EJEMPLO 3(qqq). Sal de acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-piridin-3-iletil)amino]metil}azetidin-3-ol: ^{1}H NMR (400 MHz, DMSO): 8,58 (s, 1H), 8,42-8,37 (m, 2H), 7,62-7,54 (m, 2H), 7,38-7,27 (m, 3H), 7,21-7,14 (m, 1H), 6,71-6,66 (m, 1H), 4,06-4,02 (m, 1H), 3,90-3,86 (m, 2H), 3,72-3,68 (m, 1H), 2,80-2,64 (m, 6H), 1,90 (s, 3H); MS (EI) para $C_{24}H_{22}F_3IN_4O_2$: 583 (MH^+).

EJEMPLO 3(rrr). Sal de acetato de *N*-ciclohexil-N2-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}-2-metilalaninamida: ^{1}H NMR (400 MHz, DMSO): 8,66 (br s 1H), 8,55 (s, 1H), 7,93-7,90 (m, 1H), 7,58 (d, 1H), 7,40-7,31 (m, 2H), 7,24-7,17 (m, 1H), 6,71-6,66 (m, 1H), 6,60 (br s, 1H), 4,28-4,23 (m, 1H), 4,14-4,02 (m, 2H), 3,89-3,83 (m, 1H), 3,12 (br s, 2H), 1,90 (s, 3H), 1,74-1,42 (m, 11H), 1,31-1,02 (m, 6H); MS (EI) para $C_{27}H_{32}F_3IN_4O_3$: 645 (MH^+).

EJEMPLO 3(sss). Sal de acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(tetrahidro-2H-

piran-4-ilmetil)amino]metil}azetidin-3-ol: ^{1}H NMR (400 MHz, DMSO): 8,56 (s, 1H), 7,56 (d, 1H), 7,38-7,27 (m, 2H), 7,20-7,14 (m, 1H), 6,71-6,66 (m, 1H), 4,05-4,01 (m, 1H), 3,91-3,78 (m, 4H), 3,71-3,67 (m, 1H), 3,25-3,18 (m, 2H), 2,60 (s, 2H), 2,36 (d, 2H), 1,90 (s, 3H), 1,57-1,50 (m, 3H), 1,13-1,02 (m, 2H); MS (EI) para $C_{23}H_{25}F_3IN_3O_3$: 576 (MH^+).

EJEMPLO 3(ttt). Sal de trifluoroacetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(dimetilamino)-1-metiletil]amino}metil)azetidin-3-ol: ^{1}H NMR (400 MHz, DMSO): 8,59-8,54 (m, 1H), 7,56 (d, 1H), 7,38-7,28 (m, 2H), 7,21-7,13 (m, 1H), 6,71-6,63 (m, 1H), 4,04-3,95 (m, 1H), 3,88-3,78 (m, 2H), 3,73-3,68 (m, 1H), 2,70-2,50 (m, 3H), 2,08 (s, 6H), 1,88 (s, 2H), 0,85-0,82 (m, 3H); MS (EI) para $C_{22}H_{26}F_3IN_4O_2$: 563 (MH^+).

EJEMPLO 3(uuu). Sal de trifluoroacetato de *N*-ciclopropil-1-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)ciclopentanocarboxamida: ^{1}H NMR (400 MHz, DMSO): 8,80 (br s, 1H), 8,58 (s, 1H), 8,04 (s, 1H), 7,59 (d, 1H), 7,40-7,31 (m, 2H), 7,25-7,16 (m, 1H), 6,74-6,58 (m, 2H), 4,26-3,82 (m, 4H), 3,10 (br s, 2H), 2,69-2,64 (m, 1H), 2,11-1,88 (m, 4H), 1,82-1,61 (m, 4H), 0,67-0,62 (m, 2H), 0,52-0,48 (m, 2H); MS (EI) para $C_{26}H_{28}F_3IN_4O_3$: 629 (MH^+).

EJEMPLO 3(vvv). Sal de acetato de N2-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-

il]metil}-*N*-etil-2-metilalaninamida: ^{1}H NMR (400 MHz, DMSO): 8,60 (s, 1H), 7,60-7,72 (m, 1H), 7,56 (d, 1H), 7,38-7,30 (m, 2H), 7,22-7,14 (m, 1H), 6,69-6,63 (m, 1H), 4,07-4,04 (m, 1H), 3,95-3,90 (m, 2H), 3,72-3,68 (m, 1H), 3,05-3,01 (m, 2H), 2,47 (br s, 2H), 1,90 (s, 3H), 1,09 (s, 6H), 0,94 (t, 3H); MS (EI) para $C_{23}H_{26}F_3IN_4O_3$: 591 (MH^+).

EJEMPLO 3(www). Sal de acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(2-metilhidrazino)metil]azetidin-3-ol: ^{1}H NMR (400 MHz, DMSO): 8,54 (s, 1H), 7,57 (d, 1H), 7,38-7,30 (m, 2H), 7,19-7,12 (m, 1H), 6,69-6,63 (m, 1H), 4,04-4,01 (m, 1H), 3,92-3,84 (m, 2H), 3,68-3,63 (m, 1H), 2,55 (s, 2H), 2,39 (s, 3H), 1,90 (s, 3H); MS (EI) para $C_{18}H_{18}F_3IN_4O_2$: 507 (MH^+).

EJEMPLO 3(xxx). Sal de acetato de 3-[(azetidin-3-ilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: ^{1}H NMR (400 MHz, DMSO): 7,57 (d, 1H), 7,39-7,30 (m, 2H), 7,20-7,13 (m, 1H), 6,70-6,65 (m, 1H), 4,10-4,04 (m, 1H), 3,90-3.83 (m, 2H), 3,78-3,67 (m, 3H), 3,61-3,53 (m, 1H), 3,48-3,42 (m, 2H), 2,61-2,54 (m, 2H), 1,90 (s, 3H); MS (EI) para $C_{20}H_{20}F_3IN_4O_2$: 533 (MH^+).

EJEMPLO 3(yyy). Sal de acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(1,3-tiazol-2-ilamino)metil]azetidin-3-ol: ^{1}H NMR (400 MHz, DMSO): 8,60 (s, 1H), 7,57 (d, 1H), 7,38-7,28 (m, 2H), 7,20-7,13 (m, 1H), 6,75 (d, 1H), 6,70-6,64 (m, 1H), 5,93 (d, 1H), 4,26-4,22 (m, 1H),

4,11-4,08 (m, 1H), 4,00-3,88 (m, 3H), 3,74-3,70 (m, 1H), 1,90 (s, 3H); MS (EI) para $C_{20}H_{16}F_3IN_4O_2S$: 561 (MH^+).

EJEMPLO 3(zzz). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[3-(metiloxi)fenil]amino}metil)azetidin-3-ol: ^1H NMR (400 MHz, DMSO): 8,57 (s, 1H), 7,56 (d, 1H), 7,38-7,30 (m, 2H), 7,20-7,12 (m, 1H), 6,95-6,91 (m, 1H), 6,70-6,66 (m, 1H), 6,21-6,17 (m, 2H), 6,14-6,10 (m, 1H), 5,94 (s, 1H), 5,49-5,44 (m, 1H), 4,14-4,10 (m, 1H), 3,98-3,93 (m, 2H), 3,78-3,75 (m, 1H), 3,65 (s, 3H), 3,21 (d, 2H); MS (EI) para $C_{24}H_{21}F_3IN_3O_3$: 584 (MH^+).

EJEMPLO 3(ab). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[4-(metiloxi)fenil]amino}metil)azetidin-3-ol: ^1H NMR (400 MHz, DMSO): 8,56 (s, 1H), 7,58 (d, 1H), 7,39-7,30 (d, 2H), 7,20-7,13 (m, 1H), 6,71-6,66 (m, 3H), 6,55 (d, 2H), 5,93 (s, 1H), 5,00-4,95 (m, 1H), 4,14-4,08 (m, 1H), 3,98-3,92 (m, 2H), 3,79-3,74 (m, 1H), 3,63 (s, 3H), 3,13 (d, 2H); MS (EI) para $C_{24}H_{21}F_3IN_3O_3$: 584 (MH^+).

EJEMPLO 3(ac). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(etiloxi)etil]amino}metil)azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7,48-7,43 (d, 1H), 7,36-7,33 (d, 1H), 7,31-7,26 (m, 1H), 7,08-7,00 (q, 1H), 6,65-6,58 (t, 1H), 4,24-4,16 (d, 1H), 4,08-3,98 (t, 2H), 3,92-3,85 (d, 1H), 3,60-3,55 (t, 2H), 3,54-

3,47 (q, 2H), 3,01-2,96 (s, 2H), 2,94-2,89 (t, 2H), 1,20-1,15 (t, 3H); MS (EI) para $C_{21}H_{23}F_3IN_3O_3$: 550 (MH^+).

EJEMPLO 3(ad). Sal de acetato 3-({[2,2-bis(metiloxi)etil]amino}metil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7,48-7,43 (d, 1H), 7,37-7,32 (d, 1H), 7,30-7,24 (m, 1H), 7,08-7,00 (q, 1H), 6,65-6,57 (t, 1H), 4,48-4,42 (t, 1H), 4,20-4,11 (d, 1H), 4,02-3,93 (t, 2H), 3,86-3,80 (d, 1H), 3,38-3,34 (s, 6H), 2,84-2,80 (s, 2H), 2,75-2,70 (d, 2H), 1,93-1,87 (s, 3H); MS (EI) para $C_{21}H_{23}F_3IN_3O_4$: 566 (MH^+).

EJEMPLO 3(ae). Sal de acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(3-hidroxipropil)amino]metil}azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7,48-7,43 (d, 1H), 7,38-7,33 (d, 1H), 7,32-7,26 (m, 1H), 7,09-7,00 (q, 1H), 6,66-6,58 (t, 1H), 4,31-4,23 (d, 1H), 4,16-4,05 (t, 2H), 3,99-3,89 (d, 1H), 3,70-3,64 (t, 2H), 3,26-3,22 (s, 2H), 3,11-3,04 (t, 2H), 1,93-1,89 (s, 3H), 1,89-1,82 (t, 3H); MS (EI) para $C_{20}H_{21}F_3IN_3O_3$: 536 (MH^+).

EJEMPLO 3(af). Sal de acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-piridin-4-iletil)amino]metil}azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 8,36-8,32 (d, 2H), 7,38-7,33 (d, 1H), 7,26-7,14 (m, 3H), 7,00-6,91 (q, 1H), 4,12-4,04 (d, 1H), 3,96-3,88 (t, 2H), 3,80-3,73 (d, 2H), 2,92-2,74 (m, 6H), 1,87-1,84 (s, 3H); MS (EI) para $C_{24}H_{22}F_3IN_4O_2$: 583 (MH^+).

EJEMPLO 3(ag). Sal de acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[1-(fenilmetil)pirrolidin-3-il]amino}metil)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7,47-7,24 (m, 8H), 7,08-7,00 (q, 1H), 6,64-6,57 (t, 1H), 4,19-4,11 (d, 1H), 4,05-3,81 (m, 5H), 3,52-3,44 (m, 1H), 3,09-2,99 (m, 2H), 2,91-2,76 (m, 3H), 1,93-1,91 (s, 3H), 1,82-1,71 (m, 1H); MS (EI) para $C_{28}H_{28}F_3IN_4O_2$: 637 (MH^+).

EJEMPLO 3(ah). Sal de acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(2-tienil)etil]amino}metil)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7,47-7,42 (d, 1H), 7,36-7,31 (d, 1H), 7,30-7,24 (m, 1H), 7,21-7,17 (d, 1H), 7,08-7,00 (q, 1H), 6,93-6,89 (t, 1H), 6,86-6,83 (d, 1H), 6,64-6,57 (t, 1H), 4,18-4,11 (d, 1H), 4,01-3,93 (t, 2H), 3,85-3,78 (d, 1H), 3,04-2,97 (t, 2H), 2,92-2,87 (t, 2H), 2,82-2,78 (s, 2H), 1,92-1,87 (s, 3H); MS (EI) para $C_{23}H_{21}F_3IN_3O_2S$: 588 (MH^+).

EJEMPLO 3(ai). Sal de acetato de 3-[({2-[bis(1-metiletil)amino]etil}amino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7,48-7,43 (d, 1H), 7,36-7,33 (d, 1H), 7,31-7,26 (m, 1H), 7,08-7,00 (q, 1H), 6,65-6,58 (t, 1H), 4,18-4,13 (d, 1H), 4,06-3,98 (t, 2H), 3,88-3,82 (d, 2H), 3,57-3,47 (q, 2H), 3,05-2,99 (t, 2H), 2,92-2,85 (t, 4H), 1,92-1,88 (s, 3H), 1,28-1,22 (d, 12H); MS (EI) para $C_{25}H_{32}F_3IN_4O_2$: 605 (MH^+).

EJEMPLO 3(aj). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(feniloxi)etil]amino}metil)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7,36-7,31 (d, 1H), 7,26-7,22 (d, 1H), 7,20-7,13 (m, 3H), 6,97-6,89 (t, 1H), 6,86-6,80 (m, 3H), 6,54-6,47 (t, 1H), 4,13-4,07 (d, 1H), 4,01-3,96 (t, 2H), 3,79-3,74 (d, 1H), 2,97-2,91 (t, 2H), 2,84-2,79 (s, 2H), 1,84-1,81 (s, 3H); MS (EI) para $C_{25}H_{23}F_3IN_3O_3$: 598 (MH^+).

EJEMPLO 3(ak). Sal de acetato 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-hidroxipropil)amino]metil}azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7,48-7,43 (d, 1H), 7,36-7,33 (d, 1H), 7,31-7,26 (m, 1H), 7,08-7,00 (q, 1H), 6,65-6,58 (t, 1H), 4,27-4,19 (d, 1H), 4,10-4,00 (m, 2H), 3,15-3,00 (t, 2H), 3,57-3,47 (q, 2H), 3,15-3,00 (t, 2H), 2,87-2,81 (d, 1H), 2,72-2,64 (t, 1H), 1,94-1,91 (s, 3H), 1,19-1,15 (d, 3H); MS (EI) para $C_{20}H_{21}F_3IN_3O_3$: 536 (MH^+).

EJEMPLO 3(am). Sal de acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[({2-[(1-metiletil)oxi]etil}amino)metil]azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7,48-7,43 (d, 1H), 7,36-7,33 (d, 1H), 7,31-7,26 (m, 1H), 7,08-7,00 (q, 1H), 6,65-6,58 (t, 1H), 4,21-4,13 (d, 1H), 4,04-3,95 (t, 2H), 3,88-3,82 (d, 1H), 3,64-3,51 (m, 3H), 2,89-2,84 (s, 2H), 2,83-2,77 (t, 2H), 1,91-1,89 (s, 3H), 1,15-1,12 (d, 6H); MS (EI) para $C_{22}H_{25}F_3IN_3O_3$: 564 (MH^+).

EJEMPLO 3(an). Sal de acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1-etilpiperidin-3-il)amino]metil}azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7,48-7,43 (d, 1H), 7,36-7,33 (d, 1H), 7,31-7,26 (m, 1H), 7,08-7,00 (q, 1H), 6,65-6,58 (t, 1H), 4,17-4,10 (d, 1H), 4,04-3,95 (t, 2H), 3,88-3,82 (d, 1H), 3,24-3,06 (m, 2H), 2,95-2,75 (m, 6H), 2,76-2,46 (m, 2H), 1,93-1,90 (s, 3H), 1,74-1,62 (m, 1H), 1,44-1,31 (m, 1H), 1,28-1,20 (t, 3H); MS (EI) para $C_{24}H_{28}F_3IN_4O_2$: 589 (MH^+).

EJEMPLO 3(ao). Sal de acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(5-metil-1,3,4-oxadiazol-2-il)metil]amino}metil)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7,48-7,43 (d, 1H), 7,36-7,33 (d, 1H), 7,31-7,26 (m, 1H), 7,08-7,00 (q, 1H), 6,65-6,58 (t, 1H), 4,20-4,13 (d, 1H), 4,00-3,90 (t, 2H), 3,83-3,75 (d, 1H), 2,84-2,78 (s, 2H), 2,53-2,48 (s, 2H), 1,93-1,87 (s, 3H); MS (EI) para $C_{21}H_{19}F_3IN_5O_3$: 574 (MH^+).

EJEMPLO 3(ap). Sal de acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1-metilbutil)amino]metil}azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7,48-7,43 (d, 1H), 7,38-7,33 (d, 1H), 7,32-7,27 (m, 1H), 7,09-7,01 (q, 1H), 6,65-6,58 (t, 1H), 4,25-4,19 (d, 1H), 4,12-4,02 (t, 2H), 3,96-3,90 (d, 1H), 3,16-2,96 (m, 3H), 1,91-1,89 (s, 3H), 1,68-1,57 (m, 1H), 1,49-1,29 (m, 3H), 1,23-1,18 (d, 3H), 0,99-0,92 (t, 3H); MS (EI) para $C_{22}H_{25}F_3IN_3O_2$: 548 (MH^+).

EJEMPLO 3(aq). Sal de acatato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1-metilpropil)amino]metil}azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7,48-7,43 (d, 1H), 7,37-7,33 (d, 1H), 7,32-7,26 (m, 1H), 7,09-7,01 (q, 1H), 6,65-6,58 (t, 1H), 4,27-4,20 (d, 1H), 4,14-4,03 (t, 2H), 3,98-3,92 (d, 1H), 3,20-3,16 (s, 2H), 3,07-2,97 (m, 1H), 1,91-1,89 (s, 3H), 1,80-1,70 (m, 1H), 1,54-1,41 (m, 1H), 1,26-1,22 (d, 3H), 1,00-0,94 (t, 3H); MS (EI) para $C_{21}H_{23}F_3IN_3O_2$: 534 (MH^+).

EJEMPLO 3(ar). Sal de acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-metilbutil)amino]metil}azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7,48-7,43 (d, 1H), 7,37-7,33 (d, 1H), 7,32-7,26 (m, 1H), 7,09-7,01 (q, 1H), 6,65-6,58 (t, 1H), 4,26-4,19 (d, 1H), 4,10-4,01 (t, 2H), 3,94-3,87 (d, 1H), 3,05-2,99 (s, 2H), 2,77-2,70 (m, 1H), 2,61-2,54 (m, 1H), 1,91-1,89 (s, 3H), 1,73-1,61 (m, 1H), 1,49-1,39 (m, 1H), 1,24-1,12 (m, 1H), 0,94-0,84 (m, 6H); MS (EI) para $C_{22}H_{25}F_3IN_3O2$: 548 (MH^+).

EJEMPLO 3(as). Sal de acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(pentilamino)metil]azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7,48-7,43 (d, 1H), 7,37-7,33 (d, 1H), 7,32-7,26 (m, 1H), 7,09-7,01 (q, 1H), 6,65-6,58 (t, 1H), 4,29-4,23 (d, 1H), 4,15-4,05 (t, 2H), 3,98-3,90 (d, 1H), 3,21-3,18 (s, 2H), 2,93-2,86 (m,

2H), 1,91-1,89 (s, 3H), 1,70-1,60 (m, 2H), 1,42-1,29 (m, 4H), 0,97-0,90 (t, 3H); MS (EI) para $C_{22}H_{25}F_3IN_3O_2$: 548 (MH^+).

EJEMPLO 3(at). Sal de acetato de 3-[(ciclohexilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7,48-7,43 (d, 1H), 7,38-7,34 (d, 1H), 7,33-7,27 (m, 1H), 7,09-7,01 (q, 1H), 6,65-6,58 (t, 1H), 4,25-4,19 (d, 1H), 4,14-4,03 (t, 2H), 3,98-3,90 (d, 1H), 3,21-3,18 (s, 2H), 2,93-2,86 (m, 1H), 2,07-2,00 (d, 2H), 1,92-1,90 (s, 3H), 1,89-1,82 (d, 2H), 1,73-1,66 (d, 1H), 1,42-1,14 (m, 5H); MS (EI) para $C_{23}H_{25}F_3IN_3O_2$: 560 (MH^+).

EJEMPLO 3(au). Sal de acetato de 3-[(azepan-3-ilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7,48-7,43 (d, 1H), 7,37-7,33 (d, 1H), 7,32-7,26 (m, 1H), 7,09-7,01 (q, 1H), 6,65-6,58 (t, 1H), 4,19-4,13 (d, 1H), 4,05-3,95 (t, 2H), 3,90-3,81 (d, 1H), 3,37-3,34 (s, 2H), 3,22-3,03 (m, 2H), 2,91-2,64 (m, 3H), 1,93-1,89 (s, 3H), 1,88-1,52 (m, 6H); MS (EI) para $C_{23}H_{26}F_3IN_4O_2$: 575 (MH^+).

EJEMPLO 3(av). Sal de acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(2,3-dihidro-1*H*-indol-3-il)etil]amino}metil)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7,58-7,54 (d, 1H), 7,48-7,43 (d, 1H), 7,36-7,33 (d, 1H), 7,31-7,26 (m, 1H), 7,14-6,99 (m, 4H), 6,65-6,58 (t, 1H), 4,25-4,19 (d, 1H), 4,10-4,02 (t, 2H), 3,95-3,88 (d, 1H), 3,23-

3,03 (m, 9H), 1,94-1,92 (s, 3H); MS (EI) para $C_{27}H_{26}F_3IN_4O_2$: 623 (MH^+).

EJEMPLO 3(aw). Sal de acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(1,3,5-triazin-2-ilamino)metil]azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 8,48-8,46 (s, 1H), 8,36-8,34 (s, 1H), 7,48-7,43 (d, 1H), 7,37-7,33 (d, 1H), 7,28-7,22 (m, 1H), 7,06-6,98 (q, 1H), 6,65-6,58 (t, 1H), 4,24-4,18 (d, 1H), 4,10-3,96 (t, 2H), 3,84-3,78 (d, 1H), 3,69-3,67 (s, 2H), 1,99-1,97 (s, 3H); MS (EI) para $C_{20}H_{16}F_3IN_6O_2$: 557 (MH^+).

EJEMPLO 3(ax). Sal de acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(4-hidroxiciclohexil)amino]metil}azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7,48-7,43 (d, 1H), 7,37-7,33 (d, 1H), 7,32-7,26 (m, 1H), 7,09-7,01 (q, 1H), 6,65-6,58 (t, 1H), 4,22-4,15 (d, 1H), 4,08-3,99 (t, 2H), 3,93-3,87 (d, 1H), 3,56-3,47 (m, 1H), 3,05-3,02 (s, 2H), 2,76-2,68 (m, 1H), 2,03-1,96 (m, 4H), 1,93-1,89 (s, 3H), 1,35-1,23 (m, 4H); MS (EI) para $C_{23}H_{25}F_3IN_3O_3$: 576 (MH^+).

EJEMPLO 3(ay). Sal de acetato de 3-[(ciclopent-3-en-1-ilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7,48-7,43 (d, 1H), 7,37-7,33 (d, 1H), 7,32-7,26 (m, 1H), 7,09-7,01 (q, 1H), 6,65-6,58 (t, 1H), 5,70-5,65 (s, 2H), 4,20-4,14 (d, 1H), 4,03-3,95 (t, 2H), 3,90-3,81 (d, 1H), 3,58-

3,50 (m, 1H), 2,90-2,86 (s, 2H), 2,68-2,58 (m, 2H), 2,26-2,16 (m, 2H), 1,93-1,89 (s, 3H); MS (EI) para $C_{22}H_{21}F_3IN_3O_2$: 544 (MH^+).

EJEMPLO 3(az). Sal de acetato de *N*-[4-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)fenil]acetamida: ^{1}H NMR (400 MHz, CD_3OD): 7,48-7,43 (d, 1H), 7,37-7,33 (d, 1H), 7,27-7,20 (m, 3H), 7,09-7,01 (q, 1H), 6,65-6,55 (m, 3H), 4,22-4,16 (d, 1H), 4,08-3,98 (t, 2H), 3,88-3,82 (d, 1H), 3,28-3,24 (s, 2H), 2,08-2,05 (s, 3H), 2,91-2,64 (m, 3H), 1,93-1,89 (s, 3H); MS (EI) para $C_{25}H_{22}F_3IN_4O_3$: 611 (MH^+).

EJEMPLO 3(ba). Sal de acetato de *N*-[3-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)fenil]acetamida: ^{1}H NMR (400 MHz, CD_3OD): 7,48-7,43 (d, 1H), 7,36-7,33 (d, 1H), 7,27-7,20 (m, 1H), 7,04-6,96 (m, 3H), 6,72-6,68 (d, 1H), 6,65-6,58 (t, 1H), 6,40-6,35 (d, 1H), 4,24-4,18 (d, 1H), 4,08-3,98 (t, 2H), 3,87-3,81 (d, 1H), 3,28-3,25 (s, 2H), 2,10-2,07 (s, 3H), 1,97-1,95 (s, 3H); MS (EI) para $C_{25}H_{22}F_3IN_4O_3$: 611 (MH^+).

EJEMPLO 3(bc). Sal de acetato de (1R,2S)-4-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)ciclopentano-1,2-diol: ^{1}H NMR (400 MHz, DMSO): 8,58-8,54 (s, 1H), 7,61-7,53 (d, 1H), 7,39-7,28 (m, 2H), 7,21-7,13 (m, 1H), 6,71-6,63 (t, 1H), 5,58-5,64 (s, 1H), 5,63-5,58 (s, 1H), 4,06-4,01 (d, 1H), 3,90-3,84 (t,

2H), 3,72-3,66 (d, 1H), 3,31-3,26 (m, 3H), 2,61-2,57 (s, 2H), 2,46-2,36 (m, 2H), 2,02-1,93 (dd, 2H), 1,91-1,88 (s, 3H); MS (EI) para $C_{22}H_{23}F_3IN_3O_4$: 578 (MH^+).

EJEMPLO 3(bd). Sal de acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[1-(hidroximetil)ciclohexil]amino}metil)azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7,48-7,43 (d, 1H), 7,37-7,33 (d, 1H), 7,32-7,26 (m, 1H), 7,09-7,01 (q, 1H), 6,65-6,58 (t, 1H), 4,22-4,15 (d, 1H), 4,08-3,99 (t, 2H), 3,89-3,83 (d, 1H), 3,49-3,45 (s, 2H), 2,86-2,80 (s, 2H), 1,91-1,89 (s, 3H), 1,67-1,34 (m, 10H); MS (EI) para $C_{24}H_{27}F_3IN_3O_3$: 590 (MH^+).

EJEMPLO 3(be). Sal de acetato de 3-{[(3-clorofenil)amino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7,48-7,43 (d, 1H), 7,37-7,33 (d, 1H), 7,32-7,26 (m, 1H), 7,08-6,98 (m, 2H), 6,65-6,55 (m, 3H), 6,53-6,44 (d, 1H), 4,22-4,15 (d, 1H), 4,06-3,98 (t, 2H), 3,88-3,82 (d, 1H), 3,27-3,24 (s, 2H), 1,91-1,89 (s, 3H); MS (EI) para $C_{23}H_{18}ClF_3IN_3O_2$: 588 (MH^+).

EJEMPLO 3(bf). Sal de acetato de 3-{[(4-clorofenil)amino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7,45-7,40 (d, 1H), 7,35-7,30 (d, 1H), 7,28-7,22 (m, 1H), 7,06-6,97 (m, 3H), 6,62-6,54 (m, 3H), 6,53-6,44 (d, 1H), 4,22-4,15 (d, 1H), 4,06-3,98 (t, 2H), 3,88-3,82 (d, 1H), 3,26-

3,22 (s, 2H), 1,96-1,94 (s, 3H); MS (EI) para $C_{23}H_{18}ClF_3IN_3O_2$: 588 (MH^+).

EJEMPLO 3(bg). Sal de acetato de 3-[(5-amino-3-metil-1*H*-pirazol-1-il)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7,38-7,33 (d, 1H), 7,28-7,24 (d, 1H), 7,21-7,15 (m, 1H), 6,98-6,90 (q, 1H), 6,56-6,49 (t, 1H), 5,16-5,14 (s, 1H), 4,36-4,30 (d, 1H), 4,22-4,16 (d, 1H), 3,99-3,97 (s, 1H), 3,95-3,90 (d, 1H), 3,77-3,71 (d, 1H), 1,96-1,92 (s, 3H), 1,85-1,82 (s, 3H); MS (EI) para $C_{21}H_{19}F_3IN_5O_2$: 558 (MH^+).

EJEMPLO 3(bh). Sal de acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(5-metil-1*H*-pirazol-3-il)amino]metil}azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7,38-7,33 (d, 1H), 7,28-7,24 (d, 1H), 7,21-7,15 (m, 1H), 6,98-6,90 (q, 1H), 6,56-6,49 (t, 1H), 5,22-5,19 (s, 1H), 4,15-4,08 (d, 1H), 4,02-3,88 (m, 2H), 3,75-3,68 (d, 1H), 3,20-3,18 (s, 2H), 2,07-2,05 (s, 3H), 1,85-1,82 (s, 3H); MS (EI) para $C_{21}H_{19}F_3IN_5O_2$: 558 (MH^+).

EJEMPLO 3(bi). 3-[(diethylamino)methyl]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: ^1H NMR (400 MHz, d_6-DMSO): 8,54 (s, 1H), 7,58-7,55 (dd, 1H), 7,38-7,35 (dt, 1H), 7,33-7,31 (m, 1H), 7,22-7,15 (m, 1H), 6,69-6,64 (m, 1H), 5,56 (b, 1H), 4,06-4,04 (d, 1H), 3,90-3,88 (m, 2H), 3,72-3,69 (d 1H), 2,51-2,49 (m, 6H), 0,86-0,83 (t, 6H); MS (EI) para $C_{21}H_{23}F_3IN_3O_2$: 534 (MH^+).

EJEMPLO 3(bj). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(dimetilamino)metil]azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8,56 (s, 1H), 7,59-7,56 (dd, 1H), 7,38-7,36 (dt, 1H), 7,34-7,33 (m, 1H), 7,21-7,14 (m, 1H), 6,71-6,65 (m, 1H), 5,55 (b, 1H), 4,07-4,05 (d, 1H), 3,89-3,84 (t, 2H), 3,74-3,719 (d, 1H), 2,46 (m, 2H), 2,19 (br s, 6H); MS (EI) para $C_{19}H_{19}F_3IN_3O_2$: 506 (MH^+).

EJEMPLO 3(bk). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-hidroxi-1,1-dimetiletil)amino]metil}azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8,40 (s, 1H), 7,38 (dd, 1H), 7,33-7,30 (m, 1H), 7,12 (m, 1H), 6,85-6,79 (m, 1H), 6,63-6,57 (m, 1H), 4,22-4,11(br m, 4H), 3,55 (s, 2H), 3,15 (s, 2H), 1,32 (s, 6H); MS (EI) para $C_{21}H_{23}F_3IN_3O_3$: 550 (MH^+).

EJEMPLO 3(bm). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(prop-2-en-1-ilamino)metil]azetidin-3-ol): ^{1}H NMR (400MHz, $CDCl_3$): 8,47 (s, 1H), 7,40 (dd, 1H), 7,34-7,31 (m, 1H), 7,12 (m, 1H), 6,83-6,77 (m, 1H), 6,64-6,59 (m, 1H), 6,64-6,59 (m, 1H), 5,88-5,78 (m, 1H), 5,00-5,12 (m, 2H), 4,13 (br m, 4H), 3,26 (d, 2H), 2,88 (d, 2H), 2,02 (s, 1H); MS (EI) para $C_{21}H_{19}F_3IN_3O_2$: 518 (MH^+).

EJEMPLO 3(bn). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(tetrahidro-2H-piran-4-

il)etil]amino}metil)azetidin-3-ol): ^{1}H NMR (400MHz, $CDCl_3$): 8,45 (s, 1H), 7,39 (dd, 1H), 7,34-7,31 (m, 1H), 7,14-7,10 (m, 1H), 6,84-6,77 (m, 1H), 6,63-6,58 (m, 1H), 4,26-4,04 (m, 4H), 3,95 (dd, 2H), 3,35 (t, 2H), 2,92 (d, 2H), 2,67 (m, 2H), 1,40-1,25 (m, 8H); MS (EI) para $C_{24}H_{27}F_3IN_3O_3$: 590 (MH^+).

EJEMPLO 3(bo). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1,1-dimetilprop-2-in-1-il)amino]metil}azetidin-3-ol): ^{1}H NMR (400MHz, $CDCl_3$): 8,46 (s, 1H), 7,39 (dd, 1H), 7,33-7,30 (m, 1H), 7,15-7,11 (m, 1H), 6,84-6,77 (m, 1H), 6,64-6,58 (m, 1H), 4,20 (br, 1H), 4,07 (br, 1H), 2,92 (s, 2H), 1,58 (m, 4H), 0,92 (dd, 6h); MS (EI) para $C_{22}H_{21}F_3IN_3O_2$: 572 (MH^+).

EJEMPLO 3(bp). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(1*H*-imidazol-4-il)etil]amino}metil)azetidin-3-ol): ^{1}H NMR (400MHz, $CDCl_3$): 8,44 (s, 1H), 7,33-7,14 (m, 3H), 7,00 (m, 1H), 6,67 (dd, 1H), 6,59 (s, 1H), 6,44 (m, 1H), 3,93 (d, 2H), 2,75 (m, 2H), 2,60 (m, 1H), 2,42 (m, 1H) 2,02 (AcOH; s, 3H), 1,86 (m, 4H); MS (EI) para $C_{22}H_{21}F_3IN_5O_2$: 572 (MH^+).

EJEMPLO 3(bq). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[3-(etiloxi)propil]amino}metil)azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8,49 (s, 1H), 7,39 (dd, 1H), 7,34-7,31 (m, 1H), 7,14-7,10 (m, 1H), 6,83-6,76 (m, 1H), 6,64-6,58 (m, 1H), 4,26-4,03

(br m, 4H), 3,53-3,44 (m, 4H), 2,92-2,73 (m, 4H), 1,72 (m, 2H) 1,18 (t, 3H); MS (EI) para $C_{22}H_{23}F_3IN_3O_3$: 564 (MH^+).

EJEMPLO 3(br). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(3,3-dimetilbutil)amino]metil}azetidin-3-ol: ^1H NMR (400MHz, $CDCl_3$): 8,46 (s, 1H), 7,39 (dd, 1H), 7,34-7,31 (m, 1H), 7,14-7,10 (m, 1H), 6,84-6,77 (m, 1H), 6,63-6,58 (m, 1H), 4,18 (br, 3H), 3,15 (s, 2H), 2,71 (m, 2H) 2,05 (AcOH; s, 3H), 1,43 (m, 2H), 0,90 (s, 9H); MS (EI) para $C_{23}H_{27}F_3IN_3O_2$: 562 (MH^+).

EJEMPLO 3(bs). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(3-metilbutil)amino]metil}azetidin-3-ol: ^1H NMR (400MHz, $CDCl_3$): 8,46 (s, 1H), 7,39 (dd, 1H), 7,34-7,30 (m, 1H), 7,14-7,11 (m, 1H), 6,84-6,77 (m, 1H), 6,63-6,59 (m, 1H), 4,27-3,61 (br m, 6H), 2,98 (m, 2H), 2,72 (t, 2H) 2,05 (AcOH; s, 3H), 1,61 (m,1H), 1,43 (m, 2H), 0,90 (d, 6H); MS (EI) para $C_{22}H_{25}F_3IN_3O_2$: 547 (MH^+).

EJEMPLO 3(bt). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[3-(dimetilamino)propil]amino}metil)azetidin-3-ol: MS (EI) para $C_{22}H_{26}F_3IN_4O_2$: 563 (MH^+).

EJEMPLO 3(bu). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[3-(1*H*-imidazol-1-il)propil]amino}metil)azetidin-3-ol: ^1H NMR (400MHz, $CDCl_3$): 8,46 (s, 1H), 7,53 (s, 1H), 7,40 (dd, 1H), 7,34-7,30 (m, 1H),

7,14-7,09 (m, 1H), 7,05 (s, 1H), 6,89 (s, 1H), 6,84-6,77 (m, 1H), 6,63-6,59 (m, 1H), 4,24-4,00 (br m, 6H), 2,84 (m, 2H), 2,61 (m, 2H), 1,94 (m, 2H); MS (EI) para $C_{23}H_{21}F_3IN_5O_2$: 586 (MH^+).

EJEMPLO 3(bv). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(metiltio)etil]amino}metil)azetidin-3-ol: ^1H NMR (400MHz, $CDCl_3$): 8,49 (s, 1H), 7,39 (dd, 1H), 7,34-7,31 (m, 1H), 7,14-7,11 (m, 1H), 6,83-6,77 (m, 1H), 6,63-6,59 (m, 1H), 4,26-4,03 (br m, 4H), 2,88 (s, 2H), 2,82 (t, 2H), 2,62 (t, 2H), 2,08 (s, 3H); MS (EI) para $C_{23}H_{21}F_3IN_3O_2S$: 552 (MH^+).

EJEMPLO 3(bw). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1,1,3,3-tetrametilbutil)amino]metil}azetidin-3-ol: ^1H NMR (400MHz, $CDCl_3$): 8,49 (s, 1H), 7,38 (dd, 1H), 7,34-7,30 (m, 1H), 7,14-7,11 (m, 1H), 6,83-6,77 (m, 1H), 6,64-6,59 (m, 1H), 4,25-4,01 (br m, 4H), 2,82 (s, 2H), 1,45 (s, 2H), 1,15 (s, 6H), 0,90 (s, 9H); MS (EI) para $C_{25}H_{31}F_3IN_3O_2$: 590 (MH^+).

EJEMPLO 3(bx). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1,1-dimetilpropil)amino]metil}azetidin-3-ol: ^1H NMR (400MHz, $CDCl_3$): 8,50 (s, 1H), 7,39 (dd, 1H), 7,35-7,30 (m, 1H), 7,15-7,11 (m, 1H), 6,83-6,77 (m, 1H), 6,65-6,59 (m, 1H), 4,27-4,01 (br m, 4H), 2,82 (s, 2H), 1,46 (s, 2H), 1,08 (s, 6H), 0,89 (s, 3H); MS (EI) para $C_{22}H_{21}F_3IN_4O_3$: 548 (MH^+).

EJEMPLO 3(by). 3-{[(3-amino-2-hidroxipropil)amino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: MS (EI) para $C_{23}H_{22}F_3IN_4O_3$: 551 (MH^+).

EJEMPLO 3(bz). 1-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}pirrolidin-3-ol: MS (EI) para $C_{21}H_{21}F_3IN_3O_3$: 548 (MH^+).

EJEMPLO 3(ca). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({(2S)-2-[(metiloxi)metil]pirrolidin-1-il}metil)azetidin-3-ol: MS (EI) para $C_{23}H_{25}F_3IN_3O_3$: 576 (MH^+).

EJEMPLO 3(cb). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-hidroxifenil)amino]metil}azetidin-3-ol: ^1H NMR (400MHz, $CDCl_3$): 8,46 (s, 1H), 7,41 (dd, 1H), 7,35-7,30 (m, 1H), 7,15-7,11 (m, 1H), 6,89-5,98 (m, 6H), 4,92 (s, 1H), 4,28-4,05 (br m, 4H), 3,44 (s, 2H); MS (EI) para $C_{23}H_{19}F_3IN_3O_3$: 570 (MH^+).

EJEMPLO 3(cd). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(4-hidroxifenil)amino]metil}azetidin-3-ol: ^1H NMR (400MHz, $CDCl_3$): 8,46 (s, 1H), 7,78 (s, 1H), 7,40-7,05 (m, 4H), 6,72 (m, 1H), 6,62 (d, 1H), 6,50 (m, 1H), 6,42 (d, 1H) 4,04-3,98 (m, 4H), 3,18 (s, 2H); MS (EI) para $C_{23}H_{19}F_3IN_3O_3$: 570 (MH^+).

EJEMPLO 3(ce). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(3-hidroxifenil)amino]metil}azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8,52 (s, 1H), 8,22 (s, 1H), 7,39 (dd, 1H), 7,34-7,31 (m, 1H), 7,14-7,11 (m, 1H), 6,85 (dd, 1H), 6,84-6,77 (m, 1H), 6,63-6,59 (m, 1H), 6,15 (d, 1H) 6,09-6,01 (m, 3H), 4,16-3,95 (br m, 4H), 3,22 (d, 2H) 2,15 (AcOH; s, 3H); MS (EI) para $C_{23}H_{19}F_3IN_3O_3$: 570 (MH^+).

EJEMPLO 3(cf). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(feniloxi)metil]azetidin-3-ol: MS (EI) para $C_{23}H_{18}F_3IN_2O_3$: 555 (MH^+).

EJEMPLO 3(cg). 3-({[1-({3, 4-difluoro-2-[(2-fluoro-4-yodofhenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)propano-1,2-diol: MS (EI) para $C_{20}H_{21}F_3IN_3O_4$: 552 (MH^+).

EJEMPLO 3(ch). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(feniltio)metil]azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8,46 (s, 1H), 7,45-7,23 (m, 5H), 7,14-7,05 (m, 1H), 6,78 (dd, 1H), 6,60 (m, 1H), 4,14-3,92 (br m, 4H), 3,33 (s, 2H); MS (EI) para $C_{23}H_{18}F_3IN_2O_2$: 571 (MH^+).

EJEMPLO 3(ci). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(4-hidroxibutil)amino]metil}azetidin-3-ol): ^{1}H NMR (400MHz, $CDCl_3$): 8,43 (s, 1H), 7,38 (dd, 1H), 7,34-7,30 (m, 1H), 7,14-7,10 (m, 1H), 6,84-6,77 (m, 1H), 6,63-6,58 (m, 1H), 4,26-4,04

(m, 4H), 3,61 (m, 2H), 2,96 (s, 2H), 2,73 (s, 2H); MS (EI) para $C_{21}H_{23}F_3IN_3O_3$: 550 (MH^+).

EJEMPLO 3(cj). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-hidroxietil)oxi]metil}azetidin-3-ol: ^1H NMR (400MHz, $CDCl_3$): 8,51 (s, 1H), 7,39 (dd, 1H), 7,35-7,31 (m, 1H), 7,14-7,11 (m, 1H), 6,84-6,77 (m, 1H), 6,63-6,59 (m, 1H), 4,21-4,05 (br m, 4H), 3,77 (m, 2H), 3,66 (m, 2H); MS (EI) para $C_{19}H_{18}F_3IN_2O_4$: 523 (MH^+).

EJEMPLO 3(ck). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(1S,2S)-2-hidroxiciclohexil]amino}metil)azetidin-3-ol): MS (EI) para $C_{23}H_{25}F_3IN_3O_3$: 576 (MH^+).

EJEMPLO 3(cm). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1,1-dimetil-2-pirrolidin-1-iletil)amino]metil}azetidin-3-ol: ^1H NMR (400MHz, $CDCl_3$): 8,49 (s, 1H), 7,39 (dd, 1H), 7,34-7,29 (m, 1H), 7,14-7,11 (m, 1H), 6,83-6,77 (m, 1H), 6,64-6,59 (m, 1H), 4,25-4,07 (br m, 4H), 2,88 (d, 2H), 2,62 (m, 4H), 2,58 (m, 2H), 1,78 (m, 4H), 2,05 (AcOH; s, 3H); MS (EI) para $C_{25}H_{30}F_3IN_4O_2$: 603 (MH^+).

EJEMPLO 3(cn). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(1-metil-1*H*-imidazol-4-il)metil]amino}metil)azetidin-3-ol: ^1H NMR (400MHz, $CDCl_3$): 8,50 (s, 1H), 7,41-7,11 (m, 3H), 7,12 (m, 1H), 6,85-6,79 (m, 2H), 4,12-3,98 (br m, 4H), 3,78 (s, 2H), 3,66 (s, 3H), 2,95

(s, 2H), 2,08 (AcOH; s, 4H), 2,05 (AcOH; s, 3H); MS (EI) para $C_{22}H_{21}F_3IN_5O_2$: 572 (MH^+).

EJEMPLO 3(co). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(1-metil-1*H*-imidazol-5-il)metil]amino}metil)azetidin-3-ol: ^1H NMR (400MHz, $CDCl_3$): 8,45 (s, 1H), 7,47 (s, 1H), 7,39 (dd, 1H), 7,33-7,30 (m, 1H), 7,15-7,10 (m, 1H), 6,91 (s, 1H), 6,87-6,77 (m, 1H), 6,63-6,58 (m, 1H), 4,18-4,02 (m, 4H), 3,3,80 (s, 2H), 3,62 (s, 3H), 2,90 (s, 1H), 2,05 (AcOH; s, 3H); MS (EI) para $C_{22}H_{21}F_3IN_5O_2$: 572 (MH^+).

EJEMPLO 3(cp). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(2S)-2-(metiloxi)ciclopentil]amino}metil)azetidin-3-ol): MS (EI) para $C_{23}H_{25}F_3IN_3O_3$: 576 (MH^+).

EJEMPLO 3(cq). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(1R)-2-hidroxiciclohexil]amino}metil)azetidin-3-ol): MS (EI) para $C_{23}H_{25}F_3IN_3O_3$: 576 (MH^+).

EJEMPLO 3(cr). *N*-[3-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)fenil]metanosulfonamida: ^1H NMR (400MHz, $CDCl_3$): 7,33 (dd, 1H), 7,22 (m, 1H), 7,08 (dd, 1H), 6,83-6,77 (m, 1H), 6,03-5,98 (m, 2H), 6,64-6,59 (m, 1H), 4,08-3,77 (br m, 5H), 2,88 (s, 3H); MS (EI) para $C_{24}H_{22}F_3IN_4O_4S$: 647 (MH^+).

EJEMPLO 3(cs). 3-{[(4-aminofenil)amino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8,44 (s, 1H), 7,39 (dd, 1H), 7,34-7,30 (m, 1H), 7,14-7,10 (m, 1H), 6,84-6,77 (m, 1H), 6,64-6,53 (m, 5H), 4,22-4,04 (br m, 4H), 3,34 (s, 2H); MS (EI) para $C_{23}H_{20}F_3IN_4O_2$: 569 (MH^+).

EJEMPLO 3(ct). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-hidroxi-2-metilciclopentil)amino]metil}azetidin-3-ol: MS (EI) para $C_{23}H_{25}F_3IN_3O_3$: 576 (MH^+).

EJEMPLO 3(cu). 3-[(ciclopentilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7,44 (dd, 1H), 7,36-7,31 (m, 1H), 7,30-7,24 (m, 1H), 7,09-6,99 (m, 1H), 6,64-6,57 (m, 1H), 4,17-4,10 (m,1H), 4,01-3,91 (m, 2H), 3,87-3,79 (m, 1H), 3,07-2,97 (m, 1H), 2,75 (s, 2H), 1,92-1,79 (m, 2H), 1,75-1,62 (m, 2H), 1,61-1,47 (m, 2H), 1,37-1,22 (m, 2H). MS (EI) para $C_{22}H_{23}F_3IN_3O_2$: 546 (MH^+)

EJEMPLO 3(cv). Acetato (sal) de 3-{[(ciclohexilmetil)amino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7,46 (dd, 1H), 7,39-7,32 (m, 1H), 7,31-7,25 (m, 1H), 7,11-6,99 (m, 1H), 6,67-6,57 (m, 1H), 4,27-4,15 (m, 1H), 4,12-3,97 (m, 2H), 3,96-3,85 (m, 1H), 3 (s,2H), 2,62 (d, 2H),

1,90 (s, 3H), 1,82-1,45 (m, 6H), 1,40-1,07 (m, 3H), 1,04-0,80 (m, 2H). MS (EI) para $C_{24}H_{27}F_3IN_3O_2$: 574 (MH^+).

EJEMPLO 3(cw). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(propilamino)metil]azetidin-3-ol: ^1H NMR (400 MHz, d_6-DMSO): δ 8,56 (s, 1H), 7,57 (dd, 1H), 7,37 (dd, 1H), 7,32 (m, 1H), 7,18 (m, 1H), 6,67 (m, 1H), 4,03 (d, 1H), 3,89 (m, 2H), 3,69 (d, 1H), 2,59 (s, 2H), 2,42 (t, 2H), 1,90 (s, 3H), 1,32 (m, 2H), 0,81 (t, 3H); MS (EI) para $C_{20}H_{21}F_3IN_3O_2$: 520 (MH^+).

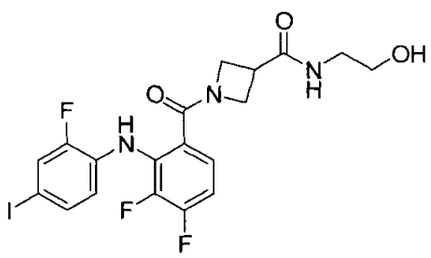
EJEMPLO 3(cx). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-metilpropil)amino]metil}azetidin-3-ol: ^1H NMR (400 MHz, d_6-DMSO): δ 8,56 (s, 1H), 7,56 (dd, 1H), 7,36 (dd, 1H), 7,31 (m, 1H), 7,18 (m, 1H), 6,67 (m, 1H), 4,02 (d, 1H), 3,89 (m, 2H), 3,70 (d, 1H), 2,57 (s, 2H), 2,27 (d, 2H), 1,91 (s, 3H), 1,55 (m, 1H), 0,79 (d, 6H); MS (EI) para $C_{21}H_{23}F_3IN_3O_2$: 534 (MH^+).

EJEMPLO 3(cy). metil (2xi)-2-desoxi-2-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)-beta-D-arabino-hexopiranosida: ^1H NMR (400 MHz, d_4-metanol, 3:1 mezcla de anómeros): δ 7,46 (d, 1H), 7,34 (d, 1H), 7,28 (m, 1H), 7,04 (q, 1H), 6,62 (m, 1H), 4,19-5,92 (m, 4H), 3,87-3,78 (m, 2H), 3,68 (m, 1H), 3,56-3,18 (m, 5H), 2,99-2,82 (m, 3H), 2,56 (m, 0,25H), 2,29 (m, 0,75H) MS (EI) para $C_{24}H_{27}F_3IN_3O_7$: 652 (M-H).

EJEMPLO 3(cz). Sal de acetato de 3-({[3-(dietilamino)propil]amino}metil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7,48-7,43 (d, 1H), 7,38-7,33 (d, 1H), 7,32-7,26 (m, 1H), 7,09-7,00 (q, 1H), 6,66-6,58 (t, 1H), 4,24-4,16 (d, 1H), 4,11-3,99 (t, 2H), 3,92-3,85 (d, 1H), 3,10-3,02 (m, 8H), 2,99-2,96 (s, 2H), 2,92-2,87 (t, 2H), 1,93-1,87 (s, 3H), 1,27-1,20 (t, 6H); MS (EI) para $C_{24}H_{30}F_3IN_4O_2$: 591 (MH^+).

EJEMPLO 4

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-(2-hidroxietil)azetidina-3-carboxamida



A una solución del ácido 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidina-3-carboxílico (15 mg, 0,03 mmol), preparado usando procedimientos similares a aquellos del Ejemplo 1, en *N*,*N*-dimetilformamida (2,00 mL) se agregó HBTU (38 mg, 0,10 mmol). La mezcla se agitó durante 15 minutos a temperatura ambiente y luego se agregó 2-aminoetanol

(3,6 µL, 0,06 mmol) y *N*-metilmorfolina (110 µL, 1.00 mmol). La mezclase dejó agitar a temperatura ambiente durante 3 días, luego se diluyó la mezcla con cloroformo (20 mL), y se lavó con agua (30 mL). La fase acuosa se extrajo nuevamente con cloroformo (10 mL). Las fases orgánicas combinadas se secaron sobr sulfato de sodio, se filtraron y el filtrado se concentró en vacío. El residuo se purificó mediante cromatografía de líquidos de alta presión y se obtuvo el compuesto del título (9,20 mg, 58%) como la sal del ácido trifluoroacético: ^{1}H NMR (400MHz, $CDCl_3$): 8,54 (s, 1H), 7,41-7,37 (m, 1H), 7,34-7,31 (m, 1H), 7,18-7,14 (m, 1H), 6,85-6,77 (m, 1H), 6,64-6,58 (m, 1H), 4,66 (br, 1H), 4,40-4,24 (br, 3H), 3,83-3,23 (br m, 7H), 1,18 (t, 3H); MS (EI) para $C_{19}H_{17}F_3IN_3O_3$: 542 (MNa^+).

Usando las mismas técnicas sintéticas o análogas de ellas y sustituyendo según sea necesario con reactivos alternativos, se prepararon los siguientes compuestos de la invención.

EJEMPLO 4(a): 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-(3,4-dihidroxibutil)azetidina-3-carboxamida: ^{1}H NMR (400 MHz, $CDCl_3$): 8,55 (s, 1H), 7,40 (dd, 1H), 7,31-7,35 (m, 1H), 7,14-7,18 (m, 1H), 6,78-6,84 (m, 1H), 6,59-6,65 (m, 1H), 6,14 (br s, 1H), 4,50-4,60 (m, 1H), 4,20-4,40 (m, 3H), 3,60-3,80 (m, 3H), 3,40-3,52 (m, 2H), 3,20-3,32 (m, 2H), 1,96 (br s, 1H), 1,18-1,28 (m, 2H). MS (EI) para $C_{21}H_{21}F_3IN_3O_4$: 562 (M-H).

EJEMPLO 4 (b): *N*-butil-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidina-3-carboxamida: ^{1}H NMR (400MHz, $CDCl_3$): 8,53 (s, 1H), 7,39 (dd, 1H), 7,33-7,31 (m, 1H), 7,17-7,13 (m, 1H), 6,83-6,77 (m, 1H), 6,64-6,58 (m, 1H), 5,50 (m, 1H), 4,57 (br, 1H), 4,29 (br m, 3H), 3,27 (m, 3H), 1,49 (m, 1H), 1,33 (m, 2H), 0,92 (t, 3H); MS (EI) para $C_{21}H_{21}F_3IN_3O_2$: 532 (MH^+), 554 (MNa^+).

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-prop-2-en-1-ilazetidina-3-carboxamida: ^{1}H NMR (400MHz, $CDCl_3$): 8,54 (s, 1H), 7,39 (dd, 1H), 7,34-7,31 (m, 1H), 7,17.7,12 (m, 1H), 6,83-6,77 (m, 1H), 6,64-6,58 (m, 1H), 5,88-5,77 (m, 1H), 5,57 (br, 1H), 5,21-5,16 (m, 2H), 4,59 (br, 1H), 4,30 (br m, 3H), 3,9 (tt, 2H), 3,32-3,25 (m, 1H)); MS (EI) para $C_{20}H_{17}F_3IN_3O_2$: 516 (MH^+), 538 (MNa^+).

EJEMPLO 4 (c): 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-etilazetidina-3-carboxamida: ^{1}H NMR (400MHz, $CDCl_3$): 8,54 (s, 1H), 7,38 (dd, 1H), 7,33-7,30 (m, 1H),7,17-7,12 (m, 1H), 6,83-6,77 (m, 1H), 6,63-6,57 (m, 1H), 5,55 (br s, 1H), 4,57 (br s, 1H), 4,28 (br m, 1H), 3,36-3,29 (m, 2H), 3,27-3,20 (m, 1H), 1,15 (t, 3H); MS (EI) para $C_{19}H_{17}F_3IN_3O_2$: 504 (MH^+), 526 (MNa^+).

EJEMPLO 4 (d): 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-(2-hidroxietil)azetidina-3-carboxamida: ^{1}H NMR (400MHz, $CDCl_3$): 8,50 (s, 1H), 7,39 (dd,

1H), 7,33-7,30 (m, 1H),7,16-7,12 (m, 1H), 6,84-6,77 (m, 1H), 6,63-6,57 (m, 1H), 4,57 (br, 1H), 4,28 (br, 3H), 3,73 (t, 2H), 3,49-3,44 (m, 2H), 3,33-3,27 (m, 1H), 2,18 (br, 1H); MS (EI) para $C_{19}H_{17}F_3IN_3O_3$: 542 (MNa^+).

EJEMPLO 4(e): 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-(2-piperidin-1-iletil)azetidina-3-carboxamida: ^1H NMR (400MHz, $CDCl_3$): 11,28 (s, 1H), 8,55 (s, 1H), 7,38 (dd, 1H), 7,33-7,30 (m, 1H), 7,15-7,10 (m, 1H), 6,82-6,76 (m, 1H), 6,63-6,58 (m, 1H), 4,42 (b, 1H), 4,26 (br m, 3H), 3,68 (br s, 2H), 3,58 (br d, 2H), 3,36 (br m, 1H)3,17 (br s, 1H), 2,63 (m, 4H), 1,92 (m, 5 H); MS (EI) para $C_{24}H_{26}F_3IN_4O_2$: 587 (MH^+).

EJEMPLO 4(f): 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-fenilazetidina-3-carboxamida: ^1H NMR (400MHz, $CDCl_3$): 8,52 (s, 1H), 7,50 (d, 1H), 7,41-7,27 (m, 4H), 7,16 (m, 2H), 6,85-6,78 (m, 1H), 6,65-6,59 (m, 1H), 4,37 (br, 3H), 3,43 (m, 1H); MS (EI) para $C_{23}H_{17}F_3IN_3O_2$: 574 (MNa^+).

EJEMPLO 4(g): *N*-[2-(dietilamino)etil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidina-3-carboxamida: ^1H NMR (400MHz, $CDCl_3$): 11,43 (s, 1H), 8,90 (s, 1H), 8,55 (s, 1H), 7,39 (dd, 1H), 7,33-7,30 (m, 1H), 7,15-7,10 (m, 1H), 6,87-6,77 (m, 1H), 6,63-6,58 (m, 1H), 4,44-4,22 (m, 4H), 3,65 (m, 2H), 3,38 (m, 1H), 3,19-3,13 (m, 5H), 1,33(t, 6H); MS (EI) para $C_{21}H_{21}F_3IN_3O_2$: 575 (MH^+).

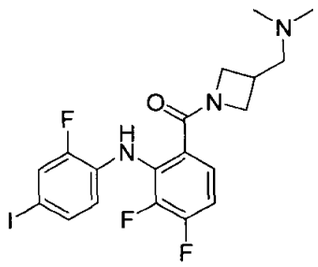
EJEMPLO 4(h): 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-[(2,3-dihidroxipropil)oxi]azetidina-3-carboxamida: MS (EI) para $C_{20}H_{19}F_3IN_3O_5$: 566 (MH^+).

EJEMPLO 4(i): 1-({3,4-Difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-(2,3-dihidroxipropil)azetidina-3-carboxamida: ^1H NMR (400 MHz, $CDCl_3$): 8,40 (br s, 1H), 7,35 (dd, 1H), 7,30 (br d, 1H), 7,16-7,09 (m, 1H), 6,89-6,76 (m, 2H), 6,58 (ddd, 1H), 4,58-4,40 (br, 1H), 4,27 (br t, 2H), 4,22-4,14 (br, 1H), 4,08-3,12 (m, 5H), 2,18-1,82 (br, 2H); MS (EI) para $C_{20}H_{19}F_3IN_3O_4$: 550 (MH^+).

EJEMPLO 4(j): 1-({3,4-Difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-hidroxiazetidina-3-carboxamida: ^1H NMR (400 MHz, $CDCl_3$): 8,23-8,10 (b, 1H), 7,35-7,28 (m, 2H), 7,14-7,07 (m, 1H), 6,86-6,80 (m, 1H), 6,60-6,54 (m, 1H), 4,52-4,38 (b, 1H), 4,32-4,08 (m, 3H), 3,30-3,21 (m, 1H); MS (EI) para $C_{17}H_{13}F_3IN_3O_3$: 492 (MH^+)

EJEMPLO 5

6-({3-[dimetilamino)metil]azetidin-1-il}carbonil)-2,3-difluoro-*N*-(2-fluoro-4-yodofenil)anilina



Una mezcla del ácido 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidina-3-carboxílico (196 mg, 0,41 mmol), preparado usando procedimientos similares a aquellos del Ejemplo 1, trietilamina (58 µL, 0,41 mmol), PyBOP (213 mg, 0,41 mmol) y borohidruro de sodio (48 mg, 1,24 mmol) en tetrahidrofurano (2 mL) se agitó a temperatura ambiente durante 15 horas. La mezcla de la reacción se concentró en vacío y el residuo resultante se repartió entre 20% ácido cítrico acuoso y acetato de etilo. La parte orgánica se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y se concentró en vacío y se obtuvo un residuo incoloro que se purificó mediante cromatografía de columna. Eluyendo con 60% acetato de etilo en hexanos, el producto aislado se concentró en vacío y se obtuvieron 48 mg, 0,11 mmol (25%) de [1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]metanol como un sólido blanco. ^{1}H NMR (400 MHz, $CDCl_3$): 7,44 (d, 1H), 7,34 (d,

1H), 7,28-7,23 (m, 1H), 7,04-6,97 (m, 1H), 4,26-4,18 (m, 1H), 4,02-3,94 (m, 2H), 3,78-3,72 (m, 1H), 3,03 (d, 2H), 3,34 (s, 1H), 2,80-2,71 (m, 1H). MS (EI) para $C_{17}H_{14}F_3IN_2O$: 463 (MH^+).

Una solución de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]metanol (48 mg, 0,11 mmol), 1,4-diazabiciclo[2.2.2]octano (18 mg, 0,16 mmol) y cloruro de metanosulfonilo (10 µL, 0,13 mmol) en tetrahidrofurano (2 mL) se agitó a temperatura ambiente durante 15 minutos. La mezcla luego repartió entre agua y acetato de etilo. La parte orgánica se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y seconcentró en vacío y se obtuvo un residuo incoloro que se purificó mediante cromatografía de columna. Eluyendo con 70% acetato de etilo en hexanos, el producto aislado se concentró en vacío y se obtuvieron 28 mg, 0,05 mmol (47%) de [1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]metil metanosulfonato como un residuo incoloro que se disolvió inmediatamente en éter de dimetilo de etilenglicol (2 mL). A la solución se agregó dimetilamina (exceso) y la solución se agitó en un tubo de sello a 50°C durante 15 horas. La mezcla de la reacción se concentró en vacío, y el residuo resultante se purificó mediante HPLC de fase invertida preparativa. El producto aislado se concentró en vacío y se obtuvieron 12 mg, 0,02 mmol (40%) de sal de acetato de 6-({3-[dimetilamino)metil]azetidin-1-il}carbonil)-2,3-

difluoro-*N*-(2-fluoro-4-yodofenil)anilina como un sólido blanco. ^{1}H NMR (400 MHz, DMSO): 8,54 (br s, 1H), 7,58 (d, 1H), 7,37 (d, 1H), 7,33-7,28 (m, 1H), 7,18-7,12 (m, 1H), 6,70-6,64 (m, 1H), 4,18-4,12 (m, 1H), 3,99-3,76 (m, 1H), 3,52-3,47 (m, 1H), 2,52-2,48 (m, 1H), 2,39 (d, 2H), 1,85 (s, 6H); MS (EI) para $C_{19}H_{19}F_3IN_3O$: 490 (MH^+).

Usando las mismas técnicas sintéticas o análogas y/o sustituyendo con reactivos alternativos, se prepararon los siguientes compuestos de la invención.

EJEMPLO 5(a): 2,3-difluoro-*N*-(2-fluoro-4-iodophenyl)-6-[(3-{[(1-metiletil)amino]metil}azetidin-1-il)carbonil]anilina: ^{1}H NMR (400 MHz, $CDCl_3$): 8,54 (s, 1H), 7,40 (dd, 1H), 7,31-7,33 (m, 1H), 7,11-7,15 (m, 1H), 6,76-6,82 (m, 1H), 6,58-6,64 (m, 1H), 4,23-4,30 (m, 2H), 3,90-4,00 (m, 1H), 3,76-3,84 (m, 1H), 2,69-2,85 (m, 4H), 1,05 (d, 6H). MS (EI) para $C_{20}H_{21}F_3IN_3O$: 502 (M-H).

EJEMPLO 5(b): 2-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-2-il]metil}amino)etanol: MS (EI) para $C_{19}H_{19}F_3IN_3O_2$: 506 (MH^+).

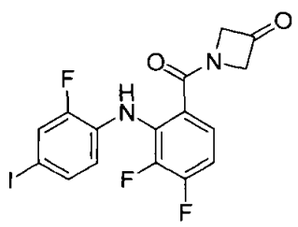
EJEMPLO 5(c): *N*-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-2-il]metil}etano-1,2-diamina: MS (EI) para $C_{19}H_{20}F_3IN_4O$: 505 (MH^+).

EJEMPLO 5(d): Sal de acetato de 6-({3-[dimetilamino)metil]azetidin-1-il}carbonil)-2,3-difluoro-*N*-(2-fluoro-4-yodofenil)anilina: ^{1}H NMR (400 MHz, DMSO): 8,54 (br

s, 1H), 7,58 (d, 1H), 7,37 (d, 1H), 7,33-7,28 (m, 1H), 7,18-7,12 (m, 1H), 6,70-6,64 (m, 1H), 4,18-4,12 (m, 1H), 3,99-3,76 (m, 1H), 3,52-3,47 (m, 1H), 2,52-2,48 (m, 1H), 2,39 (d, 2H), 1,85 (s, 6H); MS (EI) para $C_{19}H_{19}F_3IN_3O$: 490 (MH^+).

EJEMPLO 6

1-({3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-one

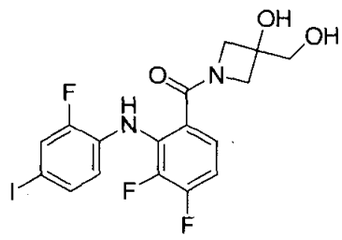


1-({3,4-Difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol (132 mg, 0,295 mmol), preparado usando procedimientos similares a aquellos del Ejemplo 1, se disolvió en diclorometano (8 mL) y se enfrió a 0°C. Se agregó peryodinano de Dess-Martin (187 mg, 0,441 mmol) y la mezcla se agitó a temperatura ambiente durante 2 horas. La mezcla se enfrió con una solución de bicarbonato de sodio saturada: 10% solución de tiosulfato de sodio (1:1; 6 mL) y se diluyó con acetato de etilo. La parte orgánica se lavó con salmuera, se secó sobre sulfato de sodio anhidro, se filtró y se concentró en vacío. La cromatografía de columna (gel de sílice, 40-50% acetato de etilo en hexanos) dio 1-({3,4-difluoro-2-[(2-fluoro-4-

yodofenil)amino]fenil}carbonil)azetidin-3-ona (122 mg, 0,273 mmol, rendimiento del 93%): ^{1}H NMR (400 MHz, $CDCl_3$): 8,43 (br s, 1H), 7,44-7,38 (m, 1H), 7,36-7,32 (m, 1H), 7,27-7,20 (m, 1H), 6,86 (ddd, 1H), 6,64 (ddd, 1H), 4,94-4,93 (m, 4H); MS (EI) para $C_{16}H_{10}F_3IN_2O_2$: 447 (MH^+).

EJEMPLO 7

1-({3,4-Difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(hidroximetil)azetidin-3-ol



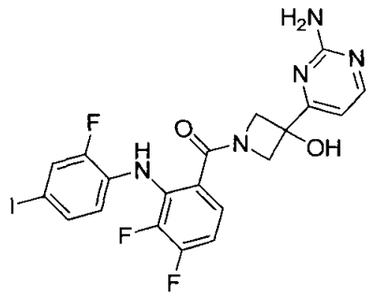
Bromuro de metil trifenilfosfonio (508 mg, 1,42 mmol) se trató con *terc*-butóxido de potasio (159 mg, 1,42 mmol) en tetrahidrofurano (5 mL) a 0°C durante 10 minutos. 1-({3,4-Difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ona (270 mg, 0,605 mmol), preparado usando procedimientos similares a aquellos descritos en el Ejemplo 6, se disolvió en tetrahidrofurano (2 mL) y se agregó a la mezcla. La mezcla se agitó a temperatura ambiente durante 15 horas y luego la mezcla se filtró y el filtrado se repartió entre acetato de etilo y agua La parte acuosa se extrajo con acetato de etilo. La parte orgánica combinada se lavó con salmuera, se secó sobre sulfato de sodio

anhidro, se filtró y se concentró en vacío. La cromatografía de columna (gel de sílice, 20% acetato de etilo en hexanos) dio 2,3-difluoro-*N*-(2-fluoro-4-yodofenil)-6-[(3-metilideneazetidin-1-il)carbonil]anilina (57 mg, 0,128 mmol, rendimiento del 21%): ^{1}H NMR (400 MHz, $CDCl_3$): 8,56 (br s, 1H), 7,39 (dd, 1H), 7,35-7,30 (m, 1H), 7,18-7,12 (m, 1H), 6,86-6,76 (m, 1H), 6,62 (ddd, 1H), 5,14-5,00 (br, 2H), 4,74 (br d, 4H); MS (EI) para $C_{17}H_{12}F_3IN_2O$: 445 (MH^+).

2,3-Difluoro-*N*-(2-fluoro-4-yodofenil)-6-[(3-metilidenazetidin-1-il)carbonil]anilina (56 mg, 0,126 mmol) y N-óxido de 4-metilmorfolina (44 mg, 0,376 mmol) se disolvieron en acetona / agua (4:1; 10 mL) y se agregó tetróxido de osmio (4% en peso en agua; 0,7 mL). La solución se agitó a temperatura ambiente durante 4 horas,luego se enfrió con bisulfito de sodio saturado (2 mL) y se concentró en vacío. El residuo se repartió entre acetato de etilo y agua. La parte orgánica se lavó con salmuera, se secó sobre sulfato de sodio anhidro, se filtró y se concentró en vacío. La cromatografía de columna (gel de sílice, 80% acetato de etilo en hexanos) y luego la HPLC de fase invertida dio 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(hidroximetil)azetidin-3-ol (17 mg, 0,036 mmol, rendimiento del 28%): ^{1}H NMR (400 MHz, $CDCl_3$): 8,43 (br s, 1H), 7,40 (dd, 1H), 7,35-7,31 (m, 1H), 7,16-7,10 (m, 1H), 6,81 (ddd, 1H), 6,61 (ddd, 1H), 4,25-4,00 (m, 4H), 3,78 (s, 2H); MS (EI) para $C_{17}H_{14}F_3IN_2O_3$: 479 (MH^+).

EXAMPLE 8

3-(2-aminopyrimidin-4-yl)-1-({3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]phenyl}carbonyl)azetidin-3-ol



A una solución de 4-yodo-2-(metiltio)pirimidina (2,00 g, 7,92 mmol) en tetrahidrofurano (4,00 ml) se agregó cloruro de isopropilmagnesio (815 mg, 7,92 mmol). La mezcla se dejó agitar durante 1 hora a 0°C, y luego se agregó 1,1-dimetiletil 3-oxoazetidieno-1-carboxilato (1,64 g, 9,60 mmol), preparado usando procedimientos similares a aquellos descritos en el Ejemplo 3. La mezcla de la reacción luego se dejó calentar a temperatura ambiente y se agitó durante 6 horas. La mezcla se enfrió con 1N ácido clorhídrico (10 mL) y se extrajo con acetato de etilo. La capa orgánica se separó, se secó sobre sulfato de sodio anhidro, se filtró y el filtrado se concentró en vacío. El residuo se purificó mediante cromatografía de columna (SiO_2, hexanos/acetato de etilo) y se obtuvo 1,1-dimetiletil 3-hidroxi-3-[2-(metiltio)pirimidin-4-il]azetidina-1-carboxilato (380 mg, 16%) como un aceite amarillo. ^1H NMR (400 MHz, $CDCl_3$): 8,62-8,59 (d, 1H), 7,36-7,33 (d, 1H), 5,14-

5,11 (s, 1H), 4,29-4,24 (d, 2H), 4,13-4,08 (d, 2H), 2,61-2,58 (s, 3H), 1,50-1,47 (s, 9H); MS (EI) para $C_{13}H_{19}N_3O_3S$: 298 (MH^+).

Una solución de 1,1-dimetiletil 3-hidroxi-3-[2-(metiltio)pirimidin-4-il]azetidina-1-carboxilato (480 mg, 1,62 mmol), y ácido 3-cloroperoxibenzoico (558 mg, 3,23 mmol) en diclorometano (25 mL) se agitó a temperatura ambiente durante 22 horas. La mezcla de la reacción se enfrió con una solución saturada de tiosulfato de sodio y el pH se ajustó a 7 con carbonato de sodio. La capa orgánica se separó, se secó sobre sulfato desodio anhidro, se filtró y el filtrado se concentró en vacío. El 1,1-dimetiletil 3-hidroxi-3-[2-(metilsulfonil)pirimidin-4-il]azetidina-1-carboxilato crudo resultante (524 mg, 98%) se usó sin nueva purificación. ^1H NMR (400 MHz, $CDCl_3$): 9,01-8,97 (d, 1H), 7,96-7,93 (d, 1H), 4,57-4,53 (s, 1H), 4,31-4,27 (d, 2H), 4,23-4,18 (d, 2H), 3,42-3,39 (s, 3H), 1,50-1,47 (s, 9H); MS (EI) para $C_{13}H_{19}N_3O_5S$: 330 (MH^+).

Una solución de 1,1-dimetiletil 3-hidroxi-3-[2-(metilsulfonil)pirimidin-4-il]azetidina-1-carboxilato (215 mg, 0,652 mmol), y amoníaco acuoso (7 mL, 28% solución) en dioxano (15 mL) dentro de un cilindro de bomba de acero sellado se calentó a 80°C durante 4 horas. La mezcla se enfrió a temperatura ambiente y el solvente se evaporó. El residuo se disolvió en diclorometano y una solución de carbonato de sodio saturado. La capa orgánica seseparó, se secó sobre suflato de sodio anhidro, se filtró y el filtrado se concentró en vacío.

El 1,1-dimetiletil 3-(2-aminopirimidin-4-il)-3-hidroxiazetidina-1-carboxilato crudo resultante (140 mg, 100%) se usó sin nueva purificación. ^{1}H NMR (400 MHz, $CDCl_3$): 8,38-8,35 (d, 1H), 6,97-6,94 (d, 1H), 5,30-5,28 (s, 2H), 4,23-4,18 (d, 2H), 4,08-4,04 (d, 2H), 1,48-1,45 (s, 9H).

A una solución de 1,1-dimetiletil 3-(2-aminopirimidin-4-il)-3-hidroxiazetidina-1-carboxilato (140 mg, 0,524 mmol) en diclorometano (10 ml) se agregó ácido trifluoroacético (3 ml). La mezcla de la reacción se agitó durante 2 horas a temperatura ambiente. La mezcla se concentró en vacío. El 3-(2-aminopirimidin-4-il)azetidin-3-ol crudo resultante (87 mg, 100%) se usó sin nueva purificación.

Una solución de ácido 3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]benzoico (201 mg, 0,512 mmol), preparado usando procedimientos similares a aquellos descritos en US 7,019,033, 3-(2-aminopirimidin-4-il)azetidin-3-ol (87 mg, 0,52 mmol), hexafluorofosfato de benzotriazol-1-il-oxi-tris(pirrolidino)fosfonio (293 mg, 0,563 mmol) y *N,N*-diisopropiletilamina (270 uL, 2,82 mmol) en *N,N*-dimetilformamida (2 mL) se agitó a temperatura ambiente durante 20 horas. La mezcla se repartió entre acetato de etilo y bicarbonato de sodio saturado. La capa orgánica se separó y se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y el filtrado seconcentró en vacío. El residuo es purificó mediante HPLC de fase invertida y se obtuvo el

compuesto del título 3-(2-aminopirimidin-4-il)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol (22 mg, 7%). ^{1}H NMR (400 MHz, CD_3OD): 8,23-8,20 (d, 1H), 7,48-7,43 (d, 1H), 7,35-7,32 (m, 2H), 7,09-7,00 (m, 1H), 6,88-6,84 (d, 1H), 6,70-6,63 (t, 1H), 4,59-4,54 (d, 1H), 4,45-4,40 (d, 1H), 4,23-4,18 (d, 1H), 3,04-3,99 (t, 1H); MS (EI) para $C_{20}H_{15}F_3IN_5O_2$: 542 (MH^+).

Usando las mismas técnicas sintéticas o análogas y sustituyendo, según fue necesario, con reactivos alternativos, se prepararon los siguientes compuestos de la invención:

EJEMPLO 8(a): 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-piridin-2-ilazetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 8,47 (m, 1H), 7,80 (m, 1H), 7,65 (d, 1H), 7,44 (m, 1H), 7,33 (m, 3H), 7,04 (m, 1H), 6,65 (m, 1H), 4,61 (d, 1H), 4,44 (d, 1H), 4,29 (d, 1H), 4,12 (d, 1H). MS (EI) para $C_{21}H_{15}F_3IN_3O_2$: 526 (MH^+).

EJEMPLO 8(b): 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1*H*-imidazol-2-il)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7,42 (m, 1H), 7,37 (m, 1H), 7,32 (m, 1H), 7,02 (m, 3H), 6,63 (m, 1H), 4,65 (d, 1H), 4,42 (d, 1H), 4,33 (d, 1H), 4,16 (d, 1H). MS (EI) para $C_{19}H_{14}F_3IN_4O_2$: 515 (MH^+).

EJEMPLO 8(c): 3-(1*H*-bencimidazol-2-il)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: ^{1}H NMR

(400 MHz, CD_3OD): 7,55 (br s, 2H), 7,42 (m, 2H), 7,33 (m, 1H), 7,23 (m, 2H), 7,04 (m, 1H), 6,65 (m, 1H), 4,76 (d, 1H), 4,57 (d, 1H), 4,43 (d, 1H), 4,25 (d, 1H). MS (EI) para $C_{23}H_{16}F_3IN_4O_2$: 565 (MH^+).

EJEMPLO 8(d): 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(5-metil-1*H*-imidazol-2-il)azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7,41 (m, 1H), 7,36 (m, 1H), 7,31 (m, 1H), 7,02 (m, 1H), 6,67 (br s, 1H), 6,63 (m, 1H), 4,63 (d, 1H), 4,39 (d, 1H), 4,30 (d, 1H), 4,13 (d, 1H), 2,18 (s, 3H). MS (EI) para $C_{20}H_{16}F_3IN_4O_2$: 529 (MH^+).

EJEMPLO 8(e): 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-prop-2-en-1-ilazetidin-3-ol: ^1H NMR (400 MHz, $CDCl_3$): 8,47 (br s, 1H), 7,40 (dd, 1H), 7,35-7,31 (m, 1H), 7,15-7,10 (m, 1H), 6,81 (ddd, 1H), 6,62 (ddd, 1H), 5,84-5,72 (m, 1H), 5,27-5,20 (m, 2H), 4,22-3,94 (m, 4H), 2,52 (d, 2H), 2,25 (s, 1H); MS (EI) para $C_{19}H_{16}F_3IN_2O_2$: 489 (MH^+).

EJEMPLO 8(f): 3-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]propano-1,2-diol: ^1H NMR (400 MHz, $CDCl_3$): 8,43 (br s, 1H), 7,39 (dd, 1H), 7,35-7,30 (m, 1H), 7,16-7,10 (m, 1H), 6,82 (ddd, 1H), 6,61 (ddd, 1H), 4,31-3,91 (m, 5H), 3,68 (br d, 1H), 3,54-3,49 (m, 1H), 2,01-1,80 (m, 2H); MS (EI) para $C_{19}H_{18}F_3IN_2O_4$: 523 (MH^+).

EJEMPLO 8(g): 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-etenilazetidin-3-ol: ^{1}H NMR (400 MHz, $CDCl_3$): 8,48 (br s, 1H), 7,40 (dd, 1H), 7,35-7,31 (m, 1H), 7,17-7,11 (m, 1H), 6,81 (ddd, 1H), 6,62 (ddd, 1H), 6,15 (dd, 1H), 5,39 (d, 1H), 5,28 (d, 1H), 4,30-4,10 (m, 4H); MS (EI) para $C_{18}H_{14}F_3IN_2O_2$: 475 (MH^+).

EJEMPLO 8(h): Clorhidrato de 1-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]etano-1,2-diol: ^{1}H NMR (400 MHz, d_6-DMSO): 8,66 (d, 1H), 7,58 (dd, 1H), 7,38 (d, 1H), 7,33-7,27 (m, 1H), 7,17 (q, 1H), 6,74-6,65 (m, 1H), 4,50-3,58 (br, 3H), 4,29 (dd, 1H), 4,14 (dd, 1H), 3,87 (t, 1H), 3,66 (t, 1H), 3,56-3,32 (m, 3H); MS (EI) para $C_{18}H_{16}F_3IN_2O_4$: 509 (MH^+).

EJEMPLO 8(i): 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-etilazetidin-3-ol: ^{1}H NMR (400 MHz, $CDCl_3$): 8,23 (br s, 1H), 7,40 (d, 1H), 7,33 (d, 1H), 7,15-7,10 (m, 1H), 6,85-6,79 (m, 1H), 6,64-6,58 (m, 1H), 4,14-3,94 (m, 4H), 1,78 (q, 2H), 0,96 (t, 3H); MS (EI) para $C_{18}H_{16}F_3IN_2O_2$: 477 (MH^+).

EJEMPLO 8(j): 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-metilazetidin-3-ol: ^{1}H NMR (400 MHz, $CDCl_3$): 8,31 (br s, 1H), 7,40 (d, 1H), 7,33 (d, 1H), 7,15-7,11 (m, 1H), 6,85-6,78 (m, 1H), 6,65-6,59 (m, 1H), 4,24-4,04 (m, 4H), 1,55 (s, 3H); MS (EI) para $C_{17}H_{14}F_3IN_2O_2$: 463 (MH^+).

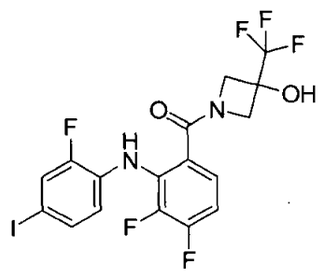
EJEMPLO 8(k): Sal de acetato de 3-(2-aminopirimidin-4-il)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 8,22-8,20 (d, 1H), 7,48-7,43 (d, 1H), 7,38-7,30 (m, 1H), 7,09-7,01 (q, 1H), 6,88-6,84 (d, 1H), 6,70-6,61 (t, 1H), 4,59-4,54 (d, 1H), 4,44-4,39 (d, 1H), 4,23-4,19 (d, 1H), 4,05-3,99 (d, 1H), 3,90-3,81 (d, 1H), 1,99-1,97 (s, 3H); MS (EI) para $C_{20}H_{15}F_3I\ N_5O_2$: 542 (MH^+).

EJEMPLO 8(m): 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1*H*-pirrol-2-il)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7,37 (dd, 1H), 7,31-7,23 (m, 2H), 7,07-6,97 (m, 1H), 6,73-6,68 (m, 1H), 6,65-6,56 (m, 1H), 6,06-5,98 (m, 2H), 4,49-4,40 (m,1H), 4,32-4,18 (m, 2H), 4,15-88-4,07 (m, 1H). MS (EI) para $C_{20}H_{15}F_3IN_3O_2$: 514 (MH^+)

EJEMPLO 8(n): 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1-metil-1*H*-imidazol-2-il)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7,34 (dd, 1H), 7,31-7,25 (m, 1H), 7,23-7,18 (m, 1H), 7,11-7,09 (m, 1H), 7,06-6,97 (m, 1H), 6,89-6,86 (m, 1H), 6,62-6,55 (m, 1H), 4,88-4,80 (m, 1H), 4,52-4,44 (m,1H), 4,38-4,30 (m, 1H), 4,21-4,12 (m, 1H), 3,68 (s, 3H). MS (EI) para $C_{20}H_{16}F_3IN_4O_2$: 529 (MH^+).

EJEMPLO 9

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(trifluorometil)azetidin-3-ol

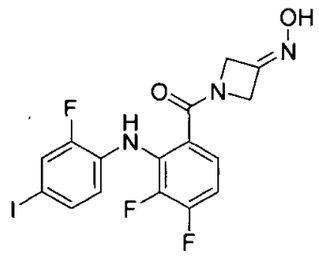


1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ona (25 mg, 0,056 mmol), preparado usando procedimientos descritos en el Ejemplo 6, se llevó a DMF (0,5 mL) luego se agregó (trifluorometil)trimetilsilano (40 µL, 0,28 mmol) y carbonato de cesio (22 mg, 0,067 mmol) y la mezcla se agitó durante una hora a temperatura ambiente. La mezcla se repartió con éter etílico y gua y la fase orgánica se lavó tres veces con agua adicional luego con salmuera y se secó sobre sulfato de sodioanhidro. La filtración y la concentración y luego la cromatografía rápida de gel de sílice del residuo usando using hexanos:acetato de etilo 3:2 como eluyente se obtuvo 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(trifluorometil)azetidin-3-ol (19,8 mg, rendimeinto del 69%) como un sólido cristalino incoloro. ^{1}H-NMR (400 MHz, $CDCl_3$): 8,31-8,26 (br, 1H), 7,40 (d, 1H), 7,33 (d, 1H), 7,13-7,10 (m,

1H), 6,86-6,80 (m, 1H), 6,65-6,60 (m, 1H), 4,42 (br s, 2H), 4,18 (br s, 2H). MS (EI) para $C_{17}H_{11}F_6IN_2O_2$: 517 (MH^+)

EJEMPLO 10

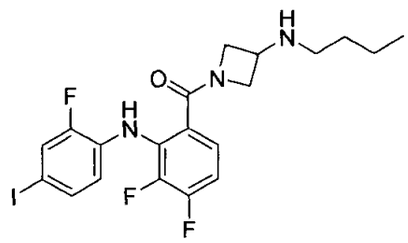
1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ona oxima



A una solución de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ona (100 mg, 0,22 mmol), preparado usando procedimientos similares a aquellos descritos en el Ejemplo 6, en dioxano (1,0 mL) se agregó hidroxilamina (0,10 mL, 50% solución en agua, 1,5 mmol), y la solución resultante se calentó a 60°C durante 18 horas. La mezcla se enfrió a temperatura ambiente y el producto crudo se purificó mediante HPLC de fase invertida y se obtuvo 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ona oxima (56 mg, rendimiento 54%): ^{1}HNMR (400MHz, $CDCl_3$), 8,43 (br s), 7,43-7,39 (m, 2H), 7,35-7,32 (dd,1H), 7,19-7,15 (m, 1H), 6,87-6,81 (m,1H), 6,65-6,59 (m, 1H), 4,89 (br s, 2H), 4,85 (br s, 2H); MS (EI) para $C_{16}H_{11}F_3IN_3O_2$: 462 (MH^+).

Ejemplo 11

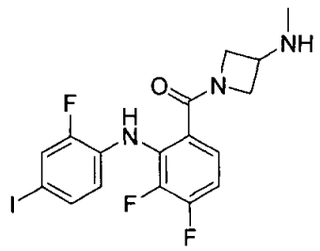
***N*-butil-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-amina**



A una solución de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-amina (0,09 M en acetonitrilo, 500 µL, 0,045 mmol), preparado usando procedimientos similares a aquellos descritos en el Ejemplo 2, se agregó trietilamina (20 µL, 0,135 mmol) y bromuro de *n*-butilo (6,14 µL, 0,054 mmol) y luego acetonitrilo adicional (1,0 mL). La mezcla de la reacción se agitó a temperatura ambiente durante 16 horas, en cuyo momento se purificó directamente mediante HPLC de fase invertida y se obtuvo el compuesto del título (8,4 mg). ^{1}H NMR (400 MHz, $CDCl_3$): 8,50 (s, 1H), 7,39 (dd, 1H), 7,32 (dd, 1H), 7,13-7,09 (m, 1H), 6,84-6,77 (m, 1H), 6,63-6,57 (m, 1H), 4,35 (br s, 2H), 4,00 (br s, 1H), 3,87 (br s, 1H), 3,74-3,68 (m, 1H), 3,20 (br s, 3,5H), 2,56 (t, 2H), 2,03 (s, 2H), 1,50-1,42 (m, 2H), 1,39-1,29 (m, 2H), 0,91 (t, 3H). MS (EI) para $C_{20}H_{21}F_3IN_3O$: 504 (MH^+).

EJEMPLO 12

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-metilazetidin-3-amina



A una solución de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-amina (0,10 M en acetonitrilo, 1,0 mL, 0,09 mmol), preparado usando procedimientos similares a aquellos descritos en el Ejemplo 2 2, a una relación de 1:1 de metanol y tetrahidrofurano (2,0 mL) se agregó formaldehído (37% en peso, 6,7 µL, 0,09 mmol) y luego con cianoborohidruro de sodio (11,0 mg, 0,18 mmol). La mezcla de la reacción se agitó a temperatura ambiente durante 16 horas, en cuyo momento se enfrió con cloruro de amonio acuoso saturado. La solución luego se purificó directamente mediante HPLC de fase invertida y se obtuvo el compuesto del título (14,9 mg). ^{1}H NMR (400 MHz, $CDCl_3$): 8,13 (br s, 1H), 7,35 (d, 1H), 7,30 (d, 1H), 7,09-7,04 (m, 1H), 6,84-6,78 (m, 1H), 6,60-6,54 (m, 1H), 4,46-4,33 (br m, 4H), 3,93 (br m, 1H), 2,64 (s, 3H). MS (EI) para $C_{17}H_{15}F_3IN_3O$: 462 (MH^+).

Usando las mismas técnicas sintéticas o análogas y sustituyendo según fue necesario, con reactivos alternativos, se prepararon los siguientes compuestos de la invención:

EJEMPLO 12(a). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-metilazetidin-3-amina: ^{1}H NMR (400 MHz, $CDCl_3$): 8,13 (br s, 1H), 7,35 (d, 1H), 7,30 (d, 1H), 7,09-7,04 (m, 1H), 6,84-6,78 (m, 1H), 6,60-6,54 (m, 1H), 4,46-4,33 (br m, 4H), 3,93 (br m, 1H), 2,64 (s, 3H). MS (EI) para $C_{17}H_{15}F_3IN_3O$: 462 (MH^+).

EJEMPLO 12(b). 2-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]amino}etanol: ^{1}H NMR (400 MHz, $CDCl_3$): 8,20 (s, 1H), 7,36 (d, 1H), 7,30 (d, 1H), 7,13-7,09 (m, 1H), 6,85-6,79 (m, 1H), 6,61-6,55 (m, 1H), 4,43 (br m, 3H), 3,98 (br m, 1H), 3,87 (br m, 1H), 3,02 (br m, 1H), 1,24-1,20 (m, 1H). MS (EI) para $C_{18}H_{17}F_3IN_3O_2$: 492 (MH^+).

EJEMPLO 12(c). *N*-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]propano-1,3-diamina: ^{1}H NMR (400 MHz, $CDCl_3$): 8,51 (s, 1H), 7,39 (d, 1H), 7,32 (d, 1H), 7,14-7,10 (m, 1H), 6,84-6,77 (m, 1H), 6,63-6,57 (m, 1H), 4,33 (br s, 2H), 3,99 (br s, 1H), 3,84 (br s, 1H), 3,71-3,64 (m, 1H), 2,91 (t, 2H), 2,70-2,66 (m, 2H), 2,01 (s, 4H), 1,76-1,69 (m, 2H). MS (EI) para $C_{19}H_{20}F_3IN_4O$: 505 (MH^+).

EJEMPLO 12(d). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-etilazetidin-3-amina: ^{1}H NMR (400 MHz, $CDCl_3$): 8,47 (s, 1H), 7,38 (d, 1H), 7,31 (d, 1H),

7,13-7,09 (m, 1H), 6,83-6,77 (m, 1H), 6,62-6,57 (m, 1H), 4,49 (br s, 3H), 4,36 (br s, 2H), 4,08 (br s, 1H), 3,94 (br s, 1H), 3,77-3,72 (m, 1H), 2,69-2,63 (m, 2H), 1,99 (s, 2H), 1,14 (t, 3H). MS (EI) para $C_{18}H_{17}F_3IN_3O$: 476 (MH^+).

EJEMPLO 12(e). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-(2-metilpropil)azetidin-3-amina: ^1H NMR (400 MHz, $CDCl_3$): 8,50 (s, 1H), 7,38 (d, 1H), 7,31 (d, 1H), 7,14-7,09 (m, 1H), 6,83-6,76 (m, 1H), 6,63-6,57 (m, 1H), 4,34 (br s, 2H), 4,00 (br s, 1H), 3,86 (br s, 1H), 3,71-3,66 (m, 1H), 3,42 (br s, 2H), 2,36 (d, 2H), 2,00 (s, 1H), 1,75-1,65 (m, 1H), 0,91 (d, 6H). MS (EI) para $C_{20}H_{21}F_3IN_3O$: 504 (MH^+).

EJEMPLO 12(f). *N*-(ciclopropilmetil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-amina: ^1H NMR (400 MHz, $CDCl_3$): 8,48 (s, 1H), 7,39 (d, 1H), 7,32 (d, 1H), 7,13-7,09 (m, 1H), 6,84-6,77 (m, 1H), 6,63-6,57 (m, 1H), 5,78 (s, 3H), 4,36 (br s, 2H), 4,10 (br s, 1H), 3,94 (br s, 1H), 3,81-3,75 (m, 1H), 2,49 (d, 2H), 2,01 (s, 4H), 0,94-0,86 (m, 1H), 0,53 (d, 2H), 0,13 (d, 2H). MS (EI) para $C_{20}H_{19}F_3IN_3O$: 502 (MH^+).

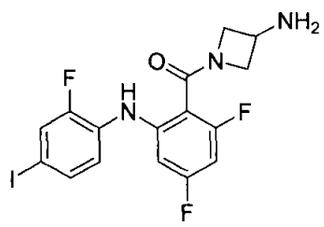
EJEMPLO 12(g). *N*-(ciclohexilmetil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-amina: ^1H NMR (400 MHz, $CDCl_3$): 8,48 (s, 1H), 7,38 (dd, 1H), 7,31 (d, 1H), 7,13-7,08 (m, 1H), 6,83-6,77 (m, 1H), 6,63-6,57 (m, 1H), 4,55 (br s, 2H), 4,33 (br m, 2H), 4,02 (br s, 1H) 3,87 (br s,

1H), 3,71-3,65 (m, 1H), 2,38 (d, 2H), 1,74-1,68 (m, 4H), 1,46-1,36 (m, 1H), 1,27-1,12 (m, 3H), 0,94-0,84 (m, 2H). MS (EI) para $C_{23}H_{25}F_3IN_3O$: 544 (MH^+).

EJEMPLO 12(h). *N*-(ciclopentilmetil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-amina: ^1H NMR (400 MHz, $CDCl_3$): 8,32 (s, 1H), 7,37 (d, 1H), 7,31 (d, 1H), 7,11-7,07 (m, 1H), 6,84-6,77 (m, 1H), 6,63-6,57 (m, 1H), 4,44-4,37 (m, 3H), 4,02-3,96 (m, 1H), 2,84 (d, 2H), 2,54 (br s, 5H), 2,20-2,12 (m, 1H), 1,88-1,81 (m, 2H), 1,68-1,54 (m, 4H), 1,24-1,15 (m, 2H). MS (EI) para $C_{22}H_{23}F_3IN_3O$: 530 (MH^+).

EJEMPLO 13

1-({2,4-difluoro-6-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-amina



Ácido 2,4,6-Trifluorobenzoico (643 mg, 3,65 mmol) y 2-fluoro-4-yodoanilina (1,0 g, 4,22 mmol) se llevaron a acetonitrilo (30 mL) y luego se agregó amida de litio (290 mg, 12,7 mmol) y la mezcla se calentó a 60°C bajo una atmósfera de nitrógeno durante una hora. Al enfriar a temperatura ambiente la mezcla se agregó a 1 N ácido clorhídrico acuoso (100 mL) y el precipitado formado se recogió mediante filtración y se lvó

con agua luego con hexanos y se secó en vacío y dio ácido 2,4-difluoro-6-[(2-fluoro-4-yodofenil)amino]benzoico (849 mg, rendimiento 59%) como un sóido tostado. ^{1}H-NMR (400 MHz, D_6-DMSO): 13,72 (br s, 1H), 9,46 (s, 1H), 7,75 (d, 1H), 7,56 (d, 1H) 7,28 (tr, 1H), 6,73-6,67 (m, 1H), 6,53 (d, 1H).

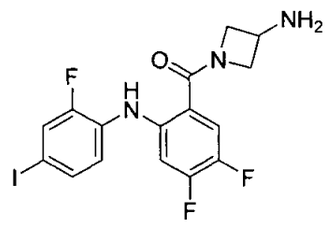
Ácido 2,4-Difluoro-6-[(2-fluoro-4-yodofenil)amino]benzoico (100 mg, 0,25 mmol) se llevó a DMF (1 mL) luego se agregó PyBOP (137 mg, 0,26 mmol) y la mezcla se agitó durante 15 minutos luego NMM (60 µL, 0,5 mmol) y después se agregó 1,1-dimetiletil azetidin-3-ilcarbamato comercialmente disponible (43 mg, 0,25 mmol). La mezcla se dejó agitar durante 12 horas a temperatura ambiente, luego se repartió con acetato de etilo y agua. La fase orgánica se lavó tres veces con agua adicional luego salmuera y se secó sobre sulfato de sodio anhidro. La filtración y la concentración y luego la cromatografía rápida de gel de sílice del residuo usando hexanos:acetato de etilo 3:1 como eluyente dió 1,1-dimetiletil [1-({2,4-difluoro-6-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]carbamato (125 mg) como un aceite incoloro.

El aceite se llevó a ácido trifluoroacético (1 mL) y se dejó en reposo a temperatura ambiente durante 5 minutos y luego se concentró en vacío. El residuo se dividió en porciones con acetato de etilo y bicarbonato de sodio acusoo saturado y la fase orgánica se lavó con salmuera y luego se secó sobre sulfato de sodio anhidro. La solución orgánica se filtró y se

concentró luego el residuo se llevó a metanol (1 mL) luego se agrgó 4 N HCl en dioxano y la solución se hizo ácida. La solución se concentró y el residuo se trituró con éter etílico y dio un precipitado espeso. El sólido se recogió mediante filtración y se secó en vacío y dio clorhidrato de 1-({2,4-difluoro-6-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-amina (58 mg, rendimiento total del 48%). ^{1}H-NMR (400 MHz, D_6-DMSO): 8,67 (br s, 3H), 8,45 (s, 1H), 7,71 (d, 1H), 7,54 (d, 1H), 7,25 (tr, 1H), 6,77 (tr, 1H), 6,48 (d, 1H), 4,28-4,23 (m, 2H), 4,13-4,06 (m, 3H). MS (EI) para $C_{16}H_{13}F_3IN_3O$: 448 (MH^+).

EJEMPLO 14

1-({4,5-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-amina



Ácido 2,4,5-trifluorobenzoico (643 mg, 3,65 mmol) y 2-fluoro-4-yodoanilina (1,0 g, 4,22 mmol) se llevaron a acetonitrilo (30 mL) luego se agregó amida de litio (290 mg, 12,7 mmol) y y la mezcla se calentó a 60° bajo una atmósfera de nitrógeno durante una hora. Al enfriar a temperatura ambiente la mezcla se agregó a 1 N ácido clorhídrico acuoso (100 mL) y el

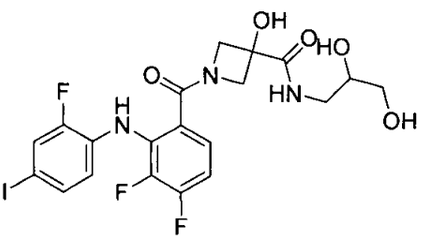
precipitado formado se recogió mediante filtración y se lavó con agua luego hexanos y se secó en vacío y dio ácido 4,5-difluoro-2-[(2-fluoro-4-yodofenil)amino]benzoico (624 mg, rendimiento del 43%) como un sólido tostado. ^{1}H-NMR (400 MHz, D_6-DMSO): 13,65 (br s, 1H), 9,63 (s, 1H), 7,84 (tr, 1H), 7,71 (d, 1H), 7,52 (d, 1H), 7,32 (tr, 1H), 7,03-6,98 (dd, 1H).

Ácido 4,5-difluoro-2-[(2-fluoro-4-yodofenil)amino]benzoico (100 mg, 0,25 mmol) se llevó a DMF (1 mL) luego se agregó PyBOP (137 mg, 0,26 mmol) y la mezcla se agitó durante 15 minutos luego NMM (60 µL, 0,5 mmol) y posteriormente se agregó 1,1-dimetiletil azetidin-3-ilcarbamato (43 mg, 0,25 mmol). La mezcla se dejó agitar durante 12 horas a temperatura ambiente luego se repartió con acetato de etilo y agua. La fase orgánica se lavó tres veces con agua adicional luego salmuera y se secó sobre sulfato de sodio. La filtración y la concentración y luego la cromatografía rápida de gel de sílice del residuo usando hexanos:acetato de etilo 3:1 como eluyente se obtuvo 1,1-dimetiletil [1-({4,5-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]carbamato (131 mg) como un aceite incoloro. El aceite se llevó a ácido trifluoroacético (1 mL) y se dejó en reposo a temperatura ambiente durante 5 minutos luego se concentró en vacío. El residuo se dividió en porciones con acetato de etilo y bicarbonato de sodio acuoso saturado y la fase orgánica se lavó con salmuera luego se secó sobre sulfato de sodio

anhidro. La solución orgánica se filtró y se concentró luego el residuo se llevó a metanol (1 mL) luego se agregó 4 N HCl en dioxano hasta que la solución fue ácida. La solución se concentró y el residuo se trituró con éter etílico y dio un pricipitado espeso. El sólido se recogió mediante filtración y se secó en vacío y dio clorhidrato de 1-({4,5-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-amina (67 mg, rendimiento total del 55%). ^{1}H-NMR (400 MHz, D_6-DMSO): 9,02 (s, 1H), 8,54 (br s, 3H), 7,68 (dd, 1H), 7,53-7,47 (m, 2H), 7,22 (tr, 1H), 7,16 (dd, 1H), 4,60 (br s, 1H), 4,23 (br s, 2H), 4,03 (br m, 2H). MS (EI) para $C_{16}H_{13}F_3IN_3O$: 448 (MH^+).

EJEMPLO 15

1-({3,4-Difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-(2,3-dihidroxipropil)-3-hidroxiazetidina-3-carboxamida



Clorhidrato de 1-(difenilmetil)azetidin-3-ol (2,75 g, 9,98 mmol), preparado usando procedimientos similares a aquellos descritos para el **Esquema 1** de la Sección de Síntesis General, se suspendieron tamices moleculares de 3Å y 4-metilmorfholina (1,1 mL, 10,0 mmol) en diclorometano (20 mL) a 0°C. Se

agregaron N-óxido de 4-metilmorfolina (2,93 g, 25,0 mmol) y perrutenato de tetrapropilamonio (140 mg, 0,399 mmol) y la mezcla se agitó a temperatura ambiente durante 24 horas. La mezcla se filtró a través de un tapón de sílice usando 5% trietilamina en acetato de etilo como eluyente. El filtrado se concentró en vacío y el residuo se repartió entre acetato de etilo y solución de bicarbonato de sodio saturado. La parte orgánica se lavó con salmuera, se secó sobre sulfato de sodio anahidro, se filtró y se concentró en vacío. La cromatografía de columna (gel de sílice, 8:1 hexanos:acetato de etilo) dio 1-(difenilmetil)azetidin-3-ona (871 mg, 3,68 mmol, rendimiento del 37%): ^{1}H NMR (400 MHz, $CDCl_3$): 7,50-7,46 (m, 4H), 7,33-7,27 (m, 4H), 7,27-7,19 (m, 2H), 4,59 (s, 1H), 4,01 (s, 4H); MS (EI) para $C_{16}H_{15}NO$: 238 (MH^+).

1-(Difenilmetil)azetidin-3-ona (600 mg, 2,53 mmol), se disolvió en diclorometano (1 mL) y se trató con trietilamina (0,5 mL, 3,59 mmol) y trimetilsililcianuro (0,8 mL, 6,01 mmol) a temperatura ambiente durante 2 horas y luego la mezcla se concentró en vacío y se obtuvo 1-(difenilmetil)-3-[(trimetilsilil)oxi]azetidina-3-carbonitrilo (774 mg, 2,30 mmol, rendimiento del 91%) como un sólido amarillo. 1-(difenilmetil)-3-[(trimetilsilil)oxi]azetidina-3-carbonitrilo (250 mg, 0,744 mmol) se disolvió en diclorometano (2 mL) a 0°C y se agregó gota a gota ácido sulfúrico concentrado (0,2 mL). La mezcla se agitó a temperatura ambiente durante 2 horas y

luego se enfrió a 0°C y se agregó 25% solución de hidróxido de amonio con cuidado gota a gota a pH 10-11. La mezcla se extrajo dos veces con diclorometano. La parte orgánica combinada se lavó con salmuera, se secó sobre sulfato de sodio anhidro, se filtró y se concentró en vacío y dio un residuo que se trituró con hexanos/éter y se obtuvo 1-(difenilmetil)-3-hidroxiazetidina-3-carboxamida (160 mg, 0,567 mmol, rendimiento 76%) como un sólido blancuzco: ^{1}H NMR (400 MHz, $CDCl_3$): 7,92 (br s, 1H), 7,39-7,34 (m, 4H), 7,33-7,27 (m, 4H), 7,27-7,19 (m, 2H), 5,61 (br s, 1H), 4,45 (s, 1H), 4,34 (s, 1H), 3,50 (dd, 2H), 3,20 (dd, 2H); MS (EI) para $C_{17}H_{18}N_2O_2$: 283 (MH^+).

1-(Difenilmetil)-3-hidroxiazetidina-3-carboxamida (1,1 g, 3,90 mmol) se trató con 10% hidróxido de sodio en etanol (15 mL) y agua (2 mL) a reflujo durante 2 horas y luego se concentró en vacío. El residuo se neutralizó con 1 N ácido clorhídrico (pH 7) y el precipitado se recogió mediante filtración y se liofilizó y se obtuvo ácido 1-(difenilmetil)-3-hidroxiazetidina-3-carboxílico (supongamos 3,90 mmol) que se usó sin nueva purificación: ^{1}H NMR (400 MHz, d_6-DMSO): 7,45-7,40 (m, 4H), 7,31-7,25 (m, 4H), 7,21-7,15 (m, 2H), 4,52 (s, 1H), 3,46 (dd, 2H), 3,02 (dd, 2H); MS (EI) para $C_{17}H_{17}NO_3$: 284 (MH^+).

Ácido 1-(difenilmetil)-3-hidroxiazetidina-3-carboxílico (supongamos 3,90 mmol) se suspendió en metanol (40 mL) y se

agregó 4 N ácido clorhídrico en dioxano (1 mL, 4 mmol). 20% em peso de hidróxido de paladio sobre carbono (100 mg) se agregó a la solución y la mezcla se trató con hidrógeno a 40 psi durante 2 h. La mezcla se filtró y el filtrado se concentró en vacío y se obtuvo clorhidrato del ácido 3-hidroxiazetidina-3-carboxílico que se disolvió en tetrahidrofurano (5 mL) y agua (5 mL) y se trató con carbonato de potasio (1,615 g, 11,7 mmol) y se agregó dicarbonato de di-*terc*-butilo (935 mg, 4,29 mmol). La mezcla se agitó a temperatura ambiente durante 17 horas y luego la mezcla se repartió entre acetato de etilo y agua. La parte de agua se extrajo con acetato de etilo y luego se acidificó a pH 3-4 y se extrajo dos veces con acetato de etilo. La parte orgánica combinada se lavó con salmuera, se secó sobre sulfato de sodio anhidro, se filtró y se concentró en vacío y se obtuvo ácido 1-{[(1,1-dimetiletil)oxi]carbonil}-3-hidroxiazetidina-3-carboxílico que se disolvió en DMF (3 mL). Se agregaron hexafluorofosfato de benzotriazol-1-iloxitris(pirrolidino)fosfonio (2,028 g, 3,90 mmol) y *N,N*-diisopropiletilamina (0,7 mL, 4,03 mmol). La mezcla se agitó a temperatura ambiente y luego se agregó alilamina (0,6 mL, 8,03 mmol) y la mezcla se agitó durante 17 horas. La mezcla se repartió entre acetato de etilo y 5% cloruro de litio. La parte orgánica se lavó con 20% ácido cítrico, bicarbonato de sodio saturado y salmuera, luego se secó sobre sulfato de sodio anhidro, se filtró y se concentró en vacío. La

cromatografía de columna (gel de sílice, acetato de etilo) dio 1,1-dimetiletil 3-hidroxi-3-[(prop-2-en-1-ilamino)carbonil]azetidina-1-carboxilato (782 mg, 3,05 mmol, rendimiento del 78% desde 1-(difenilmetil)-3-hidroxiazetidina-3-carboxamida). 1,1-Dimetiletil 3-hidroxi-3-[(prop-2-en-1-ilamino)carbonil]azetidina-1-carboxilato (782 mg, 3,05 mmol) se disolvió en metanol (10 mL) y se agregó 4 N ácido clorhídrico en dioxano (2 mL, 8 mmol). La mezcla se refluyó durante 15 minutos y luego se concentró en vacío y se obtuvo clorhidrato de 3-hidroxi-*N*-prop-2-en-1-ilazetidina-3-carboxamida (3,05 mmol).

Ácido 3,4-Difluoro-2-[(2-fluoro-4-yodofenil)amino]benzoico (1,20 g, 3,05 mmol), preparado usando procedimientos similares a aquellos descritos en US 7.019.033, 4-(dimetilamino)piridina (1,20 g, 9,86 mmol) y clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (701 mg, 3,66 mmol) se disolvieron en DMF (10 mL). La mezcla se agitó a temperatura ambiente durante 5 minutos y luego se agregó clorhidrato de 3-hidroxi-*N*-prop-2-en-1-ilazetidina-3-carboxamida (3,05 mmol) en DMF (5 mL) y la mezcla se agitó durante 15 horas. La mezcla se repartió entre acetato de etilo y 5% cloruro de litio. La parte orgánica se lavó con 20% ácido cítrico, bicarbonato de sodio saturado y salmuera, luego se secó sobre sulfato de sodio anhidro, se filtró y se concentró en vacío. La cromatografía de columna (gel de sílice, 60-85% acetato de etilo en hexanos) y luego la

HPLC de fase invertida dio 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxi-*N*-prop-2-en-1-ilazetidina-3-carboxamida (150 mg, 0,282 mmol, rendimiento del 9%): ^{1}H NMR (400 MHz, d_6-DMSO): 8,64 (br s, 1H), 8,13 (t, 1H), 7,58 (dd, 1H), 7,38 (dd, 1H), 7,34-7,28 (m, 1H), 7,21-7,12 (m, 1H), 6,84 (br s, 1H), 6,72 (ddd, 1H), 5,83-5,72 (m, 1H), 5,10-4,99 (m, 2H), 4,38 (d, 1H), 4,20 (d, 1H), 4,02 (d, 1H), 3,86 (d, 1H), 3,73-3,68 (m, 2H); MS (EI) para $C_{20}H_{17}F_3IN_3O_3$: 532 (MH^+).

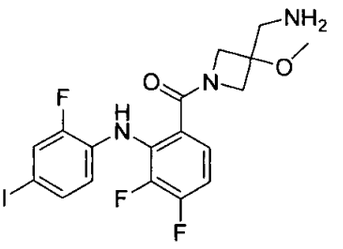
1-({3,4-Difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxi-*N*-prop-2-en-1-ilazetidina-3-carboxamida (88 mg, 0,166 mmol) y N-óxido de 4-metilmorfolina (58 mg, 0,496 mmol) se disolvieron en acetona / agua (4:1; 10 mL) y se agregó tetróxido de osmio (2,5% en peso en agua; 0,1 mL). La solución se agitó a temperatura ambiente durante 15 horas, luego se enfrió con bisulfito de de sodio saturado (2 mL) y se concentró en vacío. El residuo se repartió entre acetato de etilo y salmuera. La parte acuosa se extrajo con acetato de etilo. La parte orgánica combinada se lavó con salmuera, se secó sobre sulfato de sodio anhidro, se filtró y se concentró en vacío. La purificación mediante HPLC de fase invertida dio 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-(2,3-dihidroxipropil)-3-hidroxiazetidina-3-carboxamida (68 mg, 0,120 mmol, rendimiento del 72%): ^{1}H NMR (400 MHz, d_6-DMSO): 8,65 (br s,

1H), 7,72 (t, 1H), 7,58 (dd, 1H), 7,41-7,36 (m, 1H), 7,34-7,28 (m, 1H), 7,21-7,12 (m, 1H), 6,92 (br s, 1H), 6,72 (ddd, 1H), 5,00-4,10 (br, 2H), 5,10-4,99 (m, 2H), 4,39 (d, 1H), 4,20 (d, 1H), 4,02 (d, 1H), 3,54-3,45 (m, 1H), 3,34-3,21 (m, 2H), 3,06-2,96 (m, 1H); MS (EI) para $C_{20}H_{19}F_3IN_3O_5$: 566 (MH^+).

EJEMPLO 15(a). Usando las mismas técnicas sintéticas o análogas y sustituyendo, según fue necesario, con reactivos alternativos, se prepararon los siguientes compuestos de la invención: 1-({3,4-Difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidina-3-carboxamida: ^{1}H NMR (400 MHz, d_6-DMSO): 8,63 (br s, 1H), 7,58 (dd, 1H), 7,42-7,36 (m, 3H), 7,34-7,28 (m, 1H), 7,22-7,12 (m, 1H), 6,76-6,68 (m, 2H), 4,39 (d, 1H), 4,19 (d, 1H), 4,00 (d, 1H), 3,83 (d, 1H); MS (EI) para $C_{17}H_{13}F_3IN_3O_3$: 492 (MH^+).

EJEMPLO 16

6-{[3-(aminometil)-3-(metiloxi)azetidin-1-il]carbonil}-2,3-difluoro-*N*-(2-fluoro-4-yodofenl)anilina



Fenilmetil 1-oxa-5-azaespiro[2.3]hexano-5-carboxilato (165 mg, 0,75 mmol), preparado usando procedimientos similares a los descritos en la Referencia 3, en THF (1 mL) se agregó a amoníaco anhidro saturado en THF (10 mL) y la mezcla se dejó agitar en un recipiente sellado a temperatura ambiente durante 24 horas. La solución luego se concentró y se llevó a THF (1 mL) y luego se agregó di-*terc*-butildicarbonato (164 mg, 0,75 mmol) y se agitó durante una hora a temperatura ambiente. La mezcla luego se concentró y el residuo se purificó mediante cromatografía rápida de gel de sílice usando hexanos:acetato de etilo (1:1) como eluyente y dio fenilmetil 3-[({[(1,1-dimetiletil)oxi]carbonil}amino)metil]-3-hidroxiazetidina-1-carboxilato (16.5 mg, rendimiento del 7%) y epóxido sin reaccioanr (120 mg, recuperación del 73%). ^{1}H-NMR (400 MHz, $CDCl_3$): 7,34 (m, 5H), 5,10 (br, 1H), 5,09 (s, 2H), 4,68 (s, 1H), 3,90 (dd AB, 4H), 3,41 (d, 2H), 1,44 (s, 9H).

Fenilmetil 3-[({[(1,1-dimetiletil)oxi]carbonil}amino)metil]-3-hidroxiazetidina-1-carboxilato (16,5 mg, 0,05 mmol) y 10% Pd/C (8 mg) se llevó a metanol (2 mL) y se hidrogenó a presión ambiente durante 12 horas. El catalizador se removió mediante filtración y el filtrado se concentró y se secó en vacío. El residuo se llevó a THF (1 mL) luego se agregó DIPEA (10 µL, 0,06 mmol) y fluoruro de 3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]benzoilo (19,8 mg, 0,05 mmol), preparado usando procedimientos similares a aquellos descritos en la

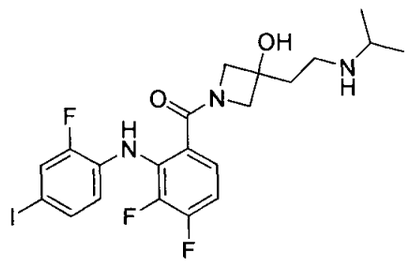
Referencia 1, y la solución se agitó a temperatura ambiente durante 30 minutos. La concentración y la purificación del residuo mediante cromatografía rápida de gel de sílice usando hexanos:acetato de etilo (1:1.5) dio 1,1-dimetiletil {[1-({3,4-difluoro-2[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidina-3-il]metil}carbamato (19 mg, rendimiento del 66% yield).

1,1-Dimetiletil {[1-({3,4-difluoro-2[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidina-3-il]metil}carbamato (8,0 mg, 0,014 mmol) y óxido de plata (I) (12 mg, 0,05 mmol) se llevaron a yoduro de metilo (0,5 mL) y la mezcla se llevó a reflujo durante 4 horas. La suspensión luego se enfrió a temperatura ambiente y se diluyó con un exceso de éter etílico luego se filtró. El filtrado se concentró y se purificó mediante cromatografía rápida de gel de sílice usando hexanos:acetato de etilo (1:1) como eluyente y dio 1,1-dimetiletil {[1-({3,4-difluoro-2[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(metiloxi)azetidina-3-il]metil}carbamato (2 mg). El material se llevó a TFA (0,5 mL) y se dejó en reposo durante 5 minutos luego se concentró en vacío. El residuo se hizo azeotrópico dos veces desde metanol (2 mL) y el residuo se secó en vacío y se obtuvo sal de trifluoroacetato de 6-{[3-(aminometil)-3-(metiloxi)azetidin-1-il]carbonil}-2,3-difluoro-*N*-(2-fluoro-4-yodofenil)anilina (2,3

mg, rendimiento del 27%) como un sólido amorfo. MS (EI) para $C_{18}H_{17}F_3IN_3O$: 492 (MH^+).

EJEMPLO 17

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{2-[(1-metiletil)amino]etil}azetidin-3-ol



Una solución de acetato de *terc*-butilo (566 µL, 4,2 mmol) en THF (10 mL) y se enfrió a -78 °C. A la solución se agregó LHMDS (5,25 mL de una solución 1,0 M en hexanos, 5,25 mmol), y la mezcla resultante se agitó durante 20 minutos a -78°C. A la solución se agregó 1-(difenilmetil)azetidin-3-ona (500 mg, 2,1 mmol), preparado usando procedimientos similares a aquellos descritos en el Ejemplo 15. Después de agitar durante 1 hora, se agregó cloruro de amonio acuoso saturado, y la mezcla se calentó a temperatura ambiente. Se agregó agua y éter, y la mezcla resultante se repartió. La fase acuosa se extrajo una vez con éter. Los extractos orgánicos combinados se secaron sobre sulfato de magnesio, se filtraron y se concentraron en vacío. El residuo se purificó mediante cromatografía rápida

(80% hexanos: 20% acetato de etilo) y dieron 1,1-dimetiletil [1-(difenilmetil)-3-hidroxiazetidin-3-il]acetato como un sólido amarillo pálido (644 mg, 1,8 mmol, rendimiento del 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7,40 (m, 4H), 7,26 (m, 4H), 7,19 (m, 2H), 4,40 (s, 1H), 4,02 (s, 1H), 3,15 (m, 2H), 3,05 (m, 2H), 2,83 (s, 2H), 1,45 (s, 9H).

A una solución de 1,1-dimetiletil [1-(difenilmetil)-3-hidroxiazetidin-3-il]acetato (333 mg, 0,94 mmol) en THF (3 mL) a 0°C se agregó hidruro de litio y aluminio (940 µL de una solución 1,0 M en THF, 0,94 mmol). La mezcla se agitó durante 3 horas 20 minutos mientras se calentaba a temperatura ambiente. Se agregó agua (36 µL) cuidadosamente a la solución, luego 15% de hidróxido de sodio (36 µL) y más agua (108 µL). El precipitado resultante se removió mediante filtración a través de celita, y el filtrado se concentró hasta secarse y dio 1-(difenilmetil)-3-(2-hidroxietil)azetidin-3-ol (228 mg, 0,80 mmol, rendimiento del 85%) como un jarabe incoloro. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7,38 (m, 4H), 7,26 (m, 4H), 7,19 (m, 2H), 4,37 (s, 1H), 3,92 (m, 2H), 3,32 (m, 2H), 2,96 (m, 2H), 2,07 (m, 2H).

Hidróxidode paladio (100 mg) se suspendió en una solución de 1-(difenilmetil)-3-(2-hidroxietil)azetidin-3-ol (228 mg, 0,80 mmol) en metanol (15 mL), y la mezcla se sometió a una atmósfera de hidrógeno a 50 psi durante 4 h. El catalizador

luego se removió mediante filtración a través de celita y el filtrado se concentró en vacío y proporcionó 3-(2-hidroxietil)azetidin-3-ol. Este material se usó en la reacción siguiente sin purificación. A una solución de ácido 3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]benzoico (314 mg, 0,80 mmol), preparado usando procedimientos similares a aquellos descritos en US 7.019.033, en DMF (4 mL) se agregó PyBOP (416 mg, 0,80 mmol) y trietilamina (223 µL, 1,6 mmol). Finalmente, el 3-(2-hidroxietil)azetidin-3-ol impurificado se agregó y la mezcla resultante se agitó a temperatura ambiente durante 16 horas. Se agregaron agua y acetato de etilo y las capas se separaron. La fase acuosa se extrajo una vez con acetato de etilo. Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre sulfato de magnesio, se filtraron y se concentraron en vacío. El residuo se purificó mediante cromatografía rápida, eluyendo con acetato de etilo, y proporcionó 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(2-hidroxietil)azetidin-3-ol como un aceite incoloro (303 mg, 0,62 mmol, rendimiento del 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8,46 (s, 1H), 7,39 (dd, 1H), 7,32 (m, 1H), 7,13 (m, 1H), 6,81 (m, 1H), 6,60 (m, 1H), 4,37 (br s, 1H), 4,28 (br m, 4H), 3,94 (br s, 2H), 2,19 (br s, 1H), 2,02 (m, 2H); MS (EI) para $C_{18}H_{16}F_3IN_2O_3$: 491 (M-H).

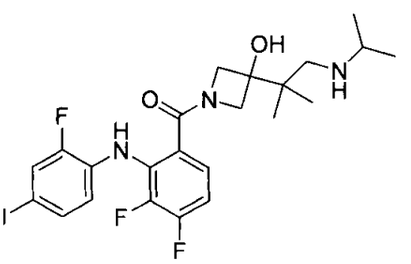
Una solución de cloruro de oxalilo (13 µL, 0,15 mmol) en diclorometano (1 mL) se enfrió a -78°C, y luego se agregó DMSO (22 µL, 0,31 mmol). A esta mezcla se agregó 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(2-hidroxietil)azetidin-3-ol (67,8 mg, 0,14 mmol) como una suspensión en diclorometano (1 mL). Después de agitar a -78°C durante 10 minutos, se agregó trietilamina (78 µL, 0,56 mmol) y la mezcla se dejó calentar a temperatura ambiente. La solución se diluyó con diclorometano y se lavó con 0,5 N HCl. La fase acuosa luego se extrajo con diclorometano. Los extractos orgánicos se combinaron, se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se purificó mediante cromatografía rápida y proporcionó [1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]acetaldehído como un sólido blanco (22,1 mg, 0,045 mmol, rendimiento del 32%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9,82 (s, 1H), 8,46 (s, 1H), 7,39 (m, 1H), 7,33 (m, 1H), 7,11 (m, 1H), 6,81 (m, 1H), 6,61 (m, 1H), 4,32-3,96 (br m, 4H), 3,41 (t, 2H), 3,07 (s, 1H); MS (EI) para $C_{18}H_{14}F_3IN_2O_3$: 491 (MH^+).

A una solución de [1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]acetaldehído (38,0 mg, 0,078 mmol) en 1,2-dicloroetano (1 mL) se agregó isopropilamina (27 µL, 0,31 mmol) luego

triacetoxiborohidruro de sodio (26 mg, 0,12 mmol). La mezcla se agitó durante 3 horas antes de enfriar con 1 gota de HCl concentrado. La mezcla enfriada se concentró hasta secarse y luego se purificó mediante HPLC preparativa y proporcionó 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{2-[(1-metiletil)amino]etil}azetidin-3-ol (21,5 mg) como un sólido amarillo. ^{1}H NMR (400 MHz, d_6-DMSO): δ 8,54 (s, 1H), 7,57 (dd, 1H), 7,38 (dd, 1H), 7,31 (m, 1H), 7,17 (m, 1H), 6,67 (m, 1H), 4,02 (m, 1H), 3,89 (m, 2H), 3,71 (m, 1H), 2,70 (m, 1H), 2,63 (m, 2H), 1,86 (s, 3H), 1,75 (m, 2H), 0,97 (d, 6H); MS (EI) para $C_{21}H_{23}F_3IN_3O_2$: 534 (MH^+).

EJEMPLO 18

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{1,1-dimetil-2-[(1-metiletil)amino]etil}azetidin-3-ol



A una solución de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ona (500 mg, 1,12 mmol), preparado usando procedimientos similares a aquellos descritos en el Ejemplo 6, en diclorometano (5 mL) enfriado a

0°C se agregó tetracloruro de titanio (125 µL, 1,12 mmol). La solución marrón oscura se agitó a 0°C durante 45 minutos, luego se agregó metiltrimetilsilil dimetilceteno acetal (550 µL, 2,24 mmol) a 0°C. Al agregar la solución se dejó calentar a temperatura ambiente y se agitó durante 1 hora. La mezcla de la reacción luego se repartió entre bicarbonato de sodio acuoso saturado y acetato de etilo. La parte acuosa se extrajo dos veces usando acetato de etilo. La parte orgánica combinada se lavó con agua, salmuera, se secó sobre sulfato de sodio, se filtró y se concentró en vacío y dio un aceite marrón que se purificó mediante cromatografía de columna. Eluyendo con 10% de éter dietílico en diclorometano, el producto aislado se concentró en vacío y se obtuvieron 520 mg, 0,95 mmol (85%) de metil 2-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]-2-metilpropanoato como una espuma blanca. ^{1}H NMR (400 MHz, $CDCl_3$): 8,34 (s, 1H), 7,38 (d, 1H), 7,31 (d, 1H), 7,13-7,08 (m, 1H), 6,85-6,77 (m, 1H), 6,63-6,56 (m, 1H), 4,26-4,20 (m, 2H), 4,13-4,09 (m, 1H), 4,00-3,93 (m, 1H), 3,70 (s, 3H), 1,23 (s, 6H). MS (EI) para $C_{21}H_{20}F_3IN_2O_4$: 547 (MH^-).

Una solución de metil 2-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]-2-metilpropanoato (520 mg, 0,95 mmol) en 4N hidróxido de potasio acuoso (5 mL) se agitó a 50°C durante 1 hora. Usando ácido

clorhídrico concentrado, la mezcla de la reacción se acidificó a pH 5 y luego se repartió con acetato de etilo. La parte acuosa se extrajo dos veces usando acetato de etilo, y la parte orgánica combinada se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y se concentró en vacío y se obtuvieron 300 mg, 0,56 mmol (59%) de ácido 2-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]-2-metilpropanoico como un sólido blanco. ^{1}H NMR (400 MHz, DMSO): 8,49 (s, 1H), 7,57-7,52 (m, 1H), 7,37-7,25 (m, 2H), 7,17-7,13 (m, 1H), 6,68-6,58 (m, 1H), 3,98-3,94 (m, 2H), 3,80-3,77 (m, 1H), 3,55-3,52 (m, 1H), 0,88 (s, 6H). MS (EI) para $C_{20}H_{18}F_3IN_2O_4$: 535 (MH^+).

A una solución del ácido 2-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]-2-metilpropanoico (300 mg, 0,56 mmol) en tetrahidrofurano (5 mL) se agregó trietilamina (80 µL, 0,56 mmol), luego PyBOP (295 mg, 0,56 mmol) y finalmente borohidruro de sodio (64 mg, 1,68 mmol). La mezcla de la reacción se enfrió agregando 20% ácido cítrico acuoso, y luego se repartió con acetato de etilo. La parte orgánica se lavó con biarbonato de sodio acuoso saturado, salmuera, se secó sobre sulfato de sodio, se filtró y se concentró en vacío y se obtuvo un sólido blanco que se purificó mediante cromatografía de columna. Eluyendo con 60% acetato de etilo en hexanos, el producto aislado se concentró en vacío y se obtuvieron 238 mg, 0,46 mmol (82%) de 1-({3,4-

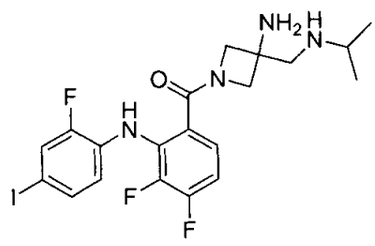
difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(2-hidroxi-1,1-dimetiletil)azetidin-3-ol como un sólido blanco. ^{1}H NMR (400 MHz, DMSO): 8,53 (s, 1H), 7,57 (d, 1H), 7,38-7,28 (m, 2H), 7,22-7,15 (m, 1H), 6,70-6,64 (m, 1H), 5,61 (s, 1H), 4,57 (br s, 1H), 4,30-4,27 (m, 1H), 4,18-4,15 (m, 1H), 3,80-3,77 (m, 1H), 3,68-3,64 (m, 1H), 3,25 (s, 2H), 0,76 (d, 6H); MS (EI) para $C_{20}H_{20}F_3IN_2O_3$: 521 (MH^+).

Una mezcla de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(2-hidroxi-1,1-dimetiletil)azetidin-3-ol (200 mg, 0,38 mmol) y peryodinano de Dess-Martin (240 mg, 0,57 mmol) en diclorometano (2 mL) se agitó a temperatura ambiente durante 2 horas. Se agregaron 10% de tiosulfito de sodio acuoso (2 mL) y bicarbonato de sodio acuoso saturado (2 mL) y la mezcla se agitó a temperatura ambiente durante 15 minutos. La mezcla se repartió y la capa acuosa se extrajo dos veces usando diclorometano. La parte orgánica combinada se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y se concentró en vacío, y se obtuvo un sólido blanco que se purificó mediante cromatografía de columna. Eluyendo con 30% acetato de etilo en hexanos, el producto aislado se concentró en vacío y se obtuvieron 100 mg, 0,20 mmol (53%) de 2-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]-2-metilpropanal como un sólido blanco, que se disolvió inmediatamente en tetrahidrofurano (2 mL). A la solución se

agregó isopropilamina (34 µL, 0,40 mmol), luego triacetoxiborohidruro (212 mg, 1,0 mmol). La solución se agitó a temperatura ambiente durante 15 horas. La mezcla de la reacción se concentró en vacío y se repartió entre 20% ácido cítrico acuoso y acetato de etilo. La parte acuosa se extrajo dos veces usando acetato de etilo y la parte orgánica combinada se lavó con bicarbonato de sodio acuoso saturado, salmuera, se secó sobre sulfato de sodio, se filtró y se concentró en vacío y dio un aceite amarillo que se purificó mediante HPLC de fase invertida preparativa. El producto aislado se concentró en vacío y se obtuvieron 50 mg, 0,07 mmol (36%) de sal de acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{1,1-dimetil-2-[(1-metiletil)amino]etil}azetidin-3-ol como un sólido blanco. ^{1}H NMR (400 MHz, DMSO): 8,47 (br s, 1H), 7,55 (d, 1H), 7,36-7,29 (m, 2H), 7,22-7,15 (m, 1H), 6,68-6,63 (m, 1H), 4,17-4,08 (m, 2H), 3,76-3,73 (m, 1H), 3,56-3,52 (m, 1H), 2,58-2,51 (m, 1H), 2,45-2,37 (m, 2H), 0,92 (t, 6H), 0,78 (d, 6H); MS (EI) para $C_{23}H_{27}F_3IN_3O_2$: 562 (MH^+).

EJEMPLO 19

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenyl)amino]fenil}carbonil)-3-{[(1-metiletil)amino]metil}azetidin-3-amina



A una solución del 1-(difenilmetil)-3-[(fenilmetil)amino]azetidina-3-carbonitrilo (0,80 g, 2,2 mol), preparado usando procedimientos similares a aquellos descritos en Kozikowski and Fauq *Synlett* **1991**, *11*, 783-4, en etanol (30 mL) se agregó hidróxido de sodio sólido (7,5 mmol), y la mezcla resultantese agitó a temperatura ambiente durante 3 días. Se agregó agua (6 mL) a la mezcla de la reacción y se continuó agitando a 90°C durante 2 horas. El pH de la mezcla de la reacción se ajustó a 5 con ácido clorhídrico concentrado y precipitó un sólido blanco. La mezcla se enfrió, se diluyó con agua (50 mL) y el sólido se recogió, se lavó con agua luego se secó en vacío y dio ácido 1-(difenilmetil)-3-[(fenilmetil)amino]azetidina-3-carboxílico (0,75g, rendimiento del 88%), MS (EI) para $C_{24}H_{24}N_2O_2$: 373 (MH^+).

A una mezcla de ácido 1-(difenilmetil)-3-[(fenilmetil)amino]azetidina-3-carboxílico (0,50 g, 1,34 mmol), *N,N*-diisopropletilamina (0,47 mL, 2,68 mmol) en DMF (3

mL) se agregó hexafluorofosfato de 1-benzotriazoliloxitripirrolidinilfosfonio (1,34g, 2,68 mol) y la mezcla resultante se agitó a temperatura ambiente durante 10 minutos. A esta mezcla se agregó 2-propilamina (0,22 mL, 2,68 mmol) y se continuó agitando durante 18 horas. La mezcla de la reacción se diluyó con acetato de etilo (100 mL) y se lavó con 2% ácido cítrico acuoso, 5% cloruro de litio, soluciones de salmuera (50 mL cada una), se secó sobre sulfato de sodio, se filtró y se concentró y dio un residuo aceitoso que se purificó mediante cromatografía rápida (gel de sílice, eluyendo con 15-25% acetato de etilo-hexano) y dio 1-(difenilmetil)-*N*-(1-metiletil)-3-[(fenilmetil)amino]azetidina-3-carboxamida (0,51 g, rendimiento del 92%), MS (EI) para $C_{27}H_{31}N_3O$: 414 (MH^+).

A una solución de la 1-(difenilmetil)-*N*-(1-metiletil)-3-[(fenilmetil)amino]azetidina-3-carboxamida (0,40 g, 0,97 mmol) en tetrahidrofurano (10 mL) a temperatura ambiente se agregó una solución de hidruro de litio y aluminio en tetrahidrofurano (1M, 2,90 mL, 2,90 mmol), y la mezcla reultante se agitó a 50°C durante 3 horas. La mezcla de la reacción se enfrió a temperatura ambiente, se enfrió con 20% solución de hidróxido acuoso (1 mL), se diluyó con éter (50 mL) y se filtró. El filtrado se lavó con solución de salmuera (20 mL dada una), se secó sobre sulfato de sodio, se filtró y se concentró y dio un residuo aceitoso que se purificó

mediante cromatografía rápida (gel de sílice, eluyendo con 5% metanol-diclorometano) y dio 1-(difenilmetil)-3-{[(1-metiletil)amino]metil}-*N*-(fenilmetil)azetidin-3-amina (0,35g, rendimiento del 90%), ^{1}H NMR (400 MHz, $CDCl_3$): 7,42-7,14 (m, 15H), 4,34 (s, 1H), 3,66 (s, 2H), 3,22-3,18 (d, 2H), 2,97 (s, 2H), 2,90-2,86 (d, 2H), 2,68-2,62 (p, 1H), 1,09-1,07 (d, 6H); MS (EI) para $C_{27}H_{33}N_3$: 400 (MH^+).

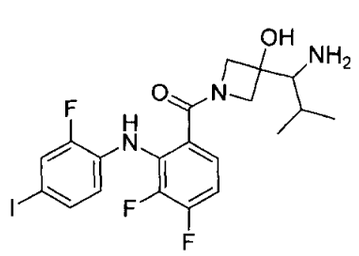
A una solución de la 1-(difenilmetil)-3-{[(1-metiletil)amino]metil}-*N*-(fenilmetil)azetidin-3-amina (0,35 g, 0,88 mmol) en metanol se agregó una solución de cloruro de hidrógeno en dioxano (solución 4 molar, 0,96 mL, 4,40 mmol) y la mezcla resultante se concentró y dio un sólido blanco que se llevó nuevamente a metanol. A esta solución se agregó hidróxido de paladio (20% sobre carbono, 0,50 g, 0,19 mmol) y la mezcla resultante se agitó a 50 psi en un aparato de Parr durante 3 horas. La mezcla de la reacción se filtró y se concentró y dio un sólido, que se lavó con éter y se secó en vacío y dio clorhidrato de 3-{[(1-metiletil)amino]metil}azetidin-3-amina como un sólido blanco (0,18 g, rendimiento del 81%). MS (EI) para $C_7H_{17}N_3$: 144 (MH^+).

A una mezcla del clorhidrato de 3-{[(1-metiletil)amino]metil}azetidin-3-amina (20 mg, 0,079 mmol) en una solución de bicarbonato de sodio saturado (1,0 mL) y dioxano (1,0 mL) se agregó fluoruro de 3,4-difluoro-2-[(2-

fluoro-4-yodofenil)amino]benzoilo (31 mg, 0,079 mmol), preparado usando procedimientos similares a aquellos descritos en la Referencia 1, y la mezcla resultante se agitó a temperatura ambiente durante 18 horas. La mezcla de la reacción se diluyó con agua (5 mL) y se extrajo con acetato de etilo (3 x 5 mL). El extracto combinado se lavó con agua y luego solución de salmuera (5 mL cada una), se secó sobre sulfato de sodio, se filtró y se concentró y dio un residuo aceitoso que purificó mediante HPLC de fase invertida y se obtuvo 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1-metiletil)amino]metil}azetidin-3-amina (15 mg, rendimiento del 37%). ^{1}H NMR (400 MHz, d_4-Metanol): 7,46-7,43 (dd, 1H), 7,35-7,33 (dd, 1H), 7,31-7,27 (m, 1H), 7,08-7,01 (dd, 1H), 6,63, 6,58 (td, 1H), 4,09-4,07 (d, 1H), 3,91-3,85 (dd, 2H), 3,76-3,73 (d, 1H). 2,80-2,74 (m, 1H), 2,73 (s, 2H), 1,07-1,05 (d, 6H); MS (EI) para $C_{20}H_{22}F_3IN_4O$: 519 (MH^+).

EJEMPLO 20

3-(1-amino-2-metilpropil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol



1,1-Dimetiletil 3-oxoazetidina-1-carboxilato (677,2 mg, 3,96 mmol), preparado usando procedimientos similares a aquellos descritos en el Ejemplo 3, se llevó a 2-metil-1-nitropropano (5 mL) luego se enfrió a 0°C luego se agregó terc-butóxido de potasio (444 mg, 3,96 mmol) y la mezcla resultante se dejó calentar a temperatura ambiente durante 30 minutos. La mezcla se reaprtió con acetato de etilo y 0,5 N ácido clorhídrico acuoso luego una vez con agua y salmuera luego se secó sobre sulfato de magnesio anhidro. La filtración y la concentración produjo un residuo (1,5 g) que se purificó adicionalmente mediante cromatografía rápida de gel de sílice usando 3:1 hexanos:acetato de etilo como eluyentes para dar 1,1-dimetiletil 3-hidroxi-3-(2-metil-1-nitropropil)azetidina-1-carboxilato (730 mg, rendimiento del 67%) como un sólido cristalino incoloro. ^{1}H-NMR (400 MHz, $CDCl_3$): 4,50 (d, 1H), 3,93 (dd AB, 2H), 3,85 (s, 2H), 3,58 (s, 1H), 2,54-2,48 (m, 1H), 1,44 (s, 9H), 1,04 (d, 6H).

1,1-Dimetiletil 3-hidroxi-3-(2-metil-1-nitropropil)azetidina-1-carboxilato (105 mg, 0,38 mmol) se llevó a metanol (1 mL) luego se agregó 4 N cloruro de hidrógeno anhidro en dioxano (1 mL) y la solución ácida se dejó en reposo durante 15 minutos a temperatura ambiente luego se concentró y se secó en vacío a un residuo amorfo. Ácido 3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]benzoico (150 mg, 0,38 mmol), preparado usando procedimientos similares a aquellos descritos en US 7.019.033,

se llevó a DMF (0,7 mL) luego se agregó PyBOP (198 mg, 0,38 mmol) y la solución se dejó agitar durante 10 minutos a temperatura ambiente. La sal de clorhidrato precedente y DIPEA (190 µL, 1,1 mmol) en solución de DMF (0,7 mL) se agregó y la mezcla se dejó agitar durante una hora a temperatura ambiente. La mezcla se repartió con acetato de etilo y 0,5 N ácido clorhídrico acuoso y la fase orgánica se lavó tres veces con agua luego salmuera y se secó sobre sulfato de magnesio anhidro. La filtración y la concentración produjeron un residuo que se purificó adicionalmente mediante cromatografía rápida de gel de sílice usando 1,5:1 hexanos:acetato de etilo como eluyente y dio 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenyl)amino]fenil}carbonil)-3-(2-metil-1-nitropropil)azetidin-3-ol (189 mg, rendimiento del 90%) como un sólido amorfo. ^{1}H-NMR (400 MHz, $CDCl_3$): 8,41 (br s, 1H), 7,41 (dd, 1H), 7,34 (d, 1H), 7,09 (br m, 1H), 6,81 (q, 1H), 6,65-6,60 (m, 1H), 4,49 (d, 1H), 4,15-4,09 (m, 4H), 3,66 (s, 1H), 2,56-2.46 (m, 1H) 1,03 (d, 6H).

1-({3,4-Difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(2-metil-1-nitropropil)azetidin-3-ol (189 mg, 0,34 mmol) se llevó a 4:1 THF:agua (5 mL) luego se agregó hierro en polvo (192 mg, 3,4 mmol) y formato de amonio (429 mg, 6,8 mmol) y la mezcla se calentó a reflujo. Después de cuatro horas se agregaron alícuotas adicionales de hierro en polvo (192 mg, 3,4 mmol) y

formato de amonio (429 mg, 6,8 mmol) y la mezcla se dejó refluir otras 12 horas. La mezcla se enfrió a temperatura ambiente y se diluyó con acetato de etilo y luego se filtró. El filtrado se repartió con acetato de etilo y bicarbonato de sodio acuoso saturado luego la capa orgánica se lavó con salmuera y se secó sobre sulfato de sodio anhidro. La filtración y la concentración dio un residuo que se purificó adicionalmente mediante cromatografía rápida de gel de sílice usando acetato de etilo a 10% metanol en diclorometano coo eluyentes para dar un residuo (36,5 mg) que se purificó adicionalmente mediante HPLC de fase invertida preparativa para dar sal de trifluoroacetato de 3-(1-amino-2-metilpropil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol (7,9 mg) como un sólido amorfo incoloro después de la liofilización de las fracciones puras combinadas. ^{1}H-NMR (400 MHz, D_6-DMSO): 8,63 (s, 1H), 7,58 (dd, 1H), 7,37 (d, 1H), 7,35-7,31 (m, 1H), 7,17 (q, 1H), 6,71-6,66 (m, 1H), 4,23 (dd, 1H), 4,03 (dd, 1H), 3,80 (dd, 1H), 3,66 (dd, 1H), 2,34 (dd, 1H), 1,79-1,70 (m, 1H), 0,84-0,77 (m, 6H). MS (EI) para $C_{20}H_{21}F_3IN_3O_2$: 520 (MH^+).

Usando las mismas técnicas sintéticas o análogas y sustituyendo, según fue necesario, con reactivos alternativos, se prepararon los siguientes compuestos de la invención:

EJEMPLO 20(a). 3-(1-aminoetil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: ^{1}H NMR (400

MHz, d_6-DMSO): 8,56 (s, 1H), 7,91 (br s, 2H), 7,58 (d, 1H), 7,39 (d, 1H), 7,36-7,32 (m, 1H), 7,24-7,17 (m, 1H), 6,72-6,65 (m, 2H), 4,33-4,29 (m, 1H), 4,23-4,19 (m, 1H), 4,16-4,14 (m, 1H), 4,07-3,94 (m, 1H), 3,82-3,77 (m, 1H), 3,51-3,45 (m, 1H), 1,15-1,12 (m, 1H), 1,10-1,08 (m, 1H). MS (EI) para $C_{18}H_{17}F_3IN_3O_2$: 492 (MH^+).

EJEMPLO 20(b). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[1-(etilamino)etil]azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8,61 (d, 1H), 8,50 (s, 1H), 8,20 (s, 1H), 7,59 (d, 1H), 7,39 (d, 1H), 7,36-7,32 (m, 1H), 7,24-7,17 (m, 1H), 6,82 (s, 1H), 6,74-6,67 (m, 1H), 4,38 (d, 1H), 4,27 (d, 1H), 4,18 (d, 1H), 4,06 (d, 2H), 3,99 (d, 1H), 3,89 (d, 1H), 3,82 (d, 1H), 3,49-3,43 (m, 1H), 3,04-2,80 (m, 4H), 1,21-1,12 (m, 6H). MS (EI) para $C_{20}H_{21}F_3IN_3O_2$: 520 (MH^+).

EJEMPLO 20(c). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1-nitroetil)azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 8,57 (d, 1H), 7,58 (d, 1H), 7,38 (d, 1H), 7,37-7,33 (m, 1H), 7,22-7,17 (m, 1H), 6,73-6,66 (m, 1H), 6,57 (s, 1H), 5,06-4,97 (m, 1H), 4,54 (d, 0,5H), 4,37 (d, 0,5 H), 4,29 (d, 0,5H), 4,14 (d, 0,5 H), 4,05 (d, 0,5 H), 3,95 (d, 0,5H), 3,86 (d, 0,5H), 3,80 (d, 0,5H), 1,44-1,38 (m, 3H). MS (EI) para $C_{18}H_{16}F_3IN_3O_4$: 523 (MH^+).

EJEMPLO 20(d). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[1-(metilamino)etil]azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO):

8,63-8,55 (m, 1H), 8,44-8,23 (m, 1H), 7,79 (br s, 1H), 7,60 (d, 1H), 7,39 (d, 1H), 7,36-7,31 (m, 1H), 7,24-7,17 (m, 1H), 6,82 (br s, 0,5H), 6,73-6,65 (m, 1H), 4,38-3,77 (m, 4H), 1,18-1,07 (m, 3H). MS (EI) para $C_{19}H_{19}F_3IN_3O_2$: 505 (M^+).

EJEMPLO 20(e). metil {1-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]etil}carbamato: ^{1}H NMR (400 MHz, d_6-DMSO): 8,59 (d, 1H), 7,58 (d, 1H), 7,41-7,05 (m, 4H), 6,72-6,64 (m, 1H), 5,84 (d, 1H), 4,20 (d, 0,5H), 4,08-4,04 (m, 1H), 3,92-3,85 (m, 1,5H), 3,76-3,71 (m, 1H), 3,69-3,63 (m, 1H), 3,46 (d, 2H), 0,99-0,95 (m, 3H). MS (EI) para $C_{20}H_{19}F_3IN_3O_4$: 550 (MH^+).

EJEMPLO 20(f). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[1-(dimetilamino)etil]azetidin-3-ol: ^{1}H NMR (400 MHz, d_6-DMSO): 9,45 (s, 1H), 8,61 (d, 1H), 760 (d, 1H), 7,39 (d, 1H), 7,38-7,33 (m, 1H), 7,24-7,18 (m, 1H), 7,05 (s, 1H), 6,73-6,66 (m, 1H), 4,48 (d, 0,5H), 4,36 (d, 0,5 H), 4,26 (d, 0,5H), 4,16-4,11 (m, 1H), 4,00-3,94 (m, 1H), 3,86 (d, 0,5H), 3,60-3,54 (m, 1H), 2,75-2,70 (m, 3H), 2,66-2,62 (br s, 3H), 1,22 (dd, 3H). MS (EI) para $C_{20}H_{21}F_3IN_3O_2$: 520 (MH^+).

EJEMPLO 20(g). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1-nitropropil)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7,46 (m, 1H), 7,35 (m, 1H), 7,28 (m, 1H), 7,07 (m, 1H), 6,61 (m, 1H), 4,65 (m, 1H), 4,44 (m, 1H), 4,25 (m, 1H), 4,02 (m, 1H), 3,86 (m, 1H), 2,04 (m, 1H),

1,76 (m, 1H), 0,94 (m, 3H). MS (EI) para $C_{19}H_{17}F_3IN_3O_4$: 536 (MH^+).

EJEMPLO 20(h). 3-(1-aminopropil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7,45 (m, 1H), 7,34 (m, 1H), 7,28 (m, 1H), 7,05 (m, 1H), 6,61 (m, 1H), 4,21 (m, 1H), 4,09-3,86 (m, 2H), 3,78 (m, 1H), 2,63 (m, 1H), 1,50 (m, 1H), 1,24 (m, 1H), 0,98 (m, 3H). MS (EI) para $C_{19}H_{19}F_3IN_3O_2$: 506 (MH^+).

EJEMPLO 20(i). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[1-(etilamino)-propil]azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7,45 (m, 1H), 7,34 (m, 1H), 7,28 (m, 1H), 7,05 (m, 1H), 6,61 (m, 1H), 4,23 (m, 1H), 4,02 (m, 1H), 3,90 (m, 1H), 3,79 (m, 1H), 2,70 (m, 1H), 2,54 (m, 1H), 1,53 (m, 1H), 1,40 (m, 1H), 1,05 (m, 3H), 0,95 (m, 3H). MS (EI) para $C_{21}H_{23}F_3IN_3O_2$: 534 (MH^+).

EJEMPLO 20(j). 3-[1-(dietilamino)propil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7,44 (m, 1H), 7,33 (m, 1H), 7,27 (m, 1H), 7,07 (m, 1H), 6,60 (m, 1H), 4,21 (m, 1H), 4,10 (m, 1H), 4,03-3,70 (m, 2H), 2,71-2,45 (m, 5H), 1,67 (m, 1H), 1,49 (m, 1H), 0,94 (m, 9H). MS (EI) para $C_{23}H_{27}F_3IN_3O_2$: 562 (MH^+).

EJEMPLO 20(k). 3-[amino(fenil)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol): MS (EI) para $C_{23}H_{19}F_3IN_3O_2$: 554 (MH^+).

EJEMPLO 20(m). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(3-metil-1-nitrobutil)azetidin-3-ol): ^{1}H NMR (400MHz, $CDCl_3$): 8,38 (s, 1H), 7,39 (dd, 1H), 7,34-7,31 (m, 1H), 7,14-7,10 (m, 1H), 6,84-6,77 (m, 1H), 6,63-6,58 (m, 1H), 4,68 (dd, 1H), 4,23-4,04 (br m, 4H), 2,13 (t, 2H), 1,64-1,44 (br m, 3H), 0,93 (d, 6H); MS (EI) para $C_{21}H_{21}F_3IN_3O_4$: 564 (MH^+).

EJEMPLO 20(n). Sal de acetato de 3-(1-aminobutil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7,48-7,43 (d, 1H); 7,38-7,33 (d, 1H), 7,32-7,26 (m, 1H), 7,09-7,00 (q, 1H), 6,66-6,58 (t, 1H), 4,33-4,22 (d, 1H), 4,13-3,81 (m, 3H), 3,17-3,09 (t, 1H), 1,93-1,89 (s, 3H), 1,89-1,82 (t, 3H), 1,56-1,24 (m, 4H), 0,97-0,88 (t, 3H); MS (EI) para $C_{20}H_{21}F_3IN_3O_2$: 520 (MH^+).

EJEMPLO 20(o). Sal de acetato de 3-(1-aminociclopentil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: ^{1}H NMR (400 MHz, $CDCl_3$): 8,27-8,21 (s, 1H), 7,42-7,36 (d, 1H), 7,34-7,29 (d, 1H), 7,15-7,09 (t, 1H), 7,09-7,01 (q, 1H), 6,88-6,79 (q, 1H), 6,63-6,53 (m, 1H), 4,18-3,92 (m, 4H), 2,12-2,08 (s, 3H), 2,06-1,70 (m, 7H), 0,92-0,68 (m, 4H); MS (EI) para $C_{21}H_{21}F_3IN_3O_2$: 532 (MH^+).

EJEMPLO 20(p). *N*-{1-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-

il]etil}acetamida: ^{1}H NMR (400 MHz, $CDCl_3$): 8,42 (s, 1H), 7,41-7,38 (dd, 1H), 7,34-7,32 (dt, 1H), 7,12-7,09 (m, 1H), 6,85-6,78 (m, 1H), 6,63-6,57 (m, 1H), 5,76 (b, 1H), 4,28-3,98 (m, 5H), 2,00 (s, 3H), 1,20-1,19 (d, 3H); MS (EI) para $C_{20}H_{19}F_3IN_3O_3$: 534 (MH^+).

EJEMPLO 20(q). (2R)-*N*-{1-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]etil}-3,3,3-trifluoro-2-(metiloxi)-2-fenilpropanamida: ^{1}H NMR (400 MHz, CDCl3): 8,47 (s, 1H), 7,45-7,40 (m, 5H), 7,33-7,31 (m, 1H), 7,21-7,19 (m, 1H), 7,12-7,05 (m, 1H), 6,85-6,76 (m, 1H), 6,63-6,58 (m, 1H), 4,20-3,99 (m, 5H), 3,36 (s, 1,5H), 3,34 (s, 1,5H), 1,27-1,25 (d, 1,5H), 1,24-1,22 (d, 1,5H); MS (EI) para $C_{28}H_{24}F_6IN_3O_4$: 708 (MH^+).

EJEMPLO 20(r). (2R)-*N*-{(1R)-1-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]etil}-3,3,3-trifluoro-2-(metiloxi)-2-fenilpropanamida: ^{1}H NMR (400 MHz, $CDCl_3$): 8,49 (s, 1H), 7,46-7,391 (m, 5H), 7,33-7,31 (m, 1H), 7,21-7,16 (m, 1H), 7,14-7,10 (m, 1H), 6,85-6,79 (m, 1H), 6,64-6,58 (m, 1H), 4,24-4,00 (m, 5H), 3,35 (s, 3H), 1,25-1,23 (d, 3H); MS (EI) para $C_{28}H_{24}F_6IN_3O_4$: 708 (MH^+).

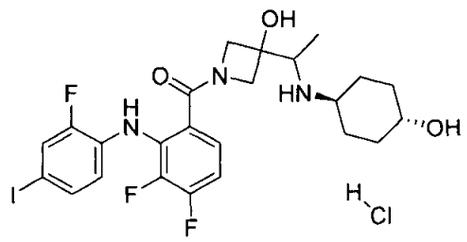
EJEMPLO 20(s). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1-metil-1-nitroetil)azetidin-3-ol: ^{1}H NMR (400 MHz, $CDCl_3$): 8,28 (s, 1H), 7,41-7,38 (dd, 1H), 7,34-7,32 (dt, 1H), 7,14-7,10 (m,

1H), 6,87-6,81 (m, 1H), 6,64-6,59 (m, 1H), 4,33-4,15 (m, 4H), 1,64 (s, 6H); MS (EI) para $C_{19}H_{17}F_3IN_3O_4$: 536 (MH^+).

EJEMPLO 20(t). 3-(1-amino-1-metiletil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol: ^1H NMR (400 MHz, $CDCl_3$): 8,30 (s, 1H), 7,39-7,36 (dd, 1H), 7,32-7,30 (dt, 1H), 7,13-7,09 (m, 1H), 6,85-6,79 (m, 1H), 6,62-6,56 (m, 1H), 4,25-3,97 (m, 4H), 1,14 (s, 6H); MS (EI) para $C_{19}H_{19}F_3IN_3O_2$: 506 (MH^+).

EJEMPLO 21

Clorhidrato de 1-({3,4-Difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{1-[(*trans*-4-hidroxiciclohexil)amino]etil}azetidin-3-ol



Terc-butóxido de potasio (1,672 g, 14,9 mmol) y bromuro de etiltrifenilfosfonio (5,538 g, 14,9 mmol) se agitó en éter (30 mL) a temperatura ambiente durante 1 hora. 1,1-Dimetiletil 3-oxoazetidina-1-carboxilato (954 mg, 6,0 mmol), preparado usando procedimientos similares a aquellos descritos en el Ejemplo 3, se agregó y la mezcla estuvo a 35°C para 4,5 h. La mezcla se filtró a través de celita y el sólido se lavó con éter 1,1-dimetiletil 3-etilidenazetidina-1-carboxilato (506

mg, 2,76 mmol, rendimiento del 49%): ^{1}H NMR (400 MHz, $CDCl_3$): 5,37-5,28 (m, 1H), 4,47-4,39 (m, 4H), 1,56-1,51 (m, 3H), 1,45 (s, 9H).

1,1-Dimetiletil 3-etilidenazetidina-1-carboxilato (506 mg, 2,76 mmol), y N-óxido de 4-metilmorfolina (1,04 g, 8,89 mmol) se disolvieron en acetona / agua (4:1; 30 mL) y se agregó tetróxido de osmio (2,5% en peso en *t*-butanol; 0,2 mL). La solución se agitó a temperatura ambiente durante 5 días, luego se enfrió con bisulfito de sodio saturado (2 mL) y se concentró en vacío. El residuo se repartió entre acetato de etilo y salmuera. La parte acuosa se extrajo con acetato de etilo. La parte orgánica combinada se lavó con salmuera, se secó sobre sulfato de sodio anhidro, se filtró y se concentró en vacío. La cromatografía de columna (gel de sílice, acetato de etilo) dio 1,1-dimetiletil 3-hidroxi-3-(1-hidroxietil)azetidina-1-carboxilato (375 mg, 1,73 mmol, rendimiento del 63%): ^{1}H NMR (400 MHz, $CDCl_3$): 4,00-3,77 (m, 5H), 2,65 (br s, 1H), 1,86, (br s, 1H), 1,44 (s, 9H), 1,25 (d, 3H).

1,1-Dimetiletil 3-hidroxi-3-(1-hidroxietil)azetidina-1-carboxilato (200 mg, 0,922 mmol) se disolvió en metanol (5 mL) y se agregó 4 N ácido clorhídrico en dioxano (1 mL, 4 mmol). La mezcla se refluyó durante 15 minutos y luego se concentró en vacío y se obtuvo clorhidrato de 3-(1-hidroxietil)azetidin-3-ol (0,922 mmol).

sílice, 50% acetato de etilo en hexanos) dio 2,3-difluoro-*N*-(2-fluoro-4-yodofenil)-6-[(2-metil-1-oxa-5-azaespiro[2.3]hex-5-il)carbonil]anilina (120 mg, 0,253 mmol, rendimiento del 99%): MS (EI) para $C_{18}H_{14}F_3IN_2O_2$: 475 (MH^+).

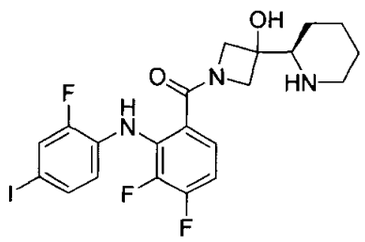
2,3-Difluoro-*N*-(2-fluoro-4-yodofenil)-6-[(2-metil-1-oxa-5-azaespiro[2.3]hex-5-il)carbonil]anilina (50 mg, 0,105 mmol) se disolvió en sulfóxido de dimetilo (0,8 mL) y se trató con *trans*-4-ciclohexanolamina (70 mg, 0,609 mmol) con 100 W de potencia de microondas a 100°C durante 45 minutos. La mezcla se purificó mediante HPLC de fase invertida y las fracciones puras se combinaron, se neutralizaron con solución de bicarbonato de sodio saturado y el solvente orgánico se removió en vacío. El residuo acuoso remanente se extrajo dos veces con acetato de etilo. La parte orgánica combinada se lavó con salmuera, se secó sobre sulfato de sodio anhidro, se filtró y se concentró en vacío y dio un residuo que se trató ácido clorhídrico acuoso y luego se liofilizó y se obtuvo clorhidrato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{1-[(*trans*-4-hidroxiciclohexil)amino]etil}azetidin-3-ol (36 mg, 0,058 mmol, rendimiento del 55%): ^{1}H NMR (400 MHz, d_6-DMSO): 8,61 (br s, 0,5H), 8,55 (br s, 0,5H), 8,49-8,33 (m, 1H), 8,08-7,90 (m, 1H), 7,59 (dd, 1H), 7,39 (br d, 1H), 7,37-7,30 (m, 1H), 7,21 (br q, 1H), 6,81 (br d, 1H), 6,77-6,65 (m, 1H), 4,20 (br d, 1H), 4,09-4,02 (m, 1H), 3,97 (br d, 1H), 3,93-3,80 (m, 1H),

3,62-3,47 (m, 1H), 3,03-2,90 (m, 1H), 2,07-1,93 (m, 2H), 1,93-1,77 (m, 2H), 1,54-1,06 (m, 8H); MS (EI) para $C_{24}H_{27}F_3IN_3O_3$: 590 (MH^+).

EJEMPLO 21(a). Usando las mismas técnicas sintéticas o análogas y sustituyendo según fue necesario con reactivos alternativos, se preparó el siguiente compuesto de la invención: 1-({3,4-Difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{1-[(1,1-dimetiletil)amino]etil}azetidin-3-ol: ^1H NMR (400 MHz, d_6-DMSO): 8,63 (br s, 0,4H), 8,53 (br s, 0,6H), 7,56 (dt, 1H), 7,40-7,34 (m, 1H), 7,32-7,26 (m, 1H), 7,25-7,13 (m, 1H), 6,72-6,62 (m, 1H), 5,43 (br s, 1H), 4,14-3,56 (m, 4H), 2,69-2,53 (m, 1H), 1,00-0,85 (br, 12H); MS (EI) para $C_{22}H_{25}F_3IN_3O_2$: 548 (MH^+).

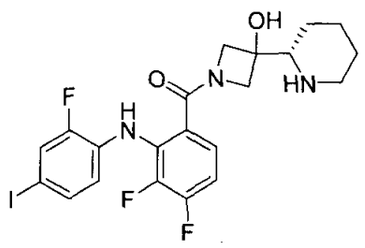
EJEMPLO 22(a) y 22(b)

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(2R)-piperidin-2-il]azetidin-3-ol



y

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(2S)-piperidin-2-il]azetidin-3-ol



A una solución de 1,1-dimetiletil 2-(3-hidroxi-1-{[(fenilmetil)oxi]carbonil}azetidin-3-il)piperidina-1-carboxilato (368 mg, 0,94 mmol), preparado usando procedimientos similares a aquellos descritos en la Referencia 5, en diclorometano (5 mL) se agregó DMAP (115 mg, 0,94 mmol) y la solución resultante se enfrió a 0°C. Se agregó cloruro de (*R*)-(-)-α-metoxi-α-trifluorometilfenilacetilo (105 µL, 0,56 mmol) a la solución con una jeringa y la mezcla se dejó calentar a temperatura ambiente luego se agitó otras 12 horas. La solución luego se repartió con bicarbonato de sodio acuoso saturado y la fase orgánica se secó sobre sulfato de magnesio anhidro luego se filtró y se concentró a un residuo aceitoso. La cromatografía rápida de gel de sílice usando hexanos:acetato de etlo 3:1 como eluyente dio el 1,1-dimetiletil (2*R*)-2-(1-{[(fenilmetil)oxi]carbonil}-3-{[(2*R*)-3,3,3-trifluoro-2-(metiloxi)-2-fenilpropanoil]oxi}azetidin-3-il)piperidina-1-carboxilato menos polar (27,5 mg, rendimiento del 5%), el 1,1-dimetiletil (2*S*)-2-(1-

{[(fenilmetil)oxi]carbonil}-3-{[(2*R*)-3,3,3-trifluoro-2-(metiloxi)-2-fenilpropanoil]oxi}azetidin-3-il)piperidina-1-carboxilato más polar (105 mg, rendimiento del 19%) y el material inicial (253 mg, recuperación del 69% recovery).

El material inicial así recuperado se llevó a diclorometano (3 mL) luego se agregó DMAP (115 mg, 0,94 mmol) y cloruro de (*R*)-(-)-α-metoxi-α-trifluorometilfenilacetilo (105 µL, 0,56 mmol) y la mezcla se dejó agitar a temperatura ambiente durante 12 horas. Procediendo como antes se obtuvo 1,1-dimetiletil (2R)-2-(1-{[(fenilmetil)oxi]carbonil}-3-{[(2*R*)-3,3,3-trifluoro-2-(metiloxi)-2-fenilpropanoil]oxi}azetidin-3-il)piperidina-1-carboxilato combinado (46,6 mg, rendimiento del 8%), y el 1,1-dimetiletil (2*S*)-2-(1-{[(fenilmetil)oxi]carbonil}-3-{[(2*R*)-3,3,3-trifluoro-2-(metiloxi)-2-fenilpropanoil]oxi}azetidin-3-il)piperidina-1-carboxilato más polar (228 mg, rendimiento del 41%) y el material inicial (100,8 mg, recuperación del 27%).

El material inicial así reuperado se llevó a tetrahidrofurano:diclorometano (1:1, 2 mL) seguido por el agregado de DMAP (47 mg, 0,39 mmol) y cloruro de (R)-(-)-α-metoxi-α-trifluorometilfenilacetilo (80 µL, 0,43 mmol) y la mezcla se calentó a 60°C durante 12 horas. Procediendo como antes se obtuvo el 1,1-dimetiletil (2*R*)-2-(1-{[(fenilmetil)oxi]carbonil}-3-{[(2*R*)-3,3,3-trifluoro-2-(metiloxi)-2-fenilpropanoil]oxi}azetidin-3-il)piperidina-1-

carboxilato menos polar combinado (144 mg, rendimiento del 26%). Los derivados de éster quirales así obtenidos es sometieron nuevamente a cromatografía rápida de gel de sílice usando hexanos:acetato de etilo 3:1 como eluyente y dieron el 1,1-dimetiletil (2*R*)-2-(1-{[(fenilmetil)oxi]carbonil}-3-{[(2*R*)-3,3,3-trifluoro-2-(metiloxi)-2-fenilpropanoil]oxi}azetidin-3-il)piperidina-1-carboxilato menos polar puro (122,8 mg, rendimiento del 22%) y el 1,1-dimetiletil (2*S*)-2-(1-{[(fenilmetil)oxi]carbonil}-3-{[(2*R*)-3,3,3-trifluoro-2-(metiloxi)-2-fenilpropanoil]oxi}azetidin-3-il)piperidina-1-carboxilato más polar puro (177,6 mg, rendimiento del 32%) ambos como residuos amorfos incoloros.

1,1-Dimetiletil (2*R*)-2-(1-{[(fenilmetil)oxi]carbonil}-3-{[(2*R*)-3,3,3-trifluoro-2-(metiloxi)-2-fenilpropanoil]oxi}azetidin-3-il)piperidina-1-carboxilato (122,8 mg, 0,21 mmol) se llevó a metanol (4 mL) y luego se agregó hidróxido de sodio acuoso 1M (1 mL) y la solución resultante se agitó durante una hora a temperatura ambiente. La solución luego se repartió con acetato de etilo y ácido clorhídrico acuoso 1N. La capa orgánica se lavó con salmuera, se secó sobre sulfato de magnesio anhidro y luego se filtró y se concentró. El residuo se purificó mediante cromatografía rápida de gel de sílice usando hexanos:acetato de etilo 2:1 y dio 1,1-dimetiletil (2*R*)-2-(3-hidroxi-1-{[(fenilmetil)oxi]carbonil}azetidin-3-il)piperidina-1-

carboxilato (60,8 mg, rendimiento del 81%) como un sólido amorfo incoloro. 1,1-dimetiletil (2*S*)-2-(3-hidroxi-1-{[(fenilmetil)oxi]carbonil}azetidin-3-il)piperidina-1-carboxilato (87,4 mg, rendimiento del 75%) se preparó en forma análoga.

1,1-Dimetiletil (2*R*)-2-(3-hidroxi-1-{[(fenilmetil)oxi]carbonil}azetidin-3-il)piperidina-1-carboxilato (60,8 mg, 0,16 mmol) y 10% Pd/C (30 mg) se llevaron a metanol (2 mL) y la mezcla se hidrogenó a presión ambiente durante una hora. La suspensión luego se filtró a través de un tampón de celita y se concentró y luego se secó en vacío hacia un sólido incoloro. La amina sólida se llevó a THF (1 mL) luego se agregó DIPEA (42 µL, 0,24 mmol) y fluoruro de 3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]benzoilo (63 mg, 0,16 mmol), preparado usando procedimientos similares a los descritos en la Referencia 1, y la mezcla se agitó a temperatura ambiente durante 30 minutos. La mezcla de la reacción se repartió con acetato de etilo y 1N ácido clorhídrico acuoso y la capa orgánica se lavó con salmuera, se secó sobre sulfato de magnesio anhidro luego se filtró y se concentró. La purificación del residuo mediante cromatografía rápida de gel de sílice usando hexanos:acetato de etilo 3:2 como eluyente dio 1,1-dimetiletil (2*R*)-2-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]piperidina-1-carboxilato (74.9 mg,

rendimiento del 74%) como un sólido amorfo. 1,1-Dimetiletil (2*R*)-2-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]piperidina-1-carboxilato ^{1}H NMR (400 MHz, $CDCl_3$): 8,53 (br s, 0,5H), 8,40 (br s, 0,5H), 7,41-7,38 (dd, 1H), 7,34-7,31(dt, 1H), 7,17-7,14 (m, 1H), 6,86-6,79 (m, 1H), 6,63-6,587 (m, 1H), 4,24-3,90 (m, 4H), 3,37-3,23 (m, 1H), 2,90-2,80 (m, 1H), 1,85-1,54 (m, 7H), 1,43 (s, 9H); MS (EI) para $C_{26}H_{29}F_3IN_3O_4$: 576 (M-$C_4H_9^+$).

1,1-Dimetiletil (2*R*)-2-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]piperidina-1-carboxilato (74,9 mg, 0,12 mmol) se llevó a metanol (1 mL) y luego se agregó 4 N HCl en dioxano (1 mL) y la solución se agitó a temperatura ambiente durante una hora. La solución luego se concentró y el residuo se repartió cn cloroformo y bicarbonato de sodio acuoso saturado. La capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio anhidro y luego se filtró y se concentró. La purificación del residuo mediante cromatografía rápida de gel de sílice usando acetato de etilo y luego se amoníaco acuoso concentrado en cloroformo y metanol (0,1:10:1) como eluyentes dio 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(2*R*)-piperidin-2-il]azetidin-3-ol (57,3 mg) como un sólido amorfo incoloro. La base libre se llevó a metanol (1 mL) luego se llevó a pH 1 agregando 4 N HCl en dioxano y la solución se

concentró. El residuo se trituró con éter etílico y se obtuvo una suspensión. El sólido se recogió mediante filtración y dio la sal de clorhidrato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(2*R*)-piperidin-2-il]azetidin-3-ol (49 mg, 72% yield) como un sólido incoloro. ^{1}H NMR (400 MHz, $CDCl_3$): 8,43-8,39 (d, 1H), 7,41-7,38 (dd, 1H), 7,33-7,31(dt, 1H), 7,14-7,10 (m, 1H), 6,84-6,80 (m, 1H), 6,63-6,57 (m, 1H), 4,12-3,99 (m, 4H), 3,10-3,08 (d, 1H), 2,72-2,69 (d, 1H), 2,64-2,62 (m, 1H), 1,61-1,58 (m, 2H), 1,36-1,16 (m, 4H); MS (EI) para $C_{21}H_{21}F_3IN_3O_2$: 532 (MH^+).

Usando las mismas técnicas sintéticas o análogas y sustituyendo según fue necesario con reactivos alternativos, se prepararon los siguientes compuestos de la invención.

EJEMPLO 22(c). 1,1-dimetiletil (2S)-2-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]piperidine-1-carboxilato: ^{1}H NMR (400 MHz, $CDCl_3$): 8,52 (br s, 0,5H), 8,39 (br s, 0,5H), 7,41-7,38 (dd, 1H), 7,34-7,31(dt, 1H), 7,17-7,12 (m, 1H), 6,85-6,79 (m, 1H), 6,63-6,57 (m, 1H), 4,25-3,88 (m, 4H), 3,34-3,26 (m, 1H), 2,80-2,90 (m, 1H), 1,85-1,54 (m, 7H), 1,43 (s, 9H); MS (EI) para $C_{26}H_{29}F_3IN_3O_4$: 576 ($M-C_4H_9^+$).

EJEMPLO 22(d). Clorhidrato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(2S)-piperidin-2-il]azetidin-3-ol: ^{1}H NMR (400 MHz, d_4-Metanol): 7,49-7,46 (dd, 1H), 7,37-7,35(dt, 1H), 7,35-7,30 (m, 1H), 7,10-7,04 (m, 1H),

6,64-6,59 (m, 1H), 4,39-4,32 (dd, 1H), 4,21-4,18 (dd, 1H), 4,13-4,07 (m, 1H), 3,97-3,88 (dd, 1H), 3,57-3,32 (m, 1H), 3,02-2,96 (dd,1H), 1,90-1,50 (m, 7H); MS (EI) para $C_{21}H_{21}F_3IN_3O_2$: 532 (MH^+).

EJEMPLO 22(e). Sal de acetato de 1-({2-[(4-bromo-2-clorofenil)amino]-3,4-difluorofenil}carbonil)-3-piperidin-2-ilazetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7,56 (d, 1H), 7,29-7,38 (m, 2H), 7,08-7,16 (m, 1H), 6,64-6,70 (m, 1H), 4,30-4,40 (m, 1H), 4,18-4,26 (m, 1H), 4,04-4,14 (m, 1H), 3,90-4,00 (m, 1H), 3,16-3,26 (m, 2H), 2,86-2,96 (m, 1H), 1,91 (s, 3H), 1,76-1,88 (m, 3H), 1,44-1,64 (m, 3H). MS (EI) para $C_{21}H_{21}BrClF_2N_3O_2$: 500 (M-H).

EJEMPLO 22(f). Sal de acetato de 1-({2-[(4-bromo-2-fluorofenilamino]-3,4-difluorofenil}carbonil)-3-piperidin-2-ilazetidin-3-ol: ^1H NMR (400 MHz, DMSO): 8,52 (br s, 1H), 7,50 (d, 1H), 7,35-7,15 (m, 3H), 6,88-6,79 (m, 1H), 4,15-3,96 (m, 1H), 3,84-3,78 (m, 1H), 3,68-3,63 (m, 1H), 2,95-2,88 (m, 1H), 2,48-2,40 (m, 2H), 1,71-1,42 (m, 3H), 1,25-1,14 (m, 2H), 1,03-0,90 (m, 1H); MS (EI) para $C_{21}H_{21}BrF_3N_3O_2$: 485 (MH^+).

EJEMPLO 22(g). 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-pirrolidin-2-ilazetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7,45 (dd, 1H), 7,37-7,31 (m, 1H), 7,30-7,25 (m, 1H), 7,13-6,99 (m, 1H), 6,67-6,54 (m, 1H), 4,20-4,09 (m,1H), 4,08-3,91 (m, 2H), 3,88-3,79 (m, 1H), 3,27 (t,

1H), 2,99-2,89 (m, 1H), 2,88-2,81 (m, 1H), 1,93-1,67 (m, 3H), 1,55-1,42 (m, 1H). MS (EI) para $C_{20}H_{19}F_3IN_3O_2$: 518 (MH^+)

EJEMPLO 22(h). Acetato (sal) de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1-metilpirrolidin-2-il)azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7,46 (dd, 1H), 7,38-7,26 (m, 2H), 7,12-6,99 (m, 1H), 6,66-6,56 (m, 1H), 4,37-3,87 (m,4H), 2,94-2,82 (m, 1H), 2,75-2,63 (m, 3H), 2,20-2,06 (m, 1H), 2,00-1,67 (m, 8H). MS (EI) para $C_{21}H_{21}F_3IN_3O_2$: 532 (MH^+).

EJEMPLO 22(i). Acetato (sal) de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1-etilpirrolidin-2-il)azetidin-3-ol: ^1H NMR (400 MHz, CD_3OD): 7,46 (d, 1H), 7,38-7,33 (m, 1H), 7,32-7,27 (m, 1H), 7,12-7,01 (m, 1H), 6,66-6,57 (m, 1H), 4,34-3,89 (m,4H), 3,57 (t, 1H), 3,51-3,40 (m, 1H), 3,28-2,81(m, 3H), 2,25-1,72 (m, 8H), 1,31-1,18 (m, 3H). MS (EI) psts $C_{22}H_{23}F_3IN_3O_2$: 546 (MH^+).

EJEMPLO 22(j). Sal de acetato de 1-({4-fluoro-5-[(2-fluoro-4-yodofenil)amino]-1-metil-1*H*-bencimidazol-6-il}carbonil)-3-[(2S)-piperidin-2-il]azetidin-3-ol: ^1H NMR (400 MHz, d_4-MeOH): 8,30 (s, 1H), 7,56 (s, 1H), 7,42 (d, 1H), 7,24 (d, 1H), 6,34 (m, 1H), 4,20 (d, 2H), 3,92 (s, 3H), 3,38-3,24 (m, 3H), 3,08 (bs, 1H), 2,88 (bs (1*H*), 1,90-1,70 (m, 3H), 1,66-1,32 (m, 3H); MS (EI) para $C_{23}H_{24}F_2IN_5O_2$: 568 (MH^+).

EJEMPLO 22(k). Sal de acetato de 1-({7-fluoro-6-[(2-fluoro-4-yodofenil)amino]-1-metil-1*H*-benimidazol-5-il}carbonil)-3-

[(2S)-piperidin-2-il]azetidin-3-ol: ^{1}H NMR (400 MHz, d_4-MeOH): 8,22 (s, 1H), 7,60 (s, 1H), 7,42 (d, 1H), 7,26 (d, 1H), 6,46 (m, 1H), 4,21 (d, 2H), 4,06 (s, 3H), 3,88 (m, 1H), 3,38-3,24 (m, 3H), 3,10 (bs, 1H), 2,88 (bs (1*H*), 1,88-1,70 (m, 3H), 1,64-1,28 (m, 3H); MS (EI) para $C_{23}H_{24}F_2IN_5O_2$: 568 (MH^+).

EJEMPLO 22(m). 4-[(4-bromo-2-fluorofenil)amino]-3-fluoro-5-({3-hidroxi-3-[(2S)-piperidin-2-il]azetidin-1-il}carbonil)-1-metilpiridin-2(1*H*)-ona: MS (EI) para $C_{21}H_{23}BrF_2N_4O_3$: 498 (MH^+).

EJEMPLO 22(n). 1-({8-cloro-7-[(2-fluoro-4-yodofenil)amino]imidazo[1,2-a]piridin-6-il}carbonil)-3-[(2S)-piperidin-2-il]azetidin-3-ol: ^{1}H NMR (400MHz, d_6-DMSO): 8,79 (s, 1H), 8,04 (d, 1H), 7,91 (d, 1H), 7,64 (dd, 1H), 7,55 (d, 1H), 6,95-7,02 (m, 1H), 4,38 (d, 1H), 4,15 (dd, 1H), 3,99 (dd, 1H), 3,72 (q, 1H), 3,32-3,39 (m, 1H), 3,00-3,12 (m, 1H), 1,93 (t, 3H), 1,51-1,70 (m, 3H); MS (EI) para $C_{22}H_{22}ClFIN_5O_2$: 532 (MH^+).

EJEMPLO 22(o). 1-({7-[(4-bromo-2-clorofenil)amino]-8-cloroimidazo[1,2-a]piridin-6-il}carbonil)-3-[(2S)-piperidin-2-il]azetidin-3-ol: ^{1}H NMR (400MHz, d_4-MeOH): 8,85 (s, 1H), 8,06 (d, 1H), 7,91 (d, 1H), 7,71 (d, 1H), 7,45 (d, 1H), 7,01 (d, 1H), 4,48 (d, 1H), 4,10-4,27 (m, 2H), 3,87 (q, 1H), 3,37 (d, 2H), 3,02 (s, 1H), 1,88-1,94 (m, 3H), 1,58-1,69 (m, 3H); $C_{22}H_{22}BrCl_2N_5O_2$: 540 (MH^+).

EJEMPLO 22(p). 1-({6-[(4-bromo-2-clorofenil)amino]-7-fluoro-3-metil-1,2-bencisoxazol-5-il}carbonil)-3-[(2S)-piperidin-2-

il]azetidin-3-ol: ^{1}H NMR (400MHz, $CDCl_3$): 8,50 (m, 1H), 7,51 (d, 1H), 7,42 (s, 1H), 7,26 (dd, 1H), 6,79 (dd, 1H), 4,20-3,98 (br m, 4H), 3,11 (d, 1H), 2,77-2,50 (br m, 5H), 1,80-1,15 (br m, 6H); MS (EI) para $C_{23}H_{23}BrClFN_4O_3$: 537 (MH^+).

EJEMPLO 22(q). 1-({3-fluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(2S)-piperidin-2-il]azetidin-3-ol: ^{1}H NMR (400 MHz, d_4-MeOH): 7,53 (2d, 1H), 7,46 (m, 2H), 7,16 (t, 1H), 6,86 (m, 1H), 6,63 (m, 1H), 4,36 (m, 1H), 4,22 (m, 1H), 4,02 (m, 1H), 3,88 (m, 1H), 3,08 (d, 1H), 2,66 (dd, 1H), 2,56 (m, 1H), 1,82 (bs, 1H), 1,66 (d, 1H), 1,58 (d, 1H), 1,38 (m, 2H), 1,22 (m, 1H); MS (EI) para $C_{21}H_{22}F_2IN_3O_2$: 514 (MH^+).

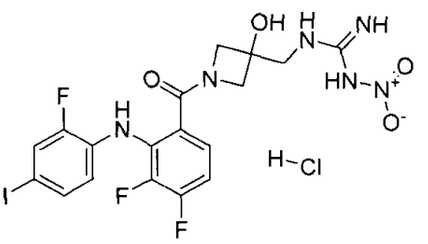
EJEMPLO 22(r). 1-({4-fluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(2S)-piperidin-2-il]azetidin-3-ol: ^{1}H NMR (400 MHz, d_4-MeOH): 7,42 (2d, 1H), 7,34-7,18 (m, 4H), 6,46 (m, 1H), 4,10 (m, 2H), 3,84 (m, 2H), 3,04 (d, 1H), 2,52 (dd, 2H), 1,76 (bs, 0,5H), 1,58 (m, 2,5H), 1,32 (m, 2H), 1,18 (m, 0,5H), 1,04 (m, 0,5H); MS (EI) para $C_{21}H_{22}F_2IN_3O_2$: 514 (MH^+).

EJEMPLO 22(s). 5-[(2-fluoro-4-yodofenil)amino]-6-({3-hidroxi-3-[(2S)-piperidin-2-il]azetidin-1-il}carbonil)-2-metilpiridazin-3(2*H*)-ona: ^{1}H NMR (400MHz, d_6-DMSO): 10,19 (s, 1H), 7,78 (dd, 1H), 7,59 (d, 1H), 7,32 (t, 1H), 5,95 (s, 1H), 4,59 (q, 1H), 4,13-4,27 (m, 2H), 3,77 (d, 1H), 3,62 (s, 3H), 3,02 (d, 2H), 2,71 (d, 1H), 1,78 (s, 1H), 1,68 (d, 1H), 1,53

(d, 1H), 1,32 (s, 2H), 1,17 (t, 1H); MS (EI) para $C_{20}H_{23}FIN_5O_3$: 528 (MH+).

Ejemplo 23

Clorhidrato de 1-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}-3-nitroguanidina



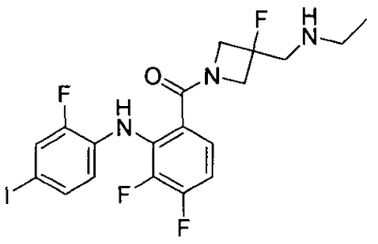
A una solución de 2,3-difluoro-*N*-(2-fluoro-4-yodofenil)-6-(1-oxa-5-azaespiro[2,3]hex-5-ilcarbonil)anilina (0,15g, 0,33 mmol), preparada usando procedimientos similares a los descritos en el Ejemplo 21, y nitroguanidina (0,1 g, 1,00 mmol) en tetrahidrofurano (3,00 mL) se agregó una solución acuosa de hidróxido de sodio (1,0 mL, 2,0 mmol) la mezcla de la reacción se agitó a 70°C durante 16 horas. La mezcla de la reacción se concentró en vacío. El producto crudo se purificó mediante HPLC de fase invertida preparativa. Las fracciones se recogieron, y el solvente se concentró. El residuo se repartió con acetato de etilo. La capa orgánica se lavó con biarbonato de sodio acuoso saturado, salmuera y se secó sobre sulfato de sodio anhidro. La filtración y la concentración derivaron en un residuo amorfo, que se disolvió en metanol y

se agregó 4 N HCl en dioxano (80 µL, 0,33 mmol) a la solución. Se formó un precipitado blanco y se recogió mediante filtración. El sólido se lavó con hexano, y se secó y se obtuvieron 76 mg (38%) de clorhidrato de 1-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}-3-nitroguanidina. ^{1}H NMR (400 MHz, d_4-MeOH): 7,46 (2d, 1H), 7,36 (m, 1H), 7,29 (m, 1H), 7,02 (m, 1H), 6,63 (m, 1H), 4,22 (m, 1H), 4,01 (m, 2H), 3,86 (m, 1H), 3,51 (d, 2H); MS (EI) para $C_{18}H_{16}F_3IN_6O_4$: 565 (MH^+).

EJEMPLO 23(a). Usando las mismas técnicas sintéticas o análogas y sustituyendo, según fue necesario, con reactivos alternativos, se prepararon los siguientes compuestos de la invención: clorhidrato de 1-ciano-3-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}guanidina. ^{1}H NMR (400 MHz, d_4-MeOH): 7,47 (2d, 1H), 7,36 (m, 1H), 7,27 (m, 1H), 7,03 (m, 1H), 6,63 (m, 1H), 4,18 (m, 1H), 3,98 (m, 2H), 3,80 (m, 1H), 3,43 (s, 2H); MS (EI) para $C_{19}H_{16}F_3IN_6O_2$: 545 (MH^+).

EJEMPLO 24

6-({3-[(etilamino)metil]-3-fluoroazetidin-1-il}carbonil)-2,3-difluoro-*N*-(2-fluoro-4-yodofenil)anilina



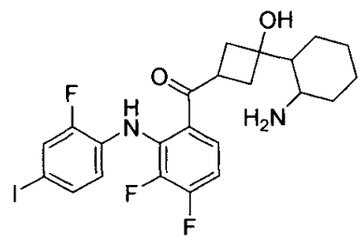
A 1,1-dimetiletil [{1-({3,4-difuoro-2-[(2-fluoro-4-yodofnil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}etilcarbamato (27 mg, 0,044 mmol), preparado usando procedimientos similares a aquellos del Ejemplo 3 y seguido por la protección con Boc, en cloroformo (2,5 mL) se agregó DAST (11,8 µL, 0,089 mmol) y se agitó durante 3,5 h a temperatura ambiente. Se enfrió con agua (15 mL), las fases se repartieron y se extrajo la fase acuosa con cloroformo (2 X 15 mL). Los extractos de cloroformo combinados se secaron sobre sulfato de sodio, se filtraron y el filtrado se concentró en vacío. El residuo se purificó sobre una columna de gel de sílice y dio 1,1-dimetiletil [{1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-fluoroazetidin-3-il]metil}etilcarbamato (19.0 mg, 70%).

Al 1,1-dimetiletil [{1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-fluoroazetidin-3-il]metil}etilcarbamato (19,0 mg, 0,031 mmol) en acetonitrilo (1,0 mL) se agregó una solución de 4.0N cloruro de hidrógeno en dioxano (1,0 mL). Después de 1,5 h la solución se concentró en vacío. El residuo se purificó mediante HPLC preparativa de fase invertida y dio el compuesto del título (4,30 mg, 27%).

^{1}H NMR (400MHz, $CDCl_3$): 8,25 (s, 1H), 7,33 (dd, 1H), 7,33-7,25 (m, 1H), 7,18-7,14 (m, 1H), 6,84-6,77 (m, 1H), 6,63-6,58 (m, 1H), 4,33-4,05 (br m, 4H), 3,07-2,95 (br m, 2H), 2,65 (q, 2H), 1,08 (t, 3H); MS (EI) para $C_{19}H_{18}F_4IN_3O$: 508 (MH^+).

EJEMPLO 25

3-(2-aminociclohexil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol



Una solución de 1-(trimetilsiloxi)ciclohexeno (200 mg, 1,17 mmol) y 3-oxoazetidina-1-carboxilato de bencilo (289 mg, 1,41 mmol), preparado usando procedimientos similares a aquellos descritos en la Referenci 3, en tetrahidrofurano (3,90 mL) se enfrió a -78°C durante 10 minutos y luego se agregó tetracloruro de titanio (0,13 mL, 1,17 mmol). La mezcla de la reacción se agitó durante otras 5 horas a -78°C. La mezcla se enfrió con bicarbonato de sodio acuoso y la capa acuosa se extrajo con éter (2x). La capa orgánica se separó, se secó sobre sulfato desodio anhidro, se filtró y el filtrado se concentró en vacío. El residuo se purificó sobre coluna de cromatografía de gel de sílice (3:2 hexanos/acetato de etilo) y dio bencil 3-hidroxi-3-(2-oxociclohexil)azetidina-1-

carboxilato (328 mg, 37%). ^{1}H NMR ($CDCl_3$): 7,28-7,34 (m, 5H), 5,08 (s, 2H), 4,02 (d, 1H), 3,89 (d, 1H), 3,87 (s, 1H), 3,55 (s, 1H), 2,71 (q, 1H), 2,29-2,43 (m, 2H), 2,11 (s, 2H), 1,95 (s, 1H), 1,66 (d, 3H); MS (EI) para $C_{17}H_{21}NO_4$: 303 (MH+).

Una solución de bencil 3-hidroxi-3-(2-oxociclohexil)azetidina-1-carboxilato (100 mg, 330 mmol) en metanol (1,60 mL) en la presencia de acetato de amonio (191 mg, 2,48 mmol se enfrió a 0°C durante 1 hora. Se agregó cianoborohidruro de sodio (81,5 mg, 1,30 mmol) y la mezcla se agitó a temperatura ambiente durante 16 horas. A la mezcla de la reacción se agregó 6 N cloruro de hidrógeno (800 µL) y se extrajo con acetato de etilo. La capa acuosa se basificó con bicarbonato de sodio acuoso (pH 9) y se extrajo con diclorometano. La parte orgánica combinada se secó sobre sulfato de sodio anhidro, se filtró y se concentró en vacío y dio bencil-3-(2-aminociclohexil)-3-hidroxiazetidina-1-carboxilato (73,7 mg, 73%). MS (EI) para $C_{17}H_{24}N_2O_3$: 305 (MH+).

A una solución de bencil-3-(2-aminociclohexil)-3-hidroxiazetidina-1-carboxilato (202 mg, 0,663 mmol) en dioxano-agua (1:1, 2,5 mL) se agregó dicarbonato de di-*terc*-butilo (138 mg, 0,630 mmol) y bicarbonato de sodio sólido (112 mg, 1,33 mmol). La mezcla de la reacción se agitó a temperatura ambiente durante 2 horas y se evaporó. El residuo se reaprtió entre acetato de etilo y agua. La capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio anhidro, se

filtró y se concentró en vacío y dio bencil 3-(2-*terc*-butoxicarbonilamino)ciclohexil)-3-hidroxiazetidina-1-carboxilato (237 mg, 100%). ^{1}H NMR (CH_3OH): 7,15-7,21 (m, 5H), 5,45 (s, 0,5H), 5,20 (d, 0,5H), 4,95 (s, 2H), 4,81 (s, 1H), 3,81 (d, 2H), 1,43-1,74 (m, 5H), 1,39 (s, 1H), 1,31 (s, 11H), 1,20 (s, 1H). MS (EI) para $C_{22}H_{32}N_2O_5$: 405 (MH+).

Una solución de bencil 3-(2-terc-butoxicarbonilamino)ciclohexil)-3-hidroxiazetidina-1-carboxilato (237 mg, 0,586 mmol) en acetato de etilo (2 mL) se hidrogenó sobre 10% paladio-carbono (200 mg, 0,586 mmol) a 40 psi durante 16 horas. La mezcla de la reacción se filtró y se concentró en vacío y proporcionó *terc*-butil 2-(3-hidroxiazetidin-3-il)ciclohexilcarbamato (181 mg, 100%). ^{1}H NMR ($CDCl_3$): 5,10 (s, 1H), 4,80 ((s, 1H), 3,78-3,86 (m, 1H), 3,61 (d, 1H), 3,57 (s, 1H), 3,36 (d, 1H), 1,77 (s, 2H). 1,40-1,53 (m, 1H), 1,36 (d, 9H), 1,25 (s, 2H). MS (EI) para $C_{14}H_{26}N_2O_3$: 271 (MH+).

A una solución de *terc*-butil 2-(3-hidroxiazetidin-3-il)ciclohexilcarbamato (181 mg, 0,669 mmol) y fluoruro de 3,4-difluoro-2-(2-fluoro-4-yodofenilamino)benzoilo (265 mg, 0,669 mmol), preparado usando procedimientos similares a los descritos en la Referencia 1, en tetrahidrofurano (2,2 mL) se agregó *N,N*-diisopropiletilamina (110 µL) a temperatura ambiente. Después de una hora, la mezcla de la reacción se calentó a 50°C y se agitó durante 45 minutos, en cuyo momento

se enfrió a temperatura ambiente y se evaporó. El residuo se reaprtió entre acetato de etilo y 10% ácido cítrico. La capara orgánica se lavó con cloruro de sodio acuoso, se secó sobre sulfato de sodio anhidro, se fltró y e concentró en vacío y dio *terc*-butil-2-(1-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)benzoil)-3-hidroxiazetidin-3-il)ciclohexilcarbamato. Este material se llevó al paso siguiente sin nueva purificación.

Terc-butil-2-(1-(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)benzoil)-3-hidroxiazetidin-3-il)ciclohexilcarbamato se disolvió en una mezcla de metanol (4 mL) y cloruro de hidrógeno (4 M en dioxano) (3 mL). La solución se calentó a reflujo luego se enfrió a temperatura ambiente y se agitó durante 16 horas. La mezcla de la reacción se concentró y se purificó mediante HPLC de fase invertida. Las fraccoines purificadas se evaporaron hasta secarse y se repartieron entre acetato de etilo y bicarbonato de sodio acuoso. La capa orgánica se secó sobre sulfato de sodio, se filtró y se concentró en vacío y dio un aceite. El residuo se llevó a metanol (2 mL) y se agregó cloruro de hidrógeno (4M en dioxano) (700 µL) y se evaporó hasta secarse y dio el compuesto del título clorhidrato de 3-(2-aminociclohexil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol (44,7 mg, 12%).

^{1}H NMR (400MHz, d_6-DMSO): 8,58 (d, 1H), 7,59 (dd, 1H), 7,54 (s, 2H), 7,38 (d, 1H), 7,33 (t, 1H), 7,16-7,25 (m, 1H), 6,69 (dt, 1H), 6,41 (s, 1H), 4,26 (d, 0,5H), 4,17 (d, 0,5H), 4,04 (t, 1H), 390 (t, 1H), 3,79 (d, 0,5H), 3,65-3,73 (m, 0,5H), 3,45-3,51 (m, 1H), 1,88 (s, 1H), 1,65-1,88 (m, 2H), 1,47 (s, 4H), 1,16-1,37 (m, 2H); MS (EI) para $C_{22}H_{23}F_3IN_3O_2$: 546 (MH^+).

Usando las mismas técnicas sintéticas o análogas y sustituyendo según fue necesario con reactivos alternativos, se prepararon los siguientes compuestos de la invención.

EJEMPLO 25(c). 3-(2-aminociclopentil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol; ^{1}H NMR (400MHz, d_6-DMSO): 8,56 (d, 1H), 7,82 (d, 1H), 7,59 (td, 1H), 7,45 (s, 1H), 7,38 (d, 1H), 7,30-7,35 (m, 1H), 7,18-7,24 (m, 1H), 6,68-6,72 (m, 1H0, 6,41 (s, 0,5H), 6,17 (s, 0,5H), 3,91-4,27 (m, 2,5H), 3,78-3,86 (m, 1H), 3,65-3,73 (m, 1H), 3,44-3,52 (m, 0,5H), 2,19-2,26 (m, 1H), 1,54-1,94 (m, 5H), 1,30-1,39 (m, 1H); MS (EI) para $C_{21}H_{21}F_3IN_3O_2$: 532 (MH^+).

EJEMPLO 25(a) y **EJEMPLO 25(b)**

(±)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(trans)-2-hidroxiciclohexil]azetidin-3-ol

y

(±)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(cis)-2-hidroxiciclohexil]azetidin-3-ol

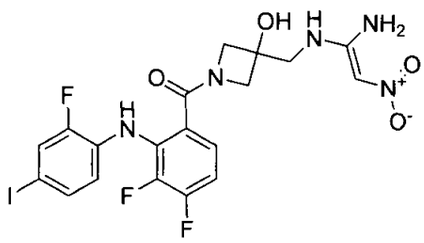
Los compeustos de los ejemplos 25a y 25b se sintetizaron partiendo desde bencil 3-hidroxi-3-(2-oxiciclohenil)azetidina-1-carboxilato preparado de acuerdo con el procedimiento que se dio en el ejemplo 25. La cetona se redujo y dio el bencil 3-hidroxi-3-(2-hidroxiciclohexil)azetidina-1-carboxilato como una mezcla de diastereómeros racémicos que se sometieron a hidrogenación y dieron 3-(2-hidroxiciclohexil)azetidin-3-ol. 3-(2-hidroxiciclohexil)azetidin-3-ol luego se transportó a un paso de acoplamiento con fluoruro de 3,4-difluoro-2-(2-fluoro-4-yodofenilamino)benzoilo en la forma habitual. El material acoplado así obtenido se purificó mediante HPLC defase invertida preparativa dnde la fracción 1 se asignó tentativamente como (±)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(trans)-2-hidroxiciclohexil]azetidin-3-ol (Ejemplo 25a) y la fracción 2 se asignó tentaivamente como (±)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(cis)-2-hidroxiciclohexil]azetidin-3-ol.

EJEMPLO 25(a). Primera fracción eluida: ^{1}H NMR (400 MHz, d_4-MeOH): 7,44 (2d, 1H), 7,34 (t, 1H), 7,25 (m, 1H), 7,03 (m, 1H), 6,60 (m, 1H), 4,46 (d, 0,5H), 4,28 (d, 0,5H), 4,22 (d, 0,5H), 3,98 (dd, 1H), 3,89 (d, 0,5H), 3,85 (s, 0,5H), 3,77 (d, 0,5H), 3,56 (m, 1H), 1,90 (m, 1H), 1,46-1,74 (m, 4H), 0,98-1,32 (m, 4H); MS (EI) para $C_{22}H_{22}F_3IN_2O_3$: 547 (MH^+).

EJEMPLO 25(b). Segunda fracción eluida: ^{1}H NMR (400 MHz, d_4-MeOH): 7,44 (2d, 1H), 7,33 (d, 1H), 7,26 (m, 1H), 7,04 (m, 1H), 6,59 (dd, 1H), 4,20 (m, 1,5H), 4,19 (s, 0,5H), 4,00 (m, 1,5H), 3,86 (dd, 1H), 3,74 (d, 0,5H), 1,76 (m, 2H), 1,50-1,68 (m, 5H), 1,18-1,46 (m, 4H); MS (EI) para $C_{22}H_{22}F_3IN_2O_3$: 547 (MH^+).

Ejemplo 26

3-({[(E)-1-amino-2-nitroetenil]amino}metil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodfenil)amino]fhenil}carbonil)azetidin-3-ol



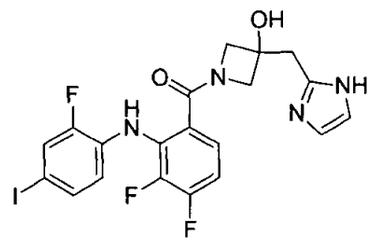
Una solución de 3-(aminometil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol (0,24 g, 0,5 mmol), praparada procedimientos similares a aquelos descritos en el Ejemplo 1, el 1,1-bis(metiltio)-2-nitroetileno comercialmente disponible (0,083 g, 0,5 mmol) en etanol (5 mL) se agitó a 70°C durante 16 horas. La mezcla de la reacción se concentró en vacío. El residuo se repartió entre acetato de etilo y agua. La capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y se concentró y dio 0,10 g, (39%) de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(Z)-1-(metiltio)-2-

nitroetenil]amino}metil)azetidin-3-ol. MS (EI) para $C_{20}H_{18}F_3IN_4O_4S$: 595 (MH^+).

A una solución de (0,05 g 0,08 mmol) 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonul)-3-({[(Z)-1-(metiltio)-2-nitroetenil]amino}metil)azetidin-3-ol en etanol (2 mL) se agregó hidróxido de amonio (0,1 mL, 0,8 mmol) y la mezcla de la reacción se agitó a 70°C durante 16 horas. La mezcla de la reacción se concentró en vacío. El producto crudo se purificó mediante HPLC preparativa defase invertida. Las fracciones se recogieron y el solvnete se concentró. El residuo se repartió con acetato de etilo. La apa orgánica se lavó con bicarbonato de sodio acuoso saturado, salmuera y se secó sobre sulfato de sodio anhidro. La filtración y la concentración derivaron en un residuo amorfo, que se disolvió en metanol y se agregó 4 N HCl en dioxano (40 µL, 0,16 mmol) a la solución. Se formó un precipitado blanco y se recogió mediante filtración en vacío. El sólido se lavó con hexano y se secó y dio 42 mg (87%) de clorhidrato de 3-({[(E)-1-amino-2-nitroetenil]amino}metil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol. ^1H NMR (400 MHz, d_4-MeOH): 7,58 (t, 0,5H), 7,44 (t, 0,5H), 7,36 (m, 1H), 7,31 (m, 1H), 7,04 (m, 1H), 6,63 (m, 1H), 3,90-4,30 (m, 4H) 3,72 (s, 2H); MS (EI) para $C_{19}H_{17}F_3IN_5O_4$: 564 (MH^+).

EJEMPLO 27

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1*H*-imidazol-2-ilmetil)azetidin-3-ol



Una solución de 2-metil-1-({[2-(trimetilsilil)etil]oxi}metil)-1*H*-imidazol (0,5 g, 2,3 mmol) (preparada usando procedimientos similares a los descritos en Clader *et. al. J. of Med. Chem.* **1995**, *38(10)*, 1600-7) en tetrahidrofurano (5 mL) se enfrió a -78°C, y se agregó *n*-butillitio (2,5 M en hexanos, 0,990 mL, 2,5 mmol). Después de 2 horas, se agregó 1,1-dimetiletil 3-oxoazetidina-1-carboxilato (0,60 g, 3,5 mmol), preparado usando procedimientos similares a los del Ejemplo 3, en 2,0 mL de tetrahidrofurano y la solución se dejó calentar a temperatura ambiente y se agitó toda la noche. La mezcla de la reacción se enfrió con un exceso de solución de cloruro de amonio acuoso saturado y se repartió entre agua y acetato de etilo. Las capas se separaron y la capa acuosa se extrajo con acetato de etilo (2 x 10 mL). Las capas orgánicas combinadas se secaron sobre sulfato de sodio, se filtraron y se concentraron en vacío. La cromatografía de columna (gel de sílice, 3:1 hexanos/acetato de etilo) dio 0,37 g (41%) de 3-

{[1-({[2-(trimetilsilil)etil]oxi}metil)-1*H*-imidazol-2-il]metil}azetidin-3-ol: ^{1}H NMR (400 MHz, $CDCl_3$): 6,96-6,92 (m, 1H), 5,23 (s, 2H), 3,98 (d, 2H), 3,79 (d, 2H), 3,52-3,47 (m, 2H), 3,13 (s, 2H), 1,43 (s, 9H), 0,94-0,88 (m, 2H), 0,00 (s, 9H).

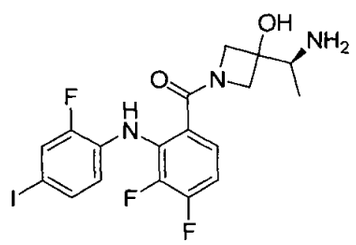
3-{[1-({[2-(trimetilsilil)etil]oxi}metil)-1*H*-imidazol-2-il]metil}azetidin-3-ol (0,19 g, 0,49 mmol) se disolvió en diclorometano (1,5 mL) y se agregó ácido trifluroacético (1,5 mL). La mezcla de la reacción se agitó a temperatura ambiente y el solvente se removió bajo vacío y dio 0,16 g de sal de trifluoroacetato de 3-(1*H*-imidazol-2-ilmetil)azetidin-3-ol (87%). El residuo crudo se usó sin nueva purificación para el paso siguiente.

A una solución de sal de trifluoroacetato de 3-(1*H*-imidazol-2-ilmetil)azetidin-3-ol (0,16 g, 0,42 mmol) y *N,N*-diisopropiletilamina (0,370 mL, 2,13 mmol) en tetrahidrofurano (2,0 mL) se agregó fluoruro de 3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]benzoilo (0,17 g, 0,42 mmol), preparado usando procedimientos similares a los descritos en la Referencia 1, y la mezcla de la reacción se agitó durante 3 horas a temperatura ambiente. La solución se repartió entre acetato de etilo y bicarbonato de sodio acuoso saturado y la capa orgánia se secó sobre sulfato de sodio y se concentró en vacío. la purificación mediante HPLC de fase invertida seguida por la liofilización de la fracción pura dio 0,032 g (13%) de sal de

acetato de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1*H*-imidazol-2-ilmetil)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7,45 (dd, 1H), 7,38-7,33 (m, 1H), 7,25-7,18 (m, 1H), 7,08-6,96 (m, 1H), 6,89 (s, 2H), 6,65-6,56 (m, 1H), 4,33-4,22 (m, 1H), 4,17-4,00 (m, 2H), 3,91-3,80 (m, 1H), 3,08 (s, 2H), 1,96 (s, 3H). MS (EI) para $C_{20}H_{16}F_3IN_4O_2$: 529 (MH^+).

EJEMPLO 28

3-[(1*R*)-1-aminoetil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol



A una solución de diisopropilamina (6,5 mL, 46,3 mmol) en THF (200 mL) a -78°C se agregó butillitio (17 mL de una solución 2,5 M en hexanos, 42,5 mmol) durante 5 minutos. La solución de diisopropilamida de litio se agitó durante 15 minutos a -78°C. Una solución de (*S*)-4-bencil-3-propionil-2-oxazolidinona (9,0 g, 38,6 mmol) en THF (100 mL) se agregó la diisopropilamida de litio con un embuodo de agregado durante 26 minutos. La temperatura de la reacción se mantuvo debajo de -70 °C durante el agrgado. Después del agregado, la mezcla de la reacción se agitó durante otros 30 minutos a -78°C. Luego se

agregó fenilmetil 3-oxoazetidina-1-carboxilato (9,5 g, 46,3 mmol) con un embudo de agregado durante 25 minutos como una solución en THF (100 mL). Nuevamente, la mezcla de la reacción se mantuvo por debajo de -70°C durante el agregado del reactivo. Después de agitar durante 1 hora adicional a -78°C, la mezcla de la reacción se enfrió con solución de cloruro de amonio saturado y luego se dejó calentar a temperatura ambiente. Se agregó agua para disolver todo el cloruro de amonio precipitado, y se agregó acetato de etilo. Las capas se repartieron, y la fase acuosa se extrajo dos veces con acetato de etilo. Los extractos orgánicos combinados se lavaron con 55 bicarbonato de sodio acuoso, se secaron sobre sulfato de sodio, se filtraron y se concentraron. El residuo se purificó mediante cromatografía de columna (50% acetato de etilo: 50% hexanos) y dio fenilmetil 3-hidroxi-3-{(1*R*)-1-metil-2-oxo-2-[(4*S*)-2-oxo-4-(fenilmetil)-1,3-oxazolidin-3-il]etil}azetidina-1-carboxilato como un sólido cristalino blanco (6,03 g, 13,8 mmol, rendimiento del 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7,37 (m, 8H), 7,20 (d, 2H), 5,12 (s, 2H), 4,66 (m, 1H), 4,27-4,20 (m, 2H), 4,10 (q, 1H), 4,03-3,93 (m, 3H), 3,28 (dd, 1H), 2,77 (dd, 1H), 1,29 (d, 3H).

Una solución de hidróxido de litio monohidratado (1,16 g, 27,6 mmol) en 30% peróxido de hidrógeno (13,2 mL, 138 mmol) se preparó y posteriormente se agregó lentamente a fenilmetil 3-hidroxi-3-{(1*R*)-1-metil-2-oxo-2-[(4*S*)-2-oxo-4-(fenilmetil)-

1,3-oxazolidin-3-il]etil}azetidina-1-carboxilato (6,03 g, 13,8 mmol) en THF (80 mL) y agua (20 mL) a 0°C. Después de que la mezcla se agitó durante 1 h a temperatura ambiente, el peróxido de hidrógeno se enfrió cuidadosamente con 1 M sulfito de sodio (150 mL, 150 mmol). El THF se removió en vacío y la mezcla luego se acidificó a pH 2 con ácido clorhídrico concentado. La mezcla acuosa se extrajo dos veces con acetato de etilo. Los extractos orgánicos combinados se secaron sobre sulfto de magnesio, se filtraron, y se concentraron en vacío. El residuo resultante se purificó mediante cromatografía de columna (gradiente, 5% metanol: 95% diclorometano a 10% metanol: 90% diclorometano) y dio ácido (2*R*)-2-(3-hidroxi-1-{[(fenilmetil)oxi]carbonil}azetidin-3-il)propanoico como un aceite incoloro (2,77 g, 9,9 mmol, rendimiento del 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7,37-7,31 (m, 5H), 5,10 (s, 2H), 3,99 (s, 2H), 3,93 (s, 2H), 2,88 (q, 1H), 1,28 (d, 3H); MS (EI) para $C_{14}H_{17}NO_5$: 280 (MH^+).

A una solución de ácido (2*R*)-2-(3-hidroxi-1-{[(fenilmetil)oxy]carbonil}azetidin-3-il)propanoico (2,77 g, 9,9 mmol) en tolueno (100 mL) se agregó trietilamina (1,52 mL, 10,9 mmol) y luego difenil fosforil azida (2,24 mL, 10,4 mmol). La mezcla se calentó a 80°C durante 2 h y luego se enfrió a temperatura ambiente. Los materiales volátiles se removieron en vacío y el residuo se purificó mediante cromatografía de columna (gradiente: 50% hexanos: 50% acetato

de etilo hasta 100% acetato de etilo). El producto deseado, éster de fenilmetilo del ácido (8*R*)-8-metil-6-oxo-5-oxa-2,7-diazaespiro[3.4]octano-2-carboxílico se aisló como un jarabe incoloro viscoso (1,84 g, 6,6 mmol, rendimiento del 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7,39-7,32 (m, 5H), 5,66 (br s, 1H), 5,12 (s, 2H), 4,34 (dd, 1H), 4,30 (dd, 1H), 4,17 (dd, 1H), 4,05 (dd, 1H), 3,98 (q, 1H), 1,34 (d, 3H).

A una solución de éster de fenilmetilo del ácido (8*R*)-8-metil-6-oxo-5-oxa-2,7-diazaespiro[3.4]octano-2-carboxílico (1,84 g, 6,6 mmol) en metanol (66 mL) se agregó 10% paladio sobre carbono (50% en masa, 500 mg). La suspensión resultante se agitó bajo 1 atmósfera de hidrógeno durante 1 hora. El catalizador luego se removió mediante filtración a través de celita. El filtrado se concentró en vacío y dio (8*R*)-8-metil-5-oxa-2,7-diazaespiro[3.4]octan-6-ona como un sólido blanco (0,99 g, rendimiento cuantitativo). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5,23 (br s, 1H), 4,07 (d, 1H), 4,02 (d, 1H), 3,92 (d, 1H), 3,79 (d, 1H), 3,58 (d, 1H), 1,38 (d, 3H); MS (EI) para $C_6H_{10}N_2O_2$: 143 (MH^+).

Una solución de (8*R*)-8-metil-5-oxa-2,7-diazarspiro[3.4]octan-6-ona (937 mg, 6,6 mmol), ácido acético (0,756 mL, 13,2 mmol), y benzaldehído (1,0 mL, 9,9 mmol) en metanol (65 mL) se trató con cianoborohidruro de sodio (829 mg, 13,2 mmol) a temperatura ambiente durante 30 minutos. La mezcla luego se

enfrió a 0°C y se agregó 3 N ácido clorhídrico (100 mL). El metanol luego se removió en vacío. La solución acuos resultante se lavó con acetato de etilo. El lavado con acetato de etilo se extrajo nuevamente con 1N ácido clorhídrico y las fases ácidas se combinaron y se basificaron con carbonato de potasio. La fase orgánica se decartó. La mezcla acuosa luego se extrajo tres veces con acetato de etilo. Los extractos orgánicos combinados se secaron sobre sulfato de magnesio, se filtraron y se concentraron en vacío. La (8*R*)-8-metil-2-(fenilmetil)-5-oxa-2,7-diazaespiro[3.4]octan-6-ona deseada se obtuvo on una pureza del 93% como un líquido incoloro (1,33 g, 5,73 mmol, rendimiento del 87%). MS (EI) para $C_{13}H_{16}N_2O_2$: 233 MH^+).

A una solución de (8*R*)-8-metil-2-(fenilmetil)-5-oxa-2,7-diazaespiro[3.4]octan-6-ona (1,33 g, 5,7 mmol) en dioxano (40 mL) y agua (20 mL) se agregó hidróxido de bario octahidratado (9,0 g, 28,5 mmol), y la mezcla se calentó a reflujo durante 2 horas. Después de enfriar a temperatura ambiente, la mezcla se acidificó con 3 N ácido clorhídrico (10 mL) y se agregó diclorometano (50 mL). La mezxcla bifásica se trató con carbonato de potasio (1,6 g, 11,4 mmol) y di-*terc*-butil dicarbonato (2,11 g, 9,7 mmol). Después de agitar vigorosamente a temperatura ambiente durante 17 horas, se remvieron los sólidos mediante filtración y las capas se reapartieron. La fase acuosa se extrajo con diclorometano y

los extractos orgánicos se combinaron y se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se recogió en metanol (60 mL) y se trató con carbonato de potasio (3,0 g, 22 mmol) agregado en dos porciones durante 4 horas a reflujo. Después de enfriar, el metanol se removió en vacío y los sólidos residuales se cargaron directamente en una columna de sílice. Después de la purificación (5% metanol: 95% diclorometano), se obtuvo 1,1-dimetiletil {(1*R*)-1-[3-hidroxi-1-(fenilmetil)azetidin-3-il]etil}carbamato como un jarabe incoloro (1,07 g, 3,5 mmol, rendimiento del 62%). MS (EI) para $C_{17}H_{26}N_2O_3$: 307 (MH^+).

A una solución de 1,1-dimetiletil {(1*R*)-1-[3-hidroxi-1-(fenilmetil)azetidin-3-il]etil}carbamato (1,07 g, 3,5 mmol) en metanol se agregó 10% paladio sobre carbono húmedo (50% en masa, 250 mg). La suspensión resultante se sometió a 1 atmósfera de hidrógeno durante 7 horas, y se agregaron 250 mg adicionales de catalizador durante la reacción. El catalizador luego se removió mediante filtración a través de celita. El filtrado luego se concentró en vacío y dio 1,1-dimetiletil [(1*R*)-1-(3-hidroxiazetidin-3-il)etil]carbamato como un jarabe incoloro (800 mg, rendimiento cuantitativo). MS (EI) para $C_{10}H_{20}N_2O_3$: 161 (M - *tert*-butyl + H).

A una solución de 1,1-dimetiletil [(1*R*)-1-(3-hidroxiazetidin-3-il)etil]carbamato (200 mg, 0,92 mmol) en diclorometano (5 mL) se agregó diisopropiletilamina (228 µL, 1,38 mmol) y

fluoruro de 3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]benzoilo (preparado de acuerdo con los procedimientos descritos en la Referencia 1) (363 mg, 0,92 mmol). La mezcla se agitó a temperatura ambiente durante 16 horas, después de cuyo tiempo los materiales volátiles se removieron en vacío. El residuo se purificó mediante cromatografía de columna (50% hexanos : 50% acetato de etilo) y proporcionó 1,1-dimetiletil {(1*R*)-1-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]etil}carbamato como una película incoloroa (333 mg, 0,56 mmol, rendimiento del 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,47 (br s, 1H), 7,40 (dd, 1H), 7,32 (d, 1H), 7,12 (m, 1H), 6,81 (m, 1H), 6,61 (m, 1H), 4,74 (br d, 1H), 4,22 (d, 1H), 4,15-4,07 (m, 2H), 3,96 (br s, 1H), 3,77 (m, 1H), 1,43 (s, 9H), 1,18 (d, 3H); MS (EI) para $C_{23}H_{25}F_3IN_3O_4$: 536 (M - *terc*-butilo + H).

Una solución de 1,1-dimetiletil {(1*R*)-1-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]etil}carbamato (333 mg, 0,56 mmol) en metanol (10 mL) se trató con ácido clorhídrico (4 N en dioxano, 1,4 mL, 5,6 mmol) a 60°C durante 30 minutos. Después de enfriar, los materiales volátiles se removieron en vacío y se proveyó clorhidrato de 3-[(1*R*)-1-aminoetil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol como un sólido blanco (285 mg, 0,54 mmol, rendimiento del 97%). ^{1}H NMR (400

MHz, DMSO-d_6) δ 8,56 (s, 1H), 7,83 (br s, 3H), 7,59 (dd, 1H), 7,39 (d, 1H), 7,34 (m, 1H), 7,21 (q, 1H), 6,69 (m, 1H), 6,65 (s, 1H), 4,25 (dd, 1H), 4,10 (dd, 1H), 3,98 (dd, 1H), 3,80 (m, 1H), 3,48 (m, 1H), 1,11 (dd, 3H); MS (EI) para $C_{18}H_{17}F_3IN_3O_2$: 492 (MH^+)

Para establecer el exceso enantiomérico (ee) de este material, clorhidrato de 3-[(1*R*)-1-aminoetil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol (21 mg, 0,040 mmol) se disolvió en diclorometano (400 µL) y se trató con diisopropiletilamina (20 µL, 0,12 mmol) y cloruro de (*R*)-(-)-α-metoxi-α-(trifluorometil)fenilacetilo a temperatura ambiente durante 15 minutos. Se removió una alícuota y se analizó mediante HPLC quiral. El exceso enantiomérico de (2*S*)-N-{(1*R*)-1-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]etil}-3,3,3-trifluoro-2-(metiloxi)-2-fenilpropanamida se halló que era 91%, y por extrapolación el ee de 3-[(1*R*)-1-aminoetil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol también se asignó que era 91%.

Ejemplo 28a. Usando la secuencia descrita anteriormente, partiendo desde (*R*)-4-bencil-3-propionil-2-oxazolidinona, 3-[(1*S*)-1-aminoetil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol se preparó usando

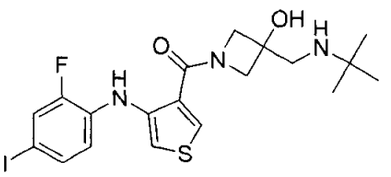
procedimientos similares excepto que el fenilmetil 3-hidroxi-3-{(1*S*)-1-metil-2-oxo-2-[(4*R*)-2-oxo-4-(fenilmetil)-1,3-oxazolidin-3-il]etil}azetidina-1-carboxilato requirió recristalizaciones adicionales desde isopropanol. Usando el mismo método descrito en el Ejemplo 28, 3-[(1*S*)-1-aminoetil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol se determinó que tenía un ee del 98,4%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8,56 (s, 1H), 7,84 (br s, 3H), 7,59 (dd, 1H), 7,39 (d, 1H), 7,34 (m, 1H), 7,21 (q, 1H), 6,69 (m, 1H), 6,65 (s, 1H), 4,25 (dd, 1H), 4,10 (dd, 1H), 3,98 (dd, 1H), 3,80 (m, 1H), 3,48 (m, 1H), 1,11 (dd, 3H); MS (EI) para $C_{18}H_{17}F_3IN_3O_2$: 492 (MH^+).

Ejemplo 28b. A 3-[(1*S*)-1-aminoetil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol (87,4 mg, 0,18 mmol), preparado usando procedimientos similares a los descritos en el Ejemplo 28, se agregó formaldehído (37% acuoso, 14 mg, 0,18 mmol) en metanol (2 mL) y borohidruro de sodio (7 mg, 0,18 mmol). La mezcla se agitó durante 3 horas a temperatura ambiente, después de cuyo tiempo se agregó borohidruro de sodio (16 mg, 0,42 mmol). Al agitar 1,25 hora adicional, se agregó más formaldehído (37% acuoso, 1 gota) y la mezcla se agitó a temperatura ambiente durante 30 minutos. Después de enfirar con 1N HCl, la mezcla de la reacción se purificó directamente mediante HPLC preparativa. El material puro se convirtió en su sal de clorhidrato para proporcionar

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(1*S*)-1-(metilamino)etil]azetidin-3-ol como un sólido blanco (21,7 mg, 0,040 mmol, rendimiento del 22%). ^{1}H NMR (400 MHz, CD_3OD) δ 7,47 (dd, 1H), 7,36 (d, 1H), 7,31 (m, 1H), 7,06 (q, 1H), 6,62 (dt, 1H), 4,36 (dd, 1H), 4,21-3,91 (m, 3H), 3,44 (q, 1H), 2,66 (s, 3H), 1,29 (br m, 3H); MS (EI) para $C_{19}H_{19}F_3IN_3O_2$: 506 (MH^+).

EJEMPLO 29

3-{[(1,1-Dimetiletil)amino]metil}-1-({4-[(2-fluoro-4-yodofenil)amino]-3-tienil}carbonil)azetidin-3-ol



A una mezcla de metil 4-oxotetrahidrotiofeno-3-carboxilato (1,75 g, 11 mmol) (comercialmente disponible o preparado usando procedimientos similares a los descritos en Rossy *et. al. J. Org. Chem.* **1980**, *45(4)*, 617-2) en 15 mL de etanol se agregó 2-fluoro-4-yodoanilina (2,6 g, 11 mmol) y luego se agregaron varias gotas de ácido acético. La mezcla se refluyó durante 3 horas. La mezcla se enfrió a temperatura ambiente y el producto precipitó. Este producto se filtró, se lavó con acetato de etilo, éter, se secó en vacío y dio el metil 4-[(2-fluoro-4-yodofenil)amino]-2,5-dihidrotiofeno-3-carboxilato

(d_6-DMSO): 13,20(s, 1H), 9,13 (s, 1H), 8,35 (d, 1H), 7,62 (dd, 1H), 7,48-7.38 (m, 2H), 7,11 (s, 1H); MS(EI) para $C_{11}H_7FINO_2S$: 362 (MH^-).

Ácido 4-[(2-fluoro-4-yodofenil)amino]tiofeno-3-carboxílico (200 mg, 0,551 mmol), 4-(dimetilamino)piridina (202 mg, 1,65 mmol) y clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (127 mg, 0,662 mmol) se disolvieron en DMF (3 mL). La mezcla se agitó a temperatura ambiente durante 5 minutos y luego se agregó clorhidrato de 3-(hidroximetil)azetidin-3-ol (72 mg, 0,516 mmol) y la mezcla se agitó durante 15 horas. La mezcla se repartió entre acetato de etilo y 20% ácido cítrico. La parte acuosa se extrajo con acetato de etilo. La parte orgánica combinada selavó con 5% cloruro de liti, bicarbonato de sodio saturado y salmuera, luego se secó sobre sulfato de sodio anhidro, se filtró y se concentró en vacío. El residuo se cristalizó desde diclorometano y dio 1-({4-[(2-fluoro-4-yodofenil)amino]-3-tienil}carbonil)-3-(hidroximetil)azetidin-3-ol (247 mg, 0,551 mmol, rendimiento cuantitativo) como cristales blancuzcos: MS (EI) para $C_{15}H_{14}FIN_2O_3S$: 449 (MH^+).

1-({4-[(2-Fluoro-4-yodofenil)amino]-3-tienil}carbonil)-3-(hidroximetil)azetidin-3-ol (247 mg, 0,551 mmol), se suspendió en diclorometano (10 mL) y se trató con 4-(dimetilamino)piridina (80 mg, 0,661 mmol), y cloruro de 2,4,6-triisopropilbencensulfonilo (183 mg, 0,604 mmol) a

temperatura ambiente durante 15 horas. La mezcla se adsorbió sobre gel de sílice y se purificó mediante cromatografía de columna (gel de sílice, 30% acetato de etilo en hexanos) y dio [1-({4-[(2-fluoro-4-yodofenil)amino]-3-tienil}carbonil)-3-hidroxiazetidin-3-il]metil 2,4,6-tris(1-metiletil)bencensulfonato (101 mg, 0,141 mmol, rendimiento del 26%): MS (EI) para $C_{30}H_{36}FIN_2O_5S_2$: 715 (MH^+).

[1-({4-[(2-Fluoro-4-yodofenil)amino]-3-tienil}carbonil)-3-hidroxiazetidin-3-il]metil 2,4,6-tris(1-metiletil)bencensulfonato (101 mg, 0,141 mmol) se disolvió en tetrahidrofurano (2 mL) y se trató con hidruro de sodio (60% en peso de dispersión en aceite; 17 mg, 0,425 mmol) a temperatura ambiente durante 20 minutos. Se agregaron tetrahidrofurano (2 mL) y *terc*-butilamina (0,1 mL) y la se agitó a temperatura ambiente durante 16 horas. Lamezcla se concentró en vacío y se repartió entre acetato de etilo y agua. La parte orgánica se lavó con salmuera, se secó sobre sulfato de sodio anhidro, se filtró y se concentró en vacío. El residuo se purificó mediante HPLC de fase invertida y las fracciones puras se combinaron, se neutralizaron con solución de bicarbonato de sodio saturado y el solvente orgánico se removió en vacío. El residuo acuoso remanente se extrajo dos veces con acetato de etilo. La parte orgánica combinada se lavó con salmuera, se secó sobre sulfato de sodio anhidro, se filtró y se concentró en vacío y dio 3-{[(1,1-

dimetiletil)amino]metil}-1-({4-[(2-fluoro-4-yodofenil)amino]-3-tienil}carbonil)azetidin-3-ol (8 mg, 0,016 mmol, rendimiento del 11%): ^{1}H NMR (400 MHz, d_6-DMSO): 9,64 (br, 1H), 8,08 (d, 1H), 7,59 (dd, 1H), 7,44 (dd, 1H), 7,36 (t, 1H), 7,12 (d, 1H), 4,39 (d, 1H), 4,22 (d, 1H), 4,03 (d, 1H), 3,80 (d, 1H), 2,68 (br, 2H) 1,04 (s, 9H); MS (EI) para $C_{19}H_{23}FIN_3O_2S$: 504 (MH^+).

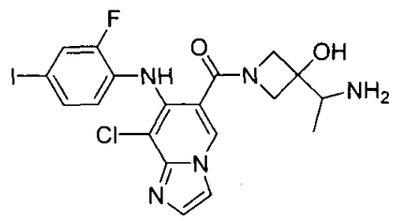
Usando las mismas técnicas sintéticas o análogas y sustituyendo según fue necesario con reactivos alternativos, se prepararon los siguientes compuestos de la invención.

EJEMPLO 29(a). 3-[(dimetilamino)metil]-1-({4-[(2-fluoro-4-yodofenil)amino]-3-tienil}carbonil)azetidin-3-ol: ^{1}H NMR (400 MHz, CD_3OD): 7,91 (d, 1H), 7,46-7,41 (m, 2H), 7,33 (t, 1H), 7,00 (d, 1H), 4,66 (s, 1H), 4,49 (s, 1H), 4,30 (s, 1H), 4,15 (s, 1H), 3,54 (s, 1H), 3,17-3,13 (m, 3H), 2,90 (s, 2H), 1,87-1,83 (m, 3H); MS(EI) para $C_{17}H_{19}FIN_3O_2S$: 476 (MH^+).

EJEMPLO 29(b). 1-({4-[(2-fluoro-4-yodofenil)amino]-3-tienil}carbonil)azetidin-3-amina: ^{1}H NMR (400 MHz, CD_3OD): 7,90 (d, 1H), 7,46-7,41 (m, 2H), 7,31 (t, 1H), 6,99 (d, 1H), 4,47 (br.s, 2H), 4,22-4,16 (m, 2H); MS(EI) para $C_{14}H_{13}FIN_3OS$: 418 (MH^+).

EJEMPLO 30

3-(1-aminoetil)-1-({8-cloro-7-[(2-fluoro-4-yodofenil)amino]imidazo[1,2-a]piridin-6-il}carbonil)azetidin-3-ol



A una suspensión de hidruro de sodio (72 mg, 1,75 mmol, 60% en peso) en tetrahidrofurano (1 mL) enfriada a 0°C se agregó nitroetano (125 µL, 1,75 mmol). La suspensión se dejó calentar a temperatura ambiente y se agitó durante 15 minutos, luego se enfrió nuevamente a 0°C. A la suspensión se agregó gota a gota una solución de 1,1-dimetiletil 3-oxoazetidina-1-carboxilato (300 mg, 1,75 mmol, en 2 mL de tetrahidrofurano), preparado usando procedimientos similares a aquellos descritos en la Referencia 3. La suspensión se agitó a temperatura ambiente durante 1 hora. La mezcla de la reacción se enfrió agregando 20% ácido cítrico acuoso y luego se repartió con acetato de etilo. La parte acuosa se extrajo dos veces usando acetato de etilo y la parte orgánica combinada se lavó con bicarbonato de sodio saturado, salmuera y se secó sobre sulfato de sodio, se filtró y se concentró en vacío y dio un aceite incoloro que se purificó mediante cromatografía de columna. Eluyendo con 30% acetato de etilo en hexanos, el producto aislado se concentró

en vacío y se obtuvieron 250 mg, 1,02 mmol (58%) de 1,1-dimetiletil 3-hidroxi-3-(1-nitroetil)azetidina-1-carboxilato como un aceite incoloro. ^{1}H NMR (400 MHz, DMSO): 6,46 (s, 1H), 5,01 (q, 1H), 4,24-3,97 (m, 2H), 3,77-3,60 (m, 2H), 1,41 (d, 3H), 1,39 (s, 9H).

1,1-Dimetiletil 3-hidroxi-3-(1-nitroetil)azetidina-1-carboxilato se disolvió en metanol (5 mL) y se trató con 4 N HCl en dioxano. La solución se calentó brevemente a reflujo y luego se concentró en vacío y dio 178 mg, 0,98 mmol (96%) de clorhidrato de 3-(1-nitroetil)azetidin-3-ol como un sólido blanco. ^{1}H NMR (400 MHz, DMSO): 9,30 (br s, 1H), 8,96 (br s, 1H), 5,12 (q, 1H), 4,44-4,38 (m, 1H), 4,22-4,17 (m, 1H), 3,94-3,87 (m, 1H), 3,85-3,77 (m, 1H), 1,44 (d, 3H).

Una solución de ácido 8-cloro-7-[(2-fluoro-4-yodofenil)amino]imidazo[1,2-*a*]piridina-6-carboxílico (150 mg, 0,35 mmol) (preparado usando procedimientos similares a aquellos descritos en US 2006030610 y US 2005054701), *N,N*-diisopropiletilamina (300 µL, 1,74 mmol), PyBOP (180 mg, 0,35 mmol) y clorhidrato de 3-(1-nitroetil)azetidin-3-ol (76 mg, 0,42 mmol) en dimetilformamida (3 mL) se agitó a temperatura ambiente durante 15 hours. La mezcla de la reacción luego se repartió entre 5% cloruro de litio y acetato de etilo. La parte acuosa se extrajo dos veces usando acetato de etilo. La parte orgánica se lavó con 20% ácido cítrico acuoso, se secó sobre sulfato de sodio, se filtró y se concentró en vacío y se

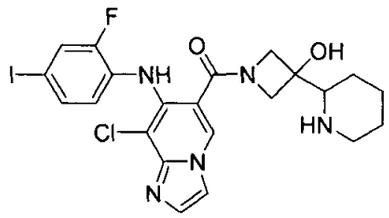
obtuvo un residuo marrón que se purificó mediante cromatografía de columna. Eluyendo con 5% metanol en diclorometano, el producto aislado se concentró en vacío y se obtuvieron 195 mg, 0,35 mmol (100%) de 1-({8-cloro-7-[(2-fluoro-4-yodofenil)amino]imidazo[1,2-*a*]piridin-6-il}carbonil)-3-(1-nitroetil)azetidin-3-ol como una espuma amarilla. ^{1}H NMR (400 MHz, $CDCl_3$): 8,28 (s, 1H), 7,68 (s, 1H), 7,59 (s, 1H), 7,43 (d, 1H), 7,31 (d, 1H), 7,23 (br s, 1H), 6,55-6,51 (m, 1H), 6,02 (br s, 1H), 4,79 (q, 1H), 4,45-3,96 (4H), 1,56 (d, 3H). MS (EI) para $C_{20}H_{19}ClFIN_6O_4$: 560 (MH^+).

A una solución de 1-({8-cloro-7-[(2-fluoro-4-yodofenil)amino]imidazo[1,2-*a*]piridin-6-il}carbonil)-3-(1-nitroetil)azetidin-3-ol (195 mg 0,35 mmol) en tetrahidrofurano/agua (5 mL, 4:1) se agregó polvo de hierro (193 mg, 3,5 mmol) y formato de amonio (438 mg, 7,0 mmol). La mezcla se agitó a 80°C durante 1 hora, luego se enfrió a temperatura ambiente y se filtró a través de un tampón de celita. La celita se lavó tres veces con etanol en ebullición (20 mL). El filtrado se concentró en vacío y el residuo se diluyó con acetato de etilo. El precipitado que se formó se filtró a través de un tampón de celita y el filtrado se repartió con agua. La parte acuosa se extrajo dos veces con acetato de etilo. La parte orgánica combinada se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y se concentró en vacío y se obtuvo un residuo amarillo que se

purificó mediante HPLC de fase invertida preparativa. El producto aislado se concentró en vacío y se obtuvieron 35 mg, 0,05 mmol (15%) de sal de acetato de 3-(1-aminoetil)-1-({8-cloro-7-[(2-fluoro-4-yodofenil)amino]imidazo[1,2-a]piridin-6-il}carbonil)azetidin-3-ol como un sólido blanco. ^{1}H NMR (400 MHz, DMSO): 8,79 (s, 1H), 8,00 (s, 1H), 7,61 (s, 1H), 7,54 (d, 1H), 7,32 (d, 1H), 6,54-6,48 (m, 1H), 4,24-4,13 (m, 1H), 3,98-3,84 (m, 2H), 3,61-3,56 (m, 1H), 2,83 (q, 1H), 0,92-0,88 (m, 3H); MS (EI) para $C_{19}H_{18}ClFIN_5O_2$: 530 (MH^+).

EJEMPLO 31

1-({8-cloro-7-[(2-fluoro-4-yodofenil)amino]imidazo[1,2-a]piridin-6-il}carbonil)-3-piperidin-2-ilazetidin-3-ol



A una solución de 1,1-dimetiletil 2-(3-hidroxi-1-{[(fenilmetil)oxi]carbonil}azetidin-3-il)piperidina-1-carboxilato (595 mg, 1,52 mmol), preparado usando procedimientos similares a aquellos descritos en la Referencia 5, en metanol (5 mL) se agregó paladio catalítico sobre carbono (5% en peso). La mezcla heterogénea se agitó bajo una atmósfera de gas hidrógeno durante 15 minutos a presión ambiente y luego se filtró. El filtrado se concentró en vacío

y se obtuvieron 385 mg, 1,50 mmol (98%) de 1,1-dimetiletil 2-(3-hidroxiazetidin-3-il)piperidine-1-carboxilato como una película incolora sin nueva purificación.

Una solución de ácido 8-cloro-7-[(2-fluoro-4-yodofenil)amino]imidazo[1,2-*a*]piridina-6-carboxílico (78 mg, 0,18 mmol) (preparado usando procedimientos similares a aquellos descritos en US 2006030610 y US 2005054701), 1,1-dimetiletil 2-(3-hidroxiazetidin-3-il)piperidina-1-carboxilato (46,7 mg, 0,18 mmol), 4-(dimetilamino)piridina (66 mg, 0,55 mmol), y finalmente clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (42 mg, 0,21 mmol) en dimetilformamida (2 mL) se agitó a temperatura ambiente durante 15 horas. La mezcla de la reacción se repartió entre 5% cloruro de litio acuoso y acetato de etilo y la parte acuosa se extrajo dos veces usando acetato de etilo. La parte orgánica combinada se lavó con 1N HCl, salmuera, se secó sobre sulfato de sodio, se filtró y se concentró en vacío y se obtuvo un residuo marrón que se purificó mediante cromatografía de columna. Eluyendo con acetato de etilo, el producto aislado se concentró en vacío y se obtuvieron 101 mg, 0,15 mmol (83%) de 1,1-dimetiletil 2-[1-({8-cloro-7-[(2-fluoro-4-yodofenil)amino]imidazo[1,2-a]piridin-6-il}carbonil)-3-hidroxiazetidin-3-il]piperidina-1-carboxilato como un sólido blanco. El sólido se disolvió inmediatamente en metanol (5 mL) y se agregó 4 N HCl en dioxano. La solución se calentó brevemente a reflujo y luego

se concentró en vacío. El residuo resultante se purificó mediante HPLC de fase invertida preparativa. El producto aislado se concentró en vacío y se obtuvieron 36 mg, 0,06 mmol (40%) de acetato de 1-({8-cloro-7-[(2-fluoro-4-yodofenil)amino]imidazo[1,2-a]piridin-6-il}carbonil)-3-piperidin-2-ilazetidin-3-ol como un sólido blanco. ^{1}H NMR (400 MHz, DMSO): 8,78 (s, 1H), 8,19 (s, 0,5H), 8,15 (s, 0,5H), 8,00 (s, 1H), 7,62 (s, 1H), 7,55 (d, 1H), 7,31 (d, 1H), 6,54-6,49 (m, 1H), 4,24-4,12 (m, 1H), 3,97-3,86 (m, 2H), 3,63-3,56 (m, 1H), 2,98-2,90 (m, 1H), 2,50-2,40 (m, 1H), 1,72-1,61 (m, 1H), 1,56-1,43 (m, 2H), 1,32-1,14 (m, 2H), 1,07-0,94 (m, 1H); MS (EI) para $C_{22}H_{22}ClFIN_5O_2$: 570 (MH^+).

Usando las mismas técnicas sintéticas o análogas y/o sustituyendo con reactivos alternativos, se prepararon los siguientes compuestos de la invención.

EJEMPLO 31(a). Sal de acetato de 1-({4-fluoro-5-[(2-fluoro-4-yodofenil)amino]-1-metil-1*H*-bencimidazol-6-il}carbonil)-3-piperidin-2-ilazetidin-3-ol: ^{1}H NMR (400 MHz, DMSO): 8,35 (s, 1H), 7,84-7,77 (m, 1H), 7,54-7,49 (m, 2H), 7,25 (d, 1H), 6,31-6,25 (m, 1H), 4,04-3,92 (m, 2H), 3,90 (s, 3H), 3,86-3,78 (m, 1H), 3,70-3,62 (m, 1H), 2,94-2,85 (m, 1H), 2,45-2,32 (m, 2H), 1,66-1,36 (m, 3H), 1,26-1,08 (m, 2H), 1,01-0,80 (m, 1H); MS (EI) para $C_{23}H_{24}F_2IN_5O_2$: 568 (MH^+).

EJEMPLO 31(a). Sal de acetato de 1-({7-[(4-bromo-2-clorofenil)amino]-8-cloroimidazo[1,2-a]piridin-6-il}carbonil)-

sulfato de sodio anhidro, se filtró y se concentró en vacío. La cromatografía de columna (gel de sílice, 20% éter en hexanos) dio fenilmetil 3-[2-(1,3-dioxolan-2-il)etilideno]azetidina-1-carboxilato (220 mg, 0,761 mmol, rendimiento del 15%): ^{1}H NMR (400 MHz, $CDCl_3$): 7,39-7,28 (m, 5H), 5,43-5,35 (m, 1H), 5,11 (s, 2H), 4,89 (t, 1H), 4,56 (br d, 4H), 4,00-3,92 (m, 2H), 3,91-3,83 (m, 2H), 2,27 (br t, 2H). Feniletil 3-[2-(1,3-dioxolan-2-il)etilideno]azetidina-1-carboxilato (220 mg, 0,761 mmol), y N-óxido de 4-metilmorfolina (287 mg, 2,45 mmol) se disolvió en acetona / agua (4:1; 10 mL) y se agregó tetróxido de osmio (4% en peso en agua; 0,05 mL). La solución se agitó a temperatura ambiente durante 20 horas, luego se enfrió con bisulfito de sodio saturado (2 mL) y se concentró en vacío. El residuo se repartió entre acetato de etilo y salmuera. La parte acuosa se extrajo con acetato de etilo. La parte orgánica combinada se lavó con salmuera, se secó sobre sulfato de sodio anhidro, se filtró y se concentró en vacío. La cromatografía de columna (gel de sílice, acetato de etilo) dio fenilmetil 3-[2-(1,3-dioxolan-2-il)-1-hidroxietil]-3-hidroxiazetidina-1-carboxilato (244 mg, 0,755 mmol, rendimiento del 99%): ^{1}H NMR (400 MHz, $CDCl_3$): 7,38-7,28 (m, 5H), 5,11-5,07 (m, 3H), 4,14-4,01 (m, 4H), 3,96-3,86 (m, 5H), 3,47 (d, 1H), 2,97-2,94 (m, 1H), 1,98-1,84 (m, 2H).

Fenilmetil 3-[2-(1,3-dioxolan-2-il)-1-hidroxietil]-3-hidroxiazetidina-1-carboxilato (235 mg, 0,728 mmol) se disolvió en metanol (5 mL) y se trató con 5% en peso de paladio sobre carbono (50 mg) bajo hidrógeno a temperatura ambiente durante 1,5 hora. La mezcla se filtró y el filtrado se concentró en vacío y se obtuvo 3-[2-(1,3-dioxolan-2-il)-1-hidroxietil]azetidin-3-ol (0,729 mmol): MS (EI) para $C_8H_{15}NO_4$: 190 (MH^+).

Ácido 3,4-Difluoro-2-[(2-fluoro-4-yodofenil)amino]benzoico (287 mg, 0,730 mmol), preparado usando procedimientos similares a aquellos descritos en US 7.019.033, 4-(dimetilamino)piridina (178 mg, 1,46 mmol) y clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (168 mg, 0,88 mmol) se disolvieron en DMF (3 mL). La mezcla se agitó a temperatura ambiente durante 10 minutos y luego se agregó 3-[2-(1,3-dioxolan-2-il)-1-hidroxietil]azetidin-3-ol (0,729 mmol) en DMF (2 mL) y la mezcla se agitó durante 15 horas. La mezcla se repartió entre acetato de etilo y 5% cloruro de litio. La parte orgánica se lavó con lavó con 20% ácido cítrico, bicarbonato de sodio saturado y salmuera, luego se secó sobre sulfato de sodio anhidro, se filtró y se concentró en vacío. La cromatografía de columna (gel de sílice, gradiente 90% de acetato de etilo en hexanos al 100% de acetato de etil) dio 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[2-(1,3-dioxolan-2-il)-1-

hidroxietil]azetidin-3-ol (148 mg, 0,262 mmol, rendimiento del 36%): MS (EI) para $C_{21}H_{20}F_3IN_2O_5$: 565 (MH^+).

1-({3,4-Difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[2-(1,3-dioxolan-2-il)-1-hidroxietil]azetidin-3-ol (148 mg, 0,262 mmol), se disolvió en diclorometano (10 mL) y se trató con 4-(dimetilamino)piridina (38 mg, 0,31 mmol), trietilamina (0,036 mL, 0,262 mmol) y cloruro de 2,4,6-triisopropilbencensulfonilo (303 mg, 1,0 mmol) a 35°C durnte 15 horas. Se agregó cloruro de 2,4,6-triisopropilbencensulfonilo (100 mg, 0,33 mmol) y la mezcla se agitó a 35°C durante 3,5 hora. La mezcla se adsorbió sobre sílice y se purificó mediante cromatografía de columna (gel de sílice, 40-50% acetato de etilo en hexanos y luego el 100% de acetato de etilo) y dio 1-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]-2-(1,3-dioxolan-2-il)etil 2,4,6-tris(1-metiletil)bencensulfonato (30 mg, 0,0361 mmol, rendimiento del 14%): MS (EI) para $C_{36}H_{42}F_3IN_2O_7S$: 831 (MH^+).

1-[1-({3,4-Difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]-2-(1,3-dioxolan-2-il)etil 2,4,6-tris(1-metiletil)bencensulfonato (50 mg, 0,060 mmol) se disolvió en tetrahidrofurano (1 mL) y se enfrió a 0°C. Se agregó hidruro de sodio (60% en peso de dispersión en aceite; 7 mg, 0,18 mmol) y la mezcla se agitó a 0°C durante 45 minutos. La mezcla se enfrió con solución de

bicarbonato de sodio saturado y se repartió con acetato de etilo. La parte acuosa se extrajo con acetato de etilo. La parte orgánica combinada se lavó con salmuera, se secó sobre sulfito de sodio anhidro, se filtró y se concentró en vacío. La cromatografía de columna (gel de sílice, 50% acetato de etilo en hexanos) dio 6-{[2-(1,3-dioxolan-2-ilmetil)-1-oxa-5-azaespiro[2.3]hex-5-il]carbonil}-2,3-difluoro-*N*-(2-fluoro-4-yodofenil)anilina (31 mg, 0,057 mmol, rendimiento del 94%): MS (EI) para $C_{21}H_{18}F_3IN_2O_4$: 547 (MH^+).

6-{[2-(1,3-Dioxolan-2-ilmetil)-1-oxa-5-azaespiro[2.3]hex-5-il]carbonil}-2,3-difluoro-*N*-(2-fluoro-4-yodofenil)anilina (31 mg, 0,057 mmol) se disolvió en dimetilformamida (0,5 mL) y se agregó azida de sodio (20 mg, 0,308 mmol). La mezcla se repartió entre acetato de etilo y 5% cloruro de litio. La parte acuosa se extrajo con acetato de etilo. La parte orgánica combinada se lavó con agua, salmuera, luego se secó sobre sulfato de sodio anhidro, se filtró y se concentró en vacío. La cromatografía de columna (gel de sílice, 50% acetato de etilo en hexanos) dio 3-[1-azido-2-(1,3-dioxolan-2-il)etil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil) azetidin-3-ol (25 mg, 0,042 mmol, rendimiento del 74%): MS (EI) para $C_{21}H_{19}F_3IN_5O_4$: 590 (MH^+).

3-[1-Azido-2-(1,3-dioxolan-2-il)etil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol (24 mg,

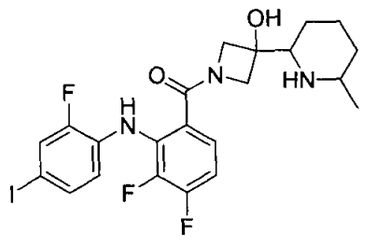
0,041 mmol) se disolvió en tetrahidrofurano (0,5 mL) y se trató con 5% ácido clorhídrico acuoso (0,5 mL) a temperatura ambiente durante 15 h. La mezcla se neutralizó con solución de bicarbonato de sodio saturado y se extrajo dos veces con acetato de etilo. La parte orgánica combinada se lavó con salmuera, se secó sobre sulfato de sodio anhidro, se filtró y se concentró en vacío y dio 3-azido-3-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]propanal (21 mg, 0,0385 mmol) que se suspendió en etanol (2 mL) y se trató con borohidruro de sodio (5 mg, 0,132 mmol) a temperatura ambiente durante 2 horas. La mezcla se enfrió con ácido acético (4 gotas) y se concentró en vacío. El residuo se repartió entre bicarbonato de sodio saturado y acetato de etilo. La parte acuosa se extrajo con acetato de etilo. La parte orgánica combinada se lavó con solución salina, se secó sobre sulfato de sodio anhidro, se filtró y se concentró en vacío. La cromatografía de columna (gel de sílice, 70-80% acetato de etilo en hexanos) dio 3-(1-azido-3-hidroxipropil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol (14 mg, 0,0255 mmol, rendimiento del 62% desde 3-[1-azido-2-(1,3-dioxolan-2-il)etil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol): ^{1}H NMR (400 MHz, $CDCl_3$): 8,33 (br s, 1H), 7,40 (dd, 1H), 7,32 (br d, 1H), 7,13 (br t, 1H), 6,83 (br q, 1H), 6,61 (ddd, 1H), 4,32-3,94 (m,

4H), 3,92-3,84 (m, 1H), 3,82-3,71 (m, 2H), 2,56 (br, 1H), 1,94 (br, 2H), 1,26 (br, 1H); MS (EI) para $C_{19}H_{17}F_3IN_5O_3$: 548 (MH^+).

3-(1-Azido-3-hidroxipropil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol (14 mg, 0,0255 mmol) se disolvió en tetrahidrofurano y agua (1:1, 0,5 mL) y se agregó trifenilfosfina soportada en polímero (3 mmol/g; 20 mg, 0,06 mmol). La mezcla se agitó a 55°C durante 1 hora. Se agregó trifenilfosfina (10 mg, 0,038 mmol) y la mezcla se agitó a 55°C durante 1,5 hora. La mezcla se filtró y el filtrado se purificó mediante HPLC de fase invertida y se obtuvo sal de trifluoroaceato de 3-(1-amino-3-hidroxipropil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol (1,7 mg, 0,003 mmol, rendimiento del 10%): ^1H NMR (400 MHz, CD_3OD): 7,47 (dd, 1H), 7,36 (br d, 1H), 7,33-7,28 (m, 1H), 7,05 (br q, 1H), 6,62 (ddd, 1H), 4,38-4,26 (m, 1H), 4,18-4,00 (m, 2H), 3,98-3,88 (m, 1H), 3,78-3,67 (m, 2H), 3,61-3,56 (m, 1H), 1,87-1,70 (m, 2H); MS (EI) para $C_{19}H_{19}F_3IN_3O_3$: 522 (MH^+).

EJEMPLO 33

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(6-metilpiperidin-2-il)azetidin-3-ol



A una solución de *N,N*-diisopropilamina (1,6 mL, 11,2 mmol) se enfrió a -78°C en THF (15 mL) se agregó 2,5 M solución de n-BuLi en hexano (4,5 mL, 11,2 mmol) gota a gota durante 15 minutos. Luego se agregó gota a gota, 6-metil-1-(fenilmetil)piperidina-2-carbonitrilo (2,4 g, 11,2 mmol) (preparado usando procedimientos similares a los descritos en Bonin *et. al. Tet. Lett.* **1982**, *23(33)*, 3369-72) en THF (10 mL) durante 20 minutos y la mezcla de la reacción se agitó durante otros 30 minutos. Luego se agregó gota a gota una solución de 1,1-dimetiletil 3-oxoazetidina-1-carboxilato (1,3 g, 7,5 mmoL), preparado usando procedimientos similares a aquellos del Ejemplo 3, en THF (10 mL) durante 30 minutos. La mezcla de la reacción se calentó gradualmente a temperatura ambiente y se dejó agitar toda la noche. La mezcla de la reacción se enfrió con 10% ácido cítrico y se extrajo con acetato de etilo (3 x 50 mL). Las capas orgánicas combinadas se lavaron con agua, salmuera, se secaron sobre sulfato de sodio anhidro luego se filtraron y se concentraron en vacío y dieron el producto crudo como un aceite amarillo. La nueva purificación mediante cromatografía rápida (30% acetato de etilo en

hexanos) dio 1,1-dimetiletil 3-[2-ciano-6-metil-1-(fenilmetil)piperidin-2-il]-3-hidroxiazetidina-1-carboxilato como un aceite amarillo pálido (0,2 g, rendimiento del 7%). ^{1}H NMR (400 MHz, $CDCl_3$): 7,17-7,40 (m, 5H), 4,42 (d, 1H), 4,04-4,18 (m, 1H), 3,83-4,00 (m, 1H), 3,70-3,75 (m, 2H), 1,70-1,87 (m, 4H), 1,45 (s, 3H), 1,41 (s, 9H), 1,22-1,26 (m,1H), 1,13-1,18 (m, 2H); MS (EI) para $C_{22}H_{31}N_3O_3$: 386 (MH^+).

A una solución agitada de 1,1-dimetiletil 3-[2-ciano-6-metil-1-(fenilmetil)piperidin-2-il]-3-hidroxiazetidina-1-carboxilato (180 mg, 0,47 mmol) en etanol (1 mL) se agregó ácido acético (53,5 µL, 0,94 mmol) y luego cianoborohidruro de sodio (58,7 mg, 0,94 mmol) y la mezcla de la reacción se agitó a 70°C toda la noche. Después de enfriar a temperatura ambiente, la suspensión se filtró a través de celita y el sólido se lavó con etanol adicional. El filtrado se concentró en vacío y se recogió en acetato de etilo (30 mL). La capa orgánica selavó con 2M solución de hidróxido de sodio. La capa de hidróxido de sodio se separó y se lavó con acetato de etilo (10 mL). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de magnesio anhidro y se concentraron en vacío y dieron 1,1-dimetiletil 3-hidroxi-3-[6-metil-1-fenilmetil)piperidin-2-il]azetidina-1-carboxilato crudo como un aceite amarillo (60 mg, rendimiento del 36%). El producto crudo se usó sin purificación. ^{1}H NMR (400 MHz, $CDCl_3$): 7,22-7,35 (m, 5H), 4,08 (d, 1H), 3,85-3,96 (m, 3H), 3,57 (d, 1H),

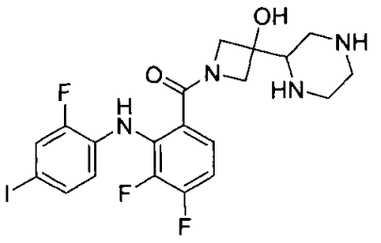
3,33-3,36 (m, 1H), 2,91-3,06 (m, 2H), 1,63-1,70 (m, 4H), 1,44 (s, 9H), 1,23 (d,3H), 1,05 (d, 2H); MS (EI) para $C_{21}H_{32}N_2O_3$: 361 (MH^+).

A una solución de 1,1-dimetiletil 3-hidroxi-3-[6-metil-1-(fenilmetil)piperidin-2-il]azetidina-1-carboxilato (60 mg, 0,16 mmol) en metanol (0,5 mL) se agregó cloruro de hidrógeno (4N en dioxano, 0,5 mL) y la mezcla de la reacción se agitó a 60°C durante una hora. La mezcla de la reacción se enfrió a temperatura ambiente y se concentró en vacío y se hizo azeotrópica 3 veces desde metanol y éter dietílico. Al secar se obtuvo la sal de clorhidrato de 3-[6-metil-1-(fenilmetil)piperidin-2-il]azetidin-3-ol como un residuo marrón (40 mg, rendimiento del 81%), que se usó sin nueva purificación. ^1H NMR (400MHz, CD_3OD): 7,58-7,63 (m, 2H), 7,47-7,49 (m, 3H), 4,78 (d, 1H), 4,44-4,62 (m, 2H), 4,29 (s, 2H), 4,22-4,26 (m, 1H), 4,12-4,18 (m, 1H), 4,08 (s, 1H), 1,60-2,00 (m, 8H), 1,48 (d, 3H); MS (EI) para $C_{16}H_{25}ClN_2O$: 261 (MH^+).

A una solución de clorhidrato de 3-[6-metil-1-(fenilmetil)piperidin-2-il]azetidin-3-ol (40 mg, 0,13 mmol) en acetato de etilo (3 mL) se agregó ácido acético (0,5 mL) y Pd/C (50 mg) y la mezcla se hidrogenó a 35 psi durante 3 horas. La mezcla de la reacción se filtró a través de celita. El filtrado se concentró en vacío. El residuo obtenido se disolvió en una pequeña cantidad de acetato de etilo y se agregó ácido clorhídrico concentrado y la mezcla se concentró

EJEMPLO 34

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-piperazin-2-ilazetidin-3-ol



A una solución de 1,4-bis(fenilmetil)piperazina-2,5-diona disponible comercialmente (2,0 g, 6,8 mmol) en dry THF seco (50 mL) a -78°C se agregó diisopropilamida de litio (2,0 M solución en heptano/THF/etilbenceno, 3,4 mL, 6,8 mmol). La suspensión marrón rojiza resultante se agitó durante 20 minutos a -78°C, y luego se agregó una solución de 1,1-dimetiletil 3-oxoazetidina-1-carboxilato (770 mg, 4,5 mmol) en THF (10 mL) durante 30 minutos con una bomba de jeringa. La mezcla se hizo una solución amarilla brillante cuando se la dejó calentar a temperatura ambiente durante 3 horas. La mezcla se enfrió con cloruro de amonio acuoso saturado. Se agregó agua para disolver las sales precipitadas, y la mezcla resultante se extrajo dos veces con acetato de etilo. Los extractos orgánicos combinados se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se purificó mediante cromatografía de columna (60% acetato de etilo: 40% hexanos) y proporcionó 1,1-dimetiletil 3-[3,6-

dioxo-1,4-bis(fenilmetil)piperazin-2-il]-3-hidroxiazetidina-1-carboxilato como una espuma incolora (1,04 g, 2,23 mmol, rendimiento 50%). ^{1}H NMR (400 MHz, $CDCl_3$): 7,39-7,29 (m, 7H), 7,23-7,19 (m, 3H), 5,34 (d, 1H), 4,82 (d, 1H), 4,58 (d, 1H), 4,37 (d, 1H), 4,37 (d, 1H), 4,22 (d, 1H), 4,15 (s, 1H), 4,08 (d, 1H), 3,97 (d, 1H), 3,75 (d, 1H), 3,74 (d, 1H), 3,67 (d, 1H), 3,64 (br s, 1H), 1,43 (s, 9H).

Una solución de 1,1-dimetiletil 3-[3,6-dioxo-1,4-bis(fenilmetil)piperazin-2-il]-3-hidroxiazetidina-1-carboxilato (1,04 g, 2,2 mmol) en metanol (10 mL) se trató con cloruro de hidrógeno en dioxano (4 N, 5,5 mL, 22 mmol) a 60°C durante 25 minutos. Después de enfriar a temperatura ambiente la solución se concentró. Se gregaron acetato de etilo y 2 N ácido clorhídrico al residuo y las fases se separaron. La fase orgánica se descartó. La fase acuosa se basificó con 5 M hidróxido de sodio y la solución resultante se extrajo 4 veces con acetato de etilo. Los extractos orgánicos combinados se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se purificó mediante cromatografía de columna (85% diclorometano: 14% metanol: 1% hidróxido de amonio acuoso) y proporcionó 3-(3-hidroxiazetidin-3-il)-1,4-bis(fenilmetil)piperazina-2,5-diona como una película incolora (493 mg, 1,35 mmol, rendimiento del 61%). ^{1}H NMR (400 MHz, $CDCl_3$): 7,39-7,28 (m, 6H), 7,25-7,20 (m, 4H), 5,39 (d, 1H), 4,80 (d, 1H), 4,44 (d, 1H), 4,36 (d, 1H), 4,26 (d, 1H), 4,11

(s, 1H), 3,97 (d, 1H), 3,83 (d, 1H), 3,71 (d, 1H), 3,27 (m, 2H); MS (EI) para $C_{21}H_{23}N_3O_3$: 366 (MH^+).

Una solución de 3-(3-hidroxiazetidin-3-il)-1,4-bis(fenilmetil)piperazina-2,5-diona (493 mg, 1,35 mmol) en éter de dimetilo de etilenglicol (12 mL) se trató con borohidruro de sodio (511 mg, 13,5 mmol) y luego se agregó lentamente trifluoruro de boro-eterato de dietilo. La mezcla de la reacción luego se calentó a reflujo durante 3 horas. Después de enfriar a 0°C se agregó metanol (17 mL) y luego se agregó cuidadosamente ácido clorhídrico concentrado (7 mL). La mezcla resultante se calentó a reflujo durante 70 minutos. Después de enfriar a temperatura ambiente, el residuo insoluble se removió mediante filtración. El filtrado se concentró a una mezcla acuosa de 10 mL en volumen. Esta mezcla se enfrió a 0°C y luego se basificó a pH 10 con 5 M hidróxido de sodio (aproximadamente 17 mL). Luego se agregó diclorometano (10 mL) y luego dicarbonato de di-*terc*-butilo (442 mg, 2,03 mmol). La mezcla se calentó a temperatura ambiente y se agitó durante 15 minutos. Las capas se separaron y la fase acuosa se extrajo dos veces con diclorometano. Los extractos orgánicos se combinaro, se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se purificó mediante cromatografí de columna (70% hexanos: 30% acetato de etilo) y proporcionaron 1,1-dimetiletil 3-[1,4-bis(fenilmetil)piperazin-2-il]-3-hidroxiazetidine-1-

carboxilato como una espuma blanca (408 mg, 0,93 mmol, rendimiento del 69%). ^{1}H NMR (400 MHz, $CDCl_3$) 7,35-7,24 (m, 10H), 4,12 (br s, 1H), 3,88 (d, 1H), 3,78-3,65 (m, 4H), 3,53 (d, 1H), 3,43 (d, 1H), 3,21 (m, 1H), 2,80 (br s, 1H), 2,66 (m, 1H), 2,57-2,37 (m, 4H), 1,41 (s, 9H); MS (EI) para $C_{26}H_{35}N_3O_3$: 438 (MH^+).

A una solución de 1,1-dimetiletil 3-[1,4-bis(fenilmetil)piperazin-2-il]-3-hidroxiazetidina-1-carboxilato (408 mg, 0,93 mmol) en metanol (15 mL) se agregó 10% paladio sobre carbono (húmedo), y la suspensión resultante se sometió a una atmósfera de hidrógeno durante 21 horas. El catalizador se removió mediante filtración a través de celita, y la torta de filtro se enjuagó con metanol. El filtrado combinado se concentró y proporcionó 1,1-dimetiletil 3-hidroxi-3-piperazin-2-ilazetidina-1-carboxilato como un jarabe marrón (227 mg, 0,88 mmol, rendimiento 95%). ^{1}H NMR (400 MHz, $CDCl_3$) 3,94-3,76 (m, 5H), 3,12 (m, 1H), 3,01 (m, 1H), 2,94-2,81 (m, 3H), 2,78-2,70 (m, 2H); MS (EI) para $C_{12}H_{23}N_3O_3$: 258 (MH^+).

A una solución de 1,1-dimetiletil 3-hidroxi-3-piperazin-2-ilazetidina-1-carboxilato (227 mg, 0,88 mmol) y *N,N*-diisopropiletilamina (436 µL, 2,64 mmol) en THF (5 mL) se agregó cloruro de 2-nitrobencensulfonilo (195 mg, 0,88 mmol). La mezcla se agitó a temperatura ambiente durante 2 horas. La solución se cocentró y el residuo se purificó mediante cromatografía de columna (95% diclorometano, 5% metanol) y

proporcionó 1,1-dimetiletil 3-hidroxi-3-{4-[(2-nitrofenil)sulfonil]piperazin-2-il}azetidina-1-carboxilato como una espuma blanca (308 mg, 0,70 mmol, rendimiento del 79%). ^{1}H NMR (400 MHz, $CDCl_3$): 7,98 (m, 1H), 7,72 (m, 2H), 7,64 (m, 1H), 3,96 (d, 1H), 3,94 (d, 1H), 3,85 (d, 1H), 3,79 (d, 1H), 3,79-3,73 (m, 2H), 3,11 (m, 1H), 3,05 (dd, 1H), 3,00 (br s, 1H), 2,94 (dt, 1H), 2,78 (dt, 1H), 2,68 (dd, 1H), 1,45 (s, 9H).

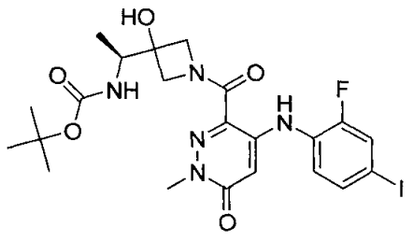
A una solución de 1,1-dimetiletil 3-hidroxi-3-{4-[(2-nitrofenil)sulfonil]piperazin-2-il}azetidina-1-carboxilato (308 mg, 0,70 mmol) en metanol (10 mL) se agregó HCl en dioxano (4 N, 1,75 mL, 7,0 mmol), y la mezcla se calentó a 60°C durante 30 minutos. La solución se concentró y proporcionó 3-{4-[(2-nitrofenil)sulfonil]piperazin-2-il}azetidin-3-ol como un sólido blanco pegajoso. Este material se disolvió en diclorometano (7 mL). A la solución se agregó *N,N*-diisopropiletilamina (1,16 mL, 7,0 mmol) y luego fluoruro de 3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]benzoilo (277 mg, 0,7 mmol), preparado usando procedimientos similares a los descritos en la Referenci 1, y la mezcla resultante se agitó a temperatura ambiente durante 16 horas. La solución se concentró y el residuo se purificó mediante cromatografía de columna (95% diclorometano: 5% metanol) y proporcionó 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{4-[(2-nitrofenil)sulfonil]piperazin-2-il}azetidin-3-ol como una

espuma amarilla pálida (453 mg, 0,63 mmol, rendimiento del 90%). ^{1}H NMR (400 MHz, $CDCl_3$): 8,49 (s, 1H), 7,96 (dd, 1H), 7,71 (m, 2H), 7,53 (dd, 1H), 7,39 (dd, 1H), 7,33 (d, 1H), 7,15 (m, 1H), 6,84 (br s, 1H), 6,62 (m, 1H), 4,29-3,97 (br m, 4H), 3,79-3,62 (m, 3H), 3,26-2,99 (br m, 3H), 2,92-2,62 (br m, 3H); MS (EI) para $C_{26}H_{23}F_3IN_5O_6S$: 718 (MH^+).

A una solución de 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{4-[(2-nitrofenil)sulfonil]piperazin-2-il}azetidin-3-ol (139,4 mg, 0,19 mmol) en DMF (1 mL) se agregó carbonato de potasio (79 mg, 0,57 mmol) y tiofenol (21 µL, 0,21 mmol). La mezcla se agitó durante 45 minutos a temperatura ambiente y luego se enfrió con agua. La mezcla acuosa se extrajo con acetato de etilo y los extractos orgánicos combinados se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se purificó mediante HPLC de fase invertida preparativa y proporcionó 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-piperazin-2-ilazetidin-3-ol como un sólido blanco (26,8 mg, 0,05 mmol). ^{1}H NMR (400 MHz, CD_3OD): 7,45 (dd, 1H), 7,36 (m, 1H), 7,32 (m, 1H), 7,03 (m, 1H), 6,62 (ddd, 1H), 4,51 (br dd, 1H), 4,31 (br dd, 1H), 4,17-3,92 (m, 4H), 3,73-3,56 (m, 3H), 3,46 (br m, 1H), 3,26 (m, 1H); MS (EI) para $C_{20}H_{20}F_3IN_4O_2$: 533 (MH^+).

EJEMPLO 36

1,1-Dimetiletil {(1*S*)-1-[1-({4-[(2-fluoro-4-yodofenil)amino]-1-metil-6-oxo-1,6-dihidropiridazin-3-il}carbonil)-3-hidroxiazetidin-3-il]etil}carbamato



A una solución de ácido 4-[(2-fluoro-4-yodofenil)amino]-1-metil-6-oxo-1,6-dihidropiridazins-3-carboxílico (50 mg, 0,13 mmol) en DMF (2 mL), preparado usando procedimientos similares a los descritos en la Referenci 4, a temperatura ambiente se agregó 1-hidroxibenzotriazol (36,3 mg, 0,27 mmol) y clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (52 mg, 0,27 mmol) y la mezcla de la reacción se agtó durante 2 horas. Se agregaron 1,1-dimetiletil [(1*S*)-1-(3-hidroxiazetidin-3-il)etil]carbamato (30 mg, 0,13 mmol), preparado usando procedimientos similares a aquellos del Ejemplo 28, y trietilamina (0,04 mL) y la mezcla se agitó durante 15 hors. La mezcla de la reacción se repartió entre cloruro de sodio saturado y acetato de etilo. La capa orgánica se lavó con 5% solución de cloruro de litio, bicarbonato de sodio saturado, se secó sobre sulfato de sodio anhidro, se

filtró y se concentró en vacío y dio el producto crudo como un aceite amarillo. El aceite se purificó mediante cromatografía de columna (gel de sílice, acetato de etilo) y dio 1,1-dimetiletil {(1*S*)-1-[1-({4-[(2-fluoro-4-yodofenil)amino]-1-metiyl-6-oxo-1,6-dihidropiridazin-3-il}carbonil)-3-hidroxiazetidin-3-il]etil}carbamato como un aceite amarillo (55 mg, rendimiento del 73%): ^{1}H NMR (400 MHz, $CDCl_3$): 10,24-10,23 (m, 1H), 7,52-7,50 (m, 2H), 7,12-7,07 (m, 1H), 6,10-6,09 (m, 1H), 5,13-5,09 (m, 1H), 4,91-4,82 (m, 1H), 4,60-4,39 (m, 2H), 4,10-4,08 (m, 1H), 4,00-3,87 (m, 2H), 3,70 (d, 3H), 1,43 (s, 9H), 1,24-1,20 (m, 3H); MS (EI) para $C_{22}H_{27}FIN_5O_5$: 588 (MH^+). Usando las mismas técnicas sintéticas o análogas y sustituyendo según fue necesario, con reactivos alternativos, se prepararon los siguientes compuestos de la invención.

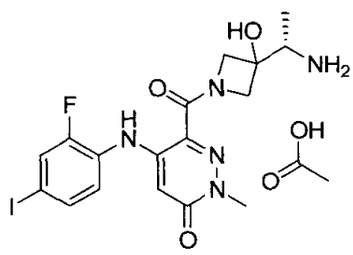
EJEMPLO 36(a). 1,1-Dimetiletil {(1*S*)-1-[1-({5-[(4-bromo-2-clorofenil)amino]-4-fluoro-1-metil-1*H*-bencimidazol-6-il}carbonil)-3-hidroxiazetidin-3-il]etil}carbamato: ^{1}H NMR (400 MHz, $CDCl_3$): 7,95 (s, 1H), 7,45-7,44 (m, 1H), 7,33-7,27 (m, 2H), 7,15-7,12 (m, 1H), 6,50-6,47 (m, 1H), 4,82-4,74 (m, 1H), 4,17-3,92 (m, 4H), 3,86 (s, 3H), 3,74-3,60 (m, 1H), 1,40 (s, 9H), 1,11-1,06 (m, 3H). MS (EI) para $C_{25}H_{28}BrClFN_5O_4$: 598 (MH^+) con patrón de isótopo de cloro, bromo.

EJEMPLO 36(b). 1,1-Dimetiletil (2*S*)-2-[1-({5-[(4-bromo-2-clorofenil)amino]-4-fluoro-1-metil-1*H*-bencimidazol-6-il}carbonil)-3-hidroxiazetidin-3-il]piperidina-1-carboxilato:

MS (EI) para $C_{28}H_{32}BrClFN_5O_4$: 638 (MH^+) con patrón de isótopo de cloro, bromo.

Ejemplo 37

Sal de aceato de 6-({3-[(1*S*)-1-aminoetil]-3-hidroxiazetidin-1-il}carbonil)-5-[(2-fluoro-4-yodofenil)amino]-2-metilpiridazin-3(2*H*)-ona



1,1-Dimetiletil {(1*S*)-1-[1-({4-[(2-fluoro-4-yodofenil)amino]-1-metil-6-oxo-1,6-dihidropiridazin-3-il}carbonil)-3-hidroxiazetidin-3-il]etil}carbamato (55 mg, 0,09 mmol), preparado usando procedimientos similares a los descritos en el Ejemplo 36, se recogió en metanol (2 mL) y se agregó ácido clorhídrico (4N en dioxano, 1 mL, 4 mmol) y la reacción se agitó a 60°C durante 2 horas. La mezcla de la racción se concentró en vacío y se purificó mediante HPLC de fase invertida seguida por la liofilización de la fracción pura que dio acetato de 6-({3-[(1*S*)-1-aminoetil]-3-hidroxiazetidin-1-il}carbonil)-5-[(2-fluoro-4-yodofenil)amino]-2-metilpiridazin-3(2*H*)-ona como un sólido amarillo (40 mg, 87%). ^1H NMR (400 MHz, $CDCl_3$): 10,17 (d, 1H), 7,52-7,46 (m, 2H), 7,09 (t, 1H),

6,13-6,12 (m, 1H), 4,51-4,48 (m, 2H), 4,18-4,03 (m, 2H), 3,73 (d, 3H), 3,35-3,28 (m, 1H), 3,22-2,80 (br, 3H), 1,21-1,19 (m, 3H); MS (EI) para $C_{17}H_{19}FIN_5O_3$: 488 (MH^+).

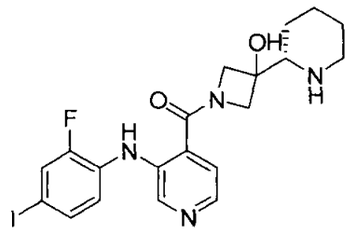
Usando las mismas técnicas sintéticas o análogas y sustituyendo según fue necesario, con reactivos alternativos, se prepararon los siguientes compuestos de la invención.

Ejemplo 37(a). Clorhidrato de 3-[(1*S*)-1-Aminoetil]-1-({5-[(4-bromo-2-clorofenil)amino]-4-fluoro-1-metil-1*H*-bencimidazol-6-il}carbonil)azetidin-3-ol. MS (EI) para $C_{20}H_{20}BrClFN_5O_2$: 498 (MH^+) con un patrón de isótopos de cloro, bromo.

Ejemplo 37(b). Clorhidrato de 1-({5-[(4-Bromo-2-clorofenil)amino]-4-fluoro-1-metiyl-1*H*-bencimidazol-6-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol. ^1H NMR (400 MHz, CD_3OD): 9,42 (s, 1H), 7,97-7,96 (m, 1H), 7,57 (s, 1H), 7,30-7,27 (m, 1H), 6,70-6,66 (m, 1H), 4,60-4,55 (m, 1H), 4,28 (t, 1H), 4,19 (s, 3H), 4,13-3,98 (m, 2H), 3,38-3,32 (m, 2H), 3,00 (t, 1H), 1,86-1,30 (m, 6H). MS (EI) para $C_{23}H_{24}BrClFN_5O_2$. HCl: 538 (MH^+) con un patrón de isótopos de cloro, bromo.

EJEMPLO 38

1-({3-[(2-fluoro-4-yodofenil)amino]piridin-4-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol



Ácido 3-[(2-Fluoro-4-yodofenil)amino]piridina-4-carboxílico (200 mg, 0,559 mmol), prparado usando procedimientos similares a los descritos en WO 2006/045514, se suspendió en DMF (7 mL) y 1-hidroxibenzotriazol (151 mg, 1,12 mmol) y se agregó clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (214 mg, 1,12 mmol). La mezcla se agitó a temperatura ambiente durante 10 minutos y luego se agregó trietilamina (0,078 mL, 0,559 mmol). Después de otros 20 minutos, se agregaron 1,1-dimetiletil (2*S*)-2-(3-hidroxiazetidin-3-il)piperidina-1-carboxilato (143 mg, 0,559 mmol), preparado usando procedimientos similares a los descritos en el Ejemplo 22(a) y 22(b), y trietilamina (0,16 mL, 1,15 mmol) y la mezcla se agitó durante 15 horas. La mezcla se repartió entre acetato de etilo y cloruro de amonio saturado. La parte orgánica se lavó con 5% cloruro de litio y dos veces con bicarbonato de sodio saturado, luego se secó sobre sulfato de sodio anhidro, se filtró y se concentró en vacío. El residuo se purificó

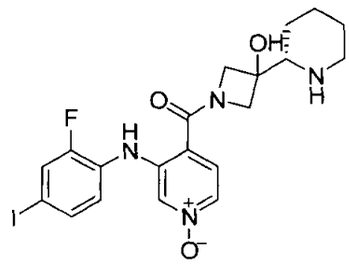
mediante cromatografía de columna (gel de sílice, 60%-80% acetato de etilo en hexanos) y dio 1,1-dimetiletil (2*S*)-2-[1-({3-[(2-fluoro-4-yodofenil)amino]piridin-4-il}carbonil)-3-hidroxiazetidin-3-il]piperidina-1-carboxilato (368 mg, 0,587 mmol, rendimiento del 74%): ^{1}H NMR (400 MHz, $CDCl_3$): 8,73 (br m, 1H), 8,62 (br s, 1H), 8,14 (d, 1H), 7,47 (dd, 1H), 7,43-7,39 (m, 1H), 7,20-7,12 (m, 2H), 4,38-4,21 (m, 2H), 4,16-4,01 (m, 2H), 4,01-3,88 (m, 1H), 3,44-3,30 (m, 1H), 2,98-2,83 (m, 1H), 2,00-1,88 (m, 1H), 1,71-1,50 (m, 6H), 1,44 (s, 9H); MS (EI) para $C_{25}H_{30}FIN_4O_4$: 597 (MH^+).

1,1-Dimetiletil (2*S*)-2-[1-({3-[(2-fluoro-4-yodofenil)amino]piridin-4-il}carbonil)-3-hidroxiazetidin-3-il]piperidina-1-carboxilato (24 mg, 0,040 mmol) se disolvió en metanol (2 mL) y se trató con ácido clorhídrico 4 N en dioxano (0,25 mL, 1 mmol) a reflujo durante 20 minutos. La mezcla se concentró en vacío y se purificó mediante HPLC de fase invertida seguida por la liofilización de las fracciones puras que dio acetatp de 1-({3-[(2-fluoro-4-yodofenil)amino]piridin-4-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol (14 mg, 0,025 mmol, rendimiento del 63%): ^{1}H NMR (400 MHz, d_6-DMSO): 8,62 (br s, 1H), 8,46 (s, 1H), 8,18 (dd, 1H), 7,65 (dd, 1H), 7,45 (d, 1H), 7,37 (t, 1H), 7,16-7,08 (m, 1H), 4,25 (dd, 1H), 4,04 (dd, 1H), 3,90 (t, 1H), 3,70 (d, 1H), 2,95 (br d, 1H), 2,52-2,42 (m, 2H), 1,78-1,68 (m, 1H),

1,57 (br t, 1H), 1,47 (br d, 1H), 1,35-1,13 (m, 2H), 1,10-0,96 (m, 1H); MS (EI) para $C_{20}H_{22}FIN_4O_2$: 497 (MH^+).

EJEMPLO 39

1-({3-[(2-fluoro-4-yodofenil)amino]-1-oxidopiridin-4-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol



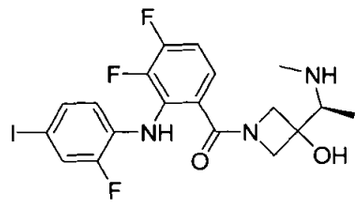
1,1-Dimetiletil (2*S*)-2-[1-({3-[(2-fluoro-4-yodofenil)amino]piridin-4-il}carbonil)-3-hidroxiazetidin-3-il]piperidina-1-carboxialto (80 mg, 0,134 mmol), preparado usando procedimientos similares a los descritos en el Ejemplo 38, se disolvió en diclorometano (3 mL) y se trató con 3-ácido cloroperoxibenzoico (73% puro; 32 mg, 0,135 mmol) a temperatura ambiente durante 7 horas. Se agregó ácido 3-cloroperoxibenzoico (73% puro; 32 mg, 0,135 mmol) y la mezcla se agitó durante 15 horas. La mezcla se purificó mediante cromatografía de columna (gel de sílice, 0-10% etanol en acetato de etilo) y dio 1,1-dimetiletil (2*S*)-2-[1-({3-[(2-fluoro-4-yodofenil)amino]-1-oxidopiridin-4-il}carbonil)-3-hidroxiazetidin-3-il]piperidina-1-carboxilato (57 mg, 0,093 mmol, rendimiento del 69%): ^{1}H NMR (400 MHz, $CDCl_3$): 9,38 (s,

1H), 8,00 (s, 1H), 7,68 (dd, 1H), 7,51 (dd, 1H), 7,46 (d, 1H), 7,19 (br d, 1H), 7,09 (t, 1H), 5,78 (br, 1H), 4,44-3,98 (m, 3H), 3,98-3,87 (m, 1H), 3,49-3,39 (m, 1H), 3,07-2,88 (m, 1H), 2,01-1,91 (m, 1H), 1,70-1,47 (m, 6H), 1,45 (s, 9H); MS (EI) para $C_{25}H_{30}FIN_4O_5$: 613 (MH^+).

1,1-Dimetiletil (2*S*)-2-[1-({3-[(2-fluoro-4-yodofenil)amino]-1-oxidopiridin-4-il}carbonil)-3-hidroxiazetidin-3-il]piperidina-1-carboxilato (57 mg, 0,093 mmol) se disolvió en metanol (2 mL) y se trató con 4N ácido clorhídrico en dioxano (0,25 mL, 1 mmol) a 50°C durante 2,25 horas. La mezcla se concentró en vacío y se purificó mediante HPLC de fase invertida seguida por la liofilización de las fracciones puras que dio acetato de 1-({3-[(2-fluoro-4-yodofenil)amino]-1-oxidopiridin-4-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol (35 mg, 0,061 mmol, rendimiento 66%): ^{1}H NMR (400 MHz, d_6-DMSO): 7,83 (s, 1H), 7,72 (dt, 2H), 7,55-7,51 (m, 1H), 7,47-7,41 (m, 1H), 7,24 (t, 1H), 4,45-4,32 (m, 1H), 4,14-3,95 (m, 2H), 3,72 (d, 1H), 2,97 (d, 1H), 2,58-2,43 (m, 2H), 1,80-1,73 (m, 1H), 1,67-1,55 (m, 1H), 1,49 (br d, 1H), 1,38-1,16 (m, 2H), 1,16-1,01 (m, 1H); MS (EI) para $C_{20}H_{22}FIN_4O_3$: 513 (MH^+).

EJEMPLO 40

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(1*S*)-1-(metilamino)etil]azetidin-3-ol



A 3-[(1*S*)-1-aminoetil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol (87,4 mg, 0,18 mmol), preparado usando procedimientos similares a los descritos en el Ejemplo 28, se agregó formaldehído (37% acuoso, 14 mg, 0,18 mmol) en metanol (2 mL) y borohidruro de sodio (7 mg, 0,18 mmol). La mezcla se agitó durante 3 horas a temperatura ambiente, después de cuyo tiempo se agregó borohidruro de sodio (16 mg, 0,42 mmol). Al agitar 1,25 hora adicional, se agrgó más formaldehído (37% acuoso, 1 gota) y la mezcla se agitó durante 3 días a temperatura ambiente. Luego se agregó otra pequeña espátula (50 mg) de borohidruro de sodio, y la mezcla se agitó a temperatura ambiente durante 30 minutos. Después de enfriar con 1 N HCl, la mezla de la reacción se purificó directamente mediante HPLC preparativa. El material puro se convirtió en su sal de clorhidrato y se proporcionó 1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(1*S*)-1-(metilamino)etil]azetidin-3-ol como un sólido amarillo (21,7 mg, 0,040 mmol, rendimienot del 22%). ^{1}H NMR (400 MHz, CD_3OD) δ 7,47 (dd, 1H), 7,36 (d, 1H), 7,31 (m, 1H), 7,06 (q, 1H), 6,62 (dt, 1H), 4,36 (dd, 1H), 4,21-3,91 (m, 3H), 3,44 (q, 1H),

2,66 (s, 3H), 1,29 (br m, 3H); MS (EI) para $C_{19}H_{19}F_3IN_3O_2$: 506 (MH^+).

Ejemplo Biológico 1

Ensayo Bioquímico

Para la medición de la actividad inhibitoria de MEK1 los compuestos de la invención se detectaron en un ensayo de cRaf-MEK-ERK2 acoplado triple usando a tecnología ALPHASCREEN (Marca Registrada de Perkin Elmer) (Perkin Elmer). El compuesto de la invención 0,5 µL de 100% solución de material de DMSO se diluyó en un compuesto tampón de ensayo de 20 mM Tris (pH = 7,5), 10 mM cloruro de magnesio, 0,03% CHAPS y 1 mM DTT. Posteriormente, se agrega 10 µL de mezcla de sustratos compuesta de MEK1 inactiva (3 nM), ATP (50 □M), ERK2 inactiva (4 nM), péptido MBP bitotinilado (b-FFKNIVTPRTPPPSQGK, 1 □M) y antifosfo MBP péptido (0.5 nM). La mezcla luego se agitó suavente durante 30 minutos a temperatura ambiente y luego se agregó cRaf activa (5 µL at 0,5 nM) para iniciar la reacción. La mezcla luego se agitó 100 minutos a temperatura ambiente y se enfrió agregando 10 µL de una mezcla de 5µg/mL duentas de donador de estreptavidina y 5µg/mL de cuentas de aceptor de proteína A en tampón de detección (75 mM Hepes pH = 7,5, 300 mM cloruro de sodio, 120 mM EDTA, 0,3% BSA y 0,03% Tween), sguido por la incubación toda la noche y la detección de

señales sobre un lector de placas ALPHAQuest® (Marca Registrada de Perkin Elmer) (Perkin Elmer).

Los compuestos de la invención son inhibidores de MEK. La magnitud a la cual estos compuestos son inhibidores de MEK se puede determinar por un experto en el arte. En particular, los compuestos se pueden ensayar en el ensayo descrito en el Ejemplo Biológico 1. Cuando se ensayaron en ensayos, ciertos compuestos de la invención demostraron la capacidad de unirse a MEK. En una realización de la invención, el inhibidor de MEK se selecciona de compuestos de la Tabla 1 que tienen una afinidad ala unión a MEK de 4 μM o menos. En otra realización, el inhibidor de MEK se selecciona de los compuestos de la Tabla 1 que tienen una afinidad a la unión a MEK de 3 μM o menos. En otra realización, el inhibidor de MEK se selecciona delos compuestos de la Tabla 1 que tienen una afinidad a la unión a MEK de 2 μM o menos. En otra realización, el inhibidor de MEK se selecciona de los compeustos de la Tabla 1 que tienen una afinidad a la unión MEK de 1,6 μM oo menos. En otra realización, el inhibidor de MEK se selecciona de los compuestos de la Tabla 1 que tienen una afinidad a la unión a MEK de 1 μM o menos. En otra realización, el inhibidor de MEK se selecciona de los compuestos de la Tabla 1 que tienen una afinidad a la unión a MEK de 0,7 μM o menos. En otra realización, el inhibidor de MEK se selecciona de los

compuestos de la Tabla 1 que tienen una afinidad a la unión a MEK de 0,3 μM o menos. En otra realización, el inhibidor de MEK se selecciona de los compuestos de la Tabla 1 que tienen una afinidad a la unión a MEK de 0,2 μM o menos. En otra realización, el inhibidor de MEK se selecciona de los compuestos de la Tabla 1 que tienen una afinidad a la unión a MEK de 0,1 μM o menos. En otra realización, el inhibidor de MEK se selecciona de los compuestos de la Tabla 1 que tienen una afinidad a la unión a MEK de 0,05 μM o menos.

Ejemplo Biológico 2

Ensayo ELISA de Fosforilación de ERK Endógena

Células MDA-MB-231T (ATCC), Calu-6 (ATCC), HCT 116 (ATCC), A2058 (ATCC), y A375 (ATCC) se sembraron a 20000, 30000, 30000, 20000, y 30000 células/receptáculo en placas de microtítulo de 96 recepáculos negras (Costar 3904), en DMEM (Cellgro) que contiene 10% FBS (Ativado por Calor, Cellgro), 1% NEAA (Cellgro), y 1% Pen/Strep (Cellgro). Las células SK-MEL-28 (ATCC) se sembraron a 20000 células/receptáculo en MEM (ATCC) que contiene 10% FBS (Activado por Calor, Cellgro), y 1% Pen/Strep (Cellgro). Las células luego se incubaron a 37°C, 5% CO_2 durante 24 horas. Se despojó de suero reemplazando el medio con DMEM o MEM libre de suero durante otras 24 horas.

La dilución final de los compuestos del ensayo en un medio libre de suero en una concentración final de 0,3% DMSO (vehículo) se agregaron a las células y se incubó durante 1 hora. Los receptáculos control negativo estaban en un medio libre de suero + 0,3% DMSO solamente. Después del tratamiento, el medio se removió y las células se fijaron con 4% formaldehído, luego enfriando peroxidasas endógenas con 0,6% H_2O_2. Las placas luego se colocaron en bloques (10% FBS, Cellgro) y se incubaron con más p44/42 MAPK anti-fosfo monoclonal de ratón, E10 (1:2000, Señalización Celular), seguido por anticuerpo secundario (IgG anti-ratón de chivo conjugado a HRP, 1:3000 de Jackson ImmunoResearch Laboratories, Inc). El lavado de las placas se realizó con PBS-T (0,1% Triton X-100) entre todos los pasos de la incubación. Luego se agregó una solución de sustrato basado en luminol y las placas se leyeron usando la máquina de Victor Wallac. Los valores de IC_{50} se determinaron basados en la fosforilación de ERK total con tratamiento con compuestos en función de la fosforilación de ERK total con tratamiento con 0,3% DMSO solo.

Ejemplo Biológico 3

Ensayo de Proliferación de Células BrdU

Células MDA-MB-231T (ATCC), Calu-6 (ATCC), HCT 116 (ATCC), A2058 (ATCC), A375 (ATCC), y Colo-205 (ATCC) se colocaron en placasa densidades de 2500, 3500, 3500, 2500, 3500, y 15000 células/receptáculo en placas de microtítulo de 96 receptáculos (Cat# 3904, Costar), en DMEM (Cellgro) que contienen 10% FBS (Inactivado por Calor, Cellgro), 1% Pen/Strep (Cellgro), y 1% NEAA (Cellgro). SK MEL-28 (ATCC) y WM-266-4 (ATCC) se colocaron en placas a densidades de 2000 y 6000 células/receptáculo en MEM (ATCC) que contiene 10% FBS (Inactivado por, Cellgro), y 1% Pen/Strep (Cellgro). Las células se incubaron toda la noche a 37°C, 5% CO_2 durante 18 h. Al día siguiente, las células se trataron con una dilución en serie de compuesto en medio (que contiene una concenración final de 0,3% DMSO). Se usaron receptáculos por triplicado para cada concentración del compuesto. Los receptáculos control recibieron medios de 0,3% DMSO. Los cultivos se incubaron a 37°C, 5% CO_2 durante otras 48 horas. Las células se ensayaron por la proliferación de acuerdo con el "kit de Proiferación Celular ELISA, Bromo Desoxiuridina (BrdU) (quimioluminiscencia)" de Roche. Las células se trataron con solución de marcado de BrdU y luego se fijaron con solución de FixDenat. Se agregó el conjugado Anti-BrdU-POD (PerOxiDasa) a

las células, después de lo cual las placas se lavaron 3x con 1X PBS. La solución de sustrato se agregó, y las placas se leyeron por la luminiscencia usando la máquina de Victor Wallac. Los valores de IC_{50} se calcularon basado en la proliferación celular con tratamiento con compuesto comparado con control vehículo.

Ejemplo Biológico 4

Modelos de ratón in vivo

Ratones desnudos atímicos hembra (NCr) de 5-8 semanas y que pesaban 20g se compraron a Taconic (Germantown, NY). Antes del inicio del estudio, se dejó que los animales se aclimataran durante un mínimo de 48 horas. Durnte estos estudios, se proporcionó a los animales alimento y agua sin límite y se los alojó en una habitación acondicionada a 70-75°F y 60% de humedad relativa. Se mantuvo un ciclo de 12 h de luz y 12 h de oscuridad con temporizadores automáticos.

Se cultivaron células de carcinoma colorectal humano Colo-205 in vitro en DMEM (Mediatech) suplementado con 10% con Suero Bovino Fetal (Hyclone), Penicilina-Estreptomicina y aminoácidos no esenciales 37°C en una atmósfera de 5% CO_2 humidificada. El día 0, las células se cosecharon mediante tripsinización, y $3x10^6$ células (pasaje N° 3, 92% viabilidad) en 0,1 ml de solución salina equilibrada de Hank helada se

implantaron vía intradérmica en el flanco posterior de ratones desnudos atímicos hembra de 5-8 semanas.

Células de melanoma humano A375 se cultivaron in vitro en DMEM (Mediatech) suplementado con 10% Suero Bovino Fetal (Hyclone), Penicilina-Estreptomicina y aminoácidos no esenciales a 37°C en un atmósfera de 5% CO_2 humidificada. El día 0, las células se cosecharon mediante tripsinización y $5x10^6$ células (pasaje N° 8, >99% viabilidad) en 0,1 mL de solución salina equilibrada de Hank helada se implantaron vía intradérmica en el flanco posterior de ratones desnudos atímicos hembra de 5-8 semanas.

Células de melanoma humano A2058 se cultivaron in vitro en DMEM (Mediatech) suplementado con 10% Suero Bovino Fetal (Hyclone), Penicilina-Estreptomicina y aminoácidos no esenciales a 37°C en una atmósfera de 5% CO_2 humidificada. El día 0, las células se cosecharon mediante tripsinización y $3x10^6$ células (pasaje N° 5, 80% viabilidad) en 0,1 mL solución salina equilibrada de Hank helada se implantaron vía transdérmica en el flanco posterior de ratones desnudos atímicos hembra de 5-8 semanas.

Células de adenocarcimona de mamas humano MDA-MB-231 se cultivaron in vitro en DMEM (Mediatech) suplementado con 10% Suero Bovino Fetal (Hyclone), Penicilina-Estreptomicina y aminoácidos no esenciales a 37°C en una atmósfera de 5% CO_2 humidificada. El día 0, las células se cosecharon mediante

tripsinización, y $1x10^6$ células (pasaje N° 6, >99% viabilidad) en 0,1 mL solución salina equilibrada de Hank helada se implantaron vía subcutánea en la almohadilla de grasa mamaria de ratones desnudos atímicos hembra de 5-8 semanas.

Células de carcinoma anaplástico de pulmón humano Calu-6 se cultivaron in vitro en DMEM (Mediatech) suplementado con 10% Suero Bovino Fetal (Hyclone), Penicilina-Estreptomicina y aminoácidos no esenciales a 37°C en una atmósfera de 5% CO_2 humidificada. El día 0, las células se cosecharon mediante tripsinización, y $5x10^6$ células (pasaje N° 8, 96% viabilidad) en 0,1 mL de solución salina equilibrada de Hank helada se implantaron vía intradérmica en el flanco posterior de raontes desnudos atímicos hembra de 5-8 semanas.

Para los tumores subcutáneos o intradérmicos, el peso medio del tumor de cada animal en los respectivos grupos control y de tratamiento se determinó dos veces por semana durante el estudio. El peso del tumor (TW) se determinó midiendo los diámetros perpendiculares con un calibre, usando la siguiente fórmula: peso del tumor (mg) = [volumen del tumor = longitud (mm) x ancho^2 (mm^2)]/2.

El porcentaje de inhibición del crecimiento del tumor (TGI) se determina con la siguiente fórmula:

$$\left[1 - \left[\frac{(X_f - X_0)}{(Y_f - X_0)} \right] \right] * 100$$

donde X_0 = TW promedio de todos los tumores un día del grupo; X_f = TW del grupo tratado el Día f; Y_f = TW del grupo control vehículo el Día f

Si los tumores remiten por debajo de sus tamaños iniciales entonces el porcentaje de remisión del tumor se determina con la siguiente fórmula:

$$\left[\frac{(X_0 - Xf)}{X_0} \right] * 100$$

TGI se calcula individualmente para cada tumor para obtener un valor de promedio ± SEM para cada grupo experimental. La relevancia estadística se determina usando el ensayo t de Student adaptado 2 (relevancia se define como $P<0,05$).

Ejemplos de Composicines Farmacéuticas

Las siguientes son formulaciones farmacéuticas representativas que contienen un compuesto de la Fórmula I

Formulación de Tableta

Los siguientes ingredientes se mezclan íntimamente y se prensan en tabletas cortadas individuales.

Ingrediente	Cantidad pir tableta, mg
Compuesto de esta invention	400
Almidón de maíz	50
croscarmelosa de sodio	25
Lactosa	120
Estearato de magnesio	5

Formulación de Cápsula

Los siguientes ingredientes se mezclaron íntimamente y se cargaron en una cápsula de gelatina dura.

Ingrediente	Cantidad por tableta, mg
Compuesto de esta invención	200
lactosa, secada por aspersión	148
estearato de magnesio	2

Formulación de Suspensión

Los siguientes ingredientes se mezclan para formar una suspensión para administración oral.

Ingrediente	Cantidad
Compuesto de esta invención	1,0 g
Ácido fumárico	0,5 g
Cloruro de sodio	2,0 g
metil parabeno	0,15 g
propil parabeno	0,05 g
azúcar granulado	25,5 g
sorbitol (70% solución)	12,85 g
Goma V K (Vanderbilt Co.)	1,0 g
Saborizante	0,035 mL
Colorantes	0,5 mg
Agua destilada	cant. Suf. a 100 mL

Formulación Inyectable

Los siguientes ingredientes se mezclan para formar una formulación inyectable

Ingrediente	Cantidad
Compuesto de esta invención	1,2 g
Solución tampón acestato de sodio	0,4 M ,.0 mL
HCl (1 N) o NaOH (1 M)	cant. Suf. a pH adecuado
agua (destilada, estéril)	cant. Suf. a 20 mL

Todos los ingredientes precedentes, excepto el agua, se combinan y se calientan a 60-70°C con agitación. Una cantidad suficiente de agua a 60°C luego se agrega con agitación vigorosa para emulsionar los ingredientes, y luego se agrega cantidad suficiente de agua hasta 100 g.

Formulación de Supositorio

Un supositorio de un peso total de 2,5 g se prepara mezclando el compuesto de la invención con Witepsol.RTM. H-15 (triglicéridos de ácido graso vegetal saturado; Riches-Nelson, Inc., New York), y tiene la siguiente composición:

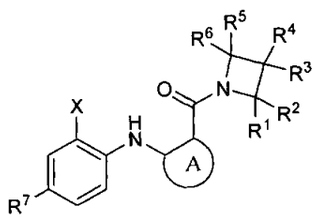
Ingrediente	Cantidad por tableta, mg
Compuesto de esta invención	500
Witepsol© H-15	resto

La invención precedente se ha descrito con algún detalle a modo de ilustración y de ejemplo, con propósitos de claridad y comprensión. La invención se ha descrito con referencia a diferentes realizaciones y técnicas. Sin embargo, se debe entender que se pueden hacer muchas variaciones y modificaciones mientras se permanece dentro del alcance y espíritu de la invención. Será obvio para un experto en el arte que se pueden hacer cambios y modificaciones dentro del alcance de las reivindicaciones adjuntas. En consecuencia. Se

debe entender que la descripción precedente es ilustrativa y no taxativa. Todas las patentes, solicitudes de patentes y publicaciones citadas en esta solicitud de patente se incorporan como referencia en la presente en su totalidad para todos los propósitos en la misma medida que si cada patente, solicitud de patente o publicación se hubiera indicado individualmente.

REIVINDICACIONES

1. Un compuesto de la Fórmula I



I

O un estereoisómero simple o una mezcla de estereoisómeros de él y optativamente como una sal o solvato farmacéuticamente aceptable de él, en donde A, X, R^1, R^2, R^3, R^4, R^5, R^6, y R^7 son lo definido en el Grupo A, el Grupo B, el Grupo C, o el Grupo D:

Grupo A:

A es arileno optativamente sustituido con uno, dos, tres o cuatro grupos seleccionados de R^{10}, R^{12}, R^{14}, y R^{16} donde R^{10}, R^{12}, R^{14} y R^{16} son independientemente hidrógeno, alquilo, alquenilo, alquinilo, halo, haloalcoxi, hidroxi, alcoxi, amino, alquilamino, dialquilamino, haloalquilo, $-NHS(O)_2R^8$, -CN, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$ y $-NR^8C(O)R^{8'}$

X es alquilo, halo, haloalquilo, o haloalcoxi;

R^1, R^2, R^3, R^4, R^5 y R^6 son independientemente hidrógeno, halo, nitro, $-NR^8R^{8'}$, $-OR^8$,

$-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$,

$-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, o heterocicloalquilo; donde el alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, y heterocicloalquilo se sustituyen independiente y optativamente con uno, dos, tres, cuatro, cinco,seeis o siete grupos selecionados independientemente de halo, alquilo, haloalquilo, nitro, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, ariko optativamente sustituido, arilalquilo optativamente sustituido, heteroarilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ y $-NR^8C(O)R^{8'}$; o uno de R^1 y R^2 junto con el carbono al cual están unidos, R^3 y R^4 junto con el carbono al cual están unidos, y R^5 y R^6 junto con el carbono al cual están unidos, forma C(O) o C(=NOH);

m es 0, 1, o 2;

R^7 es hidrógeno, halo o alquilo;

R^8, $R^{8'}$ y $R^{8''}$ se seleccionan independientemente de hidrógeno, hidroxi, alcoxi optativamente sustituido, alquilo, alquenilo, alquinilo, arilo, cicloalquilo, heteroarilo, y heterocicloalquilo; donde el alquilo, alquenilo, alquinilo,

arilo, cicloalquilo, heteroarilo y heterocicloaquilo se sustituyen independiente y optativamente con uno, dos, tres, cuatro o cinco grupos seleccionados independientemente de alquilo, halo, hidroxi, hidroxialquilo, alcoxi optativamente sustituido, alcoxialquilo, haloalquilo, carboxi, alcoxicarbonilo, alqueniloxicarbonilo, cicloalquilo optativamente sustituido, cicloalquiloxicarbonilo optativamente sustituido, arilo optativamente sustituido, ariloxi optativamente sustituido, ariloxicarbonilo optativamente sustituido, arilalquilo optativamente sustituido, arilalquiloxi optativamente sustituido, arilalquiloxicarbonilo optativamente sustituido, nitro, ciano, heterocicloalquilo optativamente sustituido, heteroarilo optativamente sustituido, $-S(O)_nR^{31}$ (donde n es 0, 1, o 2 y R^{31} es alquilo optativamente sustituido, arilo optativamente sustituido, heterocicloalquilo optativamente sustituido, o heteroarilo optativamente sustituido), $-NR^{34}SO_2R^{34a}$ (donde R^{34} es hidrógeno o alquilo y R^{34a} es alquilo, alquenilo, cicloalquilo, arilo, heteroarilo, o heterocicloalquilo), $-SO_2NR^{35}R^{35a}$ (donde R^{35} es hidrógeno o alquilo y R^{35a} es alquilo, alquenilo, cicloalquilo, arilo, heteroarilo, o heterocicloalquilo), $-NR^{32}C(O)R^{32a}$ (donde R^{32} es hidrógeno o alquilo y R^{32a} es alquilo, alquenilo, alcoxi, o cicloalquilo), $-NR^{30}R^{30'}$ (donde R^{30} y $R^{30'}$ son independientemente hidrógeno, alquilo o hidroxialquilo), y $-C(O)NR^{33}R^{33a}$ (donde R^{33} es

hidrógeno o alquilo y R^{33a} es alquilo, alquenilo, alquinilo o cicloalqulo); y

R^9 es alquilo, alquenilo, alquinilo, arilo, cicloalquilo, heteroarilo, y heterocicloalquilo; donde el alquilo, alquenilo, alquinilo, arilo, cicloalquilo, heteroarilo, y heterocicloalquilo se sustituyen optativa e independientemente con uno, dos, tres, cuatro, o cinco grupos seleccionados de halo, hidroxi, alquilo, haloalquilo, haloalcoxi, amino, alquilamino, y dialquilamino;

R^{25} y R^{25b} son independientemente hidrógeno, alquilo, alquenilo, cicloalquilo optativamente sustituido, o arilo optativamente sustituido; y

R^{25a} es hidrógeno, alquilo, o alquenilo;

Grupo B:

A es heteroarileno optativamente sustituido con uno, dos, tres o cuatro grupos seleccionados de R^{10}, R^{12}, R^{14}, R^{16} y R^{19} donde R^{10}, R^{12}, R^{14} y R^{16} son independientemente hidrógeno, alquilo, alquenilo, alquinilo, halo, haloalcoxi, hidroxi, alcoxi, ciano, amino, alquilamino, dialquilamino, haloalquilo, alquilsulfonilamino, alquilcarbonilo, alquenilcarbonilo, alcoxicarbonilo, alqueniloxicarbonilo, aminocarbonilo, alquilaminocarbonilo, dialquilaminocarbonilo, o alquilcarbonilamino; donde R^{19} es hidrógeno, alquilo o alquenilo; y donde cada alquilo y alquenilo, solo o como parte

de otro grupo dentro de R^{10}, R^{12}, R^{14}, R^{16}, y R^{19}, se sustituye optativamente con halo, hidroxi, o alcoxi;

X es alquilo, halo, haloalquilo, o haloalcoxi;

R^1, R^2, R^3, R^4, R^5 y R^6 son independintemente hidrógeno, halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, $-CN$, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, o heterocicloalquilo, donde el alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo y heterocicloalquilo se sustituyen independiente y optativamente con uno, dos, tres, cuatro, cinco, seis o siete grupos seleccionados independientemente de halo, alquilo, haloalquilo, nitro, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, heteroarilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ y $-NR^8C(O)R^{8'}$; o uno de R^1 y R^2 junto con el carbono al cual están unidos, R^3 y R^4 junto con el carbono al cual están unidos, y R^5 y R^6 junto con el carbono al cual están unidos forman C(O) o C(=NOH);

m es 1 o 2;

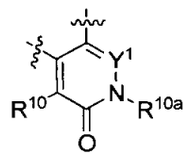
R^7 es hidrógeno, halo o alquilo; y

R^8, $R^{8'}$ y $R^{8''}$ se seleccionan independientemente de hidrógeno, hidroxi, alcoxi optativamente sustituido, alquilo, haloalquilo, alquenilo, alquinilo, arilo, cicloalquilo, heteroarilo, y heterocicloalquilo, donde el alquilo, aluqenilo, alquinilo, arilo, cicloalquilo, heteroarilo y hterocicloalquilo se sustituyen independiente y optativamente con uno, dos, tres, cuatro o cinco grupos seleccionados independientemente de alquilo, halo, hidroxi, hidroxialquilo, alcoxi optativamente sustituido, alcoxialquilo, haloalquilo, carboxi, carboxi éster, nitro, ciano, $-S(O)_nR^{31}$ (donde n es 0, 1, o 2 y R^{31} es alquilo optativamente sustituido, arilo optativamente sustituido, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, o heteroarilo optativamente sustituido), $-NR^{36}S(O)_2R^{36a}$ (donde R^{36} es hidrógeno, alquilo, o alquenilo y R^{36a} es alquilo, alquenilo, arilo optativamente sustituido, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, o heteroarilo optativamente sustituido), $-S(O)_2NR^{37}R^{37a}$ (donde R^{37} es hidrógeno, alquilo, o alquenilo y R^{37a} es alquilo, alquenilo, arilo optativamente sustituido, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, o heteroarilo optativamente sustituido), cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente

sustituido, ariloxi optativamente sustituido, arilalquiloxi optativamente sustituido, heteroarilo optativamente sustituido, $-NHC(O)R^{32}$ (donde R^{32} es alquilo, alquenilo, alcoxi, o cicloalquilo) y $-NR^{30}R^{30'}$ (donde R^{30} y $R^{30'}$ son independientemente hidrógeno, alquilo, o hidroxialquilo), y $-C(O)NHR^{33}$ (donde R^{33} es alquilo, alquenilo, alquinilo, o cicloalquilo);

Grupo C:

A es



donde R^{10} es hidrógeno, alquilo, alquenilo, alquinilo, halo, haloalcoxi, hidroxi, alcoxi, amino, alquilamino, dialquilamino, haloalquilo, $-NHS(O)_2R^8$, -CN, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$ y $-NR^8C(O)R^{8'}$;

R^{10a} es hidrógeno, alquilo, o alquenilo;

Y^1 es =CH- o =N-;

X es alquilo, halo, haloalquilo, o haloalcoxi;

R^1, R^2, R^3, R^4, R^5 and R^6 son independientemente hidrógeno, halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, -CN, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$,

$-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$,

alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, o heterocicloalquilo, donde el alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo o heterocicloalquilo se sustituyen independiente y optativamente con uno, dos, tres, cuatro, cinco, seis o siete grupos seleccionados independientemente de halo, alquilo, haloalquilo, nitro, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, heteroarilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ y $-NR^8C(O)R^{8'}$; o uno de R^1 y R^2 junto con el carbono al cual están unidos, R^3 y R^4 junto con el carbono al cual están unidos, y R^5 y R^6 junto con el carbono al cual están unidos, forman C(O) o C(=NOH);

m es 1 o 2;

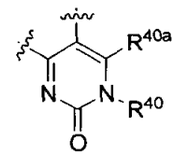
R^7 es hidrógeno, halo o alquilo; y

R^8, $R^{8'}$ y $R^{8''}$ se seleccionan independientemete de hidrógeno, hidroxi, alcoxi optativamente sustituido, alquilo, haloalquilo, alquenilo, alquinilo, arilo, cicloalquilo, heteroarilo, y heterocicloalquilo, donde el alquilo, alquenilo, alquinilo, arilo, cicloalquilo, heteroarilo y hterocicloalquio se sustituyen independiente y optativamente con uno, dos, tres, cuatro o cinco grupos seleccionados independientemente de alquilo, halo, hidroxi, hidroxialquilo,

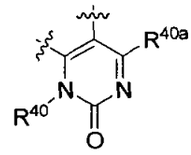
alcoxi optativamente sustituido, alcoxialquilo, haloalquilo, carboxi, carboxi éster, nitro, ciano, $-S(O)_nR^{31}$ (donde n es 0, 1, o 2 y R^{31} es alquilo optativamente sustituido, arilo optativamente sustituido, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, o heteroarilo optativamente sustituido), $-NR^{36}S(O)_2R^{36a}$ (donde R^{36} es hidrógeno, alquilo, o alquenilo y R^{36a} es alquilo, alquenilo, arilo optativamente sustituido, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, o heteroarilo optativamente sustituido), $-S(O)_2NR^{37}R^{37a}$ (donde R^{37} es hidrógeno, alquilo, o alquenilo y R^{37a} es alquilo, alquenilo, arilo optativamente sustituido, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, o heteroarilo optativamente sustituido), cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, ariloxi optativamente sustituido, arilalquiloxi optativamente sustituido, heteroarilo optativamente sustituido, $-NHC(O)R^{32}$ (donde R^{32} es alquilo, alquenilo, alcoxi, o cicloalquilo) y $-NR^{30}R^{30'}$ (donde R^{30} y $R^{30'}$ son independientemente hidrógeno, alquilo, o hidroxialquilo), y $-C(O)NHR^{33}$ (donde R^{33} es alquilo, alquenilo, alquinilo, o cicloalquilo); o

Grupo D:

A es



(b) o



(c)

R^{40} y R^{40a} son independientemente hidrógeno o alquilo;

X es alquilo, halo, haloalquilo, o haloalcoxi;

R^1, R^2, R^3, R^4, R^5 y R^6 son independientemente hidrógeno, halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, $-CN$, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, o heterocicloalquilo, donde el alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, y heterocicloalquilo se sustituyen independiente y optativamente con uno, dos, tres, cuatro, cinco, seis o siete grupos seleccionados independientemente de halo, alquilo, haloalquilo, nitro, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente

sustituido, heteroarilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ y $-NR^8C(O)R^{8'}$; o uno de R^1 y R^2 junto con el carbono al cual están unidos, R^3 y R^4 junto con el carbono al cual están unidos, y R^5 y R^6 junto con el carbono al cual están unidos, forman C(O) o C(=NOH);

m es 1 o 2;

R^7 es hidrógeno, halo o alquilo; y

R^8, $R^{8'}$ y $R^{8''}$ se seleccionan independientemente de hidrógeno, hidroxi, alcoxi optativamente sustituido, alquilo, haloalquilo, alquenilo, alquinilo, arilo, cicloalquilo, heteroarilo, y heterocicloalquilo, donde el alquilo, alquenilo, alquinilo, arilo, cicloalquilo, heteroarilo y heterocicloalquilo se sustituyen optativa e independientemente con uno, dos, tres, cuatro, o cinco grupos seleccionados independientemente de alquilo, halo, hidroxi, hidroxialquilo, alcoxi optativamente sustituido, alcoxialquilo, haloalquilo, carboxi, carboxi éster, nitro, ciano, $-S(O)_nR^{31}$ (donde n es 0, 1, o 2 y R^{31} es alquilo optativamente sustituido, arilo optativamente sustituido, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, o heteroarilo optativamente sustituido), $-NR^{36}S(O)_2R^{36a}$ (donde R^{36} es hidrógeno, alquilo, o alquenilo y R^{36a} es alquilo, alquenilo, arilo optativamente sustituido, cicloalquilo

optativamente sustituido, heterocicloalquilo optativamente sustituido, o heteroarilo optativamente sustituido), $-S(O)_2NR^{37}R^{37a}$ (donde R^{37} es hidrógeno, alquilo, o alquenilo y R^{37a} es alquilo, alquenilo, arilo, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, o heteroarilo optativamente sustituido), cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, ariloxi optativamente sustituido, arilalquiloxi optativamente sustituido, heteroarilo optativamente sustituido, $-NHC(O)R^{32}$ (donde R^{32} es alquilo, alquenilo, alcoxi, o cicloalquilo) y $-NR^{30}R^{30'}$ (donde R^{30} y $R^{30'}$ son independientemente hidrógeno, alquilo, o hidroxialquilo), y $-C(O)NHR^{33}$ (donde R^{33} es alquilo, alqienilo, alquinilo, o cicloalquilo).

2. El compuesto de acuerdo con la reivindicación 1, seleccionado del Grupo A, el Grupo B y el Grupo C, donde

Grupo A

A es fenileno optativamente sustituido con uno o dos grupos seleccionados de R^{10}, R^{12}, R^{14}, y R^{16} donde R^{10}, R^{12}, R^{14} y R^{16} son independientemente hidrógeno o halo;

X es halo;

R^1, R^2, R^5 y R^6 son hidrógeno;

R^3 es hidrógeno, halo, hidroxi, alcoxi, o amino;

R^4 es hidrógeno, $-NR^8R^{8'}$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alquilo, alquenilo, cicloalquilo, heterocicloalquilo, o heteroarilo; donde el alquilo se sustitye optativamente con uno, dos, o tres grupos seleccionados independientemente de $-OR^8$, halo, nitro, $-S(O)_mR^9$, heterocicloalquilo optativamente sustituido, $-NR^8R^{8'}$, $-NR^8C(O)R^{8'}$, $-NR^8S(O)_2R^9$, $-NR^8C(O)OR^{8'}$, y arilo; donde el cicloalquilo se sustituye optativamente con uno o dos grupós seleccionados independientemente de $-OR^8$ y $-NR^8R^{8'}$; donde el heterocicloalquilo se sustituye optativamente con uno o dos grupos seleccionados independientemente de alquilo y $-C(O)OR^8$; y donde el heteroarilo se sustituye optativamente con $-NR^8R^{8'}$; o

R^3 y R^4 junto con el carbono al cual están unidos forman C(O) o C(=NOH);

m es 0;

R^7 es halo;

R^8 y $R^{8'}$ se seleccionan independientemente de hidrógeno, hidroxi, alquilo, alquenilo, alquinilo, arilo, heterocicloalquilo, heteroarilo, y cicloalquilo;

donde el alquilo de R^8 y $R^{8'}$ se sustituye optativamente con uno, dos, o tres grupos seleccionados independientemente de hidroxi, $-NR^{30}R^{30'}$ (donde R^{30} y $R^{30'}$ son independientemente hidrógeno, alquilo, o hidroxialquilo), heteroarilo optativamente sustituido, cicloalquilo optativamente sustituido), alcoxi optativamente sustituido, cicloalquilo optativamente sustituido, arilo optativamente sustituido, heterocicloalquilo optativamente sustituido, heteroarilo optativamente sustituido, $-C(O)NR^{33}R^{33a}$ (donde R^{33} es hidrógeno o alquilo y R^{33a} es alquilo, alquenilo, alquinilo, o cicloalquilo), ariloxi optativamente sustituido, $-S(O)_nR^{31}$ (donde n es 0 y R^{31} es alquilo), carboxi, alcoxicarbonilo, y $-NR^{32}C(O)R^{32a}$ (donde R^{32} es hidrógeno o alquilo y R^{32a} es alquilo, alquenilo, alcoxi, o cicloalquilo); o donde el alquilo se sustituye optativamente con uno, dos, tres, cuatro o cinco halo;

donde el heteroarilo de R^8 y $R^{8'}$ se sustituye independiente y optativamente con uno o dos grupos seleccionados independientemente de amino y alquilo;

donde el heterocicloalquilo de R^8 y $R^{8'}$ se sustituye independiente y optativamente con uno, dos o tres grupos seleccionados independientemente de alquilo, alcoxicarbonilo, arilalquilo optativamente sustituido, hidroxi, alcoxi, y hidroxialquilo;

donde el arilo de R^8 y $R^{8'}$ se sustituye independiente y optativamente con uno o dos grupos seleccionados independientemente de hidroxi, alcoxi, halo, $-NR^{32}C(O)R^{32a}$ (donde R^{32} es hidrógeno o alquilo y R^{32a} es alquilo, alquenilo, alcox, o cicloalquilo), y $-NR^{34}SO_2R^{34a}$ (donde R^{34} es hidrógeno o alquilo y R^{34a} es alquilo, alquenilo, cicloalquilo, arilo, heteroarilo, o heterocicloalquilo); y

donde el cicloalquilo de R^8 y $R^{8'}$ se sustituye independiente y optativamente con uno, dos o tres grupos seleccionados independientemente de hidroxi, hidroxialquilo, alcoxi, carboxi, $-C(O)NR^{33}R^{33a}$ (donde R^{33} es hidrógeno o alquilo R^{33a} es alquilo, alquenilo, alquinilo, o cicloalquilo), cicloalquilo optativamente sustituido; y

R^9 es alquilo o arilo;

Grupo B

A es tien-3,4-diilo, benzo[*d*]isoxazol-5,6-diilo, 1*H*-indazol-5,6-diilo (optativamente sustituido en la posición N1 con R^{19} donde R^{19} es alquilo o alquenilo), benzo[*d*]oxazol-5,6-diilo, 1*H*-benzo[d]imidazol-5,6-diilo (optativamente sustituido en la posición N1 R^{19} donde R^{19} es alquilo o alquenilo), 1*H*-benzo[*d*][1,2,3]triazol-5,6-diilo (optativamente sustituido en la posición N1 con R^{19} donde R^{19} es alquilo o alquenilo), imidazo[1,2-*a*]piridin-6,7-diilo, cinolin-6,7-diilo, quinolin-6,7-diilo, piridin-3,4-diilo, 1-oxido-piridin-3,4-diilo, [1,2,4]triazolo[4,3-a]piridin-6,7-diilo, o

2,3-dihidroimidazo[1,2-a]piridin-6,7-diilo; donde A se sustituye optativamente con uno, dos o tres grupos seleccionados independientemente de R^{10}, R^{12}, R^{14}, R^{16} y R^{19} donde R^{10}, R^{12}, R^{14} y R^{16} son independientemente hidrógeno, alquilo, halo, o amino; y R^{19} es hidrógeno o alquilo;

X es halo;

R^1, R^2, R^5 y R^6 son hidrógeno;

R^3 es hidrógeno o hidroxi;

R^4 es $-NR^8R^{8'}$, heterocicloalquilo, heteroarilo, o alquilo; donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ y donde el heteroarilo se sustituye optativamente con alquilo;

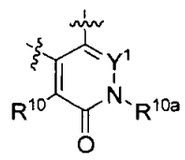
R^7 es halo;

R^8 es hidrógeno o alquilo; y

$R^{8'}$ es hidrógeno, alquilo, o cicloalquilo; donde el cicloalquilo se sustituye optativamente con uno o dos grupos seleccionados independientemente de hidroxi y alquilo;

Grupo C

A es



(a)

R^{10} es hidrógeno o halo;

R^{10a} es hidrógeno o alquilo;

Y^1 es =CH- o =N-;

X es halo;

R^1, R^2, R^5 y R^6 son hidrógeno;

R^3 es hidrógeno o hidroxi;

R^4 es $-NR^8R^{8'}$, heterocicloalquilo, heteroarilo, o alquilo; donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ y donde el heteroarilo se sustituye optativamente con alquilo;

R^7 es halo;

R^8 es hidrógeno o alquilo; y

$R^{8'}$ es hidrógeno, alquilo, o cicloalquilo; donde el cicloalquilo se sustituye optativamente con uno o dos grupos seleccionados independientemente de hidroxi y alquilo; o

un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

3. El compuesto de acuerdo con la reivindicación 1, donde R^3 is halo, nitro, $-NR^8R^{8'}$,

$-OR^8$, $-NHS(O)_2R^8$, $-CN$, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$,

$-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$,

$-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$,

$-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$,

$-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, o heterocicloalquilo; donde el

alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo y heteroicloalquilo se sustituyen independiente y optativamente con uno, dos, tres, cuatro, cicno, seis o siete grupos seleccionados independientemente de halo, alquilo, haloalquilo, nitro, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, heteroarilo optativamente sustituido, heteroarilalquilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ y $-NR^8C(O)R^{8'}$; y R^4 es lo definido en la reivindicación 1; o R^3 y R^4 junto con el carbono al cual están unidos forman C(O) o C(=NOH); o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

4. El compuesto de acuerdo con la reivindicación 1, en donde R^3 y R^4 son independientemente halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, $-CN$, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$,

$-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, o heterocicloalquilo; donde el alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, y heterocicloalquilo se sustituyen independiente y optativamente con uno, dos, tres, cuatro, cinco, seis o siete grupos seleccionados independientemente de halo, alquilo, haloalquilo, nitro, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, heteroarilo optativamente sustituido, heteroarilalquilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ y $-NR^8C(O)R^{8'}$; o R^3 y R^4 junto con el carbono al cual están unidos forman C(O) o C(=NOH); o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

5. El compuesto de acuerdo con la reivindicación 1 donde R^7 es halo; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

6. El compuesto de acuerdo con la reivindicación 1, donde X es halo; o un solo estereoisómero o una mezcla de estereoisómeros

de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

7. El compuesto de acuerdo con la reivindicación 1, donde R^1, R^2, R^5 y R^6 son hidrógeno; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

8. El compuesto de acuerdo con la reivindicación 1, seleccionado del Grupo A donde A es fenileno; y R^4 es $-NR^8R^{8'}$ (donde R^8 es hidrógeno, hidroxi, alquilo, alcoxi, arilo, cicloalquilo, heteroario, o heterocicloalquilo y $R^{8'}$ es hidroxi, alcoxi, arilo, cicloalquilo, heteroarilo, o heterocicloalquilo), $-NHS(O)_2R^8$, $-CN$, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$,
$-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$,
$-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$,
$-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alquenilo, o alquinilo; donde el alquenilo y alquinilo se sustituyen optativamente con uno, dos, tres, cuatro, cinco, seis, o siete grupos seleccionados independientemente de halo, alquilo, haloalquilo, nitro, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido,

arilalquilo optativamente sustituido, heteroarilo optativamente sustituido, heteroarilalquilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ y $-NR^8C(O)R^{8'}$; o R^3 y R^4 junto con el carbono al cual están unidos forman C(O) o C(=NOH); o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

9. El compuesto de acuerdo con la reivindicación 1, donde R^3 es hidrógeno, halo, hidroxi, amino o alcoxi; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

10. El compuesto de acuerdo con la reivindicación 1, donde R^4 es hidrógeno, $-NR^8R^{8'}$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alquilo, alquenilo, cicloalquilo, heterocicloalquilo, o heteroarilo; donde el alquilo se sustituye optativamente con uno o dos

grupos seleccionados independientemente de $-OR^8$, halo, nitro, $-S(O)_mR^9$, heterocicloalquilo optativamente sustituido, $-NR^8R^{8'}$, $-NR^8C(O)R^{8'}$, $-NR^8S(O)_2R^9$, $-NR^8C(O)OR^{8'}$, arilo; donde el arilo se sustituye optativamente con uno o dos $-NR^8R^{8'}$; donde el heterocicloalquilo se sustituye optativamente con uno o dos grupos seleccionados independientemente de alquilo y $-C(O)OR^8$; y donde el heteroarilo se sustituye optativamente cno $-NR^8R^{8'}$; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

11. El compuesto de acuerdo con la reivindicación 1, seleccionado del Grupo B donde A es fenileno optativamente sustituido con uno o dos grupos seleccionados independientemente de R^{10}, R^{12}, R^{14} y R^{16} donde R^{10}, R^{12}, R^{14} y R^{16} son independientemente hidrógeno o halo; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

12. El compuesto de acuerdo con la reivindicación 1, seleccionado del Grupo A donde A es fenileno; R^3 es hidrógeno; y R^4 ea hidrógeno, $-NR^8R^{8'}$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, alkyl, o heterocicloalquilo; donde el alquilo se sustituye optativamente con uno o dos grupos seleccionados

independientemente de $-OR^8$ y $-NR^8R^{8'}$; y donde el heterocicloalquilo se sustituye optativamente con $-NR^8R^{8'}$; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

13. El compuesto de acuerdo con la reivindicación 1, seleccionado del Grupo A donde A es fenileno; R es alcoxi; y R^4 es alqulo o heterocicloalquilo donde el alquilo se sustituye con $-NR^8R^{8'}$; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

14. El compuesto de acuerdo con la reivindicación 1, selecconado del Grupo A donde A es fenileno; R^3 es halo; y R^4 es alquilo o heterocicloalquilo donde el alquilo se sustituye con $-NR^8R^{8'}$; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

15. El compuesto de acuerdo con la reivindicación 1, seleccionado del Grupo A donde A es fenileno; y R^3 y R^4 junto con el carbono al cual están unidos forman C(O) o C(=NOH); o un solo estereoisómero o una mezcla de estereoisómeros de él y

optativamente o una sal o solvato farmacéuticamente aceptable de él.

16. El compuesto de acuerdo con la reivindicación 1, seleccionado del Grupo A donde A es fenileno; R^3 es hidroxi; y R^4 es hidrógeno, $-C(O)NR^8R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alquilo, alquenilo, heterocicloalquilo, cicloalquilo, heterocicloalquilo, o heteroarilo; donde el alquilo se sustituye optativamente con uno, dos, o tres grupos seleccionados independientemente de $-OR^8$, halo, nitro, $-S(O)_mR^9$, heterocicloalquilo optativamente sustituido, $-NR^8R^{8'}$, $-NR^8C(O)R^{8'}$, heteroarilo optativamente sustituido, $-NR^8S(O)_2R^9$, $-NR^8C(O)OR^{8'}$, y arilo; donde el cicloalquilo se sustituye optativamente con uno o dos grupos seleccionados independientemente de $-NR^8R^{8'}$ y $-C(O)NR^{33}R^{33a}$; donde el heterocicloalquilo se sustituye optativamente con uno, dos o tres grupos seleccionados independientemente de alquilo y $-C(O)OR^8$; y donde el heroarilo se sustituye optativamente con $-NR^8R^{8'}$; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

17. El compuesto de acuerdo con la reivindicación 17, seleccionado del Grupo A donde A se fenileno; R^7 es yodo o bromo; X es fluro o cloro; y R^1, R^2, R^5 y R^6 son hidrógeno; y R^{10}, R^{12}, R^{14} y R^{16} son independientemente hidrógeno o fluoro; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

18. El compuesto de acuerdo con la reivindicación 17, donde R^{10} es 3-fluoro y R^{12} y R^{14} son hidrógeno o halo; R^{10} es 3-fluoro, R^{12} es 4-fluoro y R^{14} y R^{16} son hidrógeno; R^{10} es 4-fluoro, R^{12} es 5-fluoro y R^{14} y R^{16} son hidrógeno; R^{10} es 4-fluoro, R^{12} es 6-fluoro y R^{14} y R^{16} son hidrógeno; o R^1 es 4-fluoro y R^{10}, R^{14} y R^{16} son hidrógeno; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

19. El compuesto de acuerdo con la reivindicación 1, seleccionado del Grupo A donde A es fenileno y R^3 es hidroxi; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

20. El compuesto de acuerdo con la reivindicación 19 donde R^4 es $-C(O)NR^8R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$,

$-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alquilo, cicloalquilo, heterocicloalquilo, o heteroarilo; donde el alquilo, cicloalquilo, heteroarilo y heterocicloalquilo se sustituye optativamente con uno, dos, tres o cuatro grupos seleccionados independientemente de halo, alquilo, haloalquilo, nitro, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, heteroarilo optativamente sustituido, heteroarilalquilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ y $-NR^8C(O)R^{8'}$; o donde el alquilo se sustituye optativamente con uno, dos, tres, cuatro, cinco, seis o siete halo; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

21. El compuesto de acuerdo con la reivindicación 20, donde R^4 es alquilo, heterocicloalquilo, o heteroarilo; donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$; donde el heterocicloalquilo se sustituye optativamente con alquilo o $-C(O)OR^8$; y donde el heteroarilo se sustituye optativamente con alquilo; o un solo estereoisómero o una mezcla de

estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

22. El compuesto de acuerdo con la reivindicación 1, donde R^1 es halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(O)_2R^8$, $-CN$, $-S(O)_mR^8$, $-S(O)_2NR^8R^{8'}$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$, $-NR^8C(O)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, or $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo, o heterocicloalquilo; donde el alquilo, alquenilo, alquinilo, cicloalquilo, heteroarilo y heterocicloalquilo se sustituyen independiente y optativamente con uno, dos, tres, cuatro, cinco, seis o siete grupos seleccionados independientemente de halo, alquilo, haloalquilo, nitro, cicloalquilo optativamente sustituido, heterocicloalquilo optativamente sustituido, arilo optativamente sustituido, arilalquilo optativamente sustituido, heteroarilo optativamente sustituido, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(O)_2R^9$, $-CN$, $-S(O)_mR^9$, $-C(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(O)NR^{8'}R^{8''}$, $-NR^8C(O)OR^{8'}$ y $-NR^8C(O)R^{8'}$;

R^3 es hidroxi; y R^4 es heterocicloalquilo, alquilo, o heteroarilo, donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ y donde el heteroarilo se sustituye optativamente con

alquilo; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

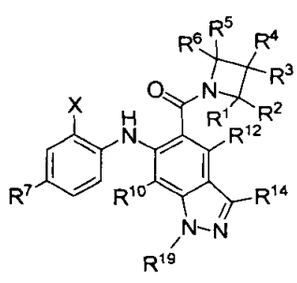
23. El compuesto de acuerdo con la reivindicación 1, seleccionado del Grupo B donde A es tien-3,4-diilo, benzo[*d*]isoxazol-5,6-diilo, 1*H*-indazol-5,6-dilo (optativamente sustituido en la posición N1 con R^{19} donde R^{19} es alquilo o alquenilo), benzo[*d*]oxazol-5,6-diilo, 1*H*-benzo[d]imidazol-5,6-diilo (optativamente sustituido en la posición N1 con R^{19} donde R^{19} es alquilo o alquenilo), 1*H*-benzo[*d*][1,2,3]triazol-5,6-diio (optativamente sustituido en la posición N1 con R^{19} donde R^{19} es alquilo o alquenilo), imidazo[1,2-*a*]piridin-6,7-diilo, cinolin-6,7-diilo, quinolin-6,7-diilo, piridin-3,4-diio, 1-oxido-piridin-3,4-diilo, [1,2,4]triazolo[4,3-a]piridin-6,7-diilo, o 2,3-dihidroimidazo[1,2-a]piridin-6,7-diilo; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

24. El compuesto de acuerdo con la reivindicación 1, donde A es tien-3,4-diilo; R^{10} y R^{12} son hidrógeno; X y R^7 son halo; y R^1, R^2, R^5, y R^6 son hidrógeno; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

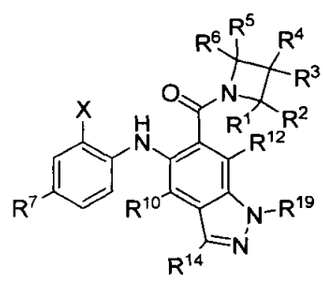
25. El compuesto de acuerdo con la reivindicación 24, donde R^3 es hidrógeno o hidroxi; y R^4 es $-NR^8R^{8'}$, heterocicloalquilo, heteroarilo, o alquilo, donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

26. El compuesto de acuerdo con la reivindicación 1, seleccionado del Grupo B donde A es benzo[*d*]isoxazol-5,6-diilo; R^{10}, R^{12}, y R^{14} son independientemente hidrógeno, halo, o alquilo; R^1, R^2, R^5, y R^6 son hidrógeno; X y R^7 son halo; R^3 es hidroxi; y R^4 es heterocicloalquilo, alquilo, o heteroarilo, donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ y donde el heteroarilo se sustituye optativamente con alquilo; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

27. El compuesto de acuerdo con la reivindicación 23, de acuerdo con la Fórmula I(g) o I(h):



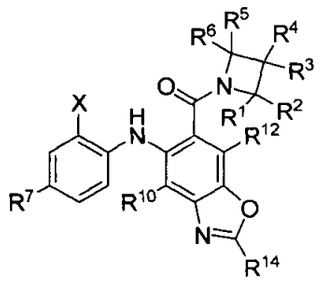
I(g);



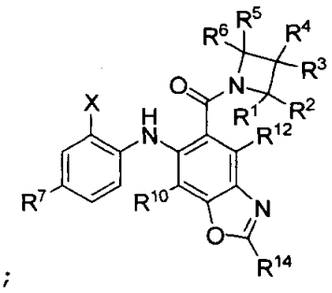
I(h);

donde R^{10}, R^{12}, y R^{14} son independientemente hidrógeno, halo, o alquilo; R^{19} es alquilo o alquenilo; R^1, R^2, R^5, y R^6 son hidrógeno; X y R^7 son halo; R^3 es hidroxi; y R^4 es heterocicloalquilo, alquilo, o heteroarilo, donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ y donde el heteroarilo se sustituye optativamente con alquilo; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

27. El compuesto de acuerdo con la reivindicación 23, de acuerdo con la Fórmula I(i) o I(j):



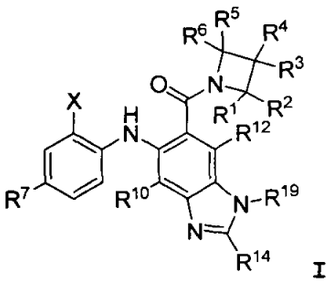
I(i);



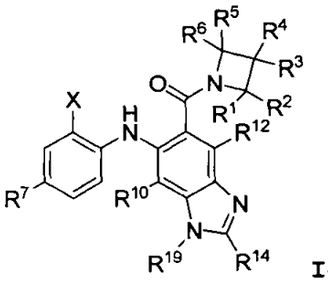
I(j);

donde R^{10}, R^{12}, y R^{14} son independientemente hidrógeno, halo, o alquilo; R^1, R^2, R^5, y R^6 sin hidrógeno; X y R^7 son halo; R^3 es hidroxi; y R^4 es heterocicloalquilo, alquilo, o heteroarilo, donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ y donde el heteroarilo se sustituye optativamente con alquilo; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

29. El compuesto de acuerdo con la reivindicación 23, de acuerdo con la Fórmula I(n) o I(o):



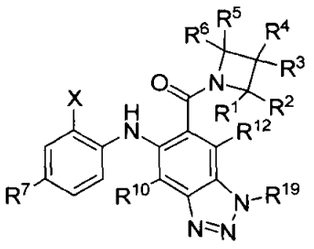
I(n);



Io);

donde R^7 es halo o alquilo; X es halo; R^{19} es alquilo; R^1, R^2, R^5, y R^6 son hidrógeno; R^{10}, R^{12}, y R^{14} son independientemente hidrógeno o halo; R^3 es hidroxi; y R^4 es heterocicloalquilo, alquilo, o heteroarilo, donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ y donde el heteroarilo se sustituye optativamente con alquilo; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

30. El compuesto de la reivindicación 23, de acuerdo con la Fórmula I(p):

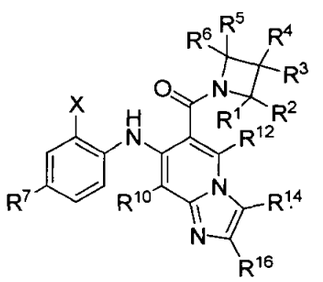


I(p)

donde R^1, R^2, R^5, y R^6 son hidrógeno; X y R^7 son halo; R^{10} y R^{12} son independientemente hidrógeno, halo, o alkyl; R^{19} es

hidrógeno o alquilo; R^3 es hidroxi; y R^4 es heterocicloalquilo, alquilo, o heteroarilo, donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ y donde el heteroarilo se sustituye optativamente con alquilo; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

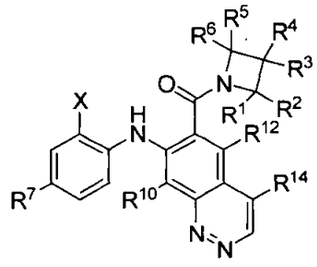
31. El compuesto de la reivindicación 23, de acuerdo con la Fórmula I(q):



I(q)

donde R^1, R^2, R^5, y R^6 son hidrógeno; X y R^7 son halo; R^{10}, R^{12}, R^{14}, y R^{16} son independientemente hidrógeno o halo; R^3 es hidroxi; y R^4 es heterocicloalquilo, alquilo, o heteroarilo, donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ y donde el heteroarilo se sustituye optativamente con alquilo; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

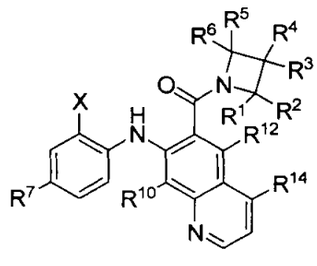
32. El compuesto de la reivindicación 23, de acuerdo con la Fórmula I(r):



I(r)

donde R^1, R^2, R^5, y R^6 son hidrógeno; X y R^7 son halo; R^{10} y R^{12} son independientemente hidrógeno, halo, o alquilo; R^{14} es hidrógeno, halo, alquilo, o amino; R^3 es hidroxi; y R^4 es heterocicloalquilo, alquilo, o heteroarilo, donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ y donde el heteroarilo se sustituye optativamente con alquilo; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

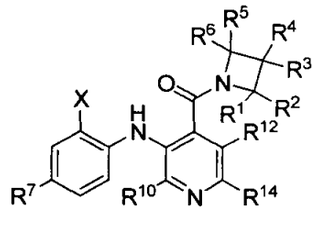
33. El compuesto de la reivindicación 23, de acuerdo con la Fórmula I(s):



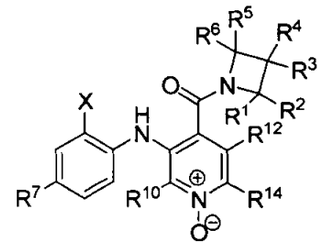
I(s)

R^1, R^2, R^5, y R^6 son hidrógeno; X y R^7 son halo; R^{10} y R^{12} son independientemente hidrógeno, halo, o alquilo; R^{14} es hidrógeno, halo, alquilo, o amino; R^3 es hidroxi; y R^4 es heterocicloalquilo, alquilo, o heteroarilo, donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ y donde el heteroarilo se sustituye optativamente con alquilo; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

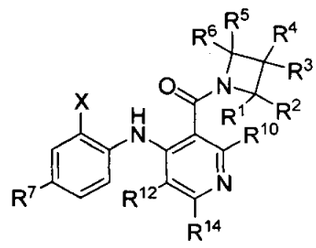
34. El compuesto de la reivindicación 23, de acuerdo con la Fórmula I(u), I(v), I(w) o I(x):



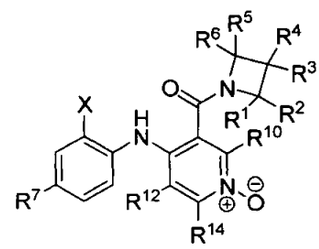
I(u);



I(v);



I(w);

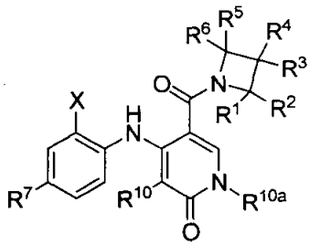


I(x);

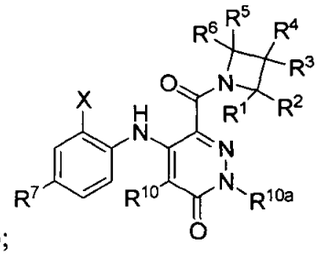
donde R^1, R^2, R^5, y R^6 son hidrógeno; X y R^7 son halo; R^{10}, R^{12}, y R^{14} son independientemente hidrógeno, halo, o alquilo; R^3 es hidroxi; y R^4 es heterocicloalquilo, alquilo, o heteroarilo, donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ y donde

el heteroarilo se sustituye optativamente con alquilo; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

35. El compuseto de la reivindicación 23, seleccionado del grupo C y de acuerdo con la Fórmula I(y) o I(z):



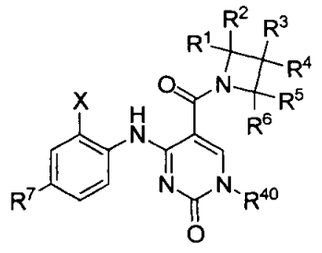
I(y);

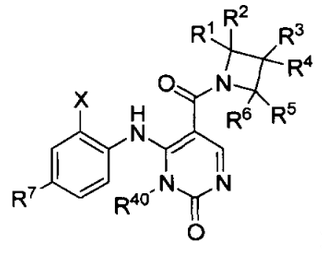


I(z)

donde R^1, R^2, R^5, y R^6 son hidrógeno; X y R^7 son halo; R^{10} es hidrógeno, halo, o alquilo; R^{10a} es alquilo; R^3 es hidroxi; y R^4 es heterocicloalquilo, alquilo, o heteroarilo, donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ y donde el heteroarilo se sustituye optativamente con alquilo; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

36. El compuesto de la reivindicación 23, seleccionado del Grupo D y de acuerodo con la Fórmula I(aa) o I(bb):



I(aa) or  **I(bb)**

donde R^1, R^2, R^5, y R^6 son hidrógeno; X y R^7 son halo; R^3 es hidroxi; y R^4 es heterocicloalquilo, alquilo, o heteroarilo, donde el alquilo se sustituye optativamente con $-NR^8R^{8'}$ y donde el heteroarilo se sustituye optativamente con alquilo; o un solo estereoisómero o una mezcla de estereoisómeros de él y optativamente o una sal o solvato farmacéuticamente aceptable de él.

37. El compuesto de acuerdo on la reivindicación 1, seleccionado del grupo formado por:

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}-carbonil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ona;

6-(azetidin-1-ilcarbonil)-2,3-difluoro-*N*-(2-fluoro-4-yodofenil)anilina;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(hidroximetil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(trifluorometil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-prop-2-en-1-ilazetidin-3-ol;

3-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]propano-1,2-diol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-etilazetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-metilazetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-etenilazetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ona; oxima;

[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]metanol;

1-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]etano-1,2-diol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-amina;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-hidroxiazetidina-3-carboxamida;

1,1-dimetiletil [1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]carbamato;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(pirrolidin-1-ilmetil)azetidin-3-ol;

3-[(dietilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(dimetilamino)metil]azetidin-3-ol;

N-butil-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidina-3-carboxamida;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-prop-2-en-1-ilazetidina-3-carboxamida;

N-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-yl]-2-metilpropanamida;

N-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]formamida;

N-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]-3,4-dihidroxibutanamida;

metil [1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]carbamato;

N-butil-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-amina;

1-({4-[(2-fluoro-4-yodofenil)amino]-3-tienil}carbonil)azetidin-3-amina;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(2*R*)-piperidin-2-il]azetidin-3-ol;

(*R*)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-pirrolidin-2-ilazetidin-3-ol;

(*S*)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-pirrolidin-2-ilazetidin-3-ol;

3-(aminometil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

3-[(1*S*)-1-aminoetil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenl}carbonil)azetidin-3-ol;

3-[(1*R*)-1-aminoetil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

(*R*)-(3-(1-aminopropil)-3-hidroxiazetidin-1-il)(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)metanona;

(*S*)-(3-(1-aminopropil)-3-hidroxiazetidin-1-il)(3,4-difluoro-2-(2-fluoro-4-yodofenilamino)fenil)metanona;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-etilazetidina-3-carboxamida;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-(2-hidroxietil)azetidina-3-carboxamida;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fhenil}carbonil)-*N*-(2-piperidin-1-iletil)azetidina-3-carboxamida;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-fenlazetidina-3-carboxamida;

N-[2-(dietilamino)etil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidina-3-carboxamida;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(morfolin-4-ilmetil)azetidin-3-ol;

1-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}piperidin-4-ol;

3-{[bis(2-hidroxietil)amino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

N-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]-2-(4-metilpiperazin-1-il)acetamida;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(4-metilpiperazin-1-il)metil]azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(4-metil-1,4-diazepan-1-il)metil]azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[metil(1-metilpirrolidin-3-il)amino]metil}azetidin-3-ol;

3-(1,4'-bipiperidin-1'-ilmetil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

N-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]-*N*,*N*-bis(2-hidroxietil)glicinamida;

3-({4-[2-(dietilamino)etil]piperazin-1-il}metil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonl)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-hidroxietil)(metil)amino]metil}azetidin-3-ol;

N-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]-2-piperidin-1-ilacetamida;

N-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]-*N*3-(2-hidroxietil)-*N*3-metil-beta-alaninamida;

N-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]-*N*3,*N*3-bis(2-hidroxietil)-beta-alaninamida;

N-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]-*N*2,*N*2-dietilglicinamida;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-metilazetidin-3-amina;

1-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]-*N*,*N*-dimetilpirrolidin-3-amina;

2-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]amino}etanol;

N-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]propano-1,3-diamina;

3-[(dimetilamino)metil]-1-({4-[(2-fluoro-4-yodofenil)amino]-3-tienil}carbonil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-metil-*N*-(2-piridin-2-iletil)azetidin-3-amina;

N-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]-*N*2-metilglicinamida;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-etilazetidin-3-amina;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-(2-metilpropil)azetidin-3-amina;

N-(ciclopropilmetil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-amina;

N-(ciclohexilmetil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-amina;

N-(ciclopentilmetil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-amina;

3-(azetidin-1-ilmetil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-[(2,3-dihidroxipropil)oxi]azetidina-3-carboxamida;

2-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-2-il]metil}amino)etanol;

N-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-2-il]metil}etano-1,2-diamina;

N-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-il]glicinamida;

6-({3-[(dimetilamino)metil]azetidin-1-il}carbonil)-2,3-difluoro-*N*-(2-fluoro-4-yodofenil)anilina;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1-metiletil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodoenil)amino]fenil}carbonil)-*N*-(3,4-dihidroxibutil)azetidina-3-carboxamida;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-(2,3-dihidroxipropil)azetidina-3-carboxamida;

1-({2,4-difluoro-6-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-amina;

1-({4,5-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-amina;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidina-3-carboxamida;

6-{[3-(aminometil)-3-(metiloxi)azetidin-1-il]carbonil}-2,3-difluoro-*N*-(2-fluoro-4-yodofenil)anilina;

N-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}acetamida;

2,3-difluoro-*N*-(2-fluoro-4-yodofenil)-6-[(3-{[(1-metiletil)amino]metil}azetidin-1-il)carbonil]anilina;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(etilamino)metil]azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{2-[(1-metiletil)amino]etil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(2-hidroxi-1,1-dimetiletil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{1,1-dimetil-2-[(1-metiletil)amino]etil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1-metiletil)amino]metil}azetidin-3-amina;

3-[(ciclopropilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2,2,2-trifluoroetil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1*H*-imidazol-1-ilmetil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1,1-dimetiletil)amino]metil}azetidin-3-ol;

3-[(ciclopentilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxi-*N*-prop-2-en-1-ilazetidina-3-carboxamida;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-*N*-(2,3-dihidroxipropil)-3-hidroxiazetidina-3-carboxamida;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1*H*-1,2,3-triazol-1-ilmetil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenl}carbonil)-3-{[(2,2-dimetilpropil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(propilamino)metil]azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-metilpropil)amino]metil}azetidin-3-ol;

3-{[(ciclopropilmetil)amino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(fenilmetil)amino]metil}azetidin-3-ol;

3-{[(ciclohexilmetil)amino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

3-[(butilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(1-etilpirrolidin-2-il)metil]amino}metili)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-hidroxietil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(dimetilamino)etil]amino}metil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-hidroxi-1,1-dimetiletil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(4-metilfenil)etil]amino}metil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(prop-2-en-1-ilamino)metil]azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(1-metilpirrolidin-2-il)etil]amino}metil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(2,3-dihidro-1*H*-inden-2-ilamino)metil]azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(tetrahidrofuran-2-ilmetil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(tetrahidro-2*H*-piran-4-il)etil]amino}metil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(1*S*,2*S*)-2-hidroxiciclopentil]amino}metil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1,1-dimetilprop-2-in-1-il)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(3-pirrolidin-1-ilpropil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1,2-dimetilpropil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(1*H*-imidazol-4-il)etil]amino}metil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[1-metil-2-(metiloxi)etil]amino}metil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[3-(etiloxi)propil]amino}metil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1-etilpropil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(3,3-dimetilbutil)amino]metil}azetidin-3-ol;

etil 4-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)piperidina-1-carboxilato;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(3-metflbutil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(etiloxi)etil]amino}metil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[3-(dimetilamino)propil]amino}metil)azetidin-3-ol;

3-[(ciclobutilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

3-({[3-(dietilamino)propil]amino}metil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[3-(1*H*-imidazol-1-il)propil]amino}metil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(metiltio)etil]amino}metil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[1-(fenilmetil)piperidin-4-il]amino}metil)azetidin-3-ol;

3-({[2,2-bis(metiloxi)etil]amino}metil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1,1,3,3-tetrametilbutil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1,1-dimetilpropil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(2,3-dihidro-1*H*-inden-1-ilamino)metil]azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[({2-[(fenilmetil)oxi]ciclopentil}amino)metil]azetidin-3-ol;

3-{[(3-amino-2-hidroxipropil)amino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-hidroxi-1-(fenilmetil)etil]amino}metil)azetidin-3-ol;

3-[(ciclooctilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

3-{[(1-ciclohexiletil)amino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-yodofhenil)amino]fenil}carbonil)azetidin-3-ol;

3-[(cicloheptilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-piridin-3-iletil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[3-(metiltio)propil]amino}metil)azetidin-3-ol;

N-ciclohexil-N^2-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}-2-metilalaninamida;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(tetrahidro-2*H*-pyran-4-ilmetil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(3-hidroxipropil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-piridin-4-iletil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofhenil)amino] fenil}carbonil)-3-({[1-(fenilmetil)pirrolidin-3-il]amino}metil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(2-tienil)etil]amino}metil)azetidin-3-ol;

3-[({2-[bis(1-metiletil)amino]etil}amino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(feniloxi)etil]amino}metil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonfl)-3-[(fenilamino)metil]azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-hidroxipropil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[({2-[(1-metiletil)oxi]etil}amino)metil]azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1-etilpiperidin-3-il)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(metiloxi)etil]amino}metil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1-nitropropil)azetidin-3-ol;

3-(1-aminoetil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(1-metilpiperidin-4-il)metil]amino}metil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[4-(dimetilamino)butil]amino}metil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-furan-2-iletil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{1-[(1,1-dimetiletil)amino]etil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-etilbutil)amino]metil}azetidin-3-ol;

1-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}pirrolidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({(2*S*)-2-[(metiloxi)metil]pirrolidin-1-il}metil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-hidroxifenil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(4-hidroxifenil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(3-hidroxifenil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(feniloxi)metil]azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1r,3r,5*R*,7*R*)-triciclo[3.3.1.1^{3,7}]dec-2-ilamino]metil}azetidin-3-ol;

3-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)propano-1,2-diol;

N-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}-L-alanina;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(feniltio)metil]azetidin-3-ol;

N-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}-D-alanina;

metil *N*-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}alaninato;

3-[({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)oxi]propano-1,2-diol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(5-metil-1,3,4-oxadiazol-2-il)metil]amino}metil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1-metilbutil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1-metilpropil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-metilbutil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(pentilamino)metil]azetidin-3-ol;

3-[(1*S*)-1-aminoetil]-1-({8-fluoro-7-[(2-fluoro-4-yodofenil)amino]imidazo[1,2-*a*]piridin-6-il}carbonil)azetidin-3-ol;

1-({8-fluoro-7-[(2-fluoro-4-yodofenil)amino]imidazo[1,2-*a*]piridin-6-il}carbonil)-3-[(1*S*)-1-(metilamino)etil]azetidin-3-ol;

3-[(ciclohexilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[1-(etilamino)etil]azetidin-3-ol;

3-[(azepan-3-ilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(dimetilamino)-1-metiletil]amino}metil)azetidin-3-ol;

N-ciclopropil-1-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)ciclopentanocarboxamida;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[2-(2,3-dihidro-1*H*-indol-3-il)etil]amino}metil)azetidin-3-ol;

N^2-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}-*N*-etil-2-metilalaninamida;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(2-metilhidrazino)metil]azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(hidroxiamino)metil]azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(metiloxi)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(etiloxi)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[1-(etilamino)propil]azetidin-3-ol;

3-[(azetidin-3-ilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(1,3-tiazol-2-ilamino)metil]azetidin-3-ol;

3-(1*H*-benzimidazol-2-il)-1-({8-fluoro-7-[(2-fluoro-4-yodofenil)amino]imidazo[1,2-*a*]piridin-6-il}carbonil)azetidin-3-ol;

3-(1*H*-benzimidazol-2-yl)-1-({7-[(4-bromo-2-fluorofenil)amino]-8-fluoroimidazo[1,2-*a*]piridin-6-il}carbonil)azetidin-3-ol;

1,1-dimetiletil [3-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metl}amino)propil]carbamato;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(pirrolidin-2-ilmetil)amino]metil}azetidin-3-ol;

1,1-dimetiletil 4-[({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)metil]piperidina-1-carboxilato;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(2-hidroxifenil)metil]amino}metil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(3-hidroxifenil)metil]amino}metil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenyl)amino]fenil}carbonil)-3-({[(4-hidroxifenil)metil]amino}metil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(4-hidroxibutil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-hidroxietil)oxi]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(1*S*,2*S*)-2-hidroxiciclohexil]amino}metil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(1,1-dimetil-2-pirrolidin-1-iletil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(1-metil-1*H*-imidazol-4-il)metil]amino}metil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(1-metil-1*H*-imidazol-5-il)metil]amino}metil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[(2*S*)-2-(metiloxi)ciclopentil]amino}metil)azetidin-3-ol;

3-{[1,1'-bi(ciclohexil)-2-ilamino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil} carbonil)-3-({[3-(metiloxi)fenil]amino}metil)azetidin-3-ol;

Ácido 1-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil) amino]fenil} carbonil)-3-hidroxiazetidin-3-il]metil}amino) ciclopentanecarboxílico;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil} carbonil)-3-{[(4-fluorofenil)amino}metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil} carbonil)-3-[(1,3,5-triazin-2-ilamino)metil]azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil} carbonil)-3-{[(*trans*-4-hidroxiciclohexil)amino]metil}azetidin-3-ol;

3-[(ciclopent-3-en-1-ilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

N-[4-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil} carbonil)-3-hidroxiazetidin-3-il]metil}amino)fenil]acetamida;

N-[3-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil} carbonil)-3-hidroxiazetidin-3-il]metil}amino)fenil]acetamida;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil} carbonil)-3-(1-metilpirrolidin-2-il)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil} carbonil)-3-[(1*H*-1,2,4-triazol-3-ilamino)metil]azetidin-3-ol;

3-[1-(dietilamino)propil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

3-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)-5-(hidroximetil)ciclopentano-1,2-diol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-piperidin-2-ilazetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(3-fluorofenil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1-metilpiperidin-2-il)azetidin-3-ol;

1-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}guanidina;

1-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}-3-nitroguanidina;

N-{1-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]etil}acetamida;

(2*R*)-*N*-{1-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]etil}-3,3,3-trifluoro-2-(metiloxi)-2-fenilpropanamida;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenyl)amino]fenil}carbonil)-3-{[(piperidin-4-ilmetil)amino]metil}azetidin-3-ol;

3-{[(3-aminopropil)amino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[({[2-(4-metilpiperazin-1-il)fenil]metil}amino)metil]azetidin-3-ol;

3-{[(1,1-dimetiletil)amino]metil}-1-({4-[(2-fluoro-4-yodofenil)amino]-3-tienil}carbonil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-hidroxiciclohexil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2,2,3,3,3-pentafluoropropil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(3,3,3-trifluoropropil)amino]metil}azetidin-3-ol;

N-[3-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)fenil]metanosulfonamida;

N-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}metanosulfonamida;

3-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)-1*H*-pirazol-5-ol;

(1*R*,2*S*)-4-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)ciclopentano-1,2-diol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[1-(hidroximetil)ciclohexil]amino}metil)azetidin-3-ol;

3-{[(3-clorofenil)amino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

3-{[(4-clorofenil)amino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

3-[(5-amino-3-metil-1*H*-pirazol-1-il)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(5-metil-1*H*-pirazol-3-il)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1-etilpirrolidin-2-il)azetidin-3-ol;

(2*R*)-*N*-{(1*S*)-1-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]etil}-3,3,3-trifluoro-2-(metiloxi)-2-fenilpropanamida;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[4-(metiloxi)fenil]amino}metil)azetidin-3-ol;

3-(1-amino-2-metilpropil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

3-{[(4-aminofenil)amino]metil}-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-hidroxi-2-metilciclopentil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{1-[(4-hidroxiciclohexil)amino]etil}azetidin-3-ol;

metil (2xi)-2-desoxi-2-({[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}amino)-beta-D-arabino-hexopiranosida;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-piridin-2-ilazetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-({[1-(hidroximetil)ciclopentil]amino}metil)azetidin-3-ol;

1-ciano-3-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonyl)-3-hidroxiazetidin-3-il]metil}guanidina;

6-({3-[(etilamino)metil]-3-fluoroazetidin-1-il}carbonil)-2,3-difluoro-*N*-(2-fluoro-4-yodofenil)anilina;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1-nitroetil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(3-fluoro-4-hidroxifenil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-{[(2-fluoro-4-hidroxifenil)amino]metil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[1-(metilamino)etil]azetidin-3-ol;

3-(1-aminoetil)-1-({8-cloro-7-[(2-fluoro-4-yodofenil)amino]imidazo[1,2-a]piridin-6-il}carbonil)azetidin-3-ol;

1-({8-fluoro-7-[(2-fluoro-4-yodofenil)amino]imidazo[1,2-*a*]piridin-6-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol;

1-({8-fluoro-7-[(2-fluoro-4-yodofenil)amino]imidazo[1,2-*a*]piridin-6-il}carbonil)-3-{(1*S*)-1-[(2-hidroxi-2-metilciclopentil)amino]etil}azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1*H*-imidazol-2-il)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1*H*-pirrol-2-il)azetidin-3-ol;

N-{[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]metil}bencencarboximidamida;

3-({[(E)-1-amino-2-nitroetenil]amino}metil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1-metil-1-nitroetil)azetidin-3-ol;

3-(1-amino-1-metiletil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

3-[(1*H*-bencimidazol-2-ilamino)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(1*H*-imidazol-2-ilamino)metil]azetidin-3-ol;

metil {1-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]etil}carbamato;

3-(1*H*-bencimidazol-2-il)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[1-(dimetilamino)etil]azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(pirimidin-2-ilamino)metil]azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(piridin-2-ilamino)metil]azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1-metil-1*H*-imidazol-2-il)azetidin-3-ol;

3-(1-aminobutil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

1-({2-fluoro-3-[(2-fluoro-4-yodofenil)amino]piridin-4-il}carbonil)-3-[(2*S*)-pirrolidin-2-il]azetidin-3-ol;

1-({8-fluoro-7-[(2-fluoro-4-yodofenil)amino]-4-metilcinolin-6-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol;

3-[amino(fenil)metil]-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(5-metil-1*H*-imidazol-2-il)azetidin-3-ol;

1,1-dimetiletil (2*S*)-2-[1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-hidroxiazetidin-3-il]piperidina-1-carboxilato;

1-({2-[(4-bromo-2-clorofenil)amino]-3,4-difluorofenil}carbonil)-3-piperidin-2-ilazetidin-3-ol;

3-(1-amino-3-hidroxipropil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(1*H*-imidazol-2-ilmetil)azetidin-3-ol;

3-(1-aminociclopentil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

3-(2-aminociclohexil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

3-(2-aminociclopentil)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-azetidin-3-ol;

1-({4-fluoro-5-[(2-fluoro-4-yodofenil)amino]-1-metil-1*H*-bencimidazol-6-il}carbonil)-3-piperidin-2-ilazetidin-3-ol;

1-({5-[(4-bromo-2-clorofenil)amino]-4-fluoro-1-metil-1*H*-bencimidazol-6-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol;

1-({8-cloro-7-[(2-fluoro-4-yodofenil)amino]imidazo[1,2-a]piridin-6-il}carbonil)-3-piperidin-2-ilazetidin-3-ol;

1-({2-[(4-bromo-2-fluorofenil)amino]-3,4-difluorofenil}carbonil)-3-piperidin-2-ilazetidin-3-ol;

1-({7-[(4-bromo-2-fluorofenil)amino]-8-fluoroimidazo[1,2-*a*]piridin-6-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(3-metil-1-nitrobutil)azetidin-3-ol;

3-(2-aminopirimidin-4-il)-1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)azetidin-3-ol;

1-({7-[(4-bromo-2-clorofenil)amino]-8-cloroimidazo[1,2-a]piridin-6-il}carbonil)-3-piperidin-2-ilazetidin-3-ol;

1-({8-cloro-7-[(2-fluoro-4-yodofenil)amino]imidazo[1,2-a]piridin-6-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol;

1-({7-[(4-bromo-2-clorofenil)amino]-8-cloroimidazo[1,2-a]piridin-6-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol;

1-({4-fluoro-5-[(2-fluoro-4-yodofenil)amino]-1-metil-1*H*-bencimidazol-6-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol;

3-[(1*S*)-1-aminoetil]-1-({5-[(4-bromo-2-clorofenil)amino]-4-fluoro-1-metil-1*H*-bencimidazol-6-il}carbonil)azetidin-3-ol;

1-({5-[(4-bromo-2-clorofenil)amino]-4-fluoro-1-metil-1*H*-benvimidazol-6-il}carbonil)-3-[(1*S*)-1-(metilamino)etil]azetidin-3-ol;

4-[(4-bromo-2-fluorofenil)amino]-3-fluoro-5-({3-hidroxi-3-[(2*S*)-piperidin-2-il]azetidin-1-il}carbonil)piridin-2(1*H*)-ona;

4-[(2-fluoro-4-yodofenil)amino]-5-({3-hidroxi-3-[(2*S*)-piperidin-2-il]azetidin-1-il}carbonil)-1-metilpiridin-2(1*H*)-ona;

4-[(2-fluoro-4-yodofenil)amino]-5-({3-hidroxi-3-[(2*S*)-piperidin-2-il]azetidin-1-il}carbonil)-1-metilpiridin-2(1*H*)-ona;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(1*S*,2*S*)-2-hidroxiciclohexil]azetidin-3-ol;

4-[(2-fluoro-4-yodofenil)amino]-5-({3-hidroxi-3-[(1*S*)-1-(metilamino)propil]azetidin-1-il}carbonil)-1-metilpiridin-2(1*H*)-ona;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(1*S*,2*R*)-2-hidroxiciclohexil]azetidin-3-ol;

5-({3-[(1*S*)-1-(dimetilamino)etil]-3-hidroxiazetidin-1-il}carbonil)-4-[(2-fluoro-4-yodofenil)amino]-1-metilpiridin-2(1*H*)-ona;

4-[(2-fluoro-4-yodofenil)amino]-5-({3-hidroxi-3-[(metilamino)metil]azetidin-1-il}carbonil)-1-metilpiridin-2(1*H*)-ona;

5-{[3-(1*H*-bencimidazol-2-il)-3-hidroxiazetidin-1-il]carbonil}-4-[(4-bromo-2-fluorofenil)amino]-1-metilpiridin-2(1*H*)-ona;

4-[(4-bromo-2-fluorofenil)amino]-5-{[3-hidroxi-3-(1-metil-1*H*-bencimidazol-2-il)azetidin-1-il]carbonil}-1-metilpiridin-2(1*H*)-ona;

4-[(4-bromo-2-fluorofenil)amino]-5-({3-hidroxi-3-[(2*S*)-pirrolidin-2-il]azetidin-1-il}carbonil)-1-metilpiridin-2(1*H*)-ona;

1-({3-fluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol;

1-({4-fluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol;

1-({6-[(4-bromo-2-clorofenil)amino]-7-fluoro-3-metil-1,2-bencisoxazol-5-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-(6-metilpiperidin-2-il)azetidin-3-ol;

1-({3,4-difluoro-2-[(2-fluoro-4-yodofenil)amino]fenil}carbonil)-3-piperazin-2-ilazetidin-3-ol;

5-[(2-fluoro-4-yodofenil)amino]-6-({3-hidroxi-3-[(2*S*)-piperidin-2-il]azetidin-1-il}carbonil)-2-metilpiridazin-3(2*H*)-ona;

5-[(4-bromo-2-clorofenil)amino]-6-({3-hidroxi-3-[(2*S*)-piperidin-2-il]azetidin-1-il}carbonil)-2-metilpiridazin-3(2*H*)-ona;

5-[(4-bromo-2-clorofenil)amino]-4-fluoro-6-({3-hidroxi-3-[(2*S*)-pirrolidin-2-il]azetidin-1-il}carbonil)-2-metilpiridazin-3(2*H*)-ona;

1-({3-[(2-fluoro-4-yodofenil)amino]-1-oxidopiridin-4-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol;

1-({2-fluoro-3-[(2-fluoro-4-bromofenil)amino]piridin-4-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol;

3-[(1*S*)-1-aminopropil]-1-({3-[(2-fluoro-4-yodofenil)amino]piridin-4-il}carbonil)azetidin-3-ol;

1-({3-[(2-fluoro-4-yodofenil)amino]piridin-4-il}carbonil)-3-[(1*S*)-1-(metilamino)propil]azetidin-3-ol;

(1*R*,2*S*)-4-({(1*S*)-1-[1-({2-fluoro-3-[(2-fluoro-4-yodofenil)amino]piridin-4-il}carbonil)-3-hidroxiazetidin-3-il]propil}amino)ciclopentano-1,2-diol;

1-({7-[(4-bromo-2-clorofenil)amino]-8-fluoro-4-metilcinolin-6-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol;

1-({7-[(4-bromo-2-fluorofhenil)amino]-8-fluoro-4-metilcinolin-6-il}carbonil)-3-[(2*S*)-piperidin-2-il]azetidin-3-ol;

3-[(1*S*)-1-aminoetil]-1-({7-[(4-bromo-2-fluorofenil)amino]cinolin-6-il}carbonil)azetidin-3-ol;

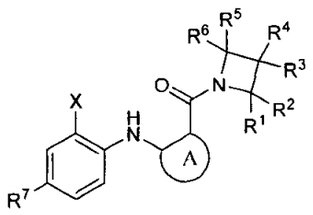
1-({7-[(4-bromo-2-fluorogenil)amino]cinolin-6-il}carbonil)-3-{(1*S*)-1-[(2-hidroxy-2-metilciclopentil)amino]etil}azetidin-3-ol;

1-({7-[(4-bromo-2-fluorofenil)amino]cinolin-6-il}carbonil)-3-[(1*S*)-1-(dimetilamino)etil]azetidin-3-ol;

3-[(1*S*)-1-aminoetil]-1-({5-[(2-fluoro-4-yodofenil)amino]-1*H*-1,2,3-benzotriazol-6-il}carbonil)azetidin-3-ol;

RESUMEN DE LA INVENCIÓN

Se describen compuestos de la Fórmula I:



I

y sales y solvatos farmacéuticamente aceptables de ellos. Dichos compuestos son inhibidores de MEK y son útiles en el tratamiento de enfermedades proliferativas, tales como el cáncer. También se revelan composiciones farmacéuticas que contienen dichos compuestos así como métodos de uso de los compuestos y las composiciones de la invención en el tratamiento del cáncer.

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EN MEDIO MAGNETICO

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(71) Applicant *(for all designated States except US)*: **EXELIXIS, INC.** [US/US]; 210 East Grand Avenue, P.O. Box 511, South San Francisco, CA 94083-0511 (US).

(72) Inventors; and

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(74) Agents: **WADE, Janice V.** et al.; EXELIXIS, INC, 210 East Grand Avenue, P.O. Box 511, South San Francisco, CA 94083-0511 (US).

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

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Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: AZETIDINES AS MEK INHIBITORS FOR THE TREATMENT OF PROLIFERATIVE DISEASES

(57) Abstract: Disclosed are compounds of Formula (I) and pharmaceutically acceptable salts and solvates thereof. Such compounds are MEK inhibitors and are useful in the treatment of proliferative diseases, such as cancer. Also disclosed are pharmaceutical compositions containing such compounds as well as methods of using the compounds and compositions of the invention in the treatment of cancer.

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Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [X] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [X]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- Descripción de la invención [X]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [X]

COMPLETA [X] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

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

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

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

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha_____

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910

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
MAYA RODRIGUEZ CARLOS ORLANDO
Apoderado(a) y/o Representante de
EXELIXIS, INC

REFERENCIA	Radicación No.	08 44683
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	Fecha inicio fase nacional	07/05/2008
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	6757

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

2. El solicitante deberà aclarar los nombres de los dos ùltimos inventores consignados en el petitorio fase nacional, por cuanto difieren de los presentados en la publicación internacional.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 23 MAYO 2008
adpa11