Industria y Comercio

SUPERINTENDENCIA

Organizacion CSA Ltda

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

09-126924

21. **EXPEDIENTE No.**

54. **TÍTULO** USO DE INHIBIDORES DE PIRIDOPIRIMIDINONA DE PI3K-ALFA EN EL TRATAMIENTO DEL CANCER

51. **CLASIFICACIÓN INTERNACIONAL** A61K 31/519

71. **SOLICITANTE** EXELIXIS, Inc.,

DOMICILIO South San FRANCISCO, CA, USA

74. **APODERADO** CARLOS ORLANDO MAYA RODRIGUEZ

22. **BOGOTÁ, D.C.,** 09 de NOVIEMBRE de 2009

Con. no pago tarifa
Fn. 10-11-2009

(FORMA P-10)

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-126924- -00000-0000
Fecha: 2009-11-09 16:43:13 Dep: 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 905

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

2. SOLICITANTE .(71)

Nombre: **EXELIXIS, INC**

Dirección: **220 East Grand Avenue, P.O. Box 511, South San Francisco, CA 94083, US**

Domicilio: **South Francisco, CA 94083, 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 230. Parque Central Bavaria**

Teléfono: **3419841** Fax: **2435423**

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.- LAMB, Peter

2.- MATTHEWS, David

Dirección: **1.- 814 Mandana Blvd, Oakland, California 94610, USA.**
2.- 2 Balceta Avenue, San Francisco, California 94127, USA

Nacionalidad o Domicilio: 1 Ciudadano de USA
2 Ciudadano de REINO UNIDO

5. PCT (86)

Solicitud internacional No. **PCT/US2008/004573** Fecha: **ABRIL 09/2008**

Publicación internacional No. **WO 2008/124161 A1** Fecha: **OCTUBRE 16/2008**

6. Título (54) **USO DE INHIBIDORES DE PIRIDOPIRIMIDINONA DE PI3K-ALFA EN EL TRATAMIENTO DEL CÁNCER.**

7. Clasificación Internacional (51) A61K 31/517, A61P 35/00 A61K 31/337

8. Prioridad Si [X] No [ ]

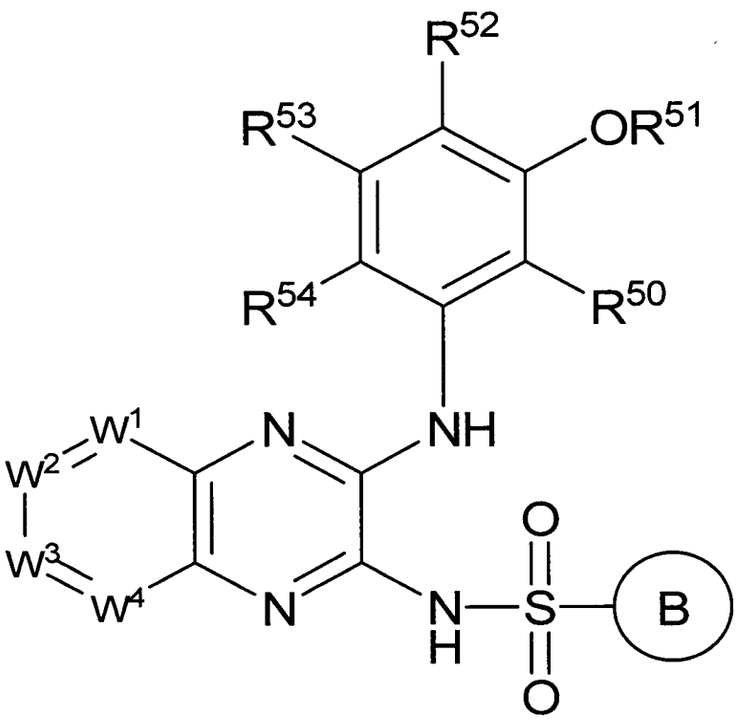
(33) País de Origen	(32) Fecha	(31) Número deSolicidud
USA	10-Abr-07	60/922,899

9. Comprobante de pago No. **09-83,652 Y 09-83,663** Fecha **NOVIEMBRE 09/2009**

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(EXP.09-113466)
- [X] Poderes, si fuere el caso (LA COPIA AUTENTICA REPOSA EN EL EXPEDIENTE 09-113466)
- [ ] 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 (CARATULA DE LA PUBLICACION INTERNACIONAL, EL COMPROBANTE DE PAGO POR EXCEDENTE PALABRAS PUBLICACION 09-83,663)

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

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 83,652
FECHA : NOVIEMBRE 9 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-126924- -00000-0000

Fecha: 2009-11-09 16:43:13 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 905

***** 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	53363170	09/11/2009	3,564,920.00

***** 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		540,000.00
		TOTAL :	$	540,000.00

SON: QUINIENTOS CUARENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 09 - 83,663
FECHA : NOVIEMBRE 9 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-126924- -00000-0000
Fecha: 2009-11-09 16:43:13 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 905

***** 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	53363170	09/11/2009	3,564,920.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS	90,180.00
		TOTAL : $	90,180.00

SON: NOVENTA MIL CIENTO OCHENTA PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

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

ACTUACION NOTARIAL
LEY 404

N 007410568

CECBA - LEY404 GCBA
LEGALIZACION
021083506
$20.00
14:42:24
19/02/2007

CECBA - LEY404 GCBA
APOSTILLA
021905388
$39.00
14:42:29
19/02/2007

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 dicho país con las siguientes facultades: "... poder amplio y suficiente para recabar 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

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 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. 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.-

ALEJANDRO M. LIPORACE
Matricula 3837
ESCRIBANO PUBLICO

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

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.**

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

Buenos Aires, Lunes 19 de Febrero de 2007

ESC. EDDA ENRIQUETA SINELLI
COLEGIO DE ESCRIBANOS
CONSEJERA

APOSTILLE

REPUBLICA ARGENTINA

(Convention de La Haye du 5 octobre 1961)

A 00104498

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: 070219053883

9. Sello / Timbre

COLEGIO DE ESCRIBANOS - APOSTILLA - CAPITAL FEDERAL - REPUBLICA ARGENTINA

10. Firma

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

GRAFICA LATINA S.R.L.

Folio 327/2007

DANIEL GOYTIA - PATENTS & TRADEMARKS

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

ALEJANDRO M. LIPORACE
Matricula 3837
ESCRIBANO PUBLICO

CERTIFICACIÓN NOTARIAL (INDIVIDUO)

A los _____ días del mes de _____

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

NOTARIAL CERTIFICATION (INDIVIDUAL)

On this _____ day of _____

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 25th day of January, 2007

ATTESTING OFFICIAL
Christoph Pereira
Vice President, Legal Affairs and Secretary

ALEJANDRO M. LIPORACE
Matricula 3837
ESCRIBANO PUBLICO

10

State of California

SECRETARY OF STATE

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. *Country: United States of America*
   This public document
2. *has been signed by 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*

Jena Bowen
Secretary of State

NP-24 A (REV. 1-07)

BY Borrego

OSP 06 99602

EL GRAN SELLO DEL ESTADO DE CALIFORNIA

ALEJANDRO M. LIPORACE
Matrícula 3837

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

J. Cohen
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
☐ Individual
☑ Corporate Officer — Title(s): Senior Vice President
☐ Partner — ☐ Limited ☐ General
☐ Attorney in Fact
☐ Trustee
☐ Guardian or Conservator
☐ Other: _____
Signer Is Representing: Exelixis, Inc.

RIGHT THUMBPRINT OF SIGNER
Top of thumb here

Signer's Name: Christoph Pereira
☐ Individual
☑ Corporate Officer — Title(s): Secretary
☐ Partner — ☐ Limited ☐ General
☐ Attorney in Fact
☐ Trustee
☐ Guardian or Conservator
☐ Other: _____
Signer Is Representing: Exelixis

RIGHT THUMBPRINT OF SIGNER
Top of thumb here

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

ALEJANDRO M. LIPORACE
Matricula 3837

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 ----------

ALEJANDRO M. LIPORACE
Matricula 3837

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 (EJ., "JANE DOE, ESCRIBANO

ALEJANDRO M. LIPONACE
Matricula 3837
ESCRIBANO PUBLICO

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.----------
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[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----------
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Persona(s) Firmante(s) distinta de la mencionada anteriormente:

ALEJANDRO M. LIPORACE
Matrícula 3837

[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----------

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

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

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

[ ] Persona Física----------

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

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

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

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

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COLEGIO DE TRADUCTORES PUBLICOS
DE LA CIUDAD DE BUENOS AIRES
Corresponde a la Legalización
Nº 74 - 3424/07
ESTEBAN SANTIAGO ALLEGRETTI

VALERIA ROSE
DANIEL GOYTIA
AGENTE Nº 464

ALEJANDRO M. LIPORACE
Matricula 3837
ESCRIBANO PUBLICO

N° 00960454 17

COLEGIO DE TRADUCTORES PÚBLICOS
DE LA CIUDAD DE BUENOS AIRES

REPÚBLICA ARGENTINA
LEY 20.305

LEGALIZACIÓN

Por la presente, el COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES, en virtud de la facultad que le confiere el artículo 10, inc. d) de la Ley 20.305, certifica únicamente que la firma y el sello que aparecen en la traducción adjunta, concuerdan con los correspondientes al Traductor Público **FIORI UGARTE, VALERIA**

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

INGLES	233	13

Buenos 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

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THIS CERTIFICATION IS NOT VALID WITHOUT THE STAMP ON THE LAST PAGE OF THE ATTACHED TRANSLATION.

ALEJANDRO M. Matricula ESCRIBANO

Vu par le *COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES* (Ordre de Traducteurs Officiels de la ville de Buenos Aires), en vertu des attributions qui lui ont été accordées par l´article 10, alinéa d) de la Loi nº 20.305, pour la seule légalisation matérielle de la signature et du sceau du *Traductor Público* (Traducteur Officiel) apposés sur la traduction du document ci-joint, qui sont conformes à ceux déposés aux archives de cette Institution.
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CERTIFICO EN SELLO DE ACTUACION NOTARIAL Nº T005904431
BUENOS AIRES 14/2/1071

ALEJANDRO M. LIPOBACE
Matricula 3837
ESCRIBANO PUBLICO

APOSTILLE

REPUBLICA ARGENTINA

(Convention de La Haye du 5 octobre 1961)

A 00104499

1. PAÍS: REPUBLICA ARGENTINA

El presente documento público

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3. Quien actúa en calidad de CONSEJERA

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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
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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
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3837
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ALEJANDRO M. LIPORACE
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(71) Applicant *(for all designated States except US)*: **EXELIXIS, INC.** [US/US]; Post Office Box 511, 210 East Grand Avenue, South San Francisco, CA 94083-0511 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **LAMB, Peter** [US/US]; 814 Mandana Blvd, Oakland, California 94610 (US). **MATTHEWS, David** [GB/US]; 2 Balceta Avenue, San Francisco, California 94127 (US).

(74) Agents: **WADE, Janice V.** et al.; EXELIXIS, Inc., 210 East Grand Avenue Post Office 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, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, 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, UZ, VC, VN, ZA, ZM, ZW.

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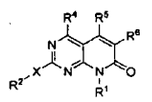
[Continued on next page]

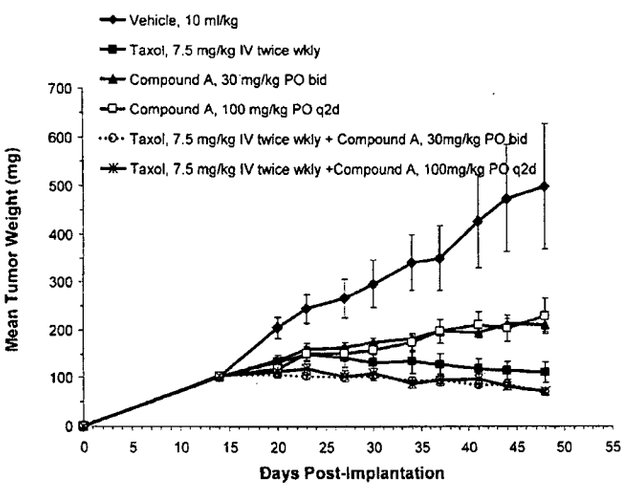
(54) Title: METHODS OF TREATING CANCER USING PYRIDOPYRIMIDINONE INHIBITORS OF PI3K ALPHA

(57) Abstract: The present invention provides methods of treating cancer by administering a compound of Formula I, optionally as a pharmaceutically acceptable salt, solvate and/or hydrate thereof, in combination with other cancer treatments. (Formula I)



(I)

Fig. 1. Compound A + Taxol in PC-3 Prostate Carcinoma Tumor Model



WO 2008/124161 A1

European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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METHODS OF TREATING CANCER USING PYRIDOPYRIMIDINONE INHIBITORS OF PI3K ALPHA

Cross-Reference to Related Applications

[0001] The Applicants claim priority under 35 U.S.C. 119(e) to copending Provisional Application No. 60/922,899 filed on April 10, 2007, the disclosure of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] This invention relates to methods of treating cancer with a compound that inhibits lipid kinase enzymatic activity and the resultant modulation of cellular activities (such as proliferation, differentiation, programmed cell death, migration, chemoinvasion and metabolism) in combination with anticancer agents.

BACKGROUND OF THE INVENTION

[0003] Improvements in the specificity of agents used to treat various disease states such as cancer, metabolic, and inflammatory diseases 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] Phosphatidylinositol 3-kinase (PI3K or PIK3CA) is composed of an 85 kDa regulatory subunit and a 110 kDa catalytic subunit. The protein encoded by this gene represents the catalytic subunit, which uses ATP to phosphorylate PtdIns, PtdIns4P and PtdIns(4,5)P2. PTEN, a tumor suppressor which inhibits cell growth through multiple mechanisms, can dephosphorylate PIP3, the major product of PIK3CA. PIP3, in turn, is required for translocation of protein kinase B (AKT1, PKB) to the cell membrane, where it is phosphorylated and activated by upstream kinases. The effect of PTEN on cell death is mediated through the PIK3CA/AKT1 pathway.

[0005] PI3Kα has been implicated in the control of cytoskeletal reorganization, apoptosis, vesicular trafficking, proliferation and differentiation processes. Increased copy number and expression of PIK3CA or activating mutations in the p110a catalytic subunit of PIK3CA are associated with a number of malignancies such as ovarian cancer (Campbell et al., *Cancer Res* **2004**, *64*, 7678-7681; Levine et al., *Clin Cancer Res* **2005**, *11*, 2875-2878; Wang et al., *Hum Mutat* **2005**, *25*, 322; Lee et al., *Gynecol Oncol* **2005**, *97*, 26-34), cervical

cancer, breast cancer (Bachman, et al. *Cancer Biol Ther* **2004**, *3,* 772-775; Levine, et al., supra; Li et al., *Breast Cancer Res Treat* **2006,** *96*, 91-95; Saal et al., *Cancer Res* **2005,** *65*, 2554-2559; Samuels and Velculescu, *Cell Cycle* **2004,** *3,* 1221-1224), colorectal cancer (Samuels, et al. *Science* **2004,** *304,* 554; Velho et al. *Eur J Cancer* **2005,** *41,* 1649-1654), endometrial cancer (Oda et al. *Cancer Res.* **2005,** *65,* 10669-10673), gastric carcinomas (Byun et al., *Int J Cancer* **2003,** *104,* 318-327; Li et al., supra; Velho et al., supra; Lee et al., *Oncogene* **2005,** *24,* 1477-1480), hepatocellular carcinoma (Lee et al., *id.*), small and non-small cell lung cancer (Tang et al., *Lung Cancer* **2006,** *51,* 181-191; Massion et al., *Am J Respir Crit Care Med* **2004,** *170,* 1088-1094), thyroid carcinoma (Wu et al., *J Clin Endocrinol Metab* **2005,** *90,* 4688-4693), acute myelogenous leukemia (AML) (Sujobert et al., *Blood* **1997,** *106,* 1063-1066), chronic myelogenous leukemia (CML) (Hickey and Cotter *J Biol Chem* **2006,** *281,* 2441-2450), and glioblastomas (Hartmann et al. *Acta Neuropathol (Berl)* **2005,** *109,* 639-642; Samuels et al., supra).

[0006] In view of the important role of PI3K-α in biological processes and disease states, inhibitors and/or modulators of this lipid kinase are desirable. In addition, it is well established that combining treatments with different mechanisms of action often leads to enhanced anti-tumor activity as compared to single treatments administered alone. This is true for combinations of chemotherapies (e.g. Kyrgiou M. et. al. *J Natl Cancer Inst* **2006**, *98*, 1655) and combinations of antibodies and chemotherapy (e.g. Pasetto LM et. al. *Anticancer Res* **2006**, *26,* 3973.

[0007] For example, activation of the PI3K pathway contributes to the resistance of human tumor cells to a wide variety of chemotherapeutic agents, including microtubule stabilizing agents such as taxol (Brognard, J., et. al. *Cancer Res* **2001,** *61*, 3986-3997; Clark, A. S., et. al. *Mol Cancer Ther* **2002,** *1*, 707-717; Kraus, A. C., et. al. *Oncogene* **2002,** *21*, 8683-8695; Krystal, G. W., et. al. *Mol Cancer Ther* **2002,** *1*, 913-922; and Yuan, Z. Q., et. al. *J Biol Chem* **2003,** *278*, 23432-23440). Taxol is widely used to treat advanced cancers including prostate carcinomas, which frequently harbor deletions in the PTEN gene, resulting in elevated signaling downstream of PI3K. A number of preclinical studies suggest that inhibiting signaling downstream of PI3K restores or enhances the ability of chemotherapeutic agents such as taxol to kill tumor cells (Brognard, J., et. al. *Cancer Res* **2001,** *61*, 3986-3997; Clark, A. S., et. al. *Mol Cancer Ther* **2002,** *1*, 707-717; Kraus, A. C., et. al. *Oncogene* **2002,** *21*, 8683-8695; Krystal, G. W., et. al. *Mol Cancer Ther* **2002,** *1*, 913-922; and Saga, Y., et. al. *Clin Cancer Res* **2002,** *8*, 1248-1252).

[0008] Rapamycin, another chemotherapeutic agent, is a potent inhibitor of the mTOR/Raptor complex. Inhibition of mTOR/Raptor prevents p70S6K and S6 phosphorylation, but also leads to relief of a negative feedback loop emanating from p70S6K that serves to downregulate PI3K (Sarbassov, D. D., et. al. *Science* **2005,** *307*, 1098-1101). As a result, rapamycin treatment can lead to upregulation of PI3K and increased phosphorylation of AKT (O'Donnell, A., et. al. paper presented at Proc Am Soc Clin Oncol. 2003; and O'Reilly, K. E., et. al. *Cancer Res* **2006,** *66*, 1500-1508). Thus, combining rapamycin with inhibitors of PI3K can enhance the efficacy of rapamycin (Powis, G. et. al. *Clinical Cancer Research* **2006,** *12,* 2964-2966; Sun, S.-Y., et. al. *Cancer Research* **2005,** *65,* 7052-7058).

[0009] A growing body of clinical and preclinical data indicates that activation of the PI3K pathway confers resistance to EGFR inhibitors such as erlotinib (Bianco, R., et. al. *Oncogene* **2003,** *22*, 2812-2822; Chakravarti, A., et. al. *Cancer Res* **2002,** *62*, 200-207; and Janmaat, M. L., et. al. *Clin Cancer Res* **2003,** *9*, 2316-2326). Both NSCLC patients with K-Ras mutations and glioblastoma patients with PTEN deletions fail to respond to erlotinib, potentially because of genetic activation of the PI3K pathway (Mellinghoff, I. K., et. al. *N. Eng. J Med.* **2006,** *353,* 2012-2024). Preclinical studies have shown that downregulation of PI3K signaling in EGFR-expressing tumor cells confers increased sensitivity to EGFR inhibitors (Ihle, N. T., et. al. *Mol Cancer Ther* **2005,** *4*, 1349-1357). Thus, treating cancer with a PI3K inhibitor in combination with an EGFR inhibitor, such as erlotinib, is desirable.

[0010] Activation of the PI3K pathway also contributes to the resistance of human tumor cells to DNA damaging agents, such as platins. A number of preclinical studies suggest that inhibiting signaling downstream of PI3K restores or enhances the ability of chemotherapeutic agents such as platins to kill tumor cells (Brognard, J., et. al. *Cancer Res* **2001,** *61*, 3986-3997; and Yuan, Z. Q., et. al. *J Biol Chem* **2003,** *278*, 23432-23440). Carboplatin is widely used to treat advanced cancers including non-small cell lung carcinomas (NSCLC), which frequently harbor activating mutations in the K-Ras gene, resulting in activation of PI3K (Aviel-Ronen S., et. al. *Clin Lung Cancer* **2006,** *8,* 30-38). NSCLC patients with K-Ras mutations do not respond to EGFR inhibitors such as Tarceva, and thus represent a significant unmet medical need (Janne PA, et. al. *J Clin Oncology* **2005,** *23*, 3227-3234). Thus, treating NSCLC with a DNA-damaging agent such as a platin in combination with an inhibitor of PI3K is desirable in light of the lack of efficacious treatments.

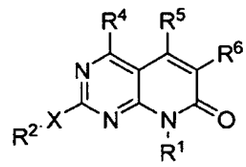
[0011] Treatments that combine an inhibitor of PI3K-α with other anti-cancer agents are desirable and needed.

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] The compositions of the invention are used to treat diseases associated with abnormal and or unregulated cellular activities. Disease states which can be treated by the methods and compositions provided herein include cancer. The invention is directed to methods of treating these diseases by administering a Compound of Formula I or II in combination with one or more treatments.

[0014] One aspect of the Invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I:



I

or a single isomer thereof where the compound is optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof; 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 combination with one or more treatments independently selected from surgery, one or more chemotherapeutic agents, one or more hormone therapys, one or more antibodys, one or more immunotherapies, radioactive iodine therapy, and radiation, where the Compound of Formula I is that wherein:

R^1 is hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

R^2 is hydrogen or alkyl where the alkyl is optionally substituted with 1, 2, 3, 4, or 5 R^8 groups;

X is $-NR^3-$;

R^3 hydrogen;

R^4 is optionally substituted alkyl;

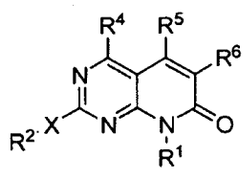
R^5 is hydrogen; and

R^6 is phenyl, acyl, or heteroaryl wherein the phenyl and heteroaryl are optionally substituted with 1, 2, 3, 4, or 5 R^9 groups;

each R^8, when present, is independently hydroxy, halo, alkoxy, haloalkoxy, amino, alkylamino, dialkylaminoalkyl, or alkoxyalkylamino; and

each R^9, when present, is independently halo, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, amino, alkylamino, dialkylamino, alkoxyalkyl, carboxyalkyl, alkoxycarbonyl, aminoalkyl, cycloalkyl, aryl, arylalkyl, aryloxy, heterocycloalkyl, or heteroaryl and where the cycloalkyl, aryl, heterocycloalkyl, and heteroaryl, each either alone or as part of another group within R^9, are independently optionally substituted with 1, 2, 3, or 4 groups selected from halo, alkyl, haloalkyl, hydroxy, alkoxy, haloalkxy, amino, alkylamino, and dialkylamino.

[0015] A second aspect of the Invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula II:



II

or a single isomer thereof where the compound is optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof; or administering a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula II and a pharmaceutically acceptable carrier, excipient, or diluent in combination with one or more treatments independently selected from surgery, one or more chemotherapeutic agents, one or more hormone therapys, one or more antibodys, one or more immunotherapies, radioactive iodine therapy, and radiation, where the Compound of Formula II is that wherein:

R^1 is hydrogen, optionally substituted alkyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

X is S, SO_2, or -NR^3-;

R^2 is hydrogen, haloalkyl, optionally substituted alkyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heterocycloalkyl-aryl- or optionally substituted heteroaryl; R^2 is optionally further substituted with one or more R^8 groups;

R^3, R^{3a}, and R^{3b} are independently hydrogen, optionally substituted alkyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted aryl, optionally substituted heterocycloalkyl or optionally substituted heteroaryl;

R^4 is hydrogen, halo, haloalkyl, haloalkoxy, -NR^{3a}-, optionally substituted alkyl, optionally substituted C_1-C_6 alkoxy, optionally substituted C_1-C_6 alkoxyalkyl, optionally substituted aminoalkyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

R^5 is hydrogen, halo, haloalkyl, haloalkoxy, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkoxy, optionally substituted C_1-C_6 alkoxyalkyl, optionally substituted aminoalkyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted aryl, optionally substituted aryl C_1-C_6 alkyl or optionally substituted heteroaryl; and

R^6 is hydrogen, halo, haloalkyl, haloalkoxy, -NR^{3b}-, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkoxy, optionally substituted C_1-C_6 alkoxyalkyl, optionally substituted acyl, optionally substituted aminoalkyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl; substitutable R^6 groups are optionally further substituted with 1, 2, 3, 4, or 5 R^9 groups;

each R^8, when present, is independently hydroxy, halo, haloalkyl, haloalkoxy, optionally substituted alkyl, optionally substituted C_1-C_6 alkoxy, optionally substituted C_1-C_6 alkoxyalkyl, optionally substituted C_1-C_6 alkoxyalkylaminoalkyl, C_1-C_6 alkylcarboxyheterocycloalkyl, oxy C_1-C_6alkylheterocycloalkyl, optionally substituted aminoalkyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted aryl, optionally substituted aryl C_1-C_6 alkyl, optionally substituted heterocycloalkyl,

optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

each R^9, when present, is independently halo, haloalkyl, haloalkoxy, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkoxy, optionally substituted C_1-C_6 alkoxyalkyl, optionally substituted C_1-C_6 carboxyalkyl, optionally substituted alkoxycarbonyl, optionally substituted aminoalkyl, optionally substituted C_3-C_7 cycloalkyl, optionally substituted aryl, optionally substituted aryl C_1-C_6 alkyl, optionally substituted aryloxy, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl.

DETAILED DESCRIPTION OF THE INVENTION

Abbreviations and Definitions

[0016] The following abbreviations and terms have the indicated meanings throughout:

Abbreviation	Meaning
Ac	acetyl
br	broad
°C	degrees Celsius
c-	cyclo
CBZ	CarboBenZoxy = benzyloxycarbonyl
d	doublet
dd	doublet of doublet
dt	doublet of triplet
DCM	dichloromethane
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphano)ferrocene
EI	Electron Impact ionization
g	gram(s)
h or hr	hour(s)
HPLC	high pressure liquid chromatography

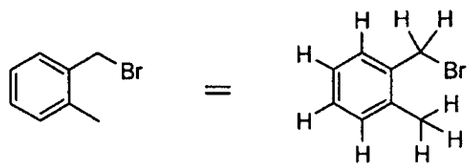
Abbreviation	Meaning
L	liter(s)
M	molar or molarity
m	Multiplet
mg	milligram(s)
MHz	megahertz (frequency)
Min	minute(s)
mL	milliliter(s)
μL	microliter(s)
μM	Micromole(s) or micromolar
mM	Millimolar
mmol	millimole(s)
mol	mole(s)
MS	mass spectral analysis
N	normal or normality
nM	Nanomolar
NMR	nuclear magnetic resonance spectroscopy
q	Quartet
RT	Room temperature
s	Singlet
t or tr	Triplet
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

Definitions for a Compound of Formula I and II

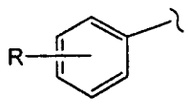
[0017] The symbol "-" means a single bond, "=" means a double bond, "≡" means a triple bond, " " means a single or double bond. The symbol " " refers to a group on a double-bond as occupying either position on the terminus of a double bond to which the symbol is attached; that is, the geometry, E- or Z-, of the double bond is ambiguous. When a group is depicted removed from its parent formula, the " " symbol will be used at the end

of the bond which was theoretically cleaved in order to separate the group from its parent structural formula.

[0018] 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.

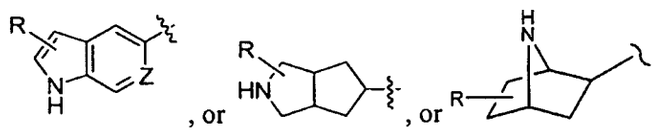


[0019] If a group "R" is depicted as "floating" on a ring system, as for example in the formula:



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.

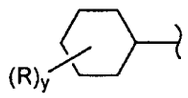
[0020] If a group "R" is depicted as floating on a fused ring system, as for example in the formulae:



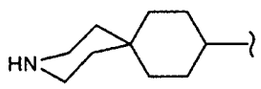
then, unless otherwise defined, a substituent "R" may reside on any atom of the fused ring system, assuming replacement of a depicted hydrogen (for example the -NH- in the formula above), implied hydrogen (for example as in the formula above, where the hydrogens are not shown but understood to be present), or expressly defined hydrogen (for example where in the formula above, "Z" 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.

[0021] 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:



[0022] "Acyl" means a -C(O)R radical where R is optionally substituted alkyl, optionally substituted alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, or heterocycloalkylalkyl, as defined herein, e.g., acetyl, trifluoromethylcarbonyl, or 2-methoxyethylcarbonyl, and the like.

[0023] "Acylamino" means a -NRR' radical where R is hydrogen, hydroxy, alkyl, or alkoxy and R' is acyl, as defined herein.

[0024] "Acyloxy" means an -OR radical where R is acyl, as defined herein, e.g. cyanomethylcarbonyloxy, and the like.

[0025] "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.

[0026] "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, and 1-pent-3-enyl, and the like.

[0027] "Alkoxy" means an -OR group where R is alkyl group as defined herein. Examples include methoxy, ethoxy, propoxy, isopropoxy, and the like.

[0028] "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.

[0029] "Alkoxyalkylamino" means an –NRR' group where R is hydrogen, alkyl, or alkoxyalkyl and R' is alkoxyalkyl, as defined herein.

[0030] "Alkoxyalkylaminoalkyl" means an alkyl group substituted with at least one, specifcially one or two, alkoxyalkylamino groups, as defined herein.

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

[0032] "Alkyl" means a linear saturated monovalent hydrocarbon radical of one to six carbon atoms or a branched saturated monovalent hydrocarbon radical of three to 6 carbon atoms, e.g., methyl, ethyl, propyl, 2-propyl, butyl (including all isomeric forms), or pentyl (including all isomeric forms), and the like.

[0033] "Alkylamino" means an -NHR group where R is alkyl, as defined herein.

[0034] "Alkylaminoalkyl" means an alkyl group substituted with one or two alkylamino groups, as defined herein.

[0035] "Alkylaminoalkyloxy" means an -OR group where R is alkylaminoalkyl, as defined herein.

[0036] "Alkylcarbonyl" means a -C(O)R group where R is alkyl, as defined herein.

[0037] "Alkynyl" 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 triple bond, e.g., ethynyl, propynyl, butynyl, pentyN-2-yl and the like.

[0038] "Amino" means $-NH_2$.

[0039] "Aminoalkyl" means an alkyl group substiuted with at least one, for example one, two or three, amino groups.

[0040] "Aminoalkyloxy" means an -OR group where R is aminoalkyl, as defined herein.

[0041] "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.

[0042] "Arylalkyl" means an alkyl radical, as defined herein, substituted with one or two aryl groups, as defined herein, e.g., benzyl and phenethyl, and the like.

[0043] "Aryloxy" means an -OR gorup where R is aryl, as defined herein.

[0044] "Carboxyalkyl" means an alkyl group, as defined herein, substituted with at least one, for example one or two, -C(O)OH groups.

[0045] "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. In another embodiment, the term cycloalkyl includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexyl, or cyclohex-3-enyl, and the like.

[0046] "Cycloalkylalkyl" means an alkyl group substituted with at least one, for example one or two, cycloalkyl groups as defined herein.

[0047] "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.

[0048] "Dialkylaminoalkyl" means an alkyl group substituted with one or two dialkylamino groups, as defined herein.

[0049] "Dialkylaminoalkyloxy" means an -OR group where R is dialkylaminoalkyl, as defined herein. Representative examples include 2-(*N,N*-diethylamino)-ethyloxy, and the like.

[0050] "Fused-polycyclic" or "fused ring system" means a polycyclic ring system that contains bridged or fused 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.

[0051] "Halogen" or "halo" refers to fluorine, chlorine, bromine or iodine.

[0052] "Haloalkoxy" means an -OR' group where R' is haloalkyl as defined herein, e.g., trifluoromethoxy or 2,2,2-trifluoroethoxy, and the like.

[0053] "Haloalkyl" mean an alkyl group substituted with one or more halogens, for example one to five halo atoms, e.g., trifluoromethyl, 2-chloroethyl, and 2,2-difluoroethyl, and the like.

[0054] "Heteroaryl" means a monocyclic, fused bicyclic, or fused tricyclic, monovalent radical of 5 to 14 ring atoms containing one or more, for example 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. Fused bicyclic radical includes bridged ring systems. Unless stated otherwise, the valency may be located on any atom of any ring of the heteroaryl group, valency rules permitting. When the point of valency is located on the nitrogen, R^x is absent. In another embodiment, 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, naphthyridi*N*-3-yl, phthalazi*N*-3-yl, phthalazi*N*-4-yl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, tetrazoyl, pyrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isooxazolyl, oxadiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl (including, for example, tetrahydroisoquinoli*N*-4-yl or tetrahydroisoquinoli*N*-6-yl, and the like), pyrrolo[3,2-c]pyridinyl (including, for example, pyrrolo[3,2-c]pyridi*N*-2-yl or pyrrolo[3,2-c]pyridi*N*-7-yl, and the like), benzopyranyl, thiazolyl, isothiazolyl, thiadiazolyl, benzothiazolyl, benzothienyl, and the derivatives thereof, or N-oxide or a protected derivative thereof.

[0055] "Heteroarylalkyl" means an alkyl group, as defined herein, substituted with at least one, for example one or two heteroaryl groups, as defined herein.

[0056] "Heteroatom" refers to O, S, N, or P.

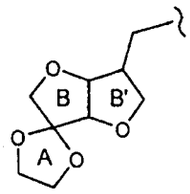
[0057] "Heterocycloalkyl" means a saturated or partially unsaturated (but not aromatic) monovalent monocyclic group of 3 to 8 ring atoms or a saturated or partially unsaturated (but not aromatic) monovalent fused bicyclic group of 5 to 12 ring atoms in which one or more, for example one, two, three, 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. In another embodiment 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.

[0058] "Heterocycloalkylalkyl" means an alkyl radical, as defined herein, substituted with one or two heterocycloalkyl groups, as defined herein, e.g., morpholinylmethyl, *N*-pyrrolidinylethyl, and 3-(*N*-azetidinyl)propyl, and the like.

[0059] "Heterocycloalkylalkyloxy means an -OR group where R is heterocycloalkylalkyl, as defined herein.

[0060] "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-1*H*-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.

[0061] "Spirocyclyl" or "spirocyclic 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. A spirocyclyl can be carbocyclic or heteroalicyclic.



[0062] "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," optional substitution may occur on 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."

[0063] "Optionally substituted alkoxy" means an -OR group where R is optionally substituted alkyl, as defined herein.

[0064] "Optionally substituted alkyl" means an alkyl radical, as defined herein, optionally substituted with one or more groups, for example 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, hydroxy, hydroxyalkoxy, halo, carboxy, alkylcarbonylamino, alkylcarbonyloxy, alkyl-$S(O)_{0-2}$-, alkenyl-$S(O)_{0-2}$-, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl-NR^c- (where R^c is hydrogen, alkyl, optionally substituted alkenyl, 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, hydroxy, alkoxy, alkenyloxy, or cyanoalkyl).

[0065] "Optionally substituted alkenyl" means an alkyl radical, as defined herein, optionally substituted with one or more groups, for example 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, hydroxy, hydroxyalkoxy, halo, carboxy, alkylcarbonylamino, alkylcarbonyloxy, alkyl-$S(O)_{0-2}$-, alkenyl-$S(O)_{0-2}$-, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonyl-NR^c- (where R^c is hydrogen, alkyl, optionally substituted alkenyl, 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, hydroxy, alkoxy, alkenyloxy, or cyanoalkyl).

[0066] "Optionally substituted amino" refers to the group -N(H)R or –N(R)R where each R is independently selected from the group: optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, acyl, carboxy, alkoxycarbonyl, -$S(O)_2$-(optionally substituted alkyl), -$S(O)_2$-optionally substituted aryl), -$S(O)_2$-(optionally substituted heterocycloalkyl), -$S(O)_2$-(optionally substitutted heteroaryl), and -$S(O)_2$-(optionally substituted heteroaryl). For example, "optionally substituted amino" includes diethylamino, methylsulfonylamino, and furanyl-oxy-sulfonamino.

[0067] "Optionally substituted aminoalkyl" means an alkyl group, as defined herein, substituted with at least one, for example one or two, optionally substituted amino groups, as defined herein.

[0068] "Optionally substituted aryl" means an aryl group, as defined herein, optionally substituted with one, two, or three substituents independently selected from acyl, acylamino, acyloxy, optionally substituted alkyl, optionally substituted alkenyl, alkoxy, alkenyloxy, halo, hydroxy, alkoxycarbonyl, alkenyloxycarbonyl, amino, alkylamino, dialkylamino, nitro, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, carboxy, cyano, alkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonylamino, aminoalkoxy, or aryl is pentafluorophenyl. Within the optional substituents on "aryl", the alkyl and alkenyl, either alone or as part of another group (including, for example, the alkyl in alkoxycarbonyl), are independently optionally substituted with one, two, three, four, or five halo.

[0069] "Optionally substituted arylalkyl" means an alkyl group, as defined herein, substituted with optionally substituted aryl, as defined herein.

[0070] "Optionally substituted cycloalkyl" means a cycloalkyl group, as defined herein, substituted with one, two, or three groups independently selected from acyl, acyloxy,

acylamino, optionally substituted alkyl, optionally substituted alkenyl, alkoxy, alkenyloxy, alkoxycarbonyl, alkenyloxycarbonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonylamino, halo, hydroxy, amino, alkylamino, dialkylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, nitro, alkoxyalkyloxy, aminoalkoxy, alkylaminoalkoxy, dialkylaminoalkoxy, carboxy, and cyano. Within the above optional substitutents on "cycloalkyl", the alkyl and alkenyl,, either alone or as part of another substituent on the cycloalkyl ring, are independently optionally substituted with one, two, three, four, or five halo, e.g. haloalkyl, haloalkoxy, haloalkenyloxy, or haloalkylsulfonyl.

[0071] "Optionally substituted cycloalkylalkyl" means an alkyl group substituted with at least one, for example one or two, optionally substituted cycloalkyl groups, as defined herein.

[0072] "Optionally substituted heteroaryl" means a heteroaryl group optionally substituted with one, two, or three substituents independently selected from acyl, acylamino, acyloxy, optionally substituted alkyl, optionally substituted alkenyl, alkoxy, alkenyloxy, halo, hydroxy, alkoxycarbonyl, alkenyloxycarbonyl, amino, alkylamino, dialkylamino, nitro, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, carboxy, cyano, alkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonylamino, aminoalkoxy, alkylaminoalkoxy, and dialkylaminoalkoxy. Within the optional substituents on "heteroaryl", the alkyl and alkenyl, either alone or as part of another group (including, for example, the alkyl in alkoxycarbonyl), are independently optionally substituted with one, two, three, four, or five halo.

[0073] "Optionally substituted heteroarylalkyl" means an alkyl group, as defined herein, substituted with at least one, for example one or two, optionally substituted heteroaryl groups, as defined herein.

[0074] "Optionally substituted heterocycloalkyl" means a heterocycloalkyl group, as defined herein, optionally substituted with one, two, or three substituents independently selected from acyl, acylamino, acyloxy, optionally substituted alkyl, optionally substituted alkenyl, alkoxy, alkenyloxy, halo, hydroxy, alkoxycarbonyl, alkenyloxycarbonyl, amino, alkylamino, dialkylamino, nitro, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, carboxy, cyano, alkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, alkylsulfonylamino, aminoalkoxy, or aryl is pentafluorophenyl. Within the optional substituents on "heterocycloalkyl", the alkyl and alkenyl, either alone or as part of another group (including, for example, the alkyl in alkoxycarbonyl), are independently optionally substituted with one, two, three, four, or five halo.

[0075] "Optionally substituted heterocycloalkylalkyl" means an alkyl group, as defined herein, substituted with at least one, for example one or two, optionally substituted heterocycloalkyl groups as defined herein.

[0076] "Yield" for each of the reactions described herein is expressed as a percentage of the theoretical yield.

Definitions for the Compound of formula 100

[0077] The terms used to describe the scope of formula 100 are defined in WO 2004/006846 (US Nat'l Stage Application Serial No. 10/522,004) which is herein incorporated by reference. For example "optionally substituted alkyl" for formula 100 has the meaning given in WO 2004/006846 (US Nat'l Stage Application Serial No. 10/522,004). Whenever a compound of formula 100 is described in this application, whether by structure or by use of the term "formula 100," the terms used to describe that compound are defined by WO 2004/006846 (US Nat'l Stage Application Serial No. 10/522,004).

Other Definitions

[0078] "AKT inhibitor" includes, for example, LY294002, PKC 412, perifosine, compounds in Table 2a, compounds in Table 2b, and compounds described in WO 2006/071819 and WO05/117909. These references also describe in vitro assays that can be used to determine the inhibitory activity of AKT.

[0079] "Alkylating agent" includes, for example, one or more of the following: Chlorambucil, Chlormethine, Cyclophosphamide, Ifosfamide, Melphalan, Carmustine, Streptozocin, Fotemustine, Lomustine, Streptozocin, Carboplatin, Cisplatin, Oxaliplatin, BBR3464, Busulfan, Dacarbazine, Mechlorethamine, Procarbazine, Temozolomide, ThioTEPA, and Uramustine.

[0080] "Antibody" includes, for example, one or more of the following: an IGF1R antibody (including, for example, $^{\alpha}$IGF-1R A12 MoAb, 19D12, h7C10 and CP-751871), an EGFR antibody (including, for example, Cetuximab (Erbitux®) and Panitumumab), an ErbB2 antibody (including, for example, Trastuzumab (Herceptin®)), a VEGF antibody (including, for example, Bevacizumab (Avastin®)), an IgG1 antibody (including, for example, Ibritumomab (tiuxetan)), a CD20 antibody (including, for example, Rituximab and Tositumomab), a CD33 antibody (including, for example, Gemtuzumab and Gemtuzumab ozogamicin), and a CD52 antibody (including, for example, Alemtuzumab).

[0081] "Antimetabolite" includes, for example, methotrexate, Pemetrexed, Raltitrexed, Cladribine, Clofarabine, Fludarabine, Mercaptopurine, Thioguanine, Capecitabine,

Cytarabine, fluorouracil (administered with or without leucovorin or folinic acid), and Gemcitabine.

[0082] "Antimicrotubule agent" includes, for example, Vincristine,Vinblastine, Vinorelbine, Vinflunine, and Vindesine.

[0083] "Aromatase inhibitor" includes, for example, one or more of the following: Aminoglutethimide, Anastrozole (Arimidex®), Letrozole (Femara®), Exemestane (Aromasin®), and Formestane (Lentaron®).

[0084] "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 deformians), 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; Adrenal Glands: neuroblastoma; and breast cancer. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

[0085] "Chemotherapeutic agent" includes, but is not limited to, an AKT inhibitor, an alkylating agent, an antimetabolite, an antimicrotubule agent, an aromatase inhibitor, a c-KIT inhibitor, a cMET inhibitor, an EGFR inhibitor, an ErbB2 inhibitor, a Flt-3 inhibitor, an HSP90 inhibitor, an IGF1R inhibitor, a platin, a Raf inhibitor, rapamycin, a Rapamycin analogue, a Receptor Tyrosine Kinase inhibitor, a taxane, a topoisomerase inhibitor, a SRC and/or ABL kinase inhibitor, and a VEGFR inhibitor. A pharmaceutically acceptable salt, solvate, and/or hydrate of a chemotherapeutic agent can be prepared by one of ordinary skill in the art and such salt, solvate, and/or hydrates thereof can be used to practice the invention.

[0086] "c-KIT inhibitor" includes, for example, imatinib, sunitinib, nilotinib, AMG 706, sorafenib, compounds in Table 3b, compounds in Table 3c, compounds in Table 8, compounds in Table 9, and compounds described in WO 2006/108059, WO/2005/020921, WO/2006/033943, and WO 2005/030140.

[0087] "cMET inhibitor" includes, for example, compounds in Table 3a, compounds in Table 3b, compounds in Table 3c, compounds described in WO06/108059, WO 2006/014325, and WO 2005/030140.

[0088] "EGFR inhibitor"includes, for example, one or more of the following: pelitinib, lapatinib (Tykerb®), gefitinib (Iressa®), erlotinib (Tarceva®), Zactima (ZD6474, vandetinib), AEE788 and HKI-272, EKB-569, CI-1033, *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5r,6a*S*)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine *N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5r,6a*S*)-2-methyloctahydrocyclo-penta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine,

N-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5s,6a*S*)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, *N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5s,6a*S*)-2-methyloctahydrocyclo-penta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, compounds in Table 4, compounds in Table 7, and compounds described in WO 2004/006846 and WO 2004/050681.

[0089] "ErbB2 inhibitor" includes, for example, lapatinib (GW572016), PKI-166, canertinib, CI-1033, HKI272, and EKB-569.

[0090] "Flt-3 inhibitor" includes, for example, CEP-701, PKC 412, MLN 518, sunitinib, sorafenib, compounds in Table 3a, compounds in Table 3b, compounds in Table 3c, compounds in Table 9, and compounds described in WO 2006/108059, WO/2006/033943, WO 2006/014325, and WO 2005/030140.

[0091] "Hormone therapy" and "hormonal therapy" include, for example, treatment with one or more of the following: steroids (e.g. dexamethasone), finasteride, tamoxifen, and an aromatase inhibitor.

[0092] "HSP90 inhibitor" includes, for example, 17-AAG, 17-DMAG, Geldanamycin, 5-(2,4-dihydroxy-5-isopropylphenyl)-*N*-ethyl-4-(4-(morpholinomethyl)phenyl)isoxazole-3-carboxamide [NVP-AUY922 (VER 52296)], 6-chloro-9-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-9*H*-purin-2-amine (CNF2024, also named BIIB021), compounds disclosed in WO2004072051 (which is herein incorporated by reference), compounds disclosed in WO2005028434 (which is herein incorporated by reference), compounds disclosed in WO2007035620 (which is herein incorporated by reference) and compounds disclosed in WO2006091963 (which is herein incorporated by reference).

[0093] "IGF1R inhibitor" includes, for example, Tyrphostin AG 1024, compounds in Table 5a, compounds in Table 5b, and compounds described in WO06/074057.

[0094] "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).

[0095] 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.

[0096] "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.

[0097] "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 preferred embodiment the patient is a mammal, and in a most preferred embodiment the patient is human.

[0098] 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.

[0099] 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.

[00100] 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 *tert*iary 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.

[00101] "Platin," and "platin-containing agent" include, for example, cisplatin, carboplatin, and oxaliplatin.

[00102] "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.

[00103] "Raf inhibitor" includes, for example, sorafenib, RAF 265 (CHIR 265), compounds in Table 6, and compounds described in WO 2005/112932. These references also describe in vitro assays that can be used to determine the inhibitory activity of RAF.

[00104] "Rapamycin analogue" includes for example, CCI-779, AP 23573, RAD 001, TAFA 93, and compounds described in WO 2004/101583 and US 7,160,867 which are each incorporated herein by reference in their entireties.

[00105] "Receptor Tyrosine Kinase inhibitor" includes, for example, inhibitors of AKT, EGFR, ErbB2, IGF1R, KIT, Met, Raf, and VEGFR2. Examples of receptor tyrosine kinase inhibitors can be found in WO 2006/108059 (US Nat'l Stage Application Serial No. 11/910,720), WO 2006/074057 (US Nat'l Stage Application Serial No. 11/722,719), WO 2006/071819 (US Nat'l Stage Application Serial No. 11/722,291), WO 2006/014325 (US Nat'l Stage Application Serial No. 11/571,140), WO 2005/117909 (US Nat'l Stage Application Serial No. 11/568,173), WO 2005/030140 (US Nat'l Stage Application Serial No. 10/573,336), WO 2004/050681 US Nat'l Stage Application Serial No. 10/533,555), WO 2005/112932 (US Nat'l Stage Application Serial No. 11/568,789), and WO 2004/006846 (US Nat'l Stage Application Serial No. 10/522,004), each of which is incorporated herein by reference for all purposes. In particular, the applications cited in this paragraph are incorporated for the purpose of providing specific examples and generic embodiments (and the definitions associated with the terms used in the embodiments) of compounds that are useful in the practice of the invention. These references also describe in vitro assays useful in the practice of this invention.

[00106] "Taxane" includes, for example, one or more of the following: Paclitaxel (Taxol®) and Docetaxel (Taxotere®).

[00107] "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.

[00108] "Topoisomerase inhibitor" includes, for example, one or more of the following: amsacrine, camptothecin, etoposide, etoposide phosphate, exatecan, irinotecan, lurtotecan, and teniposide, and topotecan.

[00109] "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.

[00110] "SRC and/or ABL kinase inhibitor" includes, for example, dasatinib, imatinib (Gleevec®), and compounds described in WO 2006/074057.

[00111] "VEGFR inhibitor" includes, for example, one or more of the following: VEGF Trap, ZD6474 (vandetanib, Zactima), sorafenib, Angiozyme, AZD2171 (cediranib), pazopanib, sorafenib, axitinib, SU5416 (semaxanib), PTK787 (vatalanib), AEE778, RAF 265, sunitinib (Sutent), *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5r,6a*S*)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, *N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5r,6a*S*)-2-methyloctahydrocyclo-penta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5s,6a*S*)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, *N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5s,6a*S*)-2-methyloctahydrocyclo-penta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, compounds in Table 7, and compounds described in WO 2004/050681 and WO 2004/006846.

Embodiments of the Invention

[00112] The following paragraphs present a number of embodiments of compounds that can be used to practice the invention. In each instance, the embodiment includes both the recited compounds as well as individual isomers and mixtures of isomers. In addtion, in each instance, the embodiment includes the pharmaceutically acceptable salts, hydrates, and/or solvates of the recited compounds and any individual isomers or mixture of isomers thereof.

[00113] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, where growth and/or survival of tumor cells of the cancer is enhanced, at least in part, by the activity of PI3K; in combination with one or more treatments selected from surgery, one or more chemotherapeutic agents, one or more hormone therapies, one or more antibodies, one or more immunotherapies, radioactive iodine therapy, and radiation.

[00114] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments independently selected from surgery, one or more chemotherapeutic agents, one or more hormone therapies, one or more antibodies, one or more immunotherapies, radioactive iodine therapy, and radiation; where the cancer is selected from breast cancer, colon cancer, rectal cancer, endometrial cancer, gastric carcinoma (including gastrointestinal carcinoid tumors and gastrointestinal stromal tumors), glioblastoma, hepatocellular carcinoma, small cell lung cancer, non-small cell lung cancer (NSCLC), melanoma, ovarian cancer, cervical cancer, pancreatic cancer, prostate carcinoma, acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), non-Hodgkin's lymphoma, and thyroid carcinoma. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments independently selected from surgery, one or more chemotherapeutic agents, one or more hormone therapies, one or more antibodies, one or more immunotherapies, radioactive iodine therapy, and radiation; where the cancer is selected from prostate cancer, NSCLC, ovarian cancer, cervical cancer, breast cancer, colon cancer, rectal cancer, and glioblastoma. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary

of the Invention, in combination with one or more treatments independently selected from surgery, one or more chemotherapeutic agents, one or more hormone therapies, one or more antibodies, one or more immunotherapies, radioactive iodine therapy, and radiation; where the cancer is selected from NSCLC, breast cancer, prostate cancer, glioblastoma, and ovarian cancer.

[00115] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or more chemotherapeutic agents.

[00116] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents independently selected from rapamycin, a rapamycin analogue, an alkylating agent, a taxane, a platin, an EGFR inhibitor, and an ErbB2 inhibitor. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents independently selected from rapamycin, temozolomide, paclitaxel, docetaxel, carboplatin, cisplatin, oxaliplatin, gefitinib (Iressa®), erlotinib (Tarceva®), Zactima (ZD6474), HKI-272, pelitinib, canertinib, a compound selected from Table 4, a compound in Table 7, and lapatinib. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents independently selected from rapamycin, temozolomide, paclitaxel, docetaxel, carboplatin, trastuzumab, erlotinib, *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5r,6a*S*)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, *N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5r,6a*S*)-2-methyloctahydrocyclo-penta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5s,6a*S*)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, *N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5s,6a*S*)-2-methyloctahydrocyclo-penta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, a compound in Table 7, and lapatinib. In another

embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents independently selected from rapamycin, paclitaxel, carboplatin, erlotinib, and *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta-[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine.

[00117] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents independently selected from a platin and a taxane. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents independently selected from carboplatin, cisplatin, oxaliplatin, and paclitaxel.

[00118] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agent is an AKT inhibitor. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is an AKT inhibitor selected from perifosine, PKC 412, a compound in Table 2a, and a compound in Table 2b.

[00119] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is a cMET inhibitor. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is a cMET inhibitor

selected from a compound in Table 3a, a compound in Table 3b, and a compound in Table 3c.

[00120] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is an EGFR inhibitor. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is an EGFR inhibitor selected from lapatinib (Tykerb®), gefitinib (Iressa®), erlotinib (Tarceva®), Zactima (ZD6474), AEE788, HKI-272, EKB-569, CI 1033, a compound selected from Table 4, and a compound in Table 7. In another embodiment, In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is an EGFR inhibitor selected from lapatinib (Tykerb®), gefitinib (Iressa®), erlotinib (Tarceva®), Zactima (ZD6474), AEE788, HKI-272, EKB-569, CI 1033, *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5r,6a*S*)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine *N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5r,6a*S*)-2-methyloctahydrocyclo-penta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5s,6a*S*)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, and *N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5s,6a*S*)-2-methyloctahydrocyclo-penta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine.

[00121] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is an ErbB2 inhibitor. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of

the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is an ErbB2 inhibitor selected from lapatinib, EKB-569, HKI272, CI 1033, PKI-166, and a compound selected from Table 4.

[00122] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is an HSP90 inhibitor. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is an HSP90 inhibitor selected from 17-AAG, 17-DMAG, Geldanamycin, and CNF2024. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is an HSP90 inhibitor selected from 17-AAG, 17-DMAG, and Geldanamycin.

[00123] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is an IGF1R inhibitor. In another embodiment, In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is an IGF1R inhibitor selected from Table 5a and Table 5b.

[00124] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is a Raf inhibitor. In another embodiment, the invention is directed

to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is a Raf inhibitor selected from sorafenib, RAF 265 (CHIR-265), and a compound in Table 6.

[00125] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is a VEGFR inhibitor. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is a VEGFR inhibitor selected from VEGF Trap, ZD6474 (Zactima), cediranib (AZ2171), pazopanib, sunitinib, sorafenib, axitinib, AEE788, RAF 265 (CHIR-265), a compound selected from Table 4, and a compound selected from Table 7.

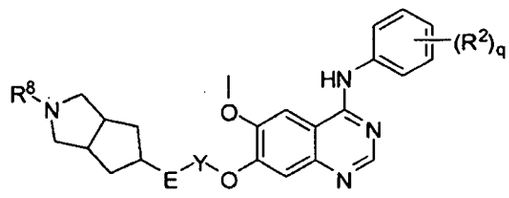
[00126] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is a cKIT inhibitor. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is a cKIT inhibitor selected from imatinib, sunitinib, nilotinib, AMG 706, sorafenib, a compound in Table 3b, a compound in Table 3c, a compound in Table 8, and a compound in Table 9.

[00127] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is a FLT3 inhibitor. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a

therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is a FLT3 inhibitor selected from CEP-701, PKC 412, sunitinib, MLN 518, sunitinib, sorafenib, a compound in Table 3a, a compound in Table 3b, a compound in Table 3c, and a compound in Table 9.

[00128] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is selected from rapamycin, a rapamycin analogue, PI103, and SF 1126. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is selected from rapamycin, CCI-779, AP 23573, RAD 001 , TAFA 93, PI103, and SF 1126. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is rapamycin.

[00129] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is of formula **100**:



100

where q is 1, 2, or 3; E is $-NR^9-$, -O-, or absent and Y is $-CH_2CH_2-$, $-CH_2-$, or absent provided that when E is $-NR^9-$ or -O-, then Y is $-CH_2CH_2-$; R^2 is selected from halogen, trihalomethyl, -CN, $-NO_2$, $-OR^3$, and lower alkyl; R^8 is selected from -H, lower alkyl, $-C(O)OR^3$,

-C(O)N(R^3)R^4, -SO_2R^4, and -C(O)R^3; R^9 is hydrogen or lower alkyl; R^3 is hydrogen or R^4; R^4 is selected from lower alkyl, aryl, lower arylalkyl, heterocyclyl, and lower heterocyclylalkyl; or R^3 and R^4, when taken together with a common nitrogen to which they are attached, form a five- to seven-membered heterocyclyl, said five- to seven-membered heterocyclyl optionally containing one or more additional heteroatom selected from N, O, S, and P; or a single geometric isomer, stereoisomer, racemate, enantiomer, or diastereomer, thereof and optionally as a pharmaceutically acceptable salt, additionally optionally as a solvate, and additionally as a hydrate thereof. The terms used to describe the scope of formula 100 are defined in WO 2004/006846 (US Nat'l Stage Application Serial No. 10/522,004) which is herein incorporated by reference. Whenever a compound of formula 100 is described in this application, whether by structure or by use of the term "formula 100," the terms used to describe that compound are defined by WO 2004/006846 (US Nat'l Stage Application Serial No. 10/522,004). In particular, "alkyl" in formula 100 is intended to include linear, branched, or cyclic hydrocarbon structures and combinations thereof, inclusively; "lower alkyl" means alkyl groups of from one to six carbon atoms. "Aryl" in formula 100 means an aromatic six- to fourteen-membered carbocyclic rings which include, for example, benzene, naphthalene, indane, tetralin, fluorene and the like. "Lower arylalkyl" in formula 100 means a residue in which an aryl moiety is attached to a parent structure via one of an alkylene, alkenylene, or alkynylene radical where the "alkyl" portion of the group has one to six carbons; examples include benzyl, phenethyl, phenylvinyl, phenylallyl and the like. In formula 100, "heterocyclyl" means a stable monocyclic, bicyclic or tricyclic three- to fifteen-membered ring radical (including fused or bridged ring systems) that consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, phosphorus, oxygen and sulfur where the nitrogen, phosphorus, carbon and sulfur atoms in the heterocyclyl radical may be optionally oxidized to various oxidation states and the nitrogen atom may be optionally quaternized; and the ring radical may be partially or fully saturated or aromatic. "Lower heterocyclylalkyl" means a residue in which a heterocyclyl is attached to a parent structure via one of an alkylene, alkenylene, and alkynylene radical having one to six carbons.

[00130] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is selected from a compound in Table 2a. In another embodiment,

the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is selected from Table 2a.

[00131] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or more chemotherapeutic agents where one of the chemotherapeutic agent is selected from a compound in Table 2b. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is one or more chemotherapeutic agents where one of the chemotherapeutic agent is selected from Table 2b.

[00132] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or more chemotherapeutic agents where one of the chemotherapeutic agent is selected from a compound in Table 3a. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is one or more chemotherapeutic agents where one of the chemotherapeutic agent is selected from Table 3a.

[00133] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or more chemotherapeutic agents where one of the chemotherapeutic agent is selected from a compound in Table 3b. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is one or more chemotherapeutic agents where one of the chemotherapeutic agent is selected from Table 3b.

[00134] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a

treatment where the treatment is one or more chemotherapeutic agents where one of the chemotherapeutic agent is selected from a compound in Table 3c. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is one or more chemotherapeutic agents where one of the chemotherapeutic agent is selected from Table 3c.

[00135] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is selected from a compound in Table 4. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is selected from Table 4.

[00136] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5r,6a*S*)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, *N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5r,6a*S*)-2-methyloctahydrocyclo-penta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5s,6a*S*)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, or *N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5s,6a*S*)-2-methyloctahydrocyclo-penta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5r,6a*S*)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, *N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5r,6a*S*)-2-

methyloctahydrocyclo-penta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5s,6a*S*)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, or *N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5s,6a*S*)-2-methyloctahydrocyclo-penta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof.

[00137] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta-[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agents is *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta-[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof.

[00138] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or more chemotherapeutic agents where one of the chemotherapeutic agent is selected from a compound in Table 5a. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is one or more chemotherapeutic agents where one of the chemotherapeutic agent is selected from Table 5a.

[00139] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or more chemotherapeutic agents where one of the

chemotherapeutic agent is selected from a compound in Table 5b. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is one or more chemotherapeutic agents where one of the chemotherapeutic agent is selected from Table 5b.

[00140] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or more chemotherapeutic agents where one of the chemotherapeutic agent is selected from a compound in Table 6. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is one or more chemotherapeutic agents where one of the chemotherapeutic agent is selected from Table 6.

[00141] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or more chemotherapeutic agents where one of the chemotherapeutic agent is selected from a compound in Table 7. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is one or more chemotherapeutic agents where one of the chemotherapeutic agent is selected from Table 7.

[00142] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or more chemotherapeutic agents where one of the chemotherapeutic agent is selected from a compound in Table 8. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is one or more chemotherapeutic agents where one of the chemotherapeutic agent is selected from Table 8.

[00143] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a

Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or more chemotherapeutic agents where one of the chemotherapeutic agent is selected from a compound in Table 9. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is one or more chemotherapeutic agents where one of the chemotherapeutic agent is selected from Table 9.

[00144] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agent is paclitaxel.

[00145] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agent is rapamycin.

[00146] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agent is carboplatin.

[00147] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agent is erlotinib.

[00148] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is one or two chemotherapeutic agents where one of the chemotherapeutic agent is lapatinib.

[00149] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a

Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is one or two antibodies where one of the antibodies is trastuzumab.

[00150] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is one or two antibodies where one of the antibodies is cetuximab.

[00151] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is one or two antibodies where one of the antibodies is panitumumab.

[00152] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is one or two antibodies where one of the antibodies is bevacizumab.

[00153] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is radiation. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is radiation.

[00154] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two antibodies. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two antibodies independently selected from an IGF1R antibody (including, for example, $^{\alpha}$IGF-1R A12 MoAb, $^{\alpha}$IGF-1R 19D12 MoAb, $^{\alpha}$IGF-1R h7C10 MoAb and $^{\alpha}$IGF-1R CP-751871 MoAb), Alemtuzumab, Bevacizumab (Avastin®), Gemtuzumab, Gemtuzumab ozogamicin, Ibritumomab tiuxetan, Panitumumab, Rituximab, Tositumomab, Omnitarg (pertuzimab), an anti-ErbB2 anibodies (including trastuzumab (Herceptin®)), and an anti-EGFR antibodies

(including, for example, cetuximab (Erbitux), panitumumab, nimotuzumab, and EMD72000)).

[00155] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is one or two antibodies. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is one or two antibodies independently selected from an IGF1R antibody (including, for example, $^{\alpha}$IGF-1R A12 MoAb, $^{\alpha}$IGF-1R 19D12 MoAb, $^{\alpha}$IGF-1R h7C10 MoAb and $^{\alpha}$IGF-1R CP-751871 MoAb), Alemtuzumab, Bevacizumab (Avastin®), Gemtuzumab, Gemtuzumab ozogamicin, Ibritumomab tiuxetan, Panitumumab, Rituximab, Tositumomab, Omnitarg (pertuzimab), an anti-ErbB2 anibodies (including trastuzumab (Herceptin®)), and an anti-EGFR antibodies (including, for example, cetuximab (Erbitux), panitumumab, nimotuzumab, and EMD72000)).

[00156] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or more chemotherapeutic agents where one of the chemotherapeutic agent is temozolomide. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is one or more chemotherapeutic agents where one of the chemotherapeutic agent is temozolomide.

[00157] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is surgery. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is surgery.

[00158] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a

treatment where the treatment is one or two hormone therapies. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two hormone therapies independently selected from tamoxifen, Toremifene (Fareston), Fulvestrant (Faslodex), Megestrol acetate (Megace), ovarian ablation, Raloxifene, a luteinizing hormone-releasing hormone (LHRH) analog (including goserelin and leuprolide), Megestrol acetate (Megace), and one or more aromatase inhibitor. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two hormone therapies where one of the hormone therapies is an aromatase inhibitor selected from letrozole (Femara), anastrozole (Arimidex), and exemestane (Aromasin). In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where the treatment is one or two hormone therapies independently selected from from tamoxifen and an aromatase inhibitor.

[00159] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where the treatment is one or two hormone therapies. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where one of the treatments is one or two hormone therapies independently selected from tamoxifen, Toremifene (Fareston), Fulvestrant (Faslodex), Megestrol acetate (Megace), ovarian ablation, Raloxifene, a luteinizing hormone-releasing hormone (LHRH) analog (including goserelin and leuprolide), Megestrol acetate (Megace), and one or two aromatase inhibitor. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where one of the treatments is one or two hormone therapies where one of the hormone therapies is an aromatase inhibitor selected from letrozole (Femara), anastrozole (Arimidex), and exemestane (Aromasin). In another embodiment, the

invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where one of the treatments is one or two hormone therapies independently selected from from tamoxifen and an aromatase inhibitor.

[00160] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with a treatment where one of the treatments is one antibody selected from an EGFR antibody and an ErbB2 antibody, or the treatment is one or two chemotherapeutic agents independently selected from a rapamycin, a rapamycin analogue, an alkylating agent, a taxane, a platin, an EGFR inhibitor, and an ErbB2 inhibitor. In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I selected from Table 1 in combination with a treatment where one of the treatments is one antibody selected from an EGFR antibody and an ErbB2 antibody, or the treatment is one or two chemotherapeutic agents independently selected from a rapamycin, rapamycin analogue, an alkylating agent, a taxane, a platin, an EGFR inhibitor, and an ErbB2 inhibitor.

[00161] In another embodiment, the invention is directed to a method of treating acute myelogenous leukemia (AML) which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments independently selected from bone marrow or peripheral blood stem cell transplantation, radiation, one or two antibodies, and one or two chemotherapeutic agents. In another embodiment, the invention is directed to a method of treating acute myelogenous leukemia (AML) which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or two treatments where one of the treatments is one antibody selected from Gemtuzumab ozogamicin (Mylotarg), $^{\alpha}$IGF-1R A12 MoAb, $^{\alpha}$IGF-1R 19D12 MoAb, $^{\alpha}$IGF-1R h7C10 MoAb, $^{\alpha}$IGF-1R CP-751871 MoAb and trastuzumab. In another embodiment, the invention is directed to a method of treating acute myelogenous leukemia (AML) which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two chemotherapeutic agents selected from Imatinib (i.e. Gleevec®), PKC 412, CEP-701, daunorubicin, doxorubicin, cytarabine (ara-C), an anthracycline drug

such as daunorubicin or idarubicin (Daunomycin, Idamycin), 6-thioguanine, and a granulocyte colony-stimulating factor (such as Neupogen or Leukine).

[00162] In another embodiment, the invention is directed to a method of treating chronic myelogenous leukemia (CML) which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments independently selected from bone marrow or peripheral blood stem cell transplantation, radiation, one or two chemotherapeutic agents, immunotherapy, and one or two antibodies. In another embodiment, the invention is directed to a method of treating chronic myelogenous leukemia (CML) which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two of the chemotherapeutic agents selected from Imatinib (i.e. Gleevec®), PKC 412, hydroxyurea (Hydrea), cytosine, cytosine arabinoside, dasatinib, AMN107, VX680 (MK0457), and cytarabine (ara-C). In another embodiment, the invention is directed to a method of treating chronic myelogenous leukemia (CML) which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two chemotherapeutic agents selected from Imatinib (i.e. Gleevec®) and dasatinib. In another embodiment, the invention is directed to a method of treating chronic myelogenous leukemia (CML) which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is immunotherapy and the immunotherapy is interferon therapy such as interferon-α.

[00163] In another embodiment, the invention is directed to a method of treating prostate cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments independently selected from surgery (including cryosurgery), radiation, one or two chemotherapeutic agents, one or two antibodies, and one or two hormone therapies. In another embodiment, the invention is directed to a method of treating prostate cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is an antibody selected from ^{a}IGF-1R A12 MoAb, ^{a}IGF-1R 19D12 MoAb, ^{a}IGF-1R h7C10 MoAb, and ^{a}IGF-1R CP-

751871 MoAb. In another embodiment, the invention is directed to a method of treating prostate cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two of the chemotherapeutic agents independently selected from rapamycin, mitoxantrone, prednisone, docetaxel (Taxotere), doxorubicin, etoposide, vinblastine, paclitaxel, and carboplatin. In another embodiment, the invention is directed to a method of treating prostate cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two of the hormone therapy indepependently selected from androgen deprivation therapy and androgen suppression therapy. In another embodiment, the invention is directed to a method of treating prostate cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two chemotherapeutic agents where one of the chemotherapeutic agents is a taxane. In another embodiment, the invention is directed to a method of treating prostate cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two chemotherapeutic agents where one of the chemotherapeutic agents is rapamycin.

[00164] In another embodiment, the invention is directed to a method of treating melanoma which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments independently selected from surgery, radiation, one or two immunotherapies, one or two hormone therapies, and one or two chemotherapeutic agents. In another embodiment, the invention is directed to a method of treating melanoma which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two chemotherapeutic agents independently selected from an alkylating agent, a taxane, a platin, and a Raf inhibitor. In another embodiment, the invention is directed to a method of treating melanoma which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with

one or more treatments where one of the treatments is one or two chemotherapeutic agents independently selected from sorafenib, Paclitaxel (Taxol®), Docetaxel (Taxotere®), dacarbazine, rapamycin, imatinib mesylate (Gleevec®), sorafenib, cisplatin, carboplatin, dacarbazine (DTIC), carmustine (BCNU), vinblastine, temozolomide (Temodar), Melphalan, and imiquimod (Aldara). In another embodiment, the invention is directed to a method of treating melanoma which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two immunotherapies independently selected from ipilimumab, interferon-alpha and interleukin-2. In another embodiment, the invention is directed to a method of treating melanoma which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is hormone therapy where the hormone therapy is tamoxifen.

[00165] In another embodiment, the invention is directed to a method of treating colon or rectal cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments independently selected from surgery, radiation, one or two antibodies, and one or two chemotherapeutic agents. In another embodiment, the invention is directed to a method of treating colon or rectal cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is surgery selected from local excision, electrofulguration, segmental colon resection, polypectomy, local transanal resection, low anterior resection, abdominoperineal resection, and pelvic exenteration. In another embodiment, the invention is directed to a method of treating colon or rectal cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two chemotherapeutic agents independently selected from a platinum-containing compound (including cisplatin, oxaliplatin, and carboplatin), 5-fluorouracil (5-FU), leucovorin, capecitabine (Xeloda), irinotecan (Camptosar), FOLFOX (Folinic acid, 5-FU, Oxaliplatin), and leucovorin. In another embodiment, the invention is directed to a method of treating colon or rectal cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as

defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two antibodies independently selected from cetuximab (Erbitux) and bevacizumab (Avastin).

[00166] In another embodiment, the invention is directed to a method of treating pancreatic cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments independently selected from surgery, radiation, one or two antibodies, and one or two chemotherapeutic agents. In another embodiment, the invention is directed to a method of treating pancreatic cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is selected from one or two chemotherapeutic agents independently selected from platinum-containing compound (including cisplatin, oxaliplatin, and carboplatin), 5-fluorouracil (5-FU), gemcitabine, a taxane (including paclitaxel and docetaxel), topotecan, irinotecan, capecitabine, streptozocin, erlotinib (Tarceva), , leucovorin, and capecitabine (Xeloda). In another embodiment, the invention is directed to a method of treating pancreatic cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is an antibody wehre the antibody is cetuximab.

[00167] In another embodiment, the invention is directed to a method of treating breast cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments independently selected from surgery, radiation, one or two chemotherapeutic agents, one or two hormone therapies, and one or two antibodies. In another embodiment, the invention is directed to a method of treating breast cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two of the chemotherapeutic agents independently selected from lapatinib (Tykerb®), Paclitaxel (Taxol®), docetaxel, capecitabine, Cyclophosphamide (Cytoxan), CMF (cyclophosphamide, fluoruracil, and methotrexate), methotrexate, fluorouracil, doxorubicin, epirubicin, gemcitabine, carboplatin (Paraplatin), cisplatin (Platinol), vinorelbine (Navelbine), capecitabine (Xeloda), pegylated liposomal doxorubicin (Doxil), albumin-bound paclitaxel (Abraxane), AC (adriamycin and

Cyclophosphamide), adriamyclin, and pamidronate or zoledronic acid (to treat bone weakness). In another embodiment, the invention is directed to a method of treating breast cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two hormone therapies independently selected from tamoxifen, Toremifene (Fareston), Fulvestrant (Faslodex), Megestrol acetate (Megace), ovarian ablation, Raloxifene, a luteinizing hormone-releasing hormone (LHRH) analogs (including goserelin and leuprolide), Megestrol acetate (Megace), and one or more aromatase inhibitors. In another embodiment, the invention is directed to a method of treating breast cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two hormone therapies and one of the hormone therapies is an aromatase inhibitor selected from letrozole (Femara), anastrozole (Arimidex), and exemestane (Aromasin). In another embodiment, the invention is directed to a method of treating breast cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two antibodies independently selected from $^{\alpha}$IGF-1R A12 MoAb, $^{\alpha}$IGF-1R 19D12 MoAb, $^{\alpha}$IGF-1R h7C10 MoAb, $^{\alpha}$IGF-1R CP-751871 MoAb, bevacizumab (Avastin), and trastuzumab.

[00168] In another embodiment, the invention is directed to a method of treating breast cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two chemotherapeutic agents and one of the chemotherapeutic agents is erlotinib.

[00169] In another embodiment, the invention is directed to a method of treating breast cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two of the chemotherapeutic agents and one or two of the chemotherapeutic agents are independently selected from rapamycin, lapatinib, erlotinib, *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5r,6a*S*)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof, *N*-(4-

bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5r,6a*S*)-2-methyloctahydrocyclo-penta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof, *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5s,6a*S*)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof, and *N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5s,6a*S*)-2-methyloctahydrocyclo-penta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof.

[00170] In another embodiment, the invention is directed to a method of treating breast cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two of the antibodies. In another embodiment, the invention is directed to a method of treating breast cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two antibodies and one of the antibodies is trastuzumab.

[00171] In another embodiment, the invention is directed to a method of treating breast cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two of the chemotherapeutic agents and one of the chemotherapeutic agents is selected from *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5r,6a*S*)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, *N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5r,6a*S*)-2-methyloctahydrocyclo-penta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5s,6a*S*)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, and *N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5s,6a*S*)-2-methyloctahydrocyclo-penta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine; optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof.

[00172] In another embodiment, the invention is directed to a method of treating breast cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two of the chemotherapeutic agents and one of the chemotherapeutic agents is *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta-[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof.

[00173] In another embodiment, the invention is directed to a method of treating non-small cell lung cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments independently selected from surgery, radiation, one or more antibodies, and one or more chemotherapeutic agents. In another embodiment, the invention is directed to a method of treating non-small cell lung cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two chemotherapeutic agents independently selected from cisplatin, oxaliplatin, carboplatin, Zactima (ZD6474), Paclitaxel, Docetaxel (Taxotere®), Gemcitabine (Gemzar®), Vinorelbine, Irinotecan, Etoposide, Vinblastine, Erlotinib (Tarceva®), gefitinib (Iressa), and Pemetrexed. In another embodiment, the invention is directed to a method of treating non-small cell lung cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is an antibody and the antibody is Bevacizumab. In another embodiment, the invention is directed to a method of treating non-small cell lung cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two chemotherapeutic agents independently selected from cisplatin, oxaliplatin, carboplatin, Paclitaxel, Docetaxel (Taxotere®), and erlotinib (Tarceva®).

[00174] In another embodiment, the invention is directed to a method of treating non-small cell lung cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention,

in combination with one or more treatments where one of the treatments is one or two chemotherapeutic agents and one of the chemotherapeutic agents is carboplatin.

[00175] In another embodiment, the invention is directed to a method of treating non-small cell lung cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two chemotherapeutic agents and one of the chemotherapeutic agents is selected from *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5r,6a*S*)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, *N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5r,6a*S*)-2-methyloctahydrocyclo-penta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5s,6a*S*)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, and *N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5s,6a*S*)-2-methyloctahydrocyclo-penta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine; optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof. In another embodiment, the invention is directed to a method of treating non-small cell lung cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two chemotherapeutic agents and one of the chemotherapeutic agents is *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta-[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof.

[00176] In another embodiment, the invention is directed to a method of treating small cell lung cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments independently selected from surgery, radiation, and one or two chemotherapeutic agents. In another embodiment, the invention is directed to a method of treating small cell lung cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two chemotherapy agents independently selected from a platin (such as cisplatin, oxaliplatin, and carboplatin), gefitinib, vinorelbine, docetaxel, paclitaxel, etoposide, fosfamide, ifosfamide, cyclophosphamide, cyclophosphamide/doxorubicin/vincristine

(CAV), doxorubicin, vincristine, gemcitabine, paclitaxel, vinorelbine, topotecan, irinotecan, methotrexate, and docetaxel.

[00177] In another embodiment, the invention is directed to a method of treating papillary or anaplastic thyroid cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments independently selected from surgery, radiation, radioactive iodine therapy, one or two hormone therapies, and one or two chemotherapeutic agents. In another embodiment, the invention is directed to a method of treating papillary or anaplastic thyroid cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two chemotherapeutic agents independently selected from thyroid hormone pills, Doxorubucin and a platin. In another embodiment, the invention is directed to a method of treating papillary or anaplastic thyroid cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is hormone therapy and the hormone therapy is radioiodine ablation.

[00178] In another embodiment, the invention is directed to a method of treating endometrial cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments independently selected from surgery, radiation, one or two hormone therapies, and one or two chemotherapeutic agents. In another embodiment, the invention is directed to a method of treating endometrial cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two hormone therapies independently selected from megestrol acetate, Tamoxifen, and a progestin including medroxyprogesterone acetate (Provera) and megestrol acetate (Megace). In another embodiment, the invention is directed to a method of treating endometrial cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two chemotherapeutic agents independently selected from a platinum-containing compound (including cisplatin, oxaliplatin, and carboplatin, more for example cisplatin), a taxane (including paclitaxel),

doxorubicin (Adriamycin), cyclophosphamide, fluorouracil (5-FU), methotrexate, and vinblastine.

[00179] In another embodiment, the invention is directed to a method of treating ovarian cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments independently selected from surgery, radiation, one or two antibodies, and one or two chemotherapeutic agents. In another embodiment, the invention is directed to a method of treating ovarian cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is an antibody and the antibody is bevacizumab. In another embodiment, the invention is directed to a method of treating ovarian cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two chemotherapeutic agents independently selected from a platinum-containing compound (including cisplatin, oxaliplatin and carboplatin), a taxane (including paclitaxel and docetaxel), topotecan, an anthracyclines (including doxorubicin and liposomal doxorubicin), gemcitabine, cyclophosphamide, vinorelbine (Navelbine), hexamethylmelamine, ifosfamide, etoposide, bleomycin, vinblastine, ifosfamide, vincristine, and cyclophosphamide. In another embodiment, the invention is directed to a method of treating ovarian cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two chemotherapeutic agents independently selected from a platin and a taxane. In another embodiment, the invention is directed to a method of treating ovarian cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two chemotherapeutic agents independently selected from cisplatin, oxaliplatin, carboplatin, paclitaxel, and docetaxel.

[00180] In another embodiment, the invention is directed to a method of treating glioblastoma which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments independently selected from surgery, radiation, one or two chemotherapeutic agents, one or two anti-seizure agents, and one or two agents to

reduce swelling. In another embodiment, the invention is directed to a method of treating glioblastoma which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is radiation selected from external beam radiation, interstitial radiotherapy, and stereotactic radiosurgery. In another embodiment, the invention is directed to a method of treating glioblastoma which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two chemotherapeutic agents independently selected from carmustine (BCNU), Erlotinib (Tarceva), bevacizumab, gefitinib (Iressa), rapamycin, temozolomide, cisplatin, BCNU, lomustine, procarbazine, and vincristine. In another embodiment, the invention is directed to a method of treating glioblastoma which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is an anti-seizure agent and the anti-seizure agent is diphenylhydantoin (Dilantin). In another embodiment, the invention is directed to a method of treating glioblastoma which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is an agents to reduce swelling and the agent is dexamethasone (Decadron). In another embodiment, the invention is directed to a method of treating glioblastoma which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two chemotherapeutic agents. In another embodiment, the invention is directed to a method of treating glioblastoma which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two chemotherapeutic agents independently selected from erlotinib and temozolomide.

[00181] In another embodiment, the invention is directed to a method of treating cervical cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments independently selected from surgery, radiation, and one or two chemotherapeutic agents. In another embodiment, the invention is directed to a method of

treating cervical cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is surgery selceted from cryosurgery, laser surgery, loop electrosurgical excision, conization, simple hysterectomy, and radical hysterectomy and pelvic lymph node dissection. In another embodiment, the invention is directed to a method of treating cervical cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is radiation selected from called external beam radiation therapy and brachytherapy. In another embodiment, the invention is directed to a method of treating cervical cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two chemotherapeutic agents independently selected from a platinum compound (such as cisplatin, carboplatin, and oxaliplatin), paclitaxel, topotecan, ifosfamide, gemcitabine, vinorelbine, and fluorouracil.

[00182] In another embodiment, the invention is directed to a method of treating a gastrointestinal carcinoid tumor which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments independently selected from surgery, radiation, immunotherapy, and one or two chemotherapeutic agents. In another embodiment, the invention is directed to a method of treating a gastrointestinal carcinoid tumor which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is surgery selected from excision and electrofulguration. In another embodiment, the invention is directed to a method of treating a gastrointestinal carcinoid tumor which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two chemotherapeutic agents independently selected from cyproheptadine, SOM230, octreotide and lanreotide. In another embodiment, the invention is directed to a method of treating a gastrointestinal carcinoid tumor which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary

of the Invention, in combination with one or more treatments where one of the treatments is immunotherapy and the immunotherapy is an interferon.

[00183] In another embodiment, the invention is directed to a method of treating a gastrointestinal stromal tumor which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments independently selected from surgery, radiation, and one or two chemotherapeutic agents. In another embodiment, the invention is directed to a method of treating a gastrointestinal stromal tumor which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two chemotherapeutic agents independently selected from imatinib mesylate (Gleevec), sunitinib (Sutent), and nilotinib (AMN107).

[00184] In another embodiment, the invention is directed to a method of treating hepatocellular carcinoma which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments independently selected from surgery, radiofrequency ablation, ethanol ablation, cryosurgery, hepatic artery embolization, chemoembolization, radiation, and one or two chemotherapeutic agents. In another embodiment, the invention is directed to a method of treating hepatocellular carcinoma which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is surgery selected from resection and transplantation. In another embodiment, the invention is directed to a method of treating hepatocellular carcinoma which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two chemotherapeutic agents independently selected from sorafenib, 5-fluorouracil and cisplatin.

[00185] In another embodiment, the invention is directed to a method of treating non-Hodgkin's lymphoma which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments independently selected from radiation, one or two chemotherapeutic agents, interferon therapy, one or two antibodies, and bone marrow or peripheral blood stem cell transplantation. In another embodiment, the invention is directed

to a method of treating non-Hodgkin's lymphoma which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is one or two chemotherapeutic agents selected from CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), chlorambucil, fludarabine, and etoposide. In another embodiment, the invention is directed to a method of treating non-Hodgkin's lymphoma which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is an antibody selected from rituximab, ibritumomab tiuxetan, tositumomab, and alemtuzumab. In another embodiment, the invention is directed to a method of treating non-Hodgkin's lymphoma which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is an antibody and the anitbody is rituximab.

[00186] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is radiation and another treatment is surgery.

[00187] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is radiation and another treatment is one or two chemotherapeutic agents.

[00188] In another embodiment, the invention is directed to a method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I, as defined in the Summary of the Invention, in combination with one or more treatments where one of the treatments is surgery and another treatment is one or two chemotherapeutic agents.

[00189] For each of the foregoing embodiments, the Compound of Formula I is selected from any of the following embodiments, including from the Representative Compounds in Table 1.

[00190] One embodiment (A) of the Invention is directed to a Compound of Formula I where R^1 is hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl. In another embodiment, R^1 is hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted arylalkyl, or optionally substituted heterocycloalkylalkyl. In another embodiment, R^1 is hydrogen, alkyl, alkyl substituted with one or two hydroxy, alkyl substituted with alkoxy, cycloalkyl, arylalkyl, or heterocycloalkylalkyl. In another embodiment, R^1 is hydrogen, methyl, ethyl, propyl, isopropyl, 2-hydroxypropyl, 3-hydroxypropyl, 2-ethoxyethyl, 3-methoxypropyl, 3-ethoxypropyl, 3-isopropoxypropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, benzyl, or 2-piperidin-1-ylethyl. In another embodiment, R^1 is ethyl, isopropyl, cyclopentyl, or cyclohexyl. In another embodiment, R^1 is ethyl.

[00191] Another embodiment (B) of the Invention is directed to a Compound of Formula I where R^2 is hydrogen or alkyl where the alkyl is optionally substituted with 1, 2, 3, 4, or 5 R^8 groups. In another embodiment, R^2 is hydrogen or alkyl where the alkyl is optionally substituted with one, two, or three R^8 groups. In another embodiment, R^2 is hydrogen or alkyl where the alkyl is optionally substitued with one, two, or three R^8 groups; and each R^8, when present, is independently selected from amino, alkylamino, dialkylamino, and halo. In another embodiment, R^2 is hydrogen, methyl, ethyl, propyl, isopropyl, *tert*-butyl, 3-aminopropyl, 3-(*N*-methylamino)-propyl, 3-(*N,N*-dimethylamino)-propyl, 2-fluoroethyl, or 2,2,2-trifluoroethyl. In another embodiment, R^2 is hydrogen or ethyl. Yet even more preferably, R^2 is hydrogen.

[00192] In another embodiment of the Invention, R^2 is hydrogen.

[00193] In another embodiment of the invention, R^2 is alkyl optionally substituted with 1, 2, 3, 4, or 5, R^8 groups. In another embodiment, R^2 is alkyl where the alkyl is optionally substitued with one, two, or three R^8 groups; and each R^8, when present, is independently selected from amino, alkylamino, dialkylamino, and halo. In another embodiment, R^2 is methyl, ethyl, propyl, isopropyl, *tert*-butyl, 3-aminopropyl, 3-(*N*-methylamino)-propyl, 3-(*N,N*-dimethylamino)-propyl, 2-fluoroethyl, or 2,2,2-trifluoroethyl. In another embodiment, R^2 is ethyl.

[00194] Another embodiment (C) of the Invention is directed to a Compound of Formula I where R^4 is optionally substituted alkyl. In another embodiment, R^4 is methyl or ethyl. In another embodiment, R^4 is methyl.

[00195] Another embodiment (D) of the Invention is directed to a Compound of Formula I where R^6 is acyl. In another embodiment, R^6 is alkylcarbonyl. In another embodiment, R^6 is acetyl.

[00196] Another embodiment (E) of the Invention is directed to a Compound of Formula I where R^6 is phenyl optionally substituted with 1, 2, 3, 4, or 5 R^9 groups. In another embodiment, R^6 is phenyl optionally substituted with one or two R^9 groups; and each R^9, when present, is independently selected from aryl, halo, alkoxy, aryloxy, and haloalkyl. In another embodiment, R^6 is phenyl optionally substituted with one or two R^9 groups; and each R^9, when present, is independently selected from phenyl, fluoro, chloro, methoxy, phenyloxy, and trifluoromethyl. In another embodiment, R^6 is phenyl, phenyl substituted with phenyl, fluorophenyl, difluorophenyl, chlorophenyl, dichlorophenyl, phenyl substituted with chloro and fluoro, methoxyphenyl, dimethoxyphenyl, phenyloxyphenyl, or trifluoromethylphenyl. In another embodiment, R^6 is phenyl, 2-phenyl-phenyl, 3-phenyl-phenyl, 4-phenyl-phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 3-chloro-4-fluoro-phenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,3-dimethoxyphenyl, 2,4-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2,6-dimethoxyphenyl, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, 4-phenyloxyphenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, or 4-trifluoromethylphenyl.

[00197] Another embodiment (F) of the Invention is directed to a Compound of Formula I where R^6 is phenyl substituted with 1, 2, 3, 4, or 5 R^9 groups.

[00198] Another embodiment (G) of the Invention is directed to a Compound of Formula I where R^6 is heteroaryl optionally substituted with 1, 2, 3, 4, or 5 R^9 groups.

[00199] Another embodiment (G1) of embodiment G is a Compound of Formula I where R^6 is a 6-membered heteroaryl optionally substituted with one or two R^9. In another embodiment, R^6 is pyridinyl, pyrazinyl, pyrimidinyl, or pyridazinyl each of which is optionally substituted with one R^9 where R^9, when present, is halo. In another embodiment, R^6 is pyridi*N*-2-yl, pyridin-3-yl, pyridi*N*-4-yl, 3-fluoropyridi*N*-4-yl, pyrazin-2-yl, pyrazin-3-

yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyridazin-3-yl, or pyridazin-4-yl, each of which is optionally substituted with one or two R^9.

[00200] In another embodiment (G2) of embodiment G is a Compound of Formula I where R^6 is pyrazinyl, pyrimidinyl, or pyridazinyl each of which is optionally substituted with one R^9 where R^9, when present, is halo. In another embodiment, R^6 is pyrazin-2-yl, pyrazin-3-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyridazin-3-yl, or pyridazin-4-yl.

[00201] Another embodiment (G3) of embodiment G is a Compound of Formula I where R^6 is 5-membered heteroaryl optionally substituted with one or two R^9. In another embodiment R^6 is pyrazolyl, imidazolyl, thienyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, furanyl, pyrrolyl, triazolyl, or tetrazolyl, each of which is optionally substituted with one R^9 where R^9, when present, is alkyl, arylalkyl, cyano, aryl, alkoxycarbonyl, or halo. In another embodiment, R^6 is pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl, pyrazol-5-yl, imidazol-1-yl, imidazol-2-yl, imidazol-4-yl, imidazol-5-yl, thien-2-yl, thien-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, 1,2,3-oxadiazol-4-yl, 1,2,3-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, furan-2-yl, furan-3-yl, pyrrol-1-yl, pyrrol-2-yl, pyrrol-3-yl, triazol-1-yl, triazol-4-yl, triazol-5-yl, tetrazol-1-yl, or tetrazol-5-yl; each of which is optionally substituted with one R^9 where R^9, when present, is methyl, benzyl, cyano, phenyl, *N-tert*-butoxycarbonyl, or chloro. In another embodiment, R^6 is pyrazol-3-yl, pyrazol-4-yl, pyrazol-5-yl, imidazol-2-yl, imidazol-4-yl, imidazol-5-yl, thien-2-yl, thien-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, 1,2,3-oxadiazol-4-yl, 1,2,3-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, furan-2-yl, furan-3-yl, pyrrol-2-yl, pyrrol-3-yl, triazol-4-yl, triazol-5-yl, or tetrazol-5-yl; each of which is optionally substituted with one R^9 where R^9, when present, is methyl, benzyl, cyano, phenyl, *N-tert*-butoxycarbonyl, or chloro.

[00202] Another embodiment (G4) of embodiment G is a Compound of Formula I where R^6 is thienyl, pyrrolyl, furanyl, pyrazolyl, thiazolyl, isoxazolyl, imidazolyl, triazolyl, or tetrazolyl, each of which is optionally substituted with one R^9 where R^9, when present, is methyl, benzyl, cyano, phenyl, *N-tert*-butoxycarbonyl, or chloro. In another embodiment, R^6 is thien-2-yl, thien-3-yl, pyrrol-2-yl, furan-2-yl, furan-3-yl, pyrazol-3-yl, pyrazol-4-yl, pyrazol-5-yl, thiazol-2-yl, thiazol-5-yl, isoxazol-4-yl, imidazol-5-yl, triazol-5-yl, tetrazol-5-yl, each of which is optionally substituted with one R^9 where R^9, when present, is methyl, benzyl, cyano, phenyl, *N-tert*-butoxycarbonyl, or chloro. In another embodiment, R^6 is thien-2-yl, thien-3-yl, 5-cyano-thien-2-yl, 4-methyl-thien-2-yl, 4-methyl-thien-3-yl, 5-chloro-thien-

5-yl, 5-phenyl-thien-2-yl, pyrrol-2-yl, *N-tert*-butoxycarbonyl-pyrrol-2-yl, *N*-methyl-pyrrol-2-yl, furan-2-yl, furan-3-yl, pyrazol-3-yl, pyrazol-4-yl, *N*-benzyl-pyrazol-4-yl, pyrazol-5-yl, thiazol-2-yl, thiazol-5-yl, isoxazol-4-yl, imidazol-5-yl, triazol-5-yl, tetrazol-5-yl,

[00203] Another embodiment (G5) of embodiment G is a Compound of Formula I where R^6 is thien-2-yl, thien-3-yl, pyrrol-2-yl, furan-2-yl, furan-3-yl, pyrazol-3-yl, pyrazol-4-yl, pyrazol-5-yl, thiazol-2-yl, thiazol-5-yl, isoxazol-4-yl, imidazol-5-yl, triazol-5-yl, or tetrazol-5-yl, each of which is optionally substituted with one R^9 where R^9, when present, is methyl, benzyl, cyano, phenyl, *N-tert*-butoxycarbonyl, or chloro.

[00204] Another embodiment (G6) of embodiment G is a Compound of Formula I where R^6 is indolyl, benzimidazolyl, benzofuranyl, benzoxazolyl, or benzoisoxazolyl each of which is optionally substituted with 1, 2, 3, 4, or 5 R^9 groups. In another embodiment, R^6 is indol-2-yl, indol-3-yl, indol-4-yl, indol-5-yl, indol-6-yl, indol-7-yl, benzimidazol-2-yl, benzimidazol-4-yl, benzimidazol-5-yl, benzimidazol-6-yl, benzimidazol-7-yl, benzofuran-2-yl, benzofuran-3-yl, benzofuran-4-yl, benzofuran-5-yl, benzofuran-6-yl, benzofuran-7-yl, benzoxazol-2-yl, benzoxazol-4-yl, benzoxazol-5-yl, benzoxazol-6-yl, benzoxazol-7-yl, benzoisoxazol-3-yl, benzoisoxazol-4-yl, benzoisoxazol-5-yl, benzoisoxazol-6-yl, or benzoisoxazol-7-yl; each of which is optionally substituted with 1, 2, 3, 4, or 5 R^9 groups. In another embodiment, R^6 is indol-6-yl.

[00205] Another embodiment of the Invention (H) is a Compound of Formula 1 where R^1 is hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkylalkyl, or optionally substituted arylalkyl; X is -NH-; R^2 is hydrogen or alkyl where the alkyl is optionally substituted with one or two R^8 groups; R^4 is alkyl; R^5 is hydrogen; R^6 is phenyl or heteroaryl wherein the phenyl and heteroaryl are optionally substituted with one, two, or three R^9 groups; each R^8, when present, is independently amino, alkylamino, dialkylamino, or halo; and each R^9, when present, is independently alkyl, arylalkyl, cyano, aryl, alkoxycarbonyl, or halo.

[00206] Another embodiment of the Invention (J) is a Compound of Formula 1 where R^6 is pyrazol-3-yl, pyrazol-4-yl, pyrazol-5-yl, imidazol-2-yl, imidazol-4-yl, imidazol-5-yl, thien-2-yl, thien-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, 1,2,3-oxadiazol-4-yl, 1,2,3-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, furan-2-yl, furan-3-yl, pyrrol-2-yl, pyrrol-3-yl, triazol-4-yl, triazol-5-yl, or tetrazol-5-yl; each of which is optionally substituted with 1, 2, 3, 4, or 5 R^9 groups.

[00207] Another embodiment (K) of the Invention is a Compound of Formula I where R^1 is alkyl or cycloalkyl; R^4 is methyl; and R^6 is heteroaryl optionally substituted with one or two R^9 groups. In another embodiment, each R^9, when present, is independently alkyl, arylalkyl, cyano, aryl, alkoxycarbonyl, or halo. In another embodiment, R^6 is pyrazol-3-yl, pyrazol-4-yl, pyrazol-5-yl, imidazol-2-yl, imidazol-4-yl, imidazol-5-yl, thien-2-yl, thien-3-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, 1,2,3-oxadiazol-4-yl, 1,2,3-oxadiazol-5-yl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, furan-2-yl, furan-3-yl, pyrrol-2-yl, pyrrol-3-yl, triazol-4-yl, triazol-5-yl, or tetrazol-5-yl; each of which is optionally substituted with one R^9 where R^9, when present, is methyl, benzyl, cyano, phenyl, or *N-tert*-butoxycarbonyl.

[00208] Another embodiment (K1) of embodiment K is a Compound of Formula I where R^2 is hydrogen.

[00209] Another embodiment (K2) of embodiment K is a Compound of Formula I where R^2 is methyl or ethyl.

[00210] Another embodiment (L) of the Invention is a Compound of Formula I where R^1 is alkyl or cycloalkyl; R^4 is methyl; and R^6 is phenyl optionally substituted with one or two R^9 groups. In another embodiment each R^9, when present, is independently halo, alkoxy, or haloalkyl.

[00211] Another embodiment (M) of the Invention is a Compound of Formula I where R^1 is alkyl or cycloalkyl; R^4 is methyl; and R^2 is hydrogen.

[00212] Another embodiment (N) of the Invention is a Compound of Formula I where R^1 is alkyl or cycloalkyl; R^4 is methyl; and R^2 is optionally substituted alkyl.

Representative Compounds

[00213] Representative compounds of Formula I and/or II 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

[00214] The Compounds in Table 1 can be prepared as pharmaceutically acceptable salts, solvates, hydrates, and/or isomers thereof. All such salt, solvate, hydrate, and isomer

combinations of the Compounds in Table 1 can be used to practice the invention. In particular, the invention can be practiced with one or two pharmaceutically acceptable salts of a Compound of Table 1 which salt(s) are formed with one or two acids independently selected from hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, 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. Any individual compound (and any optional salt, optional solvate, and optional hydrate thereof) in Table 1 can be used in combination with any of the above embodiments.

Table 1

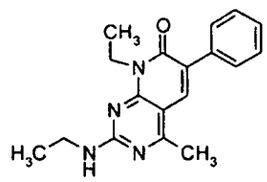
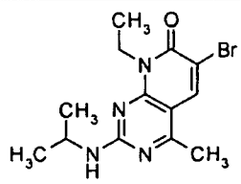
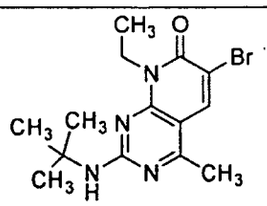
Example	Structure	Name
1		8-ethyl-2-(ethylamino)-4-methyl-6-phenylpyrido[2,3-d]pyrimidin-7(8*H*)-one
2		6-bromo-8-ethyl-4-methyl-2-[(1-methylethyl)amino]pyrido[2,3-d]pyrimidin-7(8*H*)-one
3		6-bromo-2-[(1,1-dimethylethyl)amino]-8-ethyl-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one

Table 1

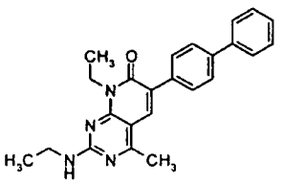
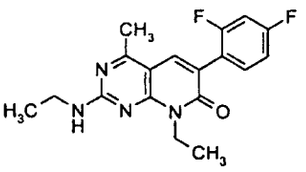
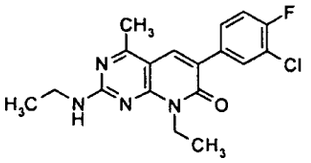
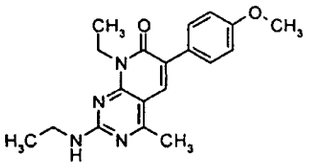
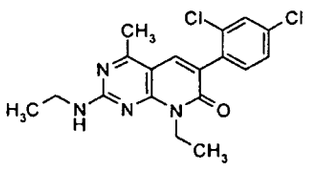
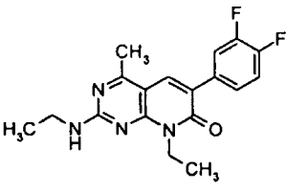
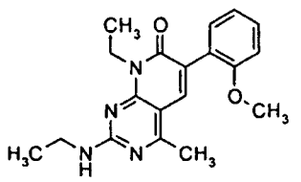
Example	Structure	Name
4		6-biphenyl-4-yl-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one
5		6-(2,4-difluorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one
6		6-(3-chloro-4-fluorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one
7		8-ethyl-2-(ethylamino)-4-methyl-6-[4-(methyloxy)phenyl]pyrido[2,3-d]pyrimidin-7(8*H*)-one
8		6-(2,4-dichlorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one
9		6-(3,4-difluorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one
10		8-ethyl-2-(ethylamino)-4-methyl-6-[2-(methyloxy)phenyl]pyrido[2,3-d]pyrimidin-7(8*H*)-one

Table 1

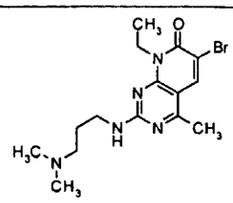
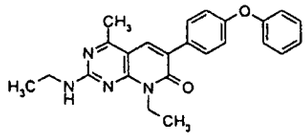
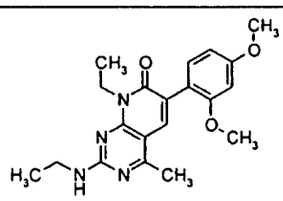
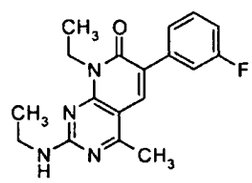
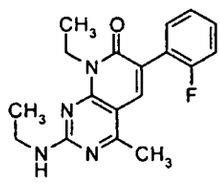
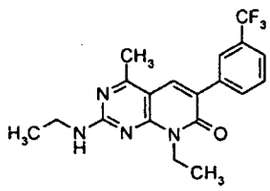
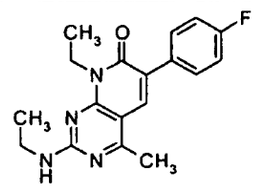
Example	Structure	Name
11		6-bromo-2-{[3-(dimethylamino)propyl]amino}-8-ethyl-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one
12		8-ethyl-2-(ethylamino)-4-methyl-6-[4-(phenyloxy)phenyl]pyrido[2,3-d]pyrimidin-7(8*H*)-one
13		6-[2,4-bis(methyloxy)phenyl]-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one
14		8-ethyl-2-(ethylamino)-6-(3-fluorophenyl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one
15		8-ethyl-2-(ethylamino)-6-(2-fluorophenyl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one
16		8-ethyl-2-(ethylamino)-4-methyl-6-[3-(trifluoromethyl)phenyl]pyrido[2,3-d]pyrimidin-7(8*H*)-one
17		8-ethyl-2-(ethylamino)-6-(4-fluorophenyl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one

Table 1

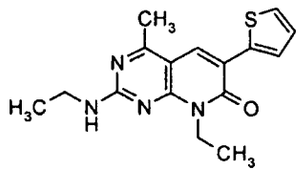
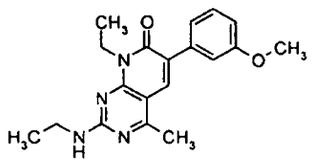
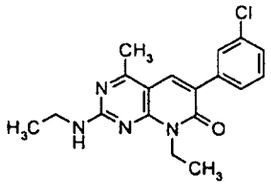
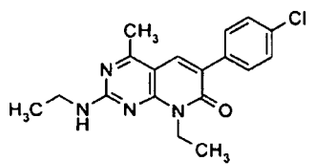
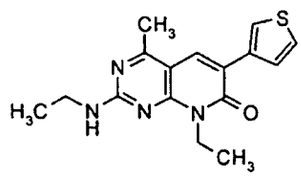
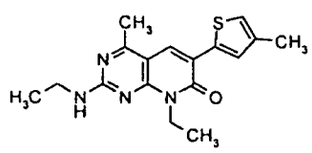
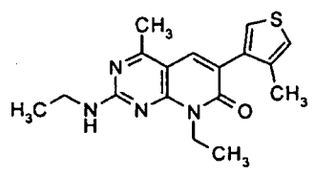
Example	Structure	Name
18		8-ethyl-2-(ethylamino)-4-methyl-6-(2-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one
19		8-ethyl-2-(ethylamino)-4-methyl-6-[3-(methyloxy)phenyl]pyrido[2,3-d]pyrimidin-7(8*H*)-one
20		6-(3-chlorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one
21		6-(4-chlorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one
22		8-ethyl-2-(ethylamino)-4-methyl-6-(3-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one
23		8-ethyl-2-(ethylamino)-4-methyl-6-(4-methyl-2-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one
24		8-ethyl-2-(ethylamino)-4-methyl-6-(4-methyl-3-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one

Table 1

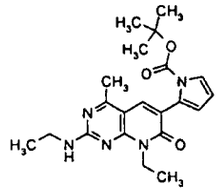
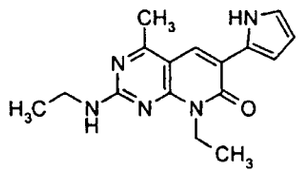
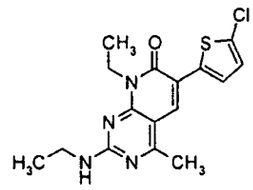
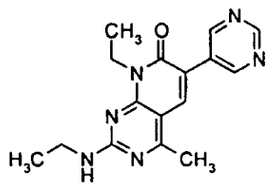
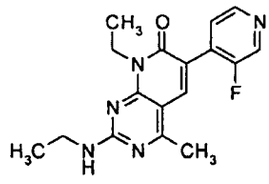
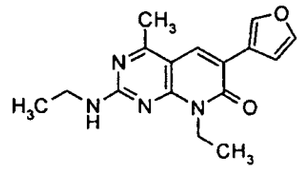
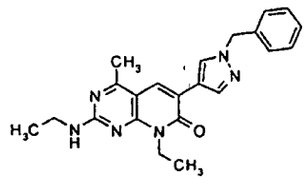
Example	Structure	Name
25		1,1-dimethylethyl 2-[8-ethyl-2-(ethylamino)-4-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl]-1*H*-pyrrole-1-carboxylate
26		8-ethyl-2-(ethylamino)-4-methyl-6-(1*H*-pyrrol-2-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one
27		6-(5-chloro-2-thienyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one
28		8-ethyl-2-(ethylamino)-4-methyl-6-pyrimidin-5-ylpyrido[2,3-d]pyrimidin-7(8*H*)-one
29		8-ethyl-2-(ethylamino)-6-(3-fluoropyridi*N*-4-yl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one
30		8-ethyl-2-(ethylamino)-6-furan-3-yl-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one
31		8-ethyl-2-(ethylamino)-4-methyl-6-[1-(phenylmethyl)-1*H*-pyrazol-4-yl]pyrido[2,3-d]pyrimidin-7(8*H*)-one

Table 1

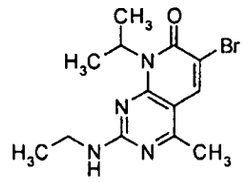
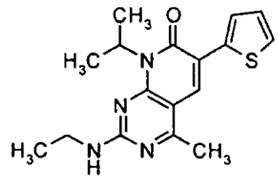
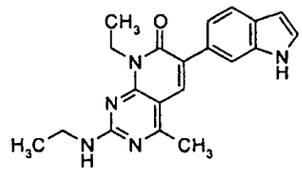
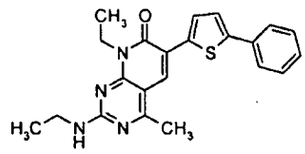
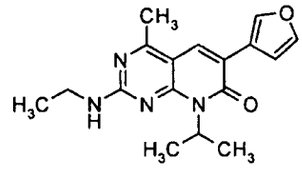
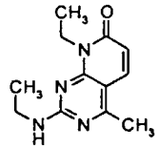
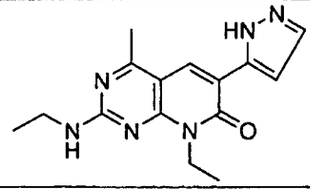
Example	Structure	Name
32		6-bromo-2-(ethylamino)-4-methyl-8-(1-methylethyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one
33		2-(ethylamino)-4-methyl-8-(1-methylethyl)-6-(2-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one
34		8-ethyl-2-(ethylamino)-6-(1*H*-indol-6-yl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one
35		8-ethyl-2-(ethylamino)-4-methyl-6-(5-phenyl-2-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one
36		2-(ethylamino)-6-furan-3-yl-4-methyl-8-(1-methylethyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one
37		8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one
38		8-ethyl-2-(ethylamino)-4-methyl-6-(1*H*-pyrazol-5-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one

Table 1

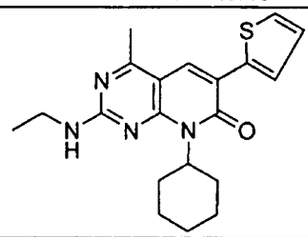
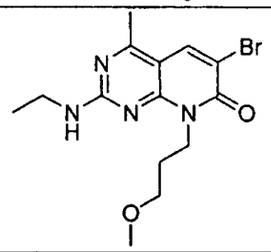
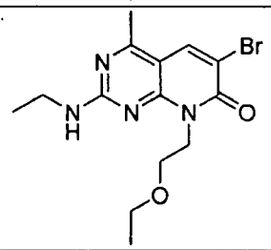
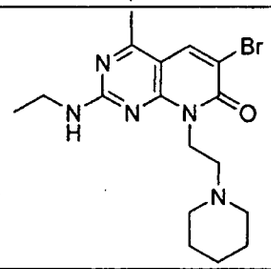
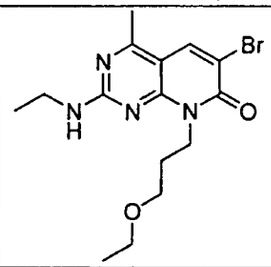
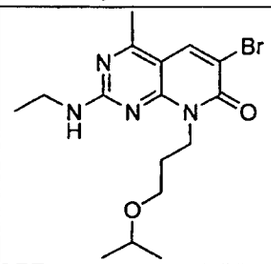
Example	Structure	Name
39		8-cyclohexyl-2-(ethylamino)-4-methyl-6-(2-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one
40		6-bromo-2-(ethylamino)-4-methyl-8-[3-(methyloxy)propyl]pyrido[2,3-d]pyrimidin-7(8*H*)-one
41		6-bromo-2-(ethylamino)-8-[2-(ethyloxy)ethyl]-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one
42		6-bromo-2-(ethylamino)-4-methyl-8-(2-piperidin-1-ylethyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one
43		6-bromo-2-(ethylamino)-8-[3-(ethyloxy)propyl]-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one
44		6-bromo-2-(ethylamino)-4-methyl-8-{3-[(1-methylethyl)oxy]propyl}pyrido[2,3-d]pyrimidin-7(8*H*)-one

Table 1

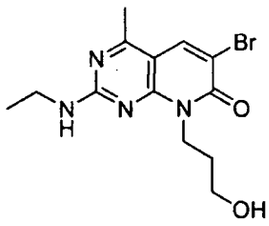
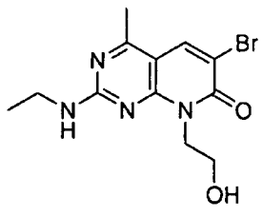
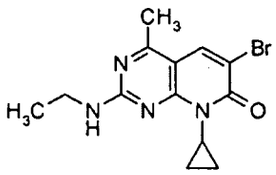
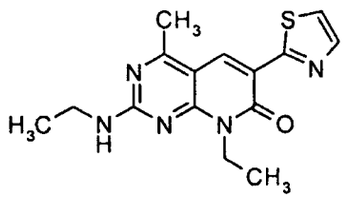
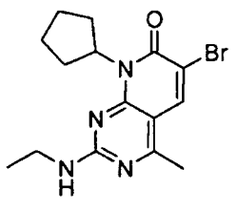
Example	Structure	Name
45		6-bromo-2-(ethylamino)-8-(3-hydroxypropyl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one
46		6-bromo-2-(ethylamino)-8-(2-hydroxyethyl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one
47		6-bromo-8-cyclopropyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one
48		8-ethyl-2-(ethylamino)-4-methyl-6-(1,3-thiazol-2-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one
49		6-bromo-8-cyclopentyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one

Table 1

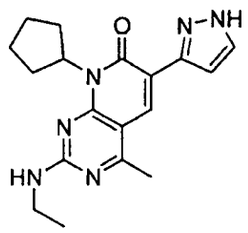
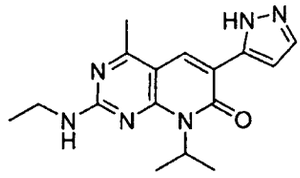
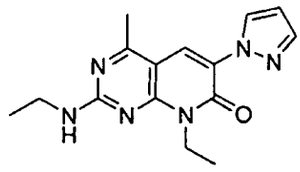
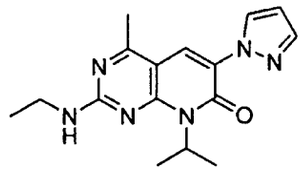
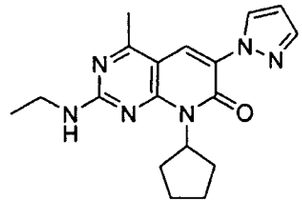
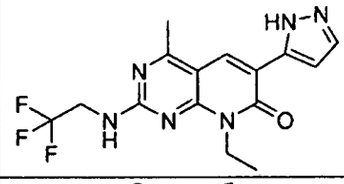
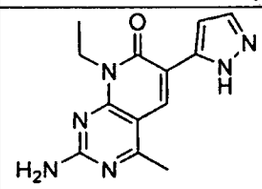
Example	Structure	Name
50		8-cyclopentyl-2-(ethylamino)-4-methyl-6-(1*H*-pyrazol-3-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one
51		2-(ethylamino)-4-methyl-8-(1-methylethyl)-6-(1*H*-pyrazol-5-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one
52		8-ethyl-2-(ethylamino)-4-methyl-6-(1*H*-pyrazol-1-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one
53		2-(ethylamino)-4-methyl-8-(1-methylethyl)-6-(1*H*-pyrazol-1-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one
54		8-cyclopentyl-2-(ethylamino)-4-methyl-6-(1*H*-pyrazol-1-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one
55		8-ethyl-4-methyl-6-(1*H*-pyrazol-5-yl)-2-[(2,2,2-trifluoroethyl)amino]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one
56		2-amino-8-ethyl-4-methyl-6-(1*H*-pyrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one

Table 1

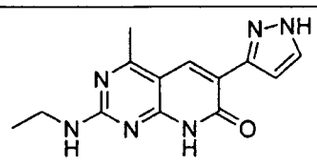
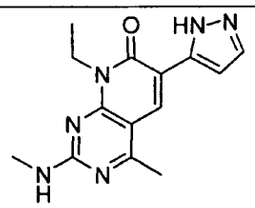
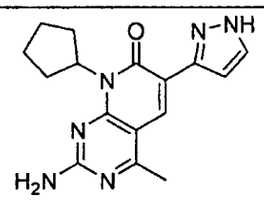
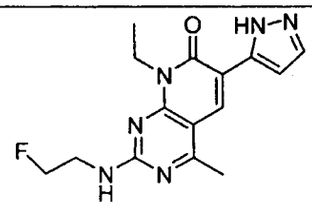
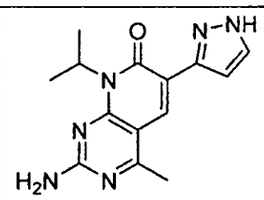
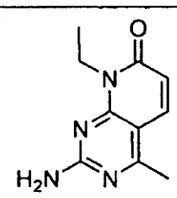
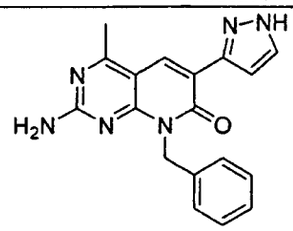
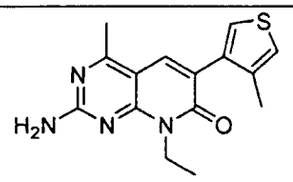
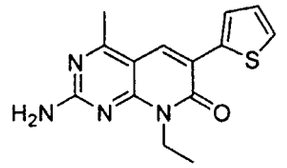
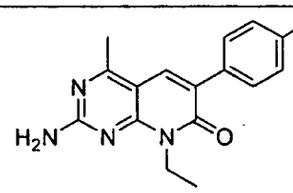
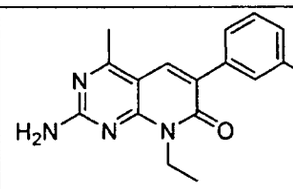
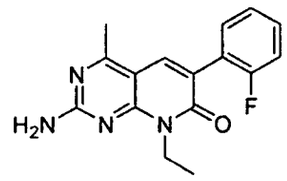
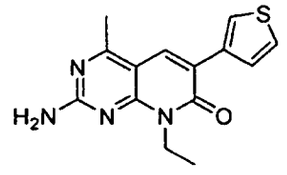
Example	Structure	Name
57		2-(ethylamino)-4-methyl-6-(1*H*-pyrazol-3-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one
58		8-ethyl-4-methyl-2-(methylamino)-6-(1*H*-pyrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one
59		2-amino-8-cyclopentyl-4-methyl-6-(1*H*-pyrazol-3-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one
60		8-ethyl-2-[(2-fluoroethyl)amino]-4-methyl-6-(1*H*-pyrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one
61		2-amino-4-methyl-8-(1-methylethyl)-6-(1*H*-pyrazol-3-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one
62		2-amino-8-ethyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one

Table 1

Example	Structure	Name
63		2-amino-4-methyl-8-(phenylmethyl)-6-(1*H*-pyrazol-3-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one
64		2-amino-8-ethyl-4-methyl-6-(4-methyl-3-thienyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one
65		2-amino-8-ethyl-4-methyl-6-(2-thienyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one
66		2-amino-8-ethyl-6-(4-fluorophenyl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one
67		2-amino-8-ethyl-6-(3-fluorophenyl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one
68		2-amino-8-ethyl-6-(2-fluorophenyl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one
69		2-amino-8-ethyl-4-methyl-6-(3-thienyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one

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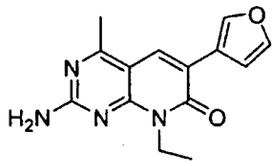
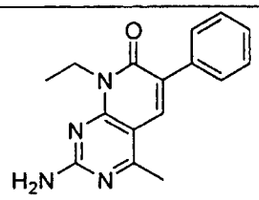
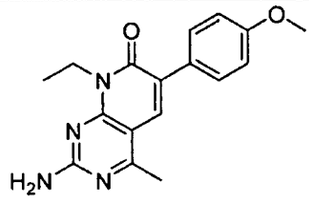
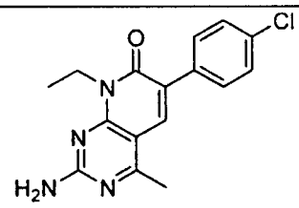
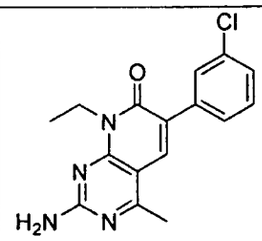
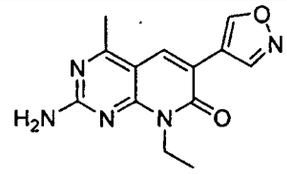
Example	Structure	Name
70		2-amino-8-ethyl-6-furan-3-yl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one
71		2-amino-8-ethyl-4-methyl-6-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one
72		2-amino-8-ethyl-4-methyl-6-[4-(methyloxy)phenyl]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one
73		2-amino-6-(4-chlorophenyl)-8-ethyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one
74		2-amino-6-(3-chlorophenyl)-8-ethyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one
75		2-amino-8-ethyl-6-isoxazol-4-yl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one

Table 1

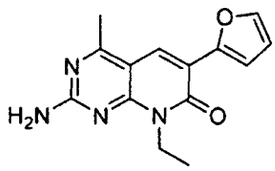
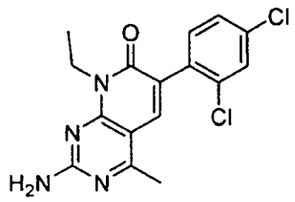
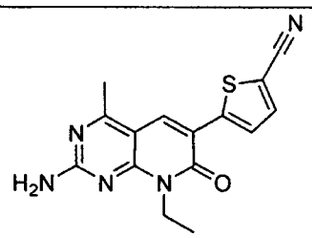
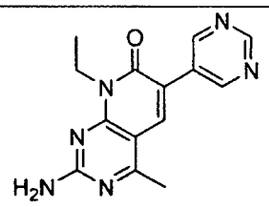
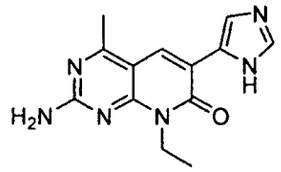
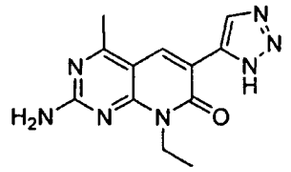
Example	Structure	Name
76		2-amino-8-ethyl-6-furan-2-yl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one
77		2-amino-6-(2,4-dichlorophenyl)-8-ethyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one
78		5-(2-amino-8-ethyl-4-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-6-yl)thiophene-2-carbonitrile
79		2-amino-8-ethyl-4-methyl-6-pyrimidin-5-ylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one
80		2-amino-8-ethyl-6-(1*H*-imidazol-5-yl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one
81		2-amino-8-ethyl-4-methyl-6-(1*H*-1,2,3-triazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one

Table 1

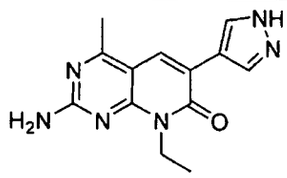
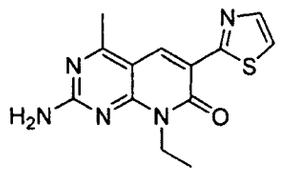
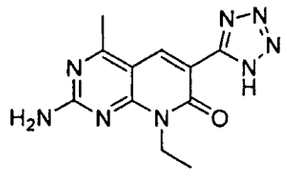
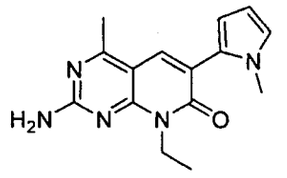
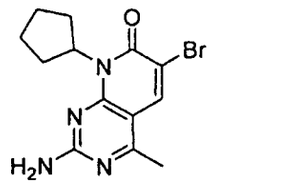
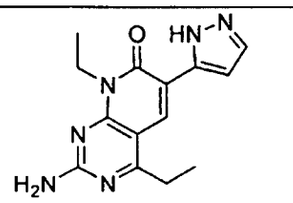
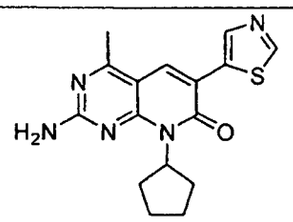
Example	Structure	Name
82		2-amino-8-ethyl-4-methyl-6-(1*H*-pyrazol-4-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one
83		2-amino-8-ethyl-4-methyl-6-(1,3-thiazol-2-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one
84		2-amino-8-ethyl-4-methyl-6-(1*H*-tetrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one
85		2-amino-8-ethyl-4-methyl-6-(1-methyl-1*H*-pyrrol-2-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one
86		2-amino-6-bromo-8-cyclopentyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one
87		2-amino-4,8-diethyl-6-(1*H*-pyrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one
88		2-amino-8-cyclopentyl-4-methyl-6-(1,3-thiazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one

Table 2a.

Representative AKT Inhibitors

[00215] The Compounds in Table 2a can be prepared as pharmaceutically acceptable salts, solvates, hydrates, and/or isomers thereof. All such salt, solvate, hydrate, and isomer combinations of the Compounds in Table 2a can be used to practice the invention.

Table 2a	
Cmpd No.	Name
1	3-(azetidin-3-ylidenemethyl)-4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
2	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-(3-fluoropyridin-4-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
3	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-(3-chloropyridin-4-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
4	2-({5-chloro-3-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methylphenyl}oxy)-*N*,*N*-dimethylethanamine
5	2-({5-chloro-3-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methylphenyl}oxy)-*N*,*N*-diethylethanamine
6	4-(4-{5-chloro-2-methyl-3-[(2-pyrrolidin-1-ylethyl)oxy]phenyl}piperazin-1-yl)-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
7	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-piperazin-1-yl-1*H*-pyrazolo[3,4-d]pyrimidine
8	*N*-(3-{4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl}prop-2-yn-1-yl)acetamide
9	*N*,*N*-diethyl-2-({3-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}oxy)ethanamine
10	3-{3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-chloro-2-methylphenyl}-*N*,*N*-diethylpropan-1-amine
11	3-bromo-4-{4-[5-chloro-2-methyl-3-(3-pyrrolidin-1-ylpropyl)phenyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
12	3-bromo-4-(4-{5-chloro-2-methyl-3-[(2-pyrrolidin-1-ylethyl)oxy]phenyl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
13	2-({3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-chloro-2-methylphenyl}oxy)-*N*,*N*-diethylethanamine
14	4-[4-(5-chloro-2-methyl-3-{[2-(1-methylpiperidin-4-yl)ethyl]oxy}phenyl)piperazin-1-yl]-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
15	5-chloro-3-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline
16	4-(4-{5-chloro-2-methyl-3-[(2-morpholin-4-ylethyl)oxy]phenyl}piperazin-1-yl)-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
17	4-(4-{5-chloro-2-methyl-3-[(2-piperidin-1-ylethyl)oxy]phenyl}piperazin-1-yl)-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
18	3-bromo-4-{4-[5-chloro-2-methyl-3-(3-morpholin-4-ylpropyl)phenyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine

Table 2a	
Cmpd No.	Name
19	3-bromo-4-(4-{5-chloro-2-methyl-3-[3-(4-methylpiperazin-1-yl)propyl]phenyl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
20	3-bromo-4-(4-{5-chloro-2-methyl-3-[(2-piperidin-1-ylethyl)oxy]phenyl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
21	3-bromo-4-(4-{5-chloro-2-methyl-3-[(2-morpholin-4-ylethyl)oxy]phenyl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
22	4-{4-[5-chloro-2-methyl-3-(3-morpholin-4-ylpropyl)phenyl]piperazin-1-yl}-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
23	*N*'-{5-chloro-3-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methylphenyl}-*N*,*N*-diethylethane-1,2-diamine
24	4-{4-[5-chloro-2-methyl-3-(3-piperidin-1-ylpropyl)phenyl]piperazin-1-yl}-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
25	4-[4-(5-chloro-3-{[2-(4-ethylpiperazin-1-yl)ethyl]oxy}-2-methylphenyl)piperazin-1-yl]-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
26	4-(4-{5-chloro-2-methyl-3-[(3-morpholin-4-ylpropyl)oxy]phenyl}piperazin-1-yl)-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
27	3-bromo-4-{4-[5-chloro-2-methyl-3-(3-piperidin-1-ylpropyl)phenyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
28	*N*'-{3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-chloro-2-methylphenyl}-*N*,*N*-diethylethane-1,2-diamine
29	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-chloro-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline
30	4-[4-(5-chloro-2-methyl-3-{[2-(4-methylpiperazin-1-yl)ethyl]oxy}phenyl)piperazin-1-yl]-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
31	4-[4-(5-chloro-2-methyl-3-{[(1-methylpiperidin-4-yl)methyl]oxy}phenyl)piperazin-1-yl]-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
32	*N*,*N*-diethyl-2-({3-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methylphenyl}oxy)ethanamine
33	2-[(5-chloro-3-{4-[1-(1,1-dimethylethyl)-3-(trifluoromethyl)-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}-2-methylphenyl)oxy]-*N*,*N*-diethylethanamine
34	2-[(5-chloro-2-methyl-3-{4-[3-(trifluoromethyl)-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}phenyl)oxy]-*N*,*N*-diethylethanamine
35	4-(4-{5-chloro-2-methyl-3-[(3-pyrrolidin-1-ylpropyl)oxy]phenyl}piperazin-1-yl)-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
36	4-[4-(5-chloro-2-methyl-3-{[3-(4-methylpiperazin-1-yl)propyl]oxy}phenyl)piperazin-1-yl]-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
37	3-bromo-4-(4-{5-chloro-2-methyl-3-[(3-piperidin-1-ylpropyl)oxy]phenyl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
38	3-bromo-4-(4-{5-chloro-2-methyl-3-[(3-morpholin-4-ylpropyl)oxy]phenyl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
39	4-(4-{5-chloro-2-methyl-3-[(2-pyrrolidin-1-ylethyl)oxy]phenyl}piperazin-1-yl)-3-(trifluoromethyl)-1*H*-pyrazolo[3,4-d]pyrimidine
40	4-(4-{5-chloro-2-methyl-3-[(3-morpholin-4-ylpropyl)oxy]phenyl}piperazin-1-yl)-3-(trifluoromethyl)-1*H*-pyrazolo[3,4-d]pyrimidine
41	4-(4-{5-chloro-2-methyl-3-[(2-morpholin-4-ylethyl)oxy]phenyl}piperazin-1-yl)-3-(trifluoromethyl)-1*H*-pyrazolo[3,4-d]pyrimidine

Table 2a	
Cmpd No.	Name
42	4-(4-{5-chloro-2-methyl-3-[(3-piperidin-1-ylpropyl)oxy]phenyl}piperazin-1-yl)-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
43	4-[4-(5-chloro-3-{[3-(4-ethylpiperazin-1-yl)propyl]oxy}-2-methylphenyl)piperazin-1-yl]-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
44	5-chloro-2-methyl-3-[4-(1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-*N*-(2-pyrrolidin-1-ylethyl)aniline
45	5-chloro-2-methyl-3-[4-(3-methyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-*N*-(2-pyrrolidin-1-ylethyl)aniline
46	*N'*-(5-chloro-2-methyl-3-{4-[3-(trifluoromethyl)-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}phenyl)-*N,N*-dimethylethane-1,2-diamine
47	3-({5-chloro-3-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methylphenyl}oxy)-*N,N*-diethylpropan-1-amine
48	*N'*-(5-chloro-2-methyl-3-{4-[3-(trifluoromethyl)-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}phenyl)-*N,N*-diethylethane-1,2-diamine
49	5-chloro-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)-3-{4-[3-(trifluoromethyl)-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}aniline
50	3-bromo-4-(4-{4-methyl-3-[(2-pyrrolidin-1-ylethyl)oxy]phenyl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
51	4-(4-{4-methyl-3-[(2-pyrrolidin-1-ylethyl)oxy]phenyl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
52	3-methyl-4-(4-{4-methyl-3-[(2-pyrrolidin-1-ylethyl)oxy]phenyl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
53	4-(4-{5-chloro-2-methyl-3-[(2-pyrrolidin-1-ylethyl)oxy]phenyl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
54	4-(4-{5-chloro-2-methyl-3-[(2-pyrrolidin-1-ylethyl)oxy]phenyl}piperazin-1-yl)-3-methyl-1*H*-pyrazolo[3,4-d]pyrimidine
55	4-(4-{5-chloro-2-methyl-3-[(2-piperidin-1-ylethyl)oxy]phenyl}piperazin-1-yl)-3-(trifluoromethyl)-1*H*-pyrazolo[3,4-d]pyrimidine
56	3-[(5-chloro-2-methyl-3-{4-[3-(trifluoromethyl)-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}phenyl)oxy]-*N,N*-diethylpropan-1-amine
57	5-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline
58	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-fluoro-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline
59	4-{4-[5-chloro-2-methyl-3-(3-pyrrolidin-1-ylpropyl)phenyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
60	3-bromo-4-{4-[5-fluoro-2-methyl-3-(3-pyrrolidin-1-ylpropyl)phenyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
61	4-{4-[5-chloro-2-methyl-3-(3-pyrrolidin-1-ylpropyl)phenyl]piperazin-1-yl}-3-(trifluoromethyl)-1*H*-pyrazolo[3,4-d]pyrimidine
62	4-(4-{5-chloro-2-methyl-3-[3-(4-methylpiperazin-1-yl)propyl]phenyl}piperazin-1-yl)-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
63	3-bromo-4-(4-pyridin-2-ylpiperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
64	3-bromo-4-[4-(2,4-dimethylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
65	3-bromo-4-{4-[3-(methyloxy)phenyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine

Table 2a	
Cmpd No.	Name
66	3-bromo-4-{4-[2-(methyloxy)phenyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
67	3-bromo-4-{4-[4-methyl-3-(3-pyrrolidin-1-ylpropyl)phenyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
68	4-(4-{5-chloro-2-methyl-3-[(3-pyrrolidin-1-ylpropyl)oxy]phenyl}piperazin-1-yl)-3-(trifluoromethyl)-1*H*-pyrazolo[3,4-d]pyrimidine
69	4-(4-{5-chloro-2-methyl-3-[(3-piperidin-1-ylpropyl)oxy]phenyl}piperazin-1-yl)-3-(trifluoromethyl)-1*H*-pyrazolo[3,4-d]pyrimidine
70	4-[4-(5-chloro-2-methyl-3-{[3-(4-methylpiperazin-1-yl)propyl]oxy}phenyl)piperazin-1-yl]-3-(trifluoromethyl)-1*H*-pyrazolo[3,4-d]pyrimidine
71	4-[4-(5-chloro-3-{[3-(4-ethylpiperazin-1-yl)propyl]oxy}-2-methylphenyl)piperazin-1-yl]-3-(trifluoromethyl)-1*H*-pyrazolo[3,4-d]pyrimidine
72	3-bromo-4-[4-(5-chloro-2-methyl-3-{[2-(4-methylpiperazin-1-yl)ethyl]oxy}phenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
73	4-[4-(5-chloro-2-methyl-3-{[2-(4-methylpiperazin-1-yl)ethyl]oxy}phenyl)piperazin-1-yl]-3-(trifluoromethyl)-1*H*-pyrazolo[3,4-d]pyrimidine
74	3-bromo-4-[4-(5-chloro-3-{[2-(4-ethylpiperazin-1-yl)ethyl]oxy}-2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
75	3-bromo-4-[4-(3,4-dichlorophenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
76	3-bromo-4-[4-(3,4-difluorophenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
77	3-bromo-4-[4-(2,4-dichlorophenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
78	3-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-fluoro-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline
79	5-fluoro-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)-3-{4-[3-(trifluoromethyl)-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}aniline
80	4-{4-[3,5-bis(methyloxy)phenyl]piperazin-1-yl}-3-bromo-1*H*-pyrazolo[3,4-d]pyrimidine
81	4-[4-(5-chloro-3-{[2-(4-ethylpiperazin-1-yl)ethyl]oxy}-2-methylphenyl)piperazin-1-yl]-3-(trifluoromethyl)-1*H*-pyrazolo[3,4-d]pyrimidine
82	*N*-{5-chloro-3-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methylphenyl}-*N*,*N*',*N*'-trimethylethane-1,2-diamine
83	3-({3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-chloro-2-methylphenyl}oxy)-*N*,*N*-diethylpropan-1-amine
84	3-bromo-4-(4-{5-chloro-2-methyl-3-[(3-pyrrolidin-1-ylpropyl)oxy]phenyl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
85	3-bromo-4-[4-(5-chloro-2-methyl-3-{[3-(4-methylpiperazin-1-yl)propyl]oxy}phenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
86	3-bromo-4-[4-(5-chloro-3-{[3-(4-ethylpiperazin-1-yl)propyl]oxy}-2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
87	3-(5-chloro-2-methyl-3-{4-[3-(trifluoromethyl)-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}phenyl)-*N*,*N*-diethylpropan-1-amine
88	3-bromo-4-[4-(5-chloro-2-methyl-3-{[(1-methylpiperidin-4-yl)methyl]oxy}phenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
89	3-bromo-4-[4-(5-chloro-2-methyl-3-{[2-(1-methylpiperidin-4-yl)ethyl]oxy}phenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
90	4-[4-(5-chloro-2-methyl-3-{[(1-methylpiperidin-4-yl)methyl]oxy}phenyl)piperazin-1-yl]-3-(trifluoromethyl)-1*H*-pyrazolo[3,4-d]pyrimidine

Table 2a	
Cmpd No.	Name
91	4-[4-(5-chloro-2-methyl-3-{[2-(1-methylpiperidin-4-yl)ethyl]oxy}phenyl)piperazin-1-yl]-3-(trifluoromethyl)-1*H*-pyrazolo[3,4-d]pyrimidine
92	4-(4-{5-chloro-2-methyl-3-[3-(4-methylpiperazin-1-yl)propyl]phenyl}piperazin-1-yl)-3-(trifluoromethyl)-1*H*-pyrazolo[3,4-d]pyrimidine
93	3-bromo-4-[4-(3-chloro-4-fluorophenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
94	1-{4-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}ethanone
95	3-bromo-4-[4-(2,5-dichlorophenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
96	3-bromo-4-[4-(3,4-dimethylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
97	3-bromo-4-[4-(4-nitrophenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
98	3-ethyl-4-(4-phenylpiperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
99	3-ethyl-4-{4-[3-(methyloxy)phenyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
100	4-{4-[5-chloro-2-methyl-3-(3-piperidin-1-ylpropyl)phenyl]piperazin-1-yl}-3-(trifluoromethyl)-1*H*-pyrazolo[3,4-d]pyrimidine
101	4-[4-(3,6-dimethylpyrazin-2-yl)piperazin-1-yl]-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
102	1-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]isoquinoline
103	3-bromo-4-[4-(2,6-dimethylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
104	3-bromo-4-{4-[4-(ethyloxy)phenyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
105	3-bromo-4-[4-(2-ethylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
106	4-{4-[2,4-bis(methyloxy)phenyl]piperazin-1-yl}-3-bromo-1*H*-pyrazolo[3,4-d]pyrimidine
107	3-bromo-4-(4-pyrazin-2-ylpiperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
108	3-bromo-4-(4-pyrimidin-2-ylpiperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
109	4-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-(trifluoromethyl)quinoline
110	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]pyrazine-2-carbonitrile
111	4-[4-(4,6-dimethylpyrimidin-2-yl)piperazin-1-yl]-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
112	ethyl 4-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-(trifluoromethyl)pyrimidine-5-carboxylate
113	4-{4-[3-chloro-5-(methyloxy)phenyl]piperazin-1-yl}-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
114	4-[4-(3-bromo-2-chloro-5-fluorophenyl)piperazin-1-yl]-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
115	2-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]pyridine-3-carboxamide
116	3-ethyl-4-{4-[4-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
117	3-bromo-4-{4-[4-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
118	3-bromo-4-{4-[4-(trifluoromethyl)pyrimidin-2-yl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
119	2-({3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]pyrazin-2-yl}oxy)-*N*,*N*-dimethylethanamine
120	4-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methylquinoline
121	3-bromo-4-[4-(2-nitrophenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
122	2-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzonitrile

Table 2a	
Cmpd No.	Name
123	4-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]benzonitrile
124	3-bromo-4-{4-[4-(trifluoromethyl)phenyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
125	3-bromo-4-(4-{4-[(phenylmethyl)oxy]phenyl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
126	4-{4-[5-chloro-2-methyl-3-(methyloxy)phenyl]piperazin-1-yl}-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
127	2-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]pyridine-3-carbonitrile
128	3-bromo-4-[4-(3,5-dichlorophenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
129	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-chloro-5-fluoro-*N*-(2-pyrrolidin-1-ylethyl)aniline
130	2-chloro-3-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-fluoro-*N*-(2-pyrrolidin-1-ylethyl)aniline
131	3-bromo-4-[4-(2,5-difluorophenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
132	4-[4-(2,5-difluorophenyl)piperazin-1-yl]-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
133	3-bromo-4-{4-[3-(methyloxy)pyrazin-2-yl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
134	3-bromo-4-[4-(3-chlorophenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
135	3-bromo-4-{4-[3-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
136	3-bromo-4-{4-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
137	4-(4-{5-chloro-2-methyl-3-[(2-pyrrolidin-1-ylethyl)oxy]phenyl}piperazin-1-yl)-3-(1-methylethyl)-1*H*-pyrazolo[3,4-d]pyrimidine
138	5-chloro-2-methyl-3-{4-[3-(1-methylethyl)-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}-*N*-(2-pyrrolidin-1-ylethyl)aniline
139	2-({3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}oxy)-*N*-ethylacetamide
140	2-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-*N*,*N*-diethylpyrimidin-4-amine
141	3-bromo-4-[4-(3-{[(3-methylphenyl)methyl]oxy}phenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
142	3-bromo-4-(4-{3-[(2-piperidin-1-ylethyl)oxy]phenyl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
143	3-bromo-4-[4-(4-furan-2-ylpyrimidin-2-yl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
144	6-{2-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]pyrimidin-4-yl}-2*H*-1,4-benzoxazin-3(4*H*)-one
145	3-ethyl-4-{4-[2-methyl-3-(methyloxy)phenyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
146	*N*'-{5-chloro-3-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methylphenyl}-*N*-methyl-*N*-(1-methylethyl)ethane-1,2-diamine
147	*N*'-{5-chloro-3-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methylphenyl}-*N*-ethyl-*N*-methylethane-1,2-diamine
148	*N*'-{3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-chloro-2-methylphenyl}-*N*,*N*-dimethylethane-1,2-diamine
149	3-({6-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-chloro-5-methylpyrimidin-4-yl}oxy)-*N*,*N*-diethylpropan-1-amine

Table 2a	
Cmpd No.	Name
150	3-bromo-4-[4-(2,3-dichlorophenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
151	3-bromo-4-{4-[2-(trifluoromethyl)phenyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
152	3-bromo-4-(4-phenylpiperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
153	3-bromo-4-[4-(4-fluorophenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
154	3-bromo-4-[4-(4-chlorophenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
155	3-bromo-4-{4-[3-(trifluoromethyl)phenyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
156	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidin-6-amine
157	3-bromo-4-[4-(4-bromophenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
158	3-bromo-4-[3-methyl-4-(3-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
159	4-[4-(3-bromo-5-chloro-2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidin-6-amine
160	4-(4-{5-chloro-2-methyl-3-[(2-pyrrolidin-1-ylethyl)oxy]phenyl}piperazin-1-yl)-3-cyclopropyl-1*H*-pyrazolo[3,4-d]pyrimidine
161	5-chloro-3-[4-(3-cyclopropyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline
162	5-chloro-2-methyl-3-{4-[3-(2-methylpropyl)-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl]piperazin-1-yl}-*N*-(2-pyrrolidin-1-ylethyl)aniline
163	4-(4-{5-chloro-2-methyl-3-[(2-pyrrolidin-1-ylethyl)oxy]phenyl}piperazin-1-yl)-3-(2-methylpropyl)-1*H*-pyrazolo[3,4-d]pyrimidine
164	3-bromo-4-[(3S)-4-(5-chloro-2-methylphenyl)-3-methylpiperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
165	5-bromo-3-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methylaniline
166	2-({3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}oxy)-*N*-cyclopropylacetamide
167	3-bromo-4-(4-{3-[(2-piperidin-1-ylethyl)oxy]pyrazin-2-yl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
168	4-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-6,7-bis(methyloxy)quinazoline
169	2-({3-chloro-5-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}oxy)-*N*,*N*-diethylethanamine
170	4-{4-[2-chloro-5-(trifluoromethyl)phenyl]piperazin-1-yl}-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
171	3-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-5-[(2-methylpropyl)oxy]-*N*-(2-pyrrolidin-1-ylethyl)aniline
172	3-({4-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-6-chloro-5-methylpyrimidin-2-yl}oxy)-*N*,*N*-diethylpropan-1-amine
173	3-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-5-[(phenylmethyl)oxy]-*N*-(2-pyrrolidin-1-ylethyl)aniline
174	3-bromo-4-[(3R)-4-(5-chloro-2-methylphenyl)-3-methylpiperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
175	3-[(2S)-4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl]-4-methyl-*N*-phenylbenzamide
176	3-[(2S)-4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)-2-methylpiperazin-1-yl]-4-methyl-*N*-(phenylmethyl)benzamide
177	methyl 3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-4-methylbenzoate

Table 2a	
Cmpd No.	Name
178	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-4-methylbenzoic acid
179	(2E)-3-(4-{4-[5-chloro-2-methyl-3-(3-pyrrolidin-1-ylpropyl)phenyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)prop-2-enoic acid
180	3-(4-{4-[5-chloro-2-methyl-3-(3-pyrrolidin-1-ylpropyl)phenyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl)prop-2-yn-1-ol
181	4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)-1-(5-chloro-2-methylphenyl)piperazin-2-one
182	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-5-[(2-methylpropyl)oxy]-*N*-(2-pyrrolidin-1-ylethyl)aniline
183	*N*'-{3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-5-[(2-methylpropyl)oxy]phenyl}-*N*,*N*-diethylethane-1,2-diamine
184	methyl 3-bromo-5-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-4-methylbenzoate
185	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-4-methyl-*N*-phenylbenzamide
186	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-*N*,4-dimethylbenzamide
187	2-({3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]phenyl}oxy)-*N*,*N*-diethylethanamine
188	methyl 3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-4-methyl-5-[(2-pyrrolidin-1-ylethyl)amino]benzoate
189	3-bromo-5-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-4-methyl-*N*-phenylbenzamide
190	3-bromo-5-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-4-methyl-*N*-phenylbenzamide
191	*N*'-{3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-chloro-2-methylphenyl}-*N*-methyl-*N*-(1-methylethyl)ethane-1,2-diamine
192	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-4-methyl-*N*-phenyl-5-[(2-pyrrolidin-1-ylethyl)amino]benzamide
193	*N*'-{3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-5-[(2-methylpropyl)oxy]phenyl}-*N*,*N*-dimethylethane-1,2-diamine
194	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-*N*,*N*,4-trimethylbenzamide
195	3-[4-(3-chloro-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-4-methyl-*N*-(2-methylpropyl)benzamide
196	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-*N*,*N*,4-trimethyl-5-[(2-pyrrolidin-1-ylethyl)amino]benzamide
197	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)-2-oxopiperazin-1-yl]-4-methyl-*N*-phenylbenzamide
198	3-[(2R)-4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)-2-(hydroxymethyl)piperazin-1-yl]-4-methyl-*N*-phenylbenzamide
199	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-5-(pyrrolidin-1-ylcarbonyl)-*N*-(2-pyrrolidin-1-ylethyl)aniline
200	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-*N*,4-dimethyl-5-[(2-pyrrolidin-1-ylethyl)amino]benzamide
201	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-*N*-(4-chlorophenyl)-4-methyl-5-[(2-pyrrolidin-1-ylethyl)amino]benzamide

Table 2a	
Cmpd No.	Name
202	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-*N*-(2-chlorophenyl)-4-methyl-5-[(2-pyrrolidin-1-ylethyl)amino]benzamide
203	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-[(cyclopropylmethyl)oxy]-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline
204	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-5-[(3-methylbutyl)oxy]-*N*-(2-pyrrolidin-1-ylethyl)aniline
205	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-[(2-ethylbutyl)oxy]-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline
206	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-(butyloxy)-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline
207	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-4-methyl-*N*-(1-methylethyl)-5-[(2-pyrrolidin-1-ylethyl)amino]benzamide
208	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-*N*,4-dimethyl-*N*-(1-methylethyl)-5-[(2-pyrrolidin-1-ylethyl)amino]benzamide
209	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-[(cyclobutylmethyl)oxy]-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline
210	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-(ethyloxy)-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline
211	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-*N*-[2-(dimethylamino)ethyl]-4-methylbenzamide
212	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-*N*-(1,1-dimethylethyl)-4-methyl-5-[(2-pyrrolidin-1-ylethyl)amino]benzamide
213	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-4-methyl-*N*-pyridin-3-yl-5-[(2-pyrrolidin-1-ylethyl)amino]benzamide
214	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-[(2-fluoro-2-methylpropyl)oxy]-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline
215	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-[(cyclohexylmethyl)oxy]-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline
216	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-[(cyclopentylmethyl)oxy]-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline
217	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-*N*-ethyl-4-methyl-5-[(2-pyrrolidin-1-ylethyl)amino]benzamide
218	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-5-[(1-methylethyl)oxy]-*N*-(2-pyrrolidin-1-ylethyl)aniline
219	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-[(2,2-dimethylpropyl)oxy]-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline
220	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)-5-[(tetrahydrofuran-2-ylmethyl)oxy]aniline
221	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-5-{[2-(methyloxy)ethyl]oxy}-*N*-(2-pyrrolidin-1-ylethyl)aniline
222	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-5-(propyloxy)-*N*-(2-pyrrolidin-1-ylethyl)aniline
223	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-{[2-(dimethylamino)ethyl]amino}-4-methyl-*N*-phenylbenzamide
224	*N*'-{3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-[(2-fluoro-2-methylpropyl)oxy]-2-methylphenyl}-*N*,*N*-dimethylethane-1,2-diamine

Table 2a	
Cmpd No.	Name
225	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-{[2-(dimethylamino)ethyl]amino}-4-methyl-*N*-(1-methylethyl)benzamide
226	1-{3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-4-methyl-5-[(2-pyrrolidin-1-ylethyl)amino]phenyl}pentan-1-one
227	*N*'-(3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-{[2,3-difluoro-2-(fluoromethyl)propyl]oxy}-2-methylphenyl)-*N*,*N*-dimethylethane-1,2-diamine
228	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-{[2,3-difluoro-2-(fluoromethyl)propyl]oxy}-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline
229	5-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-4-methyl-*N*-(2-pyrrolidin-1-ylethyl)biphenyl-3-amine
230	1-(3-{5-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-4-methylbiphenyl-3-yl}propyl)pyridinium
231	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)-5-(1,3-thiazol-2-yl)aniline
232	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-4-methyl-5-[(2-pyrrolidin-1-ylethyl)amino]benzoic acid
233	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-5-(phenylethynyl)-*N*-(2-pyrrolidin-1-ylethyl)aniline
234	{3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-4-methyl-5-[(2-pyrrolidin-1-ylethyl)amino]phenyl}(phenyl)methanone
235	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-ethynyl-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline
236	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-(3,3-dimethylbut-1-yn-1-yl)-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline
237	3-bromo-4-{4-[5-{[2,3-difluoro-2-(fluoromethyl)propyl]oxy}-2-methyl-3-(3-pyrrolidin-1-ylpropyl)phenyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
238	3-bromo-4-{4-[2-methyl-5-[(2-methylpropyl)oxy]-3-(3-pyrrolidin-1-ylpropyl)phenyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
239	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-5-(3-phenyl-1,2,4-oxadiazol-5-yl)-*N*-(2-pyrrolidin-1-ylethyl)aniline
240	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-5-(3-methyl-1,2,4-oxadiazol-5-yl)-*N*-(2-pyrrolidin-1-ylethyl)aniline
241	1-{3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-4-methyl-5-[(2-pyrrolidin-1-ylethyl)amino]phenyl}propan-1-one
242	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-(3,3-dimethylbutyl)-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline
243	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-ethyl-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline
244	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)-5-[2-(trimethylsilyl)ethyl]aniline
245	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-5-(2-phenylethyl)-*N*-(2-pyrrolidin-1-ylethyl)aniline
246	1-{3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-4-methyl-5-[(2-pyrrolidin-1-ylethyl)amino]phenyl}butan-1-one
247	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-*N*,4-dimethyl-*N*-(methyloxy)-5-[(2-pyrrolidin-1-ylethyl)amino]benzamide

Table 2a	
Cmpd No.	Name
248	3-bromo-4-[4-(3-bromo-5-{[2,3-difluoro-2-(fluoromethyl)propyl]oxy}-2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
249	4-[4-(3-bromo-5-{[2,3-difluoro-2-(fluoromethyl)propyl]oxy}-2-methylphenyl)piperazin-1-yl]-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
250	1-{3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-4-methyl-5-[(2-pyrrolidin-1-ylethyl)amino]phenyl}ethanone
251	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-[(difluoromethyl)oxy]-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline
252	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-{[(difluoromethyl)oxy]methyl}-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline
253	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-5-(methyloxy)-*N*-(2-pyrrolidin-1-ylethyl)aniline
254	5-{[2,3-difluoro-2-(fluoromethyl)propyl]oxy}-3-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline
255	2-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-3,5,6-trifluoro-*N*-(3-methylbutyl)pyridin-4-amine
256	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-*N*-[(cyclopropylmethyl)oxy]-4-methyl-5-[(2-pyrrolidin-1-ylethyl)amino]benzamide
257	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-5-(5-methyl-1,2,4-oxadiazol-3-yl)-*N*-(2-pyrrolidin-1-ylethyl)aniline
258	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-(ethylsulfonyl)-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline
259	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-5-(methylsulfonyl)-*N*-(2-pyrrolidin-1-ylethyl)aniline
260	1-{3-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-4-methyl-5-[(2-pyrrolidin-1-ylethyl)amino]phenyl}pentan-1-one
261	3-bromo-4-[4-(5-{[2,3-difluoro-2-(fluoromethyl)propyl]oxy}-2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
262	6-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-3,5-difluoro-*N*~4~-(3-methylbutyl)-*N*~2~-(2-pyrrolidin-1-ylethyl)pyridine-2,4-diamine
263	3-bromo-5-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-*N*-(2-pyrrolidin-1-ylethyl)aniline
264	3-bromo-4-[4-(3',4',6-trifluoro-4-methylbiphenyl-3-yl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
265	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-chloro-*N*-(2-pyrrolidin-1-ylethyl)aniline
266	{3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-4-methyl-5-[(2-pyrrolidin-1-ylethyl)amino]phenyl}methanol
267	3-bromo-4-(4-{4-methyl-2'-[(2-pyrrolidin-1-ylethyl)oxy]biphenyl-3-yl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
268	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-{[(2,2-difluorocyclopropyl)methyl]oxy}-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline
269	5-bromo-3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline
270	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-[(ethyloxy)methyl]-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline

Table 2a	
Cmpd No.	Name
271	3-[4-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-1-methyl-6-(trifluoromethyl)-1*H*-benzimidazol-2-yl]propan-1-ol
272	1-{3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-4-methyl-5-[(2-pyrrolidin-1-ylethyl)amino]phenyl}-4,4,4-trifluorobutan-1-one
273	{3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-4-methyl-5-[(2-pyrrolidin-1-ylethyl)amino]phenyl}(cyclopropyl)methanone
274	3-({3'-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-4'-methylbiphenyl-2-yl}oxy)-*N*,*N*-dimethylpropan-1-amine
275	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-(1,1-difluorobutyl)-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)aniline
276	3-bromo-4-(4-{4-methyl-2'-[(3-morpholin-4-ylpropyl)oxy]biphenyl-3-yl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
277	3-bromo-4-(4-{4-methyl-2'-[(2-morpholin-4-ylethyl)oxy]biphenyl-3-yl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
278	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)-5-{[(2,2,2-trifluoroethyl)oxy]methyl}aniline
279	1-[2-({3'-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-4'-methylbiphenyl-2-yl}oxy)ethyl]pyrrolidine-2,5-dione
280	3-bromo-4-(4-{3'-fluoro-4-methyl-2'-[(2-pyrrolidin-1-ylethyl)oxy]biphenyl-3-yl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
281	1-{3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-[(2-pyrrolidin-1-ylethyl)amino]phenyl}butan-1-one
282	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)-5-[(3,3,3-trifluoropropyl)oxy]aniline
283	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)-5-[(2,2,2-trifluoroethyl)oxy]aniline
284	1-{3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-4-methyl-5-[(2-pyrrolidin-1-ylethyl)amino]phenyl}butan-1-ol
285	3-bromo-4-(4-{4-chloro-2'-[(2-pyrrolidin-1-ylethyl)oxy]biphenyl-3-yl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
286	3-[4-(4-{5-{[2,3-difluoro-2-(fluoromethyl)propyl]oxy}-2-methyl-3-[(2-pyrrolidin-1-ylethyl)amino]phenyl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl]prop-2-yn-1-ol
287	3-bromo-4-(4-{4-chloro-4'-fluoro-2'-[(2-pyrrolidin-1-ylethyl)oxy]biphenyl-3-yl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
288	3-bromo-4-(4-{4-methyl-3'-[(2-pyrrolidin-1-ylethyl)oxy]biphenyl-3-yl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
289	(2E)-3-[4-(4-{5-{[2,3-difluoro-2-(fluoromethyl)propyl]oxy}-2-methyl-3-[(2-pyrrolidin-1-ylethyl)amino]phenyl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl]prop-2-enoic acid
290	3-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methyl-*N*-(2-pyrrolidin-1-ylethyl)-5-[4,4,4-trifluoro-1,1-bis(methyloxy)butyl]aniline
291	6-(4-phenylpiperazin-1-yl)-9*H*-purine
292	6-[4-(3-chlorophenyl)piperazin-1-yl]-9*H*-purine
293	4-(4-phenylpiperazin-1-yl)-7*H*-pyrrolo[2,3-d]pyrimidine
294	4-[4-(3-chlorophenyl)piperazin-1-yl]-7*H*-pyrrolo[2,3-d]pyrimidine
295	4-(4-phenylpiperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine

Table 2a	
Cmpd No.	Name
296	4-[4-(3-chlorophenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
297	6-[4-(2-chlorophenyl)piperazin-1-yl]-9*H*-purine
298	6-[4-(2-fluorophenyl)piperazin-1-yl]-9*H*-purine
299	4-[4-(2-methylphenyl)piperazin-1-yl]-7*H*-pyrrolo[2,3-d]pyrimidine
300	4-{4-[2-(methyloxy)phenyl]piperazin-1-yl}-7*H*-pyrrolo[2,3-d]pyrimidine
301	4-{4-[3-(methyloxy)phenyl]piperazin-1-yl}-7*H*-pyrrolo[2,3-d]pyrimidine
302	4-{4-[4-(methyloxy)phenyl]piperazin-1-yl}-7*H*-pyrrolo[2,3-d]pyrimidine
303	4-{4-[3-(trifluoromethyl)phenyl]piperazin-1-yl}-7*H*-pyrrolo[2,3-d]pyrimidine
304	6-{4-[4-(methyloxy)phenyl]piperazin-1-yl}-9*H*-purine
305	6-{4-[2-(methyloxy)phenyl]piperazin-1-yl}-9*H*-purine
306	6-[4-(4-chlorophenyl)piperazin-1-yl]-9*H*-purine
307	6-[4-(4-fluorophenyl)piperazin-1-yl]-9*H*-purine
308	4-[4-(4-chlorophenyl)piperazin-1-yl]-7*H*-pyrrolo[2,3-d]pyrimidine
309	4-[4-(2-chlorophenyl)piperazin-1-yl]-7*H*-pyrrolo[2,3-d]pyrimidine
310	4-[4-(4-fluorophenyl)piperazin-1-yl]-7*H*-pyrrolo[2,3-d]pyrimidine
311	4-[4-(2-fluorophenyl)piperazin-1-yl]-7*H*-pyrrolo[2,3-d]pyrimidine
312	6-{4-[3-(trifluoromethyl)phenyl]piperazin-1-yl}-9*H*-purine
313	6-[4-(2-methylphenyl)piperazin-1-yl]-9*H*-purine
314	4-{4-[3-(trifluoromethyl)phenyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
315	4-[4-(2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
316	4-[4-(3-chlorophenyl)piperazin-1-yl]-3-methyl-1*H*-pyrazolo[3,4-d]pyrimidine
317	3-methyl-4-[4-(2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
318	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
319	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-methyl-1*H*-pyrazolo[3,4-d]pyrimidine
320	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-methyl-6-phenyl-1*H*-pyrazolo[3,4-d]pyrimidine
321	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
322	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-6-methyl-1*H*-pyrazolo[3,4-d]pyrimidine
323	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-6-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
324	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-6-(1-methylethyl)-1*H*-pyrazolo[3,4-d]pyrimidine
325	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-phenyl-1*H*-pyrazolo[3,4-d]pyrimidine
326	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-({[2-(methyloxy)ethyl]oxy}methyl)-1*H*-pyrazolo[3,4-d]pyrimidine
327	3-bromo-4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
328	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-propyl-1*H*-pyrazolo[3,4-d]pyrimidine
329	4-{4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl}phenol
330	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-*N*-phenyl-1*H*-pyrazolo[3,4-d]pyrimidin-3-amine
331	4-[4-(3-chlorophenyl)piperazin-1-yl]-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine

Table 2a	
Cmpd No.	Name
332	4-{4-[5-chloro-2-(methyloxy)phenyl]piperazin-1-yl}-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
333	3-{4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl}phenol
334	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-{3-[(phenylmethyl)oxy]phenyl}-1*H*-pyrazolo[3,4-d]pyrimidine
335	3-(1,3-benzodioxol-5-yl)-4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
336	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-(2-thienyl)-1*H*-pyrazolo[3,4-d]pyrimidine
337	3-{4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl}aniline
338	3-{4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl}benzoic acid
339	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-(4-methylphenyl)-1*H*-pyrazolo[3,4-d]pyrimidine
340	*N*-(4-{4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)acetamide
341	4-[4-(3-chlorophenyl)-1,4-diazepan-1-yl]-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
342	4-[5-(3-chlorophenyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
343	4-(4-{3-chloro-4-[(2-morpholin-4-ylethyl)oxy]phenyl}piperazin-1-yl)-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
344	methyl 1-(3-chlorophenyl)-4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazine-2-carboxylate
345	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-(3-methylbut-2-en-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
346	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-(trifluoromethyl)-1*H*-pyrazolo[3,4-d]pyrimidine
347	methyl 4-(3-chlorophenyl)-1-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazine-2-carboxylate
348	4-(4-{3-chloro-4-[(2-piperidin-1-ylethyl)oxy]phenyl}piperazin-1-yl)-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
349	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-(1-methylethyl)-1*H*-pyrazolo[3,4-d]pyrimidine
350	1-(3-chlorophenyl)-4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazine-2-carboxylic acid
351	1-(3-chlorophenyl)-4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)-*N*-methylpiperazine-2-carboxamide
352	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-(phenylmethyl)-1*H*-pyrazolo[3,4-d]pyrimidine
353	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-(2-methylpropyl)-1*H*-pyrazolo[3,4-d]pyrimidine
354	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-[4-(methyloxy)phenyl]-1*H*-pyrazolo[3,4-d]pyrimidine
355	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-(4-fluorophenyl)-1*H*-pyrazolo[3,4-d]pyrimidine

Table 2a	
Cmpd No.	Name
356	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-[4-(phenyloxy)phenyl]-1*H*-pyrazolo[3,4-d]pyrimidine
357	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-{4-[(piperidin-4-ylmethyl)oxy]phenyl}-1*H*-pyrazolo[3,4-d]pyrimidine
358	1-(3-chlorophenyl)-*N*-[2-(dimethylamino)ethyl]-4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazine-2-carboxamide
359	4-[4-(5-chloro-2-methyl-3-morpholin-4-ylphenyl)piperazin-1-yl]-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
360	4-(3-chlorophenyl)-1-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)-*N*-methylpiperazine-2-carboxamide
361	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-[2-(methyloxy)phenyl]-1*H*-pyrazolo[3,4-d]pyrimidine
362	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-pyridin-4-yl-1*H*-pyrazolo[3,4-d]pyrimidine
363	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-[3-(methyloxy)phenyl]-1*H*-pyrazolo[3,4-d]pyrimidine
364	4-{4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl}benzonitrile
365	[5-chloro-3-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-(methyloxy)phenyl]methanol
366	methyl 5-chloro-3-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-(methyloxy)benzoate
367	(2E)-3-{4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl}prop-2-enoic acid
368	3-{4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl}propanoic acid
369	3-{4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl}propan-1-ol
370	methyl (2E)-3-{4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl}prop-2-enoate
371	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-{4-[(2-morpholin-4-ylethyl)oxy]phenyl}-1*H*-pyrazolo[3,4-d]pyrimidine
372	5-chloro-*N*-[2-(dimethylamino)ethyl]-3-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-(methyloxy)benzamide
373	4-(4-{5-chloro-2-(methyloxy)-3-[(4-methylpiperazin-1-yl)carbonyl]phenyl}piperazin-1-yl)-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
374	2-(dimethylamino)ethyl 5-chloro-3-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-(methyloxy)benzoate
375	1-[5-chloro-3-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-(methyloxy)phenyl]-*N*,*N*-dimethylmethanamine
376	*N*'-{[5-chloro-3-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-(methyloxy)phenyl]methyl}-*N*,*N*-dimethylethane-1,2-diamine
377	[1-(3-chlorophenyl)-4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-2-yl]methanol
378	3-[(4-{4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)oxy]-*N*,*N*-dimethylpropan-1-amine
379	2-chloro-4-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-methylphenol

Table 2a	
Cmpd No.	Name
380	1-(3-chlorophenyl)-4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)-*N*-(1-methylpiperidin-4-yl)piperazine-2-carboxamide
381	1-(3-chlorophenyl)-4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)-*N*-(2-morpholin-4-ylethyl)piperazine-2-carboxamide
382	2-{[5-chloro-3-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-(methyloxy)phenyl]oxy}-*N*,*N*-dimethylethanamine
383	3-{5-chloro-3-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methylphenyl}-*N*,*N*-dimethylprop-2-yn-1-amine
384	*N*'-{5-chloro-3-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methylphenyl}-*N*,*N*-dimethylethane-1,2-diamine
385	1,1-dimethylethyl (2E)-3-{4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl}prop-2-enoate
386	3-({2-chloro-4-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-methylphenyl}oxy)-*N*,*N*-dimethylpropan-1-amine
387	2-({2-chloro-4-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-5-methylphenyl}oxy)-*N*,*N*-dimethylethanamine
388	4-{4-[5-chloro-2-methyl-4-(methyloxy)phenyl]piperazin-1-yl}-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine
389	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-(4-methylpiperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
390	3-{4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl}-*N*,*N*-diethylprop-2-yn-1-amine
391	3-{4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl}prop-2-yn-1-ol
392	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-(piperidin-4-ylmethyl)-1*H*-pyrazolo[3,4-d]pyrimidine
393	phenylmethyl (3aR,6aS)-5-({4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl}methylidene)hexahydrocyclopenta[c]pyrrole-2(1*H*)-carboxylate
394	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-[(E)-(3aR,6aS)-hexahydrocyclopenta[c]pyrrol-5(1*H*)-ylidenemethyl]-1*H*-pyrazolo[3,4-d]pyrimidine
395	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-(3-pyrrolidin-1-ylprop-1-yn-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
396	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-[3-(4-methylpiperazin-1-yl)prop-1-yn-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
397	3-{4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl}-*N*,*N*-diethylpropan-1-amine
398	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-(3-pyrrolidin-1-ylpropyl)-1*H*-pyrazolo[3,4-d]pyrimidine
399	4-[4-(5-chloro-2-methylphenyl)piperazin-1-yl]-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
400	3-{5-chloro-3-[4-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-methylphenyl}-*N*,*N*-diethylpropan-1-amine
401	4-{4-[5-chloro-2-methyl-3-(3-pyrrolidin-1-ylpropyl)phenyl]piperazin-1-yl}-3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidine

Table 2b.

Additional Representative AKT Inhibitors

[00216] The Compounds in Table 2b can be prepared as pharmaceutically acceptable salts, solvates, hydrates, and/or isomers thereof. All such salt, solvate, hydrate, and isomer combinations of the Compounds in Table 2b can be used to practice the invention.

Table 2b

Entry	Name
1	[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methanol
2	2-{[[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]oxy}-*N*,*N*-dimethylethanamine
3	3-{[[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]oxy}-*N*,*N*-dimethylpropan-1-amine
4	3-bromo-4-{4-[(4-bromophenyl)methyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
5	{4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)-1-[(4-chlorophenyl)methyl]piperazin-2-yl}methanol
6	*N'*-[[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]-*N*,*N*-diethylethane-1,2-diamine
7	3-bromo-4-(4-{[4-(1,1-dimethylethyl)phenyl]methyl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
8	4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)-1-[(4-chlorophenyl)methyl]piperazin-2-one
9	2-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-2-(4-chlorophenyl)-*N*-[2-(dimethylamino)ethyl]acetamide
10	*N*-[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-*N*-(4-chlorophenyl)-*N'*,*N'*-diethylpropane-1,3-diamine
11	3-bromo-4-(4-{[4-(trifluoromethyl)phenyl]methyl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
12	*N*-[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-*N*-(4-chlorophenyl)-*N'*-[2-(dimethylamino)ethyl]urea
13	*N*-[[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]-*N'*-[2-(dimethylamino)ethyl]urea
14	2-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)-2-oxopiperazin-1-yl]-2-(4-chlorophenyl)-*N*-[2-(dimethylamino)ethyl]acetamide
15	2-(dimethylamino)ethyl [1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)carbamate
16	3-bromo-4-{4-[(4-chloro-3-fluorophenyl)methyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
17	3-bromo-4-{4-[(4-chloro-2-fluorophenyl)methyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
18	*N*-[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-*N*-(4-chlorophenyl)-*N'*,*N'*-diethylethane-1,2-diamine
19	3-bromo-4-{4-[(4-chlorophenyl)methyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine

Table 2b	
Entry	**Name**
20	[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-fluorophenyl)methanone
21	*N*-[[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]-*N'*,*N'*-diethyl-*N*-methylethane-1,2-diamine
22	[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-fluorophenyl)methanol
23	3-bromo-4-(4-{[2-fluoro-4-(trifluoromethyl)phenyl]methyl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
24	*N*-[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-*N*-(4-chlorophenyl)-*N*~3~,*N*~3~-diethyl-beta-alaninamide
25	2-{[[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-fluorophenyl)methyl]oxy}-*N*,*N*-dimethylethanamine
26	*N*-[[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]-*N*~3~,*N*~3~-diethyl-beta-alaninamide
27	3-bromo-4-{4-[(3,4-dichlorophenyl)methyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
28	*N*-[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-*N*-(4-chlorophenyl)-*N'*-[2-(dimethylamino)ethyl]ethanediamide
29	*N*-[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-*N*-(4-chlorophenyl)-2-(diethylamino)ethanesulfonamide
30	4-[4-(biphenyl-4-ylmethyl)piperazin-1-yl]-3-bromo-1*H*-pyrazolo[3,4-d]pyrimidine
31	3-bromo-4-{(3S)-4-[(4-chlorophenyl)methyl]-3-methylpiperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
32	3-bromo-4-(4-{[4-(methyloxy)phenyl]methyl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
33	4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)-*N*-[3-(trifluoromethyl)phenyl]piperazine-1-carboxamide
34	3-bromo-4-{4-[(4-fluorophenyl)methyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
35	*N*-[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-*N*-(4-chlorophenyl)pent-4-enamide
36	3-bromo-4-[4-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
37	4-[4-(1,3-benzodioxol-5-ylmethyl)piperazin-1-yl]-3-bromo-1*H*-pyrazolo[3,4-d]pyrimidine
38	[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methanone
39	3-bromo-4-(4-{[4-(phenyloxy)phenyl]methyl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
40	3-bromo-4-{4-[(3,4-dichlorophenyl)methyl]piperidin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
41	4-{[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]methyl}-*N*,*N*-dimethylaniline
42	methyl 4-{[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]methyl}benzoate

Table 2b	
Entry	**Name**
43	3-bromo-4-{4-[(2E)-3-phenylprop-2-enoyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
44	1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)-4-[(4-chlorophenyl)methyl]-*N*-[3-(diethylamino)propyl]piperidine-4-carboxamide
45	3-bromo-4-{4-[(2-bromophenyl)methyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
46	3-bromo-4-{4-[(2-chlorophenyl)methyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
47	3-bromo-4-{4-[(2,4-dichlorophenyl)methyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
48	3-bromo-4-{4-[(2-chloro-4-fluorophenyl)methyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
49	1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)-4-(4-chlorophenyl)-*N*-[3-(diethylamino)propyl]piperidine-4-carboxamide
50	3-bromo-4-[4-(phenylmethyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
51	2-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-*N*-pyridin-2-ylacetamide
52	3-bromo-4-[4-(1*H*-imidazol-2-ylmethyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
53	3-bromo-4-(4-{[3-(phenyloxy)phenyl]methyl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
54	3-bromo-4-{4-[(3-methylphenyl)methyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
55	3-{[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]methyl}benzonitrile
56	3-bromo-4-{4-[(2-chloro-6-fluorophenyl)methyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
57	3-bromo-4-[4-(1-phenylethyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
58	3-bromo-4-[4-(pyridin-4-ylmethyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
59	1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)-*N*-(4-chlorophenyl)piperidin-4-amine
60	3-bromo-4-[4-(pyridin-3-ylmethyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
61	3-bromo-4-(4-{[2,3,4-tris(methyloxy)phenyl]methyl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
62	3-bromo-4-[4-({3-[(phenylmethyl)oxy]phenyl}methyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
63	3-bromo-4-[4-(naphthalen-1-ylmethyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
64	3-bromo-4-(4-{[5-(4-chlorophenyl)furan-2-yl]methyl}piperazin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine

Table 2b	
Entry	**Name**
65	3-bromo-4-[4-({4-[(4-fluorophenyl)oxy]-3-nitrophenyl}methyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
66	3-bromo-4-[4-(furan-2-ylcarbonyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
67	3-bromo-4-[4-(1*H*-indol-6-ylcarbonyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
68	3-bromo-4-{4-[2-(2-thienyl)ethyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
69	3-bromo-4-[4-(3-pyrrolidin-1-ylpropyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
70	3-bromo-4-[4-(cyclohexylmethyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
71	3-bromo-4-{4-[(10-chloroanthracen-9-yl)methyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
72	3-bromo-4-[4-(1-methylpropyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
73	4-(4-{[4,6-bis(methyloxy)pyrimidin-2-yl]methyl}piperazin-1-yl)-3-bromo-1*H*-pyrazolo[3,4-d]pyrimidine
74	3-bromo-4-{4-[2-(methyloxy)ethyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
75	3-bromo-4-[4-(2-morpholin-4-yl-2-oxoethyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
76	3-bromo-4-{4-[3-(methyloxy)propyl]piperazin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
77	4-{4-[[4,6-bis(methyloxy)pyrimidin-2-yl](phenyl)methyl]piperazin-1-yl}-3-bromo-1*H*-pyrazolo[3,4-d]pyrimidine
78	3-bromo-4-[4-(6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-yl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
79	3-bromo-4-[4-({4-[(phenylmethyl)oxy]phenyl}methyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
80	3-bromo-4-[4-({3-chloro-4-[(phenylmethyl)oxy]phenyl}methyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
81	4-{[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]methyl}-*N*-(3-morpholin-4-ylpropyl)benzamide
82	4-{[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]methyl}-*N*-[3-(methyloxy)propyl]benzamide
83	2-[({4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)-1-[(4-chlorophenyl)methyl]piperazin-2-yl}methyl)oxy]-*N*,*N*-dimethylethanamine
84	3-bromo-4-[4-({4-[(4-chlorophenyl)oxy]-3-nitrophenyl}methyl)piperazin-1-yl]-1*H*-pyrazolo[3,4-d]pyrimidine
85	2-[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl]-*N*,*N*-dimethylacetamide
86	2-{[(R)-[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]oxy}-*N*,*N*-dimethylethanamine

Table 2b	
Entry	**Name**
87	*N*-(4-bromo-3-fluorophenyl)-*N*-[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-*N'*-[2-(dimethylamino)ethyl]urea
88	2-({(*R*)-(4-chlorophenyl)[1-(3-ethyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]methyl}oxy)-*N*,*N*-dimethylethanamine
89	2-{[(*S*)-[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]oxy}-*N*,*N*-dimethylethanamine
90	3-bromo-4-(4-{(*R*)-(4-chlorophenyl)[(2-pyrrolidin-1-ylethyl)oxy]methyl}piperidin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
91	1-[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-1-(4-chlorophenyl)-4-(dimethylamino)butan-1-ol
92	2-{[(*R*)-[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chloro-3-fluorophenyl)methyl]oxy}-*N*,*N*-dimethylethanamine
93	3-bromo-4-(4-{(*R*)-(4-chlorophenyl)[(2-piperidin-1-ylethyl)oxy]methyl}piperidin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
94	4-[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-4-(4-chlorophenyl)-*N*,*N*-dimethylbutan-1-amine
95	3-bromo-4-(4-{(R)-(4-chlorophenyl)[(2-morpholin-4-ylethyl)oxy]methyl}piperidin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
96	1-[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-1-(4-fluorophenyl)-*N*-(furan-2-ylmethyl)-*N*-methylmethanamine
97	1-[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]-1-(4-fluorophenyl)-*N*-methyl-*N*-(pyridin-2-ylmethyl)methanamine
98	4-{[{[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-fluorophenyl)methyl}(methyl)amino]methyl}-*N*,*N*-dimethylaniline
99	[4-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperazin-1-yl](1*H*-indol-6-yl)methanol
100	3-bromo-4-(4-{(R)-(4-chloro-3-fluorophenyl)[(2-pyrrolidin-1-ylethyl)oxy]methyl}piperidin-1-yl)-1*H*-pyrazolo[3,4-d]pyrimidine
101	3-bromo-4-{4-[(4-chlorophenyl)oxy]piperidin-1-yl}-1*H*-pyrazolo[3,4-d]pyrimidine
102	2-{[(R)-[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl](4-chlorophenyl)methyl]oxy}-*N*,*N*-diethylethanamine
103	2-{[1-(3-bromo-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)piperidin-4-yl]oxy}-5-chloro-*N*-(2-pyrrolidin-1-ylethyl)aniline

Table 3a.

Representative c-MET and/or Flt-3 Inhibitors

[00217] The Compounds in Table 3a can be prepared as pharmaceutically acceptable salts, solvates, hydrates, and/or isomers thereof. All such salt, solvate, hydrate, and isomer combinations of the Compounds in Table 3a can be used to practice the invention.

Table 3a	
Cmpd No.	**Name**
1	*N*-(4-fluorophenyl)-*N'*-[3-fluoro-4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl]propanediamide
2	*N*-(4-fluorophenyl)-*N'*-[3-fluoro-4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl]cyclopropane-1,1-dicarboxamide
3	*N*-({[3-fluoro-4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl]amino}carbonothioyl)-2-phenylacetamide
4	*N*-(4-fluorophenyl)-*N'*-(4-{[1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide
5	2-phenyl-*N*-{[(4-{[1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl]oxy}phenyl)amino]carbonothioyl}acetamide
6	*N*-(4-fluorophenyl)-*N'*-[4-(1*H*-pyrazolo[3,4-d]pyrimidin-4-yloxy)phenyl]cyclopropane-1,1-dicarboxamide
7	2-phenyl-*N*-({[4-(1*H*-pyrazolo[3,4-d]pyrimidin-4-yloxy)phenyl]amino}carbonothioyl)acetamide
8	*N*-(4-fluorophenyl)-*N'*-(4-{[9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-6-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide
9	2-phenyl-*N*-{[(4-{[9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purin-6-yl]oxy}phenyl)amino]carbonothioyl}acetamide
10	*N*-(4-fluorophenyl)-*N'*-[4-(9*H*-purin-6-yloxy)phenyl]cyclopropane-1,1-dicarboxamide
11	2-phenyl-*N*-({[4-(9*H*-purin-6-yloxy)phenyl]amino}carbonothioyl)acetamide
12	*N*-{3-fluoro-4-[(6-{[(2-morpholin-4-ylethyl)amino]carbonyl}-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)oxy]phenyl}-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

Table 3b.

Additional Representative c-MET, c-KIT, and/or Flt-3 Inhibitors

[00218] The Compounds in Table 3b can be prepared as pharmaceutically acceptable salts, solvates, hydrates, and/or isomers thereof. All such salt, solvate, hydrate, and isomer combinations of the Compounds in Table 3b can be used to practice the invention.

Table 3b	
Entry	**Name**
1	*N*-[({3-fluoro-4-[(6-(methyloxy)-7-{[(3a*R*,6a*S*)-octahydrocyclopenta[c]pyrrol-5-ylmethyl]oxy}quinazolin-4-yl)oxy]phenyl}amino)carbonothioyl]-2-phenylacetamide
2	*N*-{[(3-fluoro-4-{[7-({[(3a*R*,6a*S*)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-yl]oxy}phenyl)amino]carbonothioyl}-2-phenylacetamide

Table 3b	
Entry	**Name**
3	*N*-{[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)(methyl)amino]carbonothioyl}-2-phenylacetamide
4	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)imidazolidin-2-one
5	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylmethyl)imidazolidin-2-one
6	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylacetyl)imidazolidin-2-one
7	ethyl [(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino](oxo)acetate
8	*N*-{[(4-{[6,7-bis(methyloxy)quinazolin-4-yl]amino}-3-fluorophenyl)amino]carbonothioyl}-2-phenylacetamide
9	*N'*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N*-methyl-*N*-(2-phenylethyl)sulfamide
10	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-(phenylmethyl)-1,2,4-oxadiazol-5-amine
11	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)piperidin-2-one
12	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(phenylmethyl)ethanediamide
13	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-4-phenyl-1,3-thiazol-2-amine
14	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(2-phenylethyl)ethanediamide
15	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-1-phenylmethanesulfonamide
16	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-2-phenylethanesulfonamide
17	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-*N*-(phenylmethyl)benzenesulfonamide
18	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-*N*-methyl-*N*-(phenylmethyl)benzenesulfonamide
19	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-*N*-(2-phenylethyl)benzenesulfonamide
20	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-*N*-methyl-*N*-(2-phenylethyl)benzenesulfonamide
21	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-*N*-(3-phenylpropyl)benzenesulfonamide
22	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)pyrrolidin-2-one
23	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl (phenylmethyl)carbamate
24	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl (2-phenylethyl)carbamate
25	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-*N*-methyl-*N*-(3-phenylpropyl)benzenesulfonamide
26	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-phenylethanediamide

Table 3b	
Entry	**Name**
27	*N*-{[(3-fluoro-4-{[7-{[(2-methyloctahydrocyclopenta[c]pyrrol-5-yl)methyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}phenyl)amino]carbonothioyl}-2-phenylacetamide
28	*N*-[(Z)-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)amino](imino)methyl]-2-phenylacetamide
29	4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluoro-*N*-[2-(phenyloxy)ethyl]benzenesulfonamide
30	*N*,*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-bis-(3-phenylpropane-1-sulfonamide)
31	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-phenylpropane-1-sulfonamide
32	*N*2-[(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)sulfonyl]-*N*1-phenylglycinamide
33	*N*-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-2-phenylacetamide
34	*N*-{[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)amino]carbonothioyl}-2-phenylacetamide
35	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-1,3-benzothiazol-2-amine
36	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-amine
37	*N*-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-phenylacetamide
38	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N*'-(2-morpholin-4-ylethyl)ethanediamide
39	benzyl-{[4-(6,7-dimethoxy-quinolin-4-yloxy)-3-fluoro-phenylcarbamoyl]-methyl}-carbamic acid tert-butyl ester
40	*N*1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N*2-(phenylmethyl)glycinamide
41	*N*2-acetyl-*N*1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N*2-(phenylmethyl)glycinamide
42	*N*-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-1,3-benzothiazol-2-yl)-2-phenylacetamide
43	benzyl-{[6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-ylcarbamoyl]-methyl}-carbamic acid tert-butyl ester
44	*N*1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-*N*2-(phenylmethyl)glycinamide
45	*N*2-acetyl-*N*1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-*N*2-(phenylmethyl)glycinamide
46	*N*-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-3-phenylpropanamide
47	*N*-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-4-phenylbutanamide
48	*N*1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-*N*2-methyl-*N*2-(phenylmethyl)glycinamide
49	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N*'-{2-[4-(methyloxy)phenyl]ethyl}ethanediamide

Table 3b	
Entry	**Name**
50	*N*1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N*2-methyl-*N*2-(phenylmethyl)glycinamide
51	4-[(2-amino-1,3-benzothiazol-6-yl)oxy]-6,7-bis(methyloxy)-1-(2-oxo-2-phenylethyl)quinolinium
52	*N*-{[(4-{[6,7-bis(methyloxy)quinolin-4-yl]amino}phenyl)amino]carbonothioyl}-2-phenylacetamide
53	*N*-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-3-phenylpropanamide
54	*N*-{[(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)amino]carbonothioyl}-2-phenylacetamide
55	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(2,3-dihydro-1*H*-inden-1-yl)ethanediamide
56	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(2,3-dihydro-1*H*-inden-2-yl)ethanediamide
57	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(1,2,3,4-tetrahydronaphthalen-1-yl)ethanediamide
58	*N'*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N*-(2-phenylethyl)-*N*-(phenylmethyl)sulfamide
59	*N*1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N*2-(trifluoroacetyl)glycinamide
60	*N*-{[4-(6,7-dimethoxy-quinolin-4-yloxy)-3-fluoro-phenylcarbamoyl]-methyl}-benzamide
61	*N*-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridin-3-yl)-*N'*-(4-fluorophenyl)propanediamide
62	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-[(2*S*)-1,2,3,4-tetrahydronaphthalen-2-yl]ethanediamide
63	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-[2-(4-methylphenyl)ethyl]ethanediamide
64	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(2-phenylpropyl)ethanediamide
65	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-[2-(4-chlorophenyl)ethyl]ethanediamide
66	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N*,*N'*-bis(phenylmethyl)sulfamide
67	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N*,*N'*-bis(2-phenylethyl)sulfamide
68	ethyl [(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)amino](oxo)acetate
69	*N*-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-*N'*-(2-phenylethyl)ethanediamide
70	*N*-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-*N'*-(4-fluorophenyl)propanediamide
71	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(1,2,3,4-tetrahydronaphthalen-2-yl)ethanediamide
72	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-[2-(1-methylpyrrolidin-2-yl)ethyl]ethanediamide

Table 3b	
Entry	**Name**
73	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-[2-(phenyloxy)ethyl]ethanediamide
74	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-[2-hydroxy-1-(phenylmethyl)ethyl]urea
75	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-3-[(4-methylphenyl)sulfonyl]-4-(phenylmethyl)imidazolidin-2-one
76	*N'*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N*-methyl-*N*-(2-phenylethyl)ethanediamide
77	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-{[3-(trifluoromethyl)phenyl]methyl}ethanediamide
78	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-{2-[3-(trifluoromethyl)phenyl]ethyl}ethanediamide
79	*N*-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-3-oxo-4-phenylbutanamide
80	*N*-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-2-[3-(trifluoromethyl)phenyl]acetamide
81	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-*N*-[2-(phenyloxy)ethyl]-1,3-benzothiazol-2-amine
82	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-*N*-(2-piperidin-1-ylethyl)-1,3-benzothiazol-2-amine
83	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-*N*-methyl-*N*-(2-phenylethyl)-1,3-benzothiazol-2-amine
84	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-*N*-(2-pyrrolidin-1-ylethyl)-1,3-benzothiazol-2-amine
85	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-*N*-{[3-(trifluoromethyl)phenyl]methyl}-1,3-benzothiazol-2-amine
86	6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-*N*-{2-[3-(trifluoromethyl)phenyl]ethyl}-1,3-benzothiazol-2-amine
87	*N*-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-*N'*-[3-(trifluoromethyl)phenyl]propanediamide
88	*N*-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[3-(trifluoromethyl)phenyl]acetamide
89	*N*1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N*2-{[3-(trifluoromethyl)phenyl]methyl}glycinamide
90	*N*1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N*2-(2-phenylethyl)glycinamide
91	*N*1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N*2-{2-[3-(trifluoromethyl)phenyl]ethyl}glycinamide
92	benzyl-{[5-chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-ylcarbamoyl]-methyl}-carbamic acid tert-butyl ester
93	*N*1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-*N*2-(phenylmethyl)glycinamide
94	*N*-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[3,5-bis(trifluoromethyl)phenyl]acetamide
95	*N*-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-1,3-benzothiazol-2-yl)-2-[2-chloro-5-(trifluoromethyl)phenyl]acetamide

Table 3b	
Entry	**Name**
96	*N*-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-*N'*-(2-phenylethyl)ethanediamide
97	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(1,2,3,4-tetrahydroisoquinolin-1-ylmethyl)ethanediamide
98	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-[(2-methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl]ethanediamide
99	*N*1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N*2-methyl-*N*2-{[3-(trifluoromethyl)phenyl]methyl}glycinamide
100	*N*1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N*2-methyl-*N*2-{2-[3-(trifluoromethyl)phenyl]ethyl}glycinamide
101	*N*1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N*2-methyl-*N*2-(2-phenylethyl)glycinamide
102	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-4-(phenylmethyl)imidazolidin-2-one
103	*N*-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}pyridazin-3-yl)-*N'*-(4-fluorophenyl)propanediamide
104	*N*-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-*N'*-(2-chlorophenyl)propanediamide
105	*N*-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-*N'*-(3-chlorophenyl)propanediamide
106	*N*1-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-*N*2-methyl-*N*2-(phenylmethyl)glycinamide
107	*N*-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-*N'*-(4-chlorophenyl)propanediamide
108	(2E)-*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-[(methyloxy)imino]propanamide
109	(2E)-*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-[(ethyloxy)imino]propanamide
110	(2E)-*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-2-{[(phenylmethyl)oxy]imino}propanamide
111	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-1-(phenylmethyl)prolinamide
112	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-3-[(4-methylphenyl)sulfonyl]-4-(phenylmethyl)imidazolidin-2-one
113	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)imidazolidin-2-one
114	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)-4,5-dihydro-1,3-oxazol-2-amine
115	6,7-bis(methyloxy)-4-({4-[4-(phenylmethyl)piperazin-1-yl]phenyl}oxy)quinoline
116	1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-4-(phenylmethyl)piperazin-2-one
117	*N*1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-*N*2-(phenylmethyl)alaninamide
118	*N*1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-*N*2-methyl-*N*2-

Table 3b	
Entry	**Name**
	(phenylmethyl)alaninamide
119	*N*1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-*N*2-(phenylmethyl)leucinamide
120	*N*1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-*N*2-methyl-*N*2-(phenylmethyl)leucinamide
121	*N*1-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-*N*2-(phenylmethyl)valinamide
122	4-(6,7-dimethoxy-quinolin-4-ylamino)-*N*-(3-phenyl-propyl)-benzamide
123	4-benzyl-1-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-tetrahydro-pyrimidin-2-one
124	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-phenethyl-oxalamide
125	2-(Benzyl-methyl-amino)-*N*-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-3-methyl-butyramide (note: Alphabetic order of prefixes ignored while selecting parent chain)
126	*N*-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenyl]-2-phenoxyimino-propionamide
127	2-Benzyloxyimino-*N*-[4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-2-phenyl-acetamide
128	4-[4-(4-Benzyl-piperidin-1-yl)-phenoxy]-6,7-dimethoxy-quinoline
129	*N*-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-*N'*-(2-isopropyl-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-oxalamide
130	*N*-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-*N'*-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-oxalamide
131	4-(4-{3-Chloro-5-[2-(4-fluoro-phenylcarbamoyl)-acetylamino]-pyridin-2-yloxy}-6-methoxy-quinolin-7-yloxymethyl)-piperidine-1-carboxylic acid tert-butyl ester
132	*N*-{5-Chloro-6-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-pyridin-3-yl}-*N'*-(4-fluoro-phenyl)-malonamide
133	*N*-{5-Chloro-6-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-pyridin-3-yl}-*N'*-(4-fluoro-phenyl)-malonamide
134	*N*-{4-[7-(3-Diethylamino-propoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-*N'*-phenethyl-oxalamide
135	*N*-{3-Fluoro-4-[6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinolin-4-yloxy]-phenyl}-*N'*-phenethyl-oxalamide
136	*N*-{3-Fluoro-4-[6-methoxy-7-(3-piperidin-1-yl-propoxy)-quinolin-4-yloxy]-phenyl}-*N'*-phenethyl-oxalamide
137	*N*-{4-[7-(2-Diethylamino-ethoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-*N'*-phenethyl-oxalamide
138	*N*-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-methyl-*N'*-phenethyl-oxalamide
139	*N*-{3-Fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-phenethyl-oxalamide
140	*N*-{3-Fluoro-4-[6-methoxy-7-(2-methyl-octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-*N'*-phenethyl-oxalamide
141	2-(3,4-Dihydro-1*H*-isoquinolin-2-yl)-*N*-{3-fluoro-4-[6-methoxy-7-(1-

Table 3b	
Entry	Name
	methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-acetamide
142	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-2-(3-phenyl-pyrrolidin-1-yl)-acetamide
143	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-2-(2-phenyl-morpholin-4-yl)-acetamide
144	*N*-(2-Dimethylamino-2-phenyl-ethyl)-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
145	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(2-oxo-2-phenyl-ethyl)-oxalamide
146	*N*-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-2,2-difluoro-*N'*-(4-fluoro-phenyl)-malonamide
147	*N*-Benzyl-*N'*-{3-fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
148	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-[2-(2-fluoro-phenyl)-ethyl]-oxalamide
149	*N*-[2-(3-Chloro-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
150	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-[2-(2-methoxy-phenyl)-ethyl]-oxalamide
151	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(2-pyridin-3-yl-ethyl)-oxalamide
152	*N*-Benzyl-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
153	*N*-[2-(2,5-Dimethoxy-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
154	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-[2-(2-trifluoromethyl-phenyl)-ethyl]-oxalamide
155	*N*-[2-(2-Ethoxy-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
156	*N*-[2-(2,4-Dimethyl-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
157	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(1*S*-phenyl-2-p-tolyl-ethyl)-oxalamide
158	*N*-[2-(4-Chloro-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
159	*N*-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamic acid
160	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-[2-(3-fluoro-phenyl)-ethyl]-oxalamide
161	*N*-[2-(2-Chloro-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
162	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-[2-(3-methoxy-phenyl)-ethyl]-oxalamide
163	*N*-(1,2-Diphenyl-ethyl)-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide

Table 3b	
Entry	**Name**
164	*N*-[2-(2,4-Dichloro-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
165	*N*-[2-(3,4-Dimethoxy-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
166	*N*-[2-(4-Ethyl-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
167	*N*-[2-(4-Ethoxy-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
168	*N*-[2-(4-Ethoxy-3-methoxy-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
169	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-[2-(4-phenoxy-phenyl)-ethyl]-oxalamide
170	*N*-[2-(3-Ethoxy-4-methoxy-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
171	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(2-pyridin-2-yl-ethyl)-oxalamide
172	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(2-pyridin-4-yl-ethyl)-oxalamide
173	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-[2-(4-fluoro-phenyl)-ethyl]-oxalamide
174	*N*-[2-(2-Bromo-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
175	*N*-[2-(2-Chloro-6-fluoro-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
176	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(2*R*-phenyl-propyl)-oxalamide
177	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-indan-1-yl-oxalamide
178	*N*-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-isobutyl-oxalamide
179	*N*-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(3-methyl-butyl)-oxalamide
180	*N*-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(2*R*-phenyl-propyl)-oxalamide
181	*N*-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(2-phenyl-propyl)-oxalamide
182	*N*-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-indan-2-yl-oxalamide
183	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(1*R*-phenyl-ethyl)-oxalamide
184	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(1*S*-phenyl-ethyl)-oxalamide
185	*N*-[2-(3-Bromo-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
186	*N*-[2-(2,6-Dichloro-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide

Table 3b	
Entry	**Name**
187	*N*-[2-(2,4-Dichloro-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
188	*N*-(2-Benzo[1,3]dioxol-5-yl-ethyl)-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
189	*N*-[2-(3-Bromo-4-methoxy-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
190	*N*-[2-(3,5-Dimethoxy-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
191	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(2-o-tolyl-ethyl)-oxalamide
192	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(2-m-tolyl-ethyl)-oxalamide
193	*N*-[2-(3-Ethoxy-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
194	*N*-[2-(3,4-Dimethyl-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
195	*N*-[2-(2,5-Dimethyl-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
196	*N*-[2-(3-Chloro-4-propoxy-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
197	*N*-[2-(4-Butoxy-3-chloro-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
198	*N*-[2-(4-tert-Butyl-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
199	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-[2-(4-sulfamoyl-phenyl)-ethyl]-oxalamide
200	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-[2-(4-hydroxy-3-methoxy-phenyl)-ethyl]-oxalamide
201	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-[2-(3-hydroxy-4-methoxy-phenyl)-ethyl]-oxalamide
202	*N*-(2,4-Dichloro-benzyl)-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
203	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(4-fluoro-2-trifluoromethyl-benzyl)-oxalamide
204	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(1-p-tolyl-ethyl)-oxalamide
205	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(3-fluoro-4-trifluoromethyl-benzyl)-oxalamide
206	*N*-(3-Chloro-4-fluoro-benzyl)-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
207	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-[1-(3-methoxy-phenyl)-ethyl]-oxalamide
208	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(1-naphthalen-2-yl-ethyl)-oxalamide
209	*N*-(4-Chloro-3-trifluoromethyl-benzyl)-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide

Table 3b	
Entry	**Name**
210	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(1-p-tolyl-ethyl)-oxalamide
211	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(6-trifluoromethyl-pyridin-3-ylmethyl)-oxalamide
212	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(2-methyl-benzyl)-oxalamide
213	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(3-methyl-benzyl)-oxalamide
214	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(4-fluoro-3-trifluoromethyl-benzyl)-oxalamide
215	*N*-(3,5-Dichloro-benzyl)-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
216	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(1*R*,2,3,4-tetrahydro-naphthalen-1-yl)-oxalamide
217	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(1*S*,2,3,4-tetrahydro-naphthalen-1-yl)-oxalamide
218	*N*-Cyclopentyl-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
219	*N*-[1-(4-Bromo-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
220	*N*-(2-Fluoro-benzyl)-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
221	*N*-[2-(3,4-Dichloro-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
222	*N*-(4-Fluoro-benzyl)-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
223	*N*-(2,3-Difluoro-benzyl)-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
224	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(2-phenoxy-ethyl)-oxalamide
225	*N*-(2,2-Diphenyl-ethyl)-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
226	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-[2-(4-methoxy-phenyl)-ethyl]-oxalamide
227	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(2-phenyl-propyl)-oxalamide
228	*N*-[2-(4-Bromo-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
229	*N*-{4-[7-(1-Ethyl-piperidin-4-ylmethoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-2-oxo-2-(2-phenyl-morpholin-4-yl)-acetamide
230	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(3-fluoro-5-trifluoromethyl-benzyl)-oxalamide
231	*N*-(3,5-Difluoro-benzyl)-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
232	*N*-(2-Chloro-5-trifluoromethyl-benzyl)-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide

Table 3b	
Entry	**Name**
233	*N*-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-3-fluoro-phenyl]-*N'*-(2-dimethylamino-2-phenyl-ethyl)-oxalamide
234	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(4-methoxy-benzyl)-oxalamide
235	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(4-trifluoromethyl-benzyl)-oxalamide
236	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(3-methoxy-benzyl)-oxalamide
237	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(3-trifluoromethyl-benzyl)-oxalamide
238	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(3-trifluoromethoxy-benzyl)-oxalamide
239	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(2-methoxy-benzyl)-oxalamide
240	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(2-trifluoromethyl-benzyl)-oxalamide
241	*N*-(3-Chloro-benzyl)-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
242	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(2-trifluoromethoxy-benzyl)-oxalamide
243	*N*-(2-Chloro-benzyl)-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
244	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(4-trifluoromethoxy-benzyl)-oxalamide
245	*N*-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(4-methoxy-benzyl)-oxalamide
246	*N*-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(4-trifluoromethyl-benzyl)-oxalamide
247	*N*-{4-[7-(Azetidin-3-ylmethoxy)-6-methoxy-quinolin-4-yloxy]-3-fluoro-phenyl}-*N'*-phenethyl-oxalamide
248	*N*-{3-Fluoro-4-[6-methoxy-7-(1-methyl-azetidin-3-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-phenethyl-oxalamide
249	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(2-hydroxy-2-phenyl-ethyl)-oxalamide
250	*N*-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-*N'*-(2,4-difluoro-phenyl)-malonamide
251	*N*-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-*N'*-(4-fluoro-phenyl)-*N'*-methyl-malonamide
252	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(1*R*-phenyl-propyl)-oxalamide
253	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(1*R*-phenyl-propyl)-oxalamide
254	*N*-(3,4-Difluoro-benzyl)-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
255	*N*-(2,6-Difluoro-benzyl)-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide

Table 3b	
Entry	**Name**
256	*N*-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-[2-(4-fluoro-phenyl)-ethyl]-oxalamide
257	*N*-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-phenyl-oxalamide
258	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(3-fluoro-phenyl)-oxalamide
259	*N*-(4-Chloro-3-fluoro-phenyl)-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
260	*N*-(3,4-Dimethoxy-phenyl)-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
261	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(3-methyl-butyl)-oxalamide
262	*N*-(3,3-Dimethyl-butyl)-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
263	*N*-{5-Chloro-6-[6-methoxy-7-(3-piperidin-1-yl-propoxy)-quinolin-4-yloxy]-pyridin-3-yl}-*N'*-(4-fluoro-phenyl)-malonamide
264	*N*-{5-Chloro-6-[6-methoxy-7-(3-morpholin-4-yl-propoxy)-quinolin-4-yloxy]-pyridin-3-yl}-*N'*-(4-fluoro-phenyl)-malonamide
265	*N*-{5-Chloro-6-[7-(3-diethylamino-propoxy)-6-methoxy-quinolin-4-yloxy]-pyridin-3-yl}-*N'*-(4-fluoro-phenyl)-malonamide
266	*N*-(4-Chloro-benzyl)-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
267	*N*-(3,5-Dimethoxy-benzyl)-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
268	*N*-(4-Butyl-benzyl)-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
269	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(2-p-tolyl-ethyl)-oxalamide
270	*N*-(3,5-Bis-trifluoromethyl-benzyl)-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
271	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-pyrazin-2-ylmethyl-oxalamide
272	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-pyridin-2-ylmethyl-oxalamide
273	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-*N'*-phenethyl-oxalamide
274	*N*-{3-Fluoro-4-[6-methoxy-7-(1-methyl-piperidin-4-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-*N'*-phenethyl-oxalamide
275	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(2-fluoro-3-trifluoromethyl-benzyl)-oxalamide
276	*N*-[2-(2-Bromo-6-methoxy-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
277	*N*-[2-(3,4-Dimethoxy-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N*-methyl-oxalamide
278	*N*-[2-(5-Bromo-2-methoxy-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide

Table 3b	
Entry	**Name**
279	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(2-fluoro-5-trifluoromethyl-benzyl)-oxalamide
280	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-[1-(4-fluoro-phenyl)-ethyl]-oxalamide
281	*N*-(1*S*-Benzyl-2-oxo-2-pyrrolidin-1-yl-ethyl)-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
282	*N*-{3-Fluoro-4-[6-methoxy-7-(octahydro-cyclopenta[c]pyrrol-5-ylmethoxy)-quinazolin-4-yloxy]-phenyl}-*N'*-phenethyl-oxalamide
283	*N*-[2-(4-Amino-phenyl)-ethyl]-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
284	2-(4-Benzyl-piperidin-1-yl)-*N*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-acetamide
285	*N*-[4-(6,7-Dimethoxy-quinolin-4-yloxy)-phenyl]-*N'*-(4-fluoro-phenyl)-malonamide
286	*N*-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-*N'*-(3-fluoro-phenyl)-malonamide
287	*N*-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-*N'*-phenyl-malonamide
288	*N*-[5-Chloro-6-(6,7-dimethoxy-quinolin-4-yloxy)-pyridin-3-yl]-*N'*-(4-fluoro-phenyl)-2,2-dimethyl-malonamide
289	*N*-Ethyl-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
290	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-isopropyl-oxalamide
291	*N*-Butyl-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
292	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(2-methoxy-ethyl)-oxalamide
293	*N*-Cyclopropylmethyl-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-oxalamide
294	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N'*-(2-morpholin-4-yl-ethyl)-oxalamide
295	*N*-{3-Fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-2-oxo-2-pyrrolidin-1-yl-acetamide
296	*N*-Ethyl-*N'*-{3-fluoro-4-[6-methoxy-7-(piperidin-4-ylmethoxy)-quinolin-4-yloxy]-phenyl}-*N*-methyl-oxalamide

Table 3c.

Additional Representative c-MET, c-KIT, and/or Flt-3 Inhibitors

[00219] The Compounds in Table 3c can be prepared as pharmaceutically acceptable salts, solvates, hydrates, and/or isomers thereof. All such salt, solvate, hydrate, and isomer combinations of the Compounds in Table 3c can be used to practice the invention.

Table 3c	
Entry	**Name**
1	*N*-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
2	*N*-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-*N'*-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide
3	*N*-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-*N'*-(phenylmethyl)cyclopropane-1,1-dicarboxamide
4	*N*-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-*N'*-phenylcyclopropane-1,1-dicarboxamide
5	*N*-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
6	*N*-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
7	*N*-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperidin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-*N'*-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide
8	*N*-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloropyridin-3-yl)-*N'*-(2-phenylethyl)cyclopropane-1,1-dicarboxamide
9	*N*-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylpyridin-3-yl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
10	*N*-{4-[(7-chloroquinolin-4-yl)oxy]-3-fluorophenyl}-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
11	*N*-{4-[(7-chloroquinolin-4-yl)oxy]phenyl}-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
12	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
13	*N*-(4-{[6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
14	*N*-(4-{[6,7-bis(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
15	*N*-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
16	*N*-{5-chloro-6-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]pyridin-3-yl}-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
17	*N*-[5-chloro-6-({6-(methyloxy)-7-[(piperidin-4-ylmethyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
18	*N*-[5-chloro-6-({6-(methyloxy)-7-[(phenylmethyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
19	*N*-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-

Table 3c	
Entry	**Name**
	fluorophenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
20	*N*-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide
21	*N*-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
22	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-methylphenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
23	*N*-(4-fluorophenyl)-*N'*-[2-methyl-6-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)pyridin-3-yl]cyclopropane-1,1-dicarboxamide
24	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
25	*N*-(6-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-chloro-2-methylpyridin-3-yl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
26	*N*-[3-fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
27	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-3,5-difluorophenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
28	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,5-difluorophenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
29	*N*-[3-fluoro-4-({7-(methyloxy)-6-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
30	*N*-{3-fluoro-4-[(6-(methyloxy)-7-(2-methyl octahydrocyclo-penta[c]pyrrol-5-ylmethoxy)quinazolin-4-yl)oxy]phenyl}-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
31	*N*-{3-fluoro-4-[(7-(methyloxy)-6-{[(1-methylpiperidin-4-yl)methyl]oxy}quinazolin-4-yl)oxy]phenyl}-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
32	*N*-[5-fluoro-2-methyl-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
33	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2,3,5-trifluorophenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
34	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-5-fluoro-2-methylphenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
35	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-methylphenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
36	*N*-(3-fluoro-4-{[6-hydroxy-7-(methyloxy)quinolin-4-yl]oxy}phenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
37	*N*-(4-fluorophenyl)-*N'*-[2-methyl-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]cyclopropane-1,1-dicarboxamide
38	*N*-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
39	*N*-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

Table 3c	
Entry	**Name**
40	*N*-{3-fluoro-4-[(6-(methyloxy)-7-{[(1-methylpiperidin-4-yl)methyl]oxy}quinolin-4-yl)oxy]phenyl}-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
41	*N*-(4-fluorophenyl)-*N'*-[4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]cyclopropane-1,1-dicarboxamide
42	*N*-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
43	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-2-chloro-5-fluorophenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
44	*N*-(4-{[6,7-bis(methyloxy)-2-(methylthio)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
45	*N*-(4-fluorophenyl)-*N'*-(4-{[2-methyl-6,7-bis(methyloxy)quinazolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide
46	*N*-(4-{[2-amino-6,7-bis(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
47	*N*-(3-fluoro-4-{[2-(methylamino)-6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
48	(1*S*,2*R*)-*N*-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-*N'*-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide
49	(1*R*,2*R*)-*N*-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-*N'*-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide
50	*N*-(4-{[6-{[3-(diethylamino)propyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
51	*N*-(4-{[6-{[2-(diethylamino)ethyl]oxy}-7-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
52	1,1-dimethylethyl 4-(3-{[4-[(2-fluoro-4-{[(1-{[(4-fluorophenyl)amino]carbonyl}cyclopropyl)carbonyl]amino}phenyl)oxy]-6-(methyloxy)quinolin-7-yl]oxy}propyl)piperazine-1-carboxylate
53	(1*R*,2*R*)-*N*-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-*N'*-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide
54	(1*R*,2*R*)-*N*-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide
55	*N*-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
56	*N*-(4-{[7-{[3-(4-acetylpiperazin-1-yl)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
57	1,1-dimethylethyl 4-(3-{[4-[(2-fluoro-4-{[((1*R*,2*R*)-1-{[(4-fluorophenyl)amino]carbonyl}-2-methylcyclopropyl)carbonyl]amino}phenyl)oxy]-6-(methyloxy)quinolin-7-yl]oxy}propyl)piperazine-1-carboxylate
58	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-*N'*-(4-fluorophenyl)-1-(phenylmethyl)azetidine-3,3-dicarboxamide

Table 3c	
Entry	**Name**
59	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-*N'*-(4-fluorophenyl)azetidine-3,3-dicarboxamide
60	(1*R*,2*S*)-*N*-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-*N'*-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide
61	(1*R*,2*R*)-*N*-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-*N'*-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide
62	(1*R*,2*R*)-*N*-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-*N'*-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide
63	*N*-(3-fluoro-4-{[7-({3-[4-(1-methylethyl)piperazin-1-yl]propyl}oxy)-6-(methyloxy)quinolin-4-yl]oxy}phenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
64	*N*-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
65	(1*R*,2*R*)-*N*-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide
66	(1*R*,2*R*)-*N*-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide
67	(1*R*,2*S*)-*N*-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide
68	(1*R*,2*S*)-*N*-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide
69	*N*-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide
70	(1*R*,2*S*)-*N*-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-*N'*-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide
71	(1*R*,2*R*,3*S*)-*N*-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-*N'*-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide
72	(1*R*,2*R*,3*S*)-*N*-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-*N'*-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide
73	(1*R*,2*R*,3*S*)-*N*-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-*N'*-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide
74	(1*R*,2*R*,3*S*)-*N*-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-*N'*-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide
75	*N*-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-*N'*-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide

Table 3c	
Entry	**Name**
76	(2*R*,3*R*)-*N*-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-*N'*-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide
77	(2*R*,3*R*)-*N*-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide
78	*N*-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide
79	*N*-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-*N'*-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide
80	(1*R*,2*R*,3*S*)-*N*-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide
81	*N*-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide
82	(1*R*,2*R*,3*S*)-*N*-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide
83	*N*-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinolin-4-yl}oxy)phenyl]-*N'*-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide
84	*N*-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide
85	*N*-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)-2,2-dimethylcyclopropane-1,1-dicarboxamide
86	*N*-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide
87	*N*-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-*N'*-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide
88	*N*-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-*N'*-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide
89	(2*R*,3*R*)-*N*-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-*N'*-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide
90	*N*-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide
91	*N*-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinolin-4-yl)oxy]phenyl}-*N'*-(4-fluorophenyl)cyclobutane-1,1-dicarboxamide
92	(1*R*,2*R*)-*N*-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)-2-methylcyclopropane-1,1-

Table 3c	
Entry	**Name**
	dicarboxamide
93	(1*R*,2*R*)-*N*-{3-fluoro-4-[(6-(methyloxy)-7-{[3-(4-methylpiperazin-1-yl)propyl]oxy}quinazolin-4-yl)oxy]phenyl}-*N'*-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide
94	(2*R*,3*R*)-*N*-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide
95	(2*R*,3*R*)-*N*-(4-{[7-{[3-(diethylamino)propyl]oxy}-6-(methyloxy)quinazolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide
96	(1*R*,2*R*)-*N*-[3-fluoro-4-({6-(methyloxy)-7-[(3-piperazin-1-ylpropyl)oxy]quinazolin-4-yl}oxy)phenyl]-*N'*-(4-fluorophenyl)-2-methylcyclopropane-1,1-dicarboxamide
97	(2*R*,3*R*)-*N*-(4-{[7-{[2-(diethylamino)ethyl]oxy}-6-(methyloxy)quinolin-4-yl]oxy}-3-fluorophenyl)-*N'*-(4-fluorophenyl)-2,3-dimethylcyclopropane-1,1-dicarboxamide
98	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-*N'*-[(4-fluorophenyl)methyl]cyclopropane-1,1-dicarboxamide
99	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-*N'*-(2-morpholin-4-ylethyl)cyclopropane-1,1-dicarboxamide
100	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-*N'*-[2-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide
101	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-*N'*-[2-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide
102	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-*N'*-[3-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide
103	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-*N'*-[2-(morpholin-4-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide
104	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-*N'*-phenylcyclopropane-1,1-dicarboxamide
105	*N*-[3-(aminomethyl)phenyl]-*N'*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)cyclopropane-1,1-dicarboxamide
106	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-*N'*-[3-(piperidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide
107	*N*-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-*N'*-[3-(pyrrolidin-1-ylmethyl)phenyl]cyclopropane-1,1-dicarboxamide

Table 4.

Representative EGFR, ErbB2, and/or VEGFR Inhibitors

[00220] The Compounds in Table 4 can be prepared as pharmaceutically acceptable salts, solvates, hydrates, and/or isomers thereof. All such salt, solvate, hydrate, and isomer combinations of the Compounds in Table 4 can be used to practice the invention. In particular, the invention can be practiced with one or two pharmaceutically acceptable salts of a Compound of Table 4 which salt(s) are formed with one or two acids independently

selected from hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, 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.

Table 4

Entry	Name
1	*N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5r,6a*S*)-2-(1-methylethyl)octahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
2	*N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5r,6a*S*)-2-(1-methylethyl)octahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
3	7-({[(3a*R*,5r,6a*S*)-2-acetyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-*N*-(4-bromo-3-chloro-2-fluorophenyl)-6-(methyloxy)quinazolin-4-amine
4	*N*-(4-bromo-3-chloro-2-fluorophenyl)-6-(methyloxy)-7-{[(3a*R*,5r,6a*S*)-octahydrocyclopenta[c]pyrrol-5-ylmethyl]oxy}quinazolin-4-amine
5	ethyl (3a*R*,6a*S*)-5-({[4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydrocyclopenta[c]pyrrole-2(1*H*)-carboxylate
6	*N*-(4-bromo-3-chloro-2-fluorophenyl)-6-(methyloxy)-7-({[(3a*R*,5r,6a*S*)-2-(methylsulfonyl)octahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)quinazolin-4-amine
7	*N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5r,6a*S*)-2-ethyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
8	*N*-(3,4-dichloro-2-fluorophenyl)-6-(methyloxy)-7-({[(3a*R*,5r,6a*S*)-2-(2-methylpropyl)octahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)quinazolin-4-amine
9	*N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5s,6a*S*)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
10	*N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5s,6a*S*)-2-

Table 4	
Entry	**Name**
	methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
11	*N*-(3-chloro-2,4-difluorophenyl)-7-({[(3a*R*,5s,6a*S*)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
12	*N*-(4,5-dichloro-2-fluorophenyl)-7-({[(3a*R*,5s,6a*S*)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
13	*N*-(4-bromo-5-chloro-2-fluorophenyl)-7-({[(3a*R*,5s,6a*S*)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
14	*N*-(4-bromo-2,3-dichlorophenyl)-7-({[(3a*R*,5s,6a*S*)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
15	*N*-(3,4-dichlorophenyl)-7-({[(3a*R*,5s,6a*S*)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
16	*N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5r,6a*S*)-2-ethyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
17	*N*-(4-bromo-3-chloro-2-fluorophenyl)-6-(methyloxy)-7-({[(3a*R*,5r,6a*S*)-2-(2-methylpropyl)octahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)quinazolin-4-amine
18	*N*-(4-bromo-2,3-dichlorophenyl)-7-{[(3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
19	*N*-(4,5-dichloro-2-fluorophenyl)-7-{[(3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
20	*N*-(4-bromo-5-chloro-2-fluorophenyl)-7-{[(3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
21	*N*-(3-chloro-2,4-difluorophenyl)-7-{[(3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
22	*N*-(3,4-dichloro-2-fluorophenyl)-7-{[(3*S*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
23	*N*-(4-bromo-3-chloro-2-fluorophenyl)-7-{[(3*S*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine

Table 4	
Entry	**Name**
24	*N*-(3-chloro-2,4-difluorophenyl)-7-{[(3*S*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
25	*N*-(3,4-dichlorophenyl)-7-[(hexahydro-1*H*-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl)oxy]-6-(methyloxy)quinazolin-4-amine
26	*N*-(4,5-dichloro-2-fluorophenyl)-7-{[(3*S*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
27	*N*-(4-bromo-2,3-dichlorophenyl)-7-{[(3*S*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
28	*N*-(4-bromo-5-chloro-2-fluorophenyl)-7-{[(3*S*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
29	*N*-(3,4-dichloro-2-fluorophenyl)-7-{[(3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
30	*N*-(4-bromo-3-chloro-2-fluorophenyl)-7-{[(3*R*,9a*S*)-hexahydro-1*H*-[1,4]oxazino[3,4-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
31	*N*-(3,4-dichlorophenyl)-7-{[(3*R*,8a*R*)-hexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
32	*N*-(4-bromo-5-chloro-2-fluorophenyl)-7-{[(3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
33	*N*-(3,4-dichlorophenyl)-7-{[(3*S*,8a*R*)-hexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
34	*N*-(3,4-dichlorophenyl)-7-{[(3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
35	*N*-(3,4-dichlorophenyl)-7-{[(3*R*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
36	*N*-(3,4-dichloro-2-fluorophenyl)-7-{[(3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
37	*N*-(4-bromo-3-chloro-2-fluorophenyl)-7-{[(3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
38	*N*-(3-chloro-2,4-difluorophenyl)-7-{[(3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
39	*N*-(4-bromo-2,3-dichlorophenyl)-7-{[(3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine

Table 4	
Entry	**Name**
40	*N*-(4,5-dichloro-2-fluorophenyl)-7-{[(3*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-3-ylmethyl]oxy}-6-(methyloxy)quinazolin-4-amine
41	1,4:3,6-dianhydro-5-({[4-[(4-bromo-5-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-5-deoxy-2-O-methyl-D-xylo-hexitol
42	1,4:3,6-dianhydro-5-deoxy-5-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-2-O-methyl-D-glucitol
43	1,4:3,6-dianhydro-5-deoxy-5-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-2-O-methyl-D-xylo-hexitol
44	1,4:3,6-dianhydro-5-({[4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-5-deoxy-2-O-methyl-D-xylo-hexitol
45	1,4:3,6-dianhydro-5-({[4-[(3-chloro-2,4-difluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-5-deoxy-2-O-methyl-D-xylo-hexitol
46	1,4:3,6-dianhydro-5-({[4-[(4-bromo-2,3-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-5-deoxy-2-O-methyl-D-glucitol
47	1,4:3,6-dianhydro-2-deoxy-2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-5-O-methyl-D-threo-hexitol
48	1,4:3,6-dianhydro-5-deoxy-5-({[4-[(4,5-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-2-O-methyl-D-glucitol
49	(3*S*,9a*S*)-3-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydro-2*H*-pyrido[1,2-a]pyrazin-1(6*H*)-one
50	(3*S*,9a*R*)-3-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydro-2*H*-pyrido[1,2-a]pyrazin-1(6*H*)-one
51	(3*S*,8a*S*)-3-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydropyrrolo[1,2-a]pyrazin-1(2*H*)-one
52	(3*S*,8a*R*)-3-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydropyrrolo[1,2-a]pyrazin-1(2*H*)-one
53	(3*S*,8a*S*)-3-({[4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)hexahydropyrrolo[1,2-a]pyrazin-1(2*H*)-one
54	(3*S*,8a*S*)-3-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-2-methylhexahydropyrrolo[1,2-a]pyrazin-1(2*H*)-one
55	*N*-(3,4-dichlorophenyl)-7-({2-[(8-methyl-8-azabicyclo[3.2.1]oct-3-

Table 4	
Entry	**Name**
	yl)amino]ethyl}oxy)-6-(methyloxy)quinazolin-4-amine
56	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(8a*R*)-tetrahydro-1*H*-[1,3]thiazolo[4,3-c][1,4]oxazin-6-ylmethyl]oxy}quinazolin-4-amine
57	*N*-(3,4-dichlorophenyl)-7-{[2-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)ethyl]oxy}-6-(methyloxy)quinazolin-4-amine
58	*N*-(3,4-dichlorophenyl)-7-{[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
59	*N*-(3,4-dichlorophenyl)-7-{[(3a*R*,6a*S*)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]oxy}-6-(methyloxy)quinazolin-4-amine
60	*N*-(3,4-dichlorophenyl)-7-[(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)oxy]-6-(methyloxy)quinazolin-4-amine
61	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-5-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
62	1,4:3,6-dianhydro-2-O-[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
63	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
64	1,4:3,6-dianhydro-2-O-methyl-5-O-{6-(methyloxy)-4-[(2,3,4-trichlorophenyl)amino]quinazolin-7-yl}-L-iditol
65	1,4:3,6-dianhydro-5-O-[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-O-methyl-D-xylo-hexitol
66	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-2,3-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
67	1,4:3,6-dianhydro-5-*O*-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-L-sorbose ethylene glycol acetal
68	1,4:3,6-dianhydro-2-O-[4-[(3-chloro-2,4-difluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
69	1,4:3,6-dianhydro-2-O-[4-[(4,5-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
70	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-(difluoromethyl)-L-iditol
71	1,4:3,6-dianhydro-2-O-[4-[(3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
72	1,4:3,6-dianhydro-2-O-[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
73	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol

Table 4	
Entry	**Name**
74	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-ethyl-L-iditol
75	1,4:3,6-dianhydro-2-O-[4-[(3-bromo-2-methylphenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
76	1,4:3,6-dianhydro-2-O-[4-[(3-chloro-2-methylphenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-L-iditol
77	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-deoxy-D-xylo-hexitol
78	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-D-glucitol
79	methyl 3,6-anhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-O-methyl-alpha-L-idofuranoside
80	3,6-anhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-1,2-O-(1-methylethylidene)-beta-L-xylo-hexofuranose
81	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-deoxy-5-methylidene-D-xylo-hexitol
82	methyl 3,6-anhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-O-methyl-beta-L-idofuranoside
83	*N*-(3,4-dichloro-2-fluorophenyl)-6-(methyloxy)-7-[(octahydro-2*H*-quinolizin-3-ylmethyl)oxy]quinazolin-4-amine
84	1,4:3,6-dianhydro-2-deoxy-2-fluoro-5-O-{6-(methyloxy)-4-[(2,3,4-trifluorophenyl)amino]quinazolin-7-yl}-D-iditol
85	1,4:3,6-dianhydro-5-O-[4-[(2-chloro-4-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
86	1,4:3,6-dianhydro-5-O-[4-[(2-bromo-4-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
87	1,4:3,6-dianhydro-2-deoxy-5-O-[4-[(2,6-difluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-fluoro-D-iditol
88	1,4:3,6-dianhydro-5-O-[4-[(3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
89	1,4:3,6-dianhydro-2-deoxy-2-fluoro-5-O-[4-{[4-fluoro-3-(trifluoromethyl)phenyl]amino}-6-(methyloxy)quinazolin-7-yl]-D-iditol
90	1,4:3,6-dianhydro-2-deoxy-5-O-[4-[(2,4-difluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-fluoro-D-iditol
91	1,4:3,6-dianhydro-2-deoxy-5-O-[4-[(2,5-difluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-fluoro-D-iditol
92	1,4:3,6-dianhydro-2-deoxy-5-O-[4-[(2,3-difluorophenyl)amino]-6-

Table 4	
Entry	**Name**
	(methyloxy)quinazolin-7-yl]-2-fluoro-D-iditol
93	1,4:3,6-dianhydro-5-O-[4-[(5-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
94	1,4:3,6-dianhydro-2-deoxy-5-O-[4-[(3,5-difluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-fluoro-D-iditol
95	1,4:3,6-dianhydro-5-O-[4-[(3-chloro-4-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
96	1,4:3,6-dianhydro-5-O-[4-[(4-bromo-2-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
97	1,4:3,6-dianhydro-2-deoxy-5-O-[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-fluoro-D-iditol
98	1,4:3,6-dianhydro-5-O-[4-[(4-bromo-5-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
99	1,4:3,6-dianhydro-2-deoxy-2-fluoro-5-O-{6-(methyloxy)-4-[(2,4,5-trifluorophenyl)amino]quinazolin-7-yl}-D-iditol
100	1,4:3,6-dianhydro-2-deoxy-2-fluoro-5-O-{6-(methyloxy)-4-[(2,4,6-trifluorophenyl)amino]quinazolin-7-yl}-D-iditol
101	1,4:3,6-dianhydro-5-O-[4-({4-[(4-chlorophenyl)oxy]-3,5-difluorophenyl}amino)-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
102	1,4:3,6-dianhydro-5-O-[4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
103	1,4:3,6-dianhydro-5-O-[4-[(4-bromo-2,3-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
104	1,4:3,6-dianhydro-5-O-[4-[(4-bromo-3-chloro-5-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
105	1,4:3,6-dianhydro-2-deoxy-5-O-[4-[(4,5-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-fluoro-D-iditol
106	1,4:3,6-dianhydro-2-deoxy-2-fluoro-5-O-{6-(methyloxy)-4-[(2,3,4-trichlorophenyl)amino]quinazolin-7-yl}-D-iditol
107	1,4:3,6-dianhydro-2-deoxy-2-fluoro-5-O-{6-(methyloxy)-4-[(3,4,5-trichlorophenyl)amino]quinazolin-7-yl}-D-iditol
108	1,4:3,6-dianhydro-5-O-[4-[(4-bromo-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
109	1,4:3,6-dianhydro-5-O-[4-[(4-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
110	1,4:3,6-dianhydro-5-O-[4-[(3-chloro-2-methylphenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol

Table 4	
Entry	**Name**
111	1,4:3,6-dianhydro-2-deoxy-5-O-[4-[(3,4-difluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-fluoro-D-iditol
112	1,4:3,6-dianhydro-5-O-[4-[(2-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
113	1,4:3,6-dianhydro-2-deoxy-2-fluoro-5-O-[4-[(2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-D-iditol
114	1,4:3,6-dianhydro-5-O-[4-[(3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
115	1,4:3,6-dianhydro-2-deoxy-2-fluoro-5-O-[4-[(4-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-D-iditol
116	1,4:3,6-dianhydro-5-O-[4-[(4-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
117	1,4:3,6-dianhydro-2-deoxy-5-O-[4-[(2,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-fluoro-D-iditol
118	1,4:3,6-dianhydro-2-deoxy-5-O-[4-[(2,5-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-fluoro-D-iditol
119	1,4:3,6-dianhydro-2-deoxy-5-O-[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-fluoro-D-iditol
120	1,4:3,6-dianhydro-5-O-[4-[(2-bromo-4,6-difluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
121	1,4:3,6-dianhydro-5-O-[4-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
122	1,4:3,6-dianhydro-5-O-[4-{[2-chloro-5-(trifluoromethyl)phenyl]amino}-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
123	1,4:3,6-dianhydro-2-deoxy-2-fluoro-5-O-[4-{[2-fluoro-3-(trifluoromethyl)phenyl]amino}-6-(methyloxy)quinazolin-7-yl]-D-iditol
124	1,4:3,6-dianhydro-5-O-[4-{[2-bromo-5-(trifluoromethyl)phenyl]amino}-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
125	1,4:3,6-dianhydro-5-O-[4-{[2-bromo-4-(trifluoromethyl)phenyl]amino}-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
126	1,4:3,6-dianhydro-2-deoxy-2-fluoro-5-O-[4-{[4-fluoro-2-(trifluoromethyl)phenyl]amino}-6-(methyloxy)quinazolin-7-yl]-D-iditol
127	1,4:3,6-dianhydro-5-O-[4-{[3-bromo-5-(trifluoromethyl)phenyl]amino}-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
128	1,4:3,6-dianhydro-5-O-[4-[(2-bromophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
129	1,4:3,6-dianhydro-5-O-[4-[(3-bromophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol

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Table 4	
Entry	**Name**
130	1,4:3,6-dianhydro-5-O-[4-[(4-bromophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
131	1,4:3,6-dianhydro-5-O-[4-[(3-bromo-4-methylphenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
132	1,4:3,6-dianhydro-5-O-[4-[(5-chloro-2-methylphenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
133	1,4:3,6-dianhydro-2-deoxy-5-O-[4-[(3,5-dimethylphenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-fluoro-D-iditol
134	1,4:3,6-dianhydro-5-O-[4-{[2,5-bis(methyloxy)phenyl]amino}-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
135	1,4:3,6-dianhydro-5-O-[4-{[5-chloro-2,4-bis(methyloxy)phenyl]amino}-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
136	1,4:3,6-dianhydro-5-O-[4-{[4-chloro-2,5-bis(methyloxy)phenyl]amino}-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
137	1,4:3,6-dianhydro-5-O-[4-[(3-chloro-2,4-difluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-fluoro-D-iditol
138	*N*-(3,4-dichlorophenyl)-7-[({5-[(dimethylamino)methyl]-1,2,4-oxadiazol-3-yl}methyl)oxy]-6-(methyloxy)quinazolin-4-amine
139	*N*-(3,4-dichlorophenyl)-7-[({3-[(dimethylamino)methyl]-1,2,4-oxadiazol-5-yl}methyl)oxy]-6-(methyloxy)quinazolin-4-amine
140	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[({3-[(4-methylpiperazin-1-yl)methyl]-1,2,4-oxadiazol-5-yl}methyl)oxy]quinazolin-4-amine
141	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(5-piperidin-4-yl-1,2,4-oxadiazol-3-yl)methyl]oxy}quinazolin-4-amine
142	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[5-(1-methylpiperidin-4-yl)-1,2,4-oxadiazol-3-yl]methyl}oxy)quinazolin-4-amine
143	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[3-(morpholin-4-ylmethyl)-1,2,4-oxadiazol-5-yl]methyl}oxy)quinazolin-4-amine
144	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[(morpholin-2-ylmethyl)oxy]quinazolin-4-amine
145	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(5-piperidin-2-yl-1,2,4-oxadiazol-3-yl)methyl]oxy}quinazolin-4-amine
146	*N*-(3,4-dichlorophenyl)-7-[({2-[(dimethylamino)methyl]-1,3-thiazol-4-yl}methyl)oxy]-6-(methyloxy)quinazolin-4-amine
147	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[4-(phenylmethyl)morpholin-2-yl]methyl}oxy)quinazolin-4-amine
148	1,1-dimethylethyl 2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)morpholine-4-carboxylate

Table 4	
Entry	**Name**
149	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[2-(morpholin-4-ylmethyl)-1,3-thiazol-4-yl]methyl}oxy)quinazolin-4-amine
150	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[({2-[(4-methylpiperazin-1-yl)methyl]-1,3-thiazol-4-yl}methyl)oxy]quinazolin-4-amine
151	*N*-(3,4-dichlorophenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
152	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[(1,4-oxazepan-2-ylmethyl)oxy]quinazolin-4-amine
153	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(5-piperidin-3-yl-1,2,4-oxadiazol-3-yl)methyl]oxy}quinazolin-4-amine
154	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[5-(1-methylpiperidin-2-yl)-1,2,4-oxadiazol-3-yl]methyl}oxy)quinazolin-4-amine
155	*N*-(3,4-dichlorophenyl)-7-{[(4-methyl-1,4-oxazepan-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
156	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[5-(1-methylpiperidin-3-yl)-1,2,4-oxadiazol-3-yl]methyl}oxy)quinazolin-4-amine
157	*N*-(3,4-dichlorophenyl)-7-({[5-(1,1-dimethylethyl)-1,2,4-oxadiazol-3-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
158	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(2-phenyl-1,3-thiazol-4-yl)methyl]oxy}quinazolin-4-amine
159	7-[(2,1,3-benzothiadiazol-4-ylmethyl)oxy]-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
160	*N*-(3,4-dichlorophenyl)-7-{[(5-methylisoxazol-3-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
161	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(5-methyl-4-phenylisoxazol-3-yl)methyl]oxy}quinazolin-4-amine
162	7-[(1,3-benzothiazol-2-ylmethyl)oxy]-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
163	7-[(2,1,3-benzoxadiazol-5-ylmethyl)oxy]-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
164	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[2-(2-thienyl)-1,3-thiazol-4-yl]methyl}oxy)quinazolin-4-amine
165	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(1-phenyl-1*H*-pyrazol-4-yl)methyl]oxy}quinazolin-4-amine
166	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[({5-[3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}methyl)oxy]quinazolin-4-amine
167	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[({5-[4-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}methyl)oxy]quinazolin-4-amine

Table 4	
Entry	**Name**
168	7-({[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]methyl}oxy)-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
169	7-({[6-bromo-2-(methyloxy)naphthalen-1-yl]methyl}oxy)-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
170	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[(1,3-thiazol-4-ylmethyl)oxy]quinazolin-4-amine
171	7-{[(6-chloropyridin-3-yl)methyl]oxy}-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
172	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[(pyridin-4-ylmethyl)oxy]quinazolin-4-amine
173	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(2-methyl-1,3-thiazol-4-yl)methyl]oxy}quinazolin-4-amine
174	7-{[(6-chloro-4*H*-1,3-benzodioxin-8-yl)methyl]oxy}-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
175	7-{[(5-chloro-1-methyl-3-phenyl-1*H*-pyrazol-4-yl)methyl]oxy}-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
176	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[1-methyl-3-(trifluoromethyl)-1*H*-thieno[2,3-c]pyrazol-5-yl]methyl}oxy)quinazolin-4-amine
177	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(3-phenylisoxazol-5-yl)methyl]oxy}quinazolin-4-amine
178	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(2,4,6-trimethylphenyl)methyl]oxy}quinazolin-4-amine
179	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[(pyridin-3-ylmethyl)oxy]quinazolin-4-amine
180	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[({3-[4-(methyloxy)phenyl]isoxazol-5-yl}methyl)oxy]quinazolin-4-amine
181	*N*-(3,4-dichlorophenyl)-7-({[5-[(2,4-dichlorophenyl)oxy]-1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
182	7-[(cyclopropylmethyl)oxy]-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
183	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[(tetrahydrofuran-2-ylmethyl)oxy]quinazolin-4-amine
184	7-(cyclopentyloxy)-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
185	7-[(2-cyclohexylethyl)oxy]-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
186	7-[(cyclohexylmethyl)oxy]-*N*-(3,4-dichlorophenyl)-6-

Table 4	
Entry	**Name**
	(methyloxy)quinazolin-4-amine
187	7-[(cyclobutylmethyl)oxy]-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
188	*N*-(3,4-dichlorophenyl)-7-{[2-(1,3-dioxolan-2-yl)ethyl]oxy}-6-(methyloxy)quinazolin-4-amine
189	*N*-(3,4-dichlorophenyl)-7-{[2-(1,3-dioxan-2-yl)ethyl]oxy}-6-(methyloxy)quinazolin-4-amine
190	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[(2-morpholin-4-ylethyl)oxy]quinazolin-4-amine
191	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[(2-pyrrolidin-1-ylethyl)oxy]quinazolin-4-amine
192	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[(2-piperidin-1-ylethyl)oxy]quinazolin-4-amine
193	2-(2-{[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}ethyl)-1*H*-isoindole-1,3(2*H*)-dione
194	methyl 6-O-[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-alpha-D-glucopyranoside
195	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[(2-morpholin-4-yl-2-oxoethyl)oxy]quinazolin-4-amine
196	1,1-dimethylethyl 2-[3-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carboxylate
197	1,1-dimethylethyl 4-[3-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-1,2,4-oxadiazol-5-yl]piperidine-1-carboxylate
198	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[4-(4-pyrrolidin-1-ylphenyl)-1,3-thiazol-2-yl]methyl}oxy)quinazolin-4-amine
199	*N*-(3,4-dichlorophenyl)-7-[({4-[4-(diethylamino)phenyl]-1,3-thiazol-2-yl}methyl)oxy]-6-(methyloxy)quinazolin-4-amine
200	5-[2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-1,3-thiazol-4-yl]-2-hydroxybenzamide
201	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(4-pyridin-3-yl-1,3-thiazol-2-yl)methyl]oxy}quinazolin-4-amine
202	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(4-pyridin-2-yl-1,3-thiazol-2-yl)methyl]oxy}quinazolin-4-amine
203	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(4-pyridin-4-yl-1,3-thiazol-2-yl)methyl]oxy}quinazolin-4-amine
204	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(2-morpholin-4-yl-1,3-thiazol-4-

Table 4	
Entry	**Name**
	yl)methyl]oxy}quinazolin-4-amine
205	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(3-morpholin-4-yl-1,2,4-oxadiazol-5-yl)methyl]oxy}quinazolin-4-amine
206	*N*-(3,4-dichlorophenyl)-7-({[3-(dimethylamino)-1,2,4-oxadiazol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
207	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[({4-[(4-methylpiperazin-1-yl)methyl]-1,3-thiazol-2-yl}methyl)oxy]quinazolin-4-amine
208	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[(4,5,6,7-tetrahydro[1,3]thiazolo[5,4-c]pyridin-2-ylmethyl)oxy]quinazolin-4-amine
209	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[4-(morpholin-4-ylmethyl)-1,3-thiazol-2-yl]methyl}oxy)quinazolin-4-amine
210	*N*-(3,4-dichlorophenyl)-7-[({4-[(4-methyl-1,4-diazepan-1-yl)methyl]-1,3-thiazol-2-yl}methyl)oxy]-6-(methyloxy)quinazolin-4-amine
211	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(5-{[(phenylmethyl)oxy]methyl}-1,2,4-oxadiazol-3-yl)methyl]oxy}quinazolin-4-amine
212	*N*-(3,4-dichlorophenyl)-7-{[(4-ethylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
213	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(2-piperidin-4-yl-1,3-thiazol-4-yl)methyl]oxy}quinazolin-4-amine
214	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[2-(1-methylpiperidin-4-yl)-1,3-thiazol-4-yl]methyl}oxy)quinazolin-4-amine
215	1,1-dimethylethyl 4-[5-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-1,2,4-oxadiazol-3-yl]piperazine-1-carboxylate
217	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(3-piperazin-1-yl-1,2,4-oxadiazol-5-yl)methyl]oxy}quinazolin-4-amine
218	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[3-(4-methylpiperazin-1-yl)-1,2,4-oxadiazol-5-yl]methyl}oxy)quinazolin-4-amine
219	*N*-(3,4-dichlorophenyl)-7-({[5-(1-ethylpiperidin-2-yl)-1,2,4-oxadiazol-3-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
220	*N*-(3,4-dichlorophenyl)-7-({[3-(4-ethylpiperazin-1-yl)-1,2,4-oxadiazol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
221	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[({5-[4-(methyloxy)phenyl]-1,2,4-oxadiazol-3-yl}methyl)oxy]quinazolin-4-amine
222	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[({2-[4-(trifluoromethyl)phenyl]-1,3-thiazol-4-yl}methyl)oxy]quinazolin-4-amine
223	7-({[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}oxy)-*N*-(3,4-

Table 4	
Entry	**Name**
	dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
224	*N*-(3,4-dichlorophenyl)-7-({[5-(3,5-dimethylisoxazol-4-yl)-1,2,4-oxadiazol-3-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
225	7-{[(5-chloro-1-benzothien-3-yl)methyl]oxy}-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
226	*N*-(3,4-dichlorophenyl)-7-[({3-[4-(1,1-dimethylethyl)phenyl]-1,2,4-oxadiazol-5-yl}methyl)oxy]-6-(methyloxy)quinazolin-4-amine
227	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[({5-[2-(methyloxy)phenyl]-1,2,4-oxadiazol-3-yl}methyl)oxy]quinazolin-4-amine
228	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl]methyl}oxy)quinazolin-4-amine
229	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[1-(phenylmethyl)-1*H*-imidazol-2-yl]methyl}oxy)quinazolin-4-amine
230	*N*-(3,4-dichlorophenyl)-7-({[3-(2,6-dichlorophenyl)-5-methylisoxazol-4-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
231	*N*-(3,4-dichlorophenyl)-7-{[(6-fluoro-4*H*-1,3-benzodioxin-8-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
232	7-{[(3,5-dibromophenyl)methyl]oxy}-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
233	*N*-(3,4-dichlorophenyl)-7-{[(2,6-difluorophenyl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
234	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[({3-[(pyridin-2-ylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl}methyl)oxy]quinazolin-4-amine
235	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(5-phenyl-1,2,4-oxadiazol-3-yl)methyl]oxy}quinazolin-4-amine
236	7-({[4-chloro-2-(trifluoromethyl)quinolin-6-yl]methyl}oxy)-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
237	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[2-(1-methylpyrrolidin-2-yl)ethyl]oxy}quinazolin-4-amine
238	*N*-(3,4-dichlorophenyl)-7-({[5-(1-ethylpiperidin-4-yl)-1,2,4-oxadiazol-3-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
239	*N*-(3,4-dichlorophenyl)-7-({[5-(1-ethylpiperidin-3-yl)-1,2,4-oxadiazol-3-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
240	*N*-(3,4-dichlorophenyl)-7-({[2-(dimethylamino)-1,3-thiazol-4-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
241	*N*-(3,4-dichlorophenyl)-7-{[(4-ethyl-1,4-oxazepan-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
242	*N*-(3,4-dichlorophenyl)-7-({[2-(1-ethylpiperidin-4-yl)-1,3-thiazol-4-

Table 4	
Entry	**Name**
	yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
243	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[({3-[(2*S*)-pyrrolidin-2-yl]-1,2,4-oxadiazol-5-yl}methyl)oxy]quinazolin-4-amine
244	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[({2-[(2*S*)-pyrrolidin-2-yl]-1,3-thiazol-4-yl}methyl)oxy]quinazolin-4-amine
245	[4-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-1,3-thiazol-2-yl]methyl benzoate
246	[4-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-1,3-thiazol-2-yl]methanol
247	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(5-methyl-4,5,6,7-tetrahydro[1,3]thiazolo[5,4-c]pyridin-2-yl)methyl]oxy}quinazolin-4-amine
248	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[({2-[(4*S*)-1,3-thiazolidin-4-yl]-1,3-thiazol-4-yl}methyl)oxy]quinazolin-4-amine
249	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(2-piperidin-2-yl-1,3-thiazol-4-yl)methyl]oxy}quinazolin-4-amine
250	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[2-(1-methylpiperidin-2-yl)-1,3-thiazol-4-yl]methyl}oxy)quinazolin-4-amine
251	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(2-piperidin-3-yl-1,3-thiazol-4-yl)methyl]oxy}quinazolin-4-amine
252	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[2-(1-methylpiperidin-3-yl)-1,3-thiazol-4-yl]methyl}oxy)quinazolin-4-amine
253	*N*-(3,4-dichlorophenyl)-7-({[2-(1-ethylpiperidin-2-yl)-1,3-thiazol-4-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
254	*N*-(3,4-dichlorophenyl)-7-({[2-(1-ethylpiperidin-3-yl)-1,3-thiazol-4-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
255	*N*-(3,4-dichlorophenyl)-7-[({3-[(2*S*)-1-ethylpyrrolidin-2-yl]-1,2,4-oxadiazol-5-yl}methyl)oxy]-6-(methyloxy)quinazolin-4-amine
256	*N*-(3,4-dichlorophenyl)-7-[({2-[(2*S*)-1-ethylpyrrolidin-2-yl]-1,3-thiazol-4-yl}methyl)oxy]-6-(methyloxy)quinazolin-4-amine
257	*N*-(3,4-dichlorophenyl)-7-{[(5-ethyl-4,5,6,7-tetrahydro[1,3]thiazolo[5,4-c]pyridin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
258	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(4-propyl-1,4-oxazepan-2-yl)methyl]oxy}quinazolin-4-amine
259	7-({[4-(cyclopropylmethyl)-1,4-oxazepan-2-yl]methyl}oxy)-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
260	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[({4-[2-(methyloxy)ethyl]-1,4-oxazepan-2-yl}methyl)oxy]quinazolin-4-amine
261	*N*-(3,4-dichlorophenyl)-7-({[4-(1-methylethyl)-1,4-oxazepan-2-

Table 4	
Entry	**Name**
	yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
262	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(2-piperazin-1-yl-1,3-thiazol-4-yl)methyl]oxy}quinazolin-4-amine
263	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(5-pyrrolidin-2-yl-1,2,4-oxadiazol-3-yl)methyl]oxy}quinazolin-4-amine
264	*N*-(3,4-dichlorophenyl)-7-({[5-(1-ethylpyrrolidin-2-yl)-1,2,4-oxadiazol-3-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
265	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[({3-[(2*S*)-1-methylpyrrolidin-2-yl]-1,2,4-oxadiazol-5-yl}methyl)oxy]quinazolin-4-amine
266	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[({2-[(2*S*)-1-methylpyrrolidin-2-yl]-1,3-thiazol-4-yl}methyl)oxy]quinazolin-4-amine
267	*N*-(3,4-dichlorophenyl)-7-({[2-(4-ethylpiperazin-1-yl)-1,3-thiazol-4-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
268	*N*-(3,4-dichlorophenyl)-7-{[(1,4-dimethylpiperazin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
269	7-{[(4-cyclopentylmorpholin-2-yl)methyl]oxy}-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
270	*N*-(3,4-dichlorophenyl)-7-({[4-(1-methylethyl)morpholin-2-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
271	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[4-(3-phenylpropyl)morpholin-2-yl]methyl}oxy)quinazolin-4-amine
272	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[({4-[2-(methyloxy)ethyl]morpholin-2-yl}methyl)oxy]quinazolin-4-amine
273	ethyl 2-[2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)morpholin-4-yl]propanoate
274	*N*-(3,4-dichlorophenyl)-7-{[(4-hex-5-en-1-ylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
275	2-({2-[2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)morpholin-4-yl]ethyl}oxy)ethanol
276	methyl 3-[2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)morpholin-4-yl]propanoate
277	6-[2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)morpholin-4-yl]hexanenitrile
278	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[4-(tetrahydro-2*H*-pyran-2-ylmethyl)morpholin-2-yl]methyl}oxy)quinazolin-4-amine
279	4-[2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)morpholin-4-yl]butanenitrile
280	*N*-(3,4-dichlorophenyl)-7-[({4-[(4-fluorophenyl)methyl]morpholin-2-

Table 4	
Entry	**Name**
	yl}methyl)oxy]-6-(methyloxy)quinazolin-4-amine
281	methyl 5-[2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)morpholin-4-yl]pentanoate
282	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(4-oct-7-en-1-ylmorpholin-2-yl)methyl]oxy}quinazolin-4-amine
283	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(4-propylmorpholin-2-yl)methyl]oxy}quinazolin-4-amine
284	6-[2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)morpholin-4-yl]hexan-1-ol
285	7-{[(4-acetylmorpholin-2-yl)methyl]oxy}-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
286	7-({[4-(cyclopropylmethyl)morpholin-2-yl]methyl}oxy)-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
287	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(4-prop-2-yn-1-ylmorpholin-2-yl)methyl]oxy}quinazolin-4-amine
288	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(4-pyridin-4-ylmorpholin-2-yl)methyl]oxy}quinazolin-4-amine
289	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[4-(pyridin-2-ylmethyl)morpholin-2-yl]methyl}oxy)quinazolin-4-amine
290	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(4-pent-2-yn-1-ylmorpholin-2-yl)methyl]oxy}quinazolin-4-amine
291	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[2-(4-methylpiperazin-1-yl)-1,3-thiazol-4-yl]methyl}oxy)quinazolin-4-amine
292	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[5-(1-methylpyrrolidin-2-yl)-1,2,4-oxadiazol-3-yl]methyl}oxy)quinazolin-4-amine
293	*N*-(3-chloro-4-fluorophenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
294	7-{[(4-butyl-1,4-oxazepan-2-yl)methyl]oxy}-*N*-(3,4-dichlorophenyl)-6-(methyloxy) quinazolin-4-amine
295	(3,4-dichlorophenyl)[7-(methyloxy)-6-({[4-(2-methylpropyl)-1,4-oxazepan-2-yl]methyl}oxy) quinazolin-4-amine
296	7-{[(4-acetyl-1-ethylpiperazin-2-yl)methyl]oxy}-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
297	(3,4-dichlorophenyl)(6-(methyloxy)-7-{[(4-pentyl-1,4-oxazepan-2-yl)methyl]oxy} quinazolin-4-amine
298	(3,4-dichlorophenyl)[6-(methyloxy)-7-({[4-(tetrahydro-2*H*-pyran-2-ylmethyl)-1,4-oxazepan-2-yl]methyl}oxy)quinazolin-4-amine
299	(3,4-dichlorophenyl)[6-(methyloxy)-7-({[4-(3-thienylmethyl)-1,4-

Table 4	
Entry	**Name**
	oxazepan-2-yl]methyl}oxy) quinazolin-4-amine
300	*N*-[4-chloro-2,5-bis(methyloxy)phenyl]-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
301	*N*-(3-bromo-2-methylphenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
302	7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)-*N*-(3,4,5-trichlorophenyl)quinazolin-4-amine
303	*N*-(3-chloro-2-methylphenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
304	*N*-(3,4-dichlorophenyl)-7-{[(4-ethanimidoyl-1,4-oxazepan-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
305	*N*-(4-bromo-2-fluorophenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
306	*N*-(5-chloro-2-fluorophenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
307	*N*-(4-chloro-2-fluorophenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
308	*N*-(2,4-dichlorophenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
309	*N*-(2,4-dibromophenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
310	7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)-*N*-(2,3,4-trichlorophenyl)quinazolin-4-amine
311	*N*-(3,4-dichlorophenyl)-7-{[(1-ethyl-4-methylpiperazin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
312	*N'*-cyano-2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)morpholine-4-carboximidamide
313	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[2-(pyrrolidin-1-ylmethyl)-1,3-thiazol-4-yl]methyl}oxy)quinazolin-4-amine
314	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[4-(tetrahydro-2*H*-pyran-4-yl)morpholin-2-yl]methyl}oxy)quinazolin-4-amine
315	*N*-(3,4-dichlorophenyl)-7-({[4-(2-ethylbutyl)morpholin-2-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
316	7-({[4-(cyclohexylmethyl)morpholin-2-yl]methyl}oxy)-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
317	2-[2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)morpholin-4-yl]ethanol
318	7-{[(4-but-2-yn-1-ylmorpholin-2-yl)methyl]oxy}-*N*-(3,4-dichlorophenyl)-6-

Table 4	
Entry	**Name**
	(methyloxy)quinazolin-4-amine
319	7-{[(4-cyclobutylmorpholin-2-yl)methyl]oxy}-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
320	*N*-(3,4-dichlorophenyl)-7-[({4-[2-(1,3-dioxolan-2-yl)ethyl]morpholin-2-yl}methyl)oxy]-6-(methyloxy)quinazolin-4-amine
321	7-({[4-(2-cyclohexylethyl)morpholin-2-yl]methyl}oxy)-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
322	*N*-(3,4-dichlorophenyl)-7-[({4-[2-(1,3-dioxan-2-yl)ethyl]morpholin-2-yl}methyl)oxy]-6-(methyloxy)quinazolin-4-amine
323	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(4-pent-4-en-1-ylmorpholin-2-yl)methyl]oxy}quinazolin-4-amine
324	*N*-(3,4-dichlorophenyl)-7-[({4-[(2*R*)-2-methylbutyl]morpholin-2-yl}methyl)oxy]-6-(methyloxy)quinazolin-4-amine
325	*N*-(3,4-dichlorophenyl)-7-({[4-(4-fluorobutyl)morpholin-2-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
326	3-[2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)morpholin-4-yl]butan-2-one
327	1-[2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)morpholin-4-yl]butan-2-one
328	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(4-pentylmorpholin-2-yl)methyl]oxy}quinazolin-4-amine
329	*N*-(3,4-dichlorophenyl)-7-{[(4-hexylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
330	*N*-(3,4-dichlorophenyl)-7-{[(4-heptylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
331	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(4-octylmorpholin-2-yl)methyl]oxy}quinazolin-4-amine
332	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[4-(2-phenylethyl)morpholin-2-yl]methyl}oxy)quinazolin-4-amine
333	7-{[(4-butylmorpholin-2-yl)methyl]oxy}-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
334	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(4-prop-2-en-1-ylmorpholin-2-yl)methyl]oxy}quinazolin-4-amine
335	2-[2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)morpholin-4-yl]-1-phenylethanone
336	*N*-(3,4-dichlorophenyl)-7-({[4-(2-fluoroethyl)morpholin-2-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
337	*N*-(3,4-dichlorophenyl)-7-({[4-(3-methylbut-2-en-1-yl)morpholin-2-

Table 4	
Entry	**Name**
	yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
338	7-[({4-[(2E)-3-bromoprop-2-en-1-yl]morpholin-2-yl}methyl)oxy]-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
339	2-[2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)morpholin-4-yl]acetamide
340	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[({4-[3-(tetrahydro-2*H*-pyran-2-yloxy)propyl]-1,4-oxazepan-2-yl}methyl)oxy]quinazolin-4-amine
341	*N*-(3,4-dichlorophenyl)-7-({[4-(3-methylbutyl)-1,4-oxazepan-2-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
342	7-({[4-(cyclohexylmethyl)-1,4-oxazepan-2-yl]methyl}oxy)-4-[(3,4-dichlorophenyl)methyl]-6-(methyloxy)quinazoline
343	7-({[4-(2-cyclohexylethyl)-1,4-oxazepan-2-yl]methyl}oxy)-4-[(3,4-dichlorophenyl)methyl]-6-(methyloxy)quinazoline
345	*N*-(3,4-dichlorophenyl)-7-({[4-(2-ethylbutyl)-1,4-oxazepan-2-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
346	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[4-(methylsulfonyl)-1,4-oxazepan-2-yl]methyl}oxy)quinazolin-4-amine
347	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[4-(1-methylpiperidin-4-yl)morpholin-2-yl]methyl}oxy)quinazolin-4-amine
348	*N*-(3-chloro-2-fluorophenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
349	*N'*-cyano-2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-1,4-oxazepane-4-carboximidamide
350	*N*-(3-bromo-4-methylphenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
351	*N*-(3,4-dichlorophenyl)-7-{[(1,4-diethylpiperazin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
352	4-({[4-[(4-bromo-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-*N'*-cyanopiperidine-1-carboximidamide
353	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[4-(methylsulfonyl)morpholin-2-yl]methyl}oxy)quinazolin-4-amine
354	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[({4-[(phenylmethyl)sulfonyl]morpholin-2-yl}methyl)oxy]quinazolin-4-amine
355	*N*-(3,4-dichlorophenyl)-7-[({4-[(4-fluorophenyl)sulfonyl]morpholin-2-yl}methyl)oxy]-6-(methyloxy)quinazolin-4-amine
356	*N*-(3,4-dichlorophenyl)-7-({[4-(ethylsulfonyl)morpholin-2-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
357	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[4-(phenylsulfonyl)morpholin-2-

Table 4	
Entry	**Name**
	yl]methyl}oxy)quinazolin-4-amine
358	7-[({4-[(3-chloropropyl)sulfonyl]morpholin-2-yl}methyl)oxy]-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
359	7-({[4-(butylsulfonyl)morpholin-2-yl]methyl}oxy)-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
360	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[({4-[(4-methylphenyl)sulfonyl]morpholin-2-yl}methyl)oxy]quinazolin-4-amine
361	*N*-(3,4-dichlorophenyl)-7-[({4-[(3,5-dimethylisoxazol-4-yl)carbonyl]morpholin-2-yl}methyl)oxy]-6-(methyloxy)quinazolin-4-amine
362	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(4-{[3-(methyloxy)phenyl]acetyl}morpholin-2-yl)methyl]oxy}quinazolin-4-amine
363	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[4-(2-methylpentanoyl)morpholin-2-yl]methyl}oxy)quinazolin-4-amine
364	7-[({4-[(4-butylphenyl)carbonyl]morpholin-2-yl}methyl)oxy]-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
365	7-[({4-[(4-chlorophenyl)acetyl]morpholin-2-yl}methyl)oxy]-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
366	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[4-(2-propylpentanoyl)morpholin-2-yl]methyl}oxy)quinazolin-4-amine
367	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[4-(4-methylpentanoyl)morpholin-2-yl]methyl}oxy)quinazolin-4-amine
368	*N*-(3,4-dichlorophenyl)-7-[({4-[(2,5-difluorophenyl)carbonyl]morpholin-2-yl}methyl)oxy]-6-(methyloxy)quinazolin-4-amine
369	7-({[4-(cyclopentylcarbonyl)morpholin-2-yl]methyl}oxy)-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
370	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[4-(2-phenylbutanoyl)morpholin-2-yl]methyl}oxy)quinazolin-4-amine
371	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-[({4-[(2,3,6-trifluorophenyl)carbonyl]morpholin-2-yl}methyl)oxy]quinazolin-4-amine
372	*N*-(3,4-dichlorophenyl)-7-({[4-(furan-3-ylcarbonyl)morpholin-2-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
373	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(4-propanoylmorpholin-2-yl)methyl]oxy}quinazolin-4-amine
374	*N*-(3,4-dichlorophenyl)-7-{[(4-hexanoylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
375	*N*-(3,4-dichlorophenyl)-7-({[4-(2-ethylhexanoyl)morpholin-2-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
376	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[4-(3-

Table 4	
Entry	**Name**
	phenylpropanoyl)morpholin-2-yl]methyl}oxy)quinazolin-4-amine
377	*N*-(3,4-dichlorophenyl)-7-({[4-(2,2-dimethylpropanoyl)morpholin-2-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
378	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[4-(naphthalen-1-ylcarbonyl)morpholin-2-yl]methyl}oxy)quinazolin-4-amine
379	7-[({4-[(2-chloropyridin-3-yl)carbonyl]morpholin-2-yl}methyl)oxy]-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
380	7-[({4-[(6-chloropyridin-3-yl)carbonyl]morpholin-2-yl}methyl)oxy]-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
381	7-({[4-(1,3-benzodioxol-5-ylcarbonyl)morpholin-2-yl]methyl}oxy)-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
382	*N*-(3,4-dichlorophenyl)-6-[(1-methylethyl)oxy]-7-[(morpholin-2-ylmethyl)oxy]quinazolin-4-amine
383	*N*-(3,4-dichlorophenyl)-6-{[2-(methyloxy)ethyl]oxy}-7-[(morpholin-2-ylmethyl)oxy]quinazolin-4-amine
384	*N*-(3,4-dichlorophenyl)-6-(ethyloxy)-7-[(morpholin-2-ylmethyl)oxy]quinazolin-4-amine
385	*N*-(3,4-dichlorophenyl)-6-(ethyloxy)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}quinazolin-4-amine
386	*N*-(4-bromo-2-methylphenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
387	*N*-(4-chloro-3-methylphenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
388	*N'*-cyano-2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-*N*-methylmorpholine-4-carboximidamide
389	*N*-(4-bromo-3-chlorophenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
390	*N*-(3,4-dichlorophenyl)-6-[(1-methylethyl)oxy]-7-{[(4-methylmorpholin-2-yl)methyl]oxy}quinazolin-4-amine
391	*N*-(3,4-dichlorophenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-{[2-(methyloxy)ethyl]oxy}quinazolin-4-amine
392	*N*-(4-bromo-2-chlorophenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
393	7-{[(4-acetyl-1,4-oxazepan-2-yl)methyl]oxy}-*N*-(3,4-dichlorophenyl)-6-(methyloxy)quinazolin-4-amine
394	4-[(3,4-dichlorophenyl)amino]-7-{[(4-methylmorpholin-2-yl)methyl]oxy}quinazolin-6-ol
395	*N*-(3-bromo-4-chlorophenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-

Table 4	
Entry	**Name**
	(methyloxy)quinazolin-4-amine
396	3-[2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)morpholin-4-yl]-3-oxopropanoic acid
397	methyl 4-[2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)morpholin-4-yl]-4-oxobutanoate
398	*N*-(3,4-dichlorophenyl)-7-{[(4-methylmorpholin-3-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
399	*N*-(3-bromo-2-chlorophenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
400	*N'*-cyano-2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-*N*-[2-(methyloxy)ethyl]morpholine-4-carboximidamide
401	*N'*-cyano-2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-*N*-ethylmorpholine-4-carboximidamide
402	[(1E)-[2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)morpholin-4-yl](piperidin-1-yl)methylidene]cyanamide
403	[(1E)-[2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)morpholin-4-yl](pyrrolidin-1-yl)methylidene]cyanamide
404	[(1E)-[2-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)morpholin-4-yl](4-methylpiperazin-1-yl)methylidene]cyanamide
405	*N*-(3,4-dichlorophenyl)-7-{[(6-ethyl-4,6-dimethylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
406	*N*-(4-bromo-3-methylphenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
407	*N*-(3,4-dichlorophenyl)-7-{[(6,6-dimethylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
408	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(4,6,6-trimethylmorpholin-2-yl)methyl]oxy}quinazolin-4-amine
409	*N*-(3,4-dichlorophenyl)-7-{[2-(5,5-dimethylmorpholin-2-yl)ethyl]oxy}-6-(methyloxy)quinazolin-4-amine
410	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[2-(4,5,5-trimethylmorpholin-2-yl)ethyl]oxy}quinazolin-4-amine
411	1,1-dimethylethyl 2-(2-{[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}ethyl)-5,5-dimethylmorpholine-4-carboxylate
412	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[(4,5,5-trimethylmorpholin-2-yl)methyl]oxy}quinazolin-4-amine
413	*N*-(4-bromo-2,3-dichlorophenyl)-7-{[(4-methylmorpholin-2-

Table 4	
Entry	**Name**
	yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
414	*N*-(4,5-dichloro-2-fluorophenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
415	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-{[2-(4,6,6-trimethylmorpholin-2-yl)ethyl]oxy}quinazolin-4-amine
416	*N*-(4-bromo-2,3-difluorophenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
417	*N*-(4-bromo-2,5-difluorophenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
418	*N*-(4-bromo-3,5-difluorophenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
419	*N*-(3,4-dichloro-2-methylphenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
420	*N*-(3,4-dichlorophenyl)-7-({[(2*R*,5*S*,6*S*)-5,6-dimethylmorpholin-2-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
421	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[(2*R*,5*S*,6*S*)-4,5,6-trimethylmorpholin-2-yl]methyl}oxy)quinazolin-4-amine
422	*N*-(3,4-dichlorophenyl)-6-(methyloxy)-7-({[(2*S*,5*S*,6*S*)-4,5,6-trimethylmorpholin-2-yl]methyl}oxy)quinazolin-4-amine
423	*N*-(4-bromo-3-chloro-2-methylphenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
424	*N*-(4-bromo-5-chloro-2-fluorophenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
425	*N*-(4-bromo-3-chloro-2-fluorophenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
426	*N*-(3,4-dichloro-2-fluorophenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
427	*N*-(3-chloro-2,4-difluorophenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
428	*N*-(2,3-dichloro-4-methylphenyl)-7-{[(4-methylmorpholin-2-yl)methyl]oxy}-6-(methyloxy)quinazolin-4-amine
429	6-({[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-3,3,4-trimethylmorpholin-2-one
430	*N*-(4-bromo-2,3-dichlorophenyl)-6-(methyloxy)-7-{[(4,5,5-trimethylmorpholin-2-yl)methyl]oxy}quinazolin-4-amine
431	*N*-(4-bromo-5-chloro-2-fluorophenyl)-6-(methyloxy)-7-{[(4,5,5-trimethylmorpholin-2-yl)methyl]oxy}quinazolin-4-amine
432	*N*-(4,5-dichloro-2-fluorophenyl)-6-(methyloxy)-7-{[(4,5,5-

Table 4	
Entry	**Name**
	trimethylmorpholin-2-yl)methyl]oxy}quinazolin-4-amine
433	*N*-(3,4-dichloro-2-fluorophenyl)-6-(methyloxy)-7-{[(4,5,5-trimethylmorpholin-2-yl)methyl]oxy}quinazolin-4-amine
434	*N*-(4-bromo-3-chloro-2-fluorophenyl)-6-(methyloxy)-7-{[(4,5,5-trimethylmorpholin-2-yl)methyl]oxy}quinazolin-4-amine
435	*N*-(3-chloro-2,4-difluorophenyl)-6-(methyloxy)-7-{[(4,5,5-trimethylmorpholin-2-yl)methyl]oxy}quinazolin-4-amine
436	(6*S*)-6-({[4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-4-methylpiperazin-2-one
437	(6*S*)-6-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-4-methylpiperazin-2-one
438	(6*S*)-6-({[4-[(4-bromo-3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-1,4-dimethylpiperazin-2-one
439	(6*S*)-6-({[4-[(3,4-dichloro-2-fluorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]oxy}methyl)-1,4-dimethylpiperazin-2-one
440	*N*-(4-bromo-3-chlorophenyl)-7-{[(3a'*S*,4*R*,6'*S*,6a'*R*)-2,2-dimethyltetrahydrospiro[1,3-dioxolane-4,3'-furo[3,2-b]furan]-6'-yl]oxy}-6-(methyloxy)quinazolin-4-amine
441	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-5-C-[(methyloxy)methyl]-L-glucitol
442	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-(methylsulfonyl)-L-glucitol
443	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-L-glucitol
444	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-*S*-methyl-5-thio-D-iditol
445	1,4:3,6-dianhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-morpholin-4-yl-D-iditol
446	1,4:3,6-dianhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-(4-methylpiperazin-1-yl)-D-iditol
447	1,4:3,6-dianhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-pyrrolidin-1-yl-D-iditol
448	2-O-acetyl-1,4:3,6-dianhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-D-iditol
449	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-D-iditol
450	1,4:3,6-dianhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-

Table 4	
Entry	**Name**
	(methyloxy)quinazolin-7-yl]-2-deoxy-2-(methylsulfonyl)-D-iditol
451	2-amino-1,4:3,6-dianhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-D-iditol
452	1,4:3,6-dianhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-(dimethylamino)-D-iditol
453	1,4:3,6-dianhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-(diethylamino)-D-iditol
454	1,4:3,6-dianhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-piperidin-1-yl-D-iditol
455	2-(acetylamino)-1,4:3,6-dianhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-D-iditol
456	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-5-C-(trifluoromethyl)-L-glucitol
457	1,4:3,6-dianhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-[(methylsulfonyl)amino]-D-iditol
458	*N*-(4-bromo-3-chlorophenyl)-6-(methyloxy)-7-[(1-methylpyrrolidin-3-yl)oxy]quinazolin-4-amine
459	*N*-(4-bromo-3-chlorophenyl)-6-(methyloxy)-7-[(3*R*)-tetrahydrofuran-3-yloxy]quinazolin-4-amine
460	*N*-(4-bromo-3-chlorophenyl)-6-(methyloxy)-7-{[(3*S*,4*R*)-4-(methyloxy)tetrahydrofuran-3-yl]oxy}quinazolin-4-amine
461	1,4:3,6-dianhydro-2-deoxy-2-fluoro-5-O-(6-(methyloxy)-4-{[4-(4-methylpiperazin-1-yl)phenyl]amino}quinazolin-7-yl)-D-iditol
462	1,4:3,6-dianhydro-2-deoxy-2-fluoro-5-O-[4-{[3-fluoro-4-(4-methylpiperazin-1-yl)phenyl]amino}-6-(methyloxy)quinazolin-7-yl]-D-iditol
463	1,4:3,6-dianhydro-2-deoxy-5-O-[4-{[2,3-dichloro-4-(4-methylpiperazin-1-yl)phenyl]amino}-6-(methyloxy)quinazolin-7-yl]-2-fluoro-D-iditol
464	1,4:3,6-dianhydro-2-deoxy-5-O-[4-{[3,4-dichloro-2-(4-methylpiperazin-1-yl)phenyl]amino}-6-(methyloxy)quinazolin-7-yl]-2-fluoro-D-iditol
465	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-C-(trifluoromethyl)-D-glucitol
466	(3,4-dichlorophenyl)[6-(methyloxy)-7-({[4-(tetrahydrofuran-2-ylmethyl)-1,4-oxazepan-2-yl]methyl}oxy)quinazolin -4-amine
467	*N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta-[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
468	*N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-

Table 4	
Entry	**Name**
	methyloctahydrocyclo-penta[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
469	*N*-(3-chloro-2,4-difluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta-[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
470	*N*-(4,5-dichloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclo-penta[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
471	*N*-(4-bromo-5-chloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclo-penta[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
472	*N*-(4-bromo-2,3-dichlorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclo-penta[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
473	*N*-(3,4-dichlorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
474	*N*-(3,4-dichlorophenyl)-7-[(2-{[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]amino}ethyl)oxy]-6-(methyloxy)quinazolin-4-amine
475	*N*-(3,4-dichlorophenyl)-7-({2-[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]ethyl}oxy)-6-(methyloxy)quinazolin-4-amine
476	*N*-(3,4-dichlorophenyl)-7-({[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine
477	*N*-(3,4-dichlorophenyl)-7-{[(3-*exo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]oxy}-6-(methyloxy)quinazolin-4-amine
478	1,4:3,6-Dianhydro-5-*O*-[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-*O*-methyl-D-glucitol
479	1,4:3,6-dianhydro-5-*O*-{4-[(3-chloro-2-fluorophenyl)amino]-6-(methyloxy)quin-azolin-7-yl}-2-deoxy-2-fluoro-L-iditol
480	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-(methylsulfonyl)-D-glucitol
481	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-D-glucitol
482	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-S-methyl-5-thio-L-iditol
483	1,4:3,6-dianhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-morpholin-4-yl-L-iditol
484	1,4:3,6-dianhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-(4-methylpiperazin-1-yl)-L-iditol

Table 4	
Entry	**Name**
485	1,4:3,6-dianhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-pyrrolidin-1-yl-L-iditol
486	2-O-acetyl-1,4:3,6-dianhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-L-iditol
487	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-L-iditol
488	1,4:3,6-dianhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-(methylsulfonyl)-L-iditol
489	2-amino-1,4:3,6-dianhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-L-iditol
490	1,4:3,6-dianhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-(dimethylamino)-L-iditol
491	1,4:3,6-dianhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-(diethylamino)-L-iditol
492	1,4:3,6-dianhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-piperidin-1-yl-L-iditol
493	2-(acetylamino)-1,4:3,6-dianhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-L-iditol
494	1,4:3,6-dianhydro-2-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-O-methyl-5-C-(trifluoromethyl)-D-glucitol
495	1,4:3,6-dianhydro-5-O-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-deoxy-2-[(methylsulfonyl)amino]-L-iditol
496	1,4:3,6-dianhydro-2-deoxy-2-fluoro-5-O-(6-(methyloxy)-4-{[4-(4-methylpiperazin-1-yl)phenyl]amino}quinazolin-7-yl)-L-iditol
497	1,4:3,6-dianhydro-2-deoxy-2-fluoro-5-O-[4-{[3-fluoro-4-(4-methylpiperazin-1-yl)phenyl]amino}-6-(methyloxy)quinazolin-7-yl]-L-iditol
498	1,4:3,6-dianhydro-2-deoxy-5-O-[4-{[2,3-dichloro-4-(4-methylpiperazin-1-yl)phenyl]amino}-6-(methyloxy)quinazolin-7-yl]-2-fluoro-L-iditol
499	1,4:3,6-dianhydro-2-deoxy-5-O-[4-{[3,4-dichloro-2-(4-methylpiperazin-1-yl)phenyl]amino}-6-(methyloxy)quinazolin-7-yl]-2-fluoro-L-iditol
500	1,4:3,6-Dianhydro-5-*O*-[4-[(3,4-dichlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-2-*O*-methyl-D-glucitol
501	1,4:3,6-Dianhydro-2-*O*-[4-[(4-bromo-3-chlorophenyl)amino]-6-(methyloxy)quinazolin-7-yl]-5-*O*-methyl-L-glucitol

Representative IGF-1R Inhibitors

[00221] The Compounds in Table 5a can be prepared as pharmaceutically acceptable salts, solvates, hydrates, and/or isomers thereof. All such salt, solvate, hydrate, and isomer combinations of the Compounds in Table 5a can be used to practice the invention.

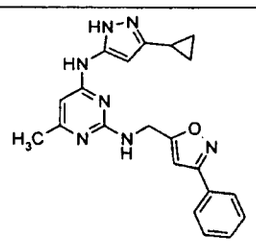
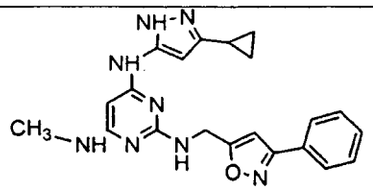
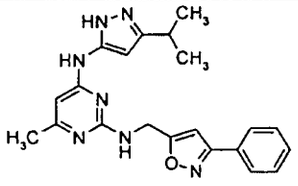
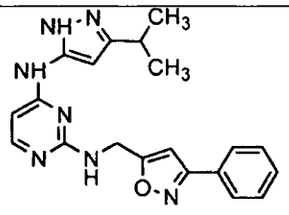
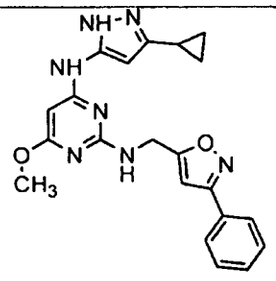
Table 5a	
Entry	Structure
1	
2	
3	
4	
5	

Table 5a	
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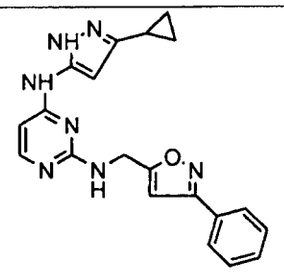
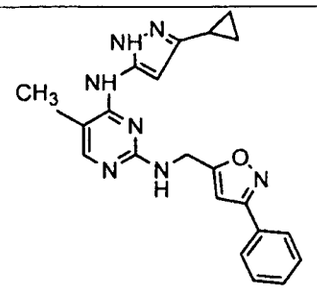
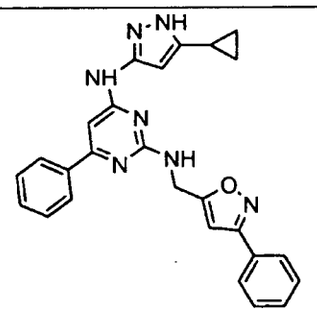
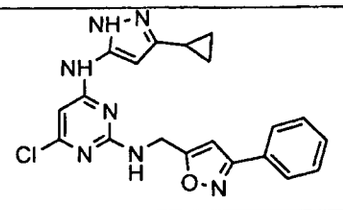
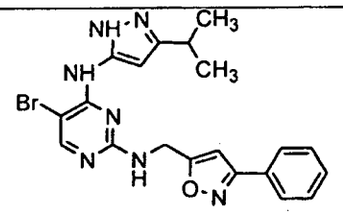
6	
7	
8	
9	
10	

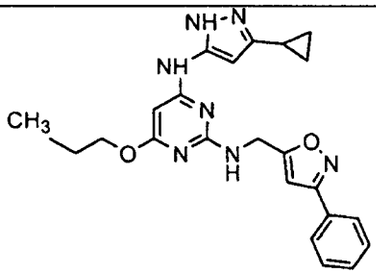
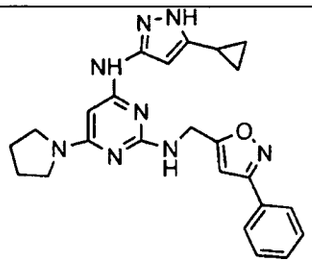
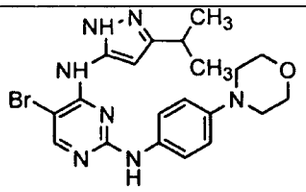
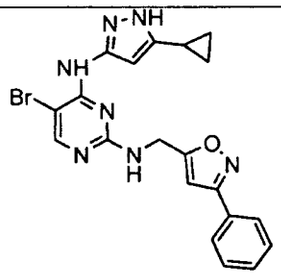
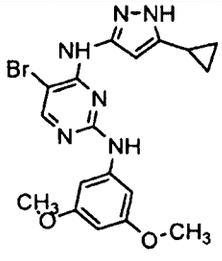
Table 5a	
Entry	Structure
11	
12	
13	
14	
15	

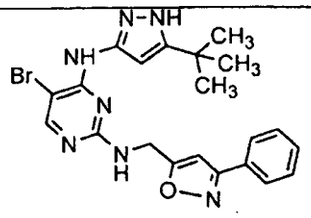
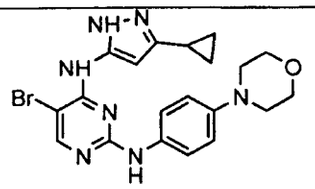
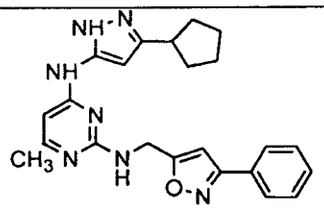
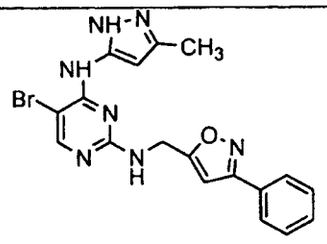
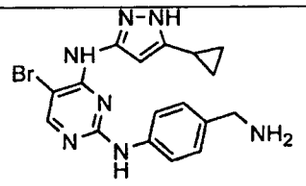
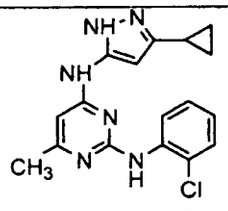
Table 5a	
Entry	Structure
16	
17	
18	
19	
20	
21	

Table 5a	
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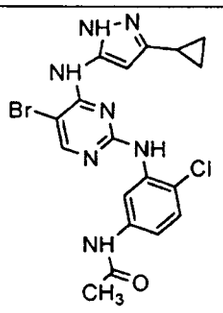
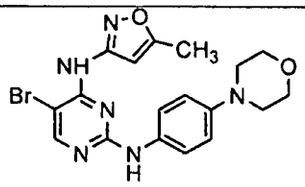
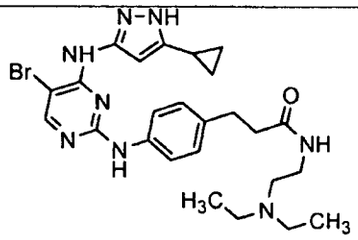
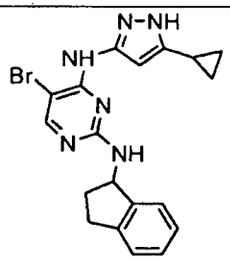
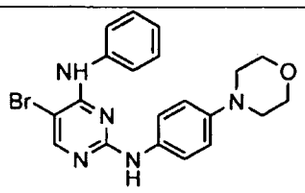
22	
23	
24	
25	
26	

Table 5a	
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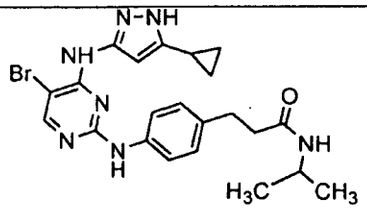
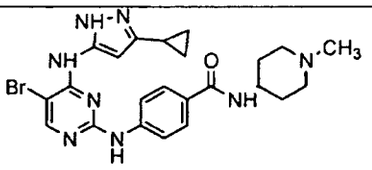
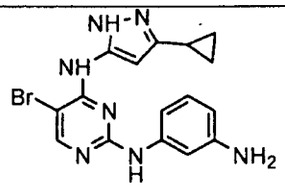
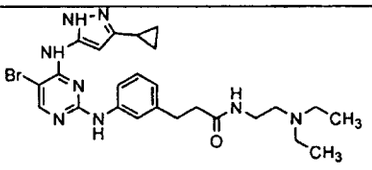
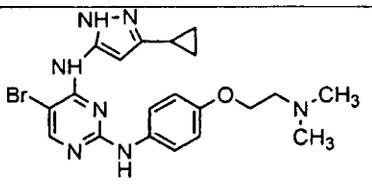
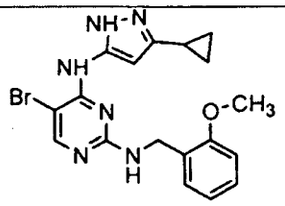
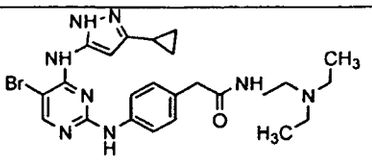
27	
28	
29	
30	
31	
32	
33	

Table 5a	
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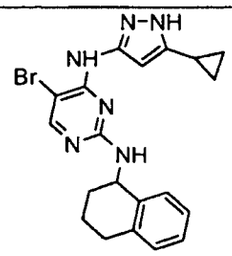
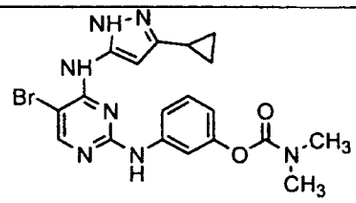
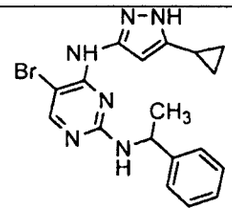
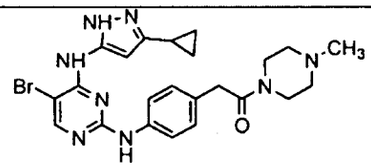
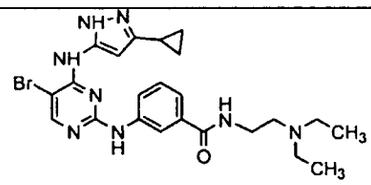
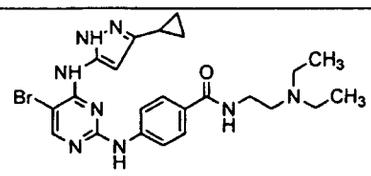
34	
35	
36	
37	
38	
39	

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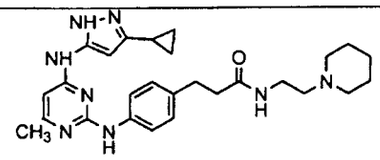
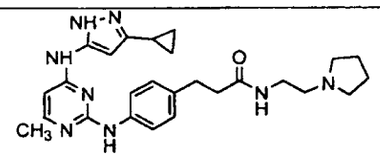
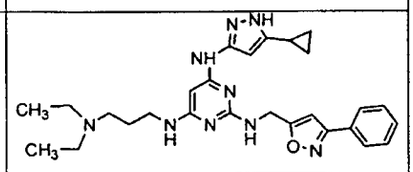
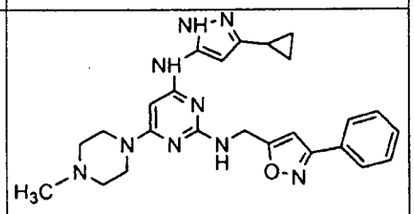
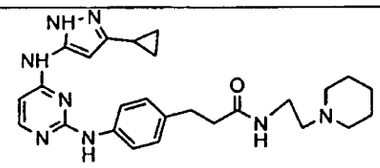
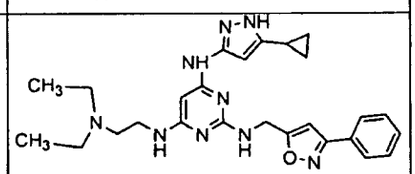
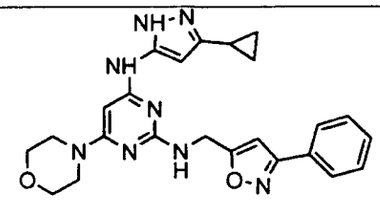
40	
41	
42	
43	
44	
45	
46	

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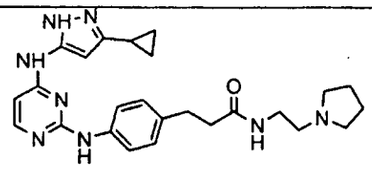
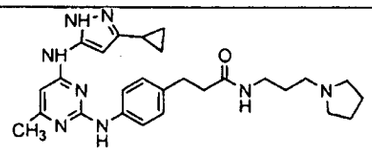
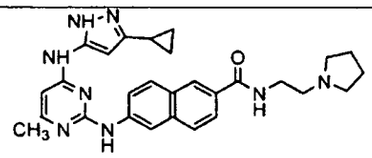
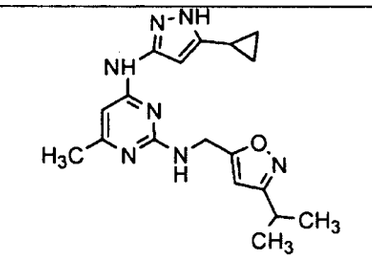
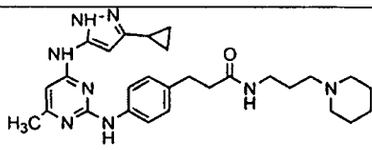
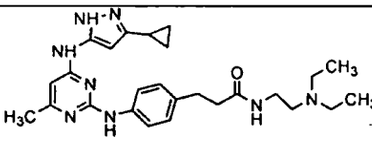
47	
48	
49	
50	
51	
52	

Table 5a	
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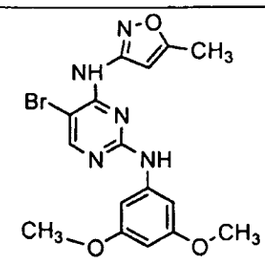
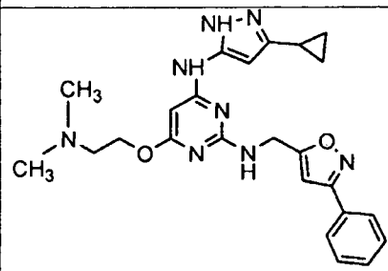
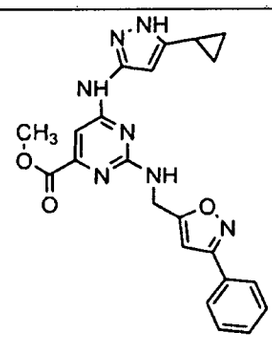
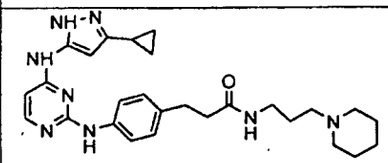
53	
54	
55	
56	

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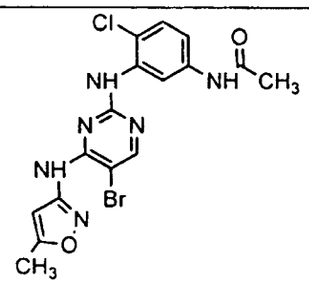
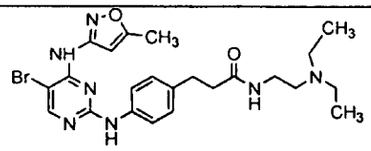
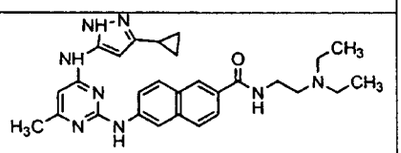
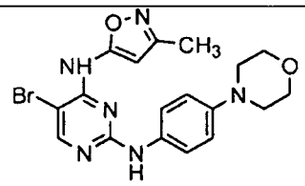
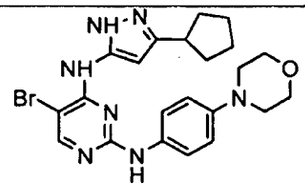
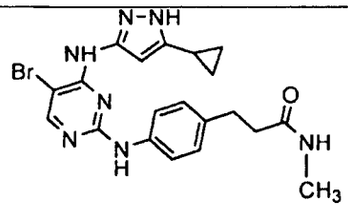
57	
58	
59	
60	
61	
62	

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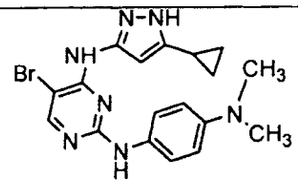
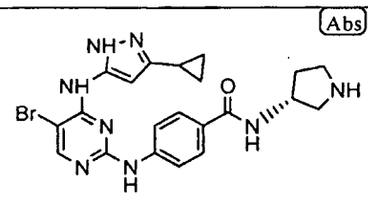
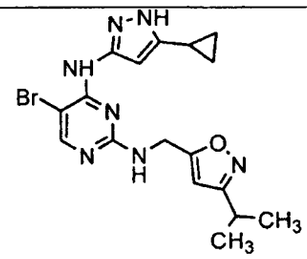
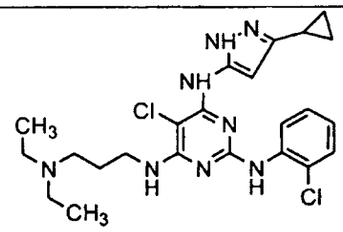
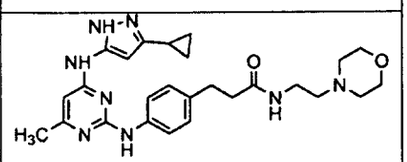
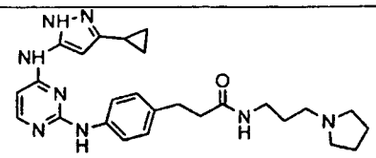
63	
64	
65	
66	
67	
68	

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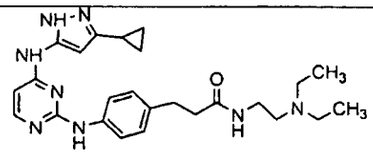
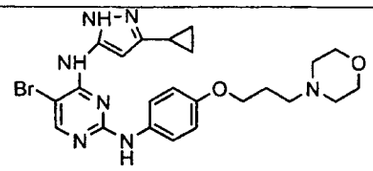
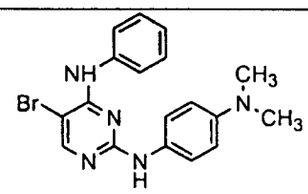
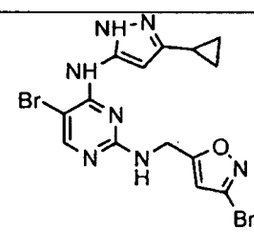
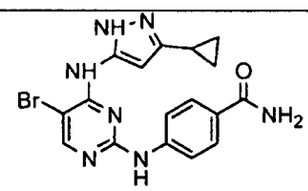
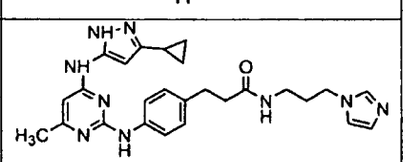
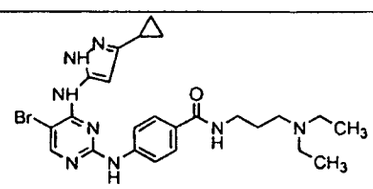
69	
70	
71	
72	
73	
74	
75	

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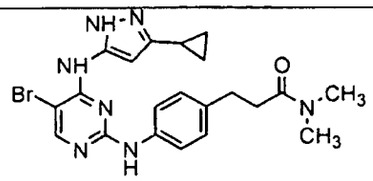
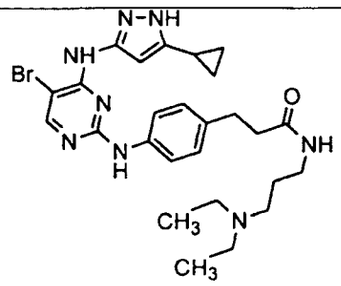
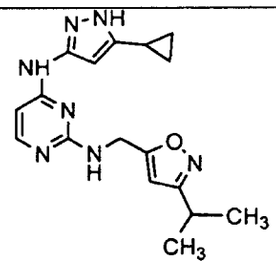
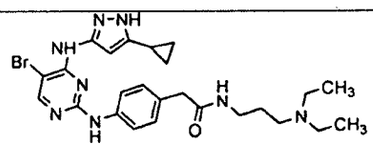
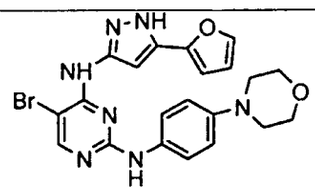
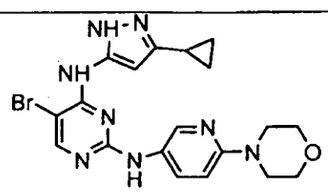
76	
77	
78	
79	
80	
81	

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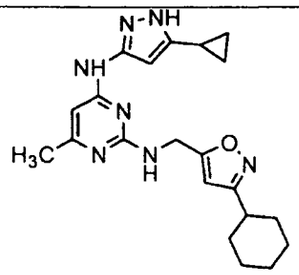
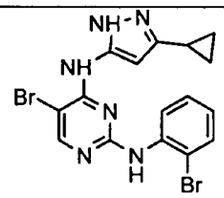
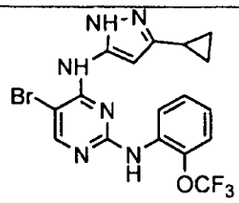
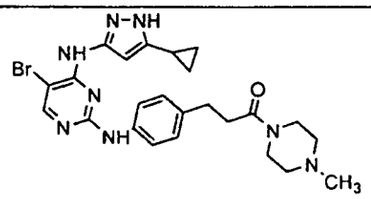
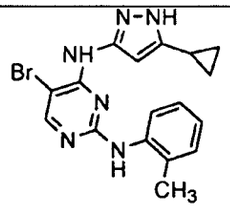
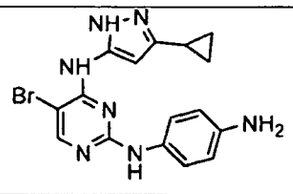
82	
83	
84	
85	
86	
87	

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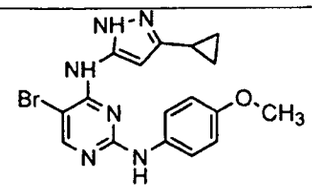
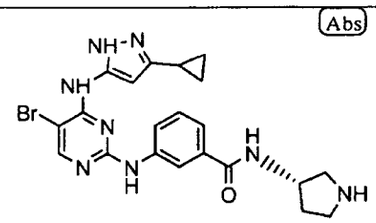
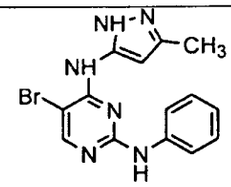
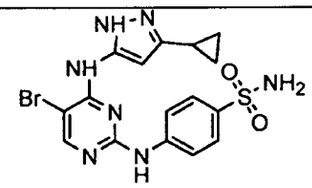
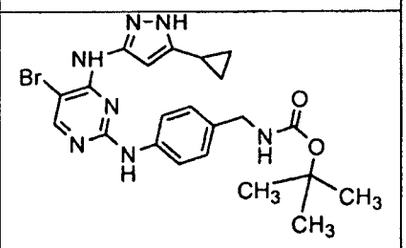
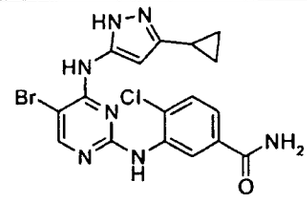
88	
89	 Abs
90	
91	
92	
93	

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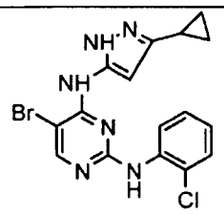
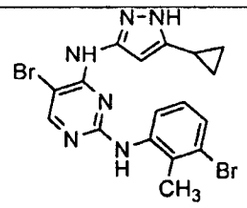
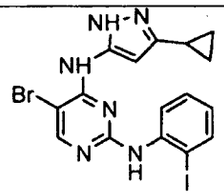
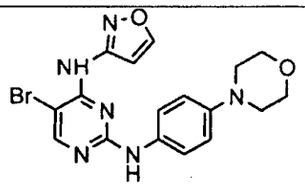
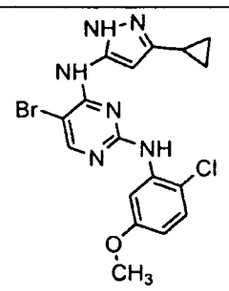
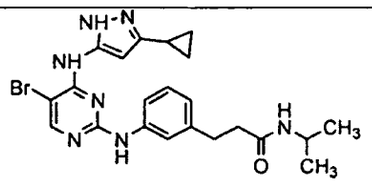
94	
95	
96	
97	
98	
99	

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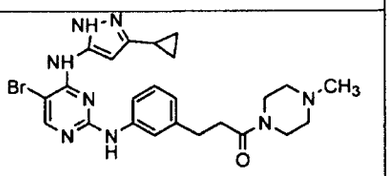
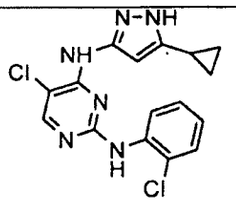
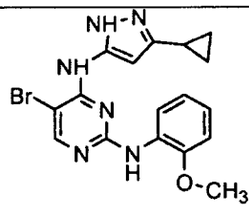
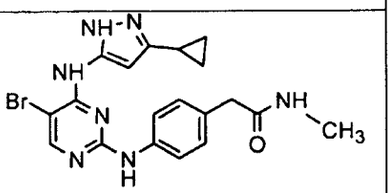
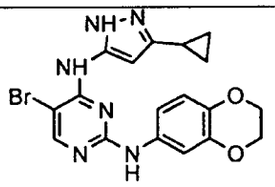
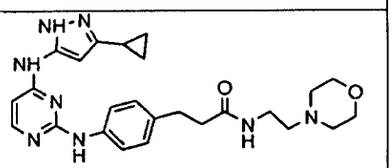
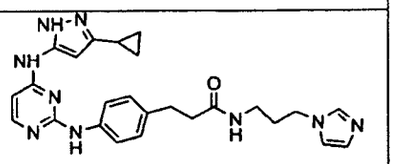
100	
101	
102	
103	
104	
105	
106	

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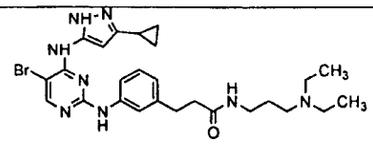
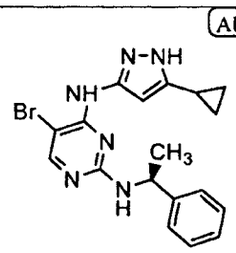
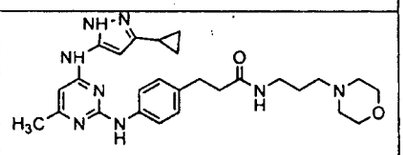
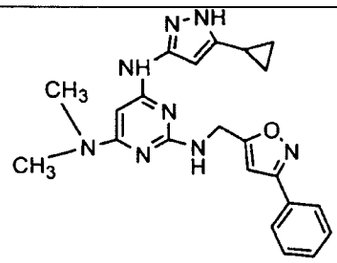
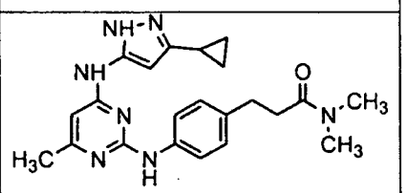
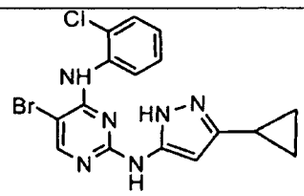
107	
108	
109	
110	
111	
112	

Table 5a	
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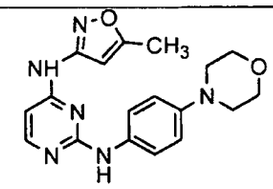
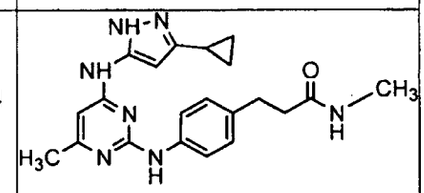
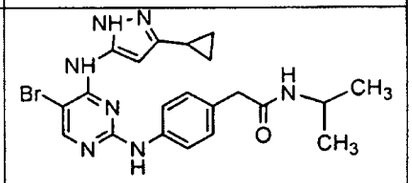
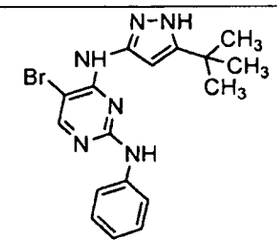
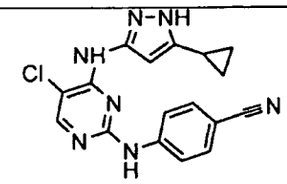
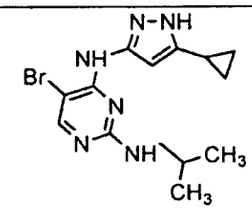
113	
114	
115	
116	
117	
118	

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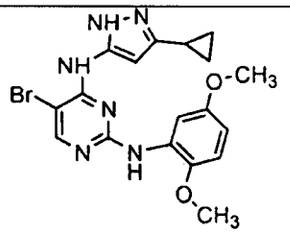
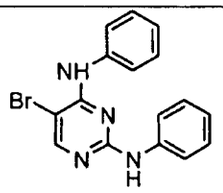
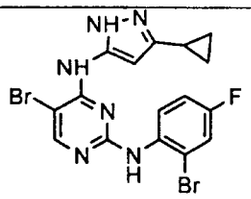
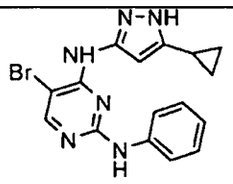
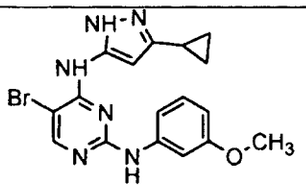
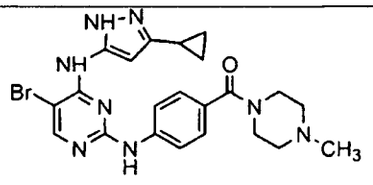
119	
120	
121	
122	
123	
124	

Table 5a	
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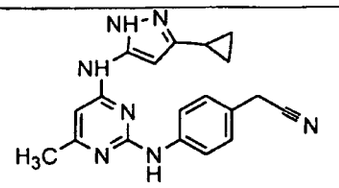
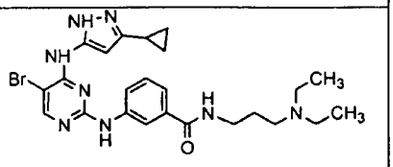
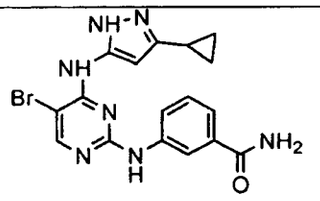
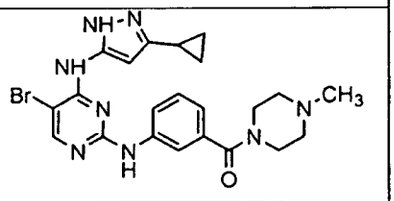
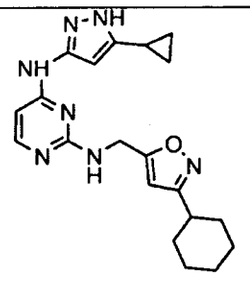
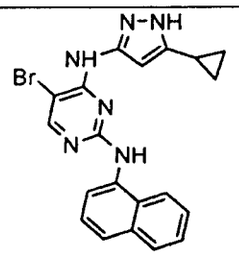
125	
126	
127	
128	
129	
130	

Table 5a	
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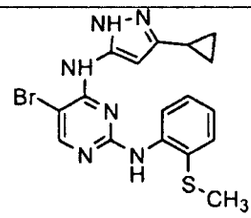
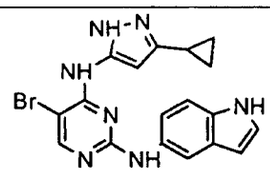
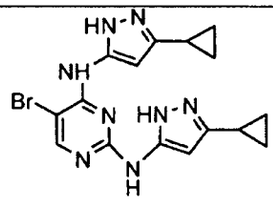
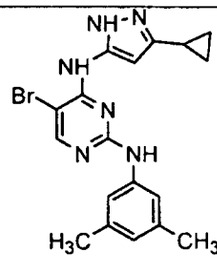
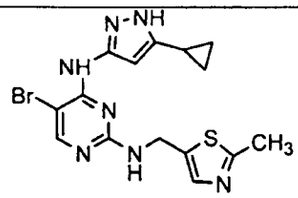
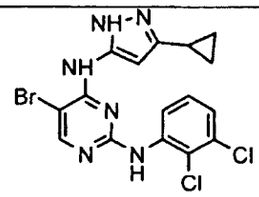
131	
132	
133	
134	
135	
136	

Table 5a	
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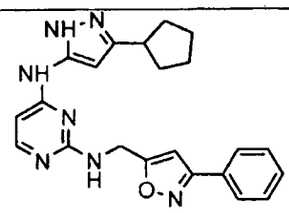
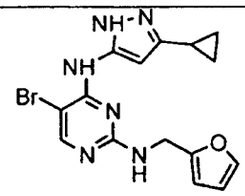
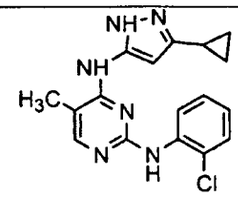
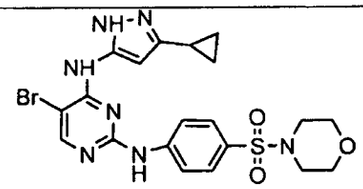
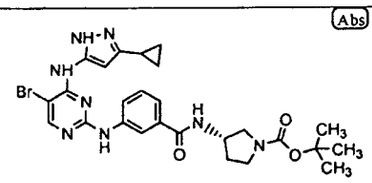
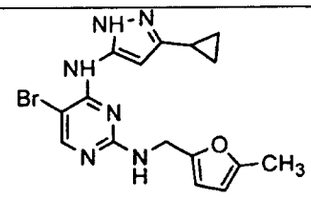
137	
138	
139	
140	
141	
142	

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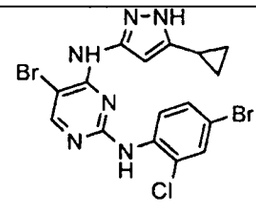
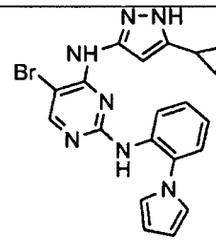
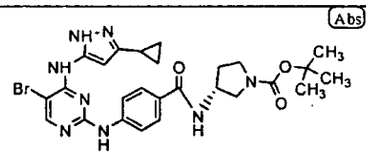
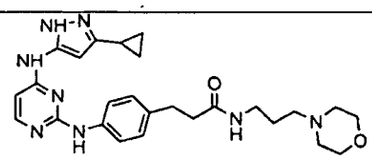
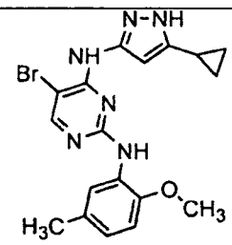
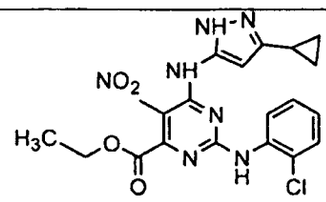
143	
144	
145	
146	
147	
148	

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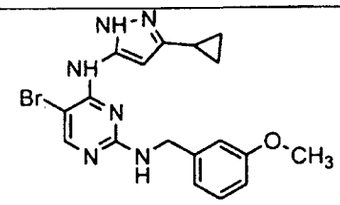
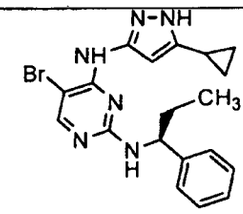
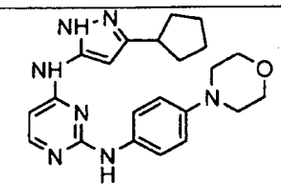
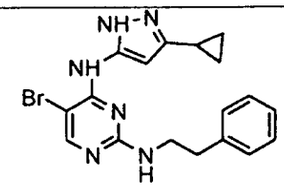
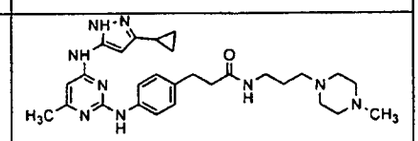
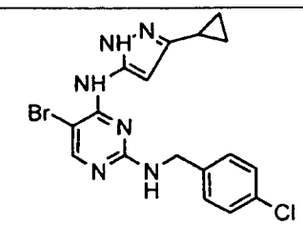
149	
150	
151	
152	
153	
154	

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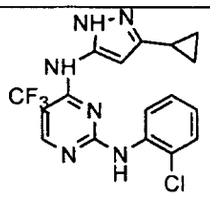
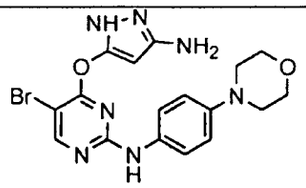
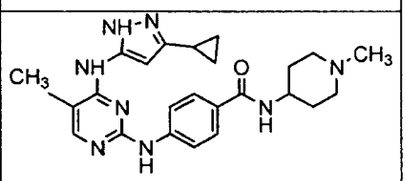
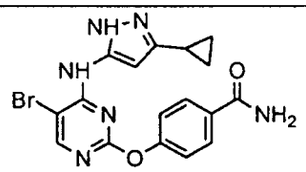
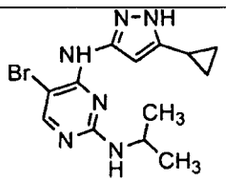
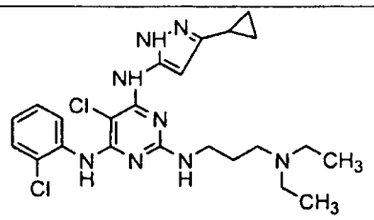
155	
156	
157	
158	
159	
160	

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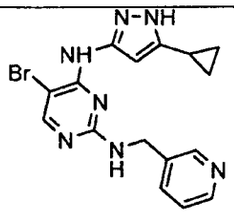
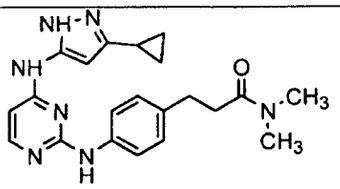
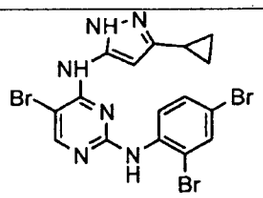
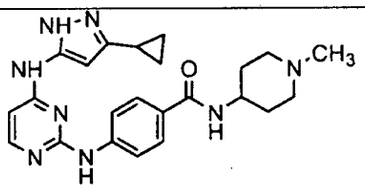
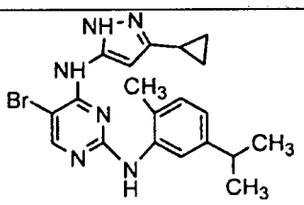
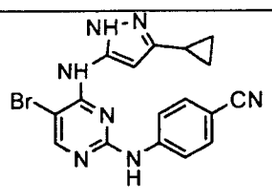
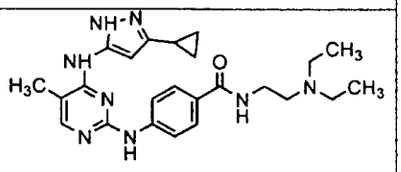
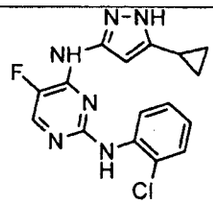
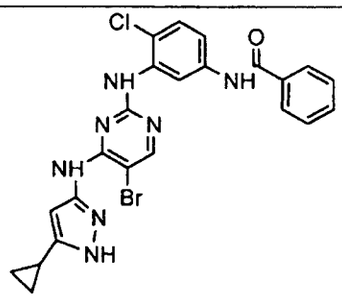
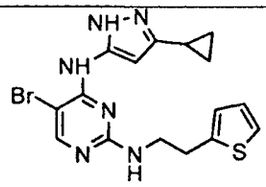
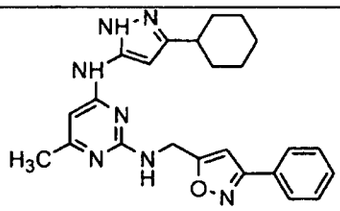
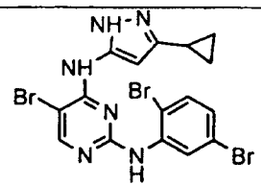
161	
162	
163	
164	
165	
166	

Table 5a	
Entry	Structure
167	
168	
169	
170	
171	
172	

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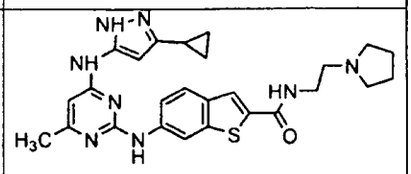
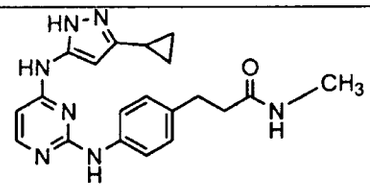
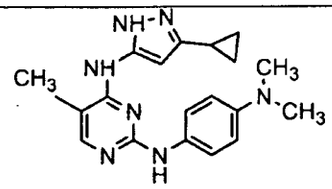
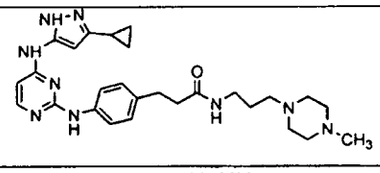
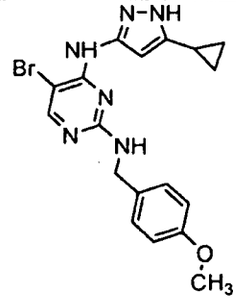
173	
174	
175	
176	
177	

Table 5a	
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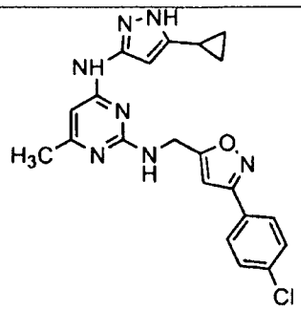
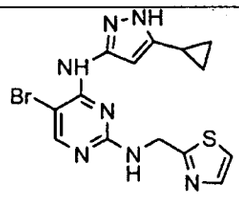
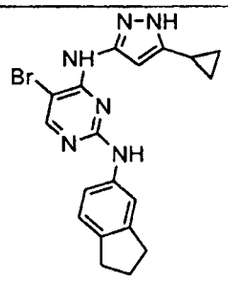
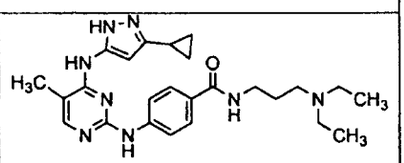
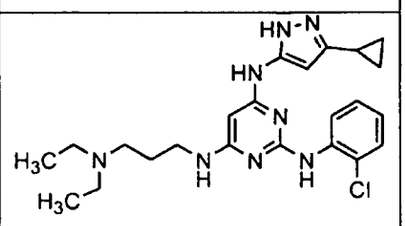
178	
179	
180	
181	
182	

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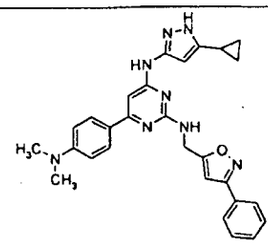
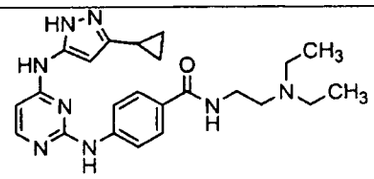
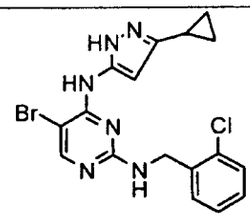
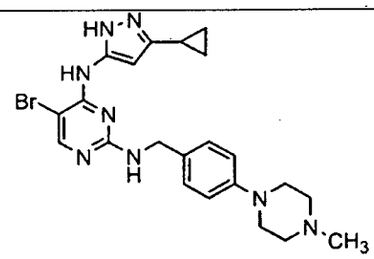
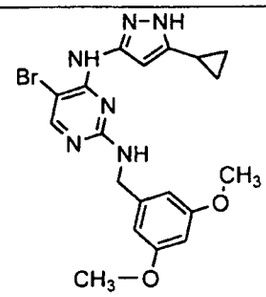
183	
184	
185	
186	
187	

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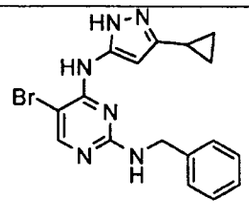
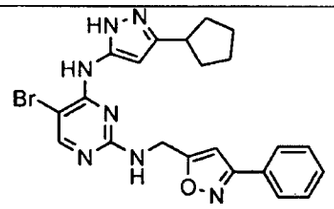
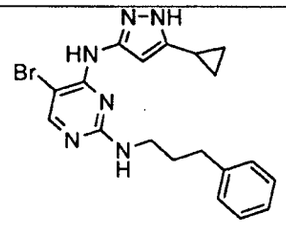
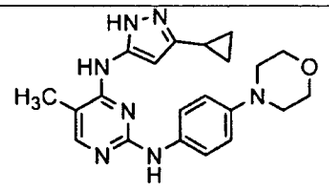
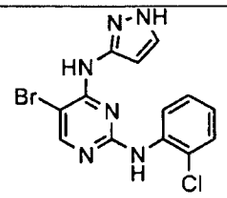
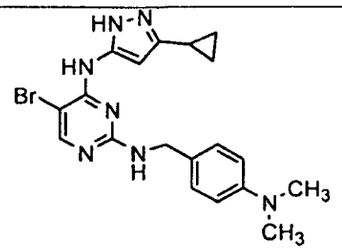
188	
189	
190	
191	
192	
193	

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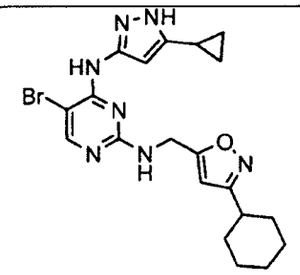
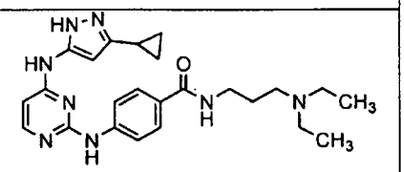
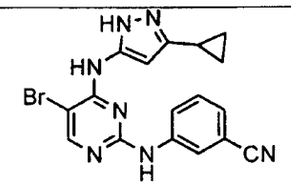
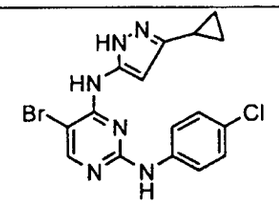
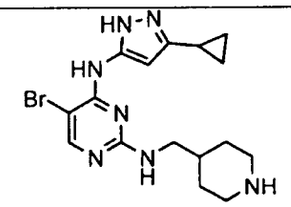
194	
195	
196	
197	
198	

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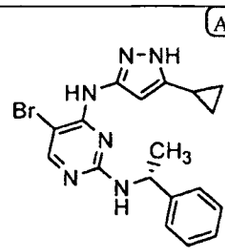
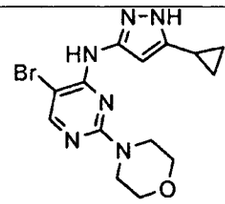
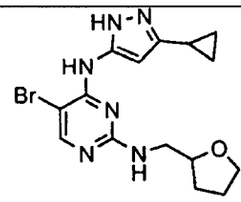
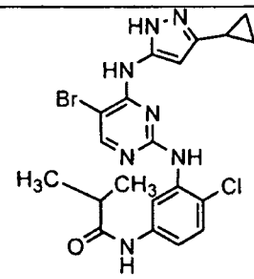
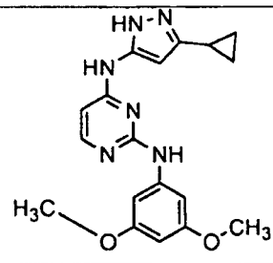
199	
200	
201	
202	
203	

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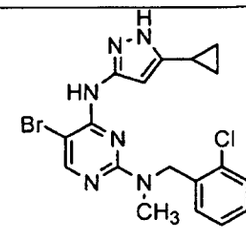
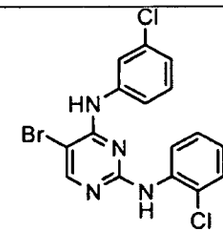
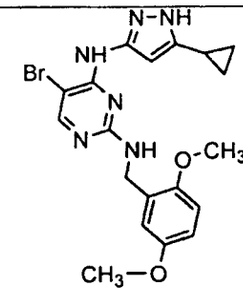
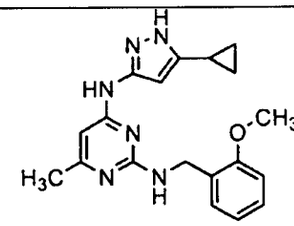
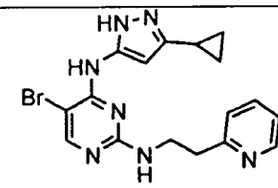
204	
205	
206	
207	
208	

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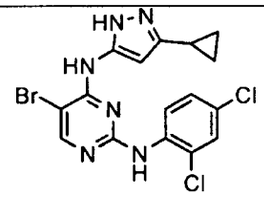
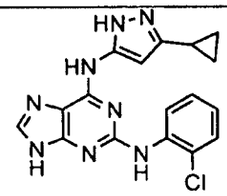
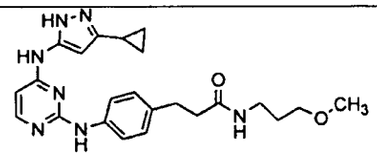
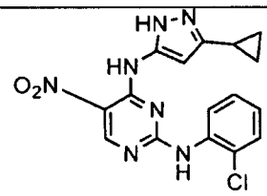
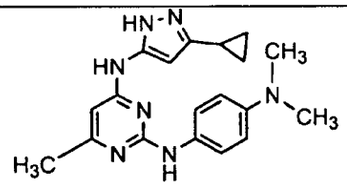
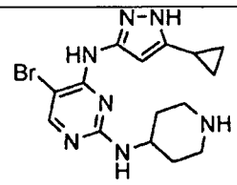
209	
210	
211	
212	
213	
214	

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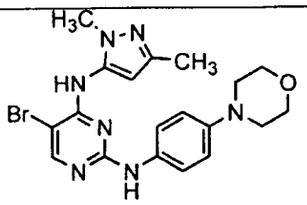
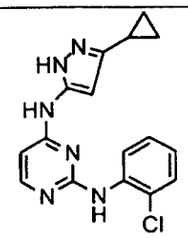
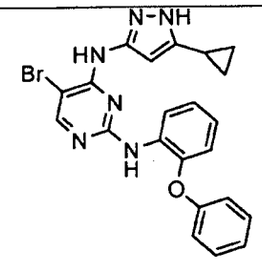
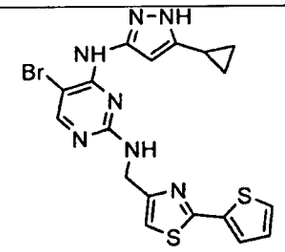
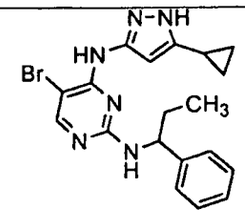
215	
216	
217	
218	
219	

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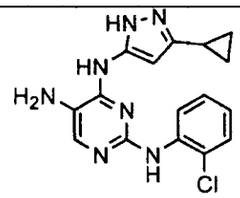
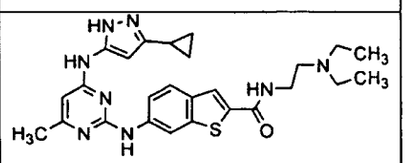
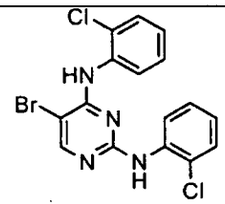
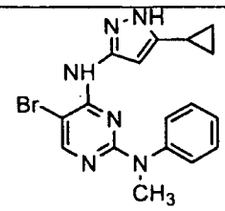
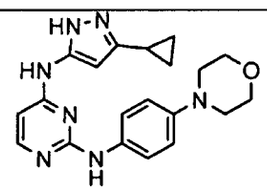
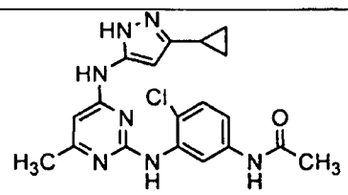
220	
221	
222	
223	
224	
225	

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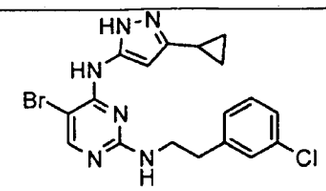
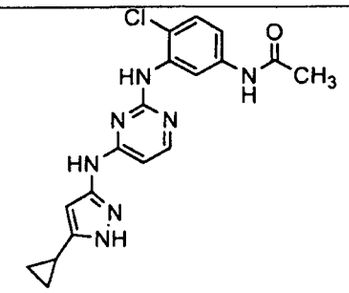
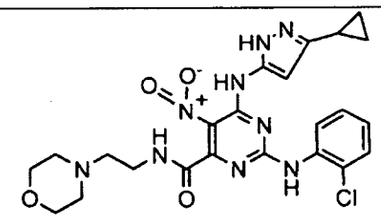
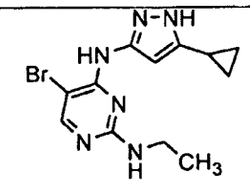
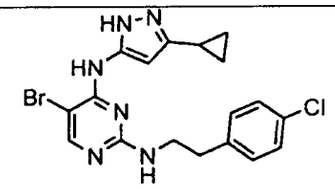
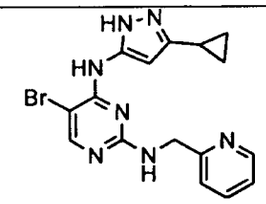
226	
227	
228	
229	
230	
231	

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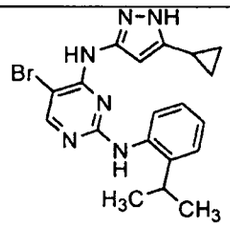
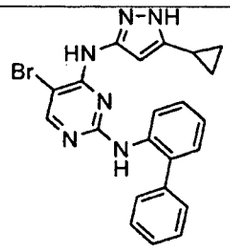
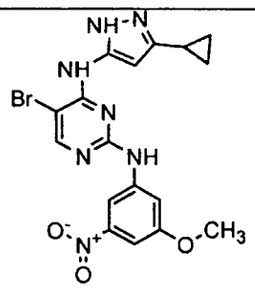
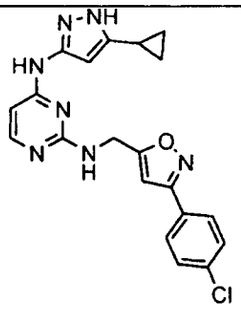
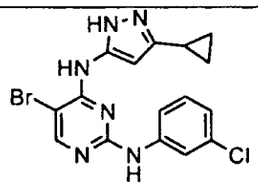
232	
233	
234	
235	
236	

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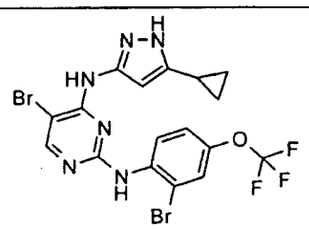
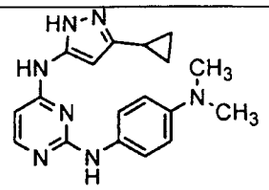
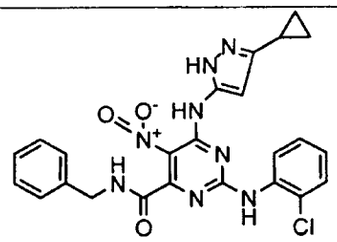
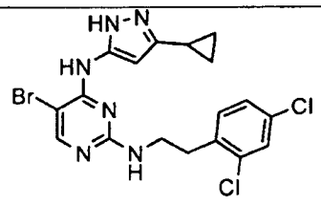
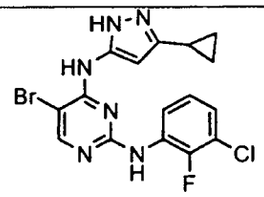
237	
238	
239	
240	
241	

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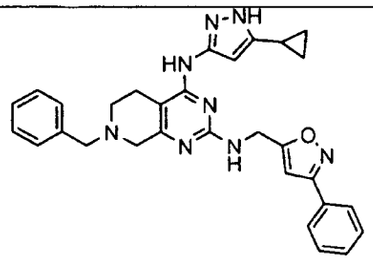
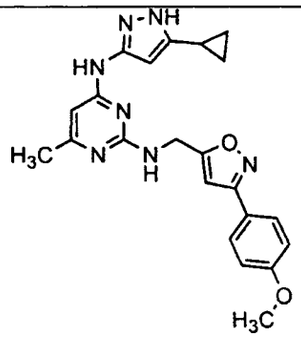
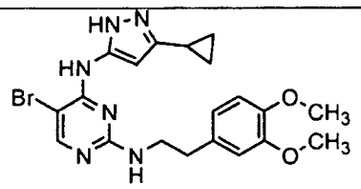
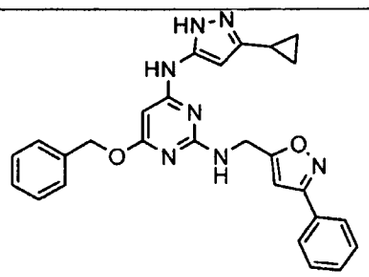
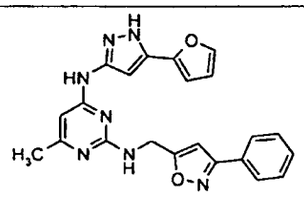
242	
243	
244	
245	
246	

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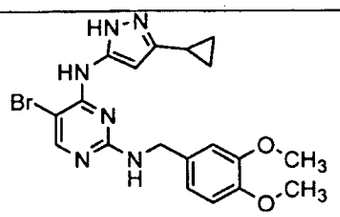
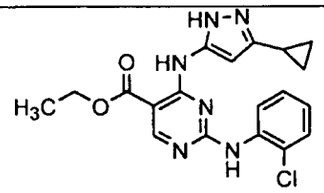
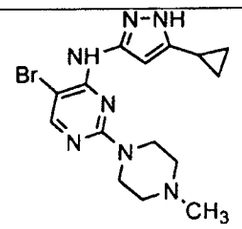
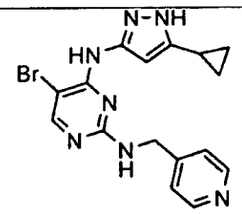
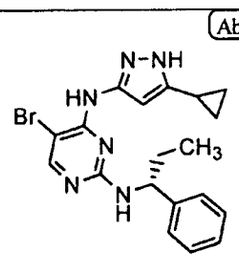
247	
248	
249	
250	
251	Abs 

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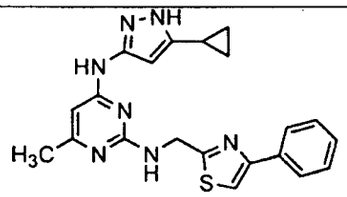
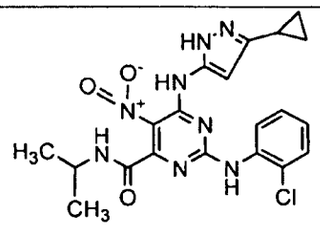
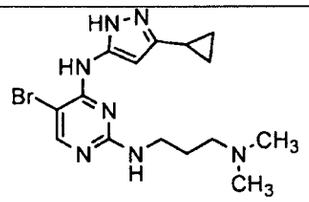
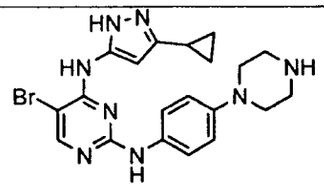
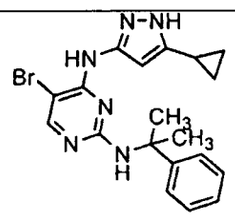
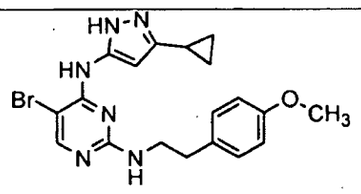
252	
253	
254	
255	
256	
257	

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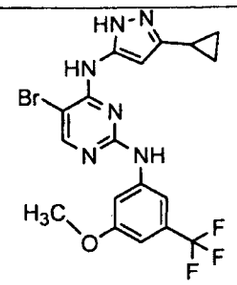
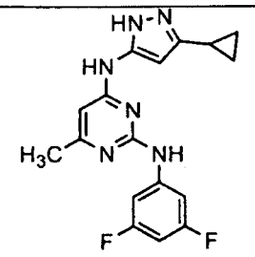
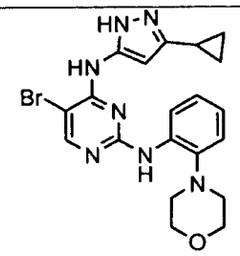
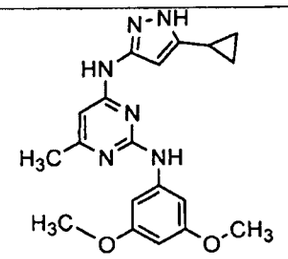
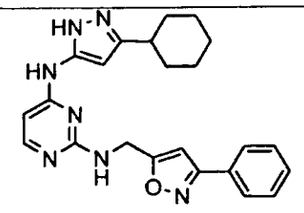
258	
259	
260	
261	
262	

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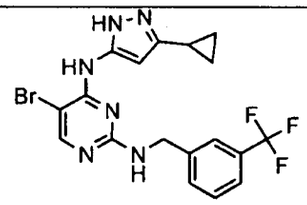
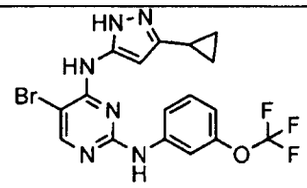
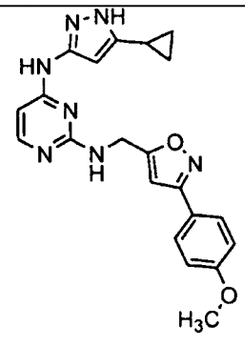
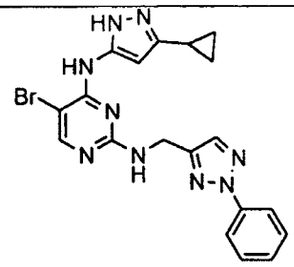
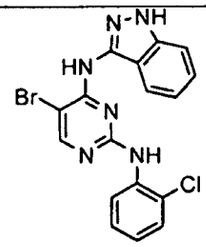
263	
264	
265	
266	
267	

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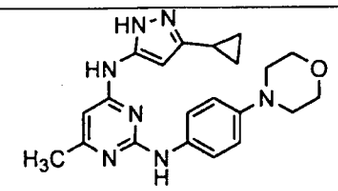
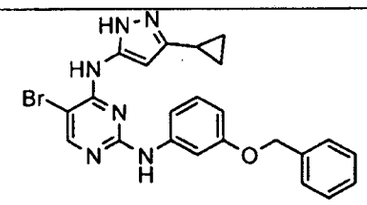
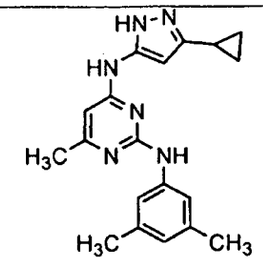
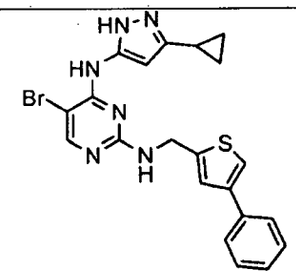
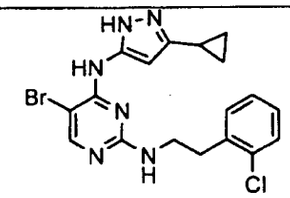
268	
269	
270	
271	
272	

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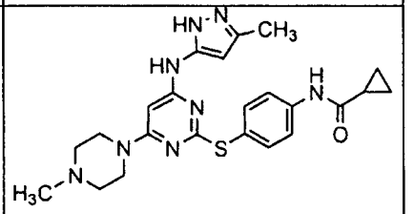
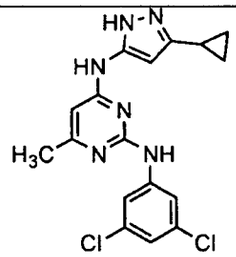
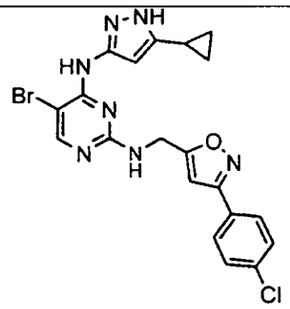
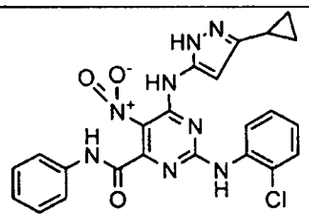
273	
274	
275	
276	

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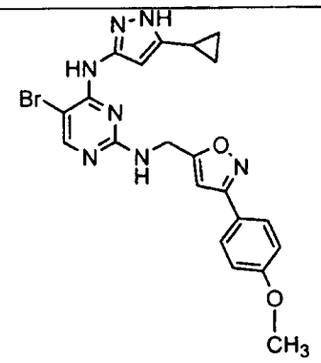
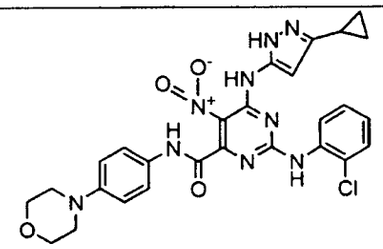
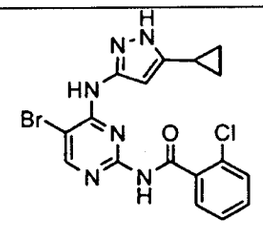
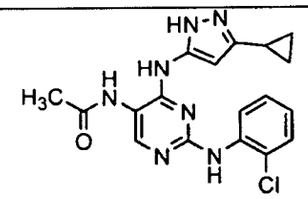
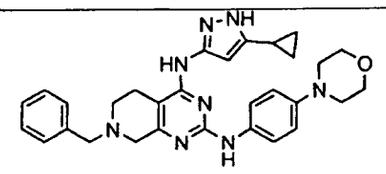
277	
278	
279	
280	
281	

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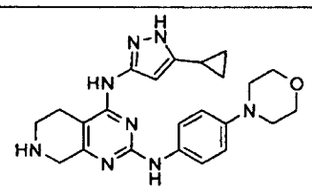
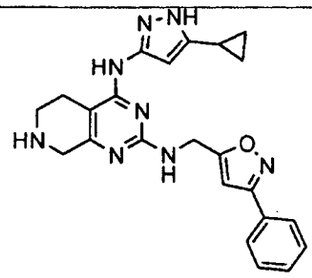
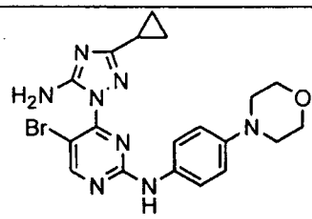
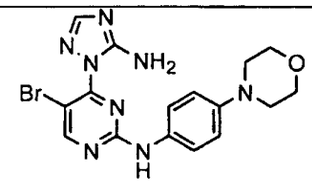
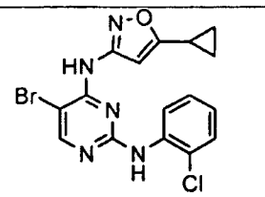
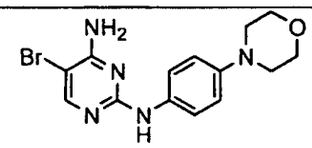
282	
283	
284	
285	
286	
287	

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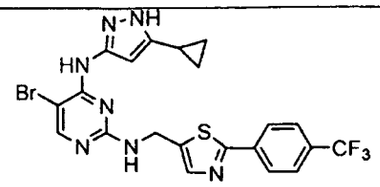
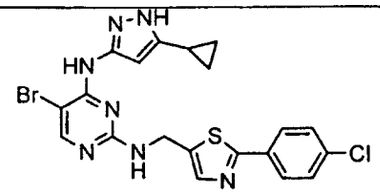
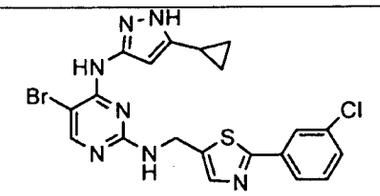
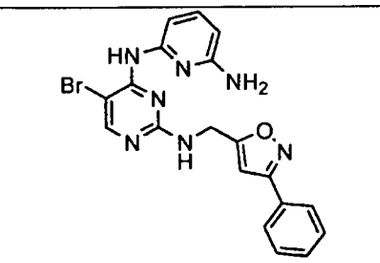
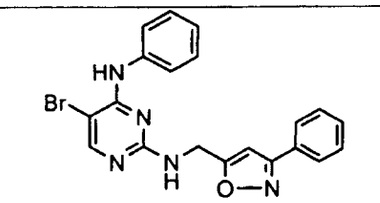
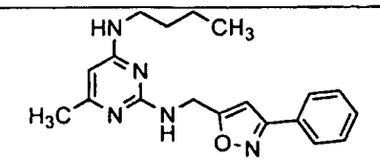
288	
289	
290	
291	
292	
293	

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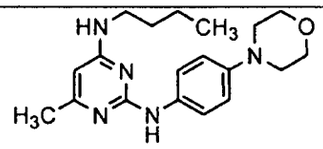
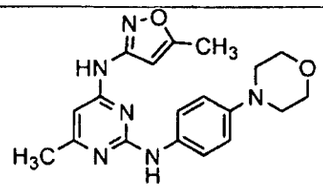
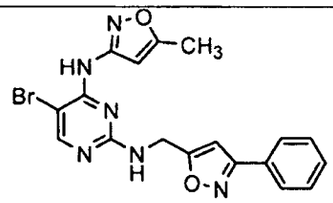
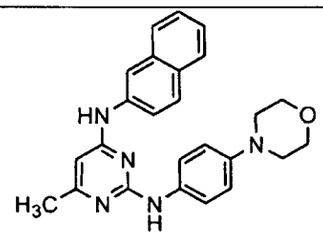
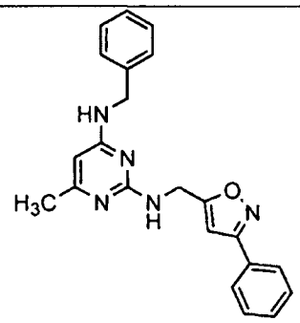
294	
295	
296	
297	
298	

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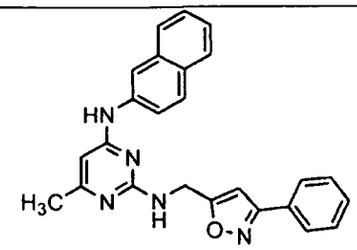
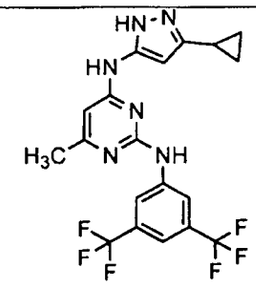
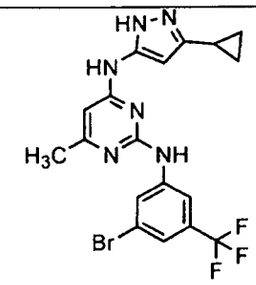
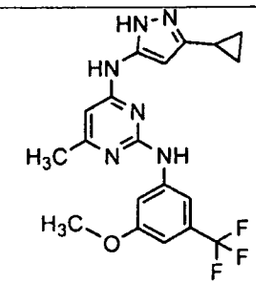
299	
300	
301	
302	

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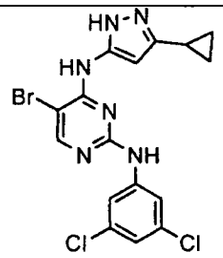
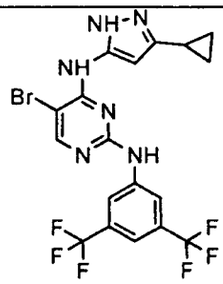
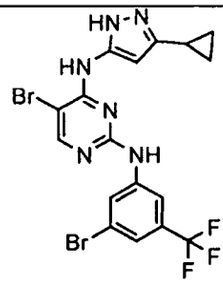
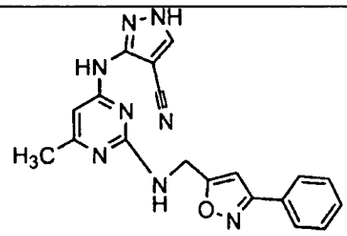
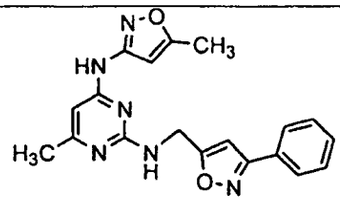
303	
304	
305	
306	
307	

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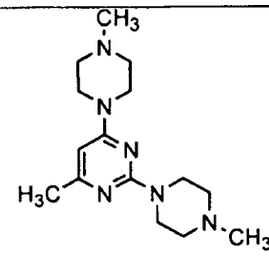
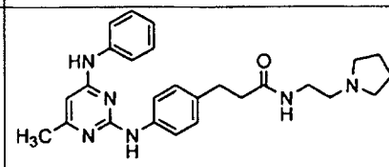
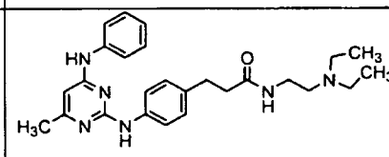
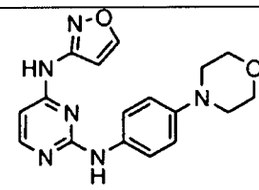
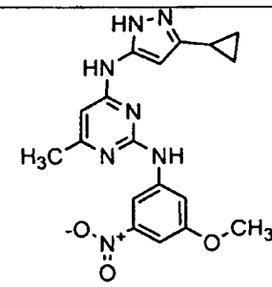
308	
309	
310	
311	
312	

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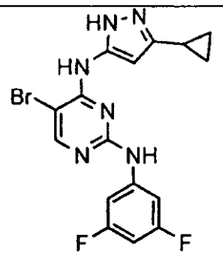
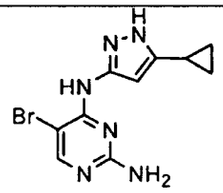
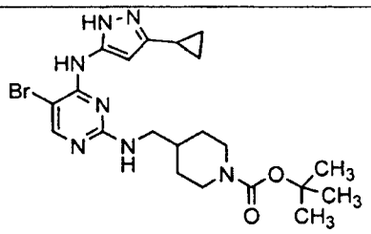
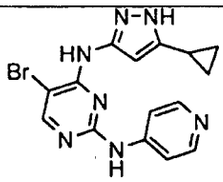
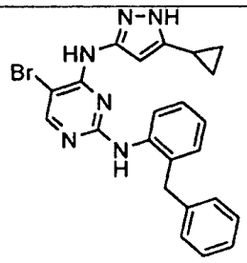
313	
314	
315	
316	
317	

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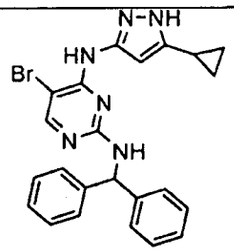
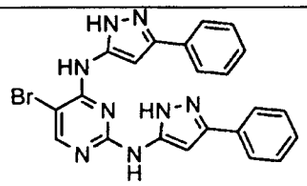
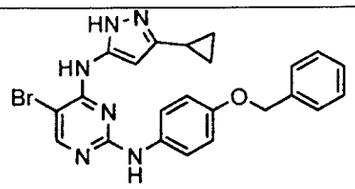
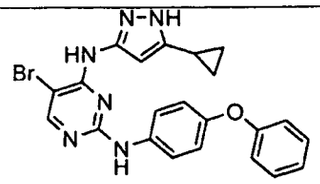
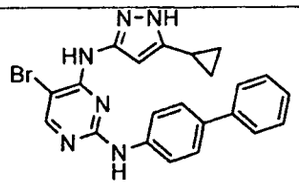
318	
319	
320	
321	
322	

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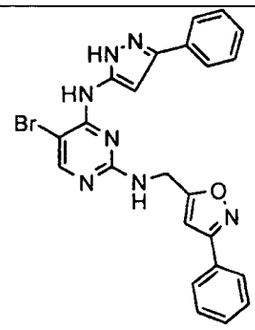
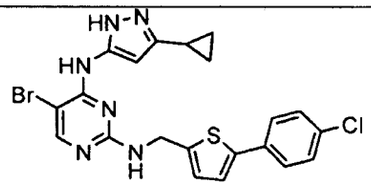
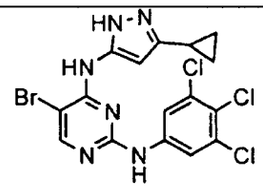
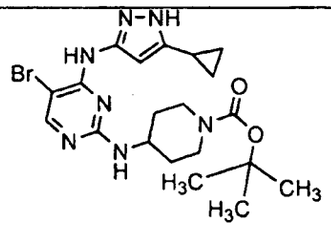
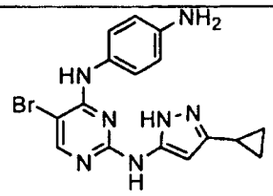
323	
324	
325	
326	
327	

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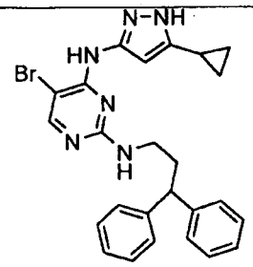
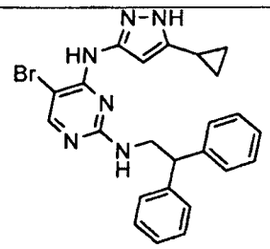
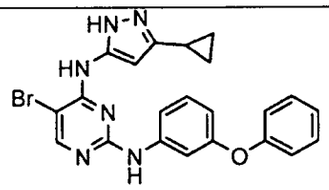
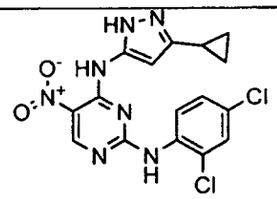
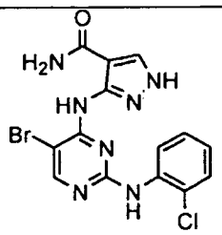
328	
329	
330	
331	
332	

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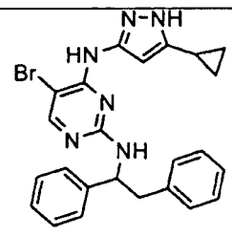
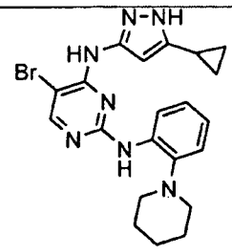
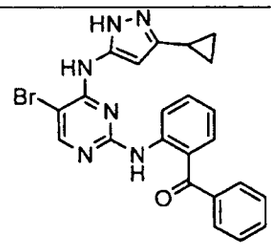
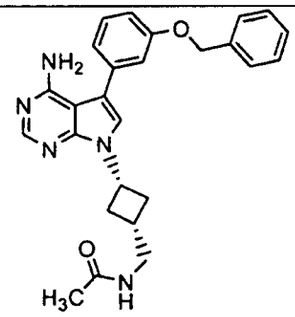
333	
334	
335	
336	

Table 5a	
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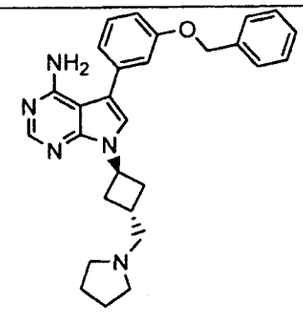
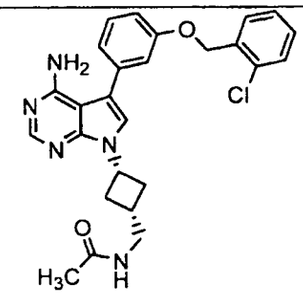
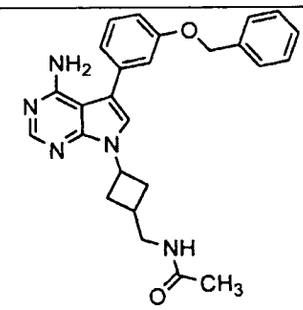
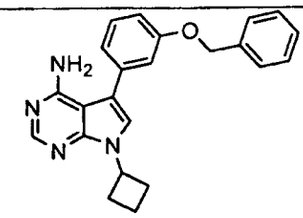
337	
338	
339	
340	

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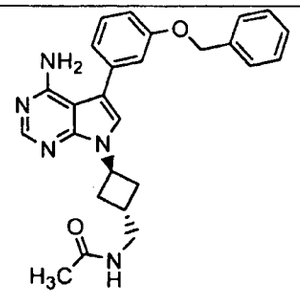
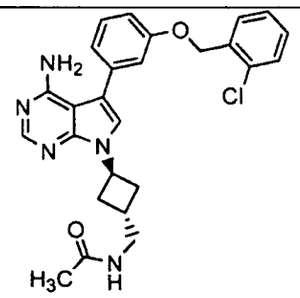
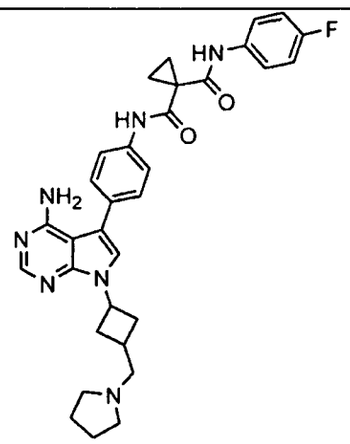
341	
342	
343	

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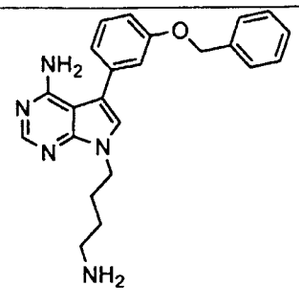
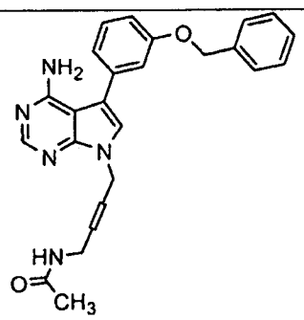
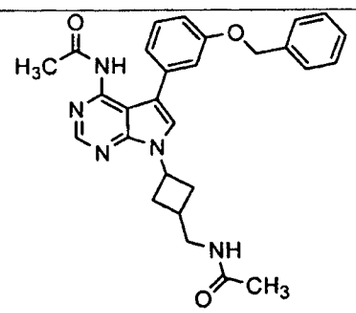
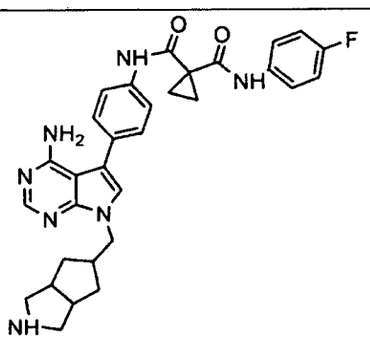
344	
345	
346	
347	

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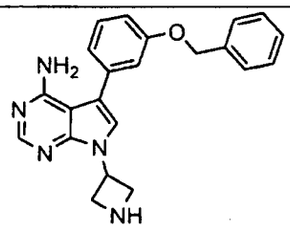
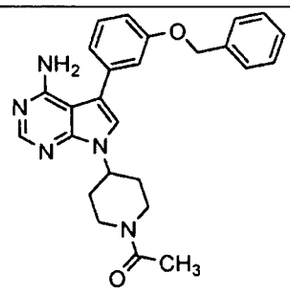
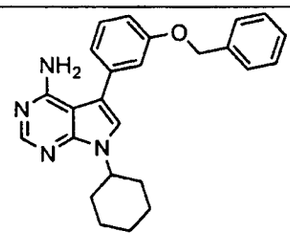
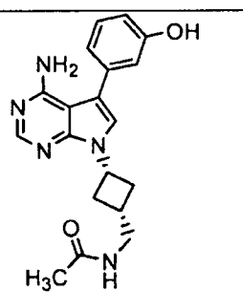
348	
349	
350	
351	

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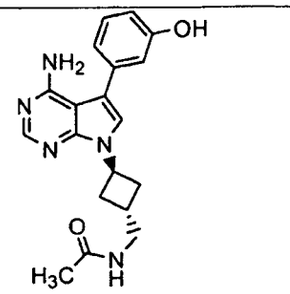
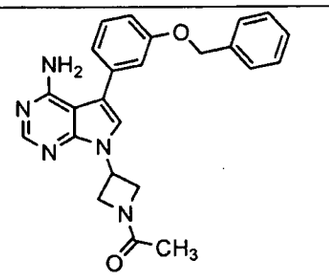
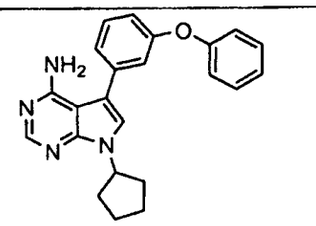
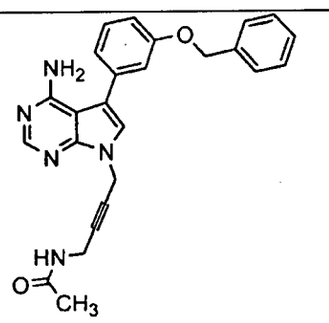
352	
353	
354	
355	

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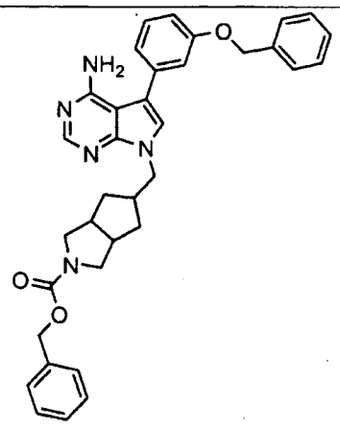
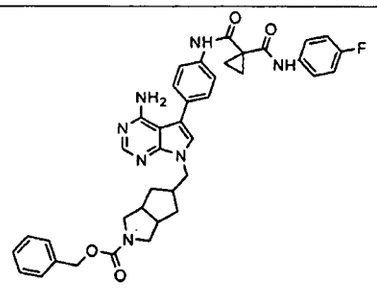
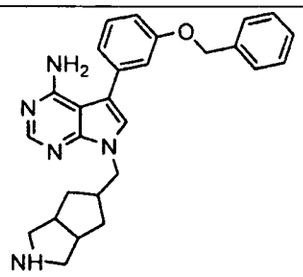
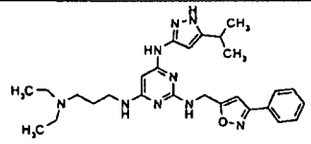
356	
357	
358	
495	

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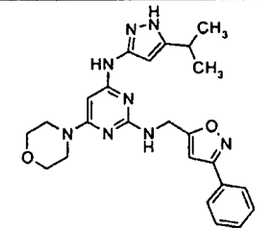
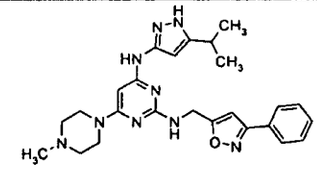
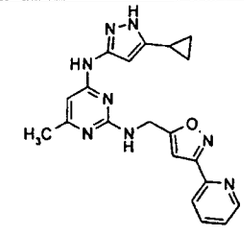
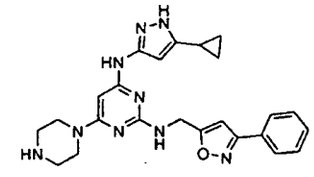
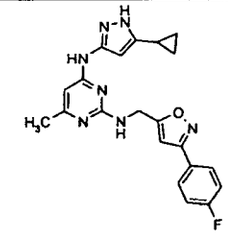
496	
497	
498	
499	
500	

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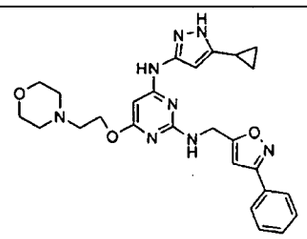
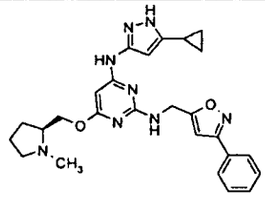
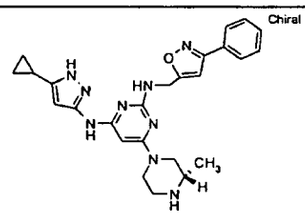
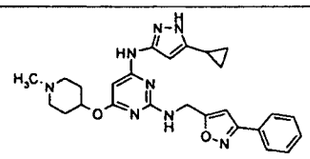
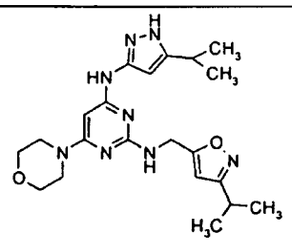
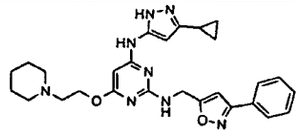
501	
502	
503	
504	
505	
506	

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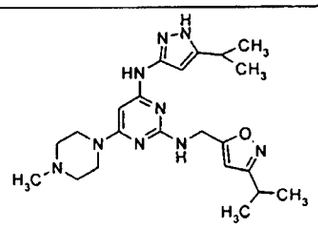
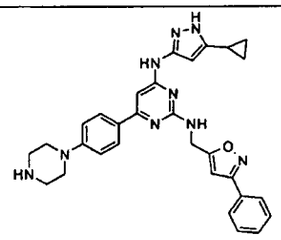
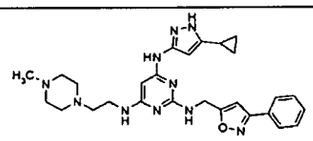
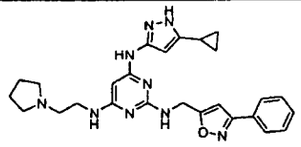
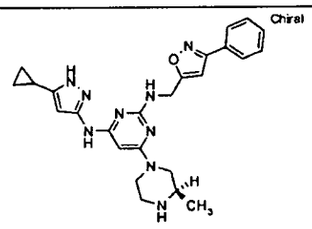
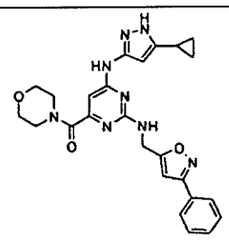
507	
508	
509	
510	
511	
512	

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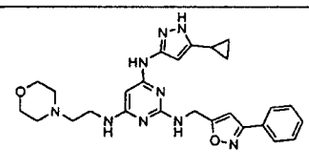
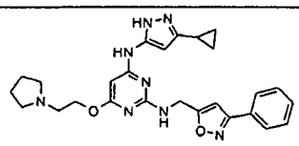
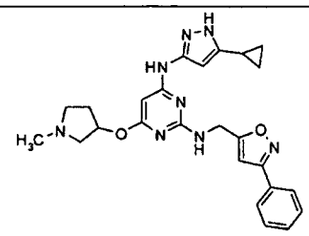
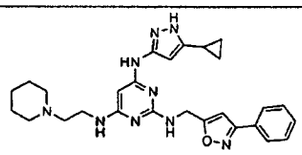
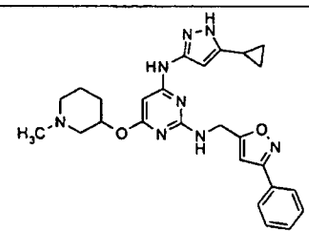
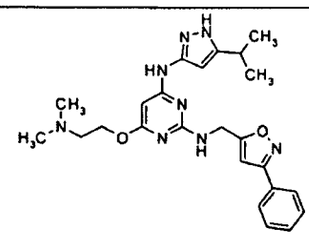
513	
514	
515	
516	
517	
518	

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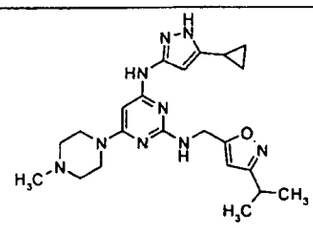
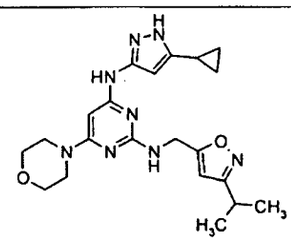
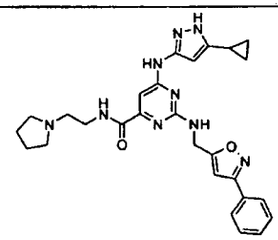
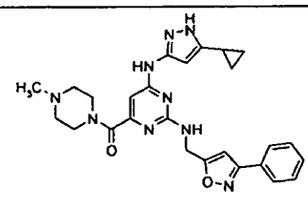
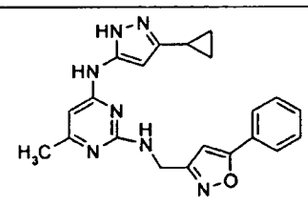
519	
520	
521	
522	
523	

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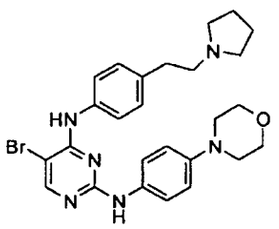
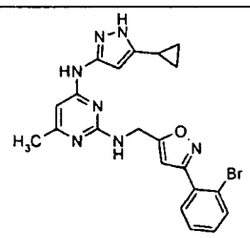
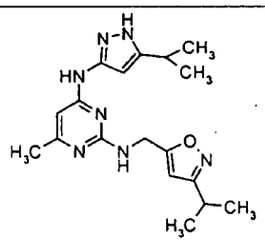
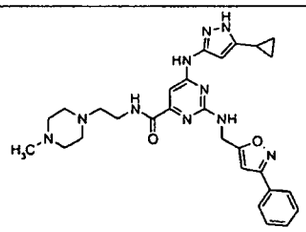
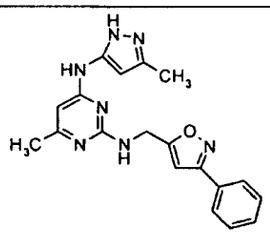
524	
525	
526	
527	
528	

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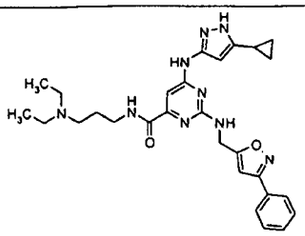
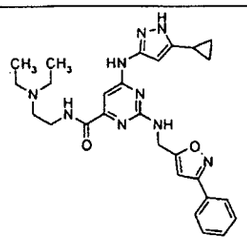
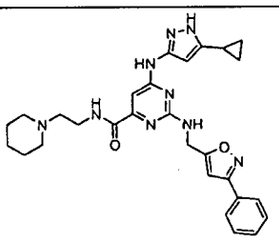
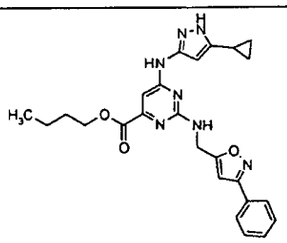
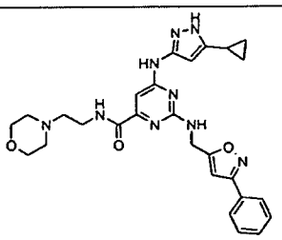
529	
530	
531	
532	
533	

Table 5a	
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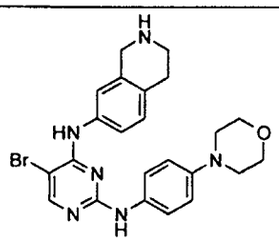
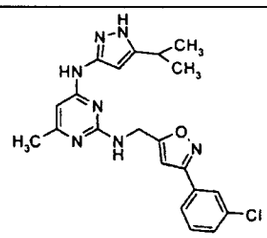
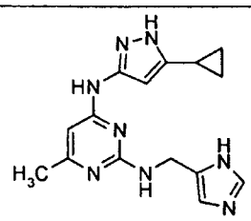
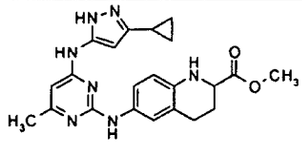
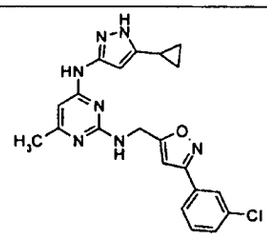
534	
535	
536	
537	
538	

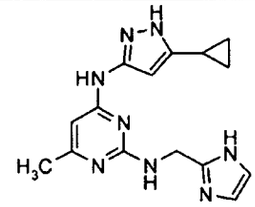
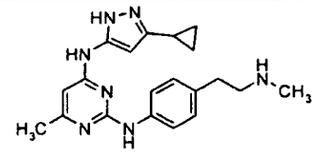
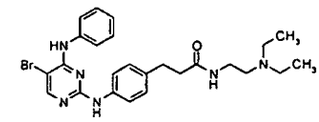
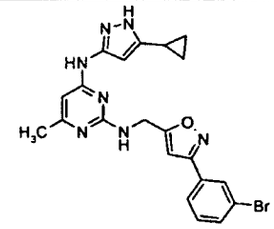
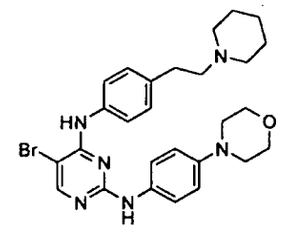
Table 5a	
Entry	Structure
539	
540	
541	
542	
543	

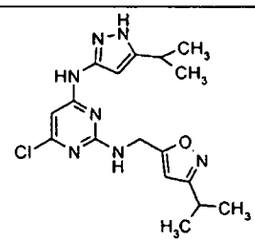
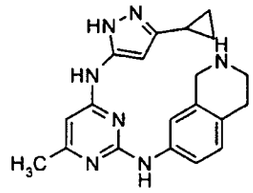
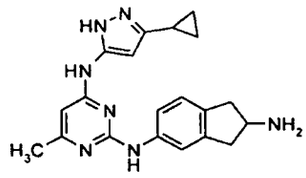
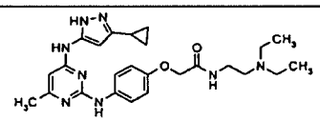
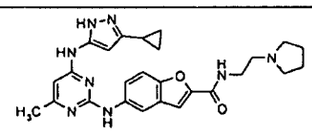
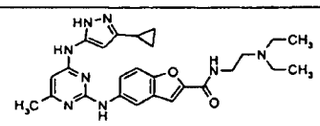
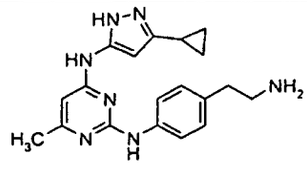
Table 5a	
Entry	Structure
544	
545	
546	
547	
548	
549	
550	

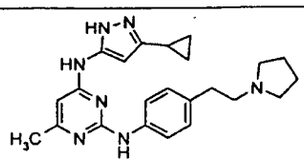
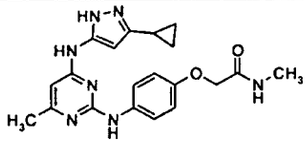
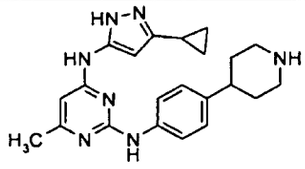
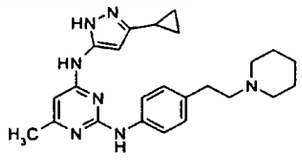
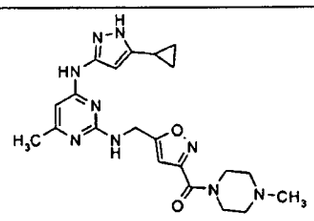
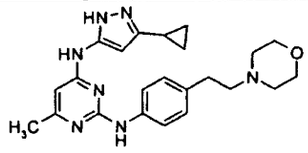
Table 5a	
Entry	Structure
551	
552	
553	
554	
555	
556	

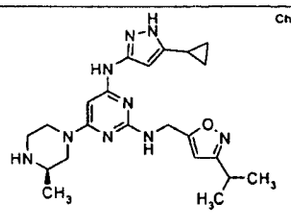
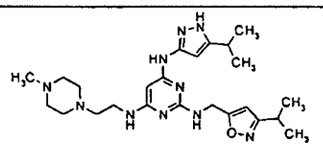
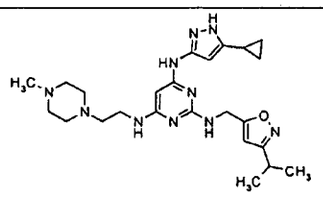
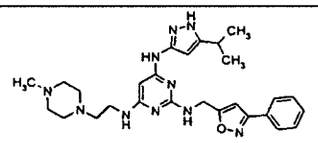
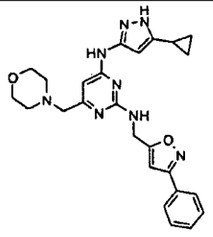
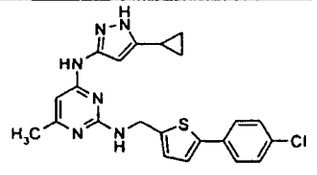
Table 5a	
Entry	Structure
557	 Chiral
558	
559	
560	
561	
562	

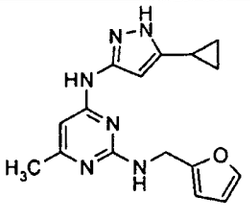
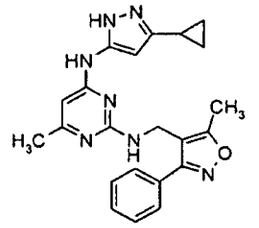
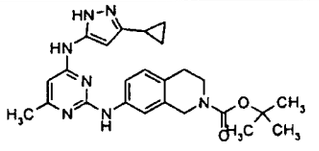
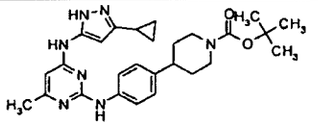
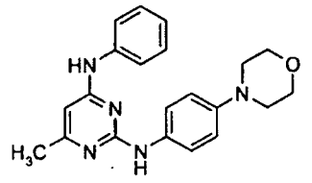
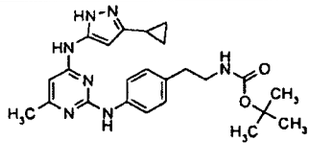
Table 5a	
Entry	Structure
563	
564	
565	
566	
567	
568	

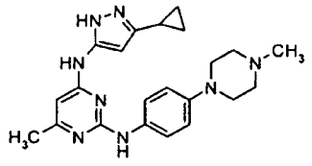
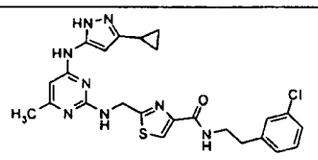
Table 5a	
Entry	Structure
569	
570	

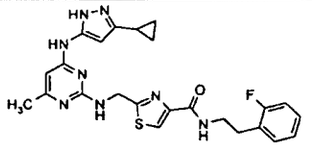
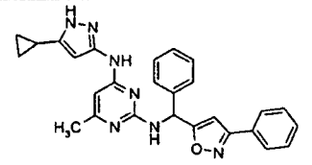
Table 5a	
Entry	Structure
571	
572	

Table 5b.

Additional Representative IGF1R Inhibitors

[00222] The Compounds in Table 5b can be prepared as pharmaceutically acceptable salts, solvates, hydrates, and/or isomers thereof. All such salt, solvate, hydrate, and isomer combinations of the Compounds in Table 5b can be used to practice the invention.

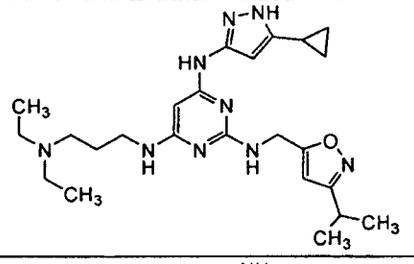
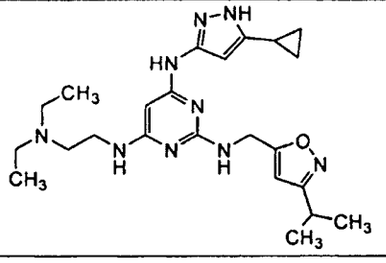
Table 5b		
Entry	Structure	Name
573		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-N^6-[3-(diethylamino)propyl]-N^2-{[3-(1-methylethyl)isoxazol-5-yl]methyl}pyrimidine-2,4,6-triamine
574		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-N^6-[2-(diethylamino)ethyl]-N^2-{[3-(1-methylethyl)isoxazol-5-yl]methyl}pyrimidine-2,4,6-triamine

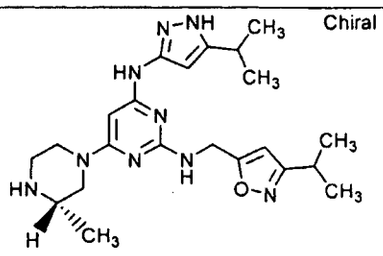
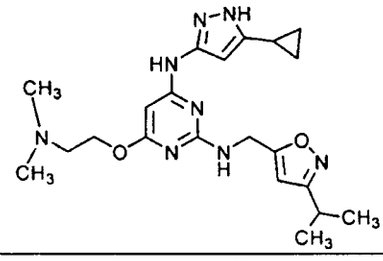
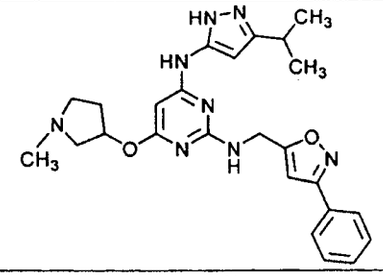
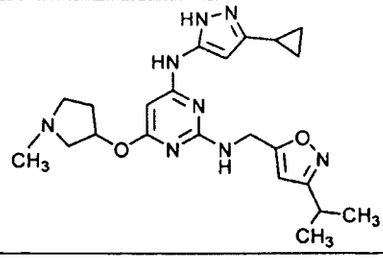
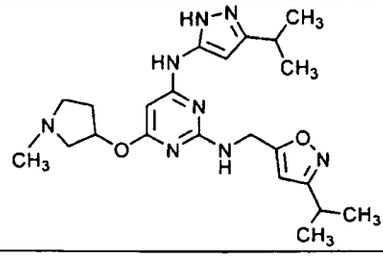
Table 5b		
Entry	**Structure**	**Name**
575	 Chiral	N^2-{[3-(1-methylethyl)isoxazol-5-yl]methyl}-N^4-[5-(1-methylethyl)-1*H*-pyrazol-3-yl]-6-[(3*S*)-3-methylpiperazin-1-yl]pyrimidine-2,4-diamine
576		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-6-{[2-(dimethylamino)ethyl]oxy}-N^2-{[3-(1-methylethyl)isoxazol-5-yl]methyl}pyrimidine-2,4-diamine
577		N^4-[3-(1-methylethyl)-1*H*-pyrazol-5-yl]-6-[(1-methylpyrrolidin-3-yl)oxy]-N^2-[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine
578		N^4-(3-cyclopropyl-1*H*-pyrazol-5-yl)-N^2-{[3-(1-methylethyl)isoxazol-5-yl]methyl}-6-[(1-methylpyrrolidin-3-yl)oxy]pyrimidine-2,4-diamine
579		N^2-{[3-(1-methylethyl)isoxazol-5-yl]methyl}-N^4-[3-(1-methylethyl)-1*H*-pyrazol-5-yl]-6-[(1-methylpyrrolidin-3-yl)oxy]pyrimidine-2,4-diamine

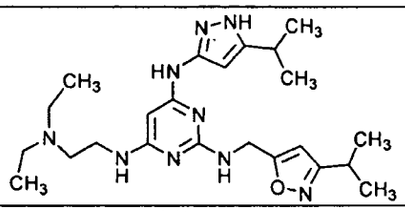
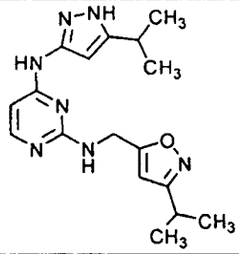
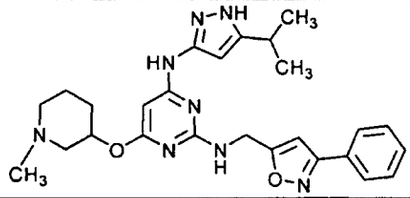
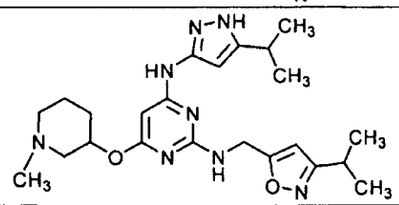
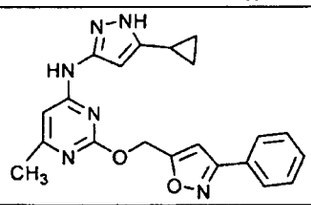
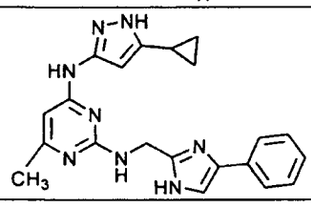
Table 5b		
Entry	**Structure**	**Name**
580		N^4-[2-(diethylamino)ethyl]-N^2-{[3-(1-methylethyl)isoxazol-5-yl]methyl}-N^6-[5-(1-methylethyl)-1H-pyrazol-3-yl]pyrimidine-2,4,6-triamine
581		N^2-{[3-(1-methylethyl)isoxazol-5-yl]methyl}-N^4-[5-(1-methylethyl)-1H-pyrazol-3-yl]pyrimidine-2,4-diamine
582		N^4-[5-(1-methylethyl)-1H-pyrazol-3-yl]-6-[(1-methylpiperidin-3-yl)oxy]-N^2-[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine
583		N^2-{[3-(1-methylethyl)isoxazol-5-yl]methyl}-N^4-[5-(1-methylethyl)-1H-pyrazol-3-yl]-6-[(1-methylpiperidin-3-yl)oxy]pyrimidine-2,4-diamine
584		N-(5-cyclopropyl-1H-pyrazol-3-yl)-6-methyl-2-{[(3-phenylisoxazol-5-yl)methyl]oxy}pyrimidin-4-amine
585		N^4-(5-cyclopropyl-1H-pyrazol-3-yl)-6-methyl-N^2-[(4-phenyl-1H-imidazol-2-yl)methyl]pyrimidine-2,4-diamine

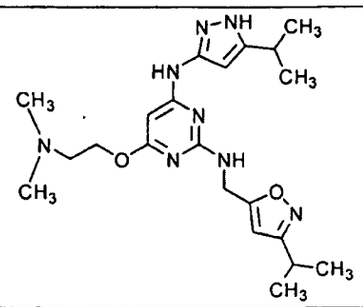
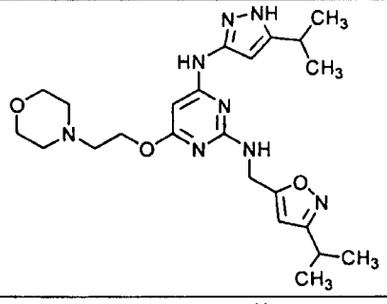
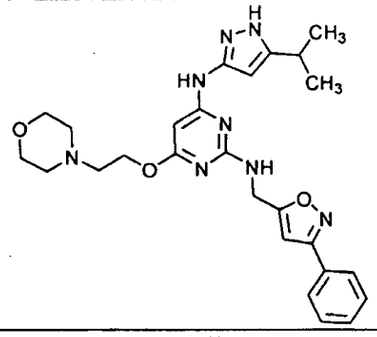
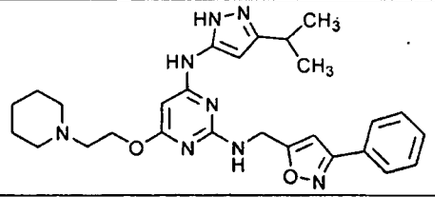
Table 5b		
Entry	**Structure**	**Name**
586		6-{[2-(dimethylamino)ethyl]oxy}-N^2-{[3-(1-methylethyl)isoxazol-5-yl]methyl}-N^4-[5-(1-methylethyl)-1*H*-pyrazol-3-yl]pyrimidine-2,4-diamine
587		N^2-{[3-(1-methylethyl)isoxazol-5-yl]methyl}-N^4-[5-(1-methylethyl)-1*H*-pyrazol-3-yl]-6-[(2-morpholin-4-ylethyl)oxy]pyrimidine-2,4-diamine
588		N^4-[5-(1-methylethyl)-1*H*-pyrazol-3-yl]-6-[(2-morpholin-4-ylethyl)oxy]-N^2-[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine
589		N^4-[3-(1-methylethyl)-1*H*-pyrazol-5-yl]-N^2-[(3-phenylisoxazol-5-yl)methyl]-6-[(2-piperidin-1-ylethyl)oxy]pyrimidine-2,4-diamine

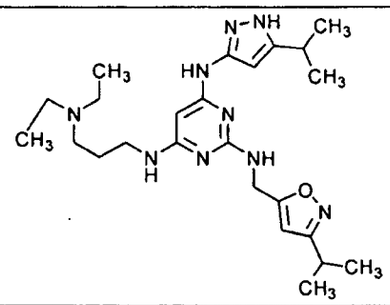
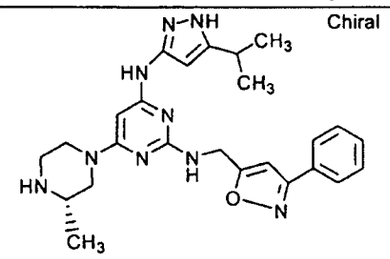
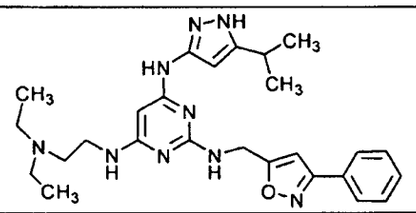
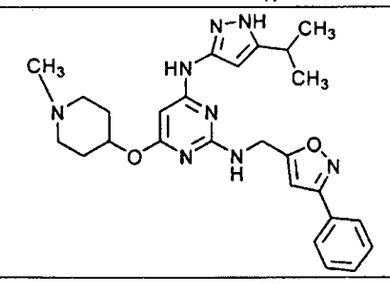
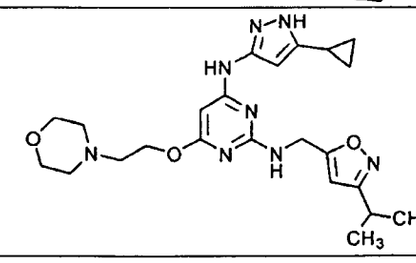
Table 5b		
Entry	**Structure**	**Name**
590		N^4-[3-(diethylamino)propyl]-N^2-{[3-(1-methylethyl)isoxazol-5-yl]methyl}-N^6-[5-(1-methylethyl)-1*H*-pyrazol-3-yl]pyrimidine-2,4,6-triamine
591		N^4-[5-(1-methylethyl)-1*H*-pyrazol-3-yl]-6-[(3*S*)-3-methylpiperazin-1-yl]-N^2-[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine
592		N^4-[2-(diethylamino)ethyl]-N^6-[5-(1-methylethyl)-1*H*-pyrazol-3-yl]-N^2-[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4,6-triamine
593		N^4-[5-(1-methylethyl)-1*H*-pyrazol-3-yl]-6-[(1-methylpiperidin-4-yl)oxy]-N^2-[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine
594		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-N^2-{[3-(1-methylethyl)isoxazol-5-yl]methyl}-6-[(2-morpholin-4-ylethyl)oxy]pyrimidine-2,4-diamine

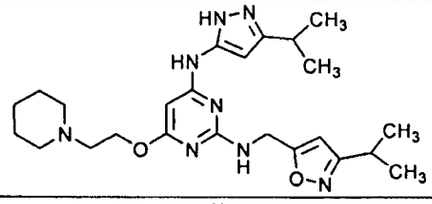
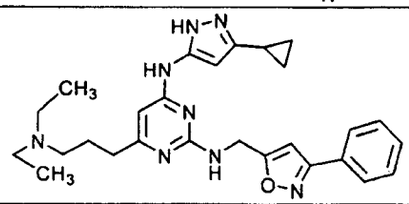
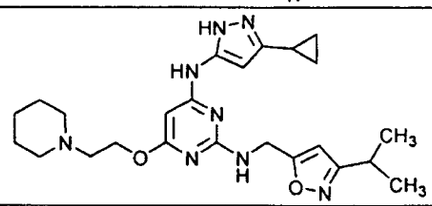
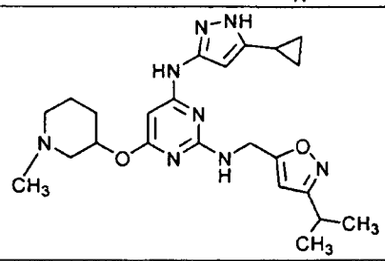
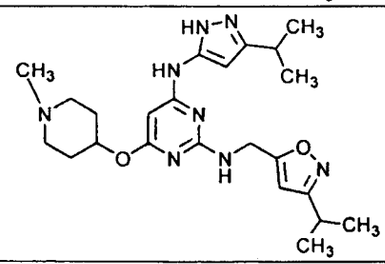
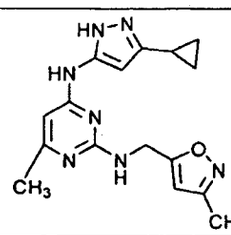
Table 5b		
Entry	**Structure**	**Name**
595		N^2-{[3-(1-methylethyl)isoxazol-5-yl]methyl}-N^4-[3-(1-methylethyl)-1H-pyrazol-5-yl]-6-[(2-piperidin-1-ylethyl)oxy]pyrimidine-2,4-diamine
596		N^4-(3-cyclopropyl-1H-pyrazol-5-yl)-6-[3-(diethylamino)propyl]-N^2-[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine
597		N^4-(3-cyclopropyl-1H-pyrazol-5-yl)-N^2-{[3-(1-methylethyl)isoxazol-5-yl]methyl}-6-[(2-piperidin-1-ylethyl)oxy]pyrimidine-2,4-diamine
598		N^4-(5-cyclopropyl-1H-pyrazol-3-yl)-N^2-{[3-(1-methylethyl)isoxazol-5-yl]methyl}-6-[(1-methylpiperidin-3-yl)oxy]pyrimidine-2,4-diamine
599		N^2-{[3-(1-methylethyl)isoxazol-5-yl]methyl}-N^4-[3-(1-methylethyl)-1H-pyrazol-5-yl]-6-[(1-methylpiperidin-4-yl)oxy]pyrimidine-2,4-diamine
600		N^4-(3-cyclopropyl-1H-pyrazol-5-yl)-6-methyl-N^2-[(3-methylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine

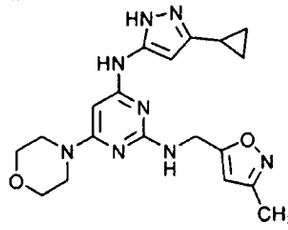
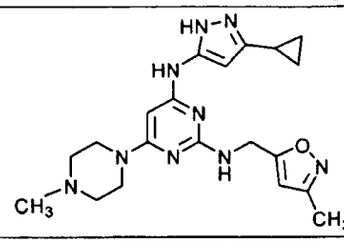
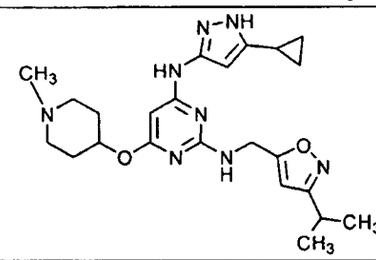
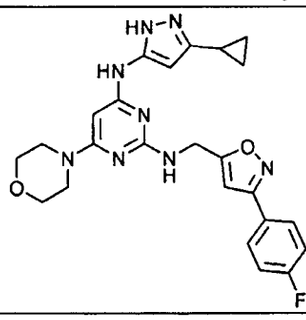
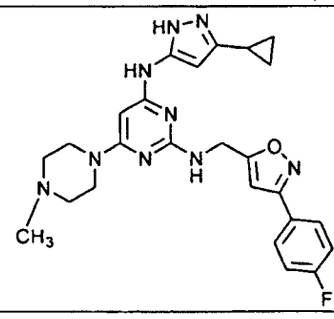
Table 5b		
Entry	**Structure**	**Name**
601		N^4-(3-cyclopropyl-1*H*-pyrazol-5-yl)-N^2-[(3-methylisoxazol-5-yl)methyl]-6-morpholin-4-ylpyrimidine-2,4-diamine
602		N^4-(3-cyclopropyl-1*H*-pyrazol-5-yl)-N^2-[(3-methylisoxazol-5-yl)methyl]-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine
603		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-N^2-{[3-(1-methylethyl)isoxazol-5-yl]methyl}-6-[(1-methylpiperidin-4-yl)oxy]pyrimidine-2,4-diamine
604		N^4-(3-cyclopropyl-1*H*-pyrazol-5-yl)-N^2-{[3-(4-fluorophenyl)isoxazol-5-yl]methyl}-6-morpholin-4-ylpyrimidine-2,4-diamine
605		N^4-(3-cyclopropyl-1*H*-pyrazol-5-yl)-N^2-{[3-(4-fluorophenyl)isoxazol-5-yl]methyl}-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine

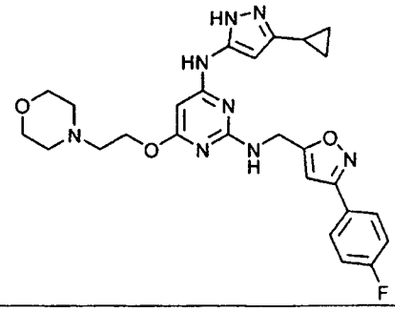
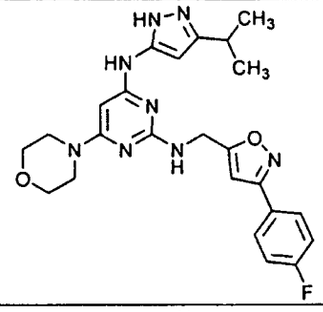
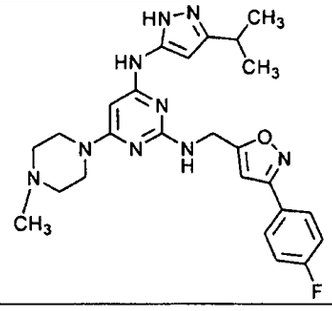
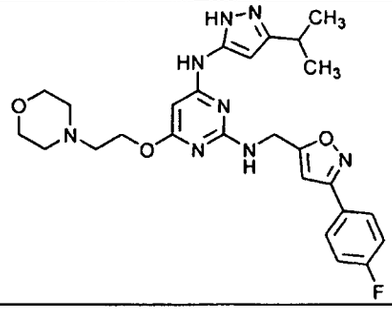
Table 5b		
Entry	**Structure**	**Name**
606		N^4-(3-cyclopropyl-1*H*-pyrazol-5-yl)-N^2-{[3-(4-fluorophenyl)isoxazol-5-yl]methyl}-6-[(2-morpholin-4-ylethyl)oxy]pyrimidine-2,4-diamine
607		N^2-{[3-(4-fluorophenyl)isoxazol-5-yl]methyl}-N^4-[3-(1-methylethyl)-1*H*-pyrazol-5-yl]-6-morpholin-4-ylpyrimidine-2,4-diamine
608		N^2-{[3-(4-fluorophenyl)isoxazol-5-yl]methyl}-N^4-[3-(1-methylethyl)-1*H*-pyrazol-5-yl]-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine
609		N^2-{[3-(4-fluorophenyl)isoxazol-5-yl]methyl}-N^4-[3-(1-methylethyl)-1*H*-pyrazol-5-yl]-6-[(2-morpholin-4-ylethyl)oxy]pyrimidine-2,4-diamine

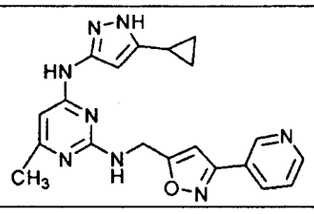
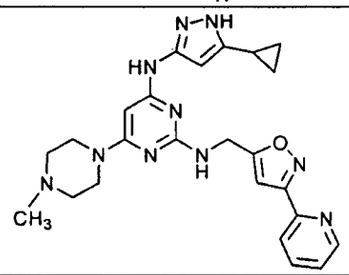
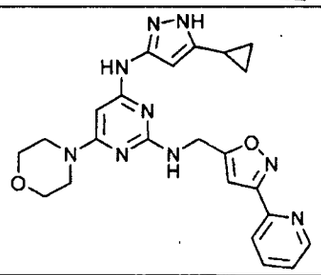
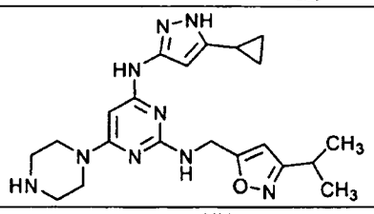
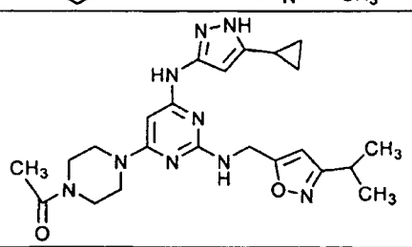
Table 5b		
Entry	**Structure**	**Name**
610		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-6-methyl-N^2-[(3-pyridin-3-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine
611		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-6-(4-methylpiperazin-1-yl)-N^2-[(3-pyridin-2-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine
612		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-6-morpholin-4-yl-N^2-[(3-pyridin-2-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine
613		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-N^2-{[3-(1-methylethyl)isoxazol-5-yl]methyl}-6-piperazin-1-ylpyrimidine-2,4-diamine
614		6-(4-acetylpiperazin-1-yl)-N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-N^2-{[3-(1-methylethyl)isoxazol-5-yl]methyl}pyrimidine-2,4-diamine

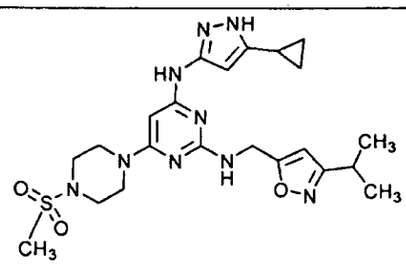
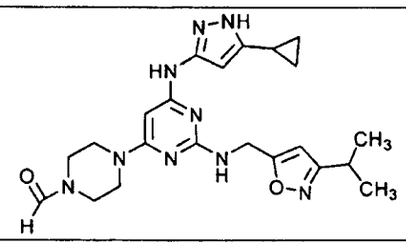
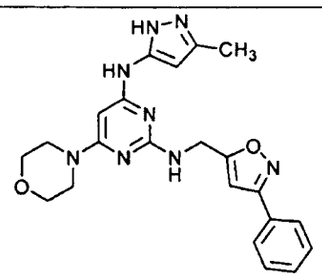
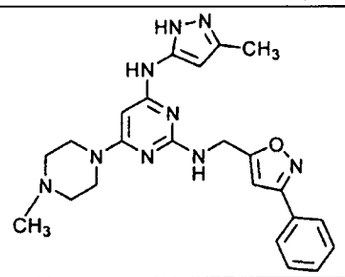
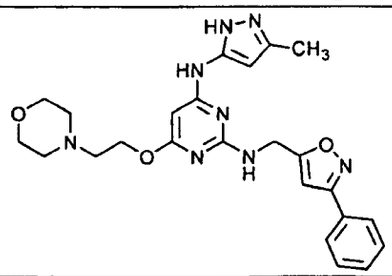
Table 5b		
Entry	**Structure**	**Name**
615		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-N^2-{[3-(1-methylethyl)isoxazol-5-yl]methyl}-6-[4-(methylsulfonyl)piperazin-1-yl]pyrimidine-2,4-diamine
616		4-{6-[(5-cyclopropyl-1*H*-pyrazol-3-yl)amino]-2-({[3-(1-methylethyl)isoxazol-5-yl]methyl}amino)pyrimidin-4-yl}piperazine-1-carbaldehyde
617		N^4-(3-methyl-1*H*-pyrazol-5-yl)-6-morpholin-4-yl-N^2-[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine
618		6-(4-methylpiperazin-1-yl)-N^4-(3-methyl-1*H*-pyrazol-5-yl)-N^2-[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine
619		N^4-(3-methyl-1*H*-pyrazol-5-yl)-6-[(2-morpholin-4-ylethyl)oxy]-N^2-[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine

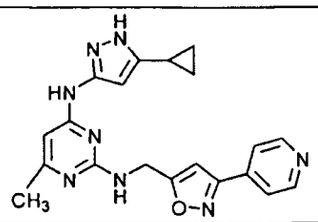
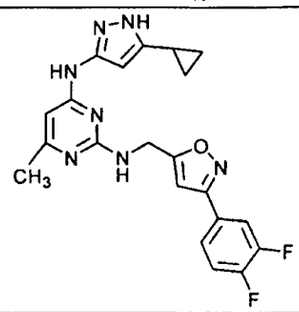
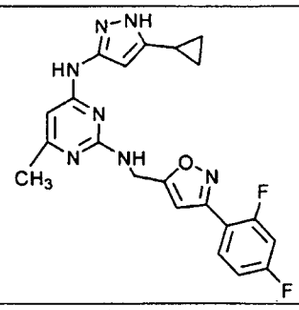
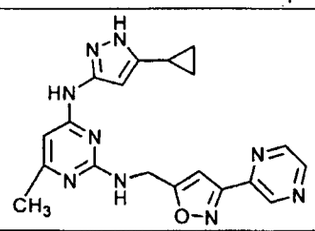
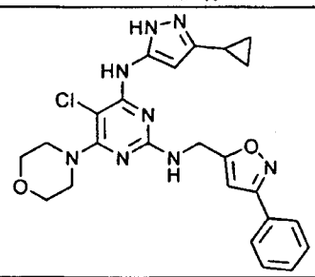
Table 5b		
Entry	**Structure**	**Name**
620		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-6-methyl-N^2-[(3-pyridin-4-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine
621		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-N^2-{[3-(3,4-difluorophenyl)isoxazol-5-yl]methyl}-6-methylpyrimidine-2,4-diamine
622		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-N^2-{[3-(2,4-difluorophenyl)isoxazol-5-yl]methyl}-6-methylpyrimidine-2,4-diamine
623		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-6-methyl-N^2-[(3-pyrazin-2-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine
624		5-chloro-N^4-(3-cyclopropyl-1*H*-pyrazol-5-yl)-6-morpholin-4-yl-N^2-[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine

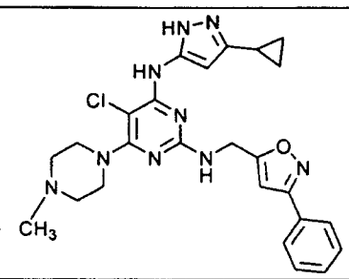
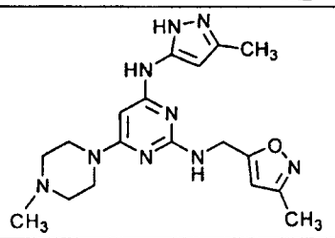
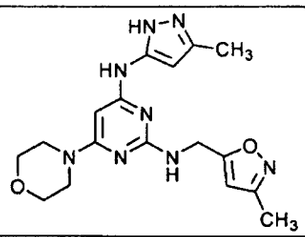
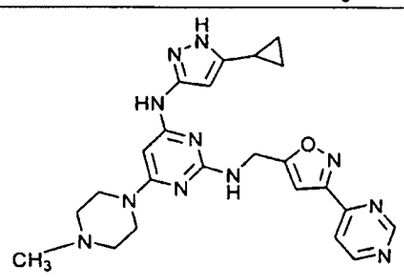
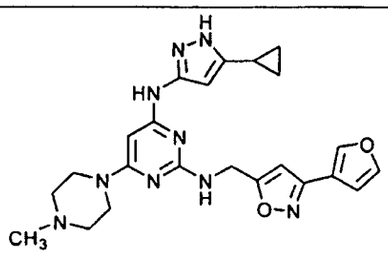
Table 5b		
Entry	**Structure**	**Name**
625		5-chloro-N^4-(3-cyclopropyl-1*H*-pyrazol-5-yl)-6-(4-methylpiperazin-1-yl)-N^2-[(3-phenylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine
626		N^2-[(3-methylisoxazol-5-yl)methyl]-6-(4-methylpiperazin-1-yl)-N^4-(3-methyl-1*H*-pyrazol-5-yl)pyrimidine-2,4-diamine
627		N^2-[(3-methylisoxazol-5-yl)methyl]-N^4-(3-methyl-1*H*-pyrazol-5-yl)-6-morpholin-4-ylpyrimidine-2,4-diamine
628		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-6-(4-methylpiperazin-1-yl)-N^2-[(3-pyrimidin-4-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine
629		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-N^2-[(3-furan-3-ylisoxazol-5-yl)methyl]-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine

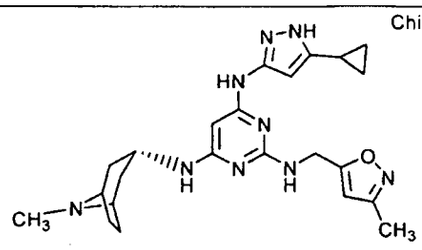
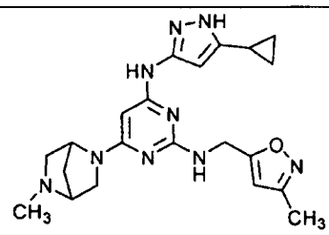
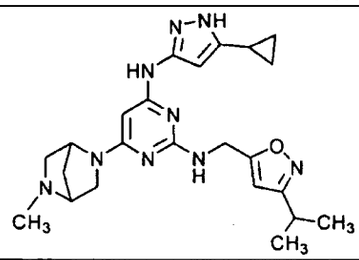
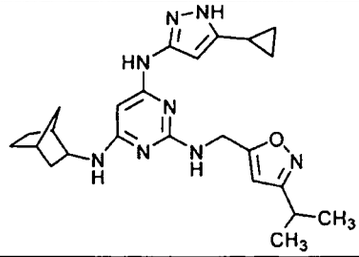
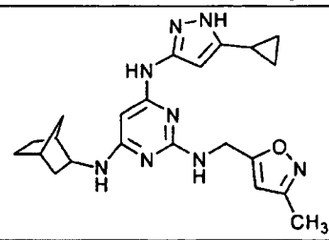
Table 5b		
Entry	**Structure**	**Name**
630	 Chiral	N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-N^6-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-N^2-[(3-methylisoxazol-5-yl)methyl]pyrimidine-2,4,6-triamine
631		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-6-(5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl)-N^2-[(3-methylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine
632		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-6-(5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl)-N^2-{[3-(1-methylethyl)isoxazol-5-yl]methyl}pyrimidine-2,4-diamine
633		N^4-bicyclo[2.2.1]hept-2-yl-N^6-(5-cyclopropyl-1*H*-pyrazol-3-yl)-N^2-{[3-(1-methylethyl)isoxazol-5-yl]methyl}pyrimidine-2,4,6-triamine
634		N^4-bicyclo[2.2.1]hept-2-yl-N^6-(5-cyclopropyl-1*H*-pyrazol-3-yl)-N^2-[(3-methylisoxazol-5-yl)methyl]pyrimidine-2,4,6-triamine

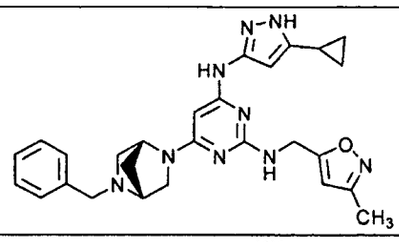
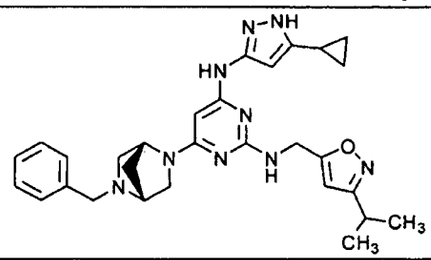
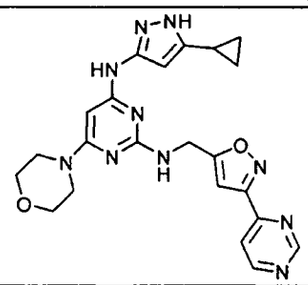
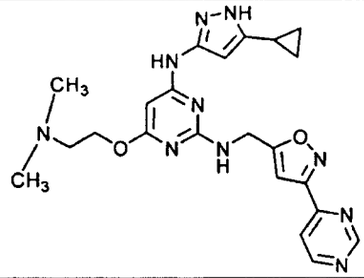
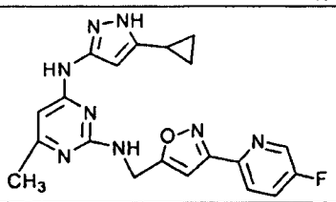
Table 5b		
Entry	**Structure**	**Name**
635		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-N^2-[(3-methylisoxazol-5-yl)methyl]-6-[(1*R*,4*R*)-5-(phenylmethyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]pyrimidine-2,4-diamine
636		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-N^2-{[3-(1-methylethyl)isoxazol-5-yl]methyl}-6-[(1*R*,4*R*)-5-(phenylmethyl)-2,5-diazabicyclo[2.2.1]hept-2-yl]pyrimidine-2,4-diamine
637		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-6-morpholin-4-yl-N^2-[(3-pyrimidin-4-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine
638		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-6-{[2-(dimethylamino)ethyl]oxy}-N^2-[(3-pyrimidin-4-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine
639		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-N^2-{[3-(5-fluoropyridin-2-yl)isoxazol-5-yl]methyl}-6-methylpyrimidine-2,4-diamine

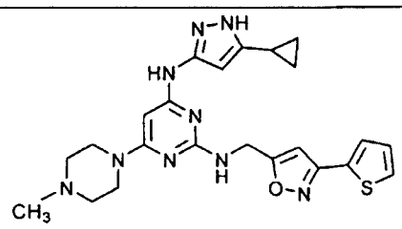
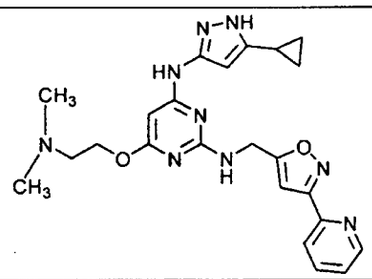
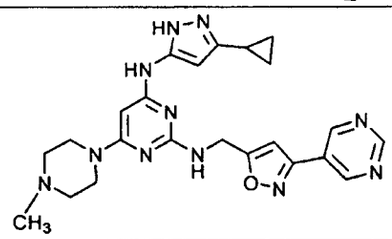
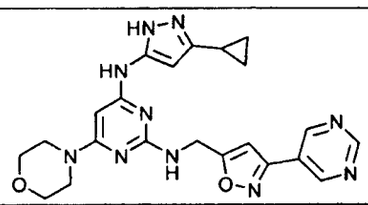
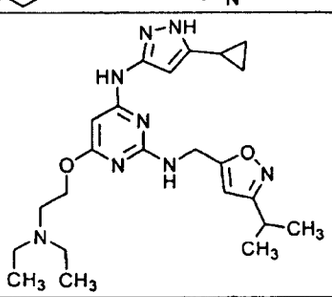
Table 5b		
Entry	**Structure**	**Name**
640		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-6-(4-methylpiperazin-1-yl)-N^2-{[3-(2-thienyl)isoxazol-5-yl]methyl}pyrimidine-2,4-diamine
641		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-6-{[2-(dimethylamino)ethyl]oxy}-N^2-[(3-pyridin-2-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine
642		N^4-(3-cyclopropyl-1*H*-pyrazol-5-yl)-6-(4-methylpiperazin-1-yl)-N^2-[(3-pyrimidin-5-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine
643		N^4-(3-cyclopropyl-1*H*-pyrazol-5-yl)-6-morpholin-4-yl-N^2-[(3-pyrimidin-5-ylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine
644		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-6-{[2-(diethylamino)ethyl]oxy}-N^2-{[3-(1-methylethyl)isoxazol-5-yl]methyl}pyrimidine-2,4-diamine

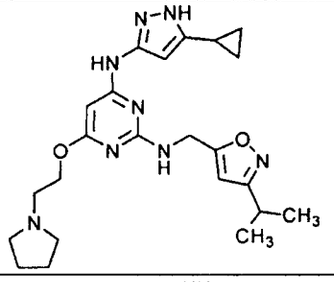
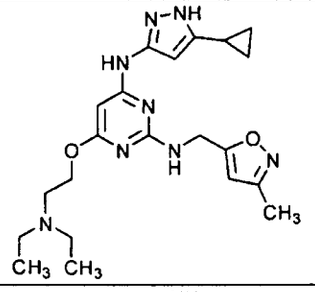
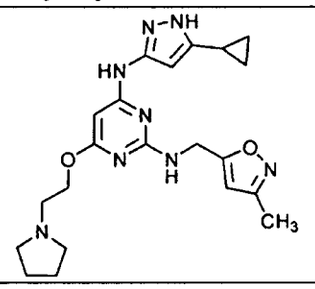
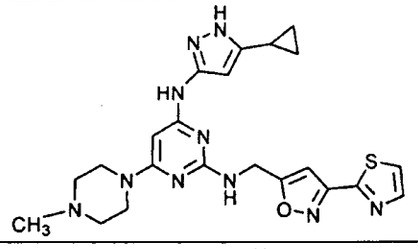
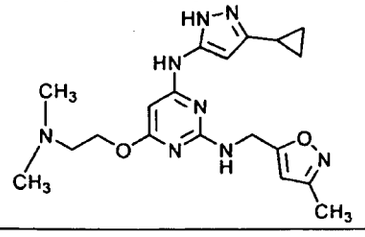
Table 5b		
Entry	**Structure**	**Name**
645		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-N^2-{[3-(1-methylethyl)isoxazol-5-yl]methyl}-6-[(2-pyrrolidin-1-ylethyl)oxy]pyrimidine-2,4-diamine
646		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-6-{[2-(diethylamino)ethyl]oxy}-N^2-[(3-methylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine
647		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-N^2-[(3-methylisoxazol-5-yl)methyl]-6-[(2-pyrrolidin-1-ylethyl)oxy]pyrimidine-2,4-diamine
648		N^4-(5-cyclopropyl-1*H*-pyrazol-3-yl)-6-(4-methylpiperazin-1-yl)-N^2-{[3-(1,3-thiazol-2-yl)isoxazol-5-yl]methyl}pyrimidine-2,4-diamine
649		N^4-(3-cyclopropyl-1*H*-pyrazol-5-yl)-6-[2-(dimethylamino)ethoxy]-N^2-[(3-methylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine

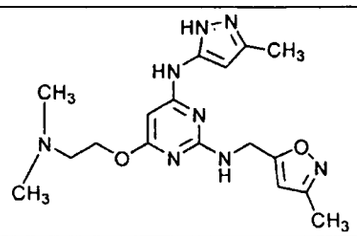
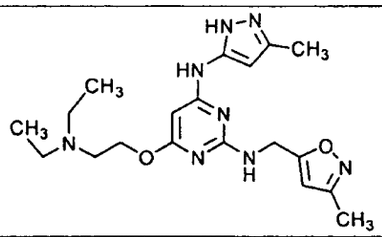
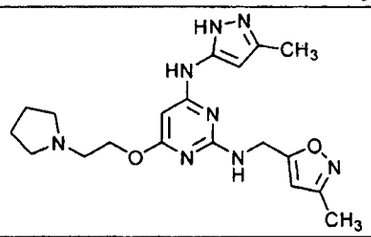
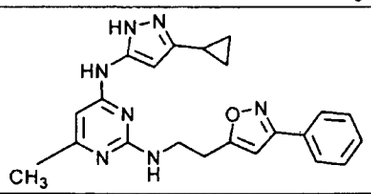
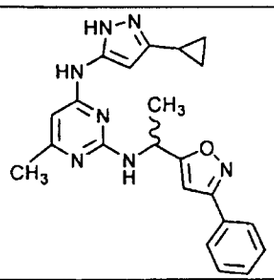
Table 5b		
Entry	**Structure**	**Name**
650		6-{[2-(dimethylamino)ethyl]oxy}-N^2-[(3-methylisoxazol-5-yl)methyl]-N^4-(3-methyl-1*H*-pyrazol-5-yl)pyrimidine-2,4-diamine
651		6-{[2-(diethylamino)ethyl]oxy}-N^2-[(3-methylisoxazol-5-yl)methyl]-N^4-(3-methyl-1*H*-pyrazol-5-yl)pyrimidine-2,4-diamine
652		N^2-[(3-methylisoxazol-5-yl)methyl]-N^4-(3-methyl-1*H*-pyrazol-5-yl)-6-[(2-pyrrolidin-1-ylethyl)oxy]pyrimidine-2,4-diamine
653		N^4-(3-cyclopropyl-1*H*-pyrazol-5-yl)-6-methyl-N^2-[2-(3-phenylisoxazol-5-yl)ethyl]pyrimidine-2,4-diamine
654		N^4-(3-cyclopropyl-1*H*-pyrazol-5-yl)-6-methyl-N^2-[1-(3-phenylisoxazol-5-yl)ethyl]pyrimidine-2,4-diamine

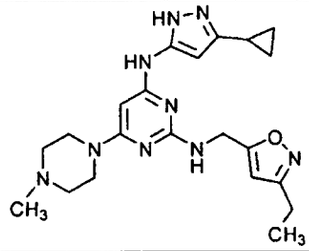
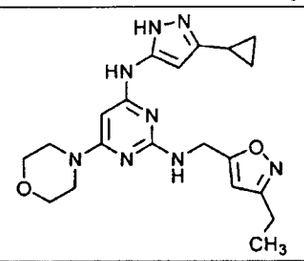
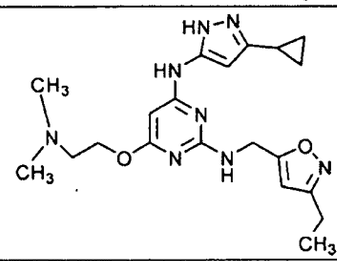
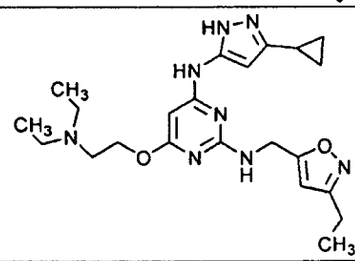
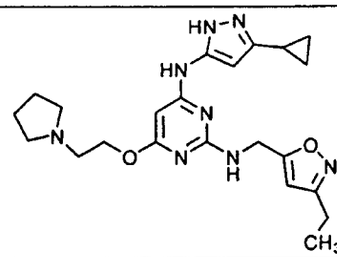
Table 5b		
Entry	**Structure**	**Name**
655		N^4-(3-cyclopropyl-1*H*-pyrazol-5-yl)-N^2-[(3-ethylisoxazol-5-yl)methyl]-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine
656		N^4-(3-cyclopropyl-1*H*-pyrazol-5-yl)-N^2-[(3-ethylisoxazol-5-yl)methyl]-6-morpholin-4-ylpyrimidine-2,4-diamine
657		N^4-(3-cyclopropyl-1*H*-pyrazol-5-yl)-6-{[2-(dimethylamino)ethyl]oxy}-N^2-[(3-ethylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine
658		N^4-(3-cyclopropyl-1*H*-pyrazol-5-yl)-6-{[2-(diethylamino)ethyl]oxy}-N^2-[(3-ethylisoxazol-5-yl)methyl]pyrimidine-2,4-diamine
659		N^4-(3-cyclopropyl-1*H*-pyrazol-5-yl)-N^2-[(3-ethylisoxazol-5-yl)methyl]-6-[(2-pyrrolidin-1-ylethyl)oxy]pyrimidine-2,4-diamine

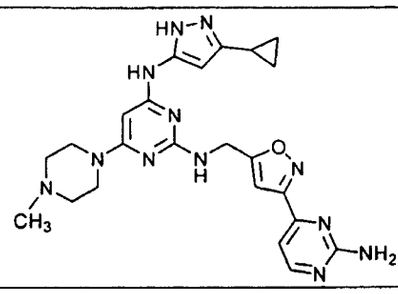
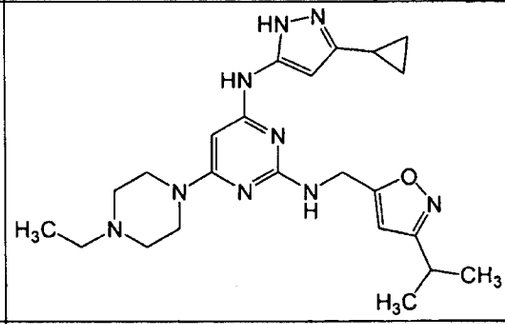
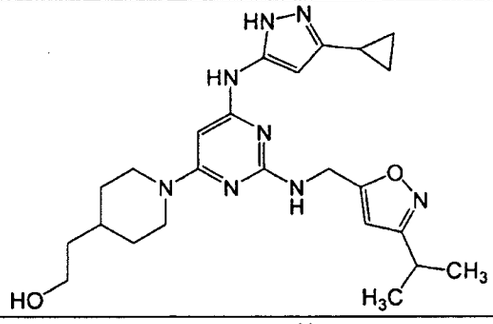
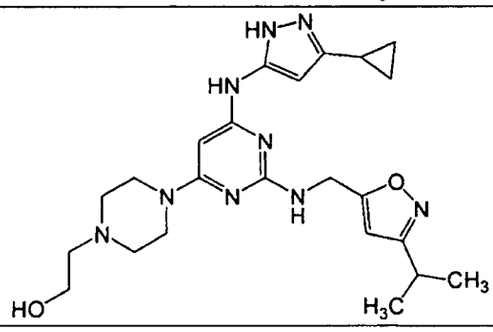
Table 5b		
Entry	**Structure**	**Name**
660		N^2-{[3-(2-aminopyrimidin-4-yl)isoxazol-5-yl]methyl}-N^4-(3-cyclopropyl-1*H*-pyrazol-5-yl)-6-(4-methylpiperazin-1-yl)pyrimidine-2,4-diamine
661		N^4-(3-cyclopropyl-1*H*-pyrazol-5-yl)-6-(4-ethylpiperazin-1-yl)-N^2-{[3-(1-methylethyl)isoxazol-5-yl]methyl}pyrimidine-2,4-diamine
662		2-(1-{6-[(3-cyclopropyl-1*H*-pyrazol-5-yl)amino]-2-({[3-(1-methylethyl)isoxazol-5-yl]methyl}amino)pyrimidin-4-yl}piperidin-4-yl)ethanol
663		2-(4-{6-[(3-cyclopropyl-1*H*-pyrazol-5-yl)amino]-2-({[3-(1-methylethyl)isoxazol-5-yl]methyl}amino)pyrimidin-4-yl}piperazin-1-yl)ethanol

Table 6.

Representative Raf Inhibitors

[00223] The Compounds in Table 6 can be prepared as pharmaceutically acceptable salts, solvates, hydrates, and/or isomers thereof. All such salt, solvate, hydrate, and isomer combinations of the Compounds in Table 6 can be used to practice the invention.

Table 6

Entry	Name
1	6-(2-butyl-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)-2*H*-1,4-benzoxazin-3(4*H*)-one
2	6-[1-hydroxy-3-oxo-2-(2-phenylethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one
3	6-(1-hydroxy-2-{[4-(methyloxy)phenyl]methyl}-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)-2*H*-1,4-benzoxazin-3(4*H*)-one
4	6-(1-hydroxy-2-{[3-(methyloxy)phenyl]methyl}-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)-2*H*-1,4-benzoxazin-3(4*H*)-one
5	6-{2-[(4-fluorophenyl)methyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-2*H*-1,4-benzoxazin-3(4*H*)-one
6	6-(1-hydroxy-3-oxo-2-phenyl-2,3-dihydro-1*H*-isoindol-1-yl)-2*H*-1,4-benzoxazin-3(4*H*)-one
7	6-{2-[(3-bromophenyl)methyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-2*H*-1,4-benzoxazin-3(4*H*)-one
8	6-{2-[(4-bromophenyl)methyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-2*H*-1,4-benzoxazin-3(4*H*)-one
9	6-[1-hydroxy-3-oxo-2-(3-phenylpropyl)-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one
10	6-{2-[(3,4-dichlorophenyl)methyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-2*H*-1,4-benzoxazin-3(4*H*)-one
11	6-{1-hydroxy-2-[(4-methylphenyl)methyl]-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-2*H*-1,4-benzoxazin-3(4*H*)-one
12	6-{2-[(4-chlorophenyl)methyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-2*H*-1,4-benzoxazin-3(4*H*)-one
13	6-[1-hydroxy-2-(1-methylethyl)-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one
14	methyl {5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
15	6-{2-[(3,4-dimethylphenyl)methyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-2*H*-1,4-benzoxazin-3(4*H*)-one
16	6-(2-{[4-chloro-3-(trifluoromethyl)phenyl]methyl}-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)-2*H*-1,4-benzoxazin-3(4*H*)-one
17	6-(2-{[4-(dimethylamino)phenyl]methyl}-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)-2*H*-1,4-benzoxazin-3(4*H*)-one
18	6-[2-(3-chlorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one

Table 6	
Entry	**Name**
19	6-[2-(4-chlorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one
20	6-[2-(3,4-dichlorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one
21	6-[1-hydroxy-2-(4-methylphenyl)-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one
22	3-(2-{[3,5-bis(methyloxy)phenyl]amino}-1*H*-benzimidazol-5-yl)-3-(methyloxy)-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-one
23	3-(2-{[3,5-bis(methyloxy)phenyl]amino}-1*H*-benzimidazol-5-yl)-2-(1-methylethyl)-3-(methyloxy)-2,3-dihydro-1*H*-isoindol-1-one
24	3-(2-{[3,5-bis(methyloxy)phenyl]amino}-1*H*-benzimidazol-5-yl)-3-hydroxy-2-phenyl-2,3-dihydro-1*H*-isoindol-1-one
25	3-(2-{[3,5-bis(methyloxy)phenyl]amino}-1*H*-benzimidazol-5-yl)-3-hydroxy-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-one
26	methyl {5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1-methyl-1*H*-benzimidazol-2-yl}carbamate
27	3-(1*H*-benzimidazol-5-yl)-3-hydroxy-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-one
28	5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-*N*-methyl-1*H*-benzimidazole-2-carboxamide
29	3-hydroxy-3-(2-methyl-1*H*-benzimidazol-5-yl)-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-one
30	7-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-3,4-dihydroquinoxalin-2(1*H*)-one
31	7-[2-(3-chlorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-3,4-dihydroquinoxalin-2(1*H*)-one
32	1,1-dimethylethyl 4-{[1-hydroxy-3-oxo-1-(3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl)-1,3-dihydro-2*H*-isoindol-2-yl]methyl}piperidine-1-carboxylate
33	6-(1-hydroxy-2-{[2-(methyloxy)phenyl]methyl}-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)-2*H*-1,4-benzoxazin-3(4*H*)-one
34	6-{2-[(3-chlorophenyl)methyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-2*H*-1,4-benzoxazin-3(4*H*)-one
35	6-{2-[(2-chlorophenyl)methyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-2*H*-1,4-benzoxazin-3(4*H*)-one
36	6-{2-[(3-fluorophenyl)methyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-2*H*-1,4-benzoxazin-3(4*H*)-one
37	6-{2-[(2-bromophenyl)methyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-2*H*-1,4-benzoxazin-3(4*H*)-one
38	6-{2-[(2-fluorophenyl)methyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-2*H*-1,4-benzoxazin-3(4*H*)-one
39	6-[2-(3-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one

Table 6	
Entry	**Name**
40	6-[1-hydroxy-2-(3-iodophenyl)-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one
41	6-[2-(3-bromophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one
42	6-[1-hydroxy-2-(3-nitrophenyl)-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one
43	6-{1-hydroxy-2-[3-(methyloxy)phenyl]-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-2*H*-1,4-benzoxazin-3(4*H*)-one
44	6-[1-hydroxy-2-(3-methylphenyl)-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one
45	3-hydroxy-3-(1*H*-indol-5-yl)-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-one
46	methyl [6-(1-hydroxy-3-oxo-2-phenyl-2,3-dihydro-1*H*-isoindol-1-yl)-1*H*-benzimidazol-2-yl]carbamate
47	6-[2-(2-aminophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one
48	6-{[2-(3-phenyl-1,2,4-oxadiazol-5-yl)phenyl]carbonyl}-2*H*-1,4-benzoxazin-3(4*H*)-one
49	6-{[2-(1*H*-benzimidazol-2-yl)phenyl]carbonyl}-2*H*-1,4-benzoxazin-3(4*H*)-one
50	6-(1-hydroxy-3-oxo-2-{[2-(trifluoromethyl)phenyl]methyl}-2,3-dihydro-1*H*-isoindol-1-yl)-2*H*-1,4-benzoxazin-3(4*H*)-one
51	6-{2-[(5-bromo-2-fluorophenyl)methyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-2*H*-1,4-benzoxazin-3(4*H*)-one
52	6-{1-hydroxy-2-[(3-nitrophenyl)methyl]-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-2*H*-1,4-benzoxazin-3(4*H*)-one
53	6-(1-hydroxy-3-oxo-2-{[3-(trifluoromethyl)phenyl]methyl}-2,3-dihydro-1*H*-isoindol-1-yl)-2*H*-1,4-benzoxazin-3(4*H*)-one
54	6-(2-{[2,3-bis(methyloxy)phenyl]methyl}-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)-2*H*-1,4-benzoxazin-3(4*H*)-one
55	6-{1-hydroxy-2-[(3-iodophenyl)methyl]-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-2*H*-1,4-benzoxazin-3(4*H*)-one
56	6-[1-hydroxy-3-oxo-2-({3-[(trifluoromethyl)oxy]phenyl}methyl)-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one
57	6-(1-hydroxy-2-{[2-(methylthio)phenyl]methyl}-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)-2*H*-1,4-benzoxazin-3(4*H*)-one
58	6-[2-(3,4-difluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one
59	6-{1-hydroxy-2-[3-(1-methylethyl)phenyl]-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-2*H*-1,4-benzoxazin-3(4*H*)-one
60	6-(1-hydroxy-3-oxo-2-{3-[(trifluoromethyl)oxy]phenyl}-2,3-dihydro-1*H*-isoindol-1-yl)-2*H*-1,4-benzoxazin-3(4*H*)-one
61	6-{1-hydroxy-3-oxo-2-[3-(trifluoromethyl)phenyl]-2,3-dihydro-1*H*-isoindol-1-yl}-2*H*-1,4-benzoxazin-3(4*H*)-one

Table 6	
Entry	**Name**
62	3-[1-hydroxy-3-oxo-1-(3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl)-1,3-dihydro-2*H*-isoindol-2-yl]benzenesulfonamide
63	6-{2-[5-chloro-2-(methyloxy)phenyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-2*H*-1,4-benzoxazin-3(4*H*)-one
64	6-{2-[4-fluoro-3-(trifluoromethyl)phenyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-2*H*-1,4-benzoxazin-3(4*H*)-one
65	3-hydroxy-3-(1*H*-indol-6-yl)-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-one
66	6-[2-(3-fluoro-5-iodophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one
67	6-[2-(3-aminophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one
68	6-[2-(3,5-difluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one
69	6-{1-hydroxy-2-[3-(methylsulfonyl)phenyl]-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-2*H*-1,4-benzoxazin-3(4*H*)-one
70	ethyl 3-[1-hydroxy-3-oxo-1-(3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl)-1,3-dihydro-2*H*-isoindol-2-yl]benzoate
71	3-[1-hydroxy-3-oxo-1-(3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl)-1,3-dihydro-2*H*-isoindol-2-yl]benzonitrile
72	6-[2-(2-chlorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one
73	6-[2-(3-amino-5-chlorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one
74	6-[2-(5-chloro-2-methylphenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one
75	6-[2-(3-chloro-2-methylphenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one
76	6-[2-(3-ethylphenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one
77	6-[2-(3-ethynylphenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one
78	6-[1-hydroxy-2-(3-hydroxyphenyl)-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one
79	6-{1-hydroxy-3-oxo-2-[3-(phenyloxy)phenyl]-2,3-dihydro-1*H*-isoindol-1-yl}-2*H*-1,4-benzoxazin-3(4*H*)-one
80	6-(1-hydroxy-3-oxo-2-{3-[(phenylmethyl)oxy]phenyl}-2,3-dihydro-1*H*-isoindol-1-yl)-2*H*-1,4-benzoxazin-3(4*H*)-one
81	3-[1-hydroxy-3-oxo-1-(3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl)-1,3-dihydro-2*H*-isoindol-2-yl]benzamide
82	6-{1-hydroxy-2-[3-(hydroxymethyl)phenyl]-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-2*H*-1,4-benzoxazin-3(4*H*)-one
83	6-[2-(2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one

Table 6	
Entry	**Name**
84	3-hydroxy-3-[2-(methylamino)-1*H*-benzimidazol-5-yl]-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-one
85	6-(2-biphenyl-3-yl-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)-2*H*-1,4-benzoxazin-3(4*H*)-one
86	6-(2-{3-[(dimethylamino)methyl]phenyl}-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)-2*H*-1,4-benzoxazin-3(4*H*)-one
87	6-[2-(3,5-dichlorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one
88	6-(1-hydroxy-3-oxo-2-piperidin-4-yl-2,3-dihydro-1*H*-isoindol-1-yl)-2*H*-1,4-benzoxazin-3(4*H*)-one
89	6-[2-(3-{[2-(dimethylamino)ethyl]oxy}phenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one
90	6-[1-hydroxy-2-(2-methylphenyl)-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-2*H*-1,4-benzoxazin-3(4*H*)-one
91	*N*-methyl-2-[(3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl)carbonyl]-*N*-phenylbenzamide
92	methyl {5-[1-(ethyloxy)-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
93	phenylmethyl 2-[(2-{[(methyloxy)carbonyl]amino}-1*H*-benzimidazol-5-yl)carbonyl]benzoate
94	3-hydroxy-3-(1*H*-indazol-5-yl)-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-one
95	3-hydroxy-3-(1*H*-indazol-6-yl)-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-one
96	ethyl {5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
97	2-methylpropyl {5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
98	methyl {5-[1-hydroxy-3-oxo-2-(2-thienylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
99	methyl {5-[1-hydroxy-3-oxo-2-(2-phenylethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
100	3-[2-amino-1-(1,1-dimethylethyl)-1*H*-benzimidazol-5-yl]-3-hydroxy-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-one
101	3-(2-amino-1*H*-benzimidazol-5-yl)-3-hydroxy-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-one
102	methyl [5-(1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)-1*H*-benzimidazol-2-yl]carbamate
103	3-(methyloxy)butyl {5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
104	methyl (5-{1-hydroxy-3-oxo-2-[(1*R*)-1-phenylethyl]-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
105	methyl (5-{1-hydroxy-3-oxo-2-[(1*S*)-1-phenylethyl]-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate

Table 6	
Entry	**Name**
106	2-(methyloxy)ethyl {5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
107	methyl {6-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1-methyl-1*H*-benzimidazol-2-yl}carbamate
108	prop-2-yn-1-yl {5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
109	but-2-yn-1-yl {5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
110	1-methylethyl {5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
111	methyl {5-[2-(2,3-dihydro-1*H*-inden-2-yl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
112	methyl {5-[1-hydroxy-3-oxo-2-(pyridin-4-ylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
113	methyl {5-[1-hydroxy-3-oxo-2-(pyridin-3-ylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
114	methyl (6-{2-[(3-fluorophenyl)methyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
115	methyl {5-[1-hydroxy-2-(3-methylphenyl)-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
116	methyl [5-(1-hydroxy-2-{[2-(methyloxy)phenyl]methyl}-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)-1*H*-benzimidazol-2-yl]carbamate
117	methyl [5-(1-hydroxy-2-{[3-(methyloxy)phenyl]methyl}-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)-1*H*-benzimidazol-2-yl]carbamate
118	methyl [5-(1-hydroxy-2-{[4-(methyloxy)phenyl]methyl}-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)-1*H*-benzimidazol-2-yl]carbamate
119	methyl (6-{2-[(4-fluorophenyl)methyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
120	methyl (6-{2-[(3-bromophenyl)methyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
121	methyl (5-{1-hydroxy-2-[(3-iodophenyl)methyl]-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
122	methyl (5-{2-[(3-chlorophenyl)methyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
123	methyl (5-{2-[(2-fluorophenyl)methyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
124	methyl {5-[1-hydroxy-3-oxo-2-(pyridin-2-ylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
125	phenylmethyl {5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
126	2-fluoroethyl {5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate

Table 6	
Entry	**Name**
127	propyl {5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
128	methyl (5-{1-hydroxy-2-[4-(methyloxy)phenyl]-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
129	methyl (5-{2-[(2-chlorophenyl)methyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
130	methyl (5-{2-[(2-bromophenyl)methyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
131	methyl (5-{1-hydroxy-2-[(3-methylphenyl)methyl]-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
132	methyl (5-{1-hydroxy-2-[(4-methylphenyl)methyl]-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
133	methyl (5-{1-hydroxy-2-[(2-methylphenyl)methyl]-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
134	methyl {5-[2-(3-bromophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
135	methyl {5-[2-(3-chlorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
136	methyl {5-[2-(3-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
137	methyl (5-{1-hydroxy-2-[3-(methyloxy)phenyl]-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
138	methyl {5-[2-(4-bromophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
139	methyl {5-[2-(4-chlorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
140	methyl {5-[2-(4-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
141	methyl {5-[2-(3,5-dimethylphenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
142	methyl {5-[2-(2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
143	methyl {5-[2-(2-chlorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
144	methyl {5-[1-hydroxy-2-(2-methylphenyl)-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
145	methyl (5-{1-hydroxy-2-[2-(methyloxy)phenyl]-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
146	methyl {5-[1-hydroxy-2-(4-methylphenyl)-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
147	methyl (5-{1-hydroxy-3-oxo-2-[3-(trifluoromethyl)phenyl]-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate

Table 6	
Entry	**Name**
148	but-2-yn-1-yl (5-{1-hydroxy-3-oxo-2-[(1*R*)-1-phenylethyl]-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
149	*N*-ethyl-*N'*-{5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}urea
150	phenylmethyl (5-{1-hydroxy-3-oxo-2-[(1*R*)-1-phenylethyl]-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
151	methyl {6-[2-(3-amino-5-chlorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
152	piperidin-4-ylmethyl {5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
153	methyl {5-[2-(cyclopropylmethyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
154	methyl {5-[2-(2,2-dimethylpropyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
155	methyl {5-[2-(3,5-dichlorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
156	methyl {5-[2-(3,5-difluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
157	*N*-ethyl-*N'*-(5-{1-hydroxy-3-oxo-2-[(1*R*)-1-phenylethyl]-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)urea
158	*N'*-{5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}-*N*,*N*-dimethylurea
159	methyl {5-[2-(3-{[2-(dimethylamino)ethyl]oxy}phenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
160	3-(4-methylpiperazin-1-yl)propyl {6-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
161	methyl {5-[2-(cyclohexylmethyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
162	methyl {5-[1-hydroxy-2-(2-methylpropyl)-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
163	methyl {5-[1-hydroxy-3-oxo-2-(1,3-thiazol-2-ylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
164	methyl {5-[2-(3,4-difluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
165	methyl (5-{2-[1-(3,5-difluorophenyl)ethyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
166	methyl (5-{2-[1-(3-fluorophenyl)ethyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
167	methyl [5-(2-cyclohexyl-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)-1*H*-benzimidazol-2-yl]carbamate
168	methyl {5-[2-(2,5-difluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate

Table 6	
Entry	**Name**
169	*N*-{5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}-*N'*-(phenylmethyl)urea
170	piperidin-4-yl {5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
171	*N*-{5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}-*N'*-methylurea
172	methyl (5-{2-[1-(2-fluorophenyl)ethyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
173	methyl (5-{1-hydroxy-3-oxo-2-[1-(2-thienyl)ethyl]-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
174	methyl (5-{2-[1-(3-chlorophenyl)ethyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
175	methyl (5-{1-hydroxy-2-[3-methyl-5-(trifluoromethyl)phenyl]-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
176	*N*-{5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}propanamide
177	methyl {5-[2-(3,4-dichlorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
178	methyl {5-[2-(3-ethylphenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
179	methyl {5-[2-(3-ethynylphenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
180	methyl {5-[2-(4-chloro-3-methylphenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
181	methyl [5-(1-hydroxy-3-oxo-2-{1-[3-(trifluoromethyl)phenyl]ethyl}-2,3-dihydro-1*H*-isoindol-1-yl)-1*H*-benzimidazol-2-yl]carbamate
182	methyl (5-{1-hydroxy-3-oxo-2-[(1*R*)-1-phenylpropyl]-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
183	methyl [5-(1-hydroxy-3-oxo-2-{2-[(trifluoromethyl)oxy]phenyl}-2,3-dihydro-1*H*-isoindol-1-yl)-1*H*-benzimidazol-2-yl]carbamate
184	methyl {5-[2-(2,3-difluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
185	cyclohexyl {5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
186	tetrahydrofuran-2-ylmethyl {5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
187	cyclopropylmethyl {5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
188	*N*-{5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}morpholine-4-carboxamide
189	methyl {5-[2-(cyclopentylmethyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate

Table 6	
Entry	Name
190	methyl {5-[2-(2,3-dimethylphenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
191	methyl {5-[2-(2,3-dihydro-1*H*-inden-1-yl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
192	methyl (2*S*)-cyclohexyl[1-hydroxy-1-(2-{[(methyloxy)carbonyl]amino}-1*H*-benzimidazol-5-yl)-3-oxo-1,3-dihydro-2*H*-isoindol-2-yl]ethanoate
193	methyl {5-[2-(2,6-difluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
194	methyl {5-[2-(3-chloro-4-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
195	but-3-en-1-yl {5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
196	2,2,2-trifluoroethyl {5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
197	methyl {5-[2-(5-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
198	methyl (5-{2-[1-(5-chloro-2-methylphenyl)ethyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
199	methyl (5-{1-hydroxy-3-oxo-2-[(1*S*)-1-phenylpropyl]-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
200	methyl (5-{2-[1-(3-chloro-2-methylphenyl)ethyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
201	methyl (5-{1-hydroxy-2-[1-(5-methyl-2-thienyl)ethyl]-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
202	methyl (5-{2-[1-(5-chloro-2-thienyl)ethyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
203	methyl {5-[1-hydroxy-2-(3-iodophenyl)-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
204	methyl (5-{1-hydroxy-2-[3-(1-methylethyl)phenyl]-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
205	methyl {5-[2-(furan-2-ylmethyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
206	methyl {5-[1-hydroxy-3-oxo-2-(3-thienylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
207	methyl {5-[2-(cyclobutylmethyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
208	3,3,3-trifluoro-2-hydroxy-*N*-{5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}-2-(trifluoromethyl)propanamide
209	methyl (5-{1-hydroxy-2-[1-(4-methyl-2-thienyl)ethyl]-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
210	methyl (5-{2-[1-(4-bromo-2-thienyl)ethyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate

Table 6	
Entry	Name
211	methyl {5-[1-hydroxy-2-(3-{[2-(methyloxy)ethyl]oxy}phenyl)-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
212	tetrahydrofuran-3-ylmethyl {5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
213	*N*-{5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}piperidine-1-carboxamide
214	methyl {5-[2-(3-bromo-4-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
215	2,3-dihydroxypropyl {5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
216	methyl {5-[1-hydroxy-3-oxo-2-(tetrahydrofuran-2-ylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
217	methyl (5-{2-[3-(aminocarbonyl)phenyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
218	4,4,4-trifluoro-3-hydroxy-*N*-{5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}-3-(trifluoromethyl)butanamide
219	methyl (5-{1-hydroxy-2-[3-(methylsulfonyl)phenyl]-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
220	methyl (5-{1-hydroxy-3-oxo-2-[3-(phenyloxy)phenyl]-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
221	methyl [5-(1-hydroxy-3-oxo-2-{3-[(phenylmethyl)oxy]phenyl}-2,3-dihydro-1*H*-isoindol-1-yl)-1*H*-benzimidazol-2-yl]carbamate
222	methyl [5-(2-biphenyl-3-yl-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)-1*H*-benzimidazol-2-yl]carbamate
223	2,2-dimethyl-3-[(phenylmethyl)oxy]propyl {5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
224	methyl {5-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
225	methyl {5-[2-(3-cyanophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
226	methyl {5-[2-(3-ethynyl-4-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
227	methyl {5-[2-(4-fluoro-3-methylphenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
228	methyl {6-[2-(3,4-dichloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
229	[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl {5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
230	methyl {5-[2-(5-bromo-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
231	methyl (5-{2-[3-(acetylamino)phenyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate

Table 6	
Entry	Name
232	methyl (5-{1-hydroxy-3-oxo-2-[3-(phenylmethyl)phenyl]-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
233	methyl (5-{2-[1-(4-chloro-2-thienyl)ethyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
234	methyl (5-{1-hydroxy-3-oxo-2-[3-(phenylcarbonyl)phenyl]-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
235	methyl [5-(2-{3-[(dimethylamino)methyl]phenyl}-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)-1*H*-benzimidazol-2-yl]carbamate
236	methyl (5-{2-[3-(aminosulfonyl)phenyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
237	methyl {5-[2-(3-acetylphenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
238	methyl {5-[2-(3-ethyl-4-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
239	methyl {5-[2-(3-chloro-5-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
240	*N*-{6-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}-2-methylpropanamide
241	methyl (5-{2-[1-(3-chloro-2-thienyl)ethyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
242	methyl [5-(1-hydroxy-3-oxo-2-pyridin-3-yl-2,3-dihydro-1*H*-isoindol-1-yl)-1*H*-benzimidazol-2-yl]carbamate
243	methyl (5-{1-hydroxy-3-oxo-2-[3-(phenylamino)phenyl]-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
244	methyl {5-[2-(5-bromo-2,4-difluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
245	methyl {5-[2-(5-chloro-2,4-difluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
246	methyl {5-[2-(3,5-dichloro-4-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
247	2,2-dimethyl-3-(methyloxy)propyl {5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
248	3-hydroxy-2,2-dimethylpropyl {5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
249	methyl (5-{2-[1-(5-bromo-2-thienyl)ethyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
250	methyl {5-[2-(4,5-dichloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
251	methyl {5-[2-(3-bromo-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
252	methyl {5-[2-(3-chloro-2,4-difluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate

Table 6	
Entry	**Name**
253	*N*-{6-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}pent-4-ynamide
254	methyl (6-{1-methyl-3-oxo-2-[3-(trifluoromethyl)phenyl]-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
255	methyl [5-(1-hydroxy-3-oxo-2-{3-[(1,1,2,2-tetrafluoroethyl)oxy]phenyl}-2,3-dihydro-1*H*-isoindol-1-yl)-1*H*-benzimidazol-2-yl]carbamate
256	methyl {5-[1-hydroxy-3-oxo-2-(3-piperidin-4-ylphenyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
257	methyl {5-[2-(3-ethenylphenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
258	methyl (5-{2-[3-(dimethylamino)phenyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
259	2,2-difluoro-*N*-{6-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}cyclopropanecarboxamide
260	*N*-ethyl-*N'*-{6-[2-(4-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}urea
261	methyl {5-[2-(3-aminophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
262	*N*-{5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}-4-[(phenylmethyl)oxy]butanamide
263	*N*-{5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}-4-piperidin-1-ylbutanamide
264	*N*-{5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}-4-(4-methylpiperazin-1-yl)butanamide
265	*N*-{6-[2-(4-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}butanamide
266	methyl {6-[2-(3-bromophenyl)-5,6-dichloro-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
267	methyl [5-(1-hydroxy-2-{3-[methyl(phenyl)amino]phenyl}-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)-1*H*-benzimidazol-2-yl]carbamate
268	methyl {5-[1-hydroxy-3-oxo-2-(phenylsulfonyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
269	methyl {5-[(2-{[(phenylamino)carbonyl]amino}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
270	methyl (5-{[2-({[(phenylmethyl)oxy]carbonyl}amino)phenyl]carbonyl}-1*H*-benzimidazol-2-yl)carbamate
271	methyl [5-({2-[(2-phenylhydrazino)carbonyl]phenyl}carbonyl)-1*H*-benzimidazol-2-yl]carbamate
272	methyl {5-[(2-{[(phenyloxy)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
273	but-2-yn-1-yl {5-[2-(4-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate

Table 6	
Entry	**Name**
274	*N*-{5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}-3-piperidin-1-ylpropanamide
275	*N*-{6-[2-(4-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}propanamide
276	*N*-(4-fluorophenyl)-2-{[2-(pent-4-ynoylamino)-1*H*-benzimidazol-6-yl]carbonyl}benzamide
277	4-(diethylamino)-*N*-{5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}butanamide
278	*N*-{5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}-4-pyrrolidin-1-ylbutanamide
279	3-piperidin-1-ylpropyl {6-[2-(4-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
280	3-(4-methylpiperazin-1-yl)propyl {6-[2-(4-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
281	methyl {5-[2-(3-bromophenyl)-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
282	methyl {5-[2-(3-ethynyl-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
283	2-piperidin-1-ylethyl {5-[2-(4-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
284	methyl {5-[2-(3-chloro-2-methylphenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
285	methyl {5-[2-(5-chloro-2-methylphenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
286	*N*-{6-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}-2,2-dimethyl-3-piperidin-1-ylpropanamide
287	*N*-{5-[2-(4-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}-4-piperidin-1-ylbutanamide
288	*N*-{5-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}-4-piperidin-1-ylbutanamide
289	methyl [6-({2-[(phenylcarbonyl)amino]phenyl}carbonyl)-1*H*-benzimidazol-2-yl]carbamate
290	methyl {5-[1-hydroxy-2-(3-morpholin-4-ylphenyl)-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
291	2-(dimethylamino)ethyl {6-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
292	2-(diethylamino)ethyl {5-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
293	2-piperidin-1-ylethyl {5-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
294	3-piperidin-1-ylpropyl {6-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate

Table 6	
Entry	**Name**
295	2-piperidin-1-ylethyl {6-[2-(3-bromophenyl)-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
296	methyl {6-[2-(3-bromophenyl)-4,7-difluoro-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
297	2-[methyl(phenylmethyl)amino]ethyl {5-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
298	methyl {5-[1-hydroxy-3-oxo-2-(3-pyrrolidin-1-ylphenyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
299	methyl {5-[2-(5-chloro-2,3-difluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
300	methyl {5-[1-hydroxy-3-oxo-2-(pyrrolidin-2-ylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
301	methyl {5-[1-hydroxy-3-oxo-2-(pyrrolidin-3-ylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
302	(1-methylpiperidin-2-yl)methyl {6-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
303	[(2*S*)-1-methylpyrrolidin-2-yl]methyl {6-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
304	octahydro-2*H*-quinolizin-1-ylmethyl {6-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
305	methyl {5-[2-(5-bromo-2-methylphenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
306	5-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1,3-dihydro-2*H*-benzimidazol-2-one
307	methyl {5-[2-(3-bromo-2,5-difluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
308	2-morpholin-4-ylethyl {6-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
309	(1-methylpiperidin-3-yl)methyl {6-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
310	methyl (5-{2-[5-chloro-2-(methyloxy)phenyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
311	methyl [5-(2-{3-[cyclohexyl(methyl)amino]phenyl}-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)-1*H*-benzimidazol-2-yl]carbamate
312	8-azabicyclo[3.2.1]oct-3-ylmethyl {6-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
313	methyl {6-[1-(3-bromophenyl)-5-oxopyrrolidin-2-yl]-1*H*-benzimidazol-2-yl}carbamate
314	(1-methylpiperidin-4-yl)methyl {5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
315	1,1-dimethylethyl 4-({[({5-[1-hydroxy-3-oxo-2-(phenylmethyl)-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}amino)carbonyl]oxy}methyl)piperidine-1-carboxylate

Table 6	
Entry	**Name**
316	(1-methylpiperidin-4-yl)methyl {5-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
317	2-(1-methylpiperidin-4-yl)ethyl {5-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
318	methyl ({6-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}amino)(oxo)acetate
319	*N*-(5-{1-hydroxy-3-oxo-2-[3-(phenyloxy)phenyl]-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)-4-piperidin-1-ylbutanamide
320	methyl {6-[2-(3-bromophenyl)-1-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
321	4-(diethylamino)but-2-yn-1-yl {6-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
322	methyl {5-[2-(3-chloro-2,6-difluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
323	2-(2-oxopyrrolidin-1-yl)ethyl {6-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
324	2-(2,5-dioxopyrrolidin-1-yl)ethyl {6-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
325	2,2,3,3-tetrafluorocyclobutyl {5-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
326	1-acetyl-*N*-{5-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}piperidine-4-carboxamide
327	*N*-{5-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}cyclobutanecarboxamide
328	methyl [5-(2-{3-[ethyl(phenyl)amino]phenyl}-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)-1*H*-benzimidazol-2-yl]carbamate
329	*N*-{6-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}-2,2-difluorocyclopropanecarboxamide
330	cyclobutyl {6-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
331	2,2-difluoroethyl {6-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
332	2-(3-chloro-2-fluorophenyl)-3-hydroxy-3-[2-(pyridin-2-ylamino)-1*H*-benzimidazol-5-yl]-2,3-dihydro-1*H*-isoindol-1-one
333	1-methylethyl {6-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
334	cyclopropylmethyl {6-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
335	*N*-{5-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}cyclopropanecarboxamide
336	2-(methyloxy)ethyl {5-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate

Table 6	
Entry	**Name**
337	tetrahydrofuran-2-ylmethyl {6-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
338	*N*-{5-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}-2-(2-thienyl)acetamide
339	methyl {6-[2-(3-chloro-2-fluorophenyl)-4,7-difluoro-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
340	ethyl {6-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
341	2-fluoroethyl {6-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
342	methyl (5-{1-hydroxy-3-oxo-2-[2-(phenyloxy)phenyl]-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
343	*N'*-{5-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}-*N,N*-diethylpentanediamide
344	cyclobutylmethyl {6-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
345	2,2,2-trifluoroethyl {6-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
346	methyl (5-{2-[3-(1,1-dimethylethyl)phenyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
347	methyl {6-[2-(3-chloro-2-fluorophenyl)-7-fluoro-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
348	2-(3-chloro-2-fluorophenyl)-3-hydroxy-3-[2-(phenylamino)-1*H*-benzimidazol-5-yl]-2,3-dihydro-1*H*-isoindol-1-one
349	methyl {6-[4,7-dichloro-2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
350	phenylmethyl 2-[(2-{[(ethyloxy)carbonyl]amino}-1,3-benzoxazol-5-yl)carbonyl]benzoate
351	methyl {5-[2-(5-chloro-3-ethynyl-2-methylphenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
352	methyl {5-[2-(5-ethynyl-2,4-difluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
353	methyl {5-[2-(3-ethynyl-2,4-difluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
354	2-(3-chloro-2-fluorophenyl)-3-hydroxy-3-[2-(pyrimidin-2-ylamino)-1*H*-benzimidazol-5-yl]-2,3-dihydro-1*H*-isoindol-1-one
355	methyl {5-[2-(3-ethynyl-2-fluorophenyl)-4,7-difluoro-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
356	2-(3-chloro-2-fluorophenyl)-3-hydroxy-3-[2-(1,3-thiazol-2-ylamino)-1*H*-benzimidazol-5-yl]-2,3-dihydro-1*H*-isoindol-1-one
357	ethyl {5-[2-(3-chloro-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1,3-benzoxazol-2-yl}carbamate

Table 6	
Entry	**Name**
358	methyl {5-[2-(5-chloro-3-iodo-2-methylphenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
359	methyl {5-[2-(3-ethyl-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
360	methyl {5-[2-(5-ethynyl-2-methylphenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
361	2-(3-chloro-2-fluorophenyl)-3-hydroxy-3-[2-(pyrazin-2-ylamino)-1*H*-benzimidazol-5-yl]-2,3-dihydro-1*H*-isoindol-1-one
362	methyl {5-[2-(2-fluoro-3-iodophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
363	methyl {6-[2-(5-ethynyl-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
364	2-(3-ethynyl-2-fluorophenyl)-3-hydroxy-3-[2-(pyrimidin-2-ylamino)-1*H*-benzimidazol-5-yl]-2,3-dihydro-1*H*-isoindol-1-one
365	methyl {5-[2-(2,5-dimethylphenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
366	methyl {5-[2-(3-ethenyl-2-fluorophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
367	methyl (6-{2-[2-fluoro-3-(methyloxy)phenyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
368	methyl (5-{1-hydroxy-2-[2-methyl-5-(methyloxy)phenyl]-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
369	methyl {5-[2-(3-ethynyl-2-fluorophenyl)-7-fluoro-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
370	methyl {5-[2-(2-fluoro-3-prop-1-yn-1-ylphenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
371	methyl {5-[2-(5-chloro-2-methylphenyl)-7-fluoro-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
372	methyl {5-[2-(3-ethynyl-2-methylphenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
373	3-hydroxy-2-[3-(methyloxy)phenyl]-3-[2-(pyrimidin-2-ylamino)-1*H*-benzimidazol-6-yl]-2,3-dihydro-1*H*-isoindol-1-one
374	3-hydroxy-2-(3-methylphenyl)-3-[2-(pyrimidin-2-ylamino)-1*H*-benzimidazol-6-yl]-2,3-dihydro-1*H*-isoindol-1-one
375	2-(5-chloro-2-methylphenyl)-3-hydroxy-3-[2-(pyrimidin-2-ylamino)-1*H*-benzimidazol-6-yl]-2,3-dihydro-1*H*-isoindol-1-one
376	methyl {6-[2-(5-chloro-2-methylphenyl)-4,7-difluoro-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
377	methyl {5-[2-(3-ethynyl-2-fluorophenyl)-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
378	2-(3-chloro-2-fluorophenyl)-3-{2-[(6-chloropyridazin-3-yl)amino]-1*H*-benzimidazol-5-yl}-3-hydroxy-2,3-dihydro-1*H*-isoindol-1-one

Table 6	
Entry	**Name**
379	2-(3-chloro-2-fluorophenyl)-4,7-difluoro-3-hydroxy-3-[2-(pyrimidin-2-ylamino)-1*H*-benzimidazol-5-yl]-2,3-dihydro-1*H*-isoindol-1-one
380	methyl {5-[2-(2-fluoro-5-methylphenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
381	methyl (5-{2-[2-fluoro-5-(methyloxy)phenyl]-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
382	methyl (5-{1-hydroxy-2-[5-methyl-2-(methyloxy)phenyl]-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl}-1*H*-benzimidazol-2-yl)carbamate
383	methyl {5-[2-(3-ethynyl-5-methylphenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
384	2-(3-chloro-2-fluorophenyl)-3-{2-[(5-chloropyrimidin-2-yl)amino]-1*H*-benzimidazol-5-yl}-3-hydroxy-2,3-dihydro-1*H*-isoindol-1-one
385	2-(3-chloro-2-fluorophenyl)-3-hydroxy-3-{2-[(4-methylpyrimidin-2-yl)amino]-1*H*-benzimidazol-5-yl}-2,3-dihydro-1*H*-isoindol-1-one
386	3-(2-{[4,6-bis(methyloxy)pyrimidin-2-yl]amino}-1*H*-benzimidazol-5-yl)-2-(3-chloro-2-fluorophenyl)-3-hydroxy-2,3-dihydro-1*H*-isoindol-1-one
387	2-(3-chloro-2-fluorophenyl)-3-hydroxy-3-(2-{[4-methyl-6-(methyloxy)pyrimidin-2-yl]amino}-1*H*-benzimidazol-5-yl)-2,3-dihydro-1*H*-isoindol-1-one
388	3-hydroxy-2-(3-methylphenyl)-3-[2-(pyrazin-2-ylamino)-1*H*-benzimidazol-6-yl]-2,3-dihydro-1*H*-isoindol-1-one
389	2-(5-chloro-2-methylphenyl)-3-hydroxy-3-[2-(pyrazin-2-ylamino)-1*H*-benzimidazol-6-yl]-2,3-dihydro-1*H*-isoindol-1-one
390	methyl {6-[2-(2-fluoro-3-methylphenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl]-1*H*-benzimidazol-2-yl}carbamate
391	3-hydroxy-2-[3-(methyloxy)phenyl]-3-[2-(pyrazin-2-ylamino)-1*H*-benzimidazol-5-yl]-2,3-dihydro-1*H*-isoindol-1-one
392	methyl {6-[(2-{[(2-thienylmethyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
393	methyl {6-[(2-{[(3-methylphenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
394	methyl {6-[(2-{[(3-bromophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
395	methyl {6-[(2-{[(3-chlorophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
396	methyl {6-[(2-{[(3-fluorophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
397	methyl (6-{[2-({[3-(methyloxy)phenyl]amino}carbonyl)phenyl]carbonyl}-1*H*-benzimidazol-2-yl)carbamate
398	methyl (6-{[2-({[3-(trifluoromethyl)phenyl]amino}carbonyl)phenyl]carbonyl}-1*H*-benzimidazol-2-yl)carbamate
399	methyl {6-[(2-{[(3-ethylphenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate

Table 6	
Entry	**Name**
400	methyl {6-[(2-{[(3-ethynylphenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
401	methyl {6-[(2-{[(3-chloro-4-fluorophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
402	methyl {6-[(2-{[(5-chloro-2-fluorophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
403	methyl {6-[(2-{[(3-iodophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
404	methyl (6-{[2-({[3-(1-methylethyl)phenyl]amino}carbonyl)phenyl]carbonyl}-1*H*-benzimidazol-2-yl)carbamate
405	methyl {6-[(2-{[(3-thienylmethyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
406	methyl {6-[(2-{[(3-bromo-4-fluorophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
407	methyl {6-[(2-{[(3-chloro-2-fluorophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
408	methyl {6-[(2-{[(4-fluoro-3-methylphenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
409	methyl {6-[(2-{[(5-bromo-2-fluorophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
410	methyl {6-[(2-{[(5-bromo-2,4-difluorophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
411	methyl {6-[(2-{[(5-chloro-2,4-difluorophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
412	methyl {6-[(2-{[(3-bromo-2-fluorophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
413	methyl {6-[(2-{[(3-ethenylphenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
414	methyl {6-[(2-{[(3-ethynyl-2-fluorophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
415	methyl {6-[(2-{[(5-chloro-2-methylphenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
416	methyl {6-[(2-{[(5-bromo-2-methylphenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
417	methyl {6-[(2-{[(2-fluoro-3-iodophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
418	methyl {6-[(2-{[(3-ethenyl-2-fluorophenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate
419	methyl {6-[(2-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenyl)carbonyl]-1*H*-benzimidazol-2-yl}carbamate

Table 7.

Representative EGFR and/or VEGFR Inhibitors

[00224] The Compounds in Table 7 can be prepared as pharmaceutically acceptable salts, solvates, hydrates, and/or isomers thereof. All such salt, solvate, hydrate, and isomer combinations of the Compounds in Table 7 can be used to practice the invention.

Table 7

Entry	Name
1	(3*Z*)-3-[[5-(methyloxy)-1*H*-benzimidazol-2-yl](phenyl)methylidene]-5-{[1-(phenylmethyl)pyrrolidin-3-yl]amino}-1,3-dihydro-2*H*-indol-2-one
2	(3*Z*)-5-[(1-ethylpiperidin-3-yl)amino]-3-[[5-(methyloxy)-1*H*-benzimidazol-2-yl](phenyl)methylidene]-1,3-dihydro-2*H*-indol-2-one
3	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[[5-(methyloxy)-1*H*-benzimidazol-2-yl](phenyl)methylidene]-1,3-dihydro-2*H*-indol-2-one
4	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[1*H*-imidazol-2-yl(phenyl)methylidene]-1,3-dihydro-2*H*-indol-2-one
5	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-{[5-(methyloxy)-1*H*-benzimidazol-2-yl][4-(methyloxy)phenyl]methylidene}-1,3-dihydro-2*H*-indol-2-one
6	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[[5-(methyloxy)-1*H*-benzimidazol-2-yl](4-methylphenyl)methylidene]-1,3-dihydro-2*H*-indol-2-one
7	(3*Z*)-3-[1*H*-benzimidazol-2-yl(4-nitrophenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
8	(3*Z*)-3-{1*H*-benzimidazol-2-yl[4-(methyloxy)phenyl]methylidene}-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
9	(3*Z*)-3-[1*H*-benzimidazol-2-yl(phenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
10	(3*Z*)-3-[[5-(methyloxy)-1*H*-benzimidazol-2-yl](phenyl)methylidene]-5-[(2,2,6,6-tetramethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
11	(3*Z*)-3-[(4-aminophenyl)(1*H*-benzimidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
12	(3*Z*)-3-[1*H*-benzimidazol-2-yl(4-methylphenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
13	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[1*H*-imidazol-2-yl(4-methylphenyl)methylidene]-1,3-dihydro-2*H*-indol-2-one
14	(3*Z*)-5-[(1-ethylpiperidin-4-yl)oxy]-3-[[5-(methyloxy)-1*H*-benzimidazol-2-yl](phenyl)methylidene]-1,3-dihydro-2*H*-indol-2-one
15	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-{1*H*-imidazol-2-yl[4-(methyloxy)phenyl]methylidene}-1,3-dihydro-2*H*-indol-2-one
16	(3*Z*)-3-[1*H*-benzimidazol-2-yl(4-fluorophenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
17	(3*Z*)-3-[1*H*-benzimidazol-2-yl(3,5-difluorophenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one

Table 7	
Entry	**Name**
18	(3*Z*)-3-[1*H*-benzimidazol-2-yl(3-fluorophenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
19	(3*Z*)-3-[1*H*-benzimidazol-2-yl(3-nitrophenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
20	3-((*Z*)-1*H*-benzimidazol-2-yl{5-[(1-ethylpiperidin-4-yl)amino]-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene}methyl)benzonitrile
21	(3*Z*)-3-[(3-aminophenyl)(1*H*-benzimidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
22	(3*Z*)-3-[1*H*-benzimidazol-2-yl(phenyl)methylidene]-5-(piperidin-4-ylamino)-1,3-dihydro-2*H*-indol-2-one
23	3-((*Z*)-1*H*-benzimidazol-2-yl{5-[(1-ethylpiperidin-4-yl)amino]-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene}methyl)benzenecarboximidamide
24	(3*Z*)-3-[1*H*-benzimidazol-2-yl(phenyl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
25	(3*Z*)-3-[1*H*-benzimidazol-2-yl(phenyl)methylidene]-5-[(2,2,6,6-tetramethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
26	(3*Z*)-3-{1*H*-benzimidazol-2-yl[3-(methyloxy)phenyl]methylidene}-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
27	(3*Z*)-3-[1*H*-benzimidazol-2-yl(3-chlorophenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
28	2-(2-{2-[(*Z*)-{5-[(1-ethylpiperidin-4-yl)amino]-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene}(phenyl)methyl]-1*H*-imidazol-4-yl}ethyl)-1*H*-isoindole-1,3(2*H*)-dione
29	(3*Z*)-3-[1*H*-benzimidazol-2-yl(phenyl)methylidene]-5-({1-[2-(dimethylamino)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
30	(3*Z*)-3-[1*H*-benzimidazol-2-yl(phenyl)methylidene]-5-{[1-(methylsulfonyl)piperidin-4-yl]amino}-1,3-dihydro-2*H*-indol-2-one
31	(3*Z*)-5-(8-azabicyclo[3.2.1]oct-3-ylamino)-3-[1*H*-benzimidazol-2-yl(phenyl)methylidene]-1,3-dihydro-2*H*-indol-2-one
32	(3*Z*)-3-{1*H*-benzimidazol-2-yl[3-(methyloxy)phenyl]methylidene}-5-[(1-ethylpiperidin-4-yl)oxy]-1,3-dihydro-2*H*-indol-2-one
33	(3*Z*)-3-[1*H*-benzimidazol-2-yl(3,5-difluorophenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)oxy]-1,3-dihydro-2*H*-indol-2-one
34	(3*Z*)-3-[1*H*-benzimidazol-2-yl(phenyl)methylidene]-5-{[1-(phenylmethyl)piperidin-4-yl]oxy}-1,3-dihydro-2*H*-indol-2-one
35	(3*Z*)-3-[1*H*-benzimidazol-2-yl(3-chlorophenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)oxy]-1,3-dihydro-2*H*-indol-2-one
36	(3*Z*)-3-[1*H*-benzimidazol-2-yl(3,5-difluorophenyl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}oxy)-1,3-dihydro-2*H*-indol-2-one
37	(3*Z*)-3-[1*H*-benzimidazol-2-yl(3-chlorophenyl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}oxy)-1,3-dihydro-2*H*-indol-2-one
38	(3*Z*)-3-[1*H*-benzimidazol-2-yl(3-chlorophenyl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one

Table 7	
Entry	**Name**
39	(3*Z*)-3-{1*H*-benzimidazol-2-yl[3-(methyloxy)phenyl]methylidene}-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
40	(3*Z*)-3-[(3-chlorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
41	(3*Z*)-3-[(3-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
42	(3*Z*)-3-[1*H*-benzimidazol-2-yl(3,5-difluorophenyl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
43	(3*Z*)-3-[1*H*-benzimidazol-2-yl(3-chlorophenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)(methyl)amino]-1,3-dihydro-2*H*-indol-2-one
44	(3*Z*)-3-[(3-chlorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)oxy]-1,3-dihydro-2*H*-indol-2-one
45	(3*Z*)-3-[1*H*-benzimidazol-2-yl(4-chlorophenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
46	(3*Z*)-3-[1*H*-benzimidazol-2-yl(3-fluorophenyl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
47	(3*Z*)-3-[1*H*-benzimidazol-2-yl(4-fluorophenyl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
48	(3*Z*)-3-[(3-chlorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
49	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[(3-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one
50	(3*Z*)-3-[1*H*-benzimidazol-2-yl(3-fluoro-4-methylphenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
51	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[(3-fluorophenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one
52	(3*Z*)-3-[1*H*-benzimidazol-2-yl(4-fluoro-3-methylphenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
53	(3*Z*)-3-[(3-chloro-4-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
54	(3*Z*)-3-[(3,4-difluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
55	(3*Z*)-3-[(5-chloro-1*H*-benzimidazol-2-yl)(phenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
56	(3*Z*)-3-[(5-chloro-1*H*-benzimidazol-2-yl)(3,5-difluorophenyl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
57	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[(3-fluoro-4-methylphenyl)(1*H*-imidazol-2-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one
58	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[(4-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one
59	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[1*H*-imidazol-2-yl(4-propylphenyl)methylidene]-1,3-dihydro-2*H*-indol-2-one

Table 7	
Entry	**Name**
60	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-{1*H*-imidazol-2-yl[4-(trifluoromethyl)phenyl]methylidene}-1,3-dihydro-2*H*-indol-2-one
61	(3*E*)-3-[(3,5-difluorophenyl)(5-fluoro-1*H*-benzimidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
62	(3*Z*)-3-[(3,5-difluorophenyl)(5-fluoro-1*H*-benzimidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
63	(3*Z*)-3-[(3-fluoro-4-methylphenyl)(1*H*-imidazol-2-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
64	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[(4-methyl-1*H*-imidazol-2-yl)(4-methylphenyl)methylidene]-1,3-dihydro-2*H*-indol-2-one
65	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[[3-fluoro-4-(trifluoromethyl)phenyl](1*H*-imidazol-2-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one
66	(3*Z*)-3-[(4-chlorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
67	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[(3-fluoro-4-methylphenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one
68	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-{1*H*-imidazol-2-yl[6-(trifluoromethyl)pyridin-3-yl]methylidene}-1,3-dihydro-2*H*-indol-2-one
69	(3*Z*)-3-[1*H*-imidazol-2-yl(4-methylphenyl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
70	(3*Z*)-3-[(3-fluorophenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
71	(3*Z*)-3-{1*H*-imidazol-2-yl[4-(trifluoromethyl)phenyl]methylidene}-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
72	(3*Z*)-3-[(5-chloro-1*H*-benzimidazol-2-yl)(phenyl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
73	(3*Z*)-3-[(3,5-difluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
74	(3*Z*)-3-[(3,5-difluorophenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
75	(3*Z*)-3-[(3,5-difluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
76	(3*Z*)-3-[(3,5-difluorophenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
77	(3*Z*)-3-[(4-methyl-1*H*-imidazol-2-yl)(4-methylphenyl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
78	(3*Z*)-3-[(4-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
79	(3*Z*)-3-[(3,4-difluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one

Table 7	
Entry	**Name**
80	(3*Z*)-3-[(3-chloro-4-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
81	(3*Z*)-3-[(3-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-(piperidin-4-ylamino)-1,3-dihydro-2*H*-indol-2-one
82	(3*Z*)-3-[(3-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-{[1-(2-piperidin-1-ylethyl)piperidin-4-yl]amino}-1,3-dihydro-2*H*-indol-2-one
83	(3*Z*)-3-[(3-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-{[1-(2-morpholin-4-ylethyl)piperidin-4-yl]amino}-1,3-dihydro-2*H*-indol-2-one
84	(3*Z*)-5-({1-[2-(diethylamino)ethyl]piperidin-4-yl}amino)-3-[(3-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one
85	(3*Z*)-3-[(3-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-{[1-(2-pyrrolidin-1-ylethyl)piperidin-4-yl]amino}-1,3-dihydro-2*H*-indol-2-one
86	(3*Z*)-3-[1*H*-imidazol-2-yl(4-methylphenyl)methylidene]-5-[(1-methylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
87	(3*Z*)-3-[(3-fluorophenyl)(1*H*-1,2,4-triazol-5-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
88	ethyl 2-{(*Z*)-(3-fluorophenyl)[5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene]methyl}-4-methyl-1*H*-imidazole-5-carboxylate
89	(3*Z*)-3-[1*H*-imidazol-2-yl(phenyl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
90	(3*Z*)-3-{1*H*-imidazol-2-yl[4-(methyloxy)phenyl]methylidene}-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
91	(3*Z*)-3-[(4-chlorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
92	(3*Z*)-3-[[3-fluoro-4-(trifluoromethyl)phenyl](1*H*-imidazol-2-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
93	(3*Z*)-3-[(3-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-{[1-(methylsulfonyl)piperidin-4-yl]amino}-1,3-dihydro-2*H*-indol-2-one
94	(3*Z*)-3-[1*H*-imidazol-2-yl(4-propylphenyl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
95	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[(3-fluorophenyl)(4-phenyl-1*H*-imidazol-2-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one
96	(3*Z*)-3-[(3-fluorophenyl)(4-phenyl-1*H*-imidazol-2-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
97	(3*Z*)-3-[(3-fluoro-4-methylphenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
98	(3*Z*)-3-{1*H*-imidazol-2-yl[6-(trifluoromethyl)pyridin-3-yl]methylidene}-5-({1-[2-(methyloxy)ethyl]piperidin-4-yl}amino)-1,3-dihydro-2*H*-indol-2-one
99	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[(3-fluorophenyl)(1*H*-1,2,4-triazol-5-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one

Table 7	
Entry	**Name**
100	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[[2-fluoro-4-(trifluoromethyl)phenyl](1*H*-imidazol-2-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one
101	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-{(4-methyl-1*H*-imidazol-2-yl)[4-(trifluoromethyl)phenyl]methylidene}-1,3-dihydro-2*H*-indol-2-one
102	(3*Z*)-3-[(4-chlorophenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
103	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[[3-fluoro-4-(trifluoromethyl)phenyl](4-methyl-1*H*-imidazol-2-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one
104	(3*Z*)-3-[(3,4-difluorophenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
105	(3*Z*)-3-[(3-chloro-4-fluorophenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
106	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[(4-fluorophenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one
107	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[(2-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one
108	(3*Z*)-5-[(1-ethylpiperidin-4-yl)amino]-3-[[2-fluoro-4-(trifluoromethyl)phenyl](4-methyl-1*H*-imidazol-2-yl)methylidene]-1,3-dihydro-2*H*-indol-2-one
109	(3*Z*)-3-[(2,3-difluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
110	(3*Z*)-3-[(2,3-difluorophenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
111	(3*Z*)-3-[(2,4-difluorophenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
112	(3*Z*)-3-[(2,4-difluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
113	(3*Z*)-3-[(2-fluorophenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
114	(3*Z*)-3-[(3-trifluoromethylphenyl)(1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
115	(3*Z*)-3-[(3-trifluoromethylphenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
116	(3*Z*)-3-[(2,4-dichloro-5-fluorophenyl)(1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
117	(3*Z*)-3-[(2,4-dichloro-5-fluorophenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one
118	(3*Z*)-3-[(4-chloro-2-fluorophenyl)(4-methyl-1*H*-imidazol-2-yl)methylidene]-5-[(1-ethylpiperidin-4-yl)amino]-1,3-dihydro-2*H*-indol-2-one

Table 8. c-KIT Inhibitors

[00225] The Compounds in Table 8 can be prepared as pharmaceutically acceptable salts, solvates, hydrates, and/or isomers thereof. All such salt, solvate, hydrate, and isomer combinations of the Compounds in Table 8 can be used to practice the invention.

Table 8

Entry	Name
1	*N*-[5-chloro-2-(methyloxy)phenyl]-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
2	*N*-phenyl-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
3	*N*-(2-methylphenyl)-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
4	*N*-(2-chlorophenyl)-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
5	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
6	ethyl 2-[({[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetyl)amino]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate
7	*N*-(3-chloro-2-methylphenyl)-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
8	*N*-(3-fluorophenyl)-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
9	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-{[3-(2*H*-tetrazol-5-yl)phenyl]oxy}acetamide
10	*N*-(4-chloro-2-fluorophenyl)-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
11	*N*-(4-bromo-3-methylphenyl)-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
12	*N*-(4-morpholin-4-ylphenyl)-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
13	*N*-[4-fluoro-3-(trifluoromethyl)phenyl]-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
14	*N*-[4-bromo-3-(trifluoromethyl)phenyl]-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
15	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-{[4-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
16	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}propanamide
17	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-{[3-(5-methyl-1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
18	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-{[2-methyl-5-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
19	*N*-(4-chlorophenyl)-*N*-methyl-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide

Table 8	
Entry	**Name**
20	*N*-[4-chloro-2-(trifluoromethyl)phenyl]-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
21	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-{[3-(2,5-dioxopyrrolidin-1-yl)phenyl]oxy}acetamide
22	(2E)-*N*-[4-chloro-3-(trifluoromethyl)phenyl]-3-[3-(1*H*-tetrazol-1-yl)phenyl]prop-2-enamide
23	*N*-[4-fluoro-3-(trifluoromethyl)phenyl]-2-{[4-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
24	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-{[3-(2-methyl-2*H*-tetrazol-5-yl)phenyl]oxy}acetamide
25	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-{[2,4-dichloro-5-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
26	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-{[3-(1*H*-tetrazol-1-yl)phenyl]thio}acetamide
27	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N*~2~-[3-(1*H*-tetrazol-1-yl)phenyl]glycinamide
28	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-{[2-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
29	methyl 1-{3-[(2-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-2-oxoethyl)oxy]phenyl}-1*H*-1,2,3-triazole-4-carboxylate
30	1,1-dimethylethyl {4-[({[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetyl)amino]phenyl}carbamate
31	1,1-dimethylethyl {4-[({[4-(1*H*-tetrazol-1-yl)phenyl]oxy}acetyl)amino]phenyl}carbamate
32	*N*-{4-[(1-ethylpiperidin-4-yl)amino]phenyl}-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
33	*N*-{4-[(1-ethylpiperidin-3-yl)amino]phenyl}-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
34	*N*-(4-aminophenyl)-2-{[4-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
35	*N*-{4-[(1-ethylpiperidin-4-yl)amino]phenyl}-2-{[4-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
36	*N*-{4-[(1-ethylpiperidin-3-yl)amino]phenyl}-2-{[4-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
37	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-[(3-pyridin-4-ylphenyl)oxy]acetamide
38	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N*~2~-methyl-*N*~2~-[3-(1*H*-tetrazol-1-yl)phenyl]glycinamide
39	*N*-1,3-benzothiazol-2-yl-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
40	*N*-quinolin-8-yl-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
41	*N*-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
42	*N*-isoquinolin-5-yl-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide

Table 8	
Entry	**Name**
43	*N*-{3-[(phenylmethyl)oxy]phenyl}-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
44	*N*-[5-methyl-2-(methyloxy)phenyl]-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
45	*N*-[2,5-bis(methyloxy)phenyl]-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
46	*N*-(6-fluoro-1,3-benzothiazol-2-yl)-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
47	methyl 3-[({[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetyl)amino]benzoate
48	5-chloro-2-[({[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetyl)amino]benzamide
49	*N*-[5-chloro-2,4-bis(methyloxy)phenyl]-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
50	*N*-[2-(phenyloxy)phenyl]-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
51	*N*-[3-(aminosulfonyl)phenyl]-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
52	*N*-[2-(methyloxy)-5-(trifluoromethyl)phenyl]-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
53	*N*-(4-{[(4-methylphenyl)sulfonyl]amino}phenyl)-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
54	*N*-(5-phenyl-1*H*-pyrazol-3-yl)-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
55	*N*-1,3-benzothiazol-2-yl-2-{[4-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
56	*N*-quinolin-8-yl-2-{[4-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
57	1,1-dimethylethyl 2-{3-[(2-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-2-oxoethyl)oxy]phenyl}-1*H*-pyrrole-1-carboxylate
58	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-{[3-(1*H*-pyrrol-2-yl)phenyl]oxy}acetamide
59	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-[(3-pyrimidin-5-ylphenyl)oxy]acetamide
60	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-{[3-(1*H*-1,2,3-triazol-1-yl)phenyl]oxy}acetamide
61	4-chloro-*N*-(2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}ethyl)-3-(trifluoromethyl)aniline
62	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N*-(2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}ethyl)formamide
63	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-[(3-pyridin-3-ylphenyl)oxy]acetamide
64	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-[(3-furan-3-ylphenyl)oxy]acetamide

Table 8	
Entry	**Name**
65	(2E)-*N*-[4-fluoro-3-(trifluoromethyl)phenyl]-3-[3-(1*H*-tetrazol-1-yl)phenyl]prop-2-enamide
66	*N*-[4-fluoro-3-(trifluoromethyl)phenyl]-3-[3-(1*H*-tetrazol-1-yl)phenyl]propanamide
67	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-{[6-(1*H*-tetrazol-1-yl)pyrimidin-4-yl]oxy}acetamide
68	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-{[3-(3,5-dimethylisoxazol-4-yl)phenyl]oxy}acetamide
69	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-[(3-quinolin-7-ylphenyl)oxy]acetamide
70	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-[(3-furan-2-ylphenyl)oxy]acetamide
71	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-[3-(1*H*-tetrazol-1-yl)phenyl]hydrazinecarboxamide
72	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-[(3-dibenzo[b,d]furan-4-ylphenyl)oxy]acetamide
73	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-[(4-pyrimidin-5-ylphenyl)oxy]acetamide
74	*N*-methyl-*N*-[4-(methyloxy)phenyl]-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
75	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-{[3-(1*H*-tetrazol-1-yl)phenyl]methyl}urea
76	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N*-methyl-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
77	*N*-[4-fluoro-3-(trifluoromethyl)phenyl]-*N*~2~-[3-(1*H*-tetrazol-1-yl)phenyl]glycinamide
78	*N*-[4-fluoro-3-(trifluoromethyl)phenyl]-2-{[3-(pyridin-2-ylamino)phenyl]oxy}acetamide
79	*N*-[2-fluoro-5-(trifluoromethyl)phenyl]-2-[3-(1*H*-tetrazol-1-yl)phenyl]hydrazinecarboxamide
80	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-[(4-pyridin-3-ylphenyl)oxy]acetamide
81	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-[(3-pyrimidin-5-ylphenyl)methyl]urea
82	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-[(4-pyrimidin-5-ylphenyl)methyl]urea
83	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-[(4-pyridin-3-ylphenyl)methyl]urea
84	[3-(1*H*-tetrazol-1-yl)phenyl]methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
85	*N*-[4-fluoro-3-(trifluoromethyl)phenyl]-2-[(4-pyrimidin-5-ylphenyl)oxy]acetamide

Table 8	
Entry	**Name**
86	*N*~2~-[4-chloro-3-(trifluoromethyl)phenyl]-*N*-[3-(1*H*-tetrazol-1-yl)phenyl]glycinamide
87	2-{[4-chloro-3-(trifluoromethyl)phenyl]oxy}-*N*-[3-(1*H*-tetrazol-1-yl)phenyl]acetamide
88	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-{[3-methyl-4-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
89	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-{[4-(1*H*-1,2,3-triazol-1-yl)phenyl]oxy}acetamide
90	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-{[3-fluoro-4-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
91	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-{[2-fluoro-4-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
92	*N*-({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)-3-(1*H*-tetrazol-1-yl)benzenesulfonamide
93	*N*-({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)-*N*-methyl-3-(1*H*-tetrazol-1-yl)benzenesulfonamide
94	*N*-[4-fluoro-3-(trifluoromethyl)phenyl]-2-[(4-pyridin-3-ylphenyl)oxy]acetamide
95	2-({4-[2,4-bis(methyloxy)pyrimidin-5-yl]phenyl}oxy)-*N*-[4-fluoro-3-(trifluoromethyl)phenyl]acetamide
96	2-({4-[2,4-bis(methyloxy)pyrimidin-5-yl]phenyl}oxy)-*N*-[4-chloro-3-(trifluoromethyl)phenyl]acetamide
97	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-[(4-pyridin-4-ylphenyl)oxy]acetamide
98	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N*~2~-[3-(methyloxy)-4-(1*H*-tetrazol-1-yl)phenyl]glycinamide
99	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N*~2~-[4-(methyloxy)-3-(1*H*-tetrazol-1-yl)phenyl]glycinamide
100	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N*~2~-[4-(1*H*-tetrazol-1-yl)phenyl]glycinamide
101	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-(2,3,5,6-tetrafluoro-4-pyrimidin-5-ylphenyl)hydrazinecarboxamide
102	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-{[4-(1*H*-tetrazol-1-yl)phenyl]methyl}urea
103	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-(4-pyrimidin-5-ylphenyl)hydrazinecarboxamide
104	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-[(3-pyridin-3-ylphenyl)methyl]urea
105	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-methyl-2-{[3-(1*H*-tetrazol-1-yl)phenyl]oxy}propanamide
106	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-{[4-(1*H*-tetrazol-1-yl)phenyl]oxy}propanamide

Table 8	
Entry	**Name**
107	*N*-({4-[2,4-bis(methyloxy)pyrimidin-5-yl]phenyl}methyl)-*N'*-[4-chloro-3-(trifluoromethyl)phenyl]urea
108	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-({3-[2-(methyloxy)pyrimidin-5-yl]phenyl}methyl)urea
109	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-({3-[6-(methyloxy)pyridin-3-yl]phenyl}methyl)urea
110	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-({4-[2-(methyloxy)pyrimidin-5-yl]phenyl}methyl)urea
111	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-({4-[6-(methyloxy)pyridin-3-yl]phenyl}methyl)urea
112	1,1-dimethylethyl 2-{4-[(2-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-2-oxoethyl)oxy]phenyl}-1*H*-indole-1-carboxylate
113	*N*-({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)-4-(1*H*-tetrazol-1-yl)benzenesulfonamide
114	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N*~2~-[3-(2*H*-tetrazol-5-yl)phenyl]glycinamide
115	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-{[2,6-difluoro-4-(1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
116	(3-pyridin-3-ylphenyl)methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
117	(3-pyrimidin-5-ylphenyl)methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
118	(3-pyridin-4-ylphenyl)methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
119	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-[4-(1*H*-tetrazol-1-yl)phenyl]hydrazinecarboxamide
120	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-(4-pyridin-3-ylphenyl)hydrazinecarboxamide
121	(4-pyridin-3-ylphenyl)methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
122	(4-pyridin-4-ylphenyl)methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
123	(4-pyrimidin-5-ylphenyl)methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
124	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-[(4-pyridin-4-ylphenyl)methyl]urea
125	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-(3-pyridin-3-ylphenyl)hydrazinecarboxamide
126	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-(3-pyrimidin-5-ylphenyl)hydrazinecarboxamide
127	*N*-[5-chloro-2,4-bis(methyloxy)phenyl]-*N'*-[(4-pyrimidin-5-ylphenyl)methyl]urea

Table 8	
Entry	**Name**
128	*N*-[5-chloro-2,4-bis(methyloxy)phenyl]-*N'*-[(4-pyridin-3-ylphenyl)methyl]urea
129	(4-pyrimidin-5-ylphenyl)methyl [5-chloro-2,4-bis(methyloxy)phenyl]carbamate
130	(4-pyridin-3-ylphenyl)methyl [5-chloro-2,4-bis(methyloxy)phenyl]carbamate
131	1-(4-pyridin-3-ylphenyl)ethyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
132	1-(4-pyrimidin-5-ylphenyl)ethyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
133	*N*-[5-chloro-2,4-bis(methyloxy)phenyl]-*N'*-[(3-pyridin-3-ylphenyl)methyl]urea
134	*N*-[5-chloro-2,4-bis(methyloxy)phenyl]-*N'*-[(3-pyrimidin-5-ylphenyl)methyl]urea
135	(3-pyridin-3-ylphenyl)methyl [5-chloro-2,4-bis(methyloxy)phenyl]carbamate
136	(3-pyrimidin-5-ylphenyl)methyl [5-chloro-2,4-bis(methyloxy)phenyl]carbamate
137	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-methyl-2-(3-pyrimidin-5-ylphenyl)hydrazinecarboxamide
138	*N*-[4-fluoro-3-(trifluoromethyl)phenyl]-*N'*-[(4-pyridin-3-ylphenyl)methyl]urea
139	*N*-{[3-(6-aminopyridin-3-yl)phenyl]methyl}-*N'*-[4-chloro-3-(trifluoromethyl)phenyl]urea
140	*N*-{[4-(6-aminopyridin-3-yl)phenyl]methyl}-*N'*-[4-chloro-3-(trifluoromethyl)phenyl]urea
141	*N*-{[3-(2-aminopyrimidin-5-yl)phenyl]methyl}-*N'*-[4-chloro-3-(trifluoromethyl)phenyl]urea
142	*N*-{[4-(2-aminopyrimidin-5-yl)phenyl]methyl}-*N'*-[4-chloro-3-(trifluoromethyl)phenyl]urea
143	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-[1-(4-pyridin-3-ylphenyl)ethyl]urea
144	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-[1-(4-pyrimidin-5-ylphenyl)ethyl]urea
145	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-{[4-(1*H*-indol-2-yl)phenyl]oxy}acetamide
146	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-(isoquinolin-7-yloxy)acetamide
147	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-(4-pyridin-4-ylphenyl)hydrazinecarboxamide
148	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-(3-pyridin-4-ylphenyl)hydrazinecarboxamide

Table 8	
Entry	**Name**
149	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-[(3-pyridin-4-ylphenyl)methyl]urea
150	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-[(3-quinoxalin-6-ylphenyl)methyl]urea
151	methyl 3-amino-6-(3-{[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]methyl}phenyl)pyrazine-2-carboxylate
152	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-[(4-quinoxalin-6-ylphenyl)methyl]urea
153	*N*-{[3-(2-amino-5-methylpyridin-3-yl)phenyl]methyl}-*N'*-[4-chloro-3-(trifluoromethyl)phenyl]urea
154	methyl 3-amino-6-(4-{[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]methyl}phenyl)pyrazine-2-carboxylate
155	[3-(1*H*-tetrazol-1-yl)phenyl]methyl [3-chloro-4-(methyloxy)phenyl]carbamate
156	*N*-[3-chloro-4-(methyloxy)phenyl]-*N'*-{[3-(1*H*-tetrazol-1-yl)phenyl]methyl}urea
157	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-2-{[4-(5-hydroxy-1*H*-tetrazol-1-yl)phenyl]oxy}acetamide
158	*N*-{[3-(2-amino-5-chloropyridin-3-yl)phenyl]methyl}-*N'*-[4-chloro-3-(trifluoromethyl)phenyl]urea
159	*N*-{[4-(2-amino-5-chloropyridin-3-yl)phenyl]methyl}-*N'*-[4-chloro-3-(trifluoromethyl)phenyl]urea
160	*N*-{[3-(6-chloropyridin-3-yl)phenyl]methyl}-*N'*-[4-chloro-3-(trifluoromethyl)phenyl]urea
161	*N*-{[4-(6-chloropyridin-3-yl)phenyl]methyl}-*N'*-[4-chloro-3-(trifluoromethyl)phenyl]urea
162	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-{[4-(pyrimidin-2-yloxy)phenyl]methyl}urea
163	*N*-({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)-3-(1*H*-tetrazol-1-yl)benzamide
164	3-amino-6-(3-{[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]methyl}phenyl)-*N*-[2-(dimethylamino)ethyl]pyrazine-2-carboxamide
165	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-{[3-(6-fluoropyridin-3-yl)phenyl]methyl}urea
166	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-({3-[2-(methyloxy)pyridin-3-yl]phenyl}methyl)urea
167	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-{[4-(6-fluoropyridin-3-yl)phenyl]methyl}urea

Table 8	
Entry	**Name**
168	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-({4-[2-(methyloxy)pyridin-3-yl]phenyl}methyl)urea
169	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-{[4-(6-methylpyridin-3-yl)phenyl]methyl}urea
170	*N*-{[4-(2-amino-5-fluoropyridin-3-yl)phenyl]methyl}-*N'*-[4-chloro-3-(trifluoromethyl)phenyl]urea
171	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-{[3-(6-methylpyridin-3-yl)phenyl]methyl}urea
172	*N*-{[4-(2-aminopyridin-3-yl)phenyl]methyl}-*N'*-[4-chloro-3-(trifluoromethyl)phenyl]urea
173	*N*-{[3-(2-aminopyridin-3-yl)phenyl]methyl}-*N'*-[4-chloro-3-(trifluoromethyl)phenyl]urea
174	[3-(6-methylpyridin-3-yl)phenyl]methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
175	[3-(2-amino-5-fluoropyridin-3-yl)phenyl]methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
176	[3-(2-aminopyridin-3-yl)phenyl]methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
177	(3-pyrazin-2-ylphenyl)methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
178	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-({3-[6-(hydroxymethyl)pyridin-3-yl]phenyl}methyl)urea
179	*N*-{[3-(6-acetylpyridin-3-yl)phenyl]methyl}-*N'*-[4-chloro-3-(trifluoromethyl)phenyl]urea
180	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-{[3-(6-cyanopyridin-3-yl)phenyl]methyl}urea
181	1,1-dimethylethyl (3*S*)-3-({[3-amino-6-(3-{[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]methyl}phenyl)pyrazin-2-yl]carbonyl}amino)piperidine-1-carboxylate
182	3-amino-6-(3-{[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]methyl}phenyl)-*N*-[(3*S*)-piperidin-3-yl]pyrazine-2-carboxamide
183	1,1-dimethylethyl (3*S*)-3-({[3-amino-6-(4-{[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]methyl}phenyl)pyrazin-2-yl]carbonyl}amino)piperidine-1-carboxylate
184	3-amino-6-(4-{[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]methyl}phenyl)-*N*-[(3*S*)-piperidin-3-yl]pyrazine-2-carboxamide
185	[3-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
186	*N*-{[3-(2-amino-5-fluoropyridin-3-yl)phenyl]methyl}-*N'*-[4-chloro-3-(trifluoromethyl)phenyl]urea

Table 8	
Entry	**Name**
187	[6-(1*H*-tetrazol-1-yl)pyridin-2-yl]methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
188	[3-(1*H*-benzimidazol-2-yl)phenyl]methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
189	[3-(6-amino-2-methylpyridin-3-yl)phenyl]methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
190	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-({3-[5-(methylthio)pyridin-3-yl]phenyl}methyl)urea
191	[4-(6-methylpyridin-3-yl)phenyl]methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
192	[4-(2-amino-5-fluoropyridin-3-yl)phenyl]methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
193	[4-(2-aminopyridin-3-yl)phenyl]methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
194	(4-pyrazin-2-ylphenyl)methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
195	[4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl]methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
196	[4-(6-amino-2-methylpyridin-3-yl)phenyl]methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
197	[3-(1*H*-tetrazol-1-yl)phenyl]methyl 1,3-benzothiazol-2-ylcarbamate
198	[3-(1*H*-tetrazol-1-yl)phenyl]methyl (5-bromopyridin-2-yl)carbamate
199	(3-pyridin-3-ylphenyl)methyl (3,5-dimethylphenyl)carbamate
200	(3-pyridin-3-ylphenyl)methyl [5-chloro-2-(methyloxy)phenyl]carbamate
201	[4-(1*H*-tetrazol-1-yl)phenyl]methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
202	(3-pyrimidin-5-ylphenyl)methyl [5-chloro-2-(methyloxy)phenyl]carbamate
203	(4-pyrimidin-5-ylphenyl)methyl (3,4-dimethylphenyl)carbamate
204	(3-pyridin-3-ylphenyl)methyl (3,4-dimethylphenyl)carbamate
205	1,1-dimethylethyl 3-({[3-amino-6-(3-{[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]methyl}phenyl)pyrazin-2-yl]carbonyl}amino)piperidine-1-carboxylate
206	1,1-dimethylethyl 3-({[3-amino-6-(4-{[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]methyl}phenyl)pyrazin-2-yl]carbonyl}amino)piperidine-1-carboxylate
207	3-amino-6-(3-{[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]methyl}phenyl)-*N*-piperidin-3-ylpyrazine-2-carboxamide

Table 8	
Entry	**Name**
208	3-amino-6-(4-{[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]methyl}phenyl)-*N*-piperidin-3-ylpyrazine-2-carboxamide
209	1,1-dimethylethyl 4-{[3-amino-6-(3-{[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]methyl}phenyl)pyrazin-2-yl]carbonyl}piperazine-1-carboxylate
210	1,1-dimethylethyl 4-{[3-amino-6-(4-{[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]methyl}phenyl)pyrazin-2-yl]carbonyl}piperazine-1-carboxylate
211	*N*-({3-[5-amino-6-(piperazin-1-ylcarbonyl)pyrazin-2-yl]phenyl}methyl)-*N'*-[4-chloro-3-(trifluoromethyl)phenyl]urea
212	*N*-({4-[5-amino-6-(piperazin-1-ylcarbonyl)pyrazin-2-yl]phenyl}methyl)-*N'*-[4-chloro-3-(trifluoromethyl)phenyl]urea
213	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-{[3-(1*H*-pyrazol-4-yl)phenyl]methyl}urea
214	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-{[4-(1*H*-pyrazol-4-yl)phenyl]methyl}urea
215	[3-(2-piperazin-1-ylpyrimidin-5-yl)phenyl]methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
216	[4-(2-piperazin-1-ylpyrimidin-5-yl)phenyl]methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
217	*N*-{[3-(2-chloropyridin-3-yl)phenyl]methyl}-*N'*-[4-chloro-3-(trifluoromethyl)phenyl]urea
218	*N*-{[4-(2-chloropyridin-3-yl)phenyl]methyl}-*N'*-[4-chloro-3-(trifluoromethyl)phenyl]urea
219	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-{[3-(2-fluoropyridin-3-yl)phenyl]methyl}urea
220	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-{[4-(2-fluoropyridin-3-yl)phenyl]methyl}urea
221	[3-(1*H*-tetrazol-1-yl)phenyl]methyl [3-(trifluoromethyl)phenyl]carbamate
222	[3-(1*H*-tetrazol-1-yl)phenyl]methyl [6-(trifluoromethyl)pyridin-2-yl]carbamate
223	[3-(1*H*-tetrazol-1-yl)phenyl]methyl [4-(trifluoromethyl)pyridin-2-yl]carbamate
224	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-({3-[5-(methylthio)pyridin-2-yl]phenyl}methyl)urea
225	[3-(2,6-dimethylpyridin-3-yl)phenyl]methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
226	{3-[5-(methyloxy)pyridin-3-yl]phenyl}methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate

Table 8	
Entry	**Name**
227	2,3'-bipyridin-6-ylmethyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
228	(6-pyrimidin-5-ylpyridin-2-yl)methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
229	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-[(3-isoquinolin-4-ylphenyl)methyl]urea
230	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-[(4-isoquinolin-4-ylphenyl)methyl]urea
231	[6-(1*H*-tetrazol-1-yl)pyridin-2-yl]methyl [4-(trifluoromethyl)pyridin-2-yl]carbamate
232	[3-(1*H*-pyrazol-4-yl)phenyl]methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate
233	[4-(1*H*-pyrazol-4-yl)phenyl]methyl [4-chloro-3-(trifluoromethyl)phenyl]carbamate

Table 9. c-KIT and/or Flt-3 Inhibitors

[00226] The Compounds in Table 9 can be prepared as pharmaceutically acceptable salts, solvates, hydrates, and/or isomers thereof. All such salt, solvate, hydrate, and isomer combinations of the Compounds in Table 9 can be used to practice the invention.

Table 9	
Entry	**Name**
1	4-((*E*)-2-{3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}ethenyl)phenol
2	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-(4-{3-[5-(4-ethylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)urea
3	*N*-(3-ethylphenyl)-*N'*-(4-{3-[5-(4-ethylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)urea
4	*N*-(4-{3-[5-(4-ethylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)-*N'*-[3-(trifluoromethyl)phenyl]urea
5	*N*-(3-acetylphenyl)-*N'*-(4-{3-[5-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)urea
6	*N*-(3,4-dichlorophenyl)-*N'*-(4-{3-[5-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)urea
7	*N*-(3-bromophenyl)-*N'*-(4-{3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)urea
8	*N*-[4-fluoro-3-(trifluoromethyl)phenyl]-*N'*-(4-{3-[5-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)urea
9	*N*-(4-{3-[5-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)-*N'*-[4-(phenyloxy)phenyl]urea

Table 9	
Entry	**Name**
10	*N*-(3-chlorophenyl)-*N'*-(4-{3-[5-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)urea
11	*N*-[3,5-bis(methyloxy)phenyl]-*N'*-(4-{3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)urea
12	*N*-(4-{3-[5-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)-*N'*-{4-[(trifluoromethyl)oxy]phenyl}urea
13	*N*-(4-{3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)-*N'*-[4-(trifluoromethyl)phenyl]urea
14	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-(4-{3-[5-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)urea
15	*N*-(4-{3-[5-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)-*N'*-[3-(trifluoromethyl)phenyl]urea
16	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-(4-{3-[4-(4-methylpiperazin-1-yl)phenyl]-1*H*-pyrazol-5-yl}phenyl)urea
17	*N*-(3,4-dimethylphenyl)-*N'*-(4-{5-[4-(4-methylpiperazin-1-yl)phenyl]-1*H*-pyrazol-3-yl}phenyl)urea
18	*N*-(4-chlorophenyl)-*N'*-(4-{3-[5-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)urea
19	*N*-(3,5-difluorophenyl)-*N'*-(4-{3-[5-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)urea
20	*N*-[3-(methyloxy)phenyl]-*N'*-(4-{3-[5-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)urea
21	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-(4-{3-[4-(4-ethylpiperazin-1-yl)phenyl]-1*H*-pyrazol-5-yl}phenyl)urea
22	*N*-(3-fluorophenyl)-*N'*-(4-{3-[5-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)urea
23	*N*-(4-fluorophenyl)-*N'*-(4-{3-[5-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)urea
24	*N*-(3-cyanophenyl)-*N'*-(4-{3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)urea
25	*N*-(3,4-difluorophenyl)-*N'*-(4-{3-[5-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)urea
26	*N*-[3,4-bis(methyloxy)phenyl]-*N'*-(4-{3-[5-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)urea
27	*N*-[5-chloro-2-(methyloxy)phenyl]-*N'*-(4-{5-[4-(4-methylpiperazin-1-yl)phenyl]-1*H*-pyrazol-3-yl}phenyl)urea
28	*N*-(4-{5-[4-(4-methylpiperazin-1-yl)phenyl]-1*H*-pyrazol-3-yl}phenyl)-*N'*-[4-(phenyloxy)phenyl]urea
29	*N*-(2,4-difluorophenyl)-*N'*-(4-{3-[6-(4-ethylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)urea
30	*N*-{4-[3-(1*H*-benzimidazol-2-yl)-1*H*-pyrazol-5-yl]phenyl}-*N'*-[4-chloro-3-(trifluoromethyl)phenyl]urea

Table 9	
Entry	**Name**
31	*N*-{4-[3-(1*H*-benzimidazol-2-yl)-1*H*-pyrazol-5-yl]phenyl}-*N'*-[2-fluoro-5-(trifluoromethyl)phenyl]urea
32	*N*-(2,4-difluorophenyl)-*N'*-(4-{3-[5-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)urea
33	*N*-{4-[3-(1*H*-benzimidazol-2-yl)-1*H*-pyrazol-5-yl]phenyl}-*N'*-phenylurea
34	*N*-[3,5-bis(trifluoromethyl)phenyl]-*N'*-(4-{3-[5-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)urea
35	*N*-(2-fluorophenyl)-*N'*-(4-{3-[5-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)urea
36	4-((*E*)-2-{5-[(*E*)-2-phenylethenyl]-1*H*-pyrazol-3-yl}ethenyl)phenol
37	2-(methyloxy)-4-((*E*)-2-{5-[(*E*)-2-phenylethenyl]-1*H*-pyrazol-3-yl}ethenyl)phenol
38	*N*-(5-fluoro-2-methylphenyl)-*N'*-(4-{3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)urea
39	*N*-(4-{3-[5-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)-*N'*-phenylurea
40	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-(4-{3-[3-(4-methylpiperazin-1-yl)phenyl]-1*H*-pyrazol-5-yl}phenyl)urea
41	*N*-(2,4-difluorophenyl)-*N'*-(4-{3-[4-(4-methylpiperazin-1-yl)phenyl]-1*H*-pyrazol-5-yl}phenyl)urea
42	*N*-(2,3-dihydro-1,4-benzodioxin-6-yl)-*N'*-(4-{5-[4-(4-methylpiperazin-1-yl)phenyl]-1*H*-pyrazol-3-yl}phenyl)urea
43	*N*-[2,4-bis(methyloxy)phenyl]-*N'*-(4-{5-[4-(4-methylpiperazin-1-yl)phenyl]-1*H*-pyrazol-3-yl}phenyl)urea
44	4-((*E*)-2-{3-[(*E*)-2-(4-fluorophenyl)ethenyl]-1*H*-pyrazol-5-yl}ethenyl)-2-(methyloxy)phenol
45	4-{(*E*)-2-[3-(1-benzofuran-2-yl)-1*H*-pyrazol-5-yl]ethenyl}phenol
46	*N*-(4-{3-[4-(4-methylpiperazin-1-yl)phenyl]-1*H*-pyrazol-5-yl}phenyl)-*N'*-(2-phenylethyl)ethanediamide
47	4-{(*E*)-2-[3-(1*H*-benzimidazol-2-yl)-1*H*-pyrazol-5-yl]ethenyl}phenol
48	4-((*E*)-2-{3-[(*E*)-2-(4-chlorophenyl)ethenyl]-1*H*-pyrazol-5-yl}ethenyl)-2-(methyloxy)phenol
49	4-{(*E*)-2-[3-(1-benzothien-2-yl)-1*H*-pyrazol-5-yl]ethenyl}phenol
50	*N*-[4-chloro-3-(trifluoromethyl)phenyl]-*N'*-[4-(3-phenyl-1*H*-pyrazol-5-yl)phenyl]urea
51	4-((*E*)-2-{3-[4-(4-methylpiperazin-1-yl)phenyl]-1*H*-pyrazol-5-yl}ethenyl)phenol
52	1,1-dimethylethyl {4-[3-(1*H*-benzimidazol-2-yl)-1*H*-pyrazol-5-yl]phenyl}carbamate
53	*N*-(5-fluoro-2-methylphenyl)-*N'*-(4-{5-[4-(4-methylpiperazin-1-yl)phenyl]-1*H*-pyrazol-3-yl}phenyl)urea
54	4-[(*E*)-2-(3-phenyl-1*H*-pyrazol-5-yl)ethenyl]phenol

Table 9	
Entry	**Name**
55	2-(methyloxy)-4-[(*E*)-2-(5-phenyl-1*H*-pyrazol-3-yl)ethenyl]phenol
56	4-[(*E*)-2-(5-naphthalen-2-yl-1*H*-pyrazol-3-yl)ethenyl]phenol
57	4-{(*E*)-2-[5-(2-fluorophenyl)-1*H*-pyrazol-3-yl]ethenyl}phenol
58	4-((*E*)-2-{3-[3-(4-methylpiperazin-1-yl)phenyl]-1*H*-pyrazol-5-yl}ethenyl)phenol
59	4-((*E*)-2-{3-[(*E*)-2-(2,4-difluorophenyl)ethenyl]-1*H*-pyrazol-5-yl}ethenyl)-2-(methyloxy)phenol
60	4-{(*E*)-2-[5-(4-fluorophenyl)-1*H*-pyrazol-3-yl]ethenyl}phenol
61	4-{(*E*)-2-[3-(4-chlorophenyl)-1*H*-pyrazol-5-yl]ethenyl}phenol
62	4-[(*E*)-2-(5-pyridin-2-yl-1*H*-pyrazol-3-yl)ethenyl]phenol
63	4-{(*E*)-2-[3-(5-chloro-1-benzofuran-2-yl)-1*H*-pyrazol-5-yl]ethenyl}phenol
64	*N*-(1,1-dimethylethyl)-*N'*-(4-{3-[5-(4-ethylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-5-yl}phenyl)urea
65	4-[(*E*)-2-(3-pyridin-4-yl-1*H*-pyrazol-5-yl)ethenyl]phenol
66	4-{(*E*)-2-[3-(3-chlorophenyl)-1*H*-pyrazol-5-yl]ethenyl}phenol
67	4-((*E*)-2-{5-[2-(methyloxy)phenyl]-1*H*-pyrazol-3-yl}ethenyl)phenol
68	4-{(*E*)-2-[3-(2-chlorophenyl)-1*H*-pyrazol-5-yl]ethenyl}phenol
69	4-[(*E*)-2-(3-pyridin-3-yl-1*H*-pyrazol-5-yl)ethenyl]phenol
70	4-((*E*)-2-{5-[3-(methyloxy)phenyl]-1*H*-pyrazol-3-yl}ethenyl)phenol
71	1,1-dimethylethyl (4-{3-[(*E*)-2-phenylethenyl]-1*H*-pyrazol-5-yl}phenyl)carbamate
72	4-{(*E*)-2-[3-(3,4-dichlorophenyl)-1*H*-pyrazol-5-yl]ethenyl}phenol
73	2-{5-[(*E*)-2-phenylethenyl]-1*H*-pyrazol-3-yl}-1-benzofuran-6-ol
74	4-{(*E*)-2-[5-(3-fluorophenyl)-1*H*-pyrazol-3-yl]ethenyl}phenol
75	2-(5-phenyl-1*H*-pyrazol-3-yl)-1*H*-benzimidazole
76	*N*-phenyl-*N'*-[4-(3-phenyl-1*H*-pyrazol-5-yl)phenyl]urea
77	4-[3-(1*H*-benzimidazol-2-yl)-1*H*-pyrazol-5-yl]aniline
78	4-[(*E*)-2-(5-biphenyl-3-yl-1*H*-pyrazol-3-yl)ethenyl]phenol
79	4-((*E*)-2-{5-[5-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]-1*H*-pyrazol-3-yl}ethenyl)phenol

General Administration

[00227] In one aspect, the invention provides pharmaceutical compositions comprising an inhibitor of PI3K according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent. In certain other specific embodiments, administration is 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, specifically in unit dosage forms suitable for simple administration of precise dosages.

[00228] 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.

[00229] 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.

[00230] 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.

[00231] 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) 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.

[00232] 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.

[00233] 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.

[00234] 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.

[00235] 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.

[00236] 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.

[00237] 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.

[00238] 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.

[00239] 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.

[00240] 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.

[00241] 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.

[00242] Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington*N*'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.

[00243] The compounds of the invention, or their pharmaceutically acceptable salts or solvates, 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.

[00244] 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 active

agents within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agents when a combination formulation is inappropriate.

[00245] Representative pharmaceutical formulations containing a compound of Formula I are described below in the Pharmaceutical Composition Examples.

UTILITY

[00246] Certain compounds of Formula I have been tested using the assay described in Biological Example 1 and have been determined to be PI3K inhibitors. As such compounds of Formula I are useful for treating diseases, particularly cancer in which PI3Kactivity contributes to the pathology and/or symptomatology of the disease. For example, cancer in which PI3K activity contributes to its pathology and/or symptomatology include breast cancer, colon cancer, rectal cancer, endometrial cancer, gastric carcinoma, glioblastoma, hepatocellular carcinoma, small cell lung cancer, non-small cell lung cancer, melanoma, ovarian cancer, pancreatic cancer, prostate carcinoma, acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), and thyroid carcinoma, and the like.

[00247] Suitable *in vitro* assays for measuring PI3K activity and the inhibition thereof by compounds are known. Typically, the assay will measure PI3K-induced ATP consumption. For further details of an *in vitro* assay for measuring PI3K activity see Biological Examples, Example 1 *infra*. Cellular activity can be determined using assays as described in Biological Examples 2, 3, and 4 *infra*. Suitable *in vivo* models of cancer are known to those of ordinary skill in the art. For further details of *in vivo* assays see Biological Examples 5-10, *infra*. Examples describing the administration of a Compound of Formula I in combination with anticancer agents are described in Biological Examples 11-14, *infra*. Following the examples disclosed herein, as well as that disclosed in the art, a person of ordinary skill in the art can determine what ombinations of a Compound of Formula I and anti-cancer agents would be effective for treating cancer.

General Synthesis

[00248] Compounds of this invention can be made by the synthetic procedures described below. The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wis.), or

Bachem (Torrance, Calif.), or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon 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.

[00249] 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, in another embodiment from about 0 °C. to about 125 °C and in another embodiment 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.

[00250] 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.

[00251] 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. In particular, imidazol-5-yl and pyrazol-5-yl each can also exist in their respective tautomeric forms imidazol-4-yl and pyrazol-3-yl. Regardless of which structure or which terminology is used, each tautomer is included within the scope of the Invention.

[00252] 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.

[00253] 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

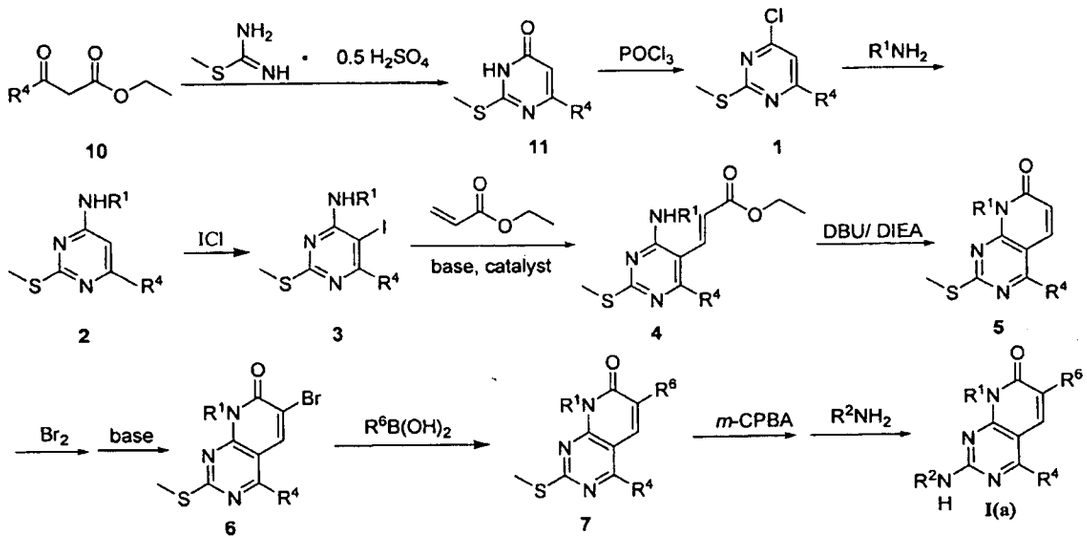
required to liberate the desired enantiomeric form. Alternatively, specific enantiomer may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents or by converting on enantiomer to the other by asymmetric transformation. For a mixture of enantiomers, enriched in a particular enantiomer, the major component enantiomer may be further enriched (with concomitant loss in yield) by recrystallization.

[00254] 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.

[00255] The chemistry for the preparation of the compounds of this invention is known to those skilled in the art. In fact, there may be more than one process to prepare the compounds of the invention. For specific examples, see M. Barvian et al. J. Med. Chem. 2000, 43, 4606-4616; S. N. VanderWei et al. J. Med. Chem. 2005, 48, 2371-2387; P. L. Toogood et al. J. Med. Chem. 2005, 48, 2388-2406; J. Kasparec et al. Tetrahedron Letters 2003, 44, 4567-4570; and references cited therein. See also U.S. Pre-grant publication US2004/0009993 A1 (M. Angiolini et al.), which is incorporated herein by reference, and references cited therein. The following examples illustrate but do not limit the invention. All references cited herein are incorporated by reference in their entirety.

[00256] A compound of the invention where R^1 is optionally substituted alkyl, R^2 is hydrogen or optionally substituted alkyl, R^4 is methyl or ethyl, R^6 is phenyl or heteroaryl each of which is optionally substituted with 1, 2, 3, 4, or 5 R^9 groups (as defined in the Summary of the Invention), and R^2 is hydrogen can be prepared according to Scheme 1.

Scheme 1



[00257] To a solution of commercially available 2-methyl-2-thiopseudourea sulfate in a solvent such as water is added a base such as sodium carbonate and an intermediate of formula **10** at room temperature. The reaction mixture is stirred for overnight or less. After neutralizing, **11** is collected through filtration and followed by drying under vacuum. **11** is then treated with $POCl_3$ and the reaction is heated to reflux for approximately 2 h and then concentrated under vacuum to dryness. **1** can be used directly in the next reaction without further purification.

[00258] An intermediate of formula **2** is prepared by reacting an intermediate of formula 1 with a primary amine R^1NH_2 in a solvent such as water and with heating. **2** is then treated with iodine monochloride in a solvent such as methanol at around 0 °C and allowed to react for approximately overnight or less as needed for the reaction to go to completion to form **3**. After completion the residue is triturated with acetone. The intermediate **3** is then reacted in a solvent, such as DMA, with ethyl acrylate in the presence of a base, such as triethylamine, and in the presence of a catalyst, such as $Pd(OAc)_2$, and (+)BINAP. The reaction is heated to approximately 100 °C and allowed to react for approximately overnight or less as needed for the reaction to go to completion to form **4**. **4** is then optionally purified by column chromatography.

[00259] **5** is prepared by treating **4** with DBU in the presence of a base such as DIPEA at room temperature. Then the reaction mixture is heated to reflux and reacted for approximately

15 h. After evaporation of solvent, the residue is triturated with acetone and collected by filtration to yield **5**.

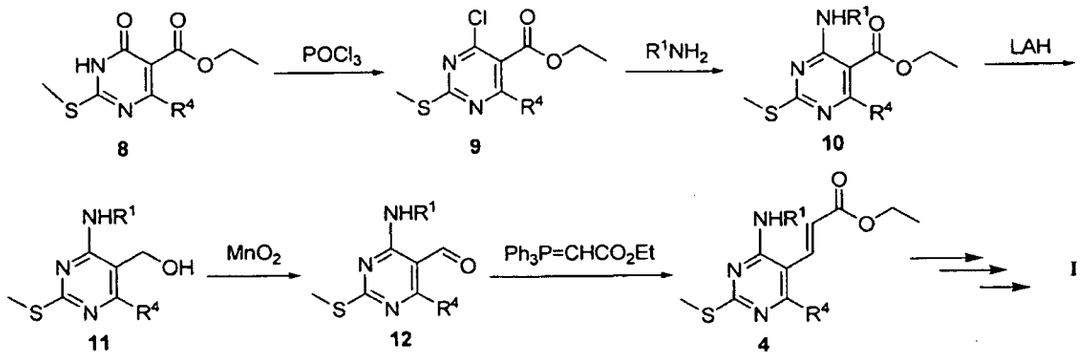
[00260] **6** is prepared by reacting **5** with a brominating agent such as Br_2 in a solvent such as DCM at room temperature. Then the reaction mixture is stirred for approximately overnight. The resulting product is filtered and then suspended in a solvent such as DCM and treated with a base such as triethylamine. The mixture is then washed with water and dried over a drying agent such as Na_2SO_4 to yield **6**.

[00261] A Suzuki coupling is then performed using **6** reacting with a boronic acid (or ester) of formula $R^6B(OH)_2$ in a solvent such as a DME-H_2O mixture, in the presence of a catalyst such as Pd(dpppf) and a base such as triethylamine at room temperature. The reaction mixture is heated to reflux for approximately 4 h. After cooling to room temperature, the reaction mixture is partitioned with water and ethyl acetate. After separation, the organic layer is dried over a drying agent such as Na_2SO_4 to yield **7**.

[00262] The methylthio group of **7** is then oxidized with *m*-CPBA in a solvent such as DCM at room temperature allowing to stir for approximately 4 h. After removal of the solvent under reduced pressure, the product is treated with with an amine of formula R^2NH_2 in a solvent such as dioxane and stirred at room temperature for approximately overnight to yield a Compound of Formula I.

[00263] Alternatively, a compound of the invention where R^1 is optionally substituted alkyl, R^4 is methyl or ethyl, R^6 is phenyl or heteroaryl each of which is optionally substituted with 1, 2, 3, 4, or 5 R^9 groups (as defined in the Summary of the Invention), and R^2 is hydrogen can be prepared according to Scheme 2.

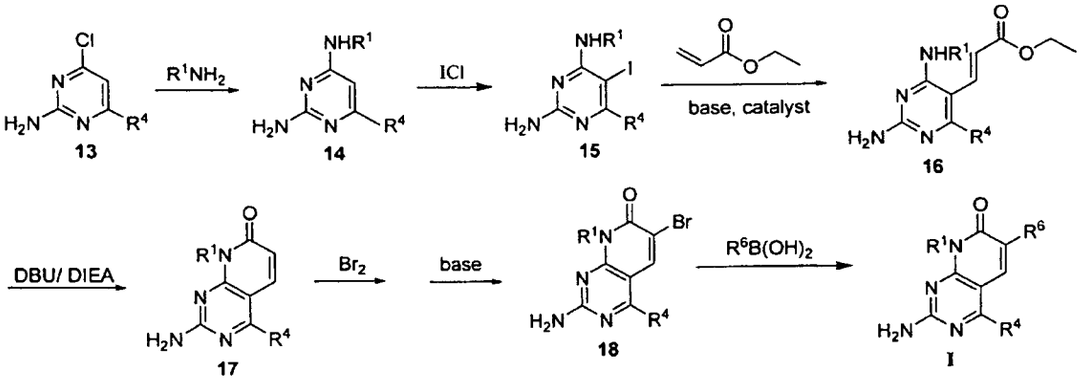
Scheme 2



[00264] An intermediate of formula **9** is prepared by reacting an intermediate of formula **8** with neat $POCl_3$ and heating. **9** is then treated with a primary amine R^1NH_2 in a solvent such as water or THF and triethylamine at 0 °C to form **10**. After removal of the solvent under reduced pressure, the intermediate **10** is then reacted with lithium aluminum hydride in a solvent such as THF at 0 °C. After quenching and aqueous workup, solvent removal provided crystalline **11** without further purification. Treatment of **11** with manganese (II) dioxide in a solvent such as methylene chloride or chloroform at room temperature provided aldehyde **12** upon filtration and solvent removal. A Wittig reaction with aldehyde **12** can be employed with (carbethoxymethylene)triphenylphosphorane in refluxing THF to provide the common intermediate **4**. **4** can then be used to prepare a Compounf of Frmula I using the procedures described in Scheme 1.

[00265] A compound of the invention where R^1 is optionally substituted alkyl, R^4 is methyl or ethyl, R^6 is phenyl or heteroaryl each of which is optionally substituted with 1, 2, 3, 4, or 5 R^9 groups (as defined in the Summary of the Invention), and R^2 is hydrogen can be prepared according to Scheme 3.

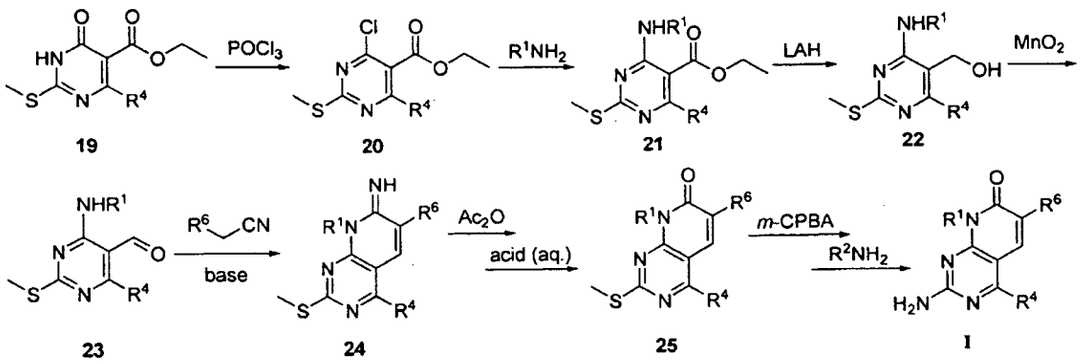
Scheme 3



[00266] An intermediate of formula **14** is prepared by reacting an intermediate of formula **13** with a primary amine R^1NH_2 in a solvent such as water and with heating. **14** is then treated with iodine monochloride in a solvent such as methanol at around 0 °C and allowed to react for approximately overnight or less as needed for the reaction to go to completion to form **15**. After completion the residue is triturated with acetone. The intermediate **15** is then reacted in a solvent, such as DMA, with ethyl acrylate in the presence of a base, such as triethylamine, and in the presence of a catalyst, such as $Pd(OAc)_2$, and (+)BINAP. The reaction is heated to approximately 100 °C and allowed to react for approximately overnight or less as needed for the reaction to go to completion to form **16**. **16** is then optionally purified by column chromatography. A Compound of Formula I can then be prepared from **16** by using the same reaction conditions as described in Scheme 1 (starting at the point of the preparation of **5** from **4**).

[00267] A compound of the invention where R^1 is optionally substituted alkyl, R^4 is methyl or ethyl, R^6 is phenyl or heteroaryl each of which is optionally substituted with 1, 2, 3, 4, or 5 R^9 groups (as defined in the Summary of the Invention), and R^2 is hydrogen can alternatively be prepared according to Scheme 4.

Scheme 4

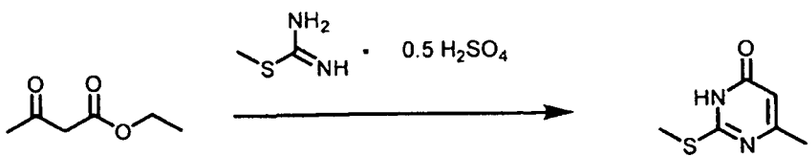


[00268] An intermediate of formula **20** is prepared by reacting an intermediate of formula **19** with neat $POCl_3$ and heating. **20** is then treated with a primary amine R^1NH_2 in a solvent such as water or THF and triethylamine at 0 °C to form **21**. After removal of the solvent under reduced pressure, the intermediate **21** is then reacted with lithium aluminum hydride in a solvent such as THF at 0 °C. After quenching and aqueous workup, solvent removal provided crystalline **22** without further purification. Treatment of **22** with manganese (II) dioxide in a solvent such as methylene chloride or chloroform at room temperature provided aldehyde **23** upon filtration and solvent removal. A Knovenegal-type condensation with **23** and an arylacetonitrile in the presence of a base such as potassium carbonate or sodium hydroxide in a protic solvent provides the cyclized imine **24**. Acetylation of the imine with acetic anhydride is required prior to hydrolysis which takes place in the presence of aqueous acid and heating to afford **25**. Subsequently, **25** can be oxidized to the corresponding sulfone with *m*-CPBA at room temperature and displaced with ammonium to provide **I**.

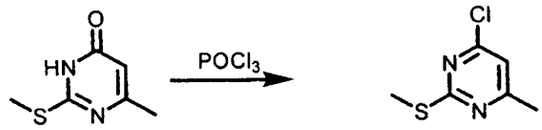
Synthetic Examples

Example 1

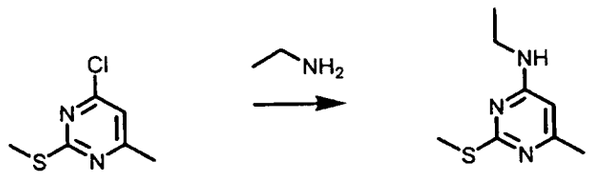
2-amino-8-ethyl-4-methyl-6-(1*H*-pyrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one



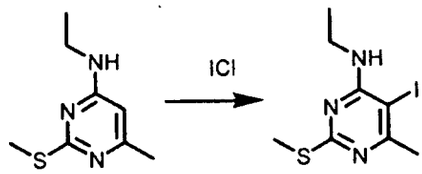
[00269] To a solution of 2-methyl-2-thiopseudourea sulfate (Aldrich, 58.74 g, 0.422 mol) in water (1000 mL) were added sodium carbonate (81.44 g, 0.768 mol) and ethyl acetoacetate (50 g, 0.384 mol) at room temperature. The reaction mixture was stirred overnight. After neutralizing to pH = 8, the solid was collected through filtration followed by drying under vacuum overnight to afford 6-methyl-2-(methylthio)pyrimidin-4(3*H*)-one (57.2 g, 95% yield) of product. ^{1}H NMR (400 MHz, DMSO-d6): δ 12.47 (bs, 1H), 5.96 (bs, 1H), 2.47(s, 3H), 2.17 (s, 3H).



[00270] To the round bottom flask containing 6-methyl-2-(methylthio)pyrimidin-4(3*H*)-one (19 g, 121.6 mmol) was added $POCl_3$ (30 mL). The reaction mixture was heated to reflux for 2 h and then concentrated on a rotary evaporator to dryness. The crude 4-chloro-6-methyl-2-(methylthio)pyrimidine was used directly in the next reaction without further purification.

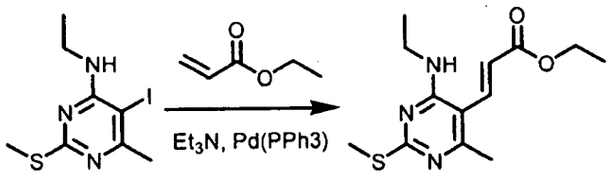


[00271] To the 4-chloro-6-methyl-2-(methylthio)pyrimidine from above was added 30 mL of a solution of 70% ethylamine in water. The reaction mixture was heated to 50 °C for 3 h. After completion, excess ethylamine was evaporated on rotary evaporator under vacuum. The solid was filtered and dried under vacuum to afford *N*-ethyl-6-methyl-2-(methylthio)pyrimidin-4-amine (20 g, 90% yield).

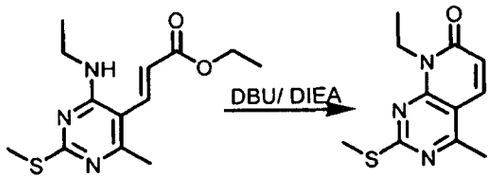


[00272] To the solution of *N*-ethyl-6-methyl-2-(methylthio)pyrimidin-4-amine (20 g, 121.6 mmol) in methanol was added iodine monochloride (26.58 g, 163.7 mmol) in small portions at 0 °C. Then the reaction mixture was stirred overnight. After evaporation of solvent, the residue

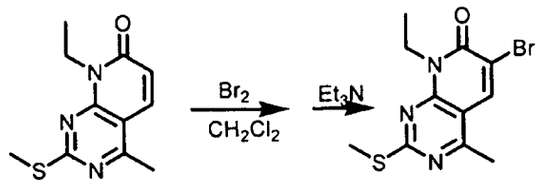
was triturated with acetone. The product *N*-ethyl-5-iodo-6-methyl-2-(methylthio)pyrimin-4-amine (25.2 g, 75% yield) was collected by filtration. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.37 (bs, 1H), 3.52 (q, J = 7.2 Hz, 1H), 2.50 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H).



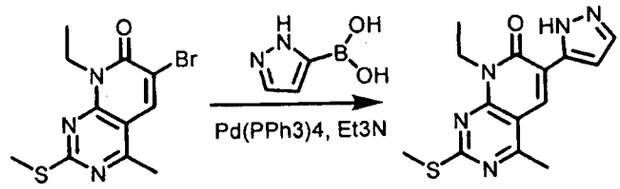
[00273] To the solution of *N*-ethyl-5-iodo-6-methyl-2-(methylthio)pyrimin-4-amine (25.2 g, 81.48 mmol) in DMA (260 mL) were added ethyl acrylate (12.23 g, 122.2 mmol), $Pd(OAc)_2$ (3.65 g, 16.25 mmol), (+)BINAP and triethyl amine (24.68 g, 244.4 mmol). Then the reaction mixture was heated to 100 °C and reacted overnight. After evaporation of solvent, the residue was diluted with water and the aqueous layer was extracted with ethyl acetate. The product (*E*)-ethyl-3-(4-(ethylamino)-6-methyl-2-(methylthio)pyrimidin-5-yl)acrylate (16.8 g, 73% yield) was isolated by silica gel column chromatography with 6-8% ethyl acetate in hexane as eluent. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 16.4Hz, 1H), 6.20 (d, J = 16.4Hz, 1H), 5.15 (bs, 1H), 4.28(q, J = 7.2 Hz, 2H), 3.54 (q, J = 7.2 Hz, 2H), 2.53 (s, 3H), 2.37 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H).



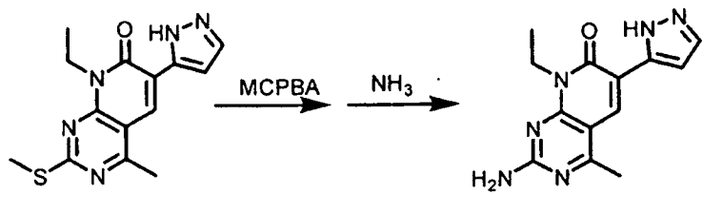
[00274] To a solution of (E)-ethyl-3-(4-(ethylamino)-6-methyl-2-(methylthio)pyrimidin-5-yl)acrylate (16.8 g, 59.8 mmol) in DIPEA was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 18.21 g, 119.6 mmol) at room temperature. Then the reaction mixture was heated to reflux and reacted for 15 h. After evaporation of solvent, the residue was triturated with acetone. The product 8-ethyl-4-methyl-2-(methylthio)pyrido[2,3-d]pyrimidin-7(8*H*)-one (10.77 g, 77% yield) was collected by filtration. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 9.6 Hz, 1H), 6.63 (d, J = 9.6 Hz, 1H), 4.5(q, J = 7.2 Hz, 2H), 2.67 (s, 3H), 2.62 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H).



[00275] To a solution of 8-ethyl-4-methyl-2-(methylthio)pyrido[2,3-d]pyrimidin-7(8*H*)-one (6.31 g, 26.84 mmol) in DCM was added Br_2 (4.79 g, 29.52 mmol) dropwise at room temperature. Then the reaction mixture was stirred at room temperature overnight. After filtration the solid was suspended in DCM (100 mL), and triethylamine (20 mL) was added. The mixture was washed with water and dried with Na_2SO_4, and the product 6-bromo-8-ethyl-4-methyl-2-(methylthio)pyrido[2,3-d]pyrimidin-7(8*H*)-one (6.96 g, 83 % yield) was obtained after evaporation of DCM. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (s, 1H), 4.56 (q, J = 7.2 Hz, 2H), 2.68 (s, 3H), 2.62 (s, 3H), 1.34 (t, J = 7.2Hz, 3H).



[00276] To a solution of 6-bromo-8-ethyl-4-methyl-2-(methylthio)pyrido[2,3-d]pyrimidin-7(8*H*)-one (0.765 g, 2.43 mmol) in DME-H_2O (10:1 11 mL) was added 1H-pyrazol-5-ylboronic acid (Frontier, 0.408 g, 3.65 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with CH_2Cl_2 (Pd(dpppf),0.198 g, 0.243 mmol) and triethylamine (0.736 g, 7.29 mmol) at room temperature. Then the reaction mixture was heated to reflux and reacted for 4 h. After cooling down to room temperature, the reaction mixture was partitioned with water and ethyl acetate. After separation, the organic layer was dried with Na_2SO_4, and the product 8-ethyl-4-methyl-2-(methylthio)-6-(1*H*-pyrazol-5-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one (0.567 g, 77% yield) was obtained by silica gel column chromatography. ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.3 (bs, 1H), 8.54 (s, 1H), 7.82-7.07 (m, 2H), 4.45 (q, J = 7.2 Hz, 2H), 2.71 (s, 3H), 2.60 (s, 3H), 1.26 (t, J = 7.2Hz, 3H).



[00277] To the solution of 8-ethyl-4-methyl-2-(methylthio)-6-(1*H*-pyrazol-5-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one (0.123 g, 0.41mmol) in DCM (2 mL) was added MCPBA (0.176 g, 77%, 0.785 mmol) in a small portion at room temperature. Then the reaction mixture was stirred for 4 h. After evaporation of DCM, dioxane (1 mL) and liquid ammonia (1 mL) were introduced. The reaction was stirred at room temperature overnight. The product 2-amino-8-ethyl-4-methyl-6-(1*H*-pyrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (50.4 mg) was obtained by silica gel column chromatography. ^{1}H NMR (400 MHz, CD_3OD): δ 8.41 (s, 1H), 7.62 (d, J = 2.0 Hz, 1H), 6.96 (d, J = 2.0Hz, 1H), 4.51 (q, J = 7.2Hz, 2H), 2.64 (s, 3H), 1.29 (t, J = 7.2Hz, 3H); MS (EI) for $C_{13}H_{14}N_6O$: 271.3 (MH^+).

[00278] Using the same or analogous synthetic techniques and substituting with appropriate reagents, the following compounds were prepared:

Example 1a. 2-(amino)-8-ethyl-4-ethyl-6-(1H-pyrazol-5-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, DMSO-D6): δ 8.40 (s, 1H), 7.27 (bs, 1H), 7.00 (s, 1H), 4.40 (q, J = 7.2 Hz, 2H), 2.95 (d, J = 7.20 Hz, 2H), 1.14 (t, J = 7.2 Hz, 3H), 1.08 (t, J = 7.2Hz, 3H), 0.89 (m, 1H), 0.24 (m, 2H), 0.01 (m, 2H); MS (EI) for $C_{14}H_{16}N_6O$: 285.2 (MH^+).

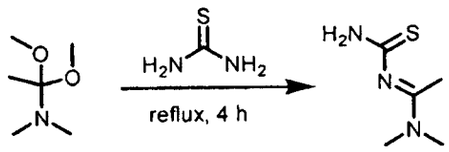
Example 1b. 8-ethyl-4-methyl-2-(methylamino)-6-(1H-pyrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, CH_3OH-d_4): δ 8.39 (s, 1H), 7.60 (bs, 1H), 6.93 (bs, 1H), 4.53 (bs, 2H), 3.02 (s, 3H), 2.84 (bs, 3H), 1.33 (bs, 3H); MS (EI) for $C_{14}H_{16}N_6O$: 285.3 (MH^+).

Example 1c. 8-Ethyl-2-[(2-fluoroethyl)amino]-4-methyl-6-(1*H*-pyrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, CH_3OH-d_4): δ 8.34 (bs, 1H), 7.25 (bs, 1H), 6.90 (bs, 1H), 4.60 (dt, *J* = 5.2, 2.2 Hz, 2H), 4.49 (q, *J* = 7.20 Hz, 2H), 3.78 (dt, *J* = 5.2, 2.2 Hz, 2H), 2.64 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H); MS (EI) for $C_{15}H_{17}FN_6O$: 317.3 (MH^+).

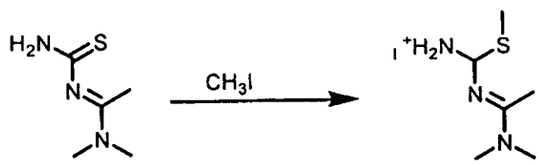
Example 1d. 2-Amino-8-cyclopentyl-4-methyl-6-(1*H*-pyrazol-3-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.10 (s, 1H), 8.42 (d, 1H), 7.70 (s, 1H), 7.20 (bs, 2H), 6.01 (m, 1H), 2.61 (s, 3H), 2.30 (m, 2H), 2.10 (m, 2H), 1.80 (m, 2H), 1.60 (m, 2H); MS (EI) for $C_{16}H_{18}N_6O$: 311.8 (M+H).

Intermediate 1

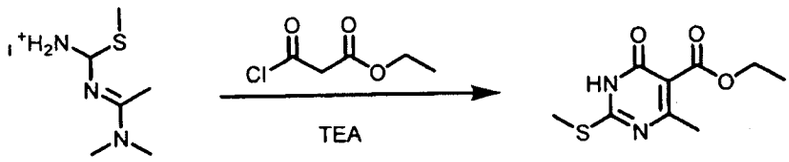
Alternate route to (E)-ethyl-3-(4-(ethylamino)-6-methyl-2-(methylthio)pyrimidin-5-yl)acrylate



[00279] *N,N*-Dimethyl acetamide dimethyl acetal (75 g, 0.56 mole) was added to a suspension of thiourea (33.0 g, 0.43 mole) in methylene chloride. The mixture was heated under reflux for 4 h. The solvent was removed and the residue was crystallized from 5% MeOH and diethyl ether affording (1E)-*N'*-(aminocarbonothioyl)-*N,N*-dimethylethanimidamide (47.8 g, 76% yield).

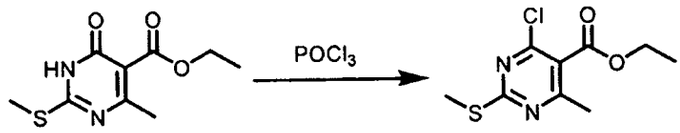


[00280] A suspension of (1E)-*N'*-(aminocarbonothioyl)-*N,N*-dimethylethanimidamide (47.8 g, 0.33 mole) in methyl iodide (150 mL) and THF (350 mL) was stirred for 18 h at room temperature. The mixture was evaporated under reduced pressure. After addition of 5% MeOH and diethyl ether, the compound precipitated and was collected by filtration affording (1*E*)-*N'*-[amino(methylthio)methyl]-*N,N*-dimethylethanimidamide hydrogen iodide salt (91.0 g, 96% yield).

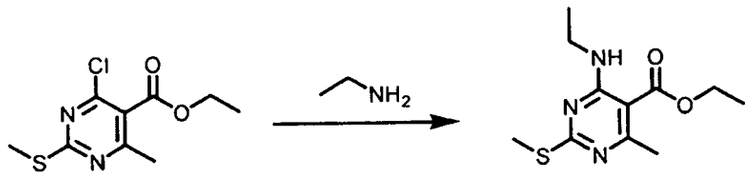


[00281] To a solution of (1E)-*N'*-[amino(methylthio)methyl]-*N,N*-dimethylethanimidamide hydrogen iodide salt (73.0 g, 0.26 mole) in dry dichloromethane (900 mL), was added ethyl 3-chloro-3-oxopropanoate (44 mL, 95% Lancaster, 0.34 mole) was added under a nitrogen

atmosphere. The mixture was stirred for 4 h at room temperature, cooled to 0 °C then triethylamine (107 mL, 0.78 mole) was added. The reaction mixture was stirred overnight. The solvent was removed and H_2O was added. The pH was adjusted to pH = 5.0 with acetic acid and extracted with ethylacetate then evaporated and crystallized from the appropriate solvent (Ethylacetate-Hexanes mixture solvent, approximately 20% ethylacetate-Hexanes). This afforded ethyl 4-methyl-2-(methylthio)-6-oxo-1,6-dihydropyrimidine-5-carboxylate (36.5 g, 62% yield) after drying under vacuum.

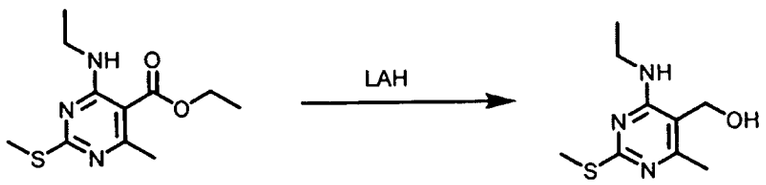


[00282] A solution of ethyl 4-methyl-2-(methylthio)-6-oxo-1,6-dihydropyrimidine-5-carboxylate (60 g, 0.26 mole) and phosphorous oxychloride ($POCl_3$, 320 mL) was heated under reflux for 4 to 5 h (monitor reaction by TLC using 30% ethylacetate and hexanes). After completion of reaction, phosphorous oxychloride was removed on a rotary evaporator. The residue was poured on to ice water and extracted with ethylacetate several times. The combined organic layers were evaporated, on a rotary evaporator, to give crude ethyl 4-chloro-6-methyl-2-(methylthio)pyrimidine-5-carboxylate (65 g). This compound was used without purification.

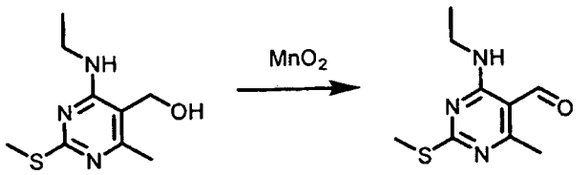


[00283] To a solution of ethyl 4-chloro-6-methyl-2-(methylthio)pyrimidine-5-carboxylate (65 g) in THF (1000 mL) and triethylamine (110 mL, 0.81 mole) was added ethylamine (2.0 M in THF, 0.81 mole) at 0 °C. This reaction mixture was stirred at room temperature overnight and then solvents were removed on a rotary evaporator. H_2O was added and the mixture extracted with ethyl acetate several times. Solvents from the combined organic layers were removed on a rotary evaporator affording 58 g (86% yield) of ethyl 4-(ethylamino)-6-methyl-2-

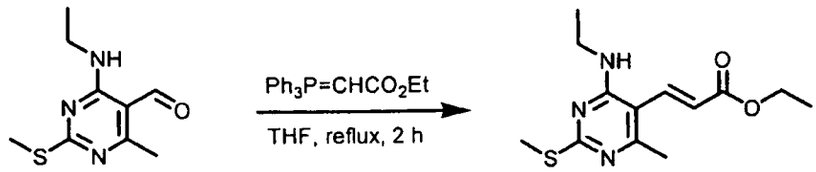
(methylthio)pyrimidine-5-carboxylate. This material was used as such without further purification.



[00284] To a lithium aluminum hydride solution (LAH, 1.0 M solution in THF, Aldrich, 450 mL) was added a solution of ethyl 4-(ethylamino)-6-methyl-2-(methylthio)pyrimidine-5-carboxylate (57 g) in THF (1000 mL). The reaction mixture was stirred overnight. After cooling to 0 °C, the reaction mixture was cautiously quenched with a 1:9 mixture of H_2O/THF until gas evolution has ceased, then diluted with H_2O (500 mL) and stirred well for 2 h. The resulting slurry was extracted with ethylacetate several times. The aqueous layer was then filtered through Celite and washed with ethylacetate again. The combined organic layers were washed with brine, dried and concentrated under reduced pressure to give 41.0 g (85% yield) of [4-(ethylamino)-6-methyl-2-(methylthio)pyrimidin-5-yl]methanol as a light yellow crystal, which was used without purification in the next step.



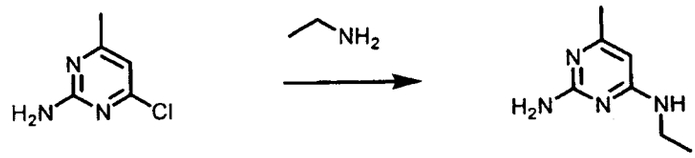
[00285] To a solution of [4-(ethylamino)-6-methyl-2-(methylthio)pyrimidin-5-yl]methanol (41.0 g) in chloroform (4000 mL) was added manganese oxide (125 g, 1.4 mole) and stirred for 4 h at room temperature. More manganese oxide was added until the disappearance of alcohol compound was observed. The reaction mixture was filtered through Celite and washed with some chloroform and evaporated all organic solvents to give 38 g (92 % yield) of 4-(ethylamino)-6-methyl-2-(methylthio)pyrimidine-5-carbaldehyde as a colorless solid, which was used without purification in the next step.



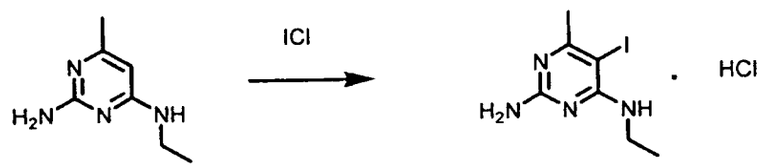
[00286] To a solution of 4-(ethylamino)-6-methyl-2-(methylthio)pyrimidine-5-carbaldehyde (38 g, 180 mmol) in THF (500 mL) was added (Carbethoxymethylene) triphenylphosphorane (95%, Aldrich, 85.18 g, 244 mmol). The reaction mixture was heated to reflux for 1.5 h and was monitered by TLC (4:1 hexanes/ethylacetate). The reaction was cooled to room temperature and was concentrated on a rotary evaporator. It was directly subjected to column chromatography (4:1 hexanes/ethylacetate) to give (E)-ethyl-3-(4-(ethylamino)-6-methyl-2-(methylthio)pyrimidin-5-yl)acrylate as a white crystal, 46.14 g (91% yield).

Example 2

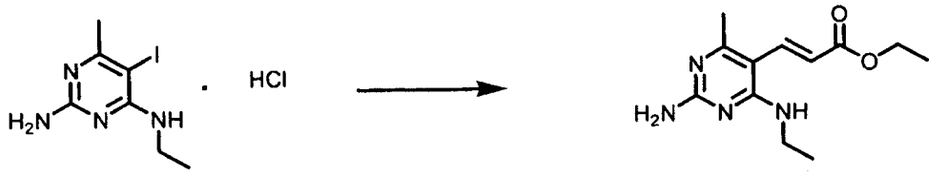
2-Amino-6-bromo-8-ethyl-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one



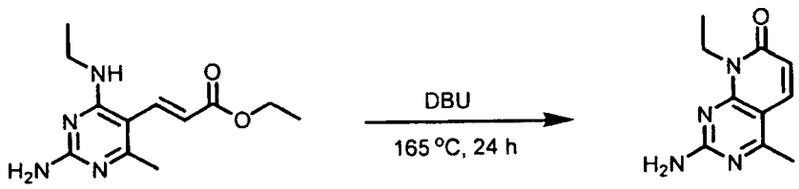
[00287] To a 3-necked 3-L flask, that was equipped with an overhead stirrer, was added in order 2-amino-4-chloro-6-methylpyrimidine (Aldrich, 100 g, 0.696 mol, 1 equiv.), ethylamine (70% ethylamine in water, Lancaster, 625 mL), 625 mL H_2O, and 125 mL TEA (0.889 mol, 1.28 equiv.). The mixture was stirred and heated at reflux for 20 h, during which time the reaction turned homogeneous. The reaction was allowed to cool to room temperature. The volatile ethylamine was removed on a rotary evaporator. A precipitate formed. The aqueous mixture containing the precipitate was allowed to stand at room temperature for 2 h and then filtered. After drying under vacuum, 106 g (100% yield) of 2-amino-6-ethylaminopyrimidine was obtained as a colorless solid. This material was used as such in the following reaction.



[00288] To a solution of 2-amino-6-ethylaminopyrimidine (98 g, 0.64 mol) in methanol (1.6 L) was added ICl (115.0 g, 0.71 mol) in a small portion at 15 °C. Then the reaction mixture was stirred at room temperature for 3 h (monitored by LC/MS). After evaporation of solvent by rotary evaporator, the residue was triturated with acetone. 2-amino-6-ethylamino-4-iodopyrimidine hydrochloride (188.5 g, 93% isolated yield) was obtained by vacuum filtration and drying. ^{1}H NMR (400 MHz, CD_3OD) δ 3.58 (q, 2H), 2.14 (s, 3H), 1.11 (t, 3H); MS (EI) for $C_7H_{11}N_4ClI$: 279.1 (MH^+).

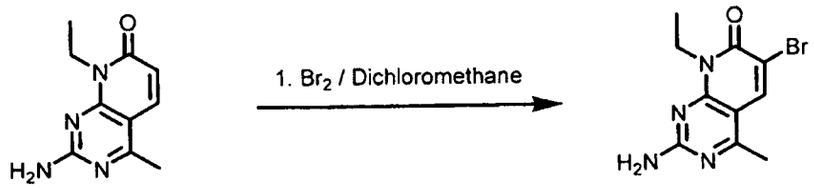


[00289] To a three-neck round bottom flask equipped with over-head mechanic stirrer were added 2-amino-6-ethylamino-4-iodopyrimidine hydrochloride (188.5 g, 0.60 mol), ethyl acrylate (221 mL, 2.0 mol), triethylamine (285 mL, 2.0 mol), DMF (1.3 L), and tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$, 31.3 g, 0.027 mol). The reaction mixture was heated to 95 °C and stirred for 3 h (monitored by LC/MC). After reaction completion, the reaction mixture was evaporated about to 1/10 of original volume and partitioned with 500 mL of ethyl acetate and 1000 mL of water. The aqueous layer was extracted with ethyl acetate 5 times. (E)-Ethyl 3-(2-amino-4-(ethylamino)-6-methylpyrimidin-5-yl)acrylate (100 g, 67% yield) was obtained by recrystalization from acetone after evaporation of ethyl acetate. ^{1}H NMR (400 MHz, CD_3OD) δ 7.48 (dd, *J1* = 16.0 Hz, *J2* = 4.0 Hz, 1H), 6.20 (dd, *J1* = 16 Hz, *J2* = 4 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 3.51 (q, *J* = 7.6 Hz, 2H), 2.39 (s, 3H), 1.3 (t, *J* = 7.2 Hz, 3H), 1.2 (t, *J* = 7.6 Hz, 3H). MS (EI) for $C_{12}H_{18}N_4O_2$: 251.3 (MH^+).



[00290] (E)-Ethyl 3-(2-amino-4-(ethylamino)-6-methylpyrimidin-5-yl)acrylate (4.50 g, 18.0 mmol) was added to DBU (10.95 g, 4.0 equiv.) and the mixture was heated to 165 °C and

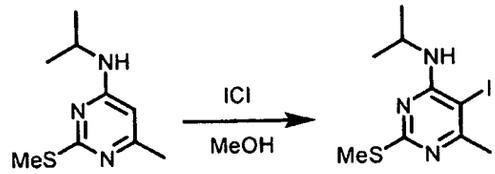
stirred for 24 h. After that, the mixture was cooled to 70 °C followed by the addition of H_2O (20 mL) to precipitate crystal and stirred for 1 h at room temperature. The crystal was collected and washed with H_2O and acetone and dried under vacuum to afford 2.70 g (73.5% yield of 2-amino-8-ethyl-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one as a light yellowish brown solid. LC/MS: Calculated for $C_{10}H_{12}N_4O$ (204.2). Found: 205.31 (M+1); HPLC analytical purity: 98.5%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.9 (d, 1H), 7.20 (bs, 2H), 6.20 (m, 1H), 4.20 (q, 2H), 2.50 (s, 3H), 1.20 (t, 3H); MS (EI) for $C_{10}H_{12}N_4O$: 205.11 (MH^+).



[00291] 2-Amino-8-ethyl-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one (2.70 g, 13.2 mmol) was added to dichloromethane (100 mL), and then bromine (0.75 mL, 1.10 equiv.) was added slowly. This reaction mixture was stirred for 3 h at room temperature. After that, the solvent was evaporated nearly 80% volume of reaction mixture under vacuum, and then acetone was added to give 3.54 g 2-Amino-6-bromo-8-ethyl-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one as a tan solid. LC/MS: Calculated for $C_{10}H_{11}BrN_4O$ (283.12). Found: 285.15 (M+2). HPLC analytical purity: 97.7%.

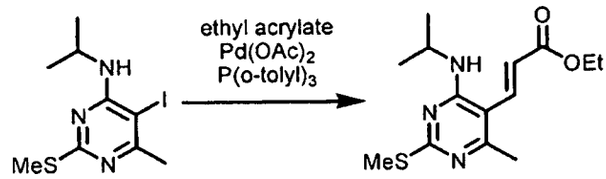
Example 3

2-Amino-4-methyl-8-(methylethyl)-6-(1*H*-pyrazol-3-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one

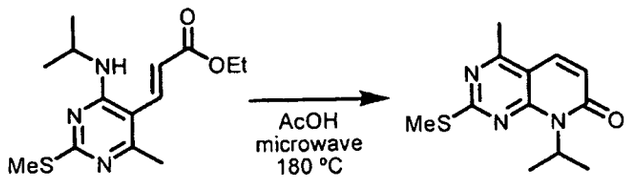


[00292] To a crude solution of *N*-isopropyl-6-methyl-2-(methylthio)pyrimidin-4-amine (44.6 g, 224 mmol), prepared using analogous procedures as described in Example 1, in 400 mL of methanol was added ICl (40.0 g, 246 mmol) in small portions at room temperature. The reaction mixture was then stirred at for 3 h monitoring by LC/MS. After evaporation of solvent

by rotary evaporator, the residue was triturated with acetone to yield 5-iodo-*N*-isopropyl-6-methyl-2-(methylthio)pyrimidin-4-amine. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 (br m, 1H), 4.47 (m, 1H), 2.78 (s, 3H), 2.67 (s, 3H), 1.41 (d, J = 6.4, 6H).

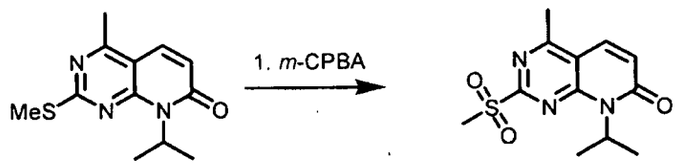


[00293] 5-Iodo-*N*-isopropyl-6-methyl-2-(methylthio)pyrimidin-4-amine (8.1 g, 26.2 mmol), ethyl acrylate (5.24 g, 52.4 mmol), triethylamine (10.6 g, 105 mmol), palladium (II) acetate (1.17 g, 5.23 mmol), and tri-o-tolyl phosphine (1.59 g, 5.23 mmol) were added in that order to 10.8 mL of DMA in a pressure tube and sealed. The reaction mixture was heated to 100 °C and allowed to stir overnight. The reaction was quenched by filtration through a short silica plug washing with ACN. The solvent was evaporated and diluted with ethyl acetate then extracted with 10 % aqueous LiCl, followed by water and brine. NOTE: Extraction is necessary to remove all DMA giving resolution in chromatography. The sample was purified by silica gel column chromatography using 20 % ethyl acetate/hexane as eluent. Desired fractions were combined and reduced to afford 2.5 g (34 % yield) of ethyl (2E)-3-[4-(isopropylamino)-6-methyl-2-(methylthio)pyrimidin-5-yl]acrylate as a yellow/orange oil.

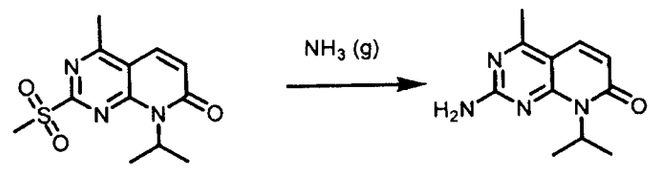


[00294] (E)-Ethyl 3-(4-(isopropylamino)-6-methyl-2-(methylthio)pyrimidin-5-yl)acrylate (2.5 g, 8.46 mmol) was dissolved in acetic acid by gentle warming. Sample was placed in microwave reactor for 6 h at 180 °C, 300 W, and 200 PSI. The product was purified by silica gel column chromatography eluting with 20 % ethyl acetate/hexane. Desired fractions were combined and reduced into 8-isopropyl-4-methyl-2-(methylthio)pyrido[2,3-d]pyrimidin-7(8*H*)-one as a yellow powder (1.20 g, 57 % yield) which was then dried under heavy vacuum

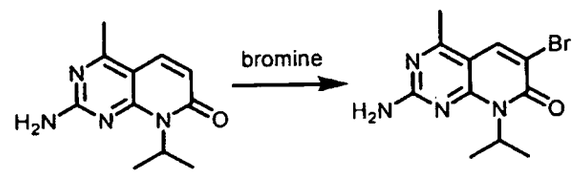
overnight. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.74 (d, J = 9.6, 1H), 6.58 (d, J = 9.6, 1H), 5.84 (br s, 1H), 2.65 (s, 3H), 2.63 (s, 3H), 1.63 (d, J = 6.8, 6H).



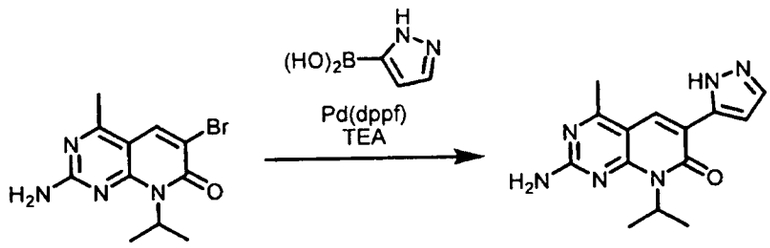
[00295] 8-Isopropyl-4-methyl-2-(methylthio)pyrido[2,3-d]pyrimidin-7(8*H*)-one (5.38 g, 21.59 mmol) was dissolved in 100 mL DCM. To the stirring solution, m-CPBA (13.97 g, 64.78 mmol) was added. The reaction was allowed to stir for 2.5 h at room temperature. LCMS indicated reaction had gone to completion. Sample was diluted with 300 mL of DCM and 300 mL K_2CO_3, upon addition of base a white precipitate formed that dissolved in excess H_2O. Organic layer was extracted further with H_2O and brine, and then dried over Na_2CO_3. The solvent was evaporated to afford the product8-isopropyl-4-methyl-2-(methylsulfonyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one (6.0 g, 99 % yield) as a light yellow oil that was used immediately in the next reaction.



[00296] 8-isopropyl-4-methyl-2-(methylsulfonyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one (approximately 3.0 g) was dissolved in 50 mL THF, in a 350 mL pressure tube. While stirring, NH_3 (g) was bubbled in through solution for 1.5 minutes. A color change was observed form light yellow to olive green in about 120 seconds. The tube was sealed and stirred at room temperature overnight. A precipitate had formed. The reaction mixture, including precipitate, was reduced to near dryness, filtered and washed with a minimal volume of cold THF, affording 2.88 g of 2-amino-8-isopropyl-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one.



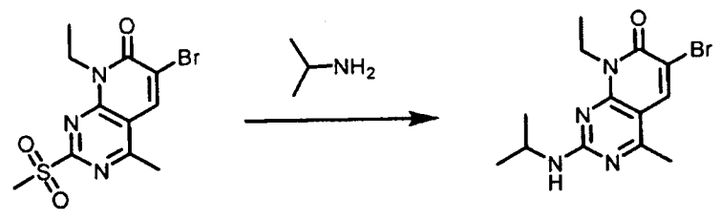
[00297] To a solution of 2-amino-8-isopropyl-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one (2.88 g, 13.19 mmol) dissolved in 80 mL of DCM at 0 °C, (4.21 g, 26.39 mmol) bromine was added. Reaction vessel was removed from ice bath and allowed to react at room temperature over night. LCMS indicated complete conversion of starting material to product. Sample was evaporated to remove DCM and excess bromine. Orange solid was diluted in ethyl acetate and extracted with 10 % $NaHSO_3$, H_2O, and brine. Organic layer was dried over Na_2SO_4, filtered, and reduced to dryness yielding 2-amino-6-bromo-8-isopropyl-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one as a light yellow powder (2.2 g, 56% yield). ^{1}H NMR (400MHz, $CDCl_3$) δ 8.08 (s, 1H), 5.83 (m, 1H), 5.69 (br s, 2H), 2.60 (s, 3H), 1.58 (d, J = 6.8, 6H).



[00298] In a 350 mL pressure tube 2-amino-6-bromo-8-isopropyl-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one (1.50 g, 5.05 mmol), 1H-pyrazol-3-yl boronic acid (1.12 g, 10.09 mmol), K_2CO_3 (336 mg, 15.1 mmol), and tetrakis(triphenylphosphine) palladium (0) (583 mg, 0.0504 mmol) were dissolved in 50 mL dioxane and 5 mL H_2O. The tube was sealed, heated to 100 °C and allowed to react overnight. A color change was observed. LCMS indicated no presence of starting material. Sample was filtered through a syringe filter and evaporated to dryness. Compound was dissolved in ethyl acetate and triturated in hexane. Light yellow powder of 2-amino-8-isopropyl-4-methyl-6-(1H-pyrazol-5-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one (195 mg, 13.7% yield) was found to be 98% pure by HPLC. ^{1}H NMR (400MHz, $CDCl_3$) δ 12.97 (br s, 1H), 8.35 (s, 1H), 7.60 (br s, 1H), 7.21 (s, 2H), 6.94 (s, 1H), 5.86 (br s, 1H), 2.50 (m, 6H), 1.54 (s, 3H), MS (EI) for $C_{14}H_{16}N_6O$: 285.0 (MH^+).

Example 4

[00299] 3-Chloroperbenzoic acid (0.565 g, 3.27 mmol) was added to a solution of 6-bromo-8-ethyl-4-methyl-2-(methylthio)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (0.308 g, 0.980 mmol) in dichloromethane (5.0 mL) at room temperature. After 30 minutes, the reaction was diluted with dichloromethane (50 mL) and washed twice with saturated $NaHCO_3$, followed by brine. The organic phase was separated and dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was precipitated with ethyl acetate to provide 8-ethyl-4-methyl-2-(methylsulfonyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one (302 mg, 89 % yield) as a yellow solid.



[00300] To a stirred solution of (76.5 mg, 0.221 mmol) in 1.5 mL of CH_2Cl_2 was added isopropyl amine (709.9 mg, 12.0 mmol, 54 eq.) The reaction was stirred for 15 h at room temperature. The reaction was diluted with CH_2Cl_2 and extracted with 2N NaOH, H_2O, and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude material was purified using preparative HPLC. Lyophillization of the product containing fractions affored 19.9 mg (27.6 %yield) of 6-bromo-8-ethyl-2-(isopropylamino)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 1H), 5.30 (bs, 1H), 4.48 (bd, 2H), 4.18 (bs, 1H), 2.52 (s, 3H), 1.62 (bs, 3H), 1.29 (m, 9H), MS (EI) for $C_{13}H_{17}BrN_4O$: 325.2 (MH^+).

[00301] Using the same or analogous synthetic techniques and substituting with appropriate reagents, the following compounds were prepared:

Example 4b. 6-bromo-2-(*tert*-butylamino)-8-ethyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 1H), 5.47 (bs, 1H), 4.48 (m, 2H), 2.50 (s, 3H), 1.58 (bs, 3H), 1.49 (s, 9H), MS (EI) for $C_{14}H_{19}BrN_4O$: 339.2 (MH^+)

Example 4c. 6-Bromo-2-(cyclopentylamino)-8-ethyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (s, 1H), 5.89 (bs, 1H), 4.49 (bd, 2H), 2.51 (s, 3H), 2.07 (m, 2H), 1.71 (m, 2H), 1.58 (m, 2H), 1.31 (t, 3H), MS (EI) for $C_{15}H_{19}BrN_4O$: 351.2 (MH^+)

Example 4d. 6-Bromo-2-(cyclohexylamino)-8-ethyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (s, 1H), 5.41 (bs, 1H), 4.47 (bd, 2H), 3.84 (bs, 1H), 2.51 (s, 3H), 2.05 (d, J = 12.4 Hz, 2H), 1.77 (m, 2H), 1.64 (br m, 4H), 1.39 (m, 2H), 1.30 (m, 3H), MS (EI) for $C_{16}H_{21}BrN_4O$: 365.2 (MH^+)

Example 4e. 6-Bromo-8-ethyl-4-methyl-2-(2-morpholinoethylamino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 1H), 6.22 (bs, 1H), 4.48 (q, J = 6.4 Hz, 2H), 3.74 (t, J = 4.4 Hz, 1H), 3.57 (q, J = 4.8 Hz, 3H), 2.98 (bs, 2H), 2.63 (t, J = 6.0 Hz, 2H), 2.53 (s, 3H), 1.30 (t, J = 6.8 Hz, 2H), MS (EI) for $C_{16}H_{22}BrN_5O$: 396.2 (MH^+)

Example 4f. 6-Bromo-8-ethyl-4-methyl-2-[(3-morpholino-4-ylpropyl)amino]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (s, 1H), 6.23 (bs, 1H), 4.47 (bs, 1H), 3.75 (m, 4H), 3.57 (m, 2H), 2.52 (m, 4H), 2.48 (m, 2H), 1.82 (m, 2H), 1.28 (s, 3H), MS (EI) for $C_{17}H_{24}BrN_5O$: 410.2 (MH^+)

Example 4g. 6-Bromo-2-{[3-(dimethylamino)propyl]amino}-8-ethyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.26 (bs, 1H), 4.47 (m, 2H), 3.54 (m, 2H), 2.78 (t, J = 7.6 Hz, 2H), 2.52 (s, 3H), 2.50 (s, 3H), 2.04 (s, 3H), 2.00 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H), MS (EI) for $C_{15}H_{22}BrN_5O$: 369.2 (MH^+)

Example 4h. 8-Ethyl-2-(ethylamino)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 9.2 Hz, 1H), 6.39 (d, J = 9.2 Hz, 1H), 5.31 (bs, 1H), 2.54 (s, 3H), 4.32 (q, J = 6.8 Hz, 2H), 3.52 (q, J = 6.8 Hz, 2H), 2.53 (s, 3H), 1.15 (m, 6H); MS (EI) for $C_{12}H_{16}N_4O$: 233.2 (MH^+).

Example 4j. 6-Bromo-2-{[2-(dimethylamino)ethyl]amino}-8-ethyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.37 (s, 1H), 7.83 (bt, J = 8.0 Hz, 1H), 4.34 (q, J = 8.0 Hz, 2H), 3.42 (q, J = 4.0 Hz, 2H), 2.51 (s, 3H), 2.45 (t, J = 4.0 Hz, 2H), 1.83 (s, 6H), 1.20 (t, J = 8.0 Hz, 3H); MS (EI) for $C_{14}H_{20}BrN_5O$: 354.3 (M^+).

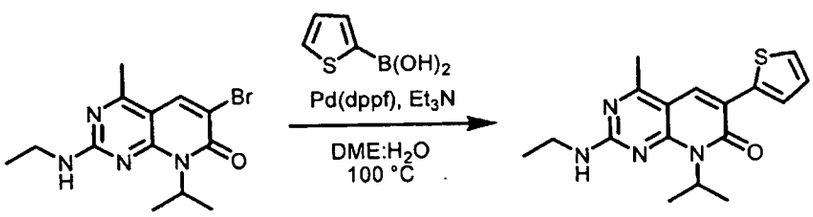
Example 4k. 6-bromo-2-(ethylamino)-4-methyl-8-(1-methylethyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H), 6.66 (bs, 1H), 5.83 (sept, J = 6.8 Hz, 1H), 3.54 (dq, J = 12.8, 7.6 Hz, 2H), 2.62 (s, 3H), 1.60 (d, J = 6.8 Hz, 6H), 1.34 (t, J = 7.2 Hz, 3H); MS (EI) for $C_{13}H_{17}BrN_4O$: 324.9 (M^+).

Example 4m. 6-Bromo-8-ethyl-4-methyl-2-morpholi*N*-4-ylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (s, 1H), 4.45 (q, *J* = 6.8 Hz, 2H), 3.92 (s, 3H), 3.79 (s, 3H), 2.55 (s, 3H), 1.30 (t, *J* = 6.8 Hz, 3H); MS (EI) for $C_{14}H_{17}Br\ N_4O_2$: 355.1 ($M2H^+$).

Example 4n. 6-Bromo-8-ethyl-4-methyl-2-[(phenylmethyl)amino]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.32 (m, 5H), 5.86 (bs, 1H), 4.68 (s, 2H), 4.43 (q, *J* = 7.2 Hz, 2H), 2.54 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 3H); MS (EI) for $C_{17}H_{17}BrN_4O$: 375.1 ($M2H^+$).**Example 4p.** 6-Bromo-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (s, 1H), 5.71 (bs, 1H), 4.48 (bs, 2H), 3.54 (q, *J* = 6.8 Hz, 2H), 2.53 (s, 3H), 1.16 (m, 6H); MS (EI) for $C_{12}H_{15}BrN_4O$: 311.9 (MH^+).

Example 5

2-(Ethylamino)-4-methyl-8-(1-methylethyl)-6-(2-thienyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one



[00302] Pd(dppf) dichloromethane adduct (0.077 g, 0.095 mmol) was added to a suspension of 6-bromo-2-(ethylamino)-4-methyl-8-(1-methylethyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (0.154 g, 0.474 mmol), 2-thiophene boronic acid (0.079 g, 0.616 mmol), and triethylamine (165 μL, 1.19 mmol) in 10:1 DME: water (1.5 mL). The reaction was heated to 100 °C. After 5 h, the reaction was cooled to room temperature, filtered though a Celite plug and concentrated in vacuo. The residue was purified on SiO_2 (3:2 hexanes: ethyl acetate) to give 2-(ethylamino)-4-methyl-8-(1-methylethyl)-6-(2-thienyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (28 mg, 18 % yield) as a light yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (s, 1H), 7.60 (dd, *J* = 4.0, 1.2 Hz, 1H), 7.38 (dd, *J* = 5.2 , 0.8 Hz, 1H), 7.10 (dd, *J* = 4.8, 3.2 Hz, 1H), 5.93 (bsept, 1H), 5.13 (bs, 1H), 3.54 (pent, *J* = 7.2 Hz, 2H), 2.61 (s, 3H), 1.66 (d, *J* = 6.8 Hz, 6H), 1.28 (t, *J* = 7.6 Hz, 3H); MS (EI) for $C_{17}H_{20}N_4OS$: 329.0 (MH^+).

[00303] Using the same or analogous synthetic techniques and substituting with appropriate reagents, the following compounds were prepared:

Example 5a. 2-(Ethylamino)-6-furan-2-yl-4-methyl-8-(1-methylethyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHZ, $CDCL_3$): δ 8.43 (S, 1H), 7.81 (S, 1H), 7.47 (T, J = 2 HZ, 1H), 6.75 (DD, J = 2.0 , 0.8 HZ, 1H), 5.92 (BSEPT, 1H), 5.25 (BS, 1H), 3.53 (DQ, J = 12.5, 7.6 HZ, 2H), 2.60 (S, 3H), 1.65 (D, J = 6.8 HZ, 6H), 1.29 (T, J = 7.2 HZ, 3H); MS (EI) FOR $C_{17}H_{20}N_4O_2$: 313.1 (MH^+).

Example 5b. 2-(Ethylamino)-4-methyl-8-(1-methylethyl)-6-(1*H*-pyrazol-3-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.61 (d, J = 2.0 Hz, 1H), 6.65 (bs, 1H), 5.93 (bs, 1H), 5.44 (bs, 1H), 3.55 (dq, J = 12.8, 6.4 Hz, 2H), 2.62 (s, 3H), 1.66 (d, J = 6.4 Hz, 6H), 1.30 (t, J = 7.6 Hz, 3H); MS (EI) for $C_{16}H_{20}N_6O$: 313.3 (MH^+).

Example 5c. 2-(Ethylamino)-4-methyl-6-(1*H*-pyrazol-3-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, MeOH-d_4:TFA-*d*, 10:1): δ 8.59 (s, 1H), 8.07 (s, 1H), 7.30 (s, 1H), 3.59 (q, J = 8.0 Hz, 2H), 2.88 (s, 3H), 1.28 (t, J = 8.0 Hz, 3H); MS (EI) for $C_{13}H_{14}N_6O$: 271.0 (MH^+).

Example 5e. 8-Cyclopentyl-2-(ethylamino)-4-methyl-6-(1*H*-pyrazol-3-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400MHz, DMSO-d_6): δ 8.32 (s, 1H), 7.80 (s, 1H), 7.59 (s, 1H), 6.916 (s, 1H), 5.95 (m, 1H), 2.35 (bs, 2H), 1.95 (bs, 2H), 1.73 (bs, 2H), 1.61 (bs, 2H), 1.12 (t, J = 6.8 Hz, 3H), MS (EI) for $C_{18H22}N_6O$: 339.1 (MH^+)

Example 5f. 6-(2,4-Difluorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, 2H), 7.52 (m, 1H), 6.85 (m, 2H), 5.38 (bs, 1H), 4.48 (m, 2H), 3.56 (m, 2H), 2.57 (s, 3H), 1.39 (m, 6H); MS (EI) for $C_{18H18}F_2N_4O$: 345.1 (MH^+).

Example 5g. 6-(3-Chloro-4-fluorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (s, 2H), 7.57 (m, 1H), 7.19 (m, 1H), 5.41 (bs, 1H), 4.45 (bs, 2H), 3.58 (m, 2H), 2.59 (m, 3H), 1.36 (m, 6H); MS (EI) for $C_{18H18}ClFN_4O$: 361.0 (MH^+).

Example 5h. 6-(2,4-Dichlorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.42 (d, 1H), 7.38 (m, 2H), 5.38 (bs, 1H), 4.42 (m, 2H), 3.59 (m, 2H), 2.56 (s, 3H), 1.24 (m, 6H); MS (EI) for $C_{18H18}Cl_2N_4O$: 377.0 (M^+), 379.0 (M+2)

Example 5i. 6-(3,4-Difluorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.59 (m, 1H), 7.39 (m, 1H), 7.18 (m,

1H), 5.39 (bs, 1H), 4.46 (m, 2H), 3.58 (m, 2H), 2.59 (s, 3H), 1.27 (m, 6H); MS (EI) for $C_{18}H_{18}F_2N_4O$: 345.1 (MH^+).

Example 5j. 8-Ethyl-2-(ethylamino)-4-methyl-6-[4-(phenyloxy)phenyl]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.63 (d, 2H), 7.39 (t, 2H), 7.16 (t, 1H), 7.04 (d, 4H), 5.38 (bs, 1H), 4.47 (m, 2H), 3.57 (m, 2H), 2.59 (s, 3H), 1.26 (m, 6H); MS (EI) for $C_{24}H_{24}N_4O_2$: 401.1 (MH^+).

Example 5k. 8-Ethyl-2-(ethylamino)-4-methyl-6-naphthale*N*-1-ylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, 2H), 7.80 (s, 1H), 7.73 (d, 1H), 7.48 (m, 4H), 539 (bs, 1H), 4.55 (bs, 2H), 3.59 (m, 2H), 2.54 (s, 3H), 1.37 (m, 6H); MS (EI) for $C_{22}H_{22}N_4O$: 359.1 (MH^+).

Example 5m. 8-Ethyl-2-(ethylamino)-4-methyl-6-[3-(trifluoromethyl)phenyl]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (m, 3H), 7.56 (m, 2H), 5.59 (bs, 1H), 4.47 (d, 2H), 3.51 (m, 2H), 2.58 (s, 3H), 1.30 (m, 6H); MS (EI) for $C_{19}H_{19}F_3N_4O$: 377.1 (MH^+).

Example 5n. 8-Ethyl-2-(ethylamino)-4-methyl-6-(2-thienyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.64 (dd, J = 3.60, 1.20 Hz, 1H), 7.38 (dd, J = 5.20, 1.20 Hz, 1H), 7.10 (dd, J = 4.78, 3.60 Hz, 2H), 3.54 (qn, 2H), 2.62 (s, 3H), 1.30 (m, 6H); MS (EI) for $C_{16}H_{18}N_4OS$: 315.0 (MH^+).

Example 5p. 6-(3-Chlorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.65 (s, 1H), 7.56 (dd, 1H), 7.34 (m, 2H), 5.39 (bs, 1H), 4.43 (m, 2H0, 3.57 (m, 2H), 2.59 (s, 3H), 1.32 (m, 6H); MS (EI) for $C_{18}H_{19}ClN_4O$: 343.0 (MH^+).

Example 5q. 6-(4-Chlorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.62 (dd, 2H0, 7.40 (dd, 2H), 5.38 (bs, 1H), 4.47 (m, 2H), 3.58 (m, 2H), 2.59 (s, 3H), 1.39 (m, 6H); MS (EI) for $C_{18}H_{19}ClN_4O$: 343.0 (MH^+).

Example 5r. 8-Ethyl-2-(ethylamino)-4-methyl-6-[4-(trifluoromethyl)phenyl]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (m, 3H), 7.63 (dd, 2H), 5.39 (bs, 1H), 4.51 (m, 2H), 3.58 (m, 2H), 2.58 (s, 3H), 1.33 (m, 6H); MS (EI) for $C_{19}H_{19}F_3N_4O$: 343.0 (MH^+).

Example 5s. 8-Ethyl-2-(ethylamino)-4-methyl-6-(3-thienyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (dd, J = 2.10, 0.90 Hz, 1H), 7.94 (s, 1H), 7.52 (dd, J = 3.90, 1.20 Hz, 1H), 7.35 (qr, 1H), 5.33 (bs, 1H), 4.52 (qr, 2H), 3.54 (m, 2H), 2.58 (s, 3H), 1.28 (m, 6H); MS (EI) for $C_{16}H_{18}N_4OS$: 315.0 (MH^+).

Example 5t. 8-Ethyl-2-(ethylamino)-4-methyl-6-(4-methyl-2-thienyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.52 (s, 1H), 6.93 (s, 1H), 5.38 (bs, 1H), 4.58 (qr, 2H), 3.57 (m, 2H), 2.61 (s, 1H), 2.33 (s, 1H), 1.60 (s, 3H); MS (EI) for $C_{17}H_{20}N_4OS$: 329.0 (MH^+).

Example 5u. 8-Ethyl-2-(ethylamino)-4-methyl-6-(4-methyl-3-thienyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (s, 1H), 7.38 (d, 1H), 6.99 (m, 1H), 5.35 (bs, 1H), 4.51 (qr, 2H), 3.57 (m, 2H), 2.58 (s, 3H), 2.22 (s, 3H), 1.32 (m, 6H); MS (EI) for $C_{17}H_{20}N_4OS$: 329.0 (MH^+).

Example 5v. 1,1-Dimethylethyl 2-[8-ethyl-2-(ethylamino)-4-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-6-yl]-1*H*-pyrrole-1-carboxylate: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.38 (d, 1H), 6.22 (m, 2H), 5.29 (bs, 1H), 4.41 (m, 2H), 3.57 (m, 2H), 2.56 (s, 3H), 1.41 (s, 9H), 1.22 (m, 6H); MS (EI) for $C_{21}H_{27}N_5O_3$: 398.0 (MH^+).

Example 5w. 8-Ethyl-2-(ethylamino)-4-methyl-6-(1H-pyrrol-2-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.1 (bs, 1H), 7.99 (s, 1H), 6.85 (d, 1H), 6.62 (d, 1H), 6.29 (d, 1H), 5.28 (bs, 1H), 4.57 (m, 2H), 3.56 (m, 2H), 2.61 (s, 3H), 1.35 (m, 6H); MS (EI) for $C_{16}H_{19}N_5O$: 298.1 (MH^+).

Example 5x. 8-Ethyl-2-(ethylamino)-6-furan-3-yl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 1H), 7.83 (s, 1H), 7.43 (s, 1H),6.76 (s, 1H), 5.37 (bs, 1H), 4.52 (m, 2H), 3.58 (m, 2H), 2.61 (s, 3H), 1.30 (m, 6H); MS (EI) for $C_{16}H_{18}N_4O_2$: 299.1 (MH^+).

Example 5y. 8-Ethyl-2-(ethylamino)-4-methyl-6-[1-(phenylmethyl)-1*H*-pyrazol-4-yl]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.98 (d, 1H), 7.96 (d, 1H), 7.35 (m, 5H), 5.39 (s, 2H), 5.35 (bs, 1H), 4.52 (m, 2H), 3.58 (m, 2H), 2.62 (s, 3H), 1.35 (m, 6H) ; MS (EI) for $C_{22}H_{24}N_6O$: 389.3 (MH^+).

Example 5z. 6-(3,5-Dimethylisoxazol-4-yl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (s, 1H), 7.24 (s, 1H), 5.43 (bs,

1H), 4.47 (bs, 2H), 3.56 (m, 2H), 2.58 (s, 3H), 2.39 (s, 3H), 2.25 (s, 3H), 1.29 (m, 6H) ; MS (EI) for $C_{17}H_{21}N_5O_2$: 328.1 (MH^+).

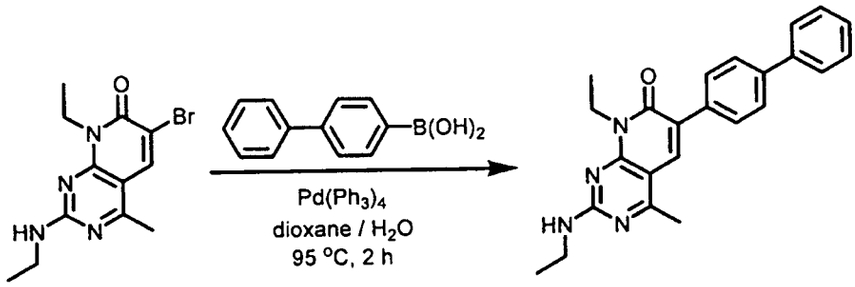
Example 5aa. 8-Ethyl-2-(ethylamino)-4-methyl-6-(1*H*-pyrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.62 (s, 1H), 6.65 (d, 1H), 5.43 (bs, 1H), 4.58 (m, 2H), 3.59 (m, 2H), 2.62 (s, 3H), 1.38 (m, 6H); MS (EI) for $C_{15}H_{18}N_6O$: 299.1 (MH^+).

Example 5bb. 8-Ethyl-4-methyl-6-(1*H*-pyrazol-5-yl)-2-[(2,2,2-trifluoroethyl)amino]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.63 (d, 1H), 6.73 (d, 1H), 5.62 (bs, 1H), 4.58 (m, 2H), 4.30 (m, 2H), 2.74 (s, 3H), 1.35 (t, 3H); MS (EI) for $C_{15}H_{15}F_3N_6O$: 353.0 (MH^+).

Example 5cc. 8-Ethyl-2-(ethylamino)-4-methyl-6-(1,3-thiazol-2-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.87 (s, 1H), 7.98 (s, 1H), 7.43 (s, 1H), 7.22 (s, 1H), 5.56 (bs, 1H), 4.58 (bs, 2H), 2.72 (s, 3H0, 1.36 (m, 6H); MS (EI) for $C_{15}H_{17}N_5OS$: 316.0 (MH^+).

Example 6

6-Biphenyl-4-yl-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-*d*]pyridimidi*N*-7(8*H*)-one



[00304] 2-Ethylamino-6-bromo-8-ethyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (60 mg, 0.194 mmol), K_2CO_3 (81.0 mg, 3.0 equiv.), biphenyl boronic acid (17.8 mg, 1.5 equiv.) and $Pd(PPh_3)_4$ (10 mol %, 225 mg) were added to dioxane / H_2O (10 mL / 3 mL). The reaction was heated to 95 °C and stirred for 2 h. The reaction mixture was partitioned between organic and aqueous layers with ethyl acetate (20 mL) and H_2O (10 mL) and saturated aqueous NaCl (5 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated to give 6-Biphenyl-4-yl-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-*d*]pyridimidi*N*-7(8*H*)-one (48.42 mg, 65 % yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.74 (m, 2H), 7.60 (m,

4H), 7.42 (m, 2H), 7.38 (m, 1H), 4.50 (q, 2H), 3.60 (q, 2H), 2.60 (s, 3H), 1.30 (m, 6H); MS (EI) for $C_{24}H_{24}N_4O$: 385.1 (MH^+).

[00305] Using the same or analogous synthetic techniques and substituting with appropriate reagents, the following compounds were prepared:

Example 6a. 8-Ethyl-2-(ethylamino)-4-methyl-6-[4-(methyloxy)phenyl]pyrido[2,3-*d*]pyridimidi*N*-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.60 (d, 2H), 6.96 (d, 2H), 4.50 (q, 2H), 3.82 (s, 3H), 3.58 (q, 2H), 2.58 (s, 3H), 1.30 (m, 6H); MS (EI) for $C_{19}H_{22}N_4O_2$: 339.1 (MH^+).

Example 6b. 8-Ethyl-2-(ethylamino)-4-methyl-6-[2-(methyloxy)phenyl]pyrido[2,3-*d*]pyridimidi*N*-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.60 (d, 2H), 6.96 (d, 2H), 4.50 (q, 2H), 3.80 (s, 3H), 3.58 (q, 2H), 2.50 (s, 3H), 1.30 (m, 6H); MS (EI) for $C_{19}H_{22}N_4O_2$: 339.1 (MH^+).

Example 6c. 6-[2,4-Bis(methyloxy)phenyl]-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.30 (s, 1H), 6.60 (m, 2H), 4.50 (q, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 3.45 (q, 2H), 2.50 (s, 3H), 1.30 (m, 6H); MS (EI) for $C_{20}H_{24}N_4O_3$: 369.1 (MH^+).

Example 6d. 8-Ethyl-2-(ethylamino)-4-methyl-6-[3-(methyloxy)phenyl]pyrido[2,3-*d*]pyridimidi*N*-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.60 (d, 2H), 6.96 (d, 2H), 4.50 (q, 2H), 3.80 (s, 3H), 3.58 (q, 2H), 2.50 (s, 3H), 1.30 (m, 6H); MS (EI) for $C_{19}H_{22}N_4O_2$: 339.1 (MH^+).

Example 6e. 8-(5-Chloro-2-thienyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.38 (d, 2H), 6.96 (d, 2H), 4.50 (q, 2H), 3.58 (q, 2H), 2.60 (s, 3H), 1.30 (m, 6H); MS (EI) for $C_{16}H_{17}ClN_4OS$: 349.2 (MH^+).

Example 6f. 8-Ethyl-2-(ethylamino)-4-methyl-6-pyrimidin-5-ylpyrido[2,3-*d*]pyridimidi*N*-7(8*H*)-one: ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.19 (s, 1H), 9.16 (s, 1H), 8.23 (s, 1H), 8.00 (m, 1H), 4.38 (q, 2H), 3.40 (q, 2H), 2.50 (s, 3H), 1.30 (m, 6H); MS (EI) for $C_{16}H_{18}N_6O$: 311.3 (MH^+).

Example 6g. 8-Ethyl-2-(ethylamino)-6-(3-fluoropyridi*N*-4-yl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (s, 1H), 8.42 (d, 1H), 7.98 (s, 1H), 7.60 (t, 1H), 4.50 (q, 2H), 3.58 (q, 2H), 2.60 (s, 3H), 1.30 (m, 6H); MS (EI) for $C_{17}H_{18}FN_5O$: 328.3 (MH^+).

Example 6h. 8-Ethyl-2-(ethylamino)-6-(1*H*-indole-6-yl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.2 (s, 1H), 7.90 (s, 1H), 7.88 (s, 1H), 7.42 (s, 2H), 7.38 (s, 1H), 6.50 (s, 1H), 4.40 (q, 2H), 3.40 (q, 2H), 2.42 (s, 3H), 1.30 (m, 6H); MS (EI) for $C_{20}H_{21}N_5O$: 348.3 (MH^+).

Example 6i. 8-Ethyl-2-(ethylamino)-4-methyl-6-(5-phenyl-2-thienyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.40 (s, 1H), 7.81 (d, 1H), 7.70 (d, 2H), 7.50 (d, 1H), 7.42 (m, 2H), 7.30 (m, 1H), 4.40 (q, 2H), 3.40 (q, 2H), 2.42 (s, 3H), 1.30 (m, 6H); MS (EI) for $C_{22}H_{22}N_4OS$: 391.3 (MH^+).

Example 6j. 8-Ethyl-2-(ethylamino)-4-methyl-6-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.46 (m, 5H), 5.41 (bs, 1H), 4.50 (q, J = 6.8 Hz, 2H), 3.60 (m, 2H), 2.57 (s, 3H), 1.30 (m, 6H); MS (EI) for $C_{18}H_{20}N_4O$: 309.2 (MH^+).

Example 6k. 8-Ethyl-2-(ethylamino)-6-(3-fluorophenyl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.46-7.02 (m, 4H), 5.41 (bs, 1H), 4.51 (q, J = 6.4 Hz, 2H), 3.55 (q, J = 6.8 Hz, 2H), 2.58 (s, 3H), 1.34 (t, J = 6.80 Hz, 3H), 1.29 (t, J = 6.40 Hz, 3H); MS (EI) for $C_{18}H_{19}FN_4O$: 327.3 (MH^+).

Example 6m. 8-ethyl-2-(ethylamino)-6-(2-fluorophenyl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.52-7.12 (m, 4H), 5.33 (bs, 1H), 4.49 (q, J = 6.8 Hz, 2H), 3.53 (q, J = 7.2 Hz, 2H), 2.55 (s, 3H), 1.34 (t, J = 7.20 Hz, 3H), 1.28 (t, J = 6.80 Hz, 3H); MS (EI) for $C_{18}H_{19}FN_4O$: 327.3 (MH^+).

Example 6n. 8-ethyl-2-(ethylamino)-6-(4-fluorophenyl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.66-7.08 (m, 4H), 5.30 (bs, 1H), 4.52 (q, J = 6.4 Hz, 2H), 3.54 (q, J = 6.8 Hz, 2H), 2.58 (s, 3H), 1.34 (t, J = 6.80 Hz, 3H), 1.29 (t, J = 6.40 Hz, 3H); MS (EI) for $C_{18}H_{19}FN_4O$: 327.3 (MH^+).

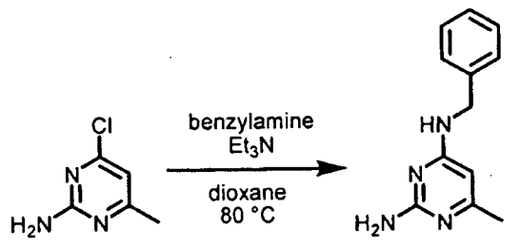
Intermediate 2

[00306] 3-Chloroperbenzoic acid (1.78 g, 10.4 mmol) was added to a solution of 6-bromo-4-methyl-8-(1-methylethyl)-2-(methylthio)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (1.33 g,

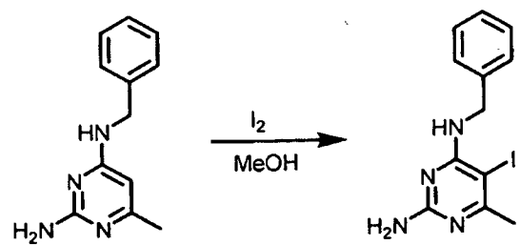
4.14 mmol), prepared using procedures similar to those described in Example 1, in dichloromethane (30.0 mL) at room temperature. After 1, the reaction was diluted with dichloromethane (50 mL) and washed twice with saturated $NaHCO_3$, followed by brine. The organic phase was separated and dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was precipitated with ethyl acetate/hexanes to provide the corresponding sulfone (1.31 g, 93 % yield) as an off-white solid.

Example 8

2-Amino-4-methyl-8-(phenylmethyl)-6-(1*H*-pyrazol-3-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one

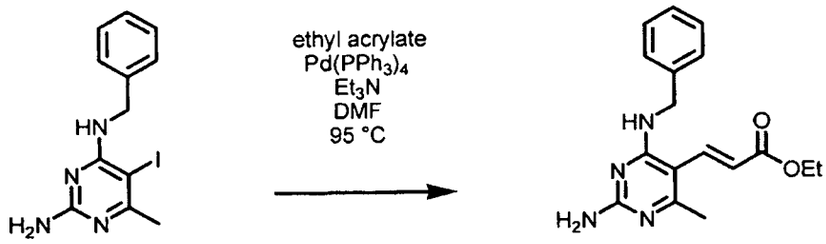


[00307] Triethylamine (3.4 mL, 24.6 mmol) was added to a suspension of 2-amino-4-chloro-6-methylpyrimidine (Aldrich, 1.77 g, 12.3 mmol) and benzylamine (1.98 g, 18.5 mmol) in anhydrous dioxane (20 mL). The reaction was heated to 80 °C and allowed to run for 12 h. Upon cooling to room temperature, a white precipitate formed which was collected by vacuum filtration. The solid was recrystallized from acetone: hexanes to afford N^4-benzyl-6-methylpyrimidine-2,4-diamine (2.33 g, 89 % yield) as a white solid.

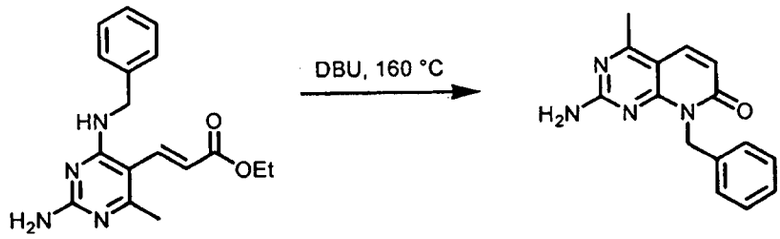


[00308] Iodine (3.04 g, 12.0 mmol) was added to a solution of N^4-benzyl-6-methylpyrimidine-2,4-diamine (2.33 g, 10.9 mmol) in anhydrous MeOH (50 mL) at 0 °C. The reaction was allowed to warm to room temperature overnight. After 12 hours, an additional 0.5 equiv of iodine was added, and the reaction warmed to 50 °C. After four hours, the reaction

was cooled to room temperature and concentrated in vacuo. The residue was diluted with ethyl acetate (200 mL) and washed with 10% $NaHSO_3$ (200 mL). The aqueous phase was separated and washed once more with ethyl acetate (200 mL). The organic phases were combined, washed with brine, separated and dried over Na_2SO_4, The filtrate was concentrated in vacuo to afford the product N^4-benzyl-5-iodo-6-methylpyrimidine-2,4-diamine (3.14 g, 85 % yield).

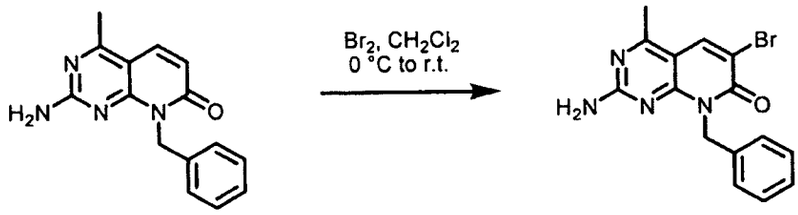


[00309] Triethylamine (7.60 mL, 54.5 mmol) was added to a suspension of N^4-benzyl-5-iodo-6-methylpyrimidine-2,4-diamine (3.14 g, 10.9 mmol), ethyl acrylate (3.55 mL, 32.7 mmol) and $Pd(PPh_3)_4$ (629 mg, 0.545 mmol) in anhydrous DMF (20 mL). The reaction was heated to 95 °C under nitrogen. After 24 h, the reaction was allowed to cool to room temperature and concentrated in vacuo. The residue was poured into a 10% solution of LiCl and washed with ethyl acetate (100 mL). The organic phase was separated and washed with brine, separated and dried over Na_2SO_4. The filtrate was concentrated in vacuo and purified on SiO_2 (3:2 methylene chloride: ethyl acetate) to afford (*E*)-ethyl-3-(2-amino-4-(benzylamino)-6-methylpyrimidin-5-yl)acrylate (0.954 g, 28 % yield) as a light yellow solid.

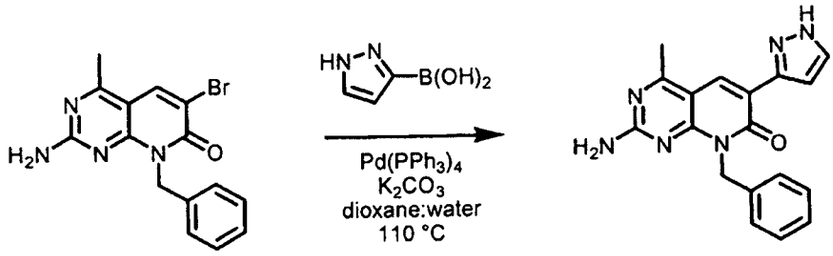


[00310] 2-amino-4-methyl-8-(phenylmethyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one Diazabicyclo[5.4.0]undec-7-ene (DBU) (1.83 mL, 12.2 mmol) was added to a flask charged with (*E*)-ethyl-3-(2-amino-4-(benzylamino)-6-methylpyrimidin-5-yl)acrylate (0.954 g, 3.05

mmol) and the reaction refluxed at 160 °C under a nitrogen atmosphere. After 20 hours, the reaction was cooled to room temperature and concentrated in vacuo. Purification on SiO_2 (1:1 methylene chloride: ethyl acetate) afforded the product (0.508 g, 62 % yield) as an off-white solid.



[00311] Bromine (72 μL, 1.40 mmol) was added to a suspension of 2-amino-4-methyl-8-(phenylmethyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (0.340 g, 1.27 mmol) in methylene chloride (20 mL) at 0 °C. The reaction was allowed to warm to room temperature over one hour and the resulting precipitate collected by vacuum filtration to afford 2-amino-6-bromo-4-methyl-(8-phenylmethyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (0.435 g, 99 % yield) after drying. The yellow solid was used in the next step without further purification.

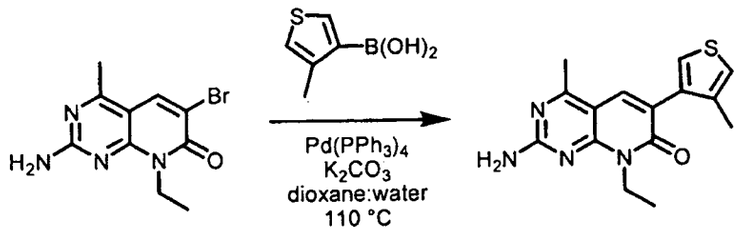


[00312] A 10:1 solution of dioxane and water (11 mL) was added to a flask charged with 2-amino-6-bromo-4-methyl-(8-phenylmethyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (0.435 g, 1.27 mmol), 1*H*-pyrazole-5-boronic acid (0.284 g, 2.54 mmol), $Pd(PPh_3)_4$ (0.073 mg, 0.063 mmol), and K_2CO_3 (0.527 g, 3.81 mmol). The flask was flushed with nitrogen and fitted with a reflux condenser and heated to 110 °C. After 12 h the reaction was cooled to room temperature and diluted with ethyl acetate (100 mL) and washed with water. The aqueous phase was acidified to pH 1.0 and washed with ethyl acetate (100 mL). The organic phases were combined and washed with brine, separated and dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was precipitated with ethyl acetate to give 2-Amino-4-methyl-8-(phenylmethyl)-6-(1*H*-

pyrazol-3-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (0.062 g, 15 % yield) as a yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.10 (bs, 1H), 12.93 (bs, 1H), 8.47 (s, 1H), 7.76 (bs, 1H), 7.51 (bs, 1H), 7.28 (m, 5H), 6.97 (s, 1H), 5.55 (s, 2H), 2.55 (bs, 3H); MS (EI) for $C_{18}H_{16}N_6O$: 333.1 (MH^+).

Example 9

2-Amino-8-ethyl-4-methyl-6-(4-methyl-3-thienyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one



[00313] A 3:1 solution of dioxane and water (4 mL) was added to a flask charged with 2-amino-6-bromo-8-ethyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (0.140 g, 0.495 mmol) from above, 4-methylthiophene-3-boronic acid (0.140 g, 0.989 mmol), $Pd(PPh_3)_4$ (0.057 mg, 0.050 mmol), and K_2CO_3 (0.205 g, 1.48 mmol). The flask was flushed with nitrogen and fitted with a reflux condenser and heated to 100 °C. After 12 hours the reaction was cooled to room temperature and diluted with ethyl acetate (70 mL) and washed with water. The aqueous phase was separated and washed with an additional amount of ethyl acetate (70 mL). The organic phases were combined and washed with brine, separated and dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified on SiO_2 (1:1 methylene chloride: ethyl acetate) to give 2-Amino-8-ethyl-4-methyl-6-(4-methyl-3-thienyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (0.081 g, 55 % yield) as an off-white solid: ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.84 (s, 1H), 7.46 (d, J = 4.0 Hz, 1H), 7.19 (m, 3H), 4.32 (q, J = 8.0 Hz, 2H), 2.52 (s, 3H), 2.11 (bs, 3H), 1.19 (t, J = 8.0 Hz, 3H); MS (EI) for $C_{15}H_{16}N_4OS$: 301.1 (MH^+).

[00314] Using the same or analogous synthetic techniques and substituting with appropriate reagents, the following compounds were prepared:

Example 9a. 2-Amino-8-ethyl-4-methyl-6-(3-thienyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (dd, J = 2.8, 1.2 Hz, 1H), 7.95 (s, 1H), 7.51 (dd, J = 5.2, 1.2 Hz, 1H), 7.37 (dd, J = 4.8, 3.2 Hz, 1H), 5.21, (bs, 2H), 4.48 (q, J = 6.8 Hz, 2H), 2.63 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); MS (EI) for $C_{14}H_{14}N_4OS$: 287.0 (MH^+).

Example 9b. 2-Amino-8-ethyl-6-furan-3-yl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (bs, 1H), 7.85 (s, 1H), 7.49 (t, *J* = 1.6 Hz, 1H), 6.77 (dd, *J* = 2.0, 0.8 Hz, 1H), 5.19, (bs, 2H), 4.48 (q, *J* = 6.8 Hz, 2H), 2.64 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); MS (EI) for $C_{14}H_{14}N_4O_2$: 271.1 (MH^+).

Example 9c. 2-Amino-6-(3,5-dimethylisoxazol-4-yl)-8-ethyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (s, 1H), 5.27, (bs, 2H), 4.44 (q, *J* = 7.2 Hz, 2H), 2.59 (s, 3H), 2.38 (s, 3H), 2.25 (s, 3H), 1.31 (t, *J* = 6.8 Hz, 3H); MS (EI) for $C_{15}H_{17}N_5O_2$: 300.1 (MH^+).

Example 9d. 2-Amino-8-ethyl-6-isoxazol-4-yl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.36 (s, 1H), 8.71 (s, 1H), 7.91 (s, 1H), 5.30, (bs, 2H), 4.48 (q, *J* = 7.2 Hz, 2H), 2.67 (s, 3H), 1.32 (t, *J* = 6.8 Hz, 3H); MS (EI) for $C_{13}H_{13}N_5O_2$: 272.0 (MH^+).

Example 9e. 2-Amino-8-ethyl-6-furan-2-yl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.48 (d, *J* = 0.8 Hz, 1H), 7.37 (d, *J* = 3.6 Hz, 1H), 6.53 (dd, *J* = 3.6, 2.0 Hz 1H), 5.21, (bs, 2H), 4.48 (q, *J* = 7.2 Hz, 2H), 2.66 (s, 3H), 1.32 (t, *J* = 6.8 Hz, 3H); MS (EI) for $C_{14}H_{14}N_4O_2$: 271.0 (MH^+).

Example 9f. 5-(2-Amino-8-ethyl-4-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-6-yl)thiophene-2-carbonitrile: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.61 (d, *J* = 4.4 Hz, 1H), 7.55 (d, *J* = 4.4 Hz, 1H), 5.33, (bs, 2H), 4.48 (q, *J* = 7.2 Hz, 2H), 2.68 (s, 3H), 1.33 (t, *J* = 6.8 Hz, 3H); MS (EI) for $C_{15}H_{13}N_5OS$: 312.0 (MH^+).

Example 9g. 2-Amino-8-ethyl-4-methyl-6-(1*H*-pyrazol-4-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.88 (s, 1H), 8.38 (s, 1H), 8.17 (s, 2H), 7.10 (bs, 2H), 4.35 (q, *J* = 7.2 Hz, 2H), 2.59 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H); MS (EI) for $C_{13}H_{14}N_6O$: 271.0 (MH^+).

Example 9h. 2-Amino-8-ethyl-4-methyl-6-(1,3-thiazol-2-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.94 (s, 1H), 7.94 (d, *J* = 3.2 Hz, 1H), 7.46 (d, *J* = 3.2 Hz, 1H), 5.34 (bs, 2H), 4.54 (q, *J* = 7.2 Hz, 2H), 2.73 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H); MS (EI) for $C_{13}H_{13}N_5OS$: 288.0 (MH^+).

Example 9i. 2-Amino-8-ethyl-4-methyl-6-(1-methyl-1*H*-pyrrol-2-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.81 (s, 1H), 7.20 (bs, 2H), 6.81 6.11 (dd, *J* = 3.6, 2 .0Hz, 1H), 6.02 (t, *J* = 3.2 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.49 (s, 3H), 2.52 (s, 3H), 1.19 (t, *J* = 7.2 Hz, 3H); MS (EI) for $C_{15}H_{17}N_5O$: 284.1 (MH^+).

Example 9j. 2-Amino-8-ethyl-4-methyl-6-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.65 (d, J = 6.8 Hz, 2H), 7.43 (d, J = 7.2 Hz, 2H), 7.36 (d, J = 7.2 Hz, 1H), 5.24 (bs, 2H), 4.47 (q, J = 7.2 Hz, 2H), 2.60 (s, 3H), 1.31 (d, J = 7.2 Hz, 3H), MS (EI) for $C_{16}H_{16}N_4O$: 281.2 (MH^+)

Example 9k 2-Amino-8-ethyl-6-(4-methoxyphenyl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.62 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 5.17 (bs, 2H), 4.47 (q, J = 6.8 Hz, 2H), 3.85 (s, 3H), 2.60 (s, 3H), 1.31 (d, J = 7.2 Hz, 3H), MS (EI) for $C_{17}H_{18}N_4O_2$: 311.2 (MH^+)

Example 9m 2-Amino-8-ethyl-6-(2-methoxyphenyl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400MHz, $CDCl_3$): δ 7.75 (m, 1H), 7.36 (m, 2H), 7.01 (m, 2H), 5.20 (bs, 2H), 4.45 (m, 2H), 3.82 (s, 3H), 2.56 (s, 3H), 1.31 (m, 3H), MS (EI) for $C_{17}H_{18}N_4O_2$: 311.2 (MH^+)

Example 9n 2-Amino-6-(4-chlorophenyl)-8-ethyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.61 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 5.23 (bs, 2H), 4.46 (q, J = 7.2 Hz, 2H), 2.61 (s, 3H), 1.31 (d, J = 6.8 Hz, 3H), MS (EI) for $C_{16}H_{15}ClN_4O$: 315.1 (MH^+)

Example 9p 2-Amino-6-(3-chlorophenyl)-8-ethyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.66 (m, 1H), 7.56 (m, 1H), 7.35 (m, 2H), 5.25 (bs, 2H), 4.46 (q, J = 5.6 Hz, 2H), 2.61 (s, 3H), 1.31 (d, J = 7.2 Hz, 3H), MS (EI) for $C_{16}H_{15}ClN_4O$: 315.1 (MH^+)

Example 9q 2-Amino-6-(2-chlorophenyl)-8-ethyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.67 (m, 1H), 7.54 (m, 2H), 7.38 (m, 1H), 7.333 (m, 1H), 5.22 (bs, 2H), 4.46 (q, J = 6.8 Hz, 2H), 2.57 (s, 3H), 1.31 (d, J = 6.8 Hz, 3H), MS (EI) for $C_{16}H_{15}ClN_4O$: 315.1 (MH^+)

Example 9r 2-Amino-6-(2,4-dichlorophenyl)-8-ethyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.67 (m, 1H), 7.49 (m, 1H), 7.32 (m, 1H), 5.24 (bs, 2H), 4.45 (q, J = 6.8 Hz, 2H), 2.58 (s, 3H), 1.30 (d, J = 7.2 Hz, 3H), MS (EI) for $C_{16}H_{14}Cl_2N_4O$: 349.1 (MH^+)

Example 9t 2-Amino-8-ethyl-4-methyl-6-(2-thienyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.39 (s, 1H), 7.85-7.13 (m, 5H), 4.37 (q, J = 7.2 Hz, 2H), 2.62 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H); MS (EI) for $C_{14}H_{14}N_4OS$: 287.1 (MH^+).

Example 9u 2-Amino-8-ethyl-6-(4-fluorophenyl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.99 (s, 1H), 7.76-7.22 (m, 6H), 4.34 (q, J = 7.2Hz, 2H), 2.56 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H); MS (EI) for $C_{16}H_{15}FN_4O$: 299.2 (MH^+).

Example 9v 2-Amino-8-ethyl-6-(3-fluorophenyl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.06 (s, 1H), 7.61-7.44 (m, 3H), 7.29 (bs, 2H), 7.20-7.15 (m, 1H), 4.34 (q, J = 7.2Hz, 2H), 2.58 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H); MS (EI) for $C_{16}H_{15}FN_4O$: 299.2 (MH^+).

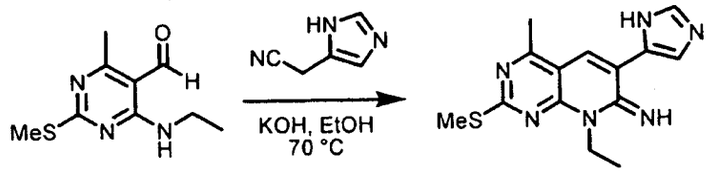
Example 9w 2-Amino-8-ethyl-6-(2-fluorophenyl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 (s, 1H), 7.50-7.23 (m, 6H), 4.32 (q, J = 6.8 Hz, 2H), 2.52 (s, 3H), 1.19 (t, J = 6.8 Hz, 3H); MS (EI) for $C_{16}H_{15}FN_4O$: 299.2 (MH^+).

Example 9x Methyl 3-(2-amino-8-ethyl-4-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-6-yl)benzoate: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.34 (s, 1H), 8.06 (s, 1H), 7.95-7.55 (m, 3H), 7.28 (bs, 1H), 4.35 (q, J = 6.8 Hz, 2H), 3.89 (s, 3H), 2.58 (s, 3H), 1.21 (t, J = 6.8 Hz, 3H); MS (EI) for $C_{18H18}N_4O_3$: 339.2 (MH^+).

Example 9y 2-Amino-8-ethyl-4-methyl-6-pyrimidin-5-ylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.39 (s, 1H), 7.65-7.30 (m, 5H), 4.31 (q, J = 7.2 Hz, 2H), 2.50 (s, 3H), 1.17 (t, J = 7.2 Hz, 3H); MS (EI) for $C_{14}H_{14}N_6O$: 283.2 (MH^+).

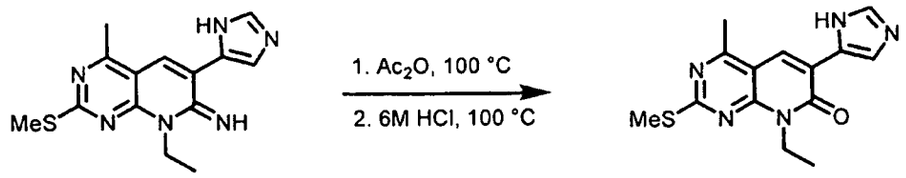
Example 10

2-Amino-8-ethyl-6-(1*H*-imidazol-5-yl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one

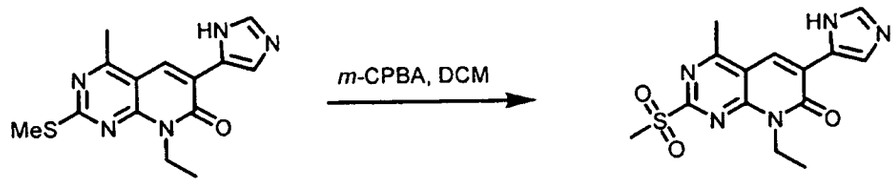


[00315] A solution of potassium hydroxide (0.139 g, 2.48 mmol) in absolute ethanol (3.0 mL) was added to a pressure tube charged with 4-(ethylamino)-6-methyl-2-(methylthio)pyrimidine-5-carbaldehyde (0.229 g, 1.08 mmol), prepared using procedures ismilar to those described for Intermediate 1, and 2-(1*H*-imidazol-5-yl)acetonitrile (0.174 g, 162 mmol) and heated to 70 °C. After 12 h, the reaction was allowed to cool to room temperature and concentrated in vacuo affording 8-ethyl-6-(1*H*-imidazol-5-yl)-4-methyl-2-

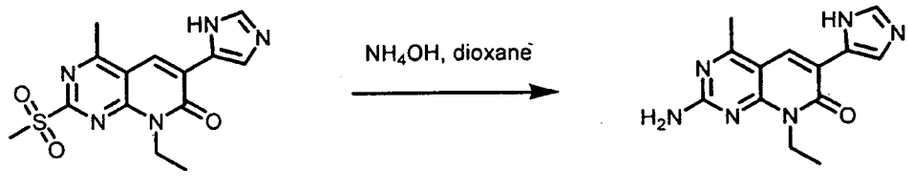
(methylthio)pyrido[2,3-*d*]pyrimidin-7(8*H*)-imine as a solid. The product was used in the subsequent step without further purification.



[00316] Acetic anhydride (15.0 mL) was added to a flask charged with crude 8-ethyl-6-(1*H*-imidazol-5-yl)-4-methyl-2-(methylthio)pyrido[2,3-*d*]pyrimidin-7(8*H*)-imine and heated to 100 °C. After 30 minutes, the reaction was allowed to cool to room temperature and concentrated in vacuo. The acetylated residue was then treated with 6 N HCl (16 mL) and heated to 95 °C for 30 minutes then transferred to a large flask. A saturated solution of $NaHCO_3$ (150 mL) was added at 0 °C to about pH = 8.0. The aqueous phase was washed thrice with ethyl acetate (100 mL) and the organic layers combined, then washed with brine and dried over Na_2SO_4. The drying agent was filtered off and the organic layers were concentrated in vacuo to afford crude 8-ethyl-6-(1*H*-imidazol-5-yl)-4-methyl-2-(methylthio)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one which was used in the subsequent step without further purification.



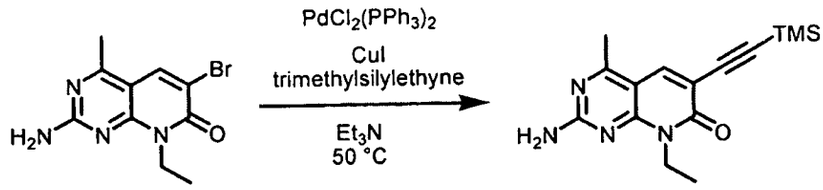
[00317] 3-Chloroperbenzoic acid (0.299 g, 1.73 mmol) was added to a solution of crude 8-ethyl-6-(1*H*-imidazol-5-yl)-4-methyl-2-(methylthio)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (0.260g, 0.866 mmol) in dichloromethane (10.0 mL) at room temperature. After 1.5 h, the reaction was diluted with dichloromethane (50 mL) and washed twice with saturated $NaHCO_3$, followed by brine. The organic phase was separated and dried over Na_2SO_4, filtered, and concentrated in vacuo. The corresponding sulfone was used in the subsequent step without further purification.



[00318] Concentrated aqueous ammonium hydroxide (400 μL) was added to a solution of the sulfone in dioxane (10 mL) at 0 °C. The reaction flask sealed, and allowed to warm to room temperature upon standing overnight. The reaction was concentrated in vacuo and purified on reverse phase HPLC (acetonitrile: water 0.1 % TFA, 20–60% gradient). The fractions containing product were collected and concentrated to one half volume and poured into saturated $NaHCO_3$ (50 mL). The aqueous phase was washed trice with ethyl acetate (50 mL) and dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was triturated with methylene chloride and ethyl acetate to afford 2-amino-8-ethyl-6-(1*H*-imidazol-5-yl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (29 mg, 12 % yield) as a light yellow solid: ^1H NMR (400 MHz, CH_3OH-d_4): δ 8.52 (bs, 1H), 7.88 (bs, 1H), 7.76 (s, 1H), 4.30 (q, J = 6.8 Hz, 2H), 2.65 (s, 3H), 1.29 (t, J = 6.8 Hz, 3H); MS (EI) for $C_{13}H_{14}N_6O$: 271.0 (MH^+).

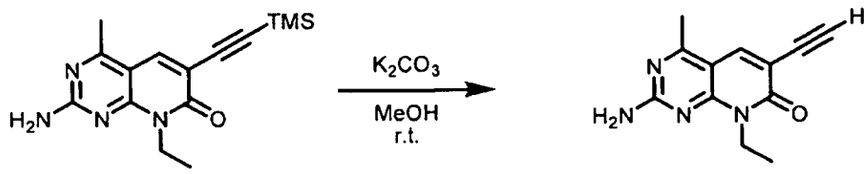
Example 11

2-Amino-8-ethyl-4-methyl-6-(1*H*-1,2,3-triazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one

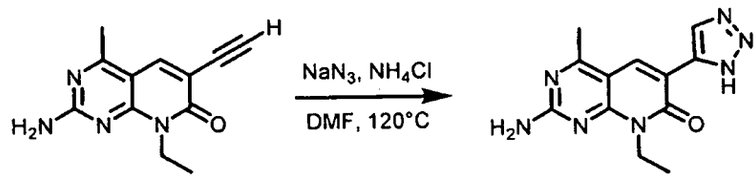


[00319] Trimethylsilylethyne (1.44 mL, 10.2 mmol) was added to a pressure tube charged with 2-amino-6-bromo-8-ethyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (1.58 g, 5.59 mmol) from above, CuI (0.053 g, 0.279 mmol), and $PdCl_2(PPh_3)_2$ (0.211 g, 0.279 mmol) in triethylamine (20 mL). The pressure tube was sealed under nitrogen and heated to 50 °C 96 h. The reaction was cooled to room temperature and poured into a saturated solution of $NaHCO_3$ (150 mL), then washed four times with ethyl acetate (50 mL). The organic layers were pooled and dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was

purified on SiO_2 (2:1, methylene chloride: ethyl acetate) to afford 2-amino-8-ethyl-4-methyl-6-((trimethylsilyl)ethynyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (1.09 g, 65 % yield) as an off white solid.



[00320] Potassium carbonate (1.00 g, 7.28 mmol) was added to a flask charged with 2-amino-8-ethyl-4-methyl-6-((trimethylsilyl)ethynyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (1.09 g, 3.64 mmol) in anhydrous methanol (15 mL). The reaction was stirred at room temperature under nitrogen for 16 h. The reaction was concentrated to one half volume and the yellow precipitate collected by vacuum filtration to afford 2-amino-8-ethyl -6-ethynyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one.

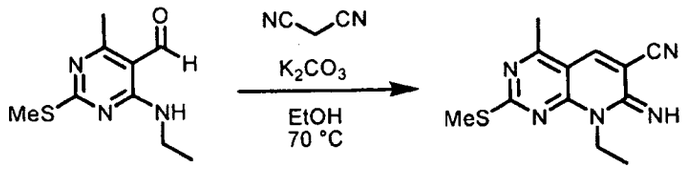


[00321] Anhydrous DMF (5.0 mL) was added to a flask charged with 2-amino-8-ethyl -6-ethynyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (0.204 g, 0.894 mmol), sodium azide (0.070 g, 1.07 mmol), and ammonium chloride (0.057 g, 1.07 mmol). The reaction was capped under nitrogen and heated to 120 °C. After 48 h, the reaction was cooled to room temperature and concentrated in vacuo. The residue was purified on reverse phase HPLC (acetonitrile: water 0.1 % TFA, 20–60% gradient). The fractions containing product were collected and concentrated to one half volume and poured into saturated $NaHCO_3$ (50 mL). The aqueous phase was washed trice with ethyl acetate (50 mL) and dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was triturated with methylene chloride and ethyl acetate to afford 2-amino-8-ethyl-4-methyl-6-(1*H*-1,2,3-triazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (14 mg, 6 % yield) as a light yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.55 (bs, 1H),

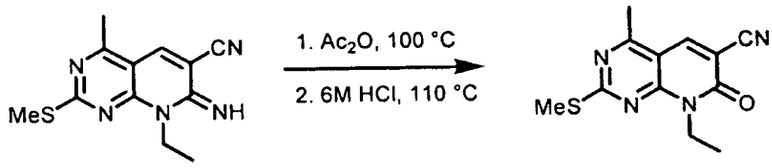
8.41 (bs, 1H), 7.32 (bs, 2H), 4.37 (q, J = 7.2 Hz, 2H), 2.60 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H); MS (EI) for $C_{12}H_{13}N_7O$: 272.0 (MH^+).

Example 12

2-Amino-8-ethyl-4-methyl-6-(1*H*-tetrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one

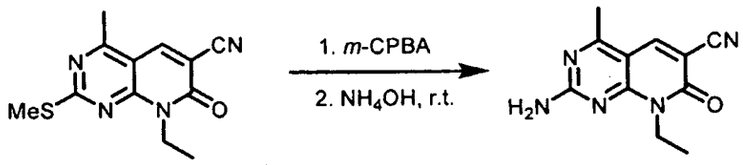


[00322] Potassium carbonate (0.539 g, 3.90 mmol) was added to a suspension of 4-(ethylamino)-6-methyl-2-(methylthio)pyrimidine-5-carbaldehyde (0.413 g, 1.95 mmol) from above, and malononitrile (0.194 g, 2.93 mmol) in absolute ethanol (15.0 mL) and heated to 70 °C. After one h, the reaction was allowed to cool to room temperature and concentrated in vacuo. The residue was diluted with ethyl acetate (50 mL) and washed with saturated $NaHCO_3$ (50 mL), and brine. The organic phase was separated and concentrated in vacuo. The residue was precipitated with ethyl acetate and hexanes to give 8-ethyl-7-imino-4-methyl-2-(methylthio)-7,8-dihydropyrido[2,3-*d*]pyrimidine-6-carbonitrile as a brown solid that was used in the subsequent step without further purification.



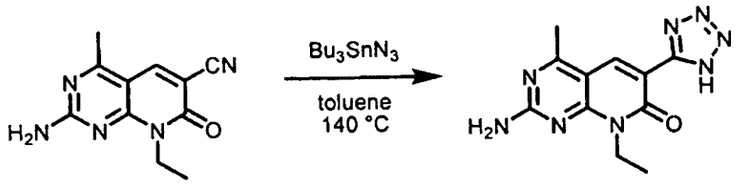
[00323] Acetic anhydride (10.0 mL) was added to a flask charged with 8-ethyl-7-imino-4-methyl-2-(methylthio)-7,8-dihydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (0.506 g, 1.95 mmol) and heated to 100 °C. After one h, the reaction was allowed to cool to room temperature and concentrated in vacuo. The acetylated residue was then treated with 6 N HCl (40 mL) and heated to 95 °C for one hour then transferred to a large flask. A saturated solution of $NaHCO_3$ (500 mL) was added slowly at 0 °C until a ~pH 8.0 was achieved. The aqueous phase was

washed thrice with ethyl acetate (100 mL) and the organic layers combined, then washed with brine and dried over Na_2SO_4. The drying agent was filtered and concentrated in vacuo to afford crude 8-ethyl-4-methyl-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidine-6-carbonitrile which was used in the subsequent step without further purification.



[00324] 3-Chloroperbenzoic acid (1.00 g, 5.85 mmol) was added to a solution of crude 8-ethyl-4-methyl-2-(methylthio)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (0.507 g, 1.95 mmol) in dichloromethane (30.0 mL) at room temperature. After 2.5 hours, the reaction was diluted with dichloromethane (50 mL) and washed twice with saturated $NaHCO_3$, followed by brine. The organic phase was separated and dried over Na_2SO_4, filtered, and concentrated in vacuo. 2-Amino-8-ethyl-4-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidine-6-carbonitrile was used in the subsequent step without further purification.

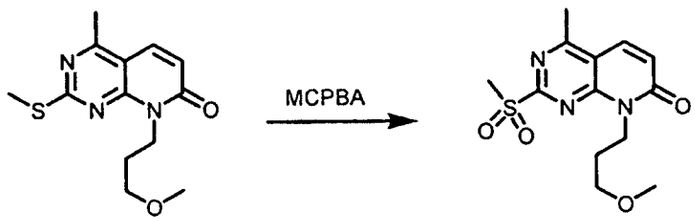
[00325] Ammonium hydroxide (500 µL) was added to a solution of the above sulfone in dioxane (10 mL) at 0 °C. The reaction flask sealed, and allowed to warm to room temperature upon standing overnight. The reaction was concentrated in vacuo triturated with ethyl acetate to afford the product which was used in the subsequent step without further purification.



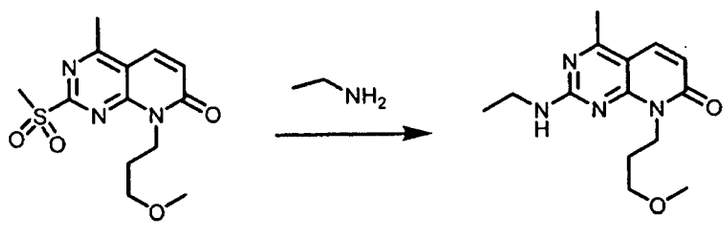
[00326] Tributyltin azide (660 µL, 2.41 mmol) was added to a flask charged with 2-amino-8-ethyl-4-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (0.184 g, 0.803 mmol) in anhydrous toluene (5.0 mL). The reaction was fitted with a reflux condenser and heated to 140 °C under a nitrogen atmosphere. After 20 h, the reaction was cooled to room temperature and the precipitate collected by vacuum filtration and washed with absolute ethanol to give 2-amino-8-ethyl-4-methyl-6-(1*H*-tetrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-

one (98 mg, 45 % yield) as a light brown solid: ^{1}H NMR (400 MHz, 20 % DCl in D_2O): δ 6.97 (s, 1H), 2.42 (q, J = 7.2 Hz, 2H), 0.953 (s, 3H), -0.73 (t, J = 7.2 Hz, 3H); MS (EI) for $C_{11}H_{11}N_8O$: 271.0 (MH^+).

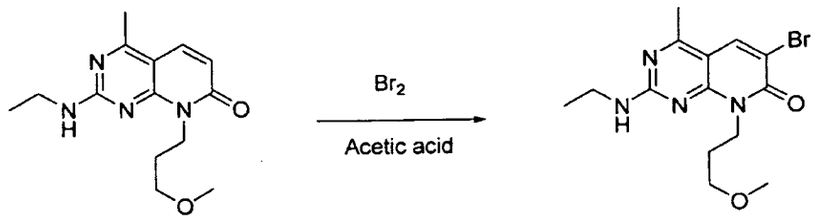
Example 13



[00327] A mixture of 8-(3-methoxypropyl)-4-methyl-2-(methylthio)pyrido[2,3-d]pyrimidin-7(8*H*)-one (0.36 g, 1.29 mmol), prepared using procedures similar to those described in Example 1, dichloromethane (10 mL), and 77 % 3-chloroperbenzoic acid with water (0.723 g, 3.23 mmol) was stirred for 1 h. The mixture was diluted with dichloromethane, washed with sat. sodium bicarbonate (3 times), brine, dried over sodium sulfate, and DCM was removed under reduced pressure. The crude 8-(3-methoxypropyl)-4-methyl-2-(methylsulfonyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one was used without further purification for subsequent step.



[00328] 8-(3-methoxypropyl)-4-methyl-2-(methylsulfonyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one, and a solution of 2M ethylamine in THF (20 mL) was stirred for 2 h. THF was removed under reduced pressure and the crude product was purified by flash column chromatography to give 2-(ethylamino)-8-(3-methoxypropyl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one (0.18 g, 50 % yield over 2 steps).



[00329] To a solution of 2-(ethylamino)-8-(3-methoxypropyl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one (0.18 g, 0.65 mmol), acetic acid (5 mL) and dichloromethane (3 mL) was added bromine (36 ul, 0.7 mmol). The mixture was stirred for 5 minutes, and then diluted with DCM and water. The organic layer was washed with sat. sodium bicarbonate (3 times), brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography to gave 0.13 g (56 % yield) of 6-bromo-2-(ethylamino)-8-(3-methoxypropyl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.09 (s, 1H), 5.44 (Br. s, 1H), 4.55 (m, 2H), 3.54-3.47 (m, 4H), 3.33 (s, 3H), 2.53 (s, 3H), 2.05-2.00 (m, 2H), 1.30- 1.23 (m, 3H); MS (EI) for $C_{14}H_{19}BrN_4O_2$: 355 (MH+).

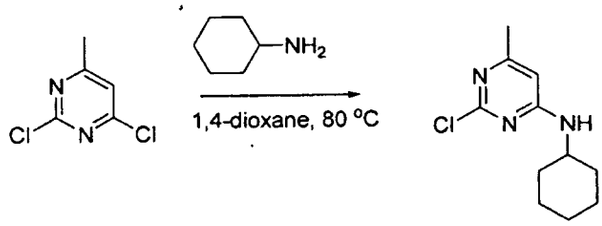
[00330] Using the same or analogous synthetic techniques and substituting with appropriate reagents, the following compounds were prepared:

Example 13a. 6-bromo-8-(2-ethoxyethyl)-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one: ^{1}H NMR (400MHz, $CDCl_3$) δ 8.09 (s, 1H), 5.37 (Br. s, 1H), 4.67 (m, 2H), 3.74 (m, 2H), 3.61-3.56 (t, 2H), 3.51 (m, 2H), 2.53 (s, 3H), 1.29-1.25 (t, 3H), 1.19-1.15 (t, 3H); MS (EI) for $C_{14}H_{19}BrN_4O_2$: 355 (MH+).

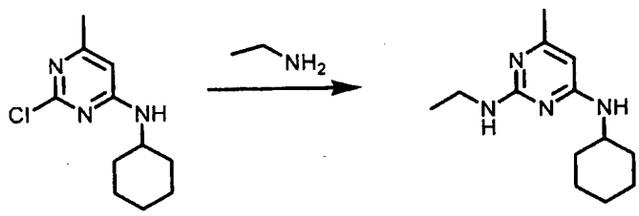
Example 13b. 6-bromo-8-(3-ethoxypropyl)-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one: ^{1}H NMR (400MHz, $CDCl_3$) δ 8.09 (s, 1H), 5.37 (Br. s, 1H), 4.53 (m, 2H), 3.52 (m, 4H), 3.48-3.43 (m, 2H), 2.53 (s, 3H), 2.04-2.00 (m, 2H), 1.29-1.25 (t, 3H), 1.19-1.15 (t, 3H); MS (EI) for $C_{15}H_{21}BrN_4O_2$: 369 (MH+).

Example 13c. 6-bromo-2-(ethylamino)-8-(3-isopropoxypropyl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one: ^{1}H NMR (400MHz, $CDCl_3$) δ 8.09 (s, 1H), 5.37 (Br. s, 1H), 4.53 (m, 2H), 3.59-3.49 (m, 5H), 2.52 (s, 3H), 2.01-1.98 (m, 2H), 1.28-1.25 (t, 3H), 1.13-1.11 (t, 6H); MS (EI) for $C_{16}H_{23}BrN_4O_2$: 383 (MH+).

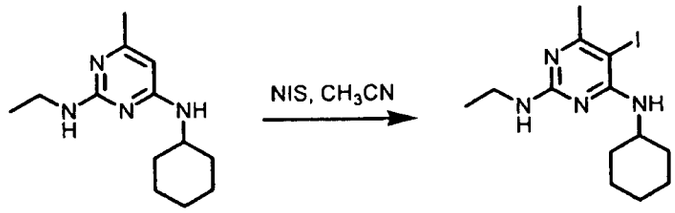
Example 14



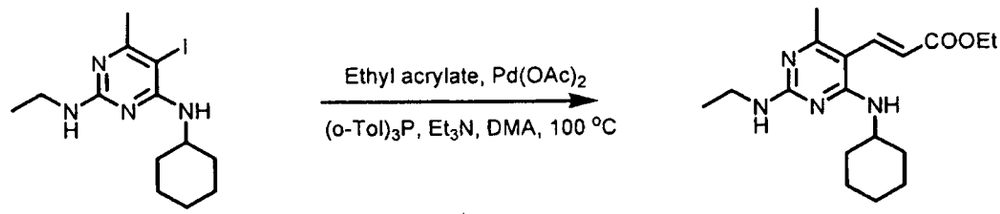
[00331] A mixture of 2,4-dichloro-6-methylpyrimidine (Aldrich, 5 g, 30 mmol), cyclohexylamine (3 g, 30 mmol) and DIEA (10 mL) was stirred at 80 °C for 12 h. The volatile material was removed under reduced pressure. The residue was loaded on a silica gel column, and was eluted with hexanes/ethyl acetate (3:1). 8-cyclohexyl-2-(ethylamino)-4-methyl-6-(thiophe*N*-2-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one was obtained as colorless oil (2.8 g, 41% yield).



[00332] The product was reacted with a solution of ethylamine (10 equiv.) in THF at 100 °C for 12 h. The crude 2-ethylamino-4-cyclohexylamino-6-methylpyrimidine was obtained from a standard workup and was used in the next step.

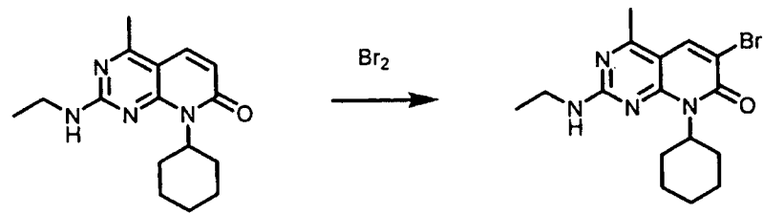


[00333] To a solution of 2-ethylamino-4-cyclohexylamino-6-methylpyrimidine (600 mg, 2.56 mmol) in CH_3CN (10 mL) was added *N*-iodosuccinimide (NIS, 658 mg, 2.92 mmol). The reaction was stirred for 2 h at room temperature. After removal of the solvent, the residue was dissolved in EtOAc. The organic phase was then washed with sodium bisulfite, brine, and dried over Na_2SO_4. Purification by flash column chromatography gave 660 mg (73% yield) of 2-ethylamino-4-cyclohexylamino-5-iodo-6-methylpyrimidine.

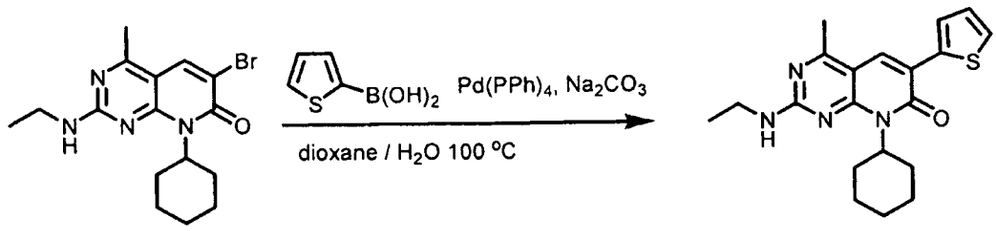


[00334] To a solution of 2-ethylamino-4-cyclohexylamino-5-iodo-6-methylpyrimidine (660 mg, 1.83 mmol) in DMA (7 mL) was added ethyl acrylate (458 mg, 4.58 mmol), $Pd(OAc)_2$ (121 mg, 0.18 mmol), $(o\text{-}Tol)_3P$ (110 mg, 0.37 mmol), and Et_3N (740 mg, 7.32 mmol). The mixture was then stirred at 100 °C for 12 h under N_2. Standard workup and purification by column chromatography gave 411 mg (67% yield) of (*E*)-ethyl 3-(4-(cyclohexylamino)-2-(ethylamino)-6-methylpyrimidin-5-yl)acrylate

[00335] (E)-ethyl 3-(4-(cyclohexylamino)-2-(ethylamino)-6-methylpyrimidin-5-yl)acrylate (200 mg, 0.6 mmol) was dissolved in AcOH (2 mL). This solution was heated in a sealed tube at 186 °C for 17 h. Standard workup and purification by column chromatography gave 65 mg (38 % yield) of 8-cyclohexyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one.



[00336] To 8-cyclohexyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one in AcOH and CH_2Cl_2 was added Br_2 (22 uL, 0.42 mmol) at 80 °C. Standard workup and purification by column chromatography gave 65 mg (0.17 mmol, 80 % yield) of 6-bromo-8-cyclohexyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one.

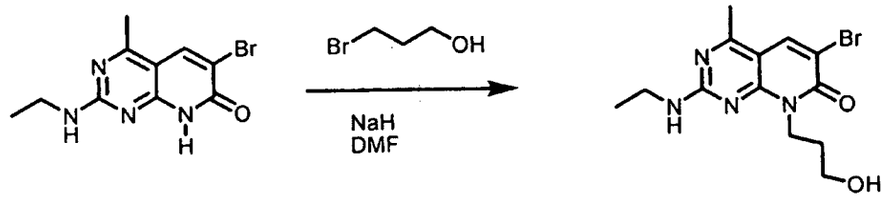


[00337] The bromide (65 mg, 0.17 mmol) obtained above was reacted with 2-thiopheneboronic acid (45 mg, 0.36 mmol) in the presence of $Pd(PPh_3)_4$ (20 mg, 0.018 mmol) and Na_2CO_3 (38 mg, 0.36 mmol) in 1,4-dioxane/H2O (1:1) at 100 °C for 2 h. Removal of solvents and purification by column chromatography gave 33 mg (50% yield) of 8-cyclohexyl-2-(ethylamino)-4-methyl-6-(thiophe*N*-2-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.01 (br s, 1 H), 7.60 (m, 1 H), 7.37 (m, 1 H), 7.10 (m, 1H), 5.60-5.40 (m, 1 H), 3.55 (m, 2 H), 2.85 (m, 1 H), 2.61 (s, 3 H), 1.90 (m, 2 H), 1.71 (m, 4 H), 1.43 (m, 2 H), 1.30-1.2 (m, 2 H),1.30 (t, 3 H); MS (EI) for $C_{20}H_{24}N_4OS$: 369 (MH+).

[00338] Using the same or analogous synthetic techniques and substituting with appropriate reagents, the following compound was prepared:

Example 14a. 6-bromo-8-cyclopropyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1 H), 5.37 (br s, 1 H), 3.54 (m, 2 H), 2.94 (br s, 1H), 2.51 (s, 3 H), 1.31-1.25 (m, 5 H), 0.91 (br s, 2 H); MS (EI) for $C_{13}H_{15}BrN_4O$: 323 (MH+).

Example 15



[00339] To a solution of 6-bromo-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one (100 mg, 0.35 mmol) in DMF (2 mL), prepared using porocedures analogous to those described in Example 14, was added NaH (30 mg, 60%, 0.7 mmol). The mixture was stirred for 30 min at room temperature and was warmed to 70 °C. 3-Bromopropanol (48 mg, 0.35 mmol) was then added. The stirring was continued for 12 h. Standard workup and purification by column chromatography gave 33 mg (27% yield) of 6-bromo-2-(ethylamino)-8-

(3-hydroxypropyl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one. ^{1}H NMR (400 MHz, CDCl3) δ 8.13 (s, 1 H), 5.42 (br s, 1 H), 4.59 (br s, 2 H), 3.50-3.47 (m, 5 H), 2.55 (s, 3 H), 2.02 (br s, 2 H), 1.28 (t, 3 H); MS (EI) for $C_{13}H_{17}BrN_4O_2$: 341 (MH+).

[00340] Using the same or analogous synthetic techniques and substituting with appropriate reagents, the following compounds were prepared:

Example 15a. 6-bromo-2-(ethylamino)-8-(2-hydroxyethyl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, DMSO-d6) δ 8.38 (s, 1 H), 4.82 (br s, 1 H), 4.40 (br s, 2 H), 3.62-3.55 (m, 2 H), 3.40-3.20 (m, 3 H), 2.55 (s, 3 H), 1.15 (t, 3 H); MS (EI) for $C_{12}H_{15}BrN_4O_2$: 327 (MH+).

Example 15b. 6-bromo-2-(ethylamino)-4-methyl-8-(2-(piperidin-1-yl)ethyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1 H), 5.39 (br s, 1 H), 4.59 (br s, 2 H), 3.55-3.40 (m, 2 H), 2.70-2.50 (m, 6 H), 2.52 (s, 3 H), 1.62-1.58 (m, 4 H), 1.46-1.40 (m, 2 H), 1.27 (t, 3 H); MS (EI) for $C_{17}H_{24}BrN_5O$: 394 (MH+).

Biological Examples

Biological Example 1

PI3Kalpha Luciferase-Coupled Chemiluminescence Assay Protocol

[00341] PI3Kα activity is measured as the percent of ATP consumed following the kinase reaction using luciferase-luciferi*N*-coupled chemiluminescence. Reactions were conducted in 384-well white, medium binding microtiter plates (Greiner). Kinase reactions were initiated by combining test compounds, ATP, substrate (PIP2), and kinase in a 20 μL volume in a buffer solution. The standard PI3Kalpha assay buffer is composed 50 mM Tris, pH 7.5, 1 mM EGTA, 10 mM $MgCl_2$, 1 mM DTT and 0.03% CHAPS. The standard assay concentrations for enzyme, ATP, and substrate are 0.5-1.1 nM, 1μM, and 7.5 μM, respectively. The reaction mixture was incubated at ambient temperature for approximately 2 h. Following the kinase reaction, a 10 μL aliquot of luciferase-luciferin mix (Promega Kinase-Glo) was added and the chemiluminescence signal measured using a Victor2 plate reader (Perkin Elmer). Total ATP consumption was limited to 40-60% and IC50 values of control compounds correlate well with literature references.

[00342] Certain compounds of the invention were tested in this assay and demonstrated the ability to bind to PI3K. For example, in one embodiment of the invention, the PI3K inhibitor is

selected from the compounds in Table 1 having a PI3K-binding affinity of about 9 μM or less. In another embodiment, the PI3K inhibitor is selected from the compounds in Table 1 having a PI3K-binding affinity of about 5 μM or less. In another embodiment, the PI3K inhibitor is selected from the compounds in Table 1 having a PI3K-binding affinity of about 3 μM or less. In another embodiment, the PI3K inhibitor is selected from the compounds in Table 1 having a PI3K-binding affinity of about 1.5 μM or less. In another embodiment, the PI3K inhibitor is selected from the compounds in Table 1 having a PI3K-binding affinity of about 1 μM or less. In another embodiment, the PI3K inhibitor is selected from the compounds in Table 1 having a PI3K-binding affinity of about 0.6 μM or less. In another embodiment, the PI3K inhibitor is selected from the compounds in Table 1 having a PI3K-binding affinity of about 0.3 μM or less. In another embodiment, the PI3K inhibitor is selected from the compounds in Table 1 having a PI3K-binding affinity of about 0.2 μM or less. In another embodiment, the PI3K inhibitor is selected from the compounds in Table 1 having a PI3K-binding affinity of about 0.1 μM or less. In another embodiment, the PI3K inhibitor is selected from the compounds in Table 1 having a PI3K-binding affinity of about 0.04 μM or less. In another embodiment, the PI3K inhibitor is selected from the compounds in Table 1 having a PI3K-binding affinity of about 0.020 μM or less.

Biological Example 2

Phospho AKT assayPC-3 cells were seeded on 6-well plates at 150,000 cells/well. Cells were cultured for 3 days, then treated with compounds in serum-free medium for 3 hr. EGF (100 ng/mL) was added for the last 10 min. Cells were lysed in TENN buffer. Phospho T308 Akt and total Akt were quantified by ELISA performed according to the Biosource assay protocol. The readings of phospho Akt were normalized to total Akt readings.

Biological Example 3

Phospho S6 assay

[00344] PC-3 cells were seeded on 96-well plates at 8,000 cells/well. For each experiment, cells were seeded and treated in duplicated plates: one plate for phospho S6 CellELISA, and one plate for total S6 CellELISA. Cells were cultured on the plates for 3 days, then treated with compounds in serum-free medium for 3 hr in triplicate. Cells were fixed with 4%

formaldehyde, quenched with 0.6% H_2O_2, blocked with 5% BSA, incubated with either phospho S6 antibody or total S6 antibody overnight, incubated with goat-anti-rabbit-IgG-HRP for 1 hr, and developed in chemiluminescent substrate.

Biological Example 4

PIP_3 assay

[00345] MCF-7 cells grown in 10-cm dishes were starved for 3 hours in DMEM, and then treated with compounds for 20 minutes. In the last 2 minutes of the incubation with the compounds, EGF (100 ng/mL) was added to stimulate the production of PIP3. The medium was aspirated and the cells were scraped with 10% trichloroacetic acid. The lipids were extracted from the pellet after the cell lysates were centrifuged. PIP3 in the cellular lipid extraction was quantified with the AlphaScreen assay in which Grp1-PH is used as the PIP3 specific probe. The amount of cellular PIP3 was calculated from the standard curve of diC_8 PI (3,4,5) P3.

Biological Example 5-10

In vivo models

[00346] Compound A is a Compound of Formula I. Compound B is *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta-[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine.

[00347] Female and male athymic nude mice (NCr) 5-8 weeks of age and weighing approximately 20-25 g were used in the following model. 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. All animals were examined daily for compound-induced or tumor-related deaths.

[00348] PC-3 human prostate adenocarcinoma cells were cultured in vitro in DMEM (Mediatech) supplemented with 20% 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 13, 99% viability) in 0.1 mL of ice-cold Hank's balanced salt solution were implanted subcutaneously into the hindflank of 5-8 week old male nude mice. A transponder was implanted in each mouse for identification, and

animals were monitored daily for clinical symptoms and survival. Body weights were recorded daily. Experiments were conducted with Compound A as a single agent as well as Compound A in combination with Taxol and Compound A in combination with Rapamycin. This model can be used to assess the desirability of treating with Compound A in combination with other anti-cancer agents.

[00349] U-87 MG human glioblastoma cells were cultured in vitro in DMEM (Mediatech) supplemented with 10% Fetal Bovine Serum (Hyclone), Penicilli*N*-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 $2x10^6$ cells (passage 5, 96% viability) in 0.1 mL of ice-cold Hank's balanced salt solution were implanted intradermally into the hindflank of 5-8 week old female nude mice. A transponder was implanted in each mouse for identification, and animals were monitored daily for clinical symptoms and survival. Body weights were recorded daily. Experiments were conducted with Compound A as a single agent and the results are not included. This model can be used to assess the desirability of treating with Compound A in combination with other anti-cancer agents.

[00350] A549 human lung carcinoma cells were cultured in vitro in DMEM (Mediatech) supplemented with 10% Fetal Bovine Serum (Hyclone), Penicilli*N*-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 $10x10^6$ cells (passage 12, 99% viability) in 0.1 mL of ice-cold Hank's balanced salt solution were implanted intradermally into the hindflank of 5-8 week old female nude mice. A transponder was implanted in each mouse for identification, and animals were monitored daily for clinical symptoms and survival. Body weights were recorded daily. Experiments were conducted with Compound A as a single agent as well as Compound A in combination with Compound B. This model can be used to assess the desirability of treating with Compound A in combination with other anti-cancer agents.

[00351] MDA-MB-468 human breast adenocarcinoma cells, passage number <6, were maintained and propagated in log-phase growth in Dulbecco's Modification of Eagles's Medium (DMEM; Mediatech) containing L-Glutamine 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 10×10^6 cells (passage 10, 98% viability) in 50% cold Hanks balanced salt solution/50% Matrigel (100

μL total volume per mouse) were implanted subcutaneously into the mammary fat pads of female nude mice. Experiments were conducted with Compound A as a single agent as well as Compound A in combination with erlotinib. This model can be used to assess the desirability of treating with Compound A in combination with other anti-cancer agents.

[00352] 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. A transponder was implanted in each mouse for identification, and animals were monitored daily for clinical symptoms and survival. Body weights were recorded daily. Experiments were conducted with Compound A as a single agent as well as Compound A in combination with carboplatin. This model can be used to assess the desirability of treating with Compound A in combination with other anti-cancer agents.

[00353] MCF7 human mammary adenocarcinoma cells were cultured in vitro in DMEM (Cellgro) supplemented with 10% Fetal Bovine Serum (Cellgro), 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 5×10^6 cells (passage 10 and 95% viability for Study 1, passage 9 and 90% viability for Study 2) in 100 μL of a solution made of 50% cold Hanks balanced salt solution with 50% growth factor reduced matrigel (R&D Systems for Study 1 and Becton Dickinson for Study 2) implanted subcutaneously into the hindflank of female nude mice. A transponder was implanted into each mouse for identification and data tracking, and animals were monitored daily for clinical symptoms and survival. During the dosing period, the tumor weight of each animal was determined twice weekly and the body weight of each animal was measured daily. Experiments were conducted with Compound A as a single agent as well as Compound A in combination with Compound B. This model can be used to assess the desirability of treating with Compound A in combination with other anti-cancer agents.

[00354] 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

[00355] These data were recorded and plotted on a tumor weight vs. days post-implantation line graph and presented graphically as an indication of tumor growth rates. 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

If tumors regress below their starting sizes, then the percent tumor regression is determined with the following formula:

$$\left[\frac{(X_0 - X_f)}{X_0}\right] * 100$$

Tumor size 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 $P<0.05$).

Biological Examples 11-14

[00356] Compound A is a Compound of Formula I and is an inhibitor of class I PI3-kinases. Compound B is *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta-[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine.

Prostate Cancer Xenograft Model – A Compound of Formula I in Combination with Taxol

[00357] Compound A was tested alone and in combination with taxol in a prostate carcinoma tumor model. PC-3 is a human prostate carcinoma cell line that harbors a homozygous deletion mutation in PTEN, which results in constitutive activation of the PI3K pathway. In single-dose pharmacodynamic experiments, oral administration of Compound A resulted in a dose-dependent decrease in the phosphorylation of AKT, p70S6K, and S6 in PC-3

tumors grown ectopically in mice. Repeat-dose administration of Compound A also inhibited the growth of these tumors, but did not induce regressions.

[00358] Oral administration of Compound A at 100mg/kg q2d or 30 mg/kg bid resulted in substantial tumor growth inhibition. See Fig. 1. Comparable tumor growth inhibition was achieved with 7.5 mg/kg taxol administered i.v. twice weekly. While tumor growth was inhibited substantially with Compound A alone, the combination of either dose of Compound A with taxol was superior to either agent alone and induced significant regression of the tumors. Body weight loss and dose skipping was minimal in all groups, and was not exacerbated in the combination group indicating that the combination was well tolerated. These results support the use of a Compound of Formula I in combination with taxol in tumors with constitutively activated PI3K signaling.

Prostate Cancer Xenograft Model – A Compound of Formula I in Combination with Rapamycin

[00359] Compound A was tested alone and in combination with rapamycin in a prostate carcinoma tumor model (PC-3 cell line). Oral administration of Compound A at 100mg/kg q2d resulted in significant tumor growth inhibition. See Fig. 2. Significant tumor growth inhibition was also observed with 5 mg/kg rapamycin administered i.p. daily. While tumor growth was inhibited substantially with Compound A alone, the combination of Compound A with rapamycin was transiently superior to either agent alone and induced regression of the tumors, although the final tumor weights were similar between rapamycin alone and the combination treatment. Body weight loss and dose skipping was minimal with each agent alone, but body weight loss was exacerbated in the combination group necessitating dose skipping. The fact that tumor regression was observed despite dose skipping suggests that using an intermittent dosing schedule would maintain efficacy and improve tolerability.

[00360] At the end of the efficacy study, tumors were resected and processed for histological analysis of markers of proliferation (Ki67) and apoptosis (TUNEL). Administration of Compound A as monotherapy (100mg/kg q2d) was associated with a significant 44% decrease in the fraction of proliferating cells. Administration of rapamycin as monotherapy was also associated with a decrease (77%) in the fraction of proliferating cells. Combined administration of Compound A and rapamycin resulted in a strong anti-proliferative effect (96% decrease)

which was significantly enhanced over that seen with monotherapy (Fig. 6). Administration of Compound A as monotherapy was associated with a significant 3.6-fold induction in the fraction of apoptotic cells, whereas rapamycin administered as monotherapy did not exert significant pro-apoptotic effects. Combined administration of Compound A and rapamycin resulted in a 7-fold induction in the fraction of apoptotic cells, which was significantly enhanced over that seen with monotherapy (Fig. 7). Together, these data indicate that coadministration of Compound A and rapamycin leads to a significant decrease in tumor cell proliferation and a significant increase in tumor cell apoptosis compared to either agent administered as monotherapy. These results support the use of a Compound of Formula I in combination with rapamycin in tumors with constitutively activated PI3K signaling.

Non-small Cell Lung Cancer Xenograft Model – A Compound of Formula I in Combination with Carboplatin

[00361] Compound A was tested both as a single agent and in combination with carboplatin in a NSCLC tumor model. Calu-6 is a human NSCLC cell line that harbors a heterozygous activating mutation in K-Ras (Q61K).

[00362] Oral administration of Compound A at 100mg/kg q2d or 30 mg/kg bid to mice bearing Calu-6 tumors resulted in substantial tumor growth inhibition. See Fig. 3. Both dose schedules resulted in similar inhibition of tumor growth. Significant tumor growth inhibition was also observed with 50 mg/kg carboplatin administered i.v. q4d, but was not as pronounced as with Compound A. The combination of Compound A 100 mg/kg q2d and carboplatin was superior to either agent alone, however, the combination of Compound A 30 mg/kg bid with carboplatin was not significantly different from Compound A 30 mg/kg bid alone. Body weight loss and dose skipping was minimal in all groups, and was not exacerbated in the combination group indicating that the combination was well tolerated. These results support the use of a Compound of Formula I in combination with platins in tumors with activating mutations in K-Ras.

Non-small Cell Lung Cancer Xenograft Model – A Compound of Formula I in Combination with Compound B

[00363] Compound A was tested both as a single agent and in combination with Compound B, an EGFR inhibitor, in a NSCLC tumor model. The A549 human non-small cell lung carcinoma cell line harbors a homozygous stop mutation in the gene encoding LKB1, and an

activating G12S mutation in K-Ras, promoting activation of both PI3K and mTOR. A549 cells also express wild-type EGFR.

[00364] Oral single-agent administration of Compound B at 30 mg/kg qd for 18 days caused a significant tumor growth inhibition of 80%. See Fig. 4a. Compound A administered qd as a single agent at 30 mg/kg caused a significant tumor growth inhibition of 80%. Oral administration of Compound B at 30 mg/kg qd followed by administration of Compound A at 30 mg/kg qd after about six hours led to a significant TGI of 93%, which trended towards an increased anti-tumor efficacy compared to the efficacy of the single treatments, although this did not reach statistical significance in these studies. One possible explanation for the modest effect of the combination is the short duration of the dosing period (14 days), which may be too short to observe the full benefit of the combination. Longer dosing regimes may produce more significant differences, as the anticipated effect of dual inhibition of PI3K/mTOR and EGFR on cell growth and survival becomes more apparent.

[00365] As a single agent Compound B dosed at 30 mg/kg qd was generally well tolerated, with a body weight loss of 1.5 to 7% with no dose omission. Compound A dosed at 30 mg/kg qd was also well tolerated with no dose skipping and non-significant body weight loss. Co-administration of Compound B at 30 mg/kg qd with Compound A at 30 mg/kg qd was associated with a body weight loss of 3 to 12%, which was necessitated minimal dose skipping (2 doses) with no dose skipping for the last 8 days.

Breast Cancer Xenograft Model – A Compound of Formula I in Combination with Compound B

[00366] Compound A, a PI3K inhibitor, was tested both as a single agent and in combination with Compound B, an EGFR inhibitor, in a breast cancer tumor model. The MCF7 human mammary adenocarcinoma cell line harbors a heterozygous, activating mutation in PI3K (PI3KCA/E545K) and expresses wild-type EGFR.

[00367] Compound B was administered orally once-daily (qd) at 30 mg/kg, and Compound A was orally administered once-daily at 30 mg/kg. Combination therapies consisted of adminstering Compound B at 30 mg/kg qd followed by administration of Compound A at 30 mg/kg qd within about 6-7 hours. Single agent administration of Compound B at 30 mg/kg qd for 14 days caused a tumor growth inhibition of 38 to 61%. See Figs. 4b-1 and 4b-2. Tumor growth inhibition of 53-76% was observed with Compound A dosed at 30 mg/kg qd. The

combination of Compound B dosed at 30 mg/kg qd with Compound A dosed at 30 mg/kg qd resulted in significant tumor growth inhibition of 83-87%, which trended towards an increased anti-tumor efficacy compared to the efficacy of the single treatments, although this did not reach statistical significance in these studies. One possible explanation for the modest effect of the combination is the short duration of the dosing period (14 days), which may be too short to observe the full benefit of the combination. Longer dosing regimes may produce more significant differences, as the anticipated effect of dual inhibition of PI3K and EGFR on cell growth and survival becomes more apparent. In both studies (Figs. 4b-1 and 4b-2) the average tumor size in the combination groups is still decreasing at the last measurement point.

[00368] At the end of the study, tumors were resected and processed for analysis of proliferating cells (Ki67 staining), determination of microvessel density (MVD) following immunostaining for CD31, and for TUNEL (apoptotic cells) analysis (see Tables 8 and 9). Administration of Compound B dosed at 30 mg/kg qd caused a significant 14 to 19% decrease in the number of viable, Ki67-positive proliferating tumor cells when compared to the vehicle control-treated group. Compound A dosed at 30 mg/kg qd did cause a significant 13% decrease in Ki67-positive cells only in Study 2. Combination of Compound B with Compound A caused a significant 23 to 37% decrease in Ki67 positive tumor cells, which was significantly more efficacious in this model than the single agent treatments (however not better than Compound B single arm in Study 1). Treatment with Compound B dosed at 30 mg/kg qd did not result in a significant induction of TUNEL-positive (apoptotic) cells compared to the vehicle control-treated group. Administration of Compound A dosed at 30 mg/kg qd did not cause a significant induction of apoptotic tumor cells. Combining Compound B with Compound A did not result in a significant induction of apoptosis compared to vehicle control. Administration of Compound B dosed at 30 mg/kg qd and Compound A dosed at 30 mg/kg qd caused a significant 31% and 32% decrease, respectively, in CD31-positive tumor vessels. The combination of Compound B with Compound A caused a 22% decrease in MVD, which was not significantly different from Compound B or Compound A single agent treatment. End-of-study immunohistochemical analyses suggest that co-administration of Compound B and Compound A may provide an additional benefit on the anti proliferative, but not the anti-angiogenic effect of the single agents in MCF-7 tumors.

[00369] As a single agent Compound B dosed at 30 mg/kg qd was generally well tolerated, with a final body weight loss of 4.5 to 6.1% (not significantly different from the vehicle-treated control group) and 7 to 13 dose omissions. The majority of the skipped doses (11 out of 13) in Study 1 came from one mouse maintaining a low body weight throughout the study from dose day 3. Administration of Compound A dosed at 30 mg/kg qd was also well tolerated with 3 to 9 doses skipped and non-significant body weight loss or gain. Co-administration of Compound B at 30 mg/kg qd with Compound A at 30 mg/kg qd was associated with a body weight loss of 0.3 to 10% throughout the study and minimal dose skipping (6 to 11 doses). By the end of the dosing period there was a non-significant loss of 0.3 to 6.2% in body weight.

Breast Cancer Xenograft Model – A Compound of Formula I in Combination with Erlotinib

[00370] Compound A was tested both as a single agent and in combination with erlotinib, in an erolitinib-resistant tumor model with elevated PI3K signaling. MDA-MB-468 is a human breast carcinoma cell line that has an increase in the copy number of the EGFR gene and a homozygous deletion of PTEN. In vitro treatment of these cells with EGFR inhibitors such as erlotinib inhibits EGFR activity but fails to downregulate the PI3K pathway.

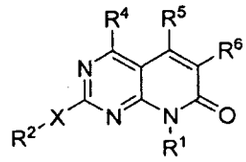
[00371] Oral administration of erlotinib at 100 mg/kg qd to mice bearing MDA-MB-468 tumors resulted in significant but incomplete tumor growth inhibition. See Fig. 5. Oral administration of Compound A at 100mg/kg q2d also resulted in tumor growth inhibition. The combination of the two agents was modestly superior to either agent alone. The relatively modest increase in efficacy in the combination group could improve with altering the dose and schedule for the administration of Compound A.

[00372] Mice administered Compound A at 100 mg/kg q2d exhibited a rate of body weight gain comparable to vehicle controls. Mice administered erlotinib exhibited an apparent decrease in their rate of body weight gain relative to vehicle controls. Coadministration with erlotinib resulted in a loss in body weight in mice treated with Compound A (10% body weight loss from start of dosing). Consistent with these data, only minimal dose-skipping was required when Compound A was administered as monotherapy (1-3 doses skipped), but substantial dose-skipping was required for Compound A when erlotinib was coadministered. These results support the use of a Compound of Formula I in combination with erlotinib in tumors expressing EGF receptors and harboring PTEN deletions.

[00373] 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. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled. 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.

What is claimed is:

1. A method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I:



I

or a single isomer thereof where the compound is optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof, or administering to a patient a pharmaceutical composition comprising a therapeutically effective amount of a Compound of Formula I and a pharmaceutically acceptable carrier, excipient, or diluent; in combination with one or more treatments independently selected from surgery, one or more chemotherapeutic agents, one or more of the hormone therapies, one or more antibodies, one or more immunotherapies, radioactive iodine therapy, and radiation wherein the Compound of Formula I is that wherein:

R^1 is hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

R^2 is hydrogen or alkyl where the alkyl is optionally substituted with 1, 2, 3, 4, or 5 R^8 groups;

X is $-NR^3-$;

R^3 hydrogen;

R^4 is optionally substituted alkyl;

R^5 is hydrogen; and

R^6 is phenyl, acyl, or heteroaryl wherein the phenyl and heteroaryl are optionally substituted with 1, 2, 3, 4, or 5 R^9 groups;

each R^8, when present, is independently hydroxy, halo, alkoxy, haloalkoxy, amino, alkylamino, dialkylaminoalkyl, or alkoxyalkylamino; and

each R^9, when present, is independently halo, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, amino, alkylamino, dialkylamino, alkoxyalkyl, carboxyalkyl, alkoxycarbonyl,

aminoalkyl, cycloalkyl, aryl, arylalkyl, aryloxy, heterocycloalkyl, or heteroaryl and where the cycloalkyl, aryl, heterocycloalkyl, and heteroaryl, each either alone or as part of another group within R^9, are independently optionally substituted with 1, 2, 3, or 4 groups selected from halo, alkyl, haloalkyl, hydroxy, alkoxy, haloalkxy, amino, alkylamino, and dialkylamino.

2. The method of Claim 1 where the cancer is selected from breast cancer, colon cancer, rectal cancer, endometrial cancer, gastrointestinal carcinoid tumors, gastrointestinal stromal tumors, glioblastoma, hepatocellular carcinoma, small cell lung cancer, non-small cell lung cancer, melanoma, ovarian cancer, cervical cancer, pancreatic cancer, prostate carcinoma, acute myelogenous leukemia, chronic myelogenous leukemia, non-Hodgkin's lymphoma, and thyroid carcinoma.

3. The method of Claim 1 or 2 where the treatment is one or two chemotherapeutic agents.

4. The method of Claims 1 or 2 where the treatment is one antibody selected from an EGFR antibody and an ErbB2 antibody, or the treatment is one or two chemotherapeutic agents independently selected from rapamycin, a rapamycin analogue, an alkylating agent, a taxane, a platin, an EGFR inhibitor, and an ErbB2 inhibitor.

5. The method of Claim 4 where the treatment is one or two chemotherapeutic agents independently selected from rapamycin, paclitaxel, carboplatin, lapatinib, erlotinib, and *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta-[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine (optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof).

6. The method of Claim 3 where the treatment is one chemotherapeutic agent and the chemotherapeutic agent is an EGFR inhibitor.

7. The method of Claim 3 where the treatment is one chemotherapeutic agent and the chemotherapeutic agent is a platin.

8. The method of Claim 3 where the treatment is one chemotherapeutic agent and the chemotherapeutic agent is a taxane.

9. The method of Claim 3 where the treatment is one chemotherapeutic agent and the chemotherapeutic agent is rapamycin or a rapamycin analogue.

10. The method of Claim 3 where the treatment is one chemotherapeutic agent and the chemotherapeutic agent is *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5r,6a*S*)-2-

methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, *N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5r,6a*S*)-2-methyloctahydrocyclo-penta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5s,6a*S*)-2-methyloctahydrocyclopenta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, or *N*-(4-bromo-3-chloro-2-fluorophenyl)-7-({[(3a*R*,5s,6a*S*)-2-methyloctahydrocyclo-penta[c]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine; each of which is optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof.

11. The method of Claim 1 where the cancer is prostate cancer and the treatment is one or two chemotherapeutic agents independently selected from rapamycin, paclitaxel, and docetaxel.

12. The method of Claim 1 where the cancer is breast cancer and the treatment is one chemotherapeutic agent and the chemotherapeutic agent is lapatinib.

13. The method of Claim 1 where the cancer is breast cancer and the treatment is one chemotherapeutic agent and the chemotherapeutic agent is erlotinib.

14. The method of Claim 1 where the cancer is breast cancer and the treatment is one chemotherapeutic agent and the chemotherapeutic agent is *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta-[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof.

15. The method of Claim 1 where the cancer is non-small cell lung cancer and the treatment is one chemotherapeutic agent where the chemotherapeutic agent is carboplatin.

16. The method of Claim 1 where the cancer is non-small cell lung cancer and the treatment is one chemotherapeutic agent where the chemotherapeutic agent is *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta-[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof.

17. The method of Claim 1 or 2 where the Compound of Formula I is selected from:

8-ethyl-2-(ethylamino)-4-methyl-6-phenylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
6-biphenyl-4-yl-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
6-(2,4-difluorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
6-(3-chloro-4-fluorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;

8-ethyl-2-(ethylamino)-4-methyl-6-[4-(methyloxy)phenyl]pyrido[2,3-d]pyrimidin-7(8*H*)-one;
6-(2,4-dichlorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
6-(3,4-difluorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-[2-(methyloxy)phenyl]pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-[4-(phenyloxy)phenyl]pyrido[2,3-d]pyrimidin-7(8*H*)-one;
6-[2,4-bis(methyloxy)phenyl]-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-6-(3-fluorophenyl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-6-(2-fluorophenyl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-[3-(trifluoromethyl)phenyl]pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-6-(4-fluorophenyl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-(2-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-[3-(methyloxy)phenyl]pyrido[2,3-d]pyrimidin-7(8*H*)-one;
6-(3-chlorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
6-(4-chlorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-(3-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-(4-methyl-2-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-(4-methyl-3-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
1,1-dimethylethyl 2-[8-ethyl-2-(ethylamino)-4-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl]-1*H*-pyrrole-1-carboxylate
8-ethyl-2-(ethylamino)-4-methyl-6-(1*H*-pyrrol-2-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
6-(5-chloro-2-thienyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-pyrimidin-5-ylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-6-(3-fluoropyridi*N*-4-yl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-6-furan-3-yl-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-[1-(phenylmethyl)-1*H*-pyrazol-4-yl]pyrido[2,3-d]pyrimidin-7(8*H*)-one;
2-(ethylamino)-4-methyl-8-(1-methylethyl)-6-(2-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-6-(1*H*-indol-6-yl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-(5-phenyl-2-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
2-(ethylamino)-6-furan-3-yl-4-methyl-8-(1-methylethyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;

8-ethyl-2-(ethylamino)-4-methyl-6-(1*H*-pyrazol-5-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-cyclohexyl-2-(ethylamino)-4-methyl-6-(2-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-(1,3-thiazol-2-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-cyclopentyl-2-(ethylamino)-4-methyl-6-(1*H*-pyrazol-3-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
2-(ethylamino)-4-methyl-8-(1-methylethyl)-6-(1*H*-pyrazol-5-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-(1*H*-pyrazol-1-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
2-(ethylamino)-4-methyl-8-(1-methylethyl)-6-(1*H*-pyrazol-1-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-cyclopentyl-2-(ethylamino)-4-methyl-6-(1*H*-pyrazol-1-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-4-methyl-6-(1*H*-pyrazol-5-yl)-2-[(2,2,2-trifluoroethyl)amino]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-(1*H*-pyrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-(ethylamino)-4-methyl-6-(1*H*-pyrazol-3-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
8-ethyl-4-methyl-2-(methylamino)-6-(1*H*-pyrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-cyclopentyl-4-methyl-6-(1*H*-pyrazol-3-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
8-ethyl-2-[(2-fluoroethyl)amino]-4-methyl-6-(1*H*-pyrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-4-methyl-8-(1-methylethyl)-6-(1*H*-pyrazol-3-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-4-methyl-8-(phenylmethyl)-6-(1*H*-pyrazol-3-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-(4-methyl-3-thienyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-(2-thienyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-6-(4-fluorophenyl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-6-(3-fluorophenyl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-6-(2-fluorophenyl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-(3-thienyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-6-furan-3-yl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-[4-(methyloxy)phenyl]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-6-(4-chlorophenyl)-8-ethyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-6-(3-chlorophenyl)-8-ethyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-6-isoxazol-4-yl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-6-furan-2-yl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-6-(2,4-dichlorophenyl)-8-ethyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;

5-(2-amino-8-ethyl-4-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-6-yl)thiophene-2-carbonitrile
2-amino-8-ethyl-4-methyl-6-pyrimidin-5-ylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-6-(1*H*-imidazol-5-yl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-(1*H*-1,2,3-triazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-(1*H*-pyrazol-4-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-(1,3-thiazol-2-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-(1*H*-tetrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-(1-methyl-1*H*-pyrrol-2-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-4,8-diethyl-6-(1*H*-pyrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one; and
2-amino-8-cyclopentyl-4-methyl-6-(1,3-thiazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;

where the Compound is optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof.

18. The method of Claims 1, 2, 4, or 17 where the treatment is one antibody selected from an EGFR antibody and an ErbB2 antibody, or the treatment is one or two chemotherapeutic agents independently selected from rapamycin, a rapamycin analogue, an alkylating agent a taxane, a platin, an EGFR inhibitor, and an ErbB2 inhibitor.

19. The method of Claim 18 where the treatment is one or two chemotherapeutic agents independently selected from rapamycin, paclitaxel, carboplatin, lapatinib, erlotinib, and *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta-[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof.

20. The method of Claim 1, 2, 3, 4, or 17 where the treatment is one chemotherapeutic agent where the chemotherapeutic agent is *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta-[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof.

21. The method of Claim 1, 2, 3, 4, or 17 where the treatment is one chemotherapeutic agent where the chemotherapeutic agent is erlotinib.

22. The method of Claim 1, 2, 3, 4, or 17 where the treatment is one chemotherapeutic agent where the chemotherapeutic agent is lapatinib.

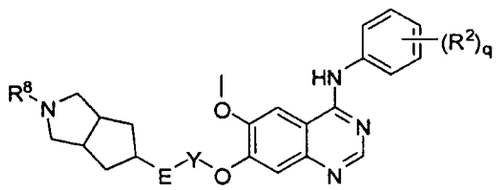
23. The method of Claim 1, 2, 3, 4, or 17 where the treatment is one chemotherapeutic agent where the chemotherapeutic agent is carboplatin.

24. The method of Claim 1, 2, 3, 4, or 17 where the treatment is one chemotherapeutic agent where the chemotherapeutic agent is paclitaxel.

25. The method of Claim 1, 2, 3, 4, or 17 where the treatment is one chemotherapeutic agent where the chemotherapeutic agent is rapamycin.

26. The method of Claim 1, 2, 3, 4, or 17 where the treatment is one antibody selected from bevacizumab, trastuzumab, cetuximab, and panitumumab.

27. The method of Claim 1, 2, 3, 4, or 17 where the treatment is one chemotherapeutic agent where the chemotherapeutic agent is of formula 100:



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where q is 1, 2, or 3; E is $-NR^9-$, -O-, or absent and Y is $-CH_2CH_2-$, $-CH_2-$, or absent provided that when E is $-NR^9-$ or -O-, then Y is $-CH_2CH_2-$; R^2 is selected from halogen, trihalomethyl, -CN, $-NO_2$, $-OR^3$, and lower alkyl; R^8 is selected from -H, lower alkyl, $-C(O)OR^3$, $-C(O)N(R^3)R^4$, $-SO_2R^4$, and $-C(O)R^3$; R^9 is hydrogen or lower alkyl; R^3 is hydrogen or R^4; R^4 is selected from lower alkyl, aryl, lower arylalkyl, heterocyclyl, and lower heterocyclylalkyl; or R^3 and R^4, when taken together with a common nitrogen to which they are attached, form a five- to seven-membered heterocyclyl, said five- to seven-membered heterocyclyl optionally containing one or more additional heteroatom selected from N, O, S, and P; or a single geometric isomer, stereoisomer, racemate, enantiomer, or diastereomer, thereof and optionally as a pharmaceutically acceptable salt, additionally optionally as a solvate, and additionally as a hydrate thereof.

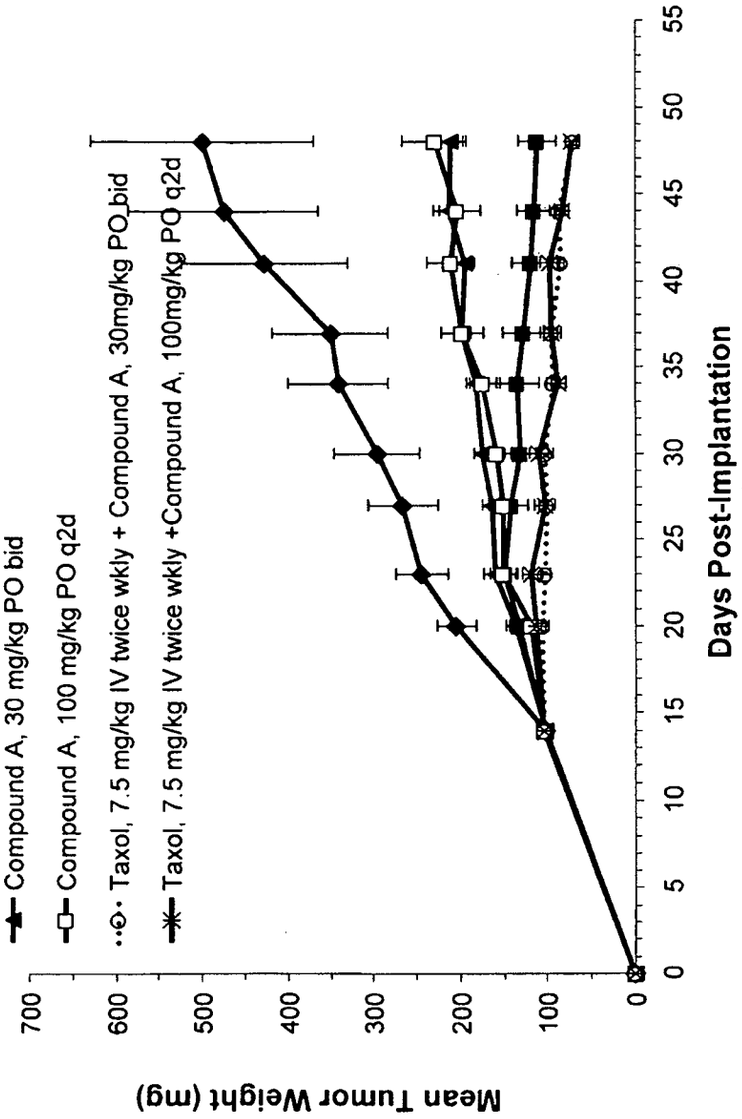


Fig. 1. Compound A + Taxol in PC-3 Prostate Carcinoma Tumor Model

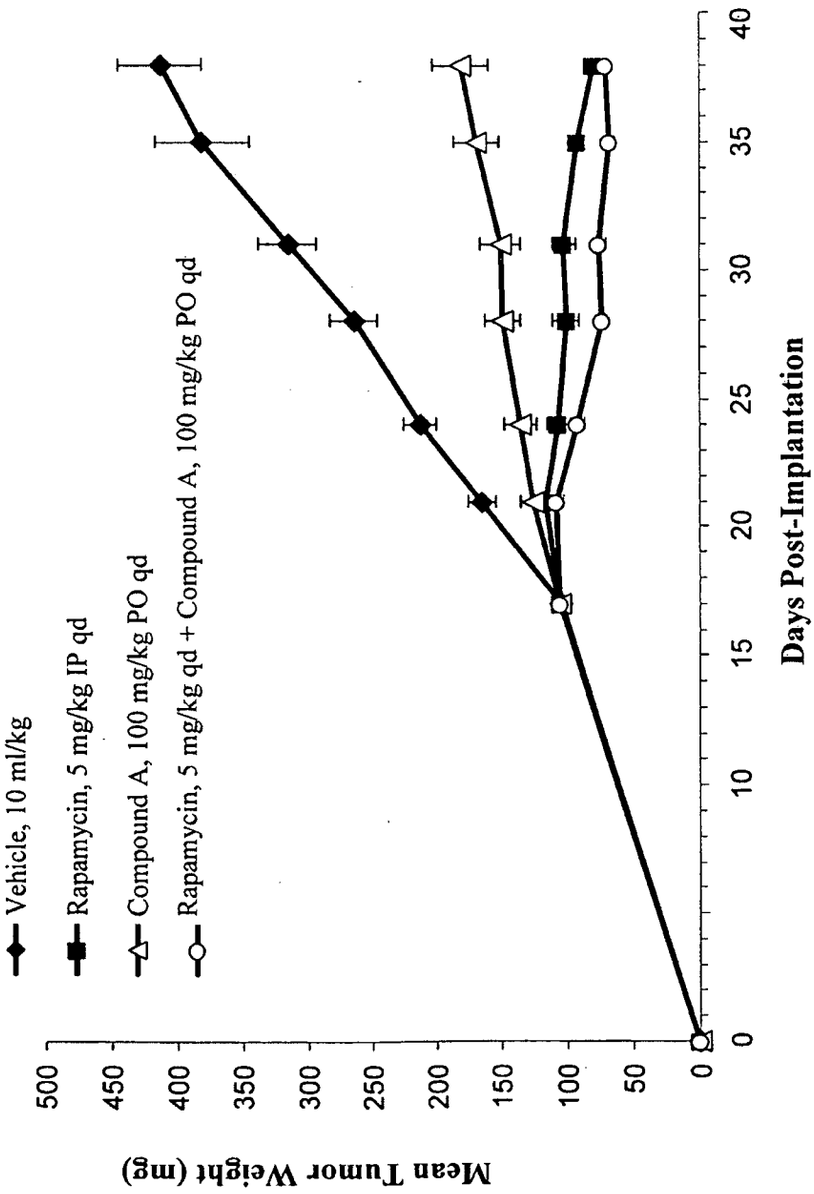


Fig. 2. Compound A + Rapamycin in PC-3 Prostate Carcinoma Tumor Model

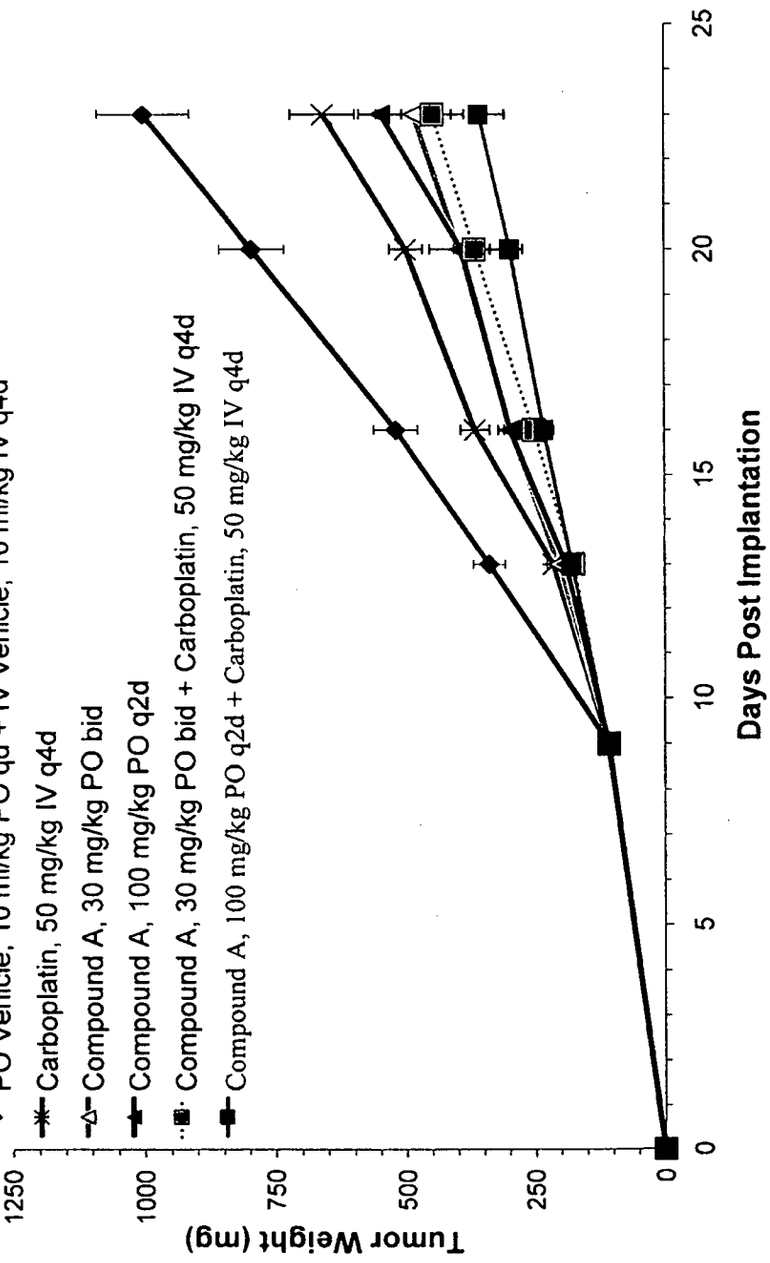


Fig. 3. Compound A + Carboplatin in Calu-6 NSCLC Tumor Model

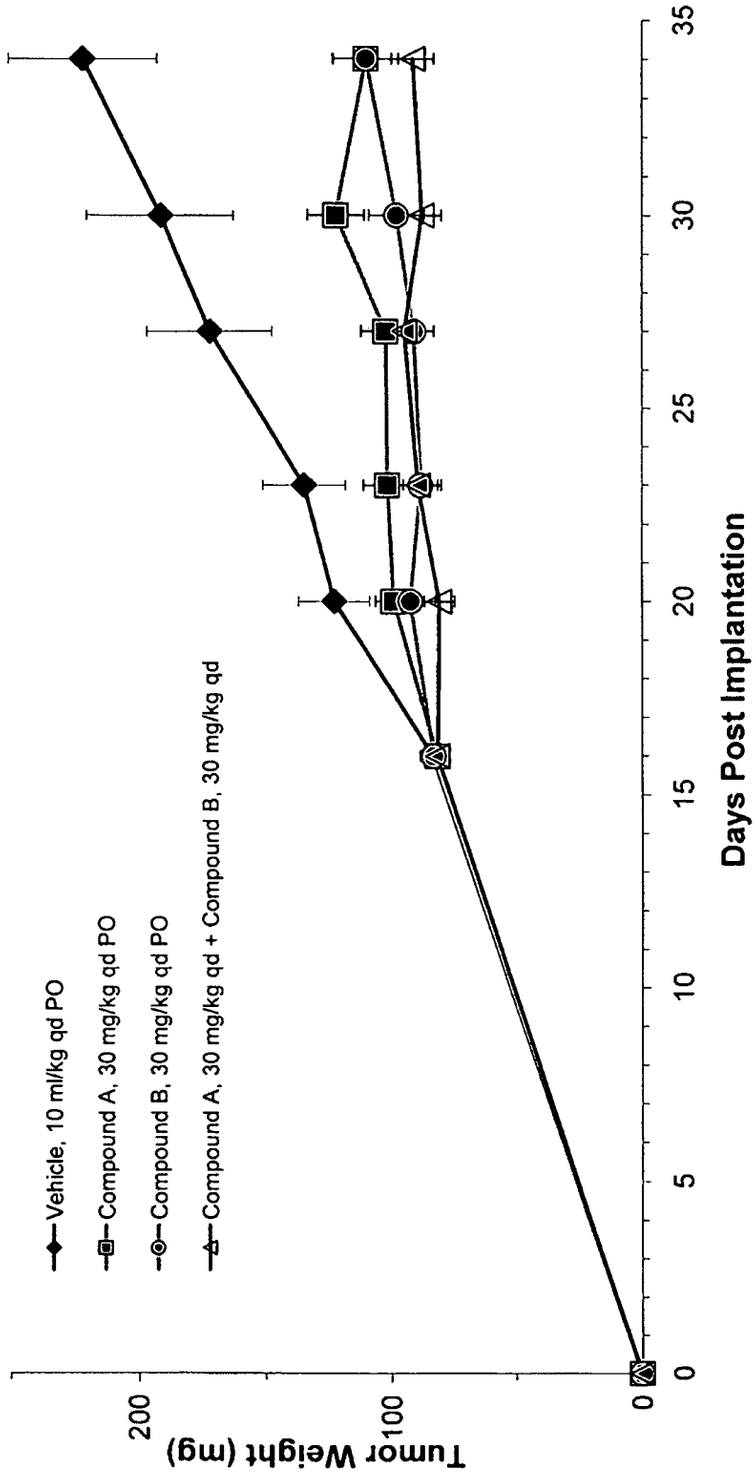


Fig. 4a. Compound A + Compound B in A549 Non-small Cell Lung Cancer Tumor Model

Fig. 4b-1. Compound A + Compound B in MCF7 Breast Cancer Tumor Model (Study 1)

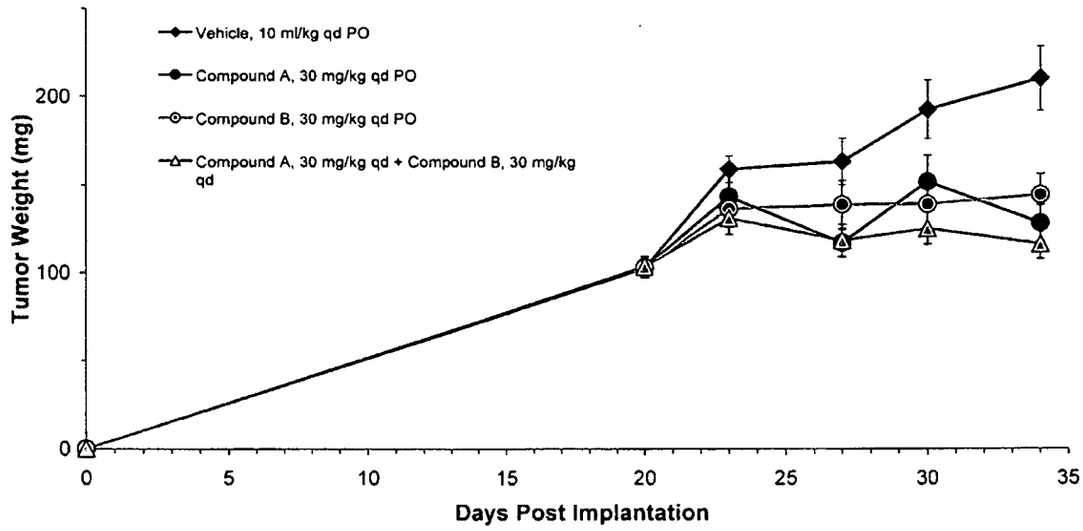
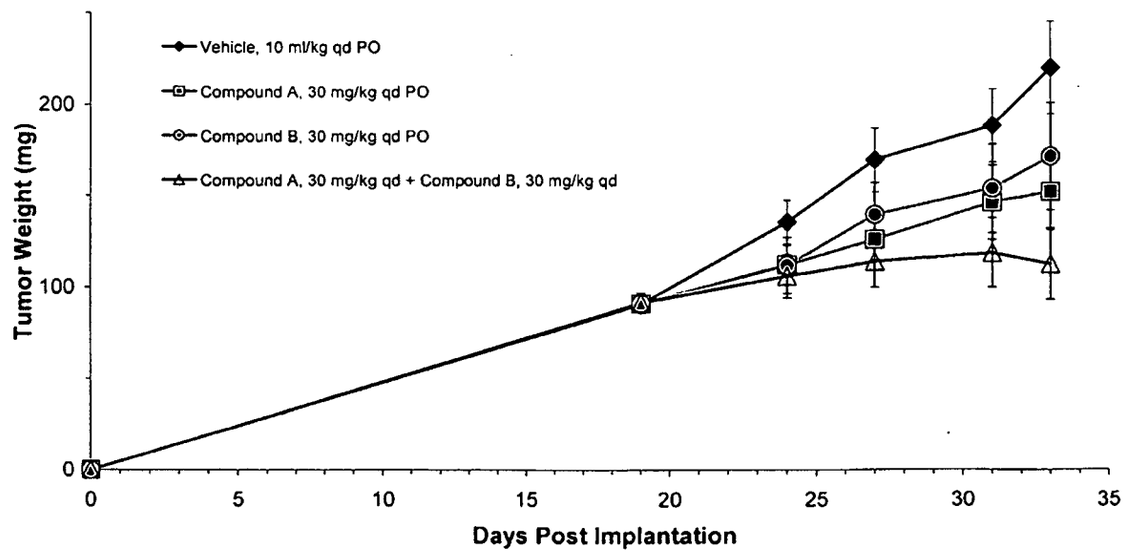


Fig. 4b-2. Compound A + Compound B in MCF7 Breast Cancer Tumor Model (Study 2)



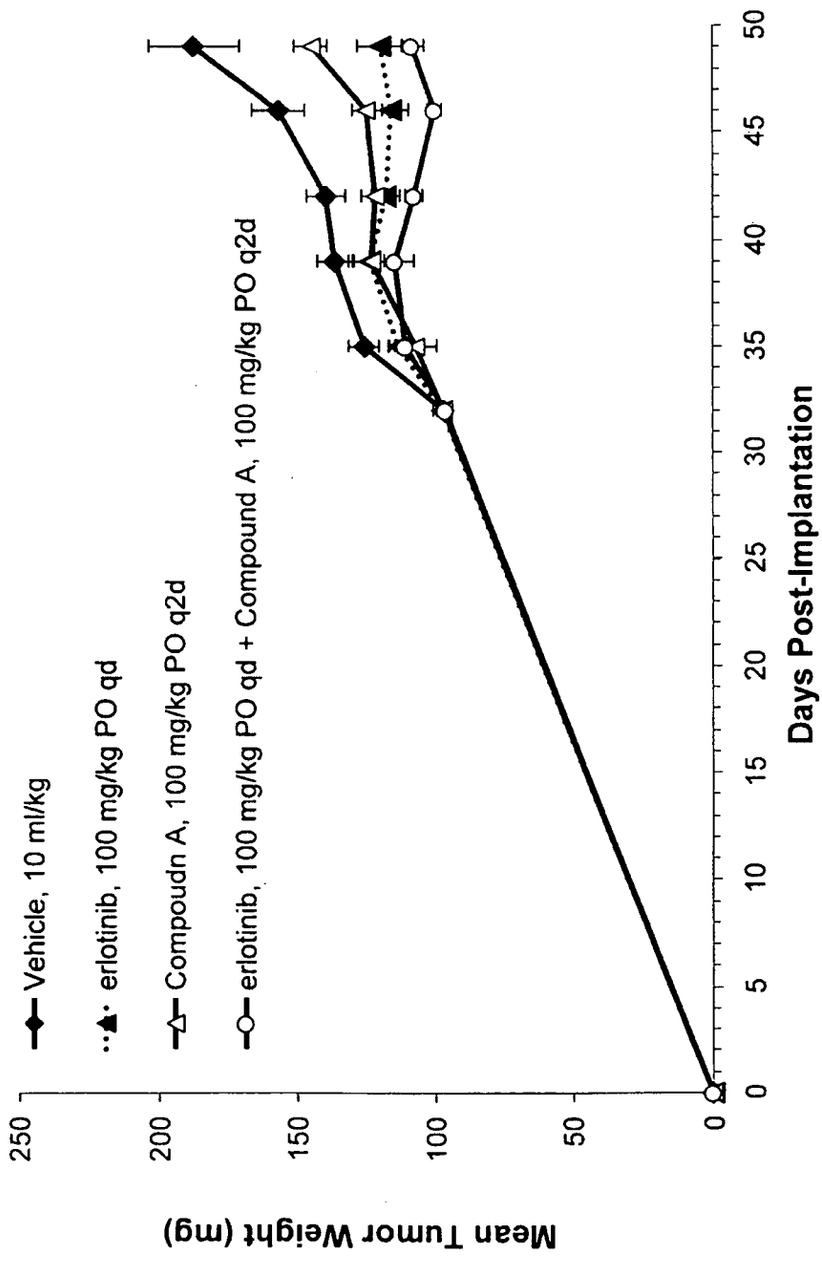


Fig. 5. Compound A + Erlotinib in MDA-MB-468 Breast Carcinoma Tumor Model

Fig. 6. Histological Analysis of Markers of Proliferation (Ki67)

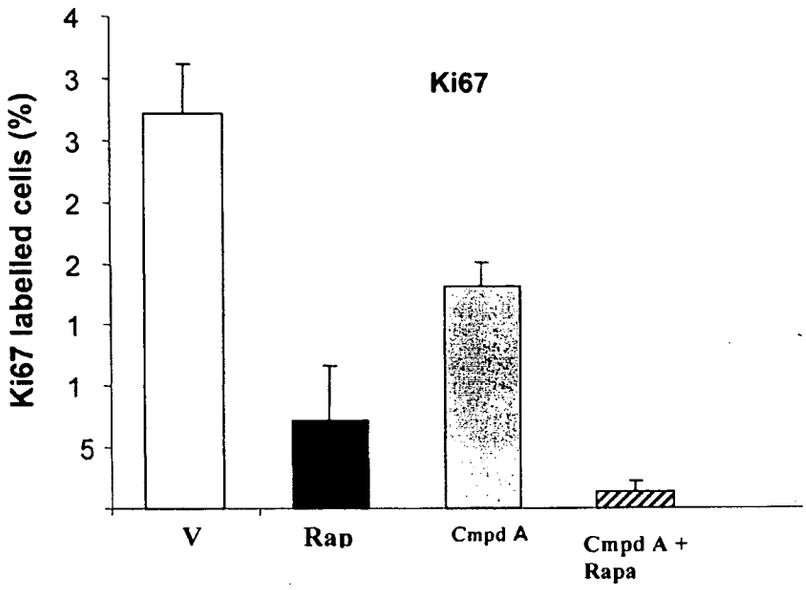


Fig. 7. Histological Analysis of Markers of Apoptosis (TUNEL)

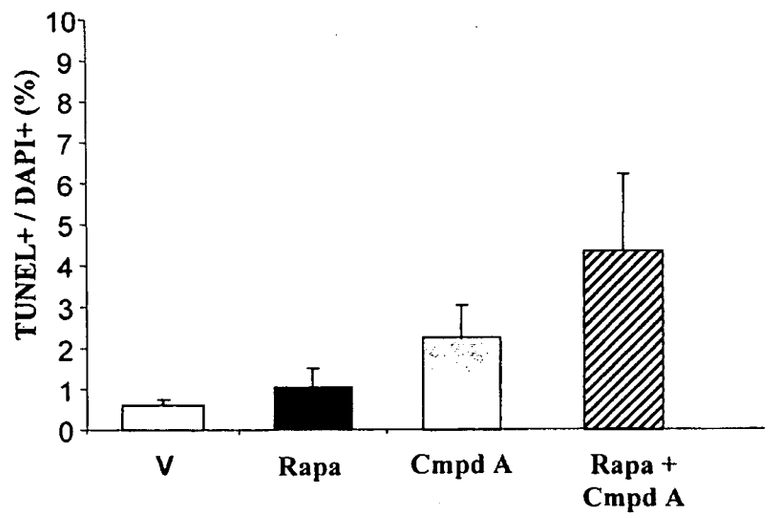


Table 8. Immunohistochemical Analysis of Proliferation, Vascularity and Apoptosis in MCF7 Xenograft Tumors (Study 1)

Group	Ki67 Expression		TUNEL Analysis		CD31 Analysis	
	% Positive Cells[a]	% Reduction[b]	% Positive Cells[a]	Fold Increase[b]	MVD[c]	% Reduction[b]
Vehicle 1 Vehicle 2	39.4 ± 2.84	na	0.95 ± 0.45	na	43.2 ± 2.45	na
Cmpd B 30 mg/kg Vehicle 2	33.7 ± 4.69	14	1.52 ± 0.60	1.6 (ns)	29.7 ± 5.13	31
Vehicle 1 Cmpd A 30 mg/kg	36.4 ± 3.54	8 (ns)	1.35 ± 0.52	1.4 (ns)	29.3 ± 5.17	32
Cmpd B 30 mg/kg Cmpd A 30 mg/kg	30.4 ± 4.34	23	1.52± 0.49	1.6 (ns)	33.8 ± 5.70	22

[a]Values are mean ± SD

[b]Values are relative to vehicle control

[c]Mean Vessel Density

na: not applicable; ns: not significant

Table 9. Immunohistochemical Analysis of Proliferation, Vascularity, and Apoptosis in MCF7 Xenograft Tumors (Study 2)

Group	Ki67 Expression		TUNEL Analysis	
	% Positive Cells[a]	% Reduction[b]	% Positive Cells[a]	Fold Increase[b]
Vehicle 1 Vehicle 2	44.5 ± 4.07	na	0.32 ± 0.19	na
Cmpd B 30 mg/kg Vehicle 2	35.9 ± 5.97	19	0.51 ± 0.26	1.6 (ns)
Vehicle 1 Cmpd A 30 mg/kg	38.7 ± 1.98	13	054 ± 0.22	1.7 (ns)
Cmpd B 30 mg/kg Cmpd A 30 mg/kg	28.0 ± 1.94	37	0.31 ± 0.04	1.0 (ns)

[a]Values are mean ± SD

[b]Values are relative to vehicle control

na: not applicable; ns: not significant

MÉTODOS DE TRATAMIENTO USANDO INHIBIDORES DE PIRIDOPIRIMIDINONA DE PI3K-ALFA

Referencia cruzada a solicitudes relacionadas

[0001] Los solicitantes reivindican prioridad bajo 35 U.S.C. 119(e) a la solicitud provisional en trámite No. 60/922.899 presentada el 10 de abril de 2007, cuya descripción se incorpora en la presente como referencia en su totalidad

CAMPO DE LA INVENCIÓN

[0002] Esta invención se refiere a los métodos de tratar el cáncer con un compuesto que inhibe la actividad enzimática de lípido quinasa y la resultante modulación de las actividades celulares (tales como proliferación, diferenciación, muerte celular programada, migración, quimioinvasión y metabolismo) en combinación con agentes anticáncer.

ANTECEDENTES DE LA INVENCIÓN

[0003] Las mejoras de la especificidad de los agentes usados para tratar diversos estados de enfermedad tales como cáncer, enfermedades metabólicas e inflamatorias es de considerable interés a causa de los beneficios terapéuticos que debería realizar si se pueden reducir los efectos secundarios asociados con la administración de estos agentes. En forma tradicional, las mejoras drásticas en el tratamiento del cáncer están asociados con la identificación de los agentes terapéuticos que actúan mediante mecanismos nuevos.

[0004] La fosfatidilinositol 3-quinasa (PI3K o PIK3CA) está compuesta de una subunidad reguladora de 85 kDa y una subunidad catalítica de 110 kDa. La proteína codificada por este gen representa la subunidad catalítica, que usa ATP para fosforilar PtdIns, PtdIns4P y PtdIns(4,5)P2. PTEN, un supresor tumor que inhibe el

crecimiento celular a través de múltiples mecanismos, puede desfosforilar PIP3, el principal producto de PIK3CA. PIP3, a su vez, es necesario para la translocación de la proteína quinasa B (AKT1, PKB) en la membrana celular, donde se fosforila y activa por quinasas corriente arriba. El efecto de PTEN en la muerte celular está mediado a través de la vía PIK3CA/AKT1.

[0005] PI3Kα ha sido implicado en el control de los procesos de reorganización citoesquelética, apoptosis, tráfico vesicular, proliferación y diferenciación. El aumento de número de copias y la expresión de PIK3CA o las mutaciones por activación en la subunidad catalítica p110a de PIK3CA están asociadas con numerosas neoplasias tales como cáncer ovárico (Campbell et al., *Cancer Res* 2004, *64,* 7678-7681; Levine et al., *Clin Cancer Res* 2005, *11,* 2875-2878; Wang et al., *Hum Mutat* 2005, *25,* 322; Lee et al., *Gynecol Oncol* 2005, *97,* 26-34), cáncer cervical, cáncer de mamas (Bachman, et al. *Cancer Biol Ther* 2004, *3,* 772-775; Levine, et al., supra; Li et al., *Cáncer de mamas Res Treat* 2006, *96,* 91-95; Saal et al., *Cancer Res* 2005, *65,* 2554-2559; Samuels y Velculescu, *Cell Cycle* 2004, *3,* 1221-1224), colocáncer rectal (Samuels, et al. *Science* 2004, *304,* 554; Velho et al. *Eur J Cancer* 2005, *41,* 1649-1654), cáncer de endometrio (Oda et al. *Cancer Res.* 2005, *65,* 10669-10673), carcinomas gástricas (Byun et al., *Int J Cancer* 2003, *104,* 318-327; Li et al., supra; Velho et al., supra; Lee et al., *Oncogene* 2005, *24,* 1477-1480), carcinoma hepatocelular (Lee et al., *id.*), small y cáncer pulmonar de células no pequeñas (Tang et al., *Lung Cancer* 2006, *51,* 181-191; Massion et al., *Am J Respir Crit Care Med* 2004, *170,* 1088-1094), carcinoma tiroideo (Wu et al., *J Clin Endocrinol Metab* 2005, *90,* 4688-4693), leucemia mielógena aguda (AML)

(Sujobert et al., *Blood* 1997, *106,* 1063-1066), leucemia mielógena crónica (CML) (Hickey y Cotter *J Biol Chem* 2006, *281,* 2441-2450), y glioblastomas (Hartmann et al. *Acta Neuropathol (Berl)* 2005, *109,* 639-642; Samuels et al., supra).

[0006] En vista del papel importante del PI3K-α en los procesos biológicos y estados de enfermedad, se desean inhibidores y/o moduladores de esta lípido quinasa. Además, está bien establecido que los tratamientos de combinación con mecanismos de acción diferentes a menudo producen aumento de actividad antitumoral en comparación con los tratamientos únicos administrados solos. Esto es verdadero para las combinaciones de quimioterapias (por ejemplo, Kyrgiou M. et. al. *J Natl Cancer Inst* 2006, *98,* 1655) y combinaciones de anticuerpos y quimioterapia (por ejemplo, Pasetto LM et. al. *Anticancer Res* 2006, *26,* 3973.

[0007] Por ejemplo, la activación de la vía PI3K contribuye a la resistencia de las células tumorales humanas a una amplia variedad de los agentes quimioterapéuticos, que incluyen agentes estabilizantes de microtúbulos tales como taxol (Brognard, J., et. al. *Cancer Res* 2001, *61,* 3986-3997; Clark, A. S., et. al. *Mol Cancer Ther* 2002, *1,* 707-717; Kraus, A. C., et. al. *Oncogene* 2002, *21,* 8683-8695; Krystal, G. W., et. al. *Mol Cancer Ther* 2002, *1,* 913-922; y Yuan, Z. Q., et. al. *J Biol Chem* 2003, *278,* 23432-23440). Taxol es ampliamente utilizado para tratar cánceres avanzados que incluyen carcinoma prostáticos, que con frecuencia albergan supresiones en el gen de PTEN, lo que produce una elevada señalización corriente abajo de PI3K. Varios estudios preclínicos sugieren que la inhibición de señalización corriente abajo de PI3K restaura o aumenta la capacidad

de los agentes quimioterapéuticos tales como taxol destruir células cancerosas (Brognard, J., et. al. *Cancer Res* 2001, *61*, 3986-3997; Clark, A. S., et. al. *Mol Cancer Ther* 2002, *1*, 707-717; Kraus, A. C., et. al. *Oncogene* 2002, *21*, 8683-8695; Krystal, G. W., et. al. *Mol Cancer Ther* 2002, *1*, 913-922; y Saga, Y., et. al. *Clin Cancer Res* 2002, *8*, 1248-1252).

[0008] La rapamicina, otro agente quimioterapéutico, es un potente inhibidor del complejo mTOR/Raptor. La inhibición de mTOR/Raptor impide la fosforilación de p70S6K y S6, pero también lleva a la reducción de un bucle de retroalimentación negativo proveniente de p70S6K que sirve para regular por disminución PI3K (Sarbassov, D. D., et. al. *Science* 2005, *307*, 1098-1101). Como resultado, el tratamiento con rapamicina puede producir regulación por aumento de PI3K y aumento de fosforilación de AKT (O'Donnell, A., et. al. documento presentado en Proc Am Soc Clin Oncol. 2003; y O'Reilly, K. E., et. al. *Cancer Res* 2006, *66*, 1500-1508). En consecuencia, la combinación de la rapamicina con los inhibidores de PI3K puede aumentar la eficacia de la rapamicina (Powis, G. et. al. *Clinical Cancer Research* 2006, *12*, 2964-2966; Sun, S.-Y., et. al. *Cancer Research* 2005, *65*, 7052-7058).

[0009] Un cantidad creciente de datos clínicos y preclínicos indica que la activación de la vía de PI3K confiere resistencia a los inhibidores de EGFR tales como erlotinib (Bianco, R., et. al. *Oncogene* 2003, *22*, 2812-2822; Chakravarti, A., et. al. *Cancer Res* 2002, *62*, 200-207; y Janmaat, M. L., et. al. *Clin Cancer Res* 2003, *9*, 2316-2326). Los pacientes con NSCLC con mutaciones K-Ras y los pacientes con glioblastoma con supresiones PTEN no pudieron responder a erlotinib, probablemente debido a la activación genética de la vía PI3K

(Mellinghoff, I. K., et. al. *N. Eng. J Med.* 2006, *353,* 2012-2024). Los estudios preclínicos han demostrado que la regulación por disminución de la señalización de PI3K en las células tumorales que expresan EGFR confiere aumento de sensibilidad a los inhibidores de EGFR (Ihle, N. T., et. al. *Mol Cancer Ther* 2005, *4,* 1349-1357). En consecuencia, es conveniente el tratamiento del cáncer con un inhibidor de PI3K en combinación con un inhibidor de EGFR, tal como erlotinib.

[0010] La activación de la vía de PI3K también contribuye a la resistencia de las células tumorales humanas a los agentes que dañan el ADN, tales como los platinos. Varios estudios preclínicos sugieren que la inhibición de la señalización corriente debajo de PI3K restaura o aumenta la capacidad de los agentes quimioterapéuticos tales como platinos de destruir células tumorales (Brognard, J., et. al. *Cancer Res* 2001, *61,* 3986-3997; y Yuan, Z. Q., et. al. *J Biol Chem* 2003, *278,* 23432-23440). El carboplatino es ampliamente usado para tratar cánceres avanzados que incluyen carcinomas pulmonares de células no pequeñas (NSCLC), que a menudo albergan mutaciones activadoras en el gen K-Ras, lo que produce la activación de PI3K (Aviel-Ronen S., et. al. *Clin Lung Cancer* 2006, *8,* 30-38). Los pacientes NSCLC con mutaciones K-Ras no responden a los inhibidores de EGFR tales como Tarceva, y en consecuencia representan una necesidad médica insatisfecha significativa (Janne PA, et. al. *J Clin Oncology* 2005, *23,* 3227-3234). En consecuencia, el tratamiento de NSCLC con un agente de que daña el ADN tal como un platino en combinación con un inhibitor de PI3K es conveniente a luz de la falta de tratamientos eficaces.

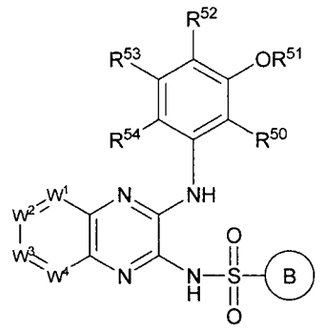
[0011] Los tratamientos que combinan un inhibidor de PI3K-α con otros agentes anti-cáncer son convenientes y necesarios.

SÍNTESIS DE LA INVENCIÓN

[0012] A continuación solo se sintetizan ciertos aspectos de la invención y no consideran de naturaleza limitante. Estos aspectos y otros aspectos y formas de realización se describen más completamente más abajo. Todas las referencias mencionadas en esta memoria descriptiva se incorporan en la presente como referencia en su totalidad. En el caso de una discrepancia entre la descripción expresa de esta memoria descriptiva y las referencias incorporadas por referencia, regirá la descripción expresa de esta memoria descriptiva.

[0013] Las composiciones de la invención se usan para tratar enfermedades asociadas con actividades celulares anormales o no reguladas. Los estados de enfermedad que se pueden tratar por los métodos y composiciones provistos en la presente incluyen cáncer. La invención se refiere a los métodos de tratar estas enfermedades por la administración de un compuesto de Fórmula I o II en combinación con uno o más tratamientos.

[0014] Un aspecto de la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un Compuesto de Fórmula I:



I

o un isómero simple de este donde el compuesto está opcionalmente en forma de sal farmacéuticamente aceptable y en forma adicional opcionalmente como un hidrato y en forma adicional opcionalmente como un solvato de este; o administrar una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de un compuesto de Fórmula I y un portador, excipiente o diluyente farmacéuticamente aceptable en combinación con uno o más tratamientos seleccionados de modo independiente cirugía, uno o más agentes quimioterapéuticos, una o más terapias hormonales, uno o más anticuerpos, una o más inmunoterapias, terapia de yodo radiactivo, y radiación, donde el Compuesto de Fórmula I es aquel donde:

R^1 is hidrógeno, alquilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, cicloalquilalquilo opcionalmente sustituido, arilo opcionalmente sustituido, arilalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, heterocicloalquilalquilo opcionalmente sustituido, heteroarilo opcionalmente sustituido o heteroarilalquilo opcionalmente sustituido;

R^2 es hidrógeno o alquilo donde el alquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 grupos R^8;

X es $-NR^3-$;

R^3 hidrógeno;

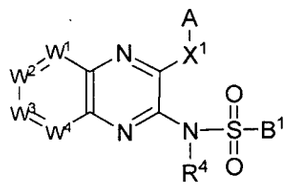
R^4 es alquilo opcionalmente sustituido;

R^5 es hidrógeno; y

R^6 es fenilo, acilo, o heteroarilo donde el fenilo y el heteroarilo están opcionalmente sustituidos con 1, 2, 3, 4, o 5 grupos R^9;

cada R^8, cuando está presente es de modo independiente hidroxi, halo, alcoxi, haloalcoxi, amino, alquilamino, dialquilaminoalquilo, o alcoxialquilamino; y cada R^9, cuando está presente, es de modo independiente halo, alquilo, haloalquilo, alcoxi, haloalcoxi, ciano, amino, alquilamino, dialquilamino, alcoxialquilo, carboxialquilo, alcoxicarbonilo, aminoalquilo, cicloalquilo, arilo, arilalquilo, ariloxi, heterocicloalquilo, o heteroarilo y donde el cicloalquilo, arilo, heterocicloalquilo, y heteroarilo, cada uno solo o como parte de otro grupo dentro de R^9, están opcionalmente sustituidos de mdo independiente con 1, 2, 3, o 4 grupos seleccionados de halo, alquilo, haloalquilo, hidroxi, alcoxi, haloalcoxi, amino, alquilamino, y dialquilamino

[0015] Un segundo aspecto de la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula II:



II

O uno de sus isómeros simples donde el compuesto está opcionalmente como una sal farmacéuticamente aceptable y en forma adicional y opcional cono un hidrato y en forma adicional y opcional como uno de sus solvatos, o

administrar una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de un compuesto de Fórmula II y a portador, excipiente o diluyente farmacéuticamente aceptable en combinación con uno o más tratamientos seleccionados de modo independiente cirugía, uno o más agentes quimioterapéuticos, una o más de las terapias hormonales, uno o más de los anticuerpos, una o más inmunoterapias, terapia de yodo radiactivo, y radiación donde el Compuesto de Fórmula II es aquel donde:

R^1 es hidrógeno, alquilo opcionalmente sustituido, cicloalquilo C3-C7 opcionalmente sustituido, arilo opcionalmente sustituido, arilalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, heterocicloalquilalquilo opcionalmente sustituido, heteroarilo opcionalmente sustituido o heteroarilalquilo opcionalmente sustituido;

X es S, SO_2, o $-NR^3-$;

R^2 es hidrógeno, haloalquilo, alquilo opcionalmente sustituido, cicloalquilo C3-C7 opcionalmente sustituido, arilo opcionalmente sustituido, arilalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, heterocicloalquilalquilo opcionalmente sustituido, heterocicloalquilarilo opcionalmente sustituido o heteroarilo opcionalmente sustituido; R^2 también esta opcionalmente sustituido con uno o más grupos R^8;

R^3, R^{3a}, y R^{3b} son de modo independiente hidrógeno, alquilo opcionalmente sustituido, cicloalquilo C3-C7 opcionalmente sustituido, arilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido o heteroarilo opcionalmente sustituido;

R^4 es hidrógeno, halo, haloalquilo, haloalcoxi, $-NR^{3a}-$, alquilo opcionalmente sustituido, alcoxi C1-C6

opcionalmente sustituido, alcoxialquilo C1-C6 opcionalmente sustituido, aminoalquilo opcionalmente sustituido, cicloalquilo C3-C7 opcionalmente sustituido, arilo opcionalmente sustituido, o heteroarilo opcionalmente sustituido;

R^5 es hidrógeno, halo, haloalquilo, haloalcoxi, alquilo C1-C6 opcionalmente sustituido, alcoxi C1-C6 opcionalmente sustituido, alcoxialquilo C1-C6 opcionalmente sustituido, aminoalquilo opcionalmente sustituido, cicloalquilo C3-C7 opcionalmente sustituido, arilo opcionalmente sustituido, arilo opcionalmente sustituido C_1-C_6 alquilo o heteroarilo opcionalmente sustituido; y

R^6 es hidrógeno, halo, haloalquilo, haloalcoxi, $-NR^{3b}-$, alquilo C1-C6 opcionalmente sustituido, alcoxi C1-C6 opcionalmente sustituido, alcoxialquilo C1-C6 opcionalmente sustituido, acilo opcionalmente sustituido, aminoalquilo opcionalmente sustituido, cicloalquilo C3-C7 opcionalmente sustituido, arilo opcionalmente sustituido, arilalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, o heteroarilo opcionalmente sustituido; los grupos sustituibles R^6 también están opcionalmente sustituidos con 1, 2, 3, 4, o 5 grupos R^9;

cada R^8, cuando está presente, es de modo independiente hidroxi, halo, haloalquilo, haloalcoxi, alquilo opcionalmente sustituido, alcoxi C1-C6 opcionalmente sustituido, alcoxialquilo C1-C6 opcionalmente sustituido, alcoxi C1-C6 alquilaminoalquilo opcionalmente sustituido, alquil C_1-C_6 carboxiheterocicloalquilo, alquiloxi C_1-C_6heterocicloalquilo, aminoalquilo opcionalmente sustituido, cicloalquilo C3-C7 opcionalmente sustituido, arilo opcionalmente sustituido, arilalquilo opcionalmente sustituido C_1-C_6, heterocicloalquilo opcionalmente sustituido, heterocicloalquilalquilo opcionalmente

sustituido, heteroarilo opcionalmente sustituido o heteroarilalquilo opcionalmente sustituido;
cada R^9, cuando está presente, es de modo independiente halo, haloalquilo, haloalcoxi, alquilo C1-C6 opcionalmente sustituido, alcoxi C1-C6 opcionalmente sustituido, alcoxialquilo C1-C6 opcionalmente sustituido, carboxialquilo C1-C6 opcionalmente sustituido, alcoxicarbonilo opcionalmente sustituido, aminoalquilo opcionalmente sustituido, cicloalquilo C3-C7 opcionalmente sustituido, arilo opcionalmente sustituido, arilo opcionalmente sustituido C_1-C_6 alquilo, ariloxi opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, o heteroarilo opcionalmente sustituido

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Abreviaturas y definiciones

[0016] Las siguientes abreviaturas y términos tiene los significados indicados a lo largo de la memoria:

Abreviatura	Significado
Ac	acetil
br	ancho
°C	grados Celsius
c-	ciclo
CBZ	CarboBenZoxi = benciloxicarbonilo
D	doblete
Dd	doblete de doblete
Dt	doblete de triplete
DCM	diclorometano
DME	1,2-dimetoxietano

Abreviatura	Significado
DMF	*N,N*-dimetilformamida
DMSO	dimetilsulfóxido
dppf	1,1'-bis(difenilfosfano)ferroceno
EI	Ionización por impacto electrónico
G	gramo(s)
h o hr	horas(s)
HPLC	Cromatografía líquida de alta presión
L	litro(s)
M	molar o molaridad
m	Multiplete
mg	miligrano(s)
MHz	megahertz (frecuencia)
Min	minuto(s)
Ml	mililitro(s)
µL	microlitro(s)
µM	Micromol(s) o micromolar
mM	Milimolar
Mmol	milimol(es)
Mol	mol(es)
EM	análisis de espectro de masa
N	normal o normalidad
nM	Nanomolar
NMR	Espectroscopia de resonancia magnética nuclear

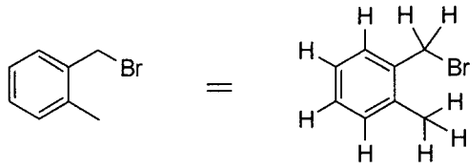
Abreviatura	Significado
Q	cuarteto
RT	Temperatura ambiente
S	Singlete
t o tr	Triplete
TFA	ácido trifluoroacético
THF	tetrahidrofurano
TLC	Cromatografía en capa delgada

Definiciones para un compuesto de Fórmula I y II

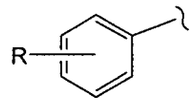
[0017] El símbolo "-" significa un enlace simple, "=" significa un enlace doble, "≡" significa un enlace triple, "----" significa un enlace simple o doble. El símbolo "~~~" se refiere a un grupo sobre un enlace doble que ocupa cualquier posición del extremo terminal de un enlace doble al que está unido el símbolo; es decir, la geometría, E- o Z-, del enlace doble es ambigua. Cuando se grafica un grupo eliminado de su fórmula original, el símbolo "~" se usará en el extremo del enlace que estaba teóricamente escindido con el fin de separar el grupo de su fórmula estructural original.

[0018] Cuando se grafican o describen estructuras químicas, a menos que se indique explícitamente lo contrario, se asume que todos los carbonos tienen sustitución de hidrógeno para conformar una valencia de cuatro. Por ejemplo, en la estructura del lado derecho del esquema siguiente hay nueve hidrógenos implicados. Los nueve hidrógenos se representan en la estructura de la derecha. Algunas veces se describe un átomo particular de la fórmula textual como portador de un hidrógeno o hidrógenos como sustitución (hidrógeno definido

expresamente), por ejemplo, $-CH_2CH_2-$. Es conocido por los expertos en la técnica que las técnicas descriptas anteriormente son comunes en las técnicas químicas para proporcionar brevedad y simplicidad a la descripción de estructuras complejas.

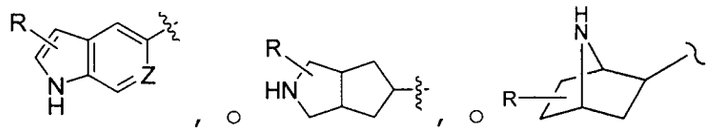


[0019] Si un grupo "R" se representa como "flotante" en un sistema anular, como por ejemplo en la fórmula:



por lo tanto, a menos que se defina de otro modo, un sustituyente del anillo "R" puede residir en cualquier átomo del sistema, lo que supone el reemplazo de un hidrógeno representado, implicado o definido expresamente de uno de los átomos del anillo, siempre que se forme una estructura estable.

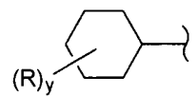
[0020] Si un grupo "R" se representa como flotante en un sistema anular fusionado, como por ejemplo en las fórmulas:



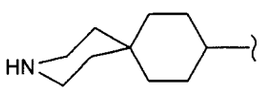
por lo tanto, a menos que se defina de otro modo, un sustituyente del anillo "R" puede residir en cualquier átomo del sistema de anillo fusionado, lo que supone el reemplazo de un hidrógeno representado (por ejemplo el -NH- de la fórmula anterior), hidrógeno implicado (por ejemplo como en la fórmula anterior, donde los hidrógenos no se muestran pero se consideran presentes), o hidrógeno definido expresamente (por ejemplo, cuando en la fórmula

anterior, "Z" equivale =CH-) de uno de los átomos anulares, siempre que se forme una estructura estable. En el ejemplo representado, el grupo "R" puede residir en cualquier anillo de 5 miembros o 6 miembros del sistema de anillos fusionados. En la fórmula representada antes, cuando y es 2 por ejemplo, por lo tanto los dos "R" pueden residir en alguno de los dos átomos del sistema anular, nuevamente se asume que cada uno reemplaza un hidrógeno representado, implicado o definido expresamente del anillo.

[0021] Cuando un grupo "R" se representa como existente en un sistema anular que contiene carbonos saturados, como por ejemplo en la fórmula:



donde, en este ejemplo, "y" puede ser más de uno, asumiendo que cada uno reemplaza un hidrógeno representado, implicado o definido expresamente en la presente sobre el anillo; por lo tanto, a menos que se defina de otro modo, cuando la estructura resultante es estable, dos "R" pueden residir en el mismo carbono. Un ejemplo simple es cuando R es un grupo metilo; puede existir un dimetilo geminal en un carbono del anillo representado (un carbono "anular"). En otro ejemplo, dos R del mismo carbono, que incluyen este carbono, pueden formar un anillo, de este modo se crea una estructura de anillo espirocíclico (un grupo "espirociclilo") con el anillo representado como por ejemplo en la fórmula:



[0022] "Acilo" significa un radical -C(O)R donde R es alquilo opcionalmente sustituido, alquenilo

opcionalmente sustituido, cicloalquilo, cicloalquilalquilo, arilo, aralquilo, heteroarilo, heteroaralquilo, heterocicloalquilo, o heterocicloalquilalquilo, como se define en la presente, por ejemplo, acetilo, trifluorometilcarbonilo, o 2-metoxietilcarbonilo, y similares.

[0023] "Acilamino" significa un radical -NRR' donde R es hidrógeno, hidroxi, alquilo o alcoxi y R' es acilo, como se define en la presente.

[0024] "Aciloxi" significa un radical -O donde R es acilo, como se define en la presente, por ejemplo cianomethilcarboniloxi, y similares.

[0025] "Administración" y sus variantes (por ejemplo, "administrar" 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 tratamiento. Cuando un compuesto de la invención o su profármaco se proporciona en combinación con uno o más agentes activos diferentes (por ejemplo, cirugía, radiación, y quimioterapia, etc.), se entiende que "administración" y sus variantes incluye la introducción concurrente y secuencial del compuesto o sus profármacos y otros agentes.

[0026] "Alquenilo" significa un radical hidrocarbonado monovalente lineal que tiene de uno a seis átomos de carbono o un radical hidrocarbonado monovalente ramificado que contiene de 3 a 6 atomos de carbono cuyo radical contiene al menos un enlace doble, por ejemplo, etenilo, propenilo, 1-but-3-enilo, 1-pent-3-enilo y similares.

[0027] "Alcoxi" significa un grupo -O donde R es alquilo, como se define en la presente. Los ejemplos incluyen etoxi, propoxi, isopropoxi y similares.

[0028] "Alcoxialquilo" significa un grupos alquilo como se define en la presente, sustituido con la menos uno, con preferencia uno, dos o tres grupos alcoxi, como se define en la presente. Los ejemplos representativos incluyen metoximetilo y similares.

[0029] "Alcoxialquilamino" significa un grupo -NRR' donde R es hidrógeno, alquilo, o alcoxialquilo y R' es alcoxialquilo, como se define en la presente.

[0030] "Alcoxialquilaminoalquilo" significa un grupo alquilo sustituido con al menos uno, en forma específica uno o dos, grupos alcoxialquilamino, como se definen en la presente.

[0031] "Alcoxicarbonilo" significa un grupo -C(O)R donde R es alcoxi, como se define en la presente.

[0032] "Alquilo" significa un radical hidrocarbonado monovalente saturado lineal de uno a seis átomos de carbono o radical hidrocarbonado monovalente saturado ramificado de tres a 6 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.

[0033] "Alquilamino" significa un grupo radical -NHR donde R es alquilo como se define en la presente.

[0034] "Alquilaminoalquilo" significa un grupo alquilo sustituido con uno o dos grupos alquilamino, como se define en la presente.

[0035] "Alquilaminoalquiloxi" significa un grupo -O donde R es alquilaminoalquilo, como se define en la presente.

[0036] "Alquilcarbonilo" significa un grupo -C(O)R donde R es alquilo, como se define en la presente.

[0037] "Alquinilo" significa un radical hidrocarbonado monovalente saturado lineal de uno a seis átomos de carbono o radical hidrocarbonado monovalente saturado ramificado de tres a 6 átomos de carbono y cuyo radical contiene al menos un enlace triple, por ejemplo, etinilo, propinilo, butinilo, pentin-2-ilo y similares.

[0038] "Amino" significa un $-NH_2$.

[0039] "Aminoalquilo" significa un grupo alquilo sustituido con al menos uno, por ejemplo uno, dos o tres, grupos amino.

[0040] "Aminoalquiloxi" significa un grupo -OR donde R es aminoalquilo, como se define en la presente.

[0041] "Arilo" significa un anillo mono o bicarbcíclico monovalente de seis a catorce miembros, donde el anillo monocíclico es aromático y al menos uno de los anillos del anillo bicíclico es aromático. A menos que se indique de otro modo, la valencia del grupo pueden estar ubicada en cualquier átomo del anillo dentro del radical, permitido por las reglas de valencia. Los ejemplos representativos incluyen fenilo, naftilo e indanilo, y similares.

[0042] "Arilalquilo" significa un radical alquilo, como se define en la presente, sustituido uno o dos grupos arilo, como se define en la presente, por ejemplo, bencilo y fenetilo y similares.

[0043] "Ariloxi" significa un grupo -OR donde R es arilo como se define en la presente.

[0044] "Carboxialquilo" significa un grupo alquilo, como se define en la presente, sustituido con uno, dos -C(O)OH.

[0045] "Cicloalquilo" significa un radical hidrocarbonado monovalente monocíclico o bicíclico fusionado, saturado o parcialmente insaturado (pero no aromático), de tres a diez átomos de carbono del anillo. El radical hidrocarbonado bicíclico fusionado incluye sistemas de anillos con puente. A menos que se indique de otro modo, la valencia del grupo pueden estar ubicada en cualquier átomo del anillo dentro del radical, permitido por las reglas de valencia. Uno o dos de los átomos de carbono anulares puede estar reemplazado con un grupo -C(O)-, -C(S)-, o -C(=NH)-. En otra realización, el término cicloalquilo incluye, pero sin limitación, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, ciclohexilo, o ciclohex-3-enilo, y similares.

[0046] "Cicloalquilalquilo" significa un grupo alquilo sustituido con al menos uno, por ejemplo, uno o dos, grupos cicloalquilo como se define en la presente.

[0047] "Dialquilamino" significa un radical -NRR' donde R y R' son de modo independiente alquilo como se define en la presente, o un derivado de N-óxido, o uno de sus derivados, por ejemplo, dimetilamino, dietilamino, *N,N*-metilpropilamino o *N,N*-metiletilamino, y similares.

[0048] "Dialquilaminoalquilo" significa un grupo alquilo sustituido con uno o dos grupos dialquilamino, como se define en la presente.

[0049] "Dialquilaminoalquiloxi" significa un grupo -OR donde R es dialquilaminoalquilo, como se define en la presente. Los ejemplos representativos incluyen 2-(*N,N*-dietilamino)-etiloxi, y similares

[0050] "Sistema policíclico fusionado" y "sistema de anillo fusionado" se refieren a un sistema de anillo policíclico que contiene anillos con puente o fusionados;

es decir, donde dos anillos tienen más de un átomo compartido en sus estructuras de anillo. En esta aplicación, los sistemas policíclicos fusionados y de anillos fusionados no todos son necesariamente sistemas de anillos aromáticos. Normalmente, pero no necesariamente, los policíclicos fusionados comparten un conjunto de átomos vecinos, por ejemplo naftaleno o 1,2,3,4-tetrahidro-naftaleno. Un sistema anular espiro no es un policíclico fusionado según esta definición, pero los sistemas de anillo policíclicos fusionados de la invención pueden de tener de por sí anillos espiro unidos por medio de un átomo anular simple del sistema policíclico fusionado. En algunos ejemplos, tal como es apreciado por los expertos en la técnica, dos grupos adyacentes en un sistema aromático pueden fusionarse juntos para formar una estructura anular. La estructura anular fusionada puede contener heteroátomos y opcionalmente puede estar sustituido con uno o más grupos. Cabe mencionar también que los carbonos saturados de dichos grupos fusionados (es decir, estructuras anulares saturadas) pueden contener dos grupos de sustitución.

[0051] Halógeno" o "halo" se refiere a flúor, cloro, bromo o yodo.

[0052] "Haloalcoxi" significa un grupo -OR' donde R' es haloalquilo como se define en la presente, por ejemplo, trifluorometoxi o 2,2,2-trifluoroetoxi, y similares.

[0053] "Haloalquilo" significa un grupo alquilo, como se define en la presente, sustituido con uno o más halógenos, por ejemplo uno a cinco átomos de halo, por ejemplo, trifluorometilo, 2-cloroetilo, y 2,2-difluoroetilo, y similares.

[0054] "Heteroarilo" significa un radical monovalente monocíclico, bicíclico fusionado o tricíclico fusionado, de 5 a 14 átomos anulares que contienen uno o más, por ejemplo uno, dos, tres, o cuatro heteroátomos en el anillo seleccionados de modo independiente de -O-, $-S(O)_n-$ (n es 0, 1, o 2), -N-, $-N(R^x)-$, y los restantes átomos anulares son carbono, en donde el anillo que comprende un radical monocíclico es aromático y en donde al menos uno de los anillos fusionados que comprende un radical bicíclico o tricíclico es aromático. Uno o dos g átomos anulares de carbono de cualquiera de los anillos no aromáticos que comprende un radical bicíclico o tricíclico puede estar reemplazado con un grupo -C(O)-, -C(S)-, o -C(=NH)-. R^x es hidrógeno, alquilo, hidroxi, alcoxi, acilo, o alquilsulfonilo. El radical bicíclico radical fusionado incluye sistemas anulares con puente. A menos que se indique de otro modo, la valencia se puede ubicar en cualquier átomo de cualquier anillo del grupo heteroarilo, permitido por las reglas de valencia. Cuando el punto de valencia se ubica en el nitrógeno, R^x está ausente. En otra forma de realización, el términio heteroarilo incluye, pero sin limitación, 1,2,4-triazolilo, 1,3,5-triazolilo, ftalimidilo, piridinilo, pirrolilo, imidazolilo, tienilo, furanilo, indolilo, 2,3-dihidro-1*H*-indolil (que incluye, por ejemplo, 2,3-dihidro-1*H*-indol-2-ilo o 2,3-dihidro-1*H*-indol-5-ilo, y similares), isoindolilo, indolinilo, isoindolinilo, bencimidazolilo, benzodioxol-4-ilo, benzofuranilo, cinnolinilo, indolizinilo, naftiridin-3-ilo, ftalazin-3-ilo, ftalazin-4-ilo, pteridinilo, purinilo, quinazolinilo, quinoxalinilo, tetrazoílo, pirazolilo, pirazinilo, pirimidinilo, piridazinilo, oxazolilo, isooxazolilo, oxadiazolilo, benzoxazolilo, quinolinilo,

isoquinolinilo, tetrahidroisoquinolinil (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, benzotiazolilo, benzotienilo, y sus derivados, N-óxido o sus derivados protegidos.

[0055] "Hetereoarilalquilo" significa un grupo alquilo, como se define en la presente, sustituido con al menos uno, por ejemplo uno o dos grupos heteroarilo, como se define en la presente.

[0056] "Heteroátomo" se refiere a O, S, N, o P.

[0057] "Heterocicloalquilo" significa un grupo monocíclico monovalente saturado o parcialmente insaturado (pero no aromático) de 3 a 8 átomos anulares o un grupo bicíclico fusionado monovalente saturado o parcialmente insaturado (pero no aromático) de 5 a 12 átomos anulares en los que uno o más, por ejemplo uno, dos, tres, o cuatro heteroátomos anulares seleccionados de modo independiente 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 de carbono del anillo se pueden reemplazar con un grupo -C(O)-, -C(S)-, o -C(=NH)-. El radical bicíclico incluye sistemas de anillo con puente. A menos que se indique de otro modo, la valencia del grupo se puede ubicar en cualquier átomo de cualquier anillo del radical, permitido por las reglas de valencia. En particular, cuando el punto de valencia se ubica en un átomo de nitrógeno, R^y está ausente. En otra forma de realización el término heterocicloalquilo incluye, pero sin limitación, 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, tetrahidropiridinilo, oxazolinilo, oxazolidinilo, isoxazolidinilo, tiazolinilo, tiazolidinilo, quinuclidinilo, isotiazolidinilo, octahidroindolilo, octahidroisoindolilo, decahidroisoquinolilo, tetrahidrofurilo, y tetrahidropiranilo, y sus derivados y N-óxido o uno de sus derivados protegidos.

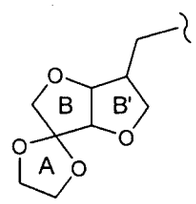
[0058] Heterocicloalquilalquilo" significa un radical alquilo radical, como se define en la presente, sustituido con uno o dos grupos heterocicloalquilo, como se define en la presente, por ejemplo, morfolinilmetilo, *N*-pirrolidiniletilo y 3-(*N*-azetidinil)propilo, y similares.

[0059] "Heterocicloalquilalquiloxi significa un grupo -OR donde R es heterocicloalquilalquilo, como se define en la presente.

[0060] "Sistema anular con puente saturado" se refiere a un sistema anular bicíclico o policíclico que no es aromático. Dicho sistema puede contener instauración aislada o conjugada, pero no anillos aromáticos o heteroaromáticos en su estructura nuclear (pero puede tener sustitución aromática en esta). Por ejemplo, hexahidro-furo[3,2-b]furano, 2,3,3a,4,7,7a-hexahidro-1*H*-indeno, 7-aza-biciclo[2.2.1]heptano, y 1,2,3,4,4a,5,8,8a-octahidro-naftaleno están incluidos en la clase de "sistema de anillo saturado".

[0061] "Espirociclilo" o "anillo espirocíclico" se refiere a un anillo que se origina de un carbono anular

particular de otro anillo. Por ejemplo, como se describe a continuación, un átomo anular de un sistema anular con puente saturado (anillos B y B'), pero no un átomo cabeza de puente, puede ser un átomo compartido entre el sistema anular saturado y un espirociclilo (anillo A) unido a este. Un espirociclilo puede ser carbocíclico o heteroalicíclico.



[0062] "Opcional" u "opcionalmente" significa que el evento o circunstancia descripto posteriormente puede ocurrir o no y que la descripción incluye casos donde dichos eventos o circunstancias no ocurren. Los expertos en la técnica deben entender que con respecto a cualquier molécula que como que contiene uno o más sustituyentes opcionales, significa que solo incluyen compuestos estéricamente prácticos y/o realizable por síntesis. "Opcionalmente sustituido" se refiere a todos los modificadores posteriores de un término. Así, por ejemplo, en el término "opcionalmente arilalquilo C_{1-8}" sustituido, la sustitución opcional se puede presentar tanto en la porción "alquilo C_{1-8}" como en la porción "arilo" de la molécula pueden estar o no sustituidas. Una liste de ejemplos de sustituciones opcionales se presentan a continuación en la definición de "sustituido".

[0063] "Alcoxi opcionalmente sustituido" significa un grupo -OR donde R es alquilo opcionalmente sustituido, como se define en la presente.

[0064] "Alquilo opcionalmente sustituido" significa un radical alquilo, como se define en la presente, opcionalmente sustituido con uno o más grupos, por ejemplo uno, dos, tres, cuatro, o cinco grupos, seleccionados de modo independiente alquilcarbonilo, alquenilcarbonilo, cicloalquilcarbonilo, alquilcarboniloxi, alquenilcarboniloxi, amino, alquilamino, dialquilamino, aminocarbonilo, alquilaminocarbonilo, dialquilaminocarbonilo, ciano, cianoalquilaminocarbonilo, alcoxi, alqueniloxi, hidroxi, hidroxialcoxi, halo, carboxi, alquilcarbonilamino, alquilcarboniloxi, alquilo-$S(O)_{0-2}$-, alquenilo-$S(O)_{0-2}$-, aminosulfonilo, alquilaminosulfonilo, dialquilaminosulfonilo, alquilsulfonil-NR^c- (donde R^c es hidrógeno, alquilo, alquenilo opcionalmente 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 de modo independiente hidrógeno, alquilo, alquenilo opcionalmente sustituido, hidroxi, alcoxi, alqueniloxi, o cianoalquilo).

[0065] "Alquenilo opcionalmente sustituido" significa un radical alquilo, como se define en la presente, opcionalmente sustituido con uno o más grupos, por ejemplo uno, dos, tres, cuatro o cinco grupos, seleccionados de modo independiente alquilcarbonilo, alquenilcarbonilo, cicloalquilcarbonilo, alquilcarboniloxi, alquenilcarboniloxi, amino, alquilamino, dialquilamino, aminocarbonilo, alquilaminocarbonilo, dialquilaminocarbonilo, ciano,

cianoalquilaminocarbonilo, alcoxi, alqueniloxi, hidroxi, hidroxialcoxi, halo, carboxi, alquilcarbonilamino, alquilcarboniloxi, alquilo-$S(O)_{0-2}$-, alquenilo-$S(O)_{0-2}$-, aminosulfonilo, alquilaminosulfonilo, dialquilaminosulfonilo, alquilsulfonil-NR^c- (donde R^c es hidrógeno, alquilo, alquenilo opcionalmente 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 de modo independiente hidrógeno, alquilo opcionalmente sustituido, alquenilo, hidroxi, alcoxi, alqueniloxi o cianoalquilo).

[0066] Amino opcionalmente sustituido" se refiere al grupo -N(H)R o -N(R)R donde cada R se selecciona de modo independiente del grupo: alquilo opcionalmente sustituido, alcoxi opcionalmente sustituido, arilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, acilo, carboxi, alcoxicarbonilo, $-S(O)_2-$(alquilo opcionalmente sustituido), $-S(O)_2-$arilo opcionalmente sustituido), $-S(O)_2-$(heterocicloalquilo opcionalmente sustituido), $-S(O)_2-$(heteroarilo opcionalmente sustituido), y $-S(O)_2-$(heteroarilo opcionalmente sustituido). Por ejemplo, "amino opcionalmente sustituido" incluye dietilamino, metilsulfonilamino, y furanil-oxi-sulfonamino.

[0067] "Aminoalquilo opcionalmente sustituido" significa un grupo alquilo, como se define en la presente, sustituido con al menos uno, por ejemplo uno o

dos, grupos amino opcionalmente sustituidos, como se define en la presente.

[0068] "Arilo opcionalmente sustituido" significa un grupo arilo, como se define en la presente, opcionalmente sustituido con uno, dos, o tres sustituyentes seleccionados independientemente de acilo, acilamino, aciloxi, alquilo opcionalmente sustituido, alquenilo opcionalmente sustituido, alcoxi, alqueniloxi, halo, hidroxi, alcoxicarbonilo, alqueniloxicarbonilo, amino, alquilamino, dialquilamino, nitro, aminocarbonilo, alquilaminocarbonilo, dialquilaminocarbonilo, carboxi, ciano, alquiltio, alquilsulfinilo, alquilsulfonilo, aminosulfonilo, alquilaminosulfonilo, dialquilaminosulfonilo, alquilsulfonilamino, aminoalcoxi, o arilo es pentafluorofenilo. Dentro de los sustituyentes opcionales en "arilo", el alquilo y alquenilo, sea solo o como parte de otro grupo (que incluyen, por ejemplo, el alquilo del alcoxicarbonilo), están opcionalmente sustituidos de modo independiente con uno, dos, tres, cuatro, o cinco halo.

[0069] "Arilalquilo opcionalmente sustituido" significa un grupo alquilo, como se define en la presente, sustituido con arilo opcionalmente sustituido, como se define en la presente.

[0070] "Cicloalquilo opcionalmente sustituido" significa a un grupo cicloalquilo, como se define en la presente, sustituido con uno, dos o tres grupos seleccionados independientemente de acilo, aciloxi, acilamino, alquilo opcionalmente sustituido, alquenilo opcionalmente sustituido, alcoxi, alqueniloxi, alcoxicarbonilo, alqueniloxicarbonilo, alquiltio, alquilsulfinilo, alquilsulfonilo, aminosulfonilo, alquilaminosulfonilo, dialquilaminosulfonilo,

alquilsulfonilamino, halo, hidroxi, amino, alquilamino, dialquilamino, aminocarbonilo, alquilaminocarbonilo, dialquilaminocarbonilo, nitro, alcoxialquiloxi, aminoalcoxi, alquilaminoalcoxi, dialquilaminoalcoxi, carboxi, y ciano. Dentro de los sustituyentes opcionales anteriores en "cicloalquilo", el alquilo y alquenilo, solo o como parte de otro sustituyente en el anillo cicloalquilo, están opcionalmente sustituidos de modo independiente con uno, dos, tres, cuatro, o cinco halo, por ejemplo haloalquilo, haloalcoxi, haloalqueniloxi, o haloalquilsulfonilo.

[0071] "Cicloalquilalquilo opcionalmente sustituido" significa un grupo alquilo sustituido con al menos uno, por ejemplo uno o dos grupos cicloalquilo opcionalmente sustituidos, como se define en la presente.

[0072] "Heteroarilo opcionalmente sustituido" significa un grupo heteroarilo opcionalmente sustituido con uno, dos o tres sustituyentes seleccionados independientemente de acilo, acilamino, aciloxi, alquilo opcionalmente sustituido, alquenilo opcionalmente sustituido, alcoxi, alqueniloxi, halo, hidroxi, alcoxicarbonilo, alqueniloxicarbonilo, amino, alquilamino, dialquilamino, nitro, aminocarbonilo, alquilaminocarbonilo, dialquilaminocarbonilo, carboxi, ciano, alquiltio, alquilsulfinilo, alquilsulfonilo, aminosulfonilo, alquilaminosulfonilo, dialquilaminosulfonilo, alquilsulfonilamino, aminoalcoxi, alquilaminoalcoxi, y dialquilaminoalcoxi. Dentro de los sustituyentes opcionales del "heteroarilo", el alquilo y alquenilo, tanto solo o como parte de otro grupo (que incluyen, por ejemplo, el alquilo del alcoxicarbonilo), están opcionalmente sustituidos de modo independiente con uno, dos, tres, cuatro, o cinco halo.

[0073] "Heteroarilalquilo opcionalmente sustituido" significa un grupo alquilo, como se define en la presente, sustituido con al menos uno, por ejemplo uno o dos, grupos heteroarilo opcionalmente sustituidos, como se define en la presente.

[0074] "Heterocicloalquilo opcionalmente sustituido" significa un grupo heterocicloalquilo, como se define en la presente, opcionalmente sustituido con uno, dos o tres sustituyentes seleccionados independientemente de acilo, acilamino, aciloxi, alquilo opcionalmente sustituido, alquenilo opcionalmente sustituido, alcoxi, alqueniloxi, halo, hidroxi, alcoxicarbonilo, alqueniloxicarbonilo, amino, alquilamino, dialquilamino, nitro, aminocarbonilo, alquilaminocarbonilo, dialquilaminocarbonilo, carboxi, ciano, alquiltio, alquilsulfinilo, alquilsulfonilo, aminosulfonilo, alquilaminosulfonilo, dialquilaminosulfonilo, alquilsulfonilamino, aminoalcoxi, o arilo es pentafluorofenilol. Dentro de los sustituyentes opcionales del "heterocicloalquilo", el alquilo y alquenilo, tanto solo o como parte de otro grupo (que incluyen, por ejemplo, el alquilo del alcoxicarbonil), están opcionalmente sustituidos de modo independiente con uno, dos, tres, cuatro, o cinco halo.

[0075] "Heterocicloalquilalquilo opcionalmente sustituido" significa un grupo alquilo, como se define en la presente, sustituido con al menos uno, por ejemplo uno o dos, grupos heterocicloalquilo.

[0076] "Rendimiento" para cada una de las reacciones que se describen en la presente se expresa como porcentaje del rendimiento teórico.

Definiciones para el Compuesto de Fórmula 100

[0077] Los términos usados para describir el alcance de la fórmula 100 se definen en WO 2004/006846 (Solicitud de etapa Nat'l US Serie No. 10/522,004) que se incorpora en la presente como referencia. Por ejemplo "opcionalmente sustituido alquilo" para la fórmula 100 tiene el significado dado en WO 2004/006846 (Solicitud de etapa Nat'l US Serie No 10/522,004). Cuando un compuesto de Fórmula 100 se describe en esta solicitud, sea por la estructura o por el uso del término "fórmula 100," los términos usados para describir este compuesto son definidos por WO 2004/006846 (Solicitud de etapa Nat'l US Serie No. 10/522,004).

Otras definiciones

[0078] "Inhibidor de AKT" incluye, por ejemplo, LY294002, PKC 412, perifosina, los compuestos de la Tabla 2a, compuestos de la Tabla 2b, y compuestos descriptos en WO 2006/071819 y WO05/117909. Estas referencias también describen los ensayos in vitro que se pueden usar para determinar la actividad inhibidora de AKT.

[0079] "Agente alquilante" incluye, por ejemplo, uno o más de los siguientes: clorambucilo, clormetina, ciclofosfamida, ifosfamida, melfalan, carmustina, etreptozocina, fotemustina, lomustina, estreptozocina, carboplatino, cisplatino, oxaliplatino, bbr3464, busulfan, dacarbazina mecloretamina, procarbazina, temozolomida, tiotepa, y uramustina.

[0080] "Anticuerpo" incluye, por ejemplo, uno o más de los siguientes: un anticuerpo de IGF1R (que incluye, por ejemplo, $^{\alpha}$IGF-1R A12 MoAb, 19D12, h7C_{10} y CP-751871), un anticuerpo EGFR (que incluye, por ejemplo, Cetuximab (Erbitux®) y Panitumumab), un anticuerpo ErbB2 (que incluye, por ejemplo, Trastuzumab (Herceptin®)), un

anticuerpo VEGF (que incluye, por ejemplo, Bevacizumab (Avastin®)), un anticuerpo IgG1 (que incluye, por ejemplo, Ibritumomab (tiuxetan)), un anticuerpo CD20 (que incluye, por ejemplo, Rituximab y Tositumomab), un anticuerpo CD33 (que incluye, por ejemplo, Gemtuzumab y Gemtuzumab ozogamicina), y un anticuerpo CD52 (que incluye, por ejemplo, Alemtuzumab).

[0081] "Antimetabolito" incluye, por ejemplo, metotrexato, pemetrexed, raltitrexed, cladribina, clofarabina, fludarabina, mercaptopurina, tioguanina, capecitabina, citarabina, fluorouracilo (administrado con o sin leucovorina o ácido folínico), y gemcitabina.

[0082] "Agente microtúbulo" incluye, por ejemplo, vincristina, vinblastina, vinorelbina, vinflunina, y vindesina.

[0083] "Inhibidor de aromatasa" incluye, por ejemplo, uno o más de los siguientes: aminoglutetimida, anastrozol (Arimidex®), letrozol (Femara®), exemestano (Aromasin®), y formestano (Lentaron®).

[0084] "Cáncer" se refiere a estados de enfermedad proliferativa celular, que incluyen pero sin limitación: Cardíaco: sarcoma (angiosarcoma, fibrosarcoma, rhabdomiosarcoma, liposarcoma), mixoma, rhabdomioma, fibroma, lipoma y teratoma; Pulmón: carcinoma broncogénico (célula escamosa, célula pequeñas no diferenciado, células grandes no diferenciadas, adenocarcinoma), alveolar (bronquiolar) carcinoma, adenoma bronquial, sarcoma, linfoma, hamartoma condromatoso, mesotelioma, Gastrointestinal: esófago (carcinoma de células esofágicas, adenocarcinoma, leiomiosarcoma, linfoma), estómago (carcinoma, linfoma, leiomiosarcoma), páncreas (adenocarcinoma ductal, insulinoma, glucagonoma, gastrinoma, tumores carcinoides,

vipoma), intestino delgado (adenocarcinoma, linfoma, tumores carcinoides, sarcoma de Karposi, leiomioma, hemangioma, lipoma, neurofibroma, fibroma), intestino grueso (adenocarcinoma, adenoma tubular, adenoma velloso, hamartoma, leiomioma); Aparato genitourinario: riñón (adenocarcinoma, tumor de Wilm [nefroblastoma], linfoma, leucemia), vejiga y uretra (carcinoma de células escamosas, carcinoma de células de transición adenocarcinoma), próstata (adenocarcinoma, sarcoma), testículos (seminoma, teratoma, carcinoma embrionario, teratocarcinoma, coriocarcinoma, sarcoma, carcinoma de células intersticiales, fibroma, fibroadenoma, tumores adenomatoides, lipoma); Hígado: hepatoma (carcinoma hepatocelular), colangiocarcinoma, hepatoblastoma, angiosarcoma, adenoma hepatocelular, hemangioma; Hueso: sarcoma osteogénico (osteosarcoma), fibrosarcoma, histiocitoma fibroso maligno, condrosarcoma, sarcoma de Ewing, linfoma maligno (sarcoma de células reticulares), mieloma múltiple, cordoma tumoral de células gigantes malignas, osteocondroma (exostosis osteocartilaginosos), condroma benigno, condroblastoma, condromixofibroma, osteoma osteoide y tumores de células gigantes; Sistema nervioso: cráneo (osteoma, hemangioma, granuloma, xantoma, osteítis deformante), meninges (meningioma, meningiosarcoma, gliomatosis), cerebro (astrocitoma, meduloblastoma, glioma, ependimoma, germinoma [pinealoma], glioblastorna multiforme, oligodendroglioma, schwannoma, retinoblastoma, tumores congénitos), neurofibroma de médula espinal, meningioma, glioma, sarcoma); Ginecológico: útero (carcinoma de endometrio), cuello uterino (carcinoma cervical, displasia cervical pre-tumoral), ovarios (carcinoma ovárico [cistadenocarcinoma seroso, cistadenocarcinoma mucinoso,

carcinoma no clasificado], tumores de células de granulosa-tecales, tumores de células de Sertoli-Leydig, disgerminoma, teratoma maligno), vulva (carcinoma de células escamosas, carcinoma intraepitelial, adenocarcinoma, fibrosarcoma, melanoma), vagina (carcinoma de células claras, carcinoma de células escamosas, sarcoma botrioide (rhabdomiosarcoma embrionario], trompas de falopio (carcinoma), Hematológico: sangre (leucemia mieloide [aguda y crónica], leucemia linfoblástica aguda, leucemia linfocítica crónica, enfermedades mieloproliferativas, mieloma múltiple, síndrome mielodisplásica), enfermedad de Hodgkin, linfoma no Hodgkin [linfoma maligna]; Piel: melanoma maligno, carcinoma de células basales, carcinoma de células escamosas, sarcoma de Karposi, molas del nervio displásico, lipoma, angioma, dermatofibroma, queloides, psoriasis; Glándulas adrenales: neuroblastoma; y cáncer de mamas. En consecuencia, el término "célula cancerosa" como se proporciona en la presente, incluye una célula afectada por alguna de las enfermedades identificadas anteriormente.

[0085] "Agente quimioterapéutico" incluye, pero sin limitación, un inhibidor de AKT, un agente alquilante, un antimetabolito, un agente antimicrotúbulo, un inhibidor de aromatasa, un inhibidor de c-KIT, un inhibidor de cMET, un inhibidor de EGFR, un inhibidor de ErbB2, un inhibidor de Flt-3, un inhibidor de HSP90, un inhibidor de IGF1R, un platino, un inhibidor de Raf, rapamicina, un análogo de rapamicina, un inhibidor del receptor de tirosina quinasa, un taxano, un inhibidor de topoisomerasa, un inhibidor de SRC y/o ABL quinasa, y un inhibidor de VEGFR. Una sal, solvato y/o hidrato farmacéuticamente aceptable de un agente

quimioterapéutico puede ser preparados por los expertos en la técnica y sus sales, solvatos y/o hidratos se pueden usar para practicar la invención

[0086] "Inhibidor de c-KIT" incluye, por ejemplo, imatinib, sunitinib, nilotinib, AMG 706, sorafenib, compuestos de la Tabla 3b, compuestos de la Tabla 3c, compuestos de la Tabla 8, compuestos de la Tabla 9, y los compuestos descriptos en WO 2006/108059, WO/2005/020921, WO/2006/033943, y WO 2005/030140.

[0087] "Inhibidor de cMET" incluye, por ejemplo, compuestos de la Tabla 3a, compuestos de la Tabla 3b, compuestos de la Tabla 3c, compuestos descriptos en WO06/108059, WO 2006/014325, y WO 2005/030140.

[0088] "Inhibidor de EGFR" incluye, por ejemplo, uno o más de los siguientes: pelitinib, lapatinib (Tykerb®), gefitinib (Iressa®), erlotinib (Tarceva®), Zactima (ZD6474, vandetinib), AEE788 y HKI-272, EKB-569, CI-1033, *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5r,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina *N*-(4-bromo-3-cloro-2-fluorofenil)-7-({[(3a*R*,5r,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5s,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, *N*-(4-bromo-3-cloro-2-fluorofenil)-7-({[(3a*R*,5s,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, compuestos de la Tabla 4, compuestos de la Tabla 7, y los compuestos descriptos en WO 2004/006846 y WO 2004/050681.

[0089] "Inhibidor de ErbB2" incluye, por ejemplo, lapatinib (GW572016), PKI-166, canertinib, CI-1033, HKI272, y EKB-569.

[0090] "Inhibidor de Flt-3" incluye, por ejemplo, CEP-701, PKC 412, MLN518, sunitinib, sorafenib, compuestos de la Tabla 3a, compuestos de la Tabla 3b, compuestos de la Tabla 3c, compuestos de la Tabla 9, y los compuestos descriptos en WO 2006/108059, WO/2006/033943, WO 2006/014325, y WO 2005/030140.

[0091] "Terapia de hormonas" y "terapia hormonal" incluye, por ejemplo, el tratamiento con uno o más de los siguientes: esteroides (por ejemplo dexametasona), finasterida, tamoxifeno y un inhibidor de aromatasa.

[0092] "Inhibidor de HSP90" incluye, por ejemplo, 17-AAG, 17-DMAG, geldanamicina, 5-(2,4-dihidroxi-5-isopropilfenil)-*N*-etil-4-(4-(morfolinometil)fenil)isoxazol-3-carboxamida [NVP-AUY922 (VER 52296)], 6-cloro-9-((4-metoxi-3,5-dimetilpiridin-2-il)metil)-9*H*-purin-2-amina (CNF2024, también llamada BIIB021), compuestos descriptos en WO2004072051 (que se incorpora en la presente como referencia), compuestos descriptos en WO2005028434 (que se incorpora en la presente como referencia), compuestos descriptos en WO2007035620 (que se incorpora en la presente como referencia) y compuestos descriptos en WO2006091963 (que se incorpora en la presente como referencia).

[0093] "Inhibidor de IGF1R" incluye, por ejemplo, Tyrphostin AG 1024, compuestos de la Tabla 5a, compuestos de la Tabla 5b, y los compuestos descriptos en WO06/074057.

[0094] "Enfermedades o patologías dependientes de quinasa" se refieren a condiciones patológicas que dependen de la actividad de una o más proteína quinasas. Las quinasas participan tanto en forma directa como indirecta 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 actividades de quinasa incluye crecimiento tumoral, la neovascularización patológica que sostiene el crecimiento del tumor sólido, y asociado con otras enfermedades donde está involucrada una excesiva vascularización local tal como enfermedades oculares (retinopatía diabética, degeneración macular relacionada con la edad y similares) e inflamación (psoriasis, artritis reumatoide, y similares)

[0095] Sin desear estar ligado a la teoría, las fosfatasas también pueden cumplir un papel en las "enfermedades o patologías dependientes de quinasa" como cognados de quinasas; es decir, las quinasas fosforilan y las fosfatasas desfosforilan, por ejemplo, sustratos proteicos. En consecuencia, los compuestos de la invención, a la vez que modulan la actividad quinasa como se describe en la presente, también pueden modular en forma directa o indirecta, la actividad de fosfatasa. Esta modulación adicional, si está presente, puede ser sinérgica (o no) con la actividad de los compuestos de la invención hacia una quinasa relacionada o quinasa interdependiente de otro modo o familia de quinasa. En cualquier caso, como se indicó previamente, los compuestos de la invención son útiles para tratar enfermedades caracterizadas en parte por niveles anormales de proliferación celular (*es decir* crecimiento tumoral), muerte celular programada (apoptosis), migración e invasión celular y angiogénesis asociada con crecimiento tumoral

[0096] "Metabolito" se refiere al producto de degradación o final de un compuesto o su sal producida

por el metabolismo o la biotransformación del cuerpo animal o humano; por ejemplo, biotransformación a una molécula más polar tal como por oxidación, reducción, o hidrólisis, o a un conjugado (ver Goodman y Gilman, "The Pharmacological Basis de Therapeutics" 8.sup.th Ed., Pergamon Press, Gilman et al.. (eds), 1990 para una discusión de biotransformación). Como se usa en la presente, el metabolito de un compuesto de la invención o su sal puede ser una forma biológicamente activa del compuesto en el cuerpo. En un ejemplo, se puede usar un profármaco de modo que la forma biológicamente activa, un metabolito, se libere *in vivo*. En otro ejemplo, un metabolito biológicamente activo se descubre casualmente, es decir, no se llevó a cabo un diseño del profármaco *per se*. Un ensayo para determinar la actividad de un metabolito de un compuesto de esta invención es conocido por los expertos en el arte a la luz de la presente descripción.

[0097] "Paciente" para los fines de la presente invención incluye seres humanos y otros animales, en particular mamíferos y otros organismos. En consecuencia los métodos son aplicables en aplicaciones de terapia humana y veterinaria. En una realización preferida el paciente es un mamífero, y en una forma de realización más preferida el paciente es humano.

[0098] Una "sal farmacéuticamente aceptable" de un compuesto significa una sal que es farmacéuticamente aceptable y que posea la actividad farmacológica deseada del compuesto original. Se considera que las sales farmacéuticamente aceptables son no tóxicas. La información adicional de las sales farmacéuticamente aceptables adecuadas 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 las cuales se incorporan en la presente como referencia.

[0099] Los ejemplos de sales de adición de ácidos farmacéuticamente aceptables incluyen los formados 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 metansulfónico, ácido etansulfónico, ácido 1,2-etandisulfónico, ácido 2-hidroxietansulfónico, ácido bencensulfónico, ácido 4-clorobencensulfónico, ácido 2-naftalenosulfónico, ácido 4-toluensulfónico, ácido canforsulfónico, ácido glucoheptónico, ácido 4,4'-metilenbis-(3-hidroxi-2-ene-1-carboxílico), ácido 3-fenilpropiónico, ácido trimetilacético, ácido ter-butilacético, ácido lauril sulfúrico, ácido glucónico, ácido glutámico, ácido hidroxinaftoico, ácido salicílico, ácido esteárico, ácido mucónico ácido p-toluensulfónico y ácido salicílico y similares.

[00100] Los ejemplos de las sales de adición de base farmacéuticamente aceptables incluyen las formadas cuando un protón ácido presente en el compuesto original está reemplazado por un ion metálico, tal como sales de sodio, potasio, litio, amonio, calcio, magnesio, hierro, zinc, cobre, manganeso, aluminio y similares. Las sales

preferibles son sales de amonio, potasio, sodio, calcio, y magnesio. Las sales derivadas de bases no tóxicas orgánicas farmacéuticamente aceptables incluyen, pero sin limitación, sales de aminas primarias, secundarias y terciarias, aminas sustituidas que incluyen aminas cíclicas y resinas de intercambio iónico. Los ejemplos de bases orgánicas incluyen isopropilamina, trimetilamina, dietilamina, trietilamina, tripropilamina, etanolamina, 2-dimetilaminoetanol, 2-dietilaminoetanol, diciclohexilamina, lisina, arginina, histidina, cafeína, procaína, hidrabamina, colina, betaína, etilendiamina, glucosamina, metilglucamina, teobromina, purinas, piperazina, piperidina, N-etilpiperidina, trometamina, *N*-metilglucamina, resinas de poliamina, y similares. Los ejemplos de bases orgánicas son isopropilamina, dietilamina, etanolamina, trimetilamina, diciclohexilamina, colina, y cafeína.

[00101] "Platino" y "agente que contiene platino" incluye por ejemplo, cisplatino, carboplatino y oxaliplatino.

[00102] Profármaco" se refiere a los compuestos que se transforman (normalmente en forma rápida) *in vivo* para producir el compuesto original de las fórmulas anteriores, por ejemplo, por hidrólisis en sangre. Los ejemplos comunes incluyen pero sin limitación, formas éster y amida de un compuesto que tiene una forma activa que porta un residuo ácido carboxílico. Los ejemplos de ésteres farmacéuticamente aceptables de los compuestos de la invención incluyen pero sin limitación, ésteres de alquilo (por ejemplo entre aproximadamente uno y aproximadamente seis carbonos), el grupo alquilo es una cadena lineal o ramificada. Los ésteres aceptables también incluyen ésteres de cicloalquilo y ésteres de

arilalquilo tales como, pero sin limitación bencilo. Los ejemplos de amidas farmacéuticamente aceptables de los compuestos de esta invención incluyen pero sin limitación, amidas primarias y alquilamidas secundarias y terciarias (por ejemplo, con entre aproximadamente uno y aproximadamente seis carbonos). Las amidas y los ésteres de los compuestos de la presente invención se pueden preparar de acuerdo con métodos convencionales. Una descripción completa de profármacos se proporciona en T. Higuchi y V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 de A.C.S. Symposio Series, y en Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association y Pergamon Press, 1987, que se incorporan en la presente como referencia para todos los fines

[00103] "Inhibidor de Raf" incluye, por ejemplo, sorafenib, RAF 265 (CHIR 265), compuestos de la Tabla 6, y los compuestos descriptos en WO 2005/112932. Estas referencias también describen ensayos in vitro que se pueden usar para determinar la actividad inhibidora de RAF.

[00104] "Análogo de rapamicina" incluye por ejemplo, CCI-779, AP23573, RAD 001, TAFA 93, y los compuestos descriptos en WO 2004/101583 y US 7,160,867 que se incorporan en la presente por referencia en su totalidad.

[00105] "Inhibidor del receptor de tirosina quinasa" incluye, por ejemplo, los inhibidores de AKT, EGFR, ErbB2, IGF1R, KIT, Met, Raf, y VEGFR2. Los ejemplos de los inhibidores del receptor de tirosina quinasa se pueden hallar en WO 2006/108059 (Solicitud de etapa Nat'l de US serie No. 11/910,720), WO 2006/074057 (Solicitud de etapa Nat'l de US serie No. 11/722,719), WO 2006/071819 (Solicitud de etapa Nat'l de US serie No. 11/722,291), WO

2006/014325 (Solicitud de etapa Nat'l de US serie No. 11/571,140), WO 2005/117909 (Solicitud de etapa Nat'l de US serie No. 11/568,173), WO 2005/030140 (Solicitud de etapa Nat'l de US serie No. 10/573,336), WO 2004/050681 Solicitud de etapa Nat'l de US serie No. 10/533,555), WO 2005/112932 (Solicitud de etapa Nat'l de US serie No. 11/568,789), y WO 2004/006846 (Solicitud de etapa Nat'l de US serie No. 10/522,004), cada una de las cuales se incorpora en la presente por referencia para todos los fines. En particular, las solicitudes mencionadas en este párrafo se incorporan para el fin de proporcionar ejemplos específicos y formas de realizaciones genéricas (y las definiciones asociadas los términos usados en las formas de realización) de los compuestos que sean útiles en la práctica de la invención. Estas referencias también describen en los ensayos in vitro útiles en la práctica de esta invención.

[00106] "Taxano" incluye, por ejemplo, uno o más de los siguientes: Paclitaxel (Taxol®) y Docetaxel (Taxotere®).

[00107] Cantidad terapéuticamente efectiva" es una cantidad de un compuesto de la invención, que cuando se administra a un paciente cuando se administra a un paciente, mejora un síntoma de la enfermedad. La cantidad de un compuesto de esta descripción que constituye una "cantidad terapéuticamente efectiva" variará de acuerdo con el compuesto, el estado de enfermedad y su gravedad, la edad del paciente tratado, y similares. La cantidad terapéuticamente efectiva puede ser determinada de rutina por los expertos en el arte tomando en cuenta su conocimiento y esta descripción.

[00108] Inhibidor de topoisomerasa" incluye, por ejemplo, no o más de los siguientes: amsacrina,

camptotecina, etopósido, fosfato de etopósido, exatecano, irinotecano, lurtotecano y tenipósido, y topotecano.

[00109] "Tratar" o "tratamiento" de una enfermedad, trastorno o síndrome, como se usa en la presente, incluye (i) prevenir la enfermedad, trastorno o síndrome que ocurren en un ser humano, es decir, provocar que los síntomas clínicos de la enfermedad, trastorno o síndrome no se desarrollen en un animal que puede estar expuesto o predispuesto a la enfermedad, trastorno o síndrome pero que aún no experimentan o exhiben síntomas de la enfermedad, trastorno o síndrome; (ii) inhibir la enfermedad, trastorno o síndrome, *es decir*, detener su desarrollo; y (iii) aliviar la enfermedad, trastorno o síndrome, *es decir*, causar regresión de la enfermedad, trastorno o síndrome. Como es conocido en el arte, se pueden necesitar ajustes para la administración sistémica versus localizada, edad, peso corporal, salud general, sexo, dieta, tiempo de administración, interacción farmacológica y la gravedad de la condición patológica y podrán ser establecidos con la experimentación de rutina por los expertos en el arte.

[00110] "Inhibidor de SRC y/o ABL quinasa" incluye, por ejemplo, dasatinib, imatinib (Gleevec®), y los compuestos descriptos en WO 2006/074057.

[00111] "Inhibidor de VEGFR" incluye, por ejemplo, uno o más de los siguientes: VEGF Trap, ZD6474 (vandetanib, Zactima), sorafenib, Angiozyme, AZD2171 (cediranib), pazopanib, sorafenib, axitinib, SU5416 (semaxanib), PTK787 (vatalanib), AEE778, RAF 265, sunitinib (Sutent), *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5r,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, *N*-(4-bromo-3-cloro-2-fluorofenil)-7-({[(3a*R*,5r,6a*S*)-2-metiloctahidrociclo-

penta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5s,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, *N*-(4-bromo-3-cloro-2-fluorofenil)-7-({[(3a*R*,5s,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, compuestos de la Tabla 7, y los compuestos descriptos en WO 2004/050681 y WO 2004/006846.

Formas de la realización de la invención

[00112] Los siguientes párrafos presentan numerosas realizaciones de compuestos que se pueden usar para practicar la invención. En cada caso, la forma de realización incluye los compuestos mencionados así como los isómeros individuales y las mezclas de isómeros. Además, en cada caso, la forma de realización incluye las sales, hidratos y/o solvatos farmacéuticamente aceptables de los compuestos mencionados y cualquiera de los isómeros individuales o mezclas de los isómeros de estos.

[00113] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, donde el crecimiento y/o la supervivencia de las células tumorales del cáncer están aumentados, al menos en parte, por la actividad de PI3K; en combinación con uno o más tratamientos seleccionado de cirugía, uno o más agentes quimioterapéuticos, una o más terapias hormonales, uno o más anticuerpos, una o más inmunoterapias, terapia de yodo radiactivo, y radiación.

[00114] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método

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comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos seleccionados de modo independiente cirugía, uno o más agentes quimioterapéuticos, una o más terapias hormonales, uno o más anticuerpos, una o más inmunoterapias, terapia de yodo radiactivo, y radiación; donde el cáncer se selecciona de cáncer de mamas, cáncer de colon, cáncer rectal, cáncer de endometrio, carcinoma gástrico (que incluye tumores carcinoides gastrointestinales y tumores estromales gastrointestinales), glioblastoma, carcinoma hepatocelular, cáncer pulmonar de células pequeñas, cáncer pulmonar de células no pequeñas (NSCLC), melanoma, cáncer ovárico, cáncer cervical, cáncer pancreático, carcinoma prostático, leucemia mielógena aguda (AML), leucemia mielógena crónica (CML), linfoma no Hodgkin, y carcinoma tiroideo. En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos seleccionados de modo independiente cirugía, uno o más agentes quimioterapéuticos, una o más terapias hormonales, uno o más anticuerpos, una o más inmunoterapias, terapia de yodo radiactivo, y radiación; donde el cáncer es seleccionado de cáncer de próstata, NSCLC, cáncer ovárico, cáncer cervical, cáncer de mamas, cáncer de colon, cáncer rectal, y glioblastoma. En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un

compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos seleccionados de modo independiente cirugía, uno o más agentes quimioterapéuticos, una o más terapias hormonales, uno o más anticuerpos, una o más inmunoterapias, terapia de yodo radiactivo, y radiación; donde el cáncer es seleccionado de NSCLC, cáncer de mamas, cáncer de próstata, glioblastoma, y cáncer ovárico.

[00115] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o más agentes quimioterapéuticos.

[00116] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos seleccionados de modo independiente rapamicina, un análogo de rapamicina, un agente alquilante, a taxano, un platino, un inhibidor de EGFR, y un inhibidor de ErbB2. En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos seleccionados de modo independiente rapamicina,

temozolomide, paclitaxel, docetaxel, carboplatino, cisplatino, oxaliplatino, gefitinib (Iressa®), erlotinib (Tarceva®), Zactima (ZD6474), HKI-272, pelitinib, canertinib, un compuesto seleccionado de Tabla 4, un compuesto de la Tabla 7, y lapatinib. En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos seleccionados de modo independiente rapamicina, temozolomide, paclitaxel, docetaxel, carboplatino, trastuzumab, erlotinib, *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5r,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, *N*-(4-bromo-3-cloro-2-fluorofenil)-7-({[(3a*R*,5r,6a*S*)-2-metiloctahidrociclo-penta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5s,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, *N*-(4-bromo-3-cloro-2-fluorofenil)-7-({[(3a*R*,5s,6a*S*)-2-metiloctahidrociclo-penta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, un compuesto de la Tabla 7, y lapatinib. En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos seleccionados de modo independiente rapamicina, paclitaxel, carboplatino, erlotinib, y *N*-(3,4-dicloro-2-

fluorofenil)-7-({[(3a*R*,5*r*,6a*S*)-2-metiloctahidrociclopenta-[*c*]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina.

[00117] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos seleccionados de modo independiente un platino y un taxano. En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos seleccionados de modo independiente carboplatino, cisplatino, oxaliplatino, y paclitaxel.

[00118] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es un inhibidor de AKT. En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes

quimioterapéuticos donde uno de los agentes quimioterapéuticos es un inhibidor de AKT seleccionado de perifosina, PKC 412, un compuesto de la Tabla 2a, y un compuesto de la Tabla 2b.

[00119] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es un inhibidor de cMET. En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es un inhibidor de cMET seleccionado de un compuesto de la Tabla 3a, un compuesto de la Tabla 3b, y un compuesto de la Tabla 3c.

[00120] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es un inhibidor de EGFR. En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente

efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es un inhibidor de EGFR seleccionado de lapatinib (Tykerb®), gefitinib (Iressa®), erlotinib (Tarceva®), Zactima (ZD6474), AEE788, HKI-272, EKB-569, CI 1033, un compuesto seleccionado de la Tabla 4, y un compuesto de la Tabla 7. En otra forma de realización, En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es un inhibidor de EGFR seleccionado de lapatinib (Tykerb®), gefitinib (Iressa®), erlotinib (Tarceva®), Zactima (ZD6474), AEE788, HKI-272, EKB-569, CI 1033, *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5r,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina *N*-(4-bromo-3-cloro-2-fluorofenil)-7-({[(3a*R*,5r,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5s,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, y *N*-(4-bromo-3-cloro-2-fluorofenil)-7-({[(3a*R*,5s,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina.

[00121] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad

terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es un inhibidor de ErbB2. En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es un inhibidor de ErbB2 seleccionado de lapatinib, EKB-569, HKI272, CI 1033, PKI-166, y un compuesto seleccionado de la Tabla 4.

[00122] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es un inhibidor de HSP90. En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es un inhibidor de HSP90 seleccionado de 17-AAG, 17-DMAG, Geldanamicina, y CNF2024. En otra forma de realización, la invención se refiere a un método

de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es un inhibidor de HSP90 seleccionado de 17-AAG, 17-DMAG, y Geldanamicina.

[00123] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es un inhibidor de IGF1R. En otra forma de realización, En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es un inhibidor de IGF1R seleccionado de la Tabla 5a y Tabla 5b.

[00124] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es un inhibidor de Raf. En otra forma de realización, la invención se refiere a un

método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es un inhibidor de Raf seleccionado de sorafenib, RAF 265 (CHIR-265), y un compuesto de la Tabla 6.

[00125] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es un inhibidor de VEGFR. En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es un inhibidor de VEGFR seleccionado de VEGF Trap, ZD6474 (Zactima), cediranib (AZ2171), pazopanib, sunitinib, sorafenib, axitinib, AEE788, RAF 265 (CHIR-265), un compuesto seleccionado de la Tabla 4, y un compuesto seleccionado de la Tabla 7.

[00126] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I,

como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es un inhibidor de cKIT. En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es un inhibidor de cKIT seleccionado de imatinib, sunitinib, nilotinib, AMG 706, sorafenib, un compuesto de la Tabla 3b, un compuesto de la Tabla 3c, un compuesto de la Tabla 8, y un compuesto de la Tabla 9.

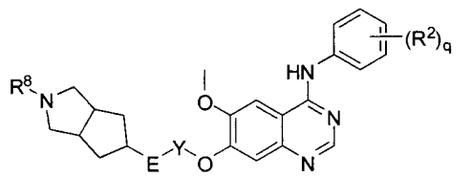
[00127] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es un inhibidor de FLT3. En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es un inhibidor de FLT3 seleccionado de CEP-701, PKC 412, sunitinib, MLN518, sunitinib, sorafenib, un compuesto de la Tabla 3a, un compuesto de

la Tabla 3b, un compuesto de la Tabla 3c, y un compuesto de la Tabla 9.

[00128] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos se selecciona de rapamicina, un análogo de rapamicina, PI103, y SF 1126. En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos se selecciona de rapamicina, CCI-779, AP23573, RAD 001, TAFA 93, PI103, y SF 1126. En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es rapamicina.

[00129] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es

uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es de fórmula 100:



100

donde q es 1, 2, o 3; E es $-NR^9-$, -O-, o ausente e Y es $-CH_2CH_2-$, $-CH_2-$, o ausente con la condición de que cuando E es $-NR^9-$ o -O-, luego Y es $-CH_2CH_2-$; R^2 se selecciona de halógeno, trihalometilo, -CN, $-NO_2$, $-OR^3$, y alquilo inferior; R^8 se selecciona de -H, alquilo inferior, $-C(O)OR^3$, $-C(O)N(R^3)R^4$, $-SO_2R^4$, y $-C(O)R^3$; R^9 es hidrógeno o alquilo inferior; R^3 es hidrógeno o R^4; R^4 se selecciona de alquilo inferior, arilo, arilalquilo inferior, heterociclilo, y heterociclilalquilo inferior; o R^3 y R^4, cuando se toman juntos con un nitrógeno común al que están unidos, forman un heterociclilo de cinco a siete miembros, dicho heterociclilo de cinco a siete miembros opcionalmente contiene uno o más heteroátomos adicionales seleccionados de N, O, S, y P; o un isómero geométrico simple, estereoisómero, racemato, enantiómero o diastereómero de este y opcionalmente en forma de sal farmacéuticamente aceptable, en forma adicional opcionalmente como un solvato, y en forma adicional como un hidrato. Los términos usados para describir el alcance de la fórmula 100 se definen en WO 2004/006846 (Solicitud de etapa Nat'l de US serie No. 10/522,004) que se incorpora en la presente como referencia. cuando se toman juntos con un nitrógeno común al que están unidas, forman un heterociclilo de cinco a siete miembros, dicho heterocicilo de cinco a siete miembros opcionalmente que contiene uno o más heteroátomos adicionales seleccionados

de N, O, S, y P; o uno de sus isómero geométricos, estereoisómeros, racematos, enantiómeros o diastereómeros simples y opcionalmente en forma de sal farmacéuticamente aceptable, en forma adicional opcionalmente como un solvato y en forma adicional como un hidrato de este. Los términos usados para describir el alcance de la fórmula 100 se definen en WO 2004/006846 (Solicitud de etapa Nat'l de US serie No. 10/522,004) que se incorpora en la presente como referencia. Cuando un compuesto de Fórmula 100 se describe en esta solicitud, sea por la estructura o por uso del término "fórmula 100", los términos usados para describir este compuesto se definen por WO 2004/006846 (Solicitud de etapa Nat'l de US serie No. 10/522,004). En particular, "alquilo" de la fórmula 100 se considera que incluye estructuras hidrocarbonados lineales, ramificados o cíclicas y sus combinaciones, inclusivamente; "alquilo inferior" significa grupos alquilo de uno a seis átomos de carbono. "Arilo" de la fórmula 100 significa anillos carbocíclicos carbocíclicos aromáticos de seis a catorce miembros que incluyen, por ejemplo, benceno, naftaleno, indano, tetralina, fluoreno y similares. "Arilalquilo inferior" de la fórmula 100 significa un residuo en que un residuo arilo se une a una estructura original por medio de un radical alquileno, alquenileno o alquinileno donde la porción "alquilo" del grupo tiene uno a seis carbonos; los ejemplos incluyen bencilo, fenetilo, fenilvinilo, fenilalilo y similares. En la fórmula 100, "heterociclilo" significa un radical anular estable monocíclico, bicíclico o tricíclico de tres a quince miembros (que incluyen sistemas anulares fusionados o on puentes) que consisten en átomos de carbono y de uno a cinco heteroátomos seleccionados del grupo que consiste en nitrógeno, fósforo, oxígeno y

azufre donde los átomos de nitrógeno, fósforo, carbono y azufre del radical heterociclilo puede estar opcionalmente oxidado a varios estados de oxidación y el átomo de nitrógeno puede estar opcionalmente cuaternizado; y el radical anular puede estar parcial o completamente saturado o aromático. "Heterociclilalquilo inferior" significa un residuo en el que un heterociclilo se une a una estructura original por medio de un radical alquileno, alquenileno y alquinileno que tiene uno a seis carbonos.

[00130] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos se selecciona de un compuesto de la Tabla 2a. En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de la tabla 1, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos se selecciona de un compuesto de la Tabla 2a.

[00131] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es

uno o más agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos se selecciona de un compuesto de la Tabla 2b. En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I de seleccionado de la Tabla 1, en combinación con un con un tratamiento donde el tratamiento es uno o más agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos se selecciona de un compuesto de la Tabla 2b.

[00132] En otra realización, la invención se refiere a un método de tratar cáncer dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, in combination con un tratamiento donde el tratamiento es uno o más agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos se selecciona de un compuesto de la Tabla 3a. En otra realización, la invención se refiere a un método de tratar cáncer dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de la Tabla 1 en combinación con un tratamiento donde el tratamiento es uno o más agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos se selecciona de un compuesto de la Tabla 3a.

[00133] En otra realización, la invención se refiere a un método de tratar cáncer dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o más agentes

quimioterapéuticos donde uno de los agentes quimioterapéuticos se selecciona de un compuesto de la Tabla 3b. En otra realización, la invención se refiere a un método de tratar cáncer dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de la Tabla 1 en combinación con un tratamiento donde el tratamiento es uno o más agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos se selecciona de un compuesto de la Tabla 3a.

[00134] En otra realización, la invención se refiere a un método de tratar cáncer dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o más agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos se selecciona de un compuesto de la Tabla 3b. En otra realización, la invención se refiere a un método de tratar cáncer dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de la Tabla 1 en combinación con un tratamiento donde el tratamiento es uno o más agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos se selecciona de un compuesto de la Tabla 3b.

[00135] En otra realización, la invención se refiere a un método de tratar cáncer dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes

quimioterapéuticos se selecciona de un compuesto de la Tabla 4. En otra realización, la invención se refiere a un método de tratar cáncer dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de la Tabla 1 en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos se seleccionade la Tabla 4.

[00136] En otra realización, la invención se refiere a un método de tratar cáncer dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5r,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, *N*-(4-bromo-3-cloro-2-fluorofenil)-7-({[(3a*R*,5r,6a*S*)-2-metiloctahidrociclo-penta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5s,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, o *N*-(4-bromo-3-cloro-2-fluorofenil)-7-({[(3a*R*,5s,6a*S*)-2-metiloctahidrociclo-penta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, opcionalmente como una sal farmacéuticamente aceptable y en forma adicional y opcional como un hidrato y en forma adicional y opcional como un solvato de este. En otra realización, la invención se refiere a un método de tratar cáncer dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un

compuesto de Fórmula I seleccionado de la Tabla 1 en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5r,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, *N*-(4-bromo-3-cloro-2-fluorofenil)-7-({[(3a*R*,5r,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5s,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, o *N*-(4-bromo-3-cloro-2-fluorofenil)-7-({[(3a*R*,5s,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, opcionalmente como una sal farmacéuticamente aceptable y en forma adicional y opcional como un hidrato y en forma adicional y opcional como un solvato de este.

[00137] En otra realización, la invención se refiere a un método de tratar cáncer dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5*r*,6a*S*)-2-metiloctahidrociclopenta-[*c*]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
opcionalmente como una sal farmacéuticamente aceptable y en forma adicional y opcional como un hidrato y en forma adicional y opcional como un solvato de este. En otra realización, la invención se refiere a un método de tratar cáncer dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un

compuesto de Fórmula I seleccionado de la Tabla 1 en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5*r*,6a*S*)-2-metiloctahidrociclopenta-[*c*]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina opcionalmente como una sal farmacéuticamente aceptable y en forma adicional y opcional como un hidrato y en forma adicional y opcional como un solvato de este.

[00138] En otra realización, la invención se refiere a un método de tratar cáncer dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o más agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos se selecciona de un compuesto de la Tabla 5a. En otra realización, la invención se refiere a un método de tratar cáncer dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de la Tabla 1 en combinación con un tratamiento donde el tratamiento es uno o más agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos se selecciona de un compuesto de la Tabla 5a.

[00139] En otra realización, la invención se refiere a un método de tratar cáncer dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o más agentes quimioterapéuticos donde uno de los agentes

quimioterapéuticos se selecciona de un compuesto de la Tabla 5b. En otra realización, la invención se refiere a un método de tratar cáncer dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de la Tabla 1 en combinación con un tratamiento donde el tratamiento es uno o más agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos se selecciona de un compuesto de la Tabla 5b.

[00140] En otra realización, la invención se refiere a un método de tratar cáncer dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o más agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos se selecciona de un compuesto de la Tabla 6. En otra realización, la invención se refiere a un método de tratar cáncer dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de la Tabla 1 en combinación con un tratamiento donde el tratamiento es uno o más agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos se selecciona de un compuesto de la Tabla 6.

[00141] En otra realización, la invención se refiere a un método de tratar cáncer dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o más agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos se selecciona de un compuesto de la

Tabla 7. En otra realización, la invención se refiere a un método de tratar cáncer dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de la Tabla 1 en combinación con un tratamiento donde el tratamiento es uno o más agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos se selecciona de un compuesto de la Tabla 7.

[00142] En otra realización, la invención se refiere a un método de tratar cáncer dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o más agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos se selecciona de un compuesto de la Tabla 8. En otra realización, la invención se refiere a un método de tratar cáncer dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de la Tabla 1 en combinación con un tratamiento donde el tratamiento es uno o más agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos se selecciona de un compuesto de la Tabla 8.

[00143] En otra realización, la invención se refiere a un método de tratar cáncer dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o más agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos se selecciona de un compuesto de la Tabla 9. En otra realización, la invención se refiere a

un método de tratar cáncer dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de la Tabla 1 en combinación con un tratamiento donde el tratamiento es uno o más agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos se selecciona de un compuesto de la Tabla 9.

[00144] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de Tabla 1 en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde el agente quimioterapéutico es paclitaxel.

[00145] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de Tabla 1 en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde el agente quimioterapéutico es rapamicina.

[00146] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de Tabla 1 en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde el agente quimioterapéutico es carboplatino.

[00147] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método

comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de Tabla 1 en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde el agente quimioterapéutico es erlotinib.

[00148] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de Tabla 1 en combinación con un tratamiento donde el tratamiento es uno o dos agentes quimioterapéuticos donde el agente quimioterapéutico es lapatinib.

[00149] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de Tabla 1 en combinación con un tratamiento donde el tratamiento es uno o dos anticuerpos donde uno de los anticuerpos es trastuzumab.

[00150] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de Tabla 1 en combinación con un tratamiento donde el tratamiento es uno o dos anticuerpos donde uno de los anticuerpos es cetuximab.

[00151] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de Tabla 1 en combinación con un tratamiento

donde el tratamiento es uno o dos anticuerpos donde uno de los anticuerpos es panitumumab.

[00152] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de Tabla 1 en combinación con un tratamiento donde el tratamiento es uno o dos anticuerpos donde uno de los anticuerpos es bevacizumab.

[00153] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es radiación. En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de Tabla 1 en combinación con un tratamiento donde el tratamiento es radiación.

[00154] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos anticuerpos. En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es

uno o dos anticuerpos seleccionados de modo independiente un anticuerpo de IGF1R (que incluye, por ejemplo, $^{\alpha}$IGF-1R A12 MoAb, $^{\alpha}$IGF-1R 19D12 MoAb, $^{\alpha}$IGF-1R h7C_{10} MoAb y $^{\alpha}$IGF-1R CP-751871 MoAb), alemtuzumab, bevacizumab (Avastin®), gemtuzumab, gemtuzumab ozogamicin, ibritumomab tiuxetan, panitumumab, rituximab, tositumomab, omnitarg (pertuzimab), anticuerpos de anti-ErbB2 (que incluyen trastuzumab (Herceptin®)), y los anticuerpos anti-EGFR (que incluye, por ejemplo, cetuximab (Erbitux), panitumumab, nimotuzumab, y EMD72000)).

[00155] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de Tabla 1 en combinación con un tratamiento donde el tratamiento es uno o dos anticuerpos. En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de Tabla 1 en combinación con un tratamiento donde el tratamiento es uno o dos anticuerpos seleccionados de modo independiente un anticuerpo de IGF1R (que incluye, por ejemplo, $^{\alpha}$IGF-1R A12 MoAb, $^{\alpha}$IGF-1R 19D12 MoAb, $^{\alpha}$IGF-1R h7C_{10} MoAb y $^{\alpha}$IGF-1R CP-751871 MoAb), alemtuzumab, bevacizumab (Avastin®), gemtuzumab, gemtuzumab ozogamicin, ibritumomab tiuxetan, panitumumab, rituximab, tositumomab, omnitarg (pertuzimab), anticuerpos anti-ErbB2 (que incluyen trastuzumab (Herceptin®)), y los anticuerpos anti-EGFR (que incluyen, por ejemplo, cetuximab (Erbitux), panitumumab, nimotuzumab, y EMD72000)).

[00156] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método

comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o más agentes quimioterapéuticos donde el agente quimioterapéutico es temozolomida. En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de Tabla 1 en combinación con un tratamiento donde el tratamiento es uno o más agentes quimioterapéuticos donde el agente quimioterapéutico es temozolomida.

[00157] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es cirugía. En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de Tabla 1 en combinación con un tratamiento donde el tratamiento es cirugía.

[00158] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos terapias hormonales. En otra forma de realización, la invención se refiere a un método de

tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos terapias hormonales seleccionadas de modo independiente tamoxifeno, torremifeno (Fareston), fulvestrant (Faslodex), acetato de megestrol (Megace), extirpación de ovarios, raloxifeno, un análogo de liberación de hormoa luteinizante (LHRH) (que incluyen goserelina y leuprolida), acetato de megestrol (Megace), y uno o más inhibidores de aromatasa. En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es una o dos terapias hormonales es un inhibidor de aromatasa seleccionado de letrozol (Femara), anastrozol (Arimidex), y exemestane (Aromasin). En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde el tratamiento es uno o dos terapias de hormonas seleccionadas de modo independiente de tamoxifeno y un inhibidor de aromatasa.

[00159] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de Tabla 1 en combinación con un tratamiento

donde el tratamiento es uno o dos terapias hormonales. En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de Tabla 1 en combinación con un tratamiento donde uno de los tratamientos es uno o dos terapias hormonales seleccionadas de modo independiente tamoxifeno, torremifeno (Fareston), Fulvestrant (Faslodex), acetato de megestrol (Megace), extirpación de ovarios, raloxifeno, un análogo de liberación de hormona luteinizante (LHRH) (que incluyen goserelina y leuprolida), acetato de megestrol (Megace), y uno o dos inhibidor de aromatasas. En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de Tabla 1 en combinación con un tratamiento donde uno de los tratamientos es uno o dos terapias hormonales donde una de las terapias hormonales es un inhibidor de aromatasas seleccionado de letrozol (Femara), anastrozol (Arimidex), y exemestano (Aromasin). En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de Tabla 1 en combinación con un tratamiento donde uno de los tratamientos es uno o dos terapias hormonales seleccionados de modo independiente de tamoxifeno y un inhibidor de aromatasa.

[00160] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad

terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con un tratamiento donde uno de los tratamientos es un anticuerpo seleccionado de un anticuerpo EGFR y un anticuerpo ErbB2, o el tratamiento es uno o dos agentes quimioterapéuticos seleccionados de modo independiente a rapamicina, análogo de rapamicina, un agente alquilante, un taxano, un platino, un inhibidor de EGFR, y un inhibidor de ErbB2. En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I seleccionado de Tabla 1 en combinación con un tratamiento donde uno de los tratamientos es un anticuerpo seleccionado de un anticuerpo EGFR y un anticuerpo ErbB2, o el tratamiento es uno o dos agentes quimioterapéuticos seleccionados de modo independiente rapamicina, un análogo de rapamicina, un agente alquilante, un taxano, un platino, un inhibidor de EGFR, y un inhibidor de ErbB2.

[00161] En otra forma de realización, la invención se refiere a un método de tratar leucemia mielógena aguda (AML) dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos seleccionados de modo independiente trasplante de médula ósea o células madre de sangre periférica, radiación, uno o dos anticuerpos, y uno o dos agentes quimioterapéuticos. En otra forma de realización, la invención se refiere a un método de tratar leucemia mielógena aguda (AML) dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I,

como se define en la Síntesis de la invención, en combinación con uno o dos tratamientos donde uno de los tratamientos es un anticuerpo seleccionado de Gemtuzumab ozogamicina (Milotarg), $^{\alpha}$IGF-1R A12 MoAb, $^{\alpha}$IGF-1R 19D12 MoAb, $^{\alpha}$IGF-1R h7C$_{10}$ MoAb, $^{\alpha}$IGF-1R CP-751871 MoAb y trastuzumab. En otra forma de realización, la invención se refiere a un método de tratar leucemia mielógena aguda (AML) dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos agentes quimioterapéuticos seleccionado de Imatinib (es decir Gleevec®), PKC 412, CEP-701, daunorrubicina, doxorrubicina, citarabina (ara-C), un fármaco antraciclina tal como daunorrubicina o idarrubicina (Daunomicina, Idamicina), 6-tioguanina, y un factor estimulante de colonia de granulocitos (tales como Neupogen o Leukine).

[00162] En otra forma de realización, la invención se refiere a un método de tratar leucemia mielógena crónica (CML) dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos seleccionados de modo independiente trasplante de médula ósea o células madre de sangre periférica, radiación, uno o dos agentes quimioterapéuticos, inmunoterapia, y uno o dos anticuerpos. En otra forma de realización, la invención se refiere a un método de tratar leucemia mielógena crónica (CML) dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos

donde uno de los tratamientos es uno o dos de los agentes quimioterapéuticos seleccionado de Imatinib (es decir Gleevec®), PKC 412, hidroxiurea (Hydrea), citosina, citosina arabinoside, dasatinib, AMN107, VX680 (MK0457), y citarabina (ara-C). En otra forma de realización, la invención se refiere a un método de tratar leucemia mielógena crónica (CML) dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos agentes quimioterapéuticos seleccionado de Imatinib (es decir Gleevec®) y dasatinib. En otra forma de realización, la invención se refiere a un método de tratar leucemia mielógena crónica (CML) dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es inmunoterapia y la inmunoterapia es terapia de interferón tales como interferón-α.

[00163] En otra forma de realización, la invención se refiere a un método de tratar cáncer de próstata dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos seleccionados de modo independiente cirugía (que incluyen criocirugía), radiación, uno o dos agentes quimioterapéuticos, uno o dos anticuerpos, y uno o dos terapias hormonales. En otra forma de realización, la invención se refiere a un método de tratar cáncer de próstata dicho método comprende administrar a un paciente una cantidad

terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es un anticuerpo seleccionado de $^{\alpha}$IGF-1R A12 MoAb, $^{\alpha}$IGF-1R 19D12 MoAb, $^{\alpha}$IGF-1R h7C$_{10}$ MoAb, y $^{\alpha}$IGF-1R CP-751871 MoAb. En otra forma de realización, la invención se refiere a un método de tratar cáncer de próstata dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos de los agentes quimioterapéuticos seleccionados de modo independiente rapamicina, mitoxantrona, prednisona, docetaxel (Taxotere), doxorrubicina, etopósido, vinblastina, paclitaxel, y carboplatino. En otra forma de realización, la invención se refiere a un método de tratar cáncer de próstata dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos de la terapia hormonal seleccionada de modo independiente de terapia de deprivación de andrógenos y terapia de supresión de andrógenos. En otra forma de realización, la invención se refiere a un método de tratar cáncer de próstata dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es un taxanos. En otra forma de realización, la invención se

refiere a un método de tratar cáncer de próstata dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos agentes quimioterapéuticos donde uno de los agentes quimioterapéuticos es rapamicina.

[00164] En otra forma de realización, la invención se refiere a un método de tratar melanoma dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos seleccionados de modo independiente cirugía, radiación, una o dos inmunoterapias, uno o dos terapias hormonales, y uno o dos agentes quimioterapéuticos. En otra forma de realización, la invención se refiere a un método de tratar melanoma dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos agentes quimioterapéuticos seleccionados de modo independiente un agente alquilante, un taxano, un platino, y un inhibidor de Raf. En otra forma de realización, la invención se refiere a un método de tratar melanoma dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos agentes quimioterapéuticos seleccionados de modo independiente sorafenib, Paclitaxel

(Taxol®), Docetaxel (Taxotere®), dacarbazina, rapamicina, imatinib mesilate (Gleevec®), sorafenib, cisplatino, carboplatino, dacarbazine (DTIC), carmustina (BCNU), vinblastina, temozolomida (Temodar), Melphalan, y imiquimod (Aldara). En otra forma de realización, la invención se refiere a un método de tratar melanoma dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es una o dos inmunoterapias seleccionadas de modo independiente ipilimumab, interferon-alfa e interleuquina-2. En otra forma de realización, la invención se refiere a un método de tratar melanoma dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es terapia hormonal donde la terapia hormonal es tamoxifeno.

[00165] En otra forma de realización, la invención se refiere a un método de tratar colon o cáncer rectal dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos seleccionados de modo independiente cirugía, radiación, uno o dos anticuerpos, y uno o dos agentes quimioterapéuticos. En otra forma de realización, la invención se refiere a un método de tratar colon o cáncer rectal dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en

combinación con uno o más tratamientos donde uno de los tratamientos es cirugía seleccionada de escisión local, electrofulguración, resección de colon segmentario, polipectomía, resección transanal local, resección anterior baja, resección abdominoperineal y exenteración pélvica. En otra forma de realización, la invención se refiere a un método de tratar colon o cáncer rectal dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos agentes quimioterapéuticos seleccionados de modo independiente un compuesto que contiene platino (que incluye cisplatino, oxaliplatino, y carboplatino), 5-fluorouracilo (5-FU), leucovorina, capecitabina (Xeloda), irinotecano (Camptosar), FOLFOX (Ácido folínico, 5-FU, oxaliplatino), y leucovorina. En otra forma de realización, la invención se refiere a un método de tratar colon o cáncer rectal dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos anticuerpos seleccionados de modo independiente cetuximab (Erbitux) y bevacizumab (Avastin).

[00166] En otra forma de realización, la invención se refiere a un método de tratar cáncer pancreático dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos seleccionados de modo independiente cirugía, radiación, uno o dos

anticuerpos, y uno o dos agentes quimioterapéuticos. En otra forma de realización, la invención se refiere a un método de tratar cáncer pancreático dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos se selecciona de uno o dos agentes quimioterapéuticos seleccionados de modo independiente compuesto que contiene platino (que incluye cisplatino, oxaliplatino, y carboplatino), 5-fluorouracilo (5-FU), gemcitabina, un taxano (que incluye paclitaxel y docetaxel), topotecano, irinotecano, capecitabina, streptozocin, erlotinib (Tarceva), leucovorina, y capecitabina (Xeloda). En otra forma de realización, la invención se refiere a un método de tratar cáncer pancreático dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es un anticuerpo donde el anticuerpo es cetuximab.

[00167] En otra forma de realización, la invención se refiere a un método de tratar cáncer de mamas dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos seleccionados de modo independiente cirugía, radiación, uno o dos agentes quimioterapéuticos, uno o dos terapias hormonales, y uno o dos anticuerpos. En otra forma de realización, la invención se refiere a un método de tratar cáncer de mamas dicho método comprende administrar a un paciente

una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos de los agentes quimioterapéuticos seleccionados de modo independiente lapatinib (Tykerb®), Paclitaxel (Taxol®), docetaxel, capecitabina, Ciclofosfamida (Cytoxan), CMF (ciclofosfamida, fluoruracilo, y metotrexato), metotrexato, fluorouracilo, doxorrubicina, epirrubicina, gemcitabina, carboplatino (Paraplatin), cisplatino (Platinol), vinorelbina (Navelbine), capecitabina (Xeloda), doxorrubicina liposómica pegilada (Doxilo), paclitaxel unida a albúmina (Abraxane), AC (adriamicina y ciclofosfamida), adriamiclina, y pamidronato o ácido zoldrónico (para tratar debilidad ósea). En otra forma de realización, la invención se refiere a un método de tratar cáncer de mamas dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos terapias hormonales seleccionados de modo independiente tamoxifeno, torremifeno (Fareston), Fulvestrant (Faslodex), acetato de megestrol (Megace), extirpación ovárica, Raloxifeno, análogos de hormona liberadora de hormona luteinizante (LHRH) (que incluye goserelina y leuprolida), acetato de megestrol (Megace), y uno o más inhibidores de aromatasas. En otra forma de realización, la invención se refiere a un método de tratar cáncer de mamas dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de

los tratamientos es uno o dos terapias hormonales y una de las terapias hormonales es un inhibidor de aromatasas seleccionado de letrozol (Femara), anastrozol (Arimidex), y exemestano (Aromasin). En otra forma de realización, la invención se refiere a un método de tratar cáncer de mamas dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos anticuerpos seleccionados de modo independiente $^{\alpha}$IGF-1R A12 MoAb, $^{\alpha}$IGF-1R 19D12 MoAb, $^{\alpha}$IGF-1R h7C$_1$0 MoAb, $^{\alpha}$IGF-1R CP-751871 MoAb, bevacizumab (Avastin), y trastuzumab.

[00168] En otra forma de realización, la invención se refiere a un método de tratar cáncer de mamas dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos agentes quimioterapéuticos y uno de los agentes quimioterapéuticos es erlotinib.

[00169] En otra forma de realización, la invención se refiere a un método de tratar cáncer de mamas dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos de los agentes quimioterapéuticos y uno o dos de los agentes quimioterapéuticos se seleccionan de modo independiente rapamicina, lapatinib, erlotinib, *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5r,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-

(metiloxi)quinazolin-4-amina opcionalmente en forma de una sal farmacéuticamente aceptable y en forma adicional opcionalmente como un hidrato y en forma adicional opcionalmente como un solvato de este, *N*-(4-bromo-3-cloro-2-fluorofenil)-7-({[(3a*R*,5r,6a*S*)-2-metiloctahidrociclo-penta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina opcionalmente en forma de sal farmacéuticamente aceptable y en forma adicional opcionalmente como un hidrato y en forma adicional opcionalmente como un solvato de este, *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5s,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina opcionalmente en forma de sal farmacéuticamente aceptable y en forma adicional opcionalmente como un hidrato y en forma adicional opcionalmente como un solvato de este, y *N*-(4-bromo-3-cloro-2-fluorofenil)-7-({[(3a*R*,5s,6a*S*)-2-metiloctahidrociclo-penta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina opcionalmente en forma de sal farmacéuticamente aceptable y en forma adicional opcionalmente como un hidrato y en forma adicional opcionalmente como un solvato de este.

[00170] En otra forma de realización, la invención se refiere a un método de tratar cáncer de mamas dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos de los anticuerpos. En otra forma de realización, la invención se refiere a un método de tratar cáncer de mamas dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en

la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos anticuerpos y uno de los anticuerpos es trastuzumab.

[00171] En otra forma de realización, la invención se refiere a un método de tratar cáncer de mamas dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos de los agentes quimioterapéuticos y uno de los agentes quimioterapéuticos se selecciona de *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5r,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, *N*-(4-bromo-3-cloro-2-fluorofenil)-7-({[(3a*R*,5r,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5s,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, y *N*-(4-bromo-3-cloro-2-fluorofenil)-7-({[(3a*R*,5s,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina; opcionalmente en forma de sal farmacéuticamente aceptable y en forma adicional opcionalmente como un hidrato y en forma adicional opcionalmente como un solvato de este.

[00172] En otra forma de realización, la invención se refiere a un método de tratar cáncer de mamas dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos de los agentes

quimioterapéuticos y uno de los agentes quimioterapéuticos es *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5*r*,6a*S*)-2-metiloctahidrociclopenta-[*c*]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina opcionalmente en forma de sal farmacéuticamente aceptable y en forma adicional opcionalmente como un hidrato y en forma adicional opcionalmente como un solvato de este.

[00173] En otra forma de realización, la invención se refiere a un método de tratar cáncer pulmonar de células no pequeñas dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos seleccionados de modo independiente cirugía, radiación, uno o más anticuerpos, y uno o más agentes quimioterapéuticos. En otra forma de realización, la invención se refiere a un método de tratar cáncer pulmonar de células no pequeñas dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos agentes quimioterapéuticos seleccionados de modo independiente cisplatino, oxaliplatino, carboplatino, zactima (zd6474), paclitaxel, docetaxel (Taxotere®), gemcitabine (Gemzar®), vinorelbina, irinotecano, etopósido, vinblastina, erlotinib (Tarceva®), gefitinib (iressa), y pemetrexed. En otra forma de realización, la invención se refiere a un método de tratar cáncer pulmonar de células no pequeñas dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más

tratamientos donde uno de los tratamientos es un anticuerpo y el anticuerpo es Bevacizumab. En otra forma de realización, la invención se refiere a un método de tratar cáncer pulmonar de células no pequeñas dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos agentes quimioterapéuticos seleccionados de modo independiente cisplatino, oxaliplatino, carboplatino, paclitaxel, docetaxel (Taxotere®), y erlotinib (Tarceva®).

[00174] En otra forma de realización, la invención se refiere a un método de tratar cáncer pulmonar de células no pequeñas dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos agentes quimioterapéuticos y uno de los agentes quimioterapéuticos es carboplatino.

[00175] En otra forma de realización, la invención se refiere a un método de tratar cáncer pulmonar de células no pequeñas dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos agentes quimioterapéuticos y uno de los agentes quimioterapéuticos se selecciona de *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5r,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, *N*-(4-bromo-3-cloro-2-

fluorofenil)-7-({[(3a*R*,5r,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5s,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, y *N*-(4-bromo-3-cloro-2-fluorofenil)-7-({[(3a*R*,5s,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina; opcionalmente en forma de sal farmacéuticamente aceptable y en forma adicional opcionalmente como un hidrato y en forma adicional opcionalmente como un solvato de este. En otra forma de realización, la invención se refiere a un método de tratar cáncer pulmonar de células no pequeñas dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos agentes quimioterapéuticos y uno de los agentes quimioterapéuticos es *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5*r*,6a*S*)-2-metiloctahidrociclopenta-[*c*]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina opcionalmente en forma de sal farmacéuticamente aceptable y en forma adicional opcionalmente como un hidrato y en forma adicional opcionalmente como un solvato de este.

[00176] En otra forma de realización, la invención se refiere a un método de tratar cáncer pulmonar de células pequeñas dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos seleccionados de modo independiente cirugía, radiación, y uno o dos agentes quimioterapéuticos. En otra forma de realización, la invención se refiere a un método de tratar cáncer

pulmonar de células pequeñas dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos agentes de quimioterapia seleccionados de modo independiente un platino (tales como cisplatino, oxaliplatino, y carboplatino), gefitinib, vinorelbina, docetaxel, paclitaxel, etopósido, fosfamida, ifosfamida, ciclofosfamida, ciclofosfamida/doxorrubicina/vincristina (CAV), doxorrubicina, vincristina, gemcitabina, paclitaxel, vinorelbina, topotecano, irinotecano, metotrexato, y docetaxel.

[00177] En otra forma de realización, la invención se refiere a un método de tratar cáncer tiroideo papilar o anaplásico dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos seleccionados de modo independiente cirugía, radiación, terapia de yodo radiactivo, uno o dos terapias hormonales, y uno o dos agentes quimioterapéuticos. En otra forma de realización, la invención se refiere a un método de tratar cáncer tiroideo papilar o anaplásico dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos agentes quimioterapéuticos seleccionados de modo independiente pastillas de hormona tiroidea, doxorrubicina y un platino. En otra forma de realización, la invención se refiere a un método de tratar cáncer tiroideo papilar o anaplásico dicho método

comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es terapia hormonal y la terapia hormonal es ablación con yodo radiactivo.

[00178] En otra forma de realización, la invención se refiere a un método de tratar cáncer de endometrio dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos seleccionados de modo independiente cirugía, radiación, uno o dos terapias hormonales, y uno o dos agentes quimioterapéuticos. En otra forma de realización, la invención se refiere a un método de tratar cáncer de endometrio dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos terapias hormonales seleccionados de modo independiente acetato de megestrol, tamoxifeno, y una progestina que incluye acetato de medroxiprogesterona (Provera) y acetato de megestrol (Megace). En otra forma de realización, la invención se refiere a un método de tratar cáncer de endometrio dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos agentes quimioterapéuticos seleccionados de modo independiente un compuesto que contiene platino (que incluye cisplatino, oxaliplatino, y

carboplatino, más particularmente por ejemplo cisplatino), un taxano (que incluye paclitaxel), doxorrubicina (Adriamicina), ciclofosfamida, fluorouracilo (5-FU), metotrexato, y vinblastina.

[00179] En otra forma de realización, la invención se refiere a un método de tratar cáncer ovárico dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos seleccionados de modo independiente cirugía, radiación, uno o dos anticuerpos, y uno o dos agentes quimioterapéuticos. En otra forma de realización, la invención se refiere a un método de tratar cáncer ovárico dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es un anticuerpo y el anticuerpo es bevacizumab. En otra forma de realización, la invención se refiere a un método de tratar cáncer ovárico dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos agentes quimioterapéuticos seleccionados de modo independiente un compuesto que contiene platino (que incluye cisplatino, oxaliplatino y carboplatino), un taxano (que incluye paclitaxel y docetaxel), topotecano, una antraciclina (que incluye doxorrubicina y doxorrubicina liposómica), gemcitabina, ciclofosfamida, vinorelbina (Navelbine), hexametilmelamina, ifosfamida, etopósido, bleomicina, vinblastina, ifosfamida,

vincristina, y ciclofosfamida. En otra forma de realización, la invención se refiere a un método de tratar cáncer ovárico dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos agentes quimioterapéuticos seleccionados de modo independiente un platino y un taxano. En otra forma de realización, la invención se refiere a un método de tratar cáncer ovárico dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos agentes quimioterapéuticos seleccionados de modo independiente cisplatino, oxaliplatino, carboplatino, paclitaxel, y docetaxel.

[00180] En otra forma de realización, la invención se refiere a un método de tratar glioblastoma, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos seleccionados de modo independiente cirugía, radiación, uno o dos agentes quimioterapéuticos, uno o dos agentes anticonvulsivantes y uno o dos agentes para reducir el edema. En otra forma de realización, la invención se refiere a un método de tratar glioblastoma dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es radiación seleccionada

de radiación de rayo externo, radioterapia intersticial y radiocirugía estereotáctica. En otra forma de realización, la invención se refiere a un método de tratar glioblastoma, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos agentes quimioterapéuticos seleccionados de modo independiente carmustina (BCNU), erlotinib (Tarceva), bevacizumab, gefitinib (Iressa), rapamicina, temozolomida, cisplatino, BCNU, lomustina, procarbazina y vincristina. En otra forma de realización, la invención se refiere a un método de tratar glioblastoma, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es un agente anticonvulsivante y el agente anticonvulsivante es difenilhidantoína (Dilantin). En otra forma de realización, la invención se refiere a un método de tratar glioblastoma, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es un agente para reducir el edema y el agente es dexametasona (Decadron). En otra forma de realización, la invención se refiere a un método de tratar glioblastoma, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos

agentes quimioterapéuticos. En otra forma de realización, la invención se refiere a un método de tratar glioblastoma dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos agentes quimioterapéuticos seleccionados de modo independiente erlotinib y temozolomida.

[00181] En otra forma de realización, la invención se refiere a un método de tratar cáncer cervical dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos seleccionados de modo independiente cirugía, radiación, y uno o dos agentes quimioterapéuticos. En otra forma de realización, la invención se refiere a un método de tratar cáncer cervical dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es cirugía seleccionado de criocirugía, cirugía láser, escisión con asa electroquirúrgica, cotización, histerectomía simple e histerectomía radical y disección de ganglios linfáticos pélvicos. En otra forma de realización, la invención se refiere a un método de tratar cáncer cervical, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es radiación seleccionada de la llamada terapia de radiación de rayo

externo y braquiterapia. En otra forma de realización, la invención se refiere a un método de tratar cáncer cervical dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos agentes quimioterapéuticos seleccionados de modo independiente un compuesto de platino (tales como cisplatino, carboplatino, y oxaliplatino), paclitaxel, topotecano, ifosfamida, gemcitabina, vinorelbina, y fluorouracilo.

[00182] En otra forma de realización, la invención se refiere a un método de tratar un tumor carcinoide gastrointestinal, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos seleccionados de modo independiente cirugía, radiación, inmunoterapia, y uno o dos agentes quimioterapéuticos. En otra forma de realización, la invención se refiere a un método de tratar a tumor carcinoide gastrointestinal dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es cirugía seleccionado de extirpación y electrofulguración. En otra forma de realización, la invención se refiere a un método de tratar a tumor carcinoide gastrointestinal dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos

agentes quimioterapéuticos seleccionados de modo independiente ciproheptadina, SOM230, octreotide y lanreotide. En otra forma de realización, la invención se refiere a un método de tratar a tumor carcinoide gastrointestinal dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es inmunoterapia y la inmunoterapia es un interferón.

[00183] En otra forma de realización, la invención se refiere a un método de tratar un tumor estromal gastrointestinal, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos seleccionados de modo independiente cirugía, radiación, y uno o dos agentes quimioterapéuticos. En otra forma de realización, la invención se refiere a un método de tratar a tumor estromal gastrointestinal, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos agentes quimioterapéuticos seleccionados de modo independiente mesilato de imatinib (Gleevec), sunitinib (Sutent), y nilotinib (AMN107).

[00184] En otra forma de realización, la invención se refiere a un método de tratar carcinoma hepatocelular, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos seleccionados

de modo independiente cirugía, ablación por radiofrecuencia, ablación por etanol, criocirugía, embolización arterial hepática, embolización química, radiación, y uno o dos agentes quimioterapéuticos. Otra forma de realización, la invención se refiere a un método de tratar carcinoma hepatocelular dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es cirugía seleccionada de resección y trasplante. En otra forma de realización, la invención se refiere a un método de tratar carcinoma hepatocelular dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos agentes quimioterapéuticos seleccionados de modo independiente sorafenib, 5-fluorouracilo y cisplatino.

[00185] En otra forma de realización, la invención se refiere a un método de tratar linfoma no Hodgkin, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos seleccionados de modo independiente radiación, uno o dos agentes quimioterapéuticos, terapia con interferón, uno o dos anticuerpos, y trasplante de médula ósea o células madre de sangre periférica. En otra forma de realización, la invención se refiere a un método de tratar linfoma no Hodgkin dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención,

en combinación con uno o más tratamientos donde uno de los tratamientos es uno o dos agentes quimioterapéuticos seleccionado de CHOP (ciclofosfamida, doxorrubicina, vincristina y prednisona), clorambucilo, fludarabina y etopósido. En otra forma de realización, la invención se refiere a un método de tratar linfoma no Hodgkin dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es un anticuerpo seleccionado de rituximab, ibritumomab tiuxetan, tositumomab, y alemtuzumab. En otra forma de realización, la invención se refiere a un método de tratar linfoma no Hodgkin dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es un anticuerpo y el anticuerpo es rituximab.

[00186] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es radiación y otro tratamiento es cirugía.

[00187] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los

tratamientos es radiación y otro tratamiento es uno o dos agentes quimioterapéuticos.

[00188] En otra forma de realización, la invención se refiere a un método de tratar cáncer, dicho método comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, como se define en la Síntesis de la invención, en combinación con uno o más tratamientos donde uno de los tratamientos es cirugía y otro tratamiento es uno o dos agentes quimioterapéuticos.

[00189] Para cada una de las formas de realización anteriores, el Compuesto de Fórmula I se selecciona de alguna de las siguientes formas de realización, que incluye los compuestos representativos de la Tabla 1.

[00190] Una forma de realización (A) de la Invención se refiere a un Compuesto de Fórmula I donde R^1 es hidrógeno, alquilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, cicloalquilalquilo opcionalmente sustituido, arilo opcionalmente sustituido, arilalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, heterocicloalquilalquilo opcionalmente sustituido, heteroarilo opcionalmente sustituido o heteroarilalquilo opcionalmente sustituido. En otra realización, R^1 es hidrógeno, alquilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, arilalquilo opcionalmente sustituido, o heterocicloalquilalquilo opcionalmente sustituido. En otra realización, R^1 es hidrógeno, alquilo, alquilo sustituido con uno o dos hidroxi, alquilo sustituido con alcoxi, cicloalquilo, arilalquilo, o heterocicloalquilalquil. En otra realización, R^1 es hidrógeno, metilo, etilo, propilo, isopropilo, 2-hidroxipropilo, 3-hidroxipropilo, 2-etoxietilo,

3-metoxipropilo, 3-etoxipropilo, 3-isopropoxipropilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, bencilo, o 2-piperidin-1-iletilo. En otra realización, R^1 es etilo, isopropilo, ciclopentilo, o ciclohexilo. En otra realización, R^1 es etilo.

[00191] Otra forma de realización (B) de la invención se refiere a un Compuesto de Fórmula I donde R^2 es hidrógeno o alquilo donde el alquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 grupos R^8. En otra realización, R^2 es hidrógeno o alquilo donde el alquilo está opcionalmente sustituido con uno, dos o tres grupos R^8. En otra realización, R^2 es hidrógeno o alquilo donde el alquilo está opcionalmente sustituido con uno, dos o tres grupos R^8; y cada R^8, cuando está presente, se selecciona de modo independiente de amino, alquilamino, dialquilamino, y halo. En otra realización, R^2 es hidrógeno, metilo, etilo, propilo, isopropilo, *ter*-butilo, 3-aminopropilo, 3-(*N*-metilamino)-propilo, 3-(*N,N*-dimetilamino)-propilo, 2-fluoroetilo o 2,2,2-trifluoroetilo. En otra realización, R^2 es hidrógeno o etilo. Aun con mayor preferencia, R^2 es hidrógeno.

[00192] En otra realización de la invención, R^2 es hidrógeno.

[00193] En otra realización de la invención, R^2 es alquilo opcionalmente sustituido con 1, 2, 3, 4, o 5 grupos R^8. En otra realización, R^2 es alquilo donde el alquilo está opcionalmente sustituido con uno, dos o tres grupos R^8; y cada R^8, cuando está presente, se selecciona de modo independiente de amino, alquilamino, dialquilamino, y halo. En otra realización, R^2 es metilo, etilo, propilo, isopropilo, *ter*-butilo, 3-aminopropilo, 3-(*N*-metilamino)-propilo, 3-(*N,N*-

dimetilamino)-propilo, 2-fluoroetilo, o 2,2,2-trifluoroetilo. En otra realización, R^2 es etilo.

[00194] Otra forma de realización (C) de la invención se refiere a un Compuesto de Fórmula I donde R^4 es alquilo opcionalmente sustituido. En otra realización, R^4 es metilo o etilo. En otra realización, R^4 es metilo.

[00195] Otra forma de realización (D) de la invención se refiere a un Compuesto de Fórmula I donde R^6 es acilo. En otra realización, R^6 is alquilcarbonil. En otra realización, R^6 es acetilo.

[00196] Otra forma de realización (E) de la invención se refiere a un Compuesto de Fórmula I donde R^6 es fenilo opcionalmente sustituido con 1, 2, 3, 4, o 5 grupos R^9. En otra realización, R^6 es fenilo opcionalmente sustituido con uno o dos grupos R^9; y cada R^9, cuando está presente, se selecciona de modo independiente de arilo, halo, alcoxi, ariloxi, y haloalquilo. En otra realización, R^6 es fenilo opcionalmente sustituido con uno o dos grupos R^9; y cada R^9, cuando está presente, se selecciona de modo independiente de fenilo, fluoro, cloro, metoxi, feniloxi, y trifluorometilo. En otra realización, R^6 es fenilo, fenilo sustituido con fenilo, fluorofenilo, difluorofenilo, clorofenilo, diclorofenilo, fenilo sustituido con cloro y fluoro, metoxifenilo, dimetoxifenilo, feniloxifenilo, o trifluorometilfenilo. En otra realización, R^6 es fenilo, 2-fenil-fenilo, 3-fenil-fenilo, 4-fenil-fenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 2,3-difluorofenilo, 2,4-difluorofenilo, 2,5-difluorofenilo, 2,6-difluorofenilo, 3,4-difluorofenilo, 3,5-difluorofenilo, 2-clorofenilo, 3-clorofenilo, 4-clorofenilo, 2,3-diclorofenilo, 2,4-diclorofenilo, 2,5-diclorofenilo, 2,6-diclorofenilo, 3,4-diclorofenilo, 3,5-diclorofenilo, 3-cloro-4-fluoro-

fenilo, 2-metoxifenilo, 3-metoxifenilo, 4-metoxifenilo, 2,3-dimetoxifenilo, 2,4-dimetoxifenilo, 2,5-dimetoxifenilo, 2,6-dimetoxifenilo, 3,4-dimetoxifenilo, 3,5-dimetoxifenilo, 4-feniloxifenilo, 2-trifluorometilfenilo, 3-trifluorometilfenilo, o 4-trifluorometilfenilo.

[00197] Otra forma de realización (F) de la invención se refiere a un Compuesto de Fórmula I donde R^6 es fenilo sustituido con 1, 2, 3, 4, o 5 grupos R^9.

[00198] Otra forma de realización (G) de la invención se refiere a un Compuesto de Fórmula I donde R^6 es heteroarilo opcionalmente sustituido con 1, 2, 3, 4 o 5 grupos R^9.

[00199] Otra forma de realización (G1) de la forma de realización G es un Compuesto de Fórmula I donde R^6 es un heteroarilo de 6 miembros opcionalmente sustituido con uno o dos R^9. En otra realización, R^6 es piridinilo, pirazinilo, pirimidinilo, o piridazinil cada uno de los cuales está opcionalmente sustituido con un R^9 donde R^9, cuando está presente, es halo. En otra realización, R^6 es piridi*N*-2-ilo, piridin-3-ilo, piridi*N*-4-ilo, 3-fluoropiridi*N*-4-ilo, pirazin-2-ilo, pirazin-3-ilo, pirimidin-2-ilo, pirimidin-4-ilo, pirimidin-5-ilo, piridazin-3-ilo, o piridazin-4-ilo, cada uno de los cuales está opcionalmente sustituido con uno o dos R^9.

[00200] En otra realización (G2) de la forma de realización G es un Compuesto de Fórmula I donde R^6 es pirazinilo, pirimidinilo, o piridazinilo cada uno de los cuales está opcionalmente sustituido con un R^9 donde R^9, cuando está presente, es halo. En otra realización, R^6 es pirazin-2-ilo, pirazin-3-ilo, pirimidin-2-ilo, pirimidin-4-ilo, pirimidin-5-ilo, piridazin-3-ilo, o piridazin-4-ilo.

[00201] Otra forma de realización (G3) de la forma de realización G es un Compuesto de Fórmula I donde R^6 es un heteroarilo de 5 miembros opcionalmente sustituido con uno o dos R^9. En otra realización R^6 es pirazolilo, imidazolilo, tienilo, tiazolilo, oxazolilo, isoxazolilo, oxadiazolilo, furanilo, pirrolilo, triazolilo, o tetrazolilo, cada uno de los cuales está opcionalmente sustituido con un R^9 donde R^9, cuando está presente, es alquilo, arilalquilo, ciano, arilo, alcoxicarbonilo, o halo. En otra realización, R^6 es pirazol-1-ilo, pirazol-3-ilo, pirazol-4-ilo, pirazol-5-ilo, imidazol-1-ilo, imidazol-2-ilo, imidazol-4-ilo, imidazol-5-ilo, tien-2-ilo, tien-3-ilo, tiazol-2-ilo, tiazol-4-ilo, tiazol-5-ilo, oxazol-2-ilo, oxazol-4-ilo, oxazol-5-ilo, isoxazol-3-ilo, isoxazol-4-ilo, isoxazol-5-ilo, 1,2,3-oxadiazol-4-ilo, 1,2,3-oxadiazol-5-ilo, 1,3,4-oxadiazol-2-ilo, 1,2,4-oxadiazol-3-ilo, 1,2,4-oxadiazol-5-ilo, furan-2-ilo, furan-3-ilo, pirrol-1-ilo, pirrol-2-ilo, pirrol-3-ilo, triazol-1-ilo, triazol-4-ilo, triazol-5-ilo, tetrazol-1-ilo, o tetrazol-5-il; cada uno de los cuales está opcionalmente sustituido con un R^9 donde R^9, cuando está presente, es metilo, bencilo, ciano, fenilo, *N-ter*-butoxicarbonilo, o cloro. En otra realización, R^6 es pirazol-3-ilo, pirazol-4-ilo, pirazol-5-ilo, imidazol-2-ilo, imidazol-4-ilo, imidazol-5-ilo, tien-2-ilo, tien-3-ilo, tiazol-2-ilo, tiazol-4-ilo, tiazol-5-ilo, oxazol-2-ilo, oxazol-4-ilo, oxazol-5-ilo, isoxazol-3-ilo, isoxazol-4-ilo, isoxazol-5-ilo, 1,2,3-oxadiazol-4-ilo, 1,2,3-oxadiazol-5-ilo, 1,3,4-oxadiazol-2-ilo, 1,2,4-oxadiazol-3-ilo, 1,2,4-oxadiazol-5-ilo, furan-2-ilo, furan-3-ilo, pirrol-2-ilo, pirrol-3-ilo, triazol-4-ilo, triazol-5-ilo, o tetrazol-5-il; cada uno de los cuales está opcionalmente sustituido con un R^9 donde R^9,

cuando está presente, es metilo, bencilo, ciano, fenilo, *N-ter*-butoxicarbonilo, o cloro.

[00202] Otra forma de realización (G4) de la forma de realización G es un Compuesto de Fórmula I donde R^6 es tienilo, pirrolilo, furanilo, pirazolilo, tiazolilo, isoxazolilo, imidazolilo, triazolilo, o tetrazolilo, cada uno de los cuales está opcionalmente sustituido con un R^9 donde R^9, cuando está presente, es metilo, bencilo, ciano, fenilo, *N-ter*-butoxicarbonilo, o cloro. En otra realización, R^6 is tien-2-ilo, tien-3-ilo, pirrol-2-ilo, furan-2-ilo, furan-3-ilo, pirazol-3-ilo, pirazol-4-ilo, pirazol-5-ilo, tiazol-2-ilo, tiazol-5-ilo, isoxazol-4-ilo, imidazol-5-ilo, triazol-5-ilo, tetrazol-5-ilo, cada uno de los cuales está opcionalmente sustituido con un R^9 donde R^9, cuando está presente, es metilo, bencilo, ciano, fenilo, *N-ter*-butoxicarbonilo, o cloro. En otra realización, R^6 es tien-2-ilo, tien-3-ilo, 5-ciano-tien-2-ilo, 4-metil-tien-2-ilo, 4-metil-tien-3-ilo, 5-cloro-tien-5-ilo, 5-fenilo-tien-2-ilo, pirrol-2-ilo, *N-ter*-butoxicarbonil-pirrol-2-ilo, *N*-metil-pirrol-2-ilo, furan-2-ilo, furan-3-ilo, pirazol-3-ilo, pirazol-4-ilo, *N*-benzil-pirazol-4-ilo, pirazol-5-ilo, tiazol-2-ilo, tiazol-5-ilo, isoxazol-4-ilo, imidazol-5-ilo, triazol-5-ilo, tetrazol-5-ilo,

[00203] Otra forma de realización (G5) de la forma de realización G es un Compuesto de Fórmula I donde R^6 es tien-2-ilo, tien-3-ilo, pirrol-2-ilo, furan-2-ilo, furan-3-ilo, pirazol-3-ilo, pirazol-4-ilo, pirazol-5-ilo, tiazol-2-ilo, tiazol-5-ilo, isoxazol-4-ilo, imidazol-5-ilo, triazol-5-ilo, o tetrazol-5-ilo, cada uno de los cuales está opcionalmente sustituido con un R^9 donde R^9, cuando está presente, es metilo, bencilo, ciano, fenilo, *N-ter*-butoxicarbonilo, o cloro.

[00204] Otra forma de realización (G6) de la forma de realización G es un Compuesto de Fórmula I donde R^6 es indolilo, benzimidazolilo, benzofuranilo, benzoxazolilo, o benzoisoxazolilo cada uno de los cuales está opcionalmente sustituido con 1, 2, 3, 4, o 5 grupos R^9. En otra realización, R^6 es indol-2-ilo, indol-3-ilo, indol-4-ilo, indol-5-ilo, indol-6-ilo, indol-7-ilo, benzimidazol-2-ilo, benzimidazol-4-ilo, benzimidazol-5-ilo, benzimidazol-6-ilo, benzimidazol-7-ilo, benzofuran-2-ilo, benzofuran-3-ilo, benzofuran-4-ilo, benzofuran-5-ilo, benzofuran-6-ilo, benzofuran-7-ilo, benzoxazol-2-ilo, benzoxazol-4-ilo, benzoxazol-5-ilo, benzoxazol-6-ilo, benzoxazol-7-ilo, benzoisoxazol-3-ilo, benzoisoxazol-4-ilo, benzoisoxazol-5-ilo, benzoisoxazol-6-ilo, o benzoisoxazol-7-ilo; cada uno de los cuales está opcionalmente sustituido con 1, 2, 3, 4, o 5 R^9 groups. En otra realización, R^6 es indol-6-ilo.

[00205] Otra forma de realización de la invención (H) es un Compuesto de Fórmula 1 donde R^1 es hidrógeno, alquilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, heterocicloalquilalquilo opcionalmente sustituido, o arilalquilo opcionalmente sustituido; X es -NH-; R^2 es hidrógeno o alquilo donde el alquilo está opcionalmente sustituido con uno o dos R^8; R^4 es alquilo; R^5 es hidrógeno; R^6 es fenilo o heteroarilo donde el fenilo y heteroarilo están opcionalmente sustituido con uno, dos o tres grupos R^9; cada R^8, cuando está presente, es de modo independiente amino, alquilamino, dialquilamino, o halo; y cada R^9, cuando está presente, es de modo independiente alquilo, arilalquilo, ciano, arilo, alcoxicarbonilo, o halo.

[00206] Otra forma de realización de la invención (J) es un Compuesto de Fórmula 1 donde R^6 es pirazol-3-ilo,

pirazol-4-ilo, pirazol-5-ilo, imidazol-2-ilo, imidazol-4-ilo, imidazol-5-ilo, tien-2-ilo, tien-3-ilo, tiazol-2-ilo, tiazol-4-ilo, tiazol-5-ilo, oxazol-2-ilo, oxazol-4-ilo, oxazol-5-ilo, isoxazol-3-ilo, isoxazol-4-ilo, isoxazol-5-ilo, 1,2,3-oxadiazol-4-ilo, 1,2,3-oxadiazol-5-ilo, 1,3,4-oxadiazol-2-ilo, 1,2,4-oxadiazol-3-ilo, 1,2,4-oxadiazol-5-ilo, furan-2-ilo, furan-3-ilo, pirrol-2-ilo, pirrol-3-ilo, triazol-4-ilo, triazol-5-ilo, o tetrazol-5-ilo; cada uno de los cuales está opcionalmente sustituido con 1, 2, 3, 4, o 5 grupos R^9.

[00207] Otra forma de realización (K) de la invención es un Compuesto de Fórmula I donde R^1 es alquilo o cicloalquilo; R^4 es metilo; y R^6 es heteroarilo opcionalmente sustituido con uno o dos grupos R^9. En otra realización, cada R^9, cuando está presente, es de modo independiente alquilo, arilalquilo, ciano, arilo, alcoxicarbonilo, o halo. En otra realización, R^6 es pirazol-3-ilo, pirazol-4-ilo, pirazol-5-ilo, imidazol-2-ilo, imidazol-4-ilo, imidazol-5-ilo, tien-2-ilo, tien-3-ilo, tiazol-2-ilo, tiazol-4-ilo, tiazol-5-ilo, oxazol-2-ilo, oxazol-4-ilo, oxazol-5-ilo, isoxazol-3-ilo, isoxazol-4-ilo, isoxazol-5-ilo, 1,2,3-oxadiazol-4-ilo, 1,2,3-oxadiazol-5-ilo, 1,3,4-oxadiazol-2-ilo, 1,2,4-oxadiazol-3-ilo, 1,2,4-oxadiazol-5-ilo, furan-2-ilo, furan-3-ilo, pirrol-2-ilo, pirrol-3-ilo, triazol-4-ilo, triazol-5-ilo, o tetrazol-5-ilo; cada uno de los cuales está opcionalmente sustituido con un R^9 donde R^9, cuando está presente, es metilo, bencilo, ciano, fenilo, o *N-ter*-butoxicarbonilo.

[00208] Otra forma de realización (K1) de la forma de realización K es un Compuesto de Fórmula I donde R^2 es hidrógeno.

[00209] Otra forma de realización (K2) de la forma de realización K es un Compuesto de Fórmula I donde R^2 es metilo o etilo.

[00210] Otra forma de realización (L) de la invención es un Compuesto de Fórmula I donde R^1 es alquilo o cicloalquilo; R^4 es metilo; y R^6 es fenilo opcionalmente sustituido con uno o dos grupos R^9. En otra realización cada R^9, cuando está presente, es de modo independiente halo, alcoxi, o haloalquilo.

[00211] Otra forma de realización (M) de la invención es un Compuesto de Fórmula I donde R^1 es alquilo o cicloalquilo; R^4 es metilo; y R^2 es hidrógeno.

[00212] Otra forma de realización (N) de la invención es un Compuesto de Fórmula I donde R^1 es alquilo o cicloalquilo; R^4 es metilo; y R^2 es alquilo opcionalmente sustituido.

Compuestos representativos

[00213] Los compuestos representativos de Fórmula I y/o II se describen a continuación. Los ejemplos son solo ilustrativos y no limitan el alcance de la invención de ninguna manera. Los compuestos de la invención se nombran de acuerdo con la aplicación sistemática de las reglas de nomenclatura de acuerdo con la International Union de Pure y Applied Chemistry (IUPAC), International Union de Biochemistry y Molecular Biology (IUBMB), y el Chemical Abstracts Service (CAS). Los nombres se generaron usando el programa de computación de denominación ACD/Labs 8,00, versión del producto 8,08.

Tabla 1

[00214] Los Compuestos de la Tabla 1 se pueden preparar como sus sales, solvatos, hidratos, y/o isómeros farmacéuticamente aceptables. Dichas sales, solvatos, hidratos y combinaciones de isómeros de los Compuestos de la Tabla 1 se pueden usar en la práctica de la invención. En particular, la invención se puede practicar con una o dos sales farmacéuticamente aceptables de un Compuesto de la Tabla 1, dichas sales se forman con uno o dos ácidos seleccionados de modo independiente de ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico, ácido fosfórico, 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 metansulfónico, ácido etansulfónico, ácido 1,2-etandisulfónico, ácido 2-hidroxietansulfónico, ácido bencensulfónico, ácido 4-clorobencensulfónico, ácido 2-naftalenosulfónico, ácido 4-toluensulfónico, ácido canforsulfónico, ácido glucoheptónico, ácido 4,4'-metilenbis-(3-hidroxi-2-ene-1-carboxílico), ácido 3-fenilpropiónico, ácido trimetilacético, ácido ter-butilacético, ácido lauril sulfúrico, ácido glucónico, ácido glutámico, ácido hidroxinaftoico, ácido salicílico, ácido esteárico, ácido mucónico ácido p-toluensulfónico y ácido salicílico. Cualquier compuesto individual (y cualquiera de sus sales opcionales, solvatos opcionales e hidratos opcionales) de la Tabla 1 se puede usar en

combinación con cualquiera de las formas de realización anteriores.

Tabla 1

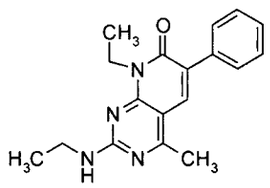
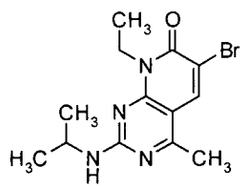
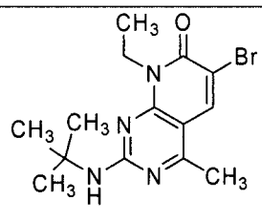
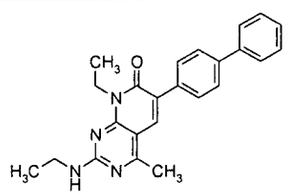
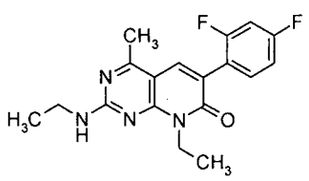
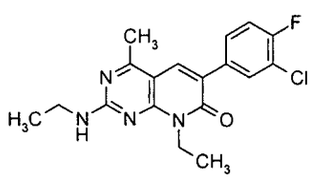
Ejemplo	Estructura	Nombre
1		8-etil-2-(etilamino)-4-metil-6-fenilpirido[2,3-d]pirimidin-7(8*H*)-one
2		6-bromo-8-etil-4-metil-2-[(1-metiletil)amino]pirido[2,3-d]pirimidin-7(8*H*)-ona
3		6-bromo-2-[(1,1-dimetiletil)amino]-8-etil-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona
4		6-bifenil-4-il-8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona
5		6-(2,4-difluorofenil)-8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona
6		6-(3-cloro-4-fluorofenil)-8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona

Tabla 1

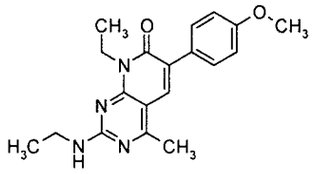
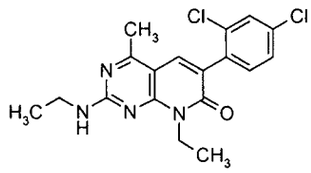
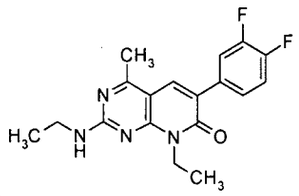
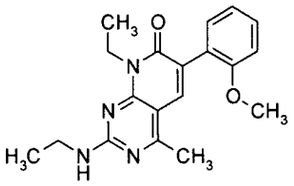
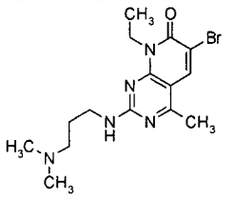
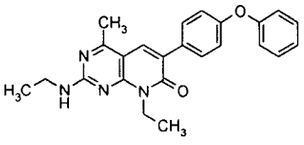
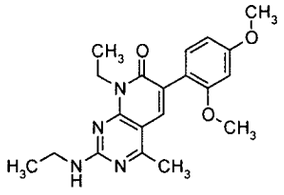
Ejemplo	Estructura	Nombre
7		8-etil-2-(etilamino)-4-metil-6-[4-(metiloxi)fenilo]pirido[2,3-d]pirimidin-7(8*H*)-ona
8		6-(2,4-diclorofenil)-8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona
9		6-(3,4-difluorofenil)-8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona
10		8-etil-2-(etilamino)-4-metil-6-[2-(metiloxi)fenilo]pirido[2,3-d]pirimidin-7(8*H*)-ona
11		6-bromo-2-{[3-(dimetilamino)propil]amino}-8-etil-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona
12		8-etil-2-(etilamino)-4-metil-6-[4-(feniloxi)fenilo]pirido[2,3-d]pirimidin-7(8*H*)-ona
13		6-[2,4-bis(metiloxi)fenilo]-8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona

Tabla 1

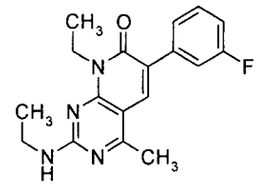
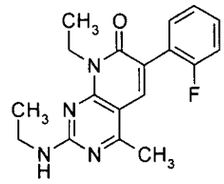
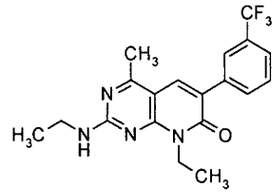
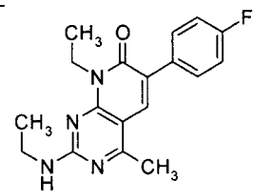
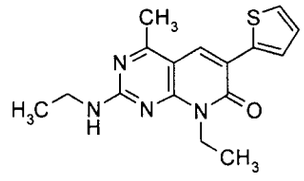
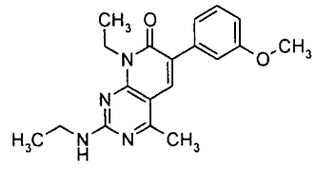
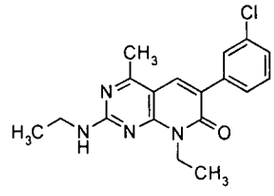
Ejemplo	Estructura	Nombre
14		8-etil-2-(etilamino)-6-(3-fluorofenil)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona
15		8-etil-2-(etilamino)-6-(2-fluorofenil)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona
16		8-etil-2-(etilamino)-4-metil-6-[3-(trifluorometil)fenilo]pirido[2,3-d]pirimidin-7(8*H*)-ona
17		8-etil-2-(etilamino)-6-(4-fluorofenil)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona
18		8-etil-2-(etilamino)-4-metil-6-(2-tienil)pirido[2,3-d]pirimidin-7(8*H*)-ona
19		8-etil-2-(etilamino)-4-metil-6-[3-(metiloxi)fenilo]pirido[2,3-d]pirimidin-7(8*H*)-ona
20		6-(3-clorofenil)-8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona

Tabla 1

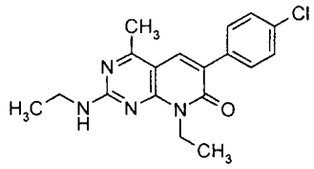
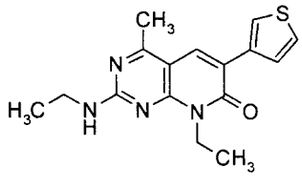
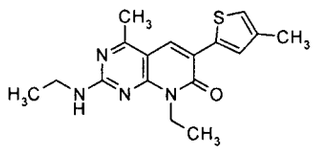
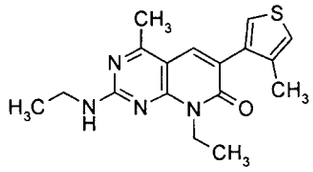
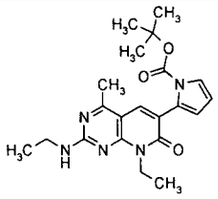
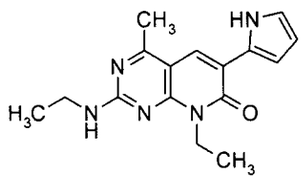
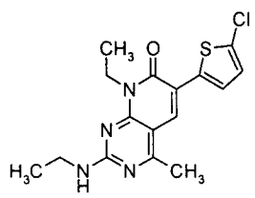
Ejemplo	Estructura	Nombre
21		6-(4-clorofenil)-8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona
22		8-etil-2-(etilamino)-4-metil-6-(3-tienil)pirido[2,3-d]pirimidin-7(8*H*)-ona
23		8-etil-2-(etilamino)-4-metil-6-(4-metil-2-tienil)pirido[2,3-d]pirimidin-7(8*H*)-ona
24		8-etil-2-(etilamino)-4-metil-6-(4-metil-3-tienil)pirido[2,3-d]pirimidin-7(8*H*)-ona
25		1,1-dimetiletil 2-[8-etil-2-(etilamino)-4-metil-7-oxo-7,8-dihidropirido[2,3-d]pirimidin-6-il]-1*H*-pirrole-1-carboxilate
26		8-etil-2-(etilamino)-4-metil-6-(1*H*-pirrol-2-il)pirido[2,3-d]pirimidin-7(8*H*)-ona
27		6-(5-cloro-2-tienil)-8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona

Tabla 1

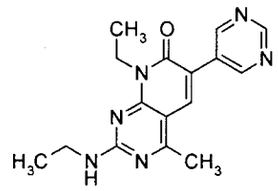
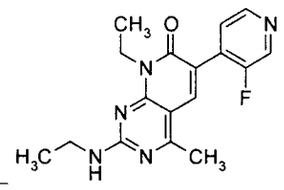
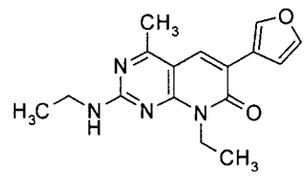
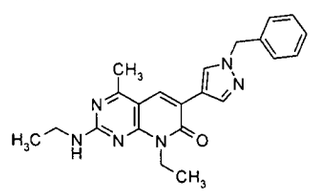
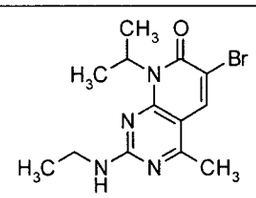
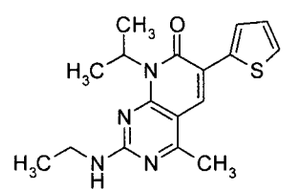
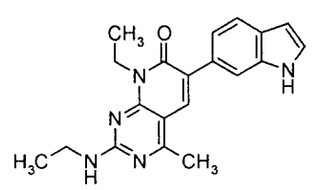
Ejemplo	Estructura	Nombre
28		8-etil-2-(etilamino)-4-metil-6-pirimidin-5-ilpirido[2,3-d]pirimidin-7(8*H*)-ona
29		8-etil-2-(etilamino)-6-(3-fluoropiridi*N*-4-il)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona
30		8-etil-2-(etilamino)-6-furan-3-il-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona
31		8-etil-2-(etilamino)-4-metil-6-[1-(fenilmetil)-1*H*-pirazol-4-il]pirido[2,3-d]pirimidin-7(8*H*)-ona
32		6-bromo-2-(etilamino)-4-metil-8-(1-metiletil)pirido[2,3-d]pirimidin-7(8*H*)-ona
33		2-(etilamino)-4-metil-8-(1-metiletil)-6-(2-tienil)pirido[2,3-d]pirimidin-7(8*H*)-ona
34		8-etil-2-(etilamino)-6-(1*H*-indol-6-il)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona

Tabla 1

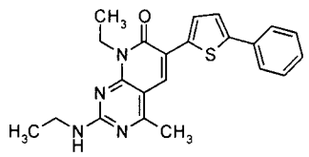
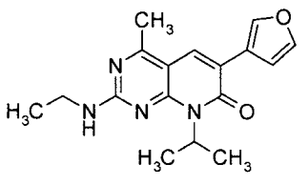
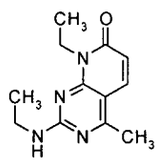
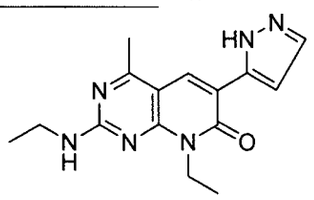
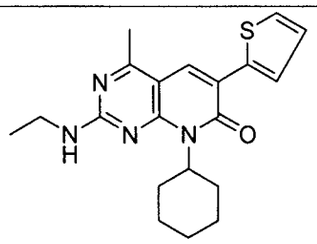
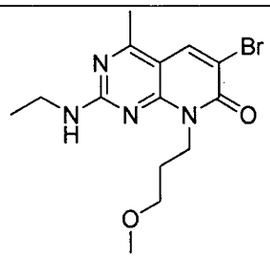
Ejemplo	Estructura	Nombre
35		8-etil-2-(etilamino)-4-metil-6-(5-fenilo-2-tienil)pirido[2,3-d]pirimidin-7(8*H*)-ona
36		2-(etilamino)-6-furan-3-il-4-metil-8-(1-metiletil)pirido[2,3-d]pirimidin-7(8*H*)-ona
37		8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona
38		8-etil-2-(etilamino)-4-metil-6-(1*H*-pirazol-5-il)pirido[2,3-d]pirimidin-7(8*H*)-ona
39		8-ciclohexil-2-(etilamino)-4-metil-6-(2-tienil)pirido[2,3-d]pirimidin-7(8*H*)-ona
40		6-bromo-2-(etilamino)-4-metil-8-[3-(metiloxi)propil]pirido[2,3-d]pirimidin-7(8*H*)-ona

Tabla 1

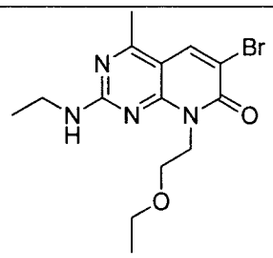
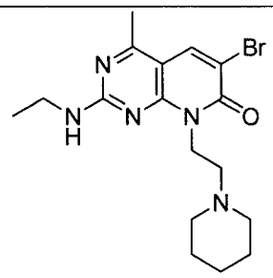
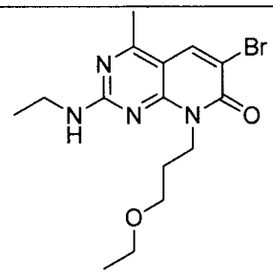
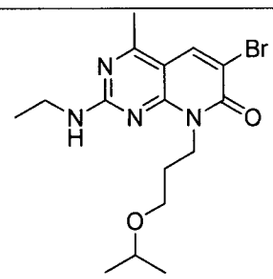
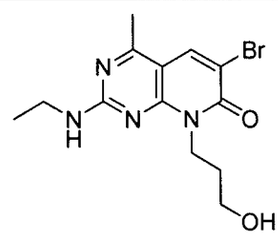
Ejemplo	Estructura	Nombre
41		6-bromo-2-(etilamino)-8-[2-(etiloxi)etilo]-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona
42		6-bromo-2-(etilamino)-4-metil-8-(2-piperidin-1-iletil)pirido[2,3-d]pirimidin-7(8*H*)-ona
43		6-bromo-2-(etilamino)-8-[3-(etiloxi)propil]-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona
44		6-bromo-2-(etilamino)-4-metil-8-{3-[(1-metiletil)oxi]propil}pirido[2,3-d]pirimidin-7(8*H*)-ona
45		6-bromo-2-(etilamino)-8-(3-hidroxipropil)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona

Tabla 1

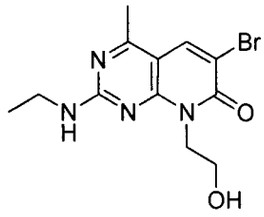
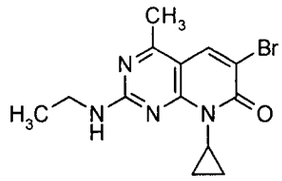
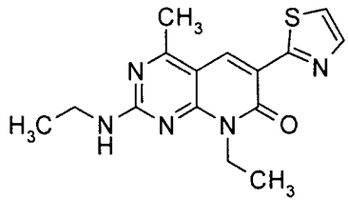
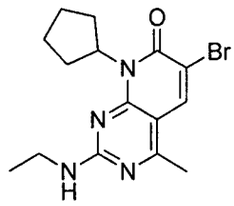
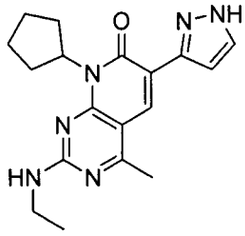
Ejemplo	Estructura	Nombre
46		6-bromo-2-(etilamino)-8-(2-hidroxietil)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona
47		6-bromo-8-ciclopropil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona
48		8-etil-2-(etilamino)-4-metil-6-(1,3-tiazol-2-il)pirido[2,3-d]pirimidin-7(8*H*)-ona
49		6-bromo-8-ciclopentil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona
50		8-ciclopentil-2-(etilamino)-4-metil-6-(1*H*-pirazol-3-il)pirido[2,3-d]pirimidin-7(8*H*)-ona

Tabla 1

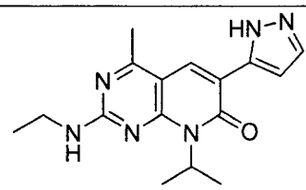
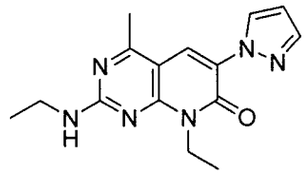
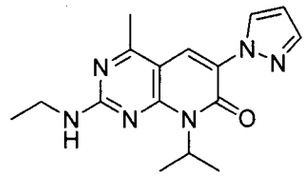
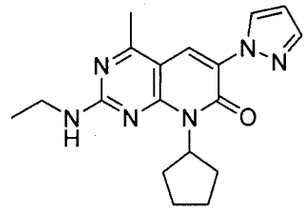
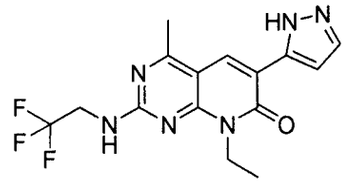
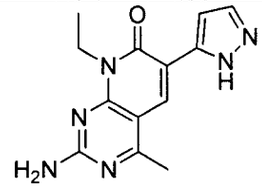
Ejemplo	Estructura	Nombre
51		2-(etilamino)-4-metil-8-(1-metiletil)-6-(1*H*-pirazol-5-il)pirido[2,3-d]pirimidin-7(8*H*)-ona
52		8-etil-2-(etilamino)-4-metil-6-(1*H*-pirazol-1-il)pirido[2,3-d]pirimidin-7(8*H*)-ona
53		2-(etilamino)-4-metil-8-(1-metiletil)-6-(1*H*-pirazol-1-il)pirido[2,3-d]pirimidin-7(8*H*)-ona
54		8-ciclopentil-2-(etilamino)-4-metil-6-(1*H*-pirazol-1-il)pirido[2,3-d]pirimidin-7(8*H*)-ona
55		8-etil-4-metil-6-(1*H*-pirazol-5-il)-2-[(2,2,2-trifluoroetil)amino]pirido[2,3-*d*]pirimidin-7(8*H*)-ona
56		2-amino-8-etil-4-metil-6-(1*H*-pirazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona

Tabla 1

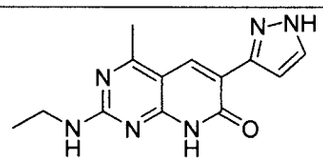
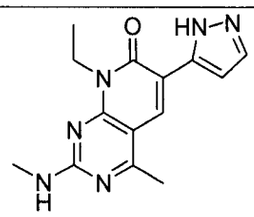
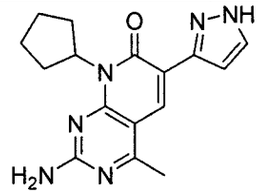
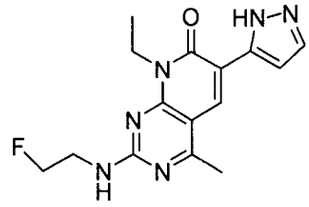
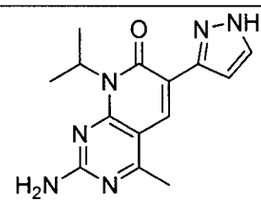
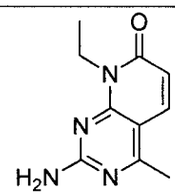
Ejemplo	Estructura	Nombre
57		2-(etilamino)-4-metil-6-(1*H*-pirazol-3-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona
58		8-etil-4-metil-2-(metilamino)-6-(1*H*-pirazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona
59		2-amino-8-ciclopentil-4-metil-6-(1*H*-pirazol-3-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona
60		8-etil-2-[(2-fluoroetil)amino]-4-metil-6-(1*H*-pirazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona
61		2-amino-4-metil-8-(1-metiletil)-6-(1*H*-pirazol-3-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona
62		2-amino-8-etil-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona

Tabla 1

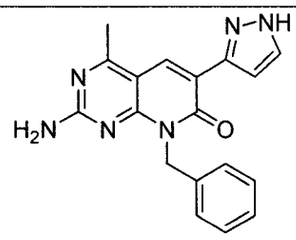
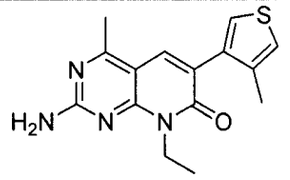
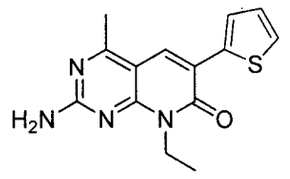
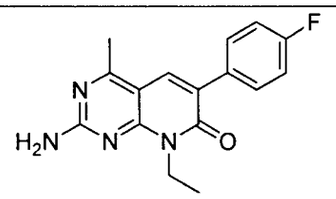
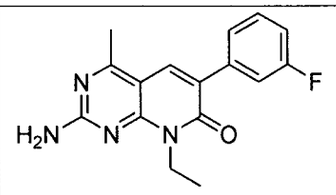
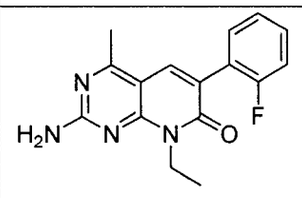
Ejemplo	Estructura	Nombre
63		2-amino-4-metil-8-(fenilmetil)-6-(1*H*-pirazol-3-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona
64		2-amino-8-etil-4-metil-6-(4-metil-3-tienil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona
65		2-amino-8-etil-4-metil-6-(2-tienil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona
66		2-amino-8-etil-6-(4-fluorofenil)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona
67		2-amino-8-etil-6-(3-fluorofenil)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona
68		2-amino-8-etil-6-(2-fluorofenil)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona

Tabla 1

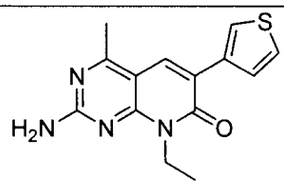
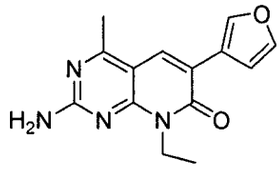
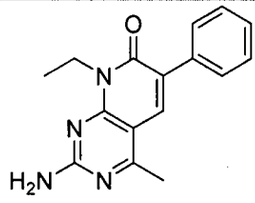
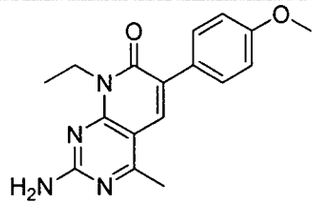
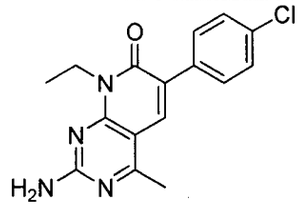
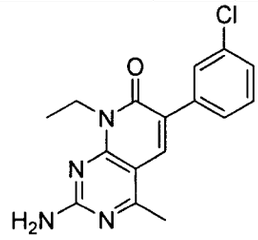
Ejemplo	Estructura	Nombre
69		2-amino-8-etil-4-metil-6-(3-tienil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona
70		2-amino-8-etil-6-furan-3-il-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona
71		2-amino-8-etil-4-metil-6-fenilpirido[2,3-*d*]pirimidin-7(8*H*)-ona
72		2-amino-8-etil-4-metil-6-[4-(metiloxi)fenilo]pirido[2,3-*d*]pirimidin-7(8*H*)-ona
73		2-amino-6-(4-clorofenil)-8-etil-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona
74		2-amino-6-(3-clorofenil)-8-etil-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona

Tabla 1

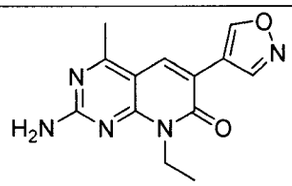
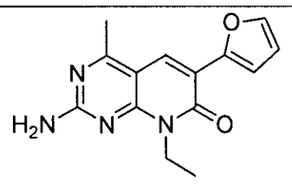
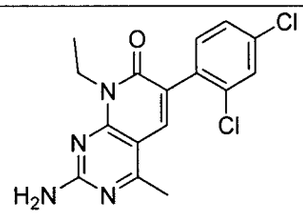
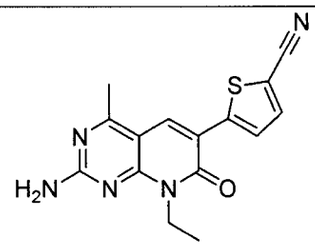
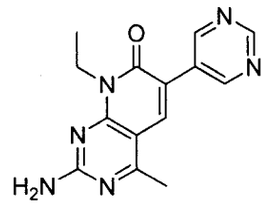
Ejemplo	Estructura	Nombre
75		2-amino-8-etil-6-isoxazol-4-il-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona
76		2-amino-8-etil-6-furan-2-il-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona
77		2-amino-6-(2,4-diclorofenil)-8-etil-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona
78		5-(2-amino-8-etil-4-metil-7-oxo-7,8-dihidropirido[2,3-*d*]pirimidin-6-il)tiofene-2-carbonitrilo
79		2-amino-8-etil-4-metil-6-pirimidin-5-ilpirido[2,3-*d*]pirimidin-7(8*H*)-ona

Tabla 1

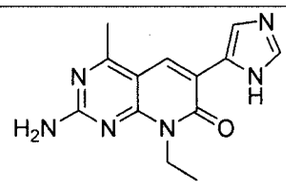
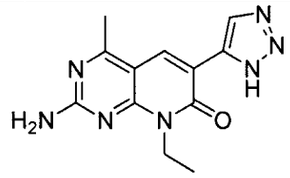
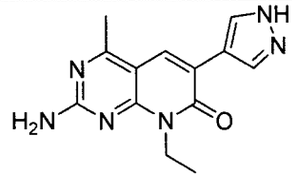
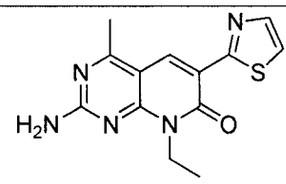
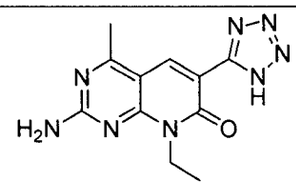
Ejemplo	Estructura	Nombre
80		2-amino-8-etil-6-(1*H*-imidazol-5-il)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona
81		2-amino-8-etil-4-metil-6-(1*H*-1,2,3-triazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona
82		2-amino-8-etil-4-metil-6-(1*H*-pirazol-4-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona
83		2-amino-8-etil-4-metil-6-(1,3-tiazol-2-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona
84		2-amino-8-etil-4-metil-6-(1*H*-tetrazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona

Tabla 1

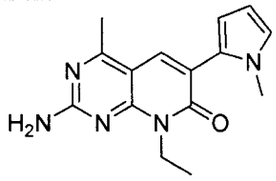
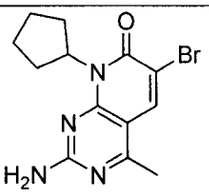
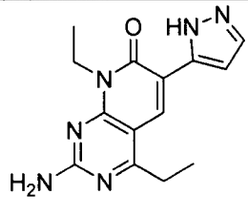
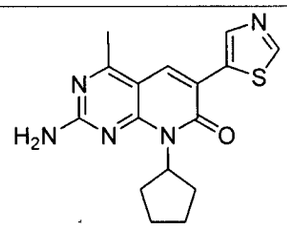
Ejemplo	Estructura	Nombre
85		2-amino-8-etil-4-metil-6-(1-metil-1*H*-pirrol-2-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona
86		2-amino-6-bromo-8-ciclopentil-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona
87		2-amino-4,8-dietil-6-(1*H*-pirazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona
88		2-amino-8-ciclopentil-4-metil-6-(1,3-tiazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona

Tabla 2a.

Inhibidores de AKT representativos

[00215] Los Compuestos de la Tabla 2a se pueden preparar como sales, solvatos, hidratos y/o isómeros farmacéuticamente aceptables de estos. Todas estas combinaciones de sal, solvato, hidrato e isómero de los Compuestos de la Tabla 2a se pueden usar para practicar la invención.

Tabla 2a

Comp No.	*Nombre*
1	3-(azetidin-3-ilidenmetil)-4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
2	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-(3-fluoropiridin-4-il)-1*H*-pirazolo[3,4-d]pirimidina
3	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-(3-cloropiridin-4-il)-1*H*-pirazolo[3,4-d]pirimidina
4	2-({5-cloro-3-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metilfenil}oxi)-*N*,*N*-dimetiletanamina
5	2-({5-cloro-3-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metilfenil}oxi)-*N*,*N*-dietiletanamina
6	4-(4-{5-cloro-2-metil-3-[(2-pirrolidin-1-iletil)oxi]fenil}piperazin-1-il)-3-etil-1*H*-pirazolo[3,4-d]pirimidina
7	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-piperazin-1-il-1*H*-pirazolo[3,4-d]pirimidina
8	*N*-(3-{4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidin-3-il}prop-2-in-1-il)acetamida
9	*N*,*N*-dietil-2-({3-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]fenil}oxi)etanamina
10	3-{3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-cloro-2-metilfenil}-*N*,*N*-dietilpropan-1-amina
11	3-bromo-4-{4-[5-cloro-2-metil-3-(3-pirrolidin-1-ilpropil)fenil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
12	3-bromo-4-(4-{5-cloro-2-metil-3-[(2-pirrolidin-1-iletil)oxi]fenil}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina

Comp No.	*Nombre*
13	2-({3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-cloro-2-metilfenil}oxi)-*N*,*N*-dietiletanamina
14	4-[4-(5-cloro-2-metil-3-{[2-(1-metilpiperidin-4-il)etil]oxi}fenil)piperazin-1-il]-3-etil-1*H*-pirazolo[3,4-d]pirimidina
15	5-cloro-3-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-*N*-(2-pirrolidin-1-iletil)anilina
16	4-(4-{5-cloro-2-metil-3-[(2-morfolin-4-iletil)oxi]fenil}piperazin-1-il)-3-etil-1*H*-pirazolo[3,4-d]pirimidina
17	4-(4-{5-cloro-2-metil-3-[(2-piperidin-1-iletil)oxi]fenil}piperazin-1-il)-3-etil-1*H*-pirazolo[3,4-d]pirimidina
18	3-bromo-4-{4-[5-cloro-2-metil-3-(3-morfolin-4-ilpropil)fenil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
19	3-bromo-4-(4-{5-cloro-2-metil-3-[3-(4-metilpiperazin-1-il)propil]fenil}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
20	3-bromo-4-(4-{5-cloro-2-metil-3-[(2-piperidin-1-iletil)oxi]fenil}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
21	3-bromo-4-(4-{5-cloro-2-metil-3-[(2-morfolin-4-iletil)oxi]fenil}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
22	4-{4-[5-cloro-2-metil-3-(3-morfolin-4-ilpropil)fenil]piperazin-1-il}-3-etil-1*H*-pirazolo[3,4-d]pirimidina

Comp No.	*Nombre*
23	*N*'-{5-cloro-3-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metilfenil}-*N*,*N*-dietiletano-1,2-diamine
24	4-{4-[5-cloro-2-metil-3-(3-piperidin-1-ilpropil)fenil]piperazin-1-il}-3-etil-1*H*-pirazolo[3,4-d]pirimidina
25	4-[4-(5-cloro-3-{[2-(4-etilpiperazin-1-il)etil]oxi}-2-metilfenil)piperazin-1-il]-3-etil-1*H*-pirazolo[3,4-d]pirimidina
26	4-(4-{5-cloro-2-metil-3-[(3-morfolin-4-ilpropil)oxi]fenil}piperazin-1-il)-3-etil-1*H*-pirazolo[3,4-d]pirimidina
27	3-bromo-4-{4-[5-cloro-2-metil-3-(3-piperidin-1-ilpropil)fenil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
28	*N*'-{3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-cloro-2-metilfenil}-*N*,*N*-dietiletano-1,2-diamine
29	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-cloro-2-metil-*N*-(2-pirrolidin-1-iletil)anilina
30	4-[4-(5-cloro-2-metil-3-{[2-(4-metilpiperazin-1-il)etil]oxi}fenil)piperazin-1-il]-3-etil-1*H*-pirazolo[3,4-d]pirimidina
31	4-[4-(5-cloro-2-metil-3-{[(1-metilpiperidin-4-il)metil]oxi}fenil)piperazin-1-il]-3-etil-1*H*-pirazolo[3,4-d]pirimidina
32	*N*,*N*-dietil-2-({3-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metilfenil}oxi)etanamina

Comp No.	*Nombre*
33	2-[(5-cloro-3-{4-[1-(1,1-dimetiletil)-3-(trifluorometil)-1*H*-pirazolo[3,4-d]pirimidin-4-il]piperazin-1-il}-2-metilfenil)oxi]-*N*,*N*-dietiletanamina
34	2-[(5-cloro-2-metil-3-{4-[3-(trifluorometil)-1*H*-pirazolo[3,4-d]pirimidin-4-il]piperazin-1-il}fenil)oxi]-*N*,*N*-dietiletanamina
35	4-(4-{5-cloro-2-metil-3-[(3-pirrolidin-1-ilpropil)oxi]fenil}piperazin-1-il)-3-etil-1*H*-pirazolo[3,4-d]pirimidina
36	4-[4-(5-cloro-2-metil-3-{[3-(4-metilpiperazin-1-il)propil]oxi}fenil)piperazin-1-il]-3-etil-1*H*-pirazolo[3,4-d]pirimidina
37	3-bromo-4-(4-{5-cloro-2-metil-3-[(3-piperidin-1-ilpropil)oxi]fenil}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
38	3-bromo-4-(4-{5-cloro-2-metil-3-[(3-morfolin-4-ilpropil)oxi]fenil}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
39	4-(4-{5-cloro-2-metil-3-[(2-pirrolidin-1-iletil)oxi]fenil}piperazin-1-il)-3-(trifluorometil)-1*H*-pirazolo[3,4-d]pirimidina
40	4-(4-{5-cloro-2-metil-3-[(3-morfolin-4-ilpropil)oxi]fenil}piperazin-1-il)-3-(trifluorometil)-1*H*-pirazolo[3,4-d]pirimidina
41	4-(4-{5-cloro-2-metil-3-[(2-morfolin-4-iletil)oxi]fenil}piperazin-1-il)-3-(trifluorometil)-1*H*-pirazolo[3,4-d]pirimidina
42	4-(4-{5-cloro-2-metil-3-[(3-piperidin-1-ilpropil)oxi]fenil}piperazin-1-il)-3-etil-1*H*-pirazolo[3,4-d]pirimidina

Comp No.	*Nombre*
43	4-[4-(5-cloro-3-{[3-(4-etilpiperazin-1-il)propil]oxi}-2-metilfenil)piperazin-1-il]-3-etil-1*H*-pirazolo[3,4-d]pirimidina
44	5-cloro-2-metil-3-[4-(1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-*N*-(2-pirrolidin-1-iletil)anilina
45	5-cloro-2-metil-3-[4-(3-metil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-*N*-(2-pirrolidin-1-iletil)anilina
46	*N*'-(5-cloro-2-metil-3-{4-[3-(trifluorometil)-1*H*-pirazolo[3,4-d]pirimidin-4-il]piperazin-1-il}fenil)-*N*,*N*-dimetiletano-1,2-diamina
47	3-({5-cloro-3-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metilfenil}oxi)-*N*,*N*-dietilpropan-1-amina
48	*N*'-(5-cloro-2-metil-3-{4-[3-(trifluorometil)-1*H*-pirazolo[3,4-d]pirimidin-4-il]piperazin-1-il}fenil)-*N*,*N*-dietiletano-1,2-diamina
49	5-cloro-2-metil-*N*-(2-pirrolidin-1-iletil)-3-{4-[3-(trifluorometil)-1*H*-pirazolo[3,4-d]pirimidin-4-il]piperazin-1-il}anilina
50	3-bromo-4-(4-{4-metil-3-[(2-pirrolidin-1-iletil)oxi]fenil}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
51	4-(4-{4-metil-3-[(2-pirrolidin-1-iletil)oxi]fenil}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
52	3-metil-4-(4-{4-metil-3-[(2-pirrolidin-1-iletil)oxi]fenil}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina

Comp No.	*Nombre*
53	4-(4-{5-cloro-2-metil-3-[(2-pirrolidin-1-iletil)oxi]fenil}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
54	4-(4-{5-cloro-2-metil-3-[(2-pirrolidin-1-iletil)oxi]fenil}piperazin-1-il)-3-metil-1*H*-pirazolo[3,4-d]pirimidina
55	4-(4-{5-cloro-2-metil-3-[(2-piperidin-1-iletil)oxi]fenil}piperazin-1-il)-3-(trifluorometil)-1*H*-pirazolo[3,4-d]pirimidina
56	3-[(5-cloro-2-metil-3-{4-[3-(trifluorometil)-1*H*-pirazolo[3,4-d]pirimidin-4-il]piperazin-1-il}fenil)oxi]-*N*,*N*-dietilpropan-1-amina
57	5-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-*N*-(2-pirrolidin-1-iletil)anilina
58	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-fluoro-2-metil-*N*-(2-pirrolidin-1-iletil)anilina
59	4-{4-[5-cloro-2-metil-3-(3-pirrolidin-1-ilpropil)fenil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
60	3-bromo-4-{4-[5-fluoro-2-metil-3-(3-pirrolidin-1-ilpropil)fenil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
61	4-{4-[5-cloro-2-metil-3-(3-pirrolidin-1-ilpropil)fenil]piperazin-1-il}-3-(trifluorometil)-1*H*-pirazolo[3,4-d]pirimidina
62	4-(4-{5-cloro-2-metil-3-[3-(4-metilpiperazin-1-il)propil]fenil}piperazin-1-il)-3-etil-1*H*-pirazolo[3,4-d]pirimidina

Comp No.	*Nombre*
63	3-bromo-4-(4-piridin-2-ilpiperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
64	3-bromo-4-[4-(2,4-dimetilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
65	3-bromo-4-{4-[3-(metiloxi)fenil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
66	3-bromo-4-{4-[2-(metiloxi)fenil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
67	3-bromo-4-{4-[4-metil-3-(3-pirrolidin-1-ilpropil)fenil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
68	4-(4-{5-cloro-2-metil-3-[(3-pirrolidin-1-ilpropil)oxi]fenil}piperazin-1-il)-3-(trifluorometil)-1*H*-pirazolo[3,4-d]pirimidina
69	4-(4-{5-cloro-2-metil-3-[(3-piperidin-1-ilpropil)oxi]fenil}piperazin-1-il)-3-(trifluorometil)-1*H*-pirazolo[3,4-d]pirimidina
70	4-[4-(5-cloro-2-metil-3-{[3-(4-metilpiperazin-1-il)propil]oxi}fenil)piperazin-1-il]-3-(trifluorometil)-1*H*-pirazolo[3,4-d]pirimidina
71	4-[4-(5-cloro-3-{[3-(4-etilpiperazin-1-il)propil]oxi}-2-metilfenil)piperazin-1-il]-3-(trifluorometil)-1*H*-pirazolo[3,4-d]pirimidina
72	3-bromo-4-[4-(5-cloro-2-metil-3-{[2-(4-metilpiperazin-1-il)etil]oxi}fenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
73	4-[4-(5-cloro-2-metil-3-{[2-(4-metilpiperazin-1-il)etil]oxi}fenil)piperazin-1-il]-3-(trifluorometil)-1*H*-pirazolo[3,4-d]pirimidina

Comp No.	*Nombre*
74	3-bromo-4-[4-(5-cloro-3-{[2-(4-etilpiperazin-1-il)etil]oxi}-2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
75	3-bromo-4-[4-(3,4-diclorofenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
76	3-bromo-4-[4-(3,4-difluorofenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
77	3-bromo-4-[4-(2,4-diclorofenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
78	3-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-fluoro-2-metil-*N*-(2-pirrolidin-1-iletil)anilina
79	5-fluoro-2-metil-*N*-(2-pirrolidin-1-iletil)-3-{4-[3-(trifluorometil)-1*H*-pirazolo[3,4-d]pirimidin-4-il]piperazin-1-il}anilina
80	4-{4-[3,5-bis(metiloxi)fenil]piperazin-1-il}-3-bromo-1*H*-pirazolo[3,4-d]pirimidina
81	4-[4-(5-cloro-3-{[2-(4-etilpiperazin-1-il)etil]oxi}-2-metilfenil)piperazin-1-il]-3-(trifluorometil)-1*H*-pirazolo[3,4-d]pirimidina
82	*N*-{5-cloro-3-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metilfenil}-*N*,*N*',*N*'-trimetiletano-1,2-diamina
83	3-({3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-cloro-2-metilfenil}oxi)-*N*,*N*-dietilpropan-1-amina
84	3-bromo-4-(4-{5-cloro-2-metil-3-[(3-pirrolidin-1-ilpropil)oxi]fenil}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina

Comp No.	*Nombre*
85	3-bromo-4-[4-(5-cloro-2-metil-3-{[3-(4-metilpiperazin-1-il)propil]oxi}fenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
86	3-bromo-4-[4-(5-cloro-3-{[3-(4-etilpiperazin-1-il)propil]oxi}-2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
87	3-(5-cloro-2-metil-3-{4-[3-(trifluorometil)-1*H*-pirazolo[3,4-d]pirimidin-4-il]piperazin-1-il}fenil)-*N*,*N*-dietilpropan-1-amina
88	3-bromo-4-[4-(5-cloro-2-metil-3-{[(1-metilpiperidin-4-il)metil]oxi}fenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
89	3-bromo-4-[4-(5-cloro-2-metil-3-{[2-(1-metilpiperidin-4-il)etil]oxi}fenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
90	4-[4-(5-cloro-2-metil-3-{[(1-metilpiperidin-4-il)metil]oxi}fenil)piperazin-1-il]-3-(trifluorometil)-1*H*-pirazolo[3,4-d]pirimidina
91	4-[4-(5-cloro-2-metil-3-{[2-(1-metilpiperidin-4-il)etil]oxi}fenil)piperazin-1-il]-3-(trifluorometil)-1*H*-pirazolo[3,4-d]pirimidina
92	4-(4-{5-cloro-2-metil-3-[3-(4-metilpiperazin-1-il)propil]fenil}piperazin-1-il)-3-(trifluorometil)-1*H*-pirazolo[3,4-d]pirimidina
93	3-bromo-4-[4-(3-cloro-4-fluorofenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
94	1-{4-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]fenil}etanona
95	3-bromo-4-[4-(2,5-diclorofenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina

Comp No.	*Nombre*
96	3-bromo-4-[4-(3,4-dimetilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
97	3-bromo-4-[4-(4-nitrofenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
98	3-etil-4-(4-fenilpiperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
99	3-etil-4-{4-[3-(metiloxi)fenil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
100	4-{4-[5-cloro-2-metil-3-(3-piperidin-1-ilpropil)fenil]piperazin-1-il}-3-(trifluorometil)-1*H*-pirazolo[3,4-d]pirimidina
101	4-[4-(3,6-dimetilpirazin-2-il)piperazin-1-il]-3-etil-1*H*-pirazolo[3,4-d]pirimidina
102	1-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]isoquinolina
103	3-bromo-4-[4-(2,6-dimetilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
104	3-bromo-4-{4-[4-(etiloxi)fenil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
105	3-bromo-4-[4-(2-etilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
106	4-{4-[2,4-bis(metiloxi)fenil]piperazin-1-il}-3-bromo-1*H*-pirazolo[3,4-d]pirimidina
107	3-bromo-4-(4-pirazin-2-ilpiperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
108	3-bromo-4-(4-pirimidin-2-ilpiperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
109	4-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-(trifluorometil)quinolina
110	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]pirazino-2-carbonitrilo

Comp No.	*Nombre*
111	4-[4-(4,6-dimetilpirimidin-2-il)piperazin-1-il]-3-etil-1*H*-pirazolo[3,4-d]pirimidina
112	4-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-(trifluorometil)pirimidino-5-carboxilato de etilo
113	4-{4-[3-cloro-5-(metiloxi)fenil]piperazin-1-il}-3-etil-1*H*-pirazolo[3,4-d]pirimidina
114	4-[4-(3-bromo-2-cloro-5-fluorofenil)piperazin-1-il]-3-etil-1*H*-pirazolo[3,4-d]pirimidina
115	2-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]piridino-3-carboxamida
116	3-etil-4-{4-[4-(trifluorometil)piridin-2-il]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
117	3-bromo-4-{4-[4-(trifluorometil)piridin-2-il]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
118	3-bromo-4-{4-[4-(trifluorometil)pirimidin-2-il]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
119	2-({3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]pirazin-2-il}oxi)-*N*,*N*-dimetiletanamina
120	4-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metilquinolina
121	3-bromo-4-[4-(2-nitrofenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
122	2-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]benzonitrilo
123	4-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]benzonitrilo
124	3-bromo-4-{4-[4-(trifluorometil)fenil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina

Comp No.	*Nombre*
125	3-bromo-4-(4-{4-[(fenilmetil)oxi]fenil}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
126	4-{4-[5-cloro-2-metil-3-(metiloxi)fenil]piperazin-1-il}-3-etil-1*H*-pirazolo[3,4-d]pirimidina
127	2-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]piridino-3-carbonitrilo
128	3-bromo-4-[4-(3,5-diclorofenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
129	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-cloro-5-fluoro-*N*-(2-pirrolidin-1-iletil)anilina
130	2-cloro-3-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-fluoro-*N*-(2-pirrolidin-1-iletil)anilina
131	3-bromo-4-[4-(2,5-difluorofenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
132	4-[4-(2,5-difluorofenil)piperazin-1-il]-3-etil-1*H*-pirazolo[3,4-d]pirimidina
133	3-bromo-4-{4-[3-(metiloxi)pirazin-2-il]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
134	3-bromo-4-[4-(3-clorofenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
135	3-bromo-4-{4-[3-(trifluorometil)piridin-2-il]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
136	3-bromo-4-{4-[3-cloro-5-(trifluorometil)piridin-2-il]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
137	4-(4-{5-cloro-2-metil-3-[(2-pirrolidin-1-iletil)oxi]fenil}piperazin-1-il)-3-(1-metiletil)-1*H*-pirazolo[3,4-d]pirimidina

Comp No.	*Nombre*
138	5-cloro-2-metil-3-{4-[3-(1-metiletil)-1*H*-pirazolo[3,4-d]pirimidin-4-il]piperazin-1-il}-*N*-(2-pirrolidin-1-iletil)anilina
139	2-({3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]fenil}oxi)-*N*-etilacetamida
140	2-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-*N*,*N*-dietilpirimidin-4-amina
141	3-bromo-4-[4-(3-{[(3-metilfenil)metil]oxi}fenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
142	3-bromo-4-(4-{3-[(2-piperidin-1-iletil)oxi]fenil}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
143	3-bromo-4-[4-(4-furan-2-ilpirimidin-2-il)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
144	6-{2-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]pirimidin-4-il}-2*H*-1,4-benzoxazin-3(4*H*)-one
145	3-etil-4-{4-[2-metil-3-(metiloxi)fenil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
146	*N*'-{5-cloro-3-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metilfenil}-*N*-metil-*N*-(1-metiletil)etano-1,2-diamina
147	*N*'-{5-cloro-3-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metilfenil}-*N*-etil-*N*-metiletano-1,2-diamina
148	*N*'-{3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-cloro-2-metilfenil}-*N*,*N*-dimetiletano-1,2-diamina

Comp No.	*Nombre*
149	3-({6-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-cloro-5-metilpirimidin-4-il}oxi)-*N*,*N*-dietilpropan-1-amina
150	3-bromo-4-[4-(2,3-diclorofenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
151	3-bromo-4-{4-[2-(trifluorometil)fenil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
152	3-bromo-4-(4-fenilpiperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
153	3-bromo-4-[4-(4-fluorofenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
154	3-bromo-4-[4-(4-clorofenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
155	3-bromo-4-{4-[3-(trifluorometil)fenil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
156	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidin-6-amina
157	3-bromo-4-[4-(4-bromofenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
158	3-bromo-4-[3-metil-4-(3-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
159	4-[4-(3-bromo-5-cloro-2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidin-6-amina
160	4-(4-{5-cloro-2-metil-3-[(2-pirrolidin-1-iletil)oxi]fenil}piperazin-1-il)-3-ciclopropil-1*H*-pirazolo[3,4-d]pirimidina
161	5-cloro-3-[4-(3-ciclopropil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-*N*-(2-pirrolidin-1-iletil)anilina

Comp No.	*Nombre*
162	5-cloro-2-metil-3-{4-[3-(2-metilpropil)-1*H*-pirazolo[3,4-d]pirimidin-4-il]piperazin-1-il}-*N*-(2-pirrolidin-1-iletil)anilina
163	4-(4-{5-cloro-2-metil-3-[(2-pirrolidin-1-iletil)oxi]fenil}piperazin-1-il)-3-(2-metilpropil)-1*H*-pirazolo[3,4-d]pirimidina
164	3-bromo-4-[(3S)-4-(5-cloro-2-metilfenil)-3-metilpiperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
165	5-bromo-3-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metilanilina
166	2-({3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]fenil}oxi)-*N*-ciclopropilacetamida
167	3-bromo-4-(4-{3-[(2-piperidin-1-iletil)oxi]pirazin-2-il}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
168	4-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-6,7-bis(metiloxi)quinazoline
169	2-({3-cloro-5-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]fenil}oxi)-*N*,*N*-dietiletanamina
170	4-{4-[2-cloro-5-(trifluorometil)fenil]piperazin-1-il}-3-etil-1*H*-pirazolo[3,4-d]pirimidina
171	3-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-5-[(2-metilpropil)oxi]-*N*-(2-pirrolidin-1-iletil)anilina
172	3-({4-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-6-cloro-5-metilpirimidin-2-il}oxi)-*N*,*N*-dietilpropan-1-amina
173	3-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-5-[(fenilmetil)oxi]-*N*-(2-pirrolidin-1-iletil)anilina
174	3-bromo-4-[(3R)-4-(5-cloro-2-metilfenil)-3-metilpiperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina

Comp No.	*Nombre*
175	3-[(2S)-4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)-2-metilpiperazin-1-il]-4-metil-*N*-fenilbenzamida
176	3-[(2S)-4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)-2-metilpiperazin-1-il]-4-metil-*N*-(fenilmetil)benzamida
177	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-4-metilbenzoato de metilo
178	Ácido 3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-4-metilbenzoico
179	Ácido (2E)-3-(4-{4-[5-cloro-2-metil-3-(3-pirrolidin-1-ilpropil)fenil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidin-3-il)prop-2-enoico
180	3-(4-{4-[5-cloro-2-metil-3-(3-pirrolidin-1-ilpropil)fenil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidin-3-il)prop-2-in-1-ol
181	4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)-1-(5-cloro-2-metilfenil)piperazin-2-ona
182	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-5-[(2-metilpropil)oxi]-*N*-(2-pirrolidin-1-iletil)anilina
183	*N*'-{3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-5-[(2-metilpropil)oxi]fenil}-*N*,*N*-dietiletano-1,2-diamina
184	3-bromo-5-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-4-metilbenzoato de metilo
185	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-4-metil-*N*-fenilbenzamida
186	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-*N*,4-dimetilbenzamida
187	2-({3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]fenil}oxi)-*N*,*N*-dietiletanamina

Comp No.	*Nombre*
188	metil 3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-4-metil-5-[(2-pirrolidin-1-iletil)amino]benzoate
189	3-bromo-5-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-4-metil-*N*-fenilbenzamida
190	3-bromo-5-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-4-metil-*N*-fenilbenzamida
191	*N*'-{3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-cloro-2-metilfenil}-*N*-metil-*N*-(1-metiletil)etano-1,2-diamina
192	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-4-metil-*N*-fenilo-5-[(2-pirrolidin-1-iletil)amino]benzamida
193	*N*'-{3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-5-[(2-metilpropil)oxi]fenil}-*N*,*N*-dimetiletano-1,2-diamina
194	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-*N*,*N*,4-trimetilbenzamida
195	3-[4-(3-cloro-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-4-metil-*N*-(2-metilpropil)benzamida
196	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-*N*,*N*,4-trimetil-5-[(2-pirrolidin-1-iletil)amino]benzamida
197	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)-2-oxopiperazin-1-il]-4-metil-*N*-fenilbenzamida
198	3-[(2R)-4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)-2-(hidroximetil)piperazin-1-il]-4-metil-*N*-fenilbenzamida
199	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-5-(pirrolidin-1-ilcarbonil)-*N*-(2-pirrolidin-1-iletil)anilina

Comp No.	*Nombre*
200	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-*N*,4-dimetil-5-[(2-pirrolidin-1-iletil)amino]benzamida
201	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-*N*-(4-clorofenil)-4-metil-5-[(2-pirrolidin-1-iletil)amino]benzamida
202	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-*N*-(2-clorofenil)-4-metil-5-[(2-pirrolidin-1-iletil)amino]benzamida
203	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-[(ciclopropilmetil)oxi]-2-metil-*N*-(2-pirrolidin-1-iletil)anilina
204	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-5-[(3-metilbutil)oxi]-*N*-(2-pirrolidin-1-iletil)anilina
205	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-[(2-etilbutil)oxi]-2-metil-*N*-(2-pirrolidin-1-iletil)anilina
206	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-(butiloxi)-2-metil-*N*-(2-pirrolidin-1-iletil)anilina
207	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-4-metil-*N*-(1-metiletil)-5-[(2-pirrolidin-1-iletil)amino]benzamida
208	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-*N*,4-dimetil-*N*-(1-metiletil)-5-[(2-pirrolidin-1-iletil)amino]benzamida
209	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-[(ciclobutilmetil)oxi]-2-metil-*N*-(2-pirrolidin-1-iletil)anilina

Comp No.	*Nombre*
210	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-(etiloxi)-2-metil-*N*-(2-pirrolidin-1-iletil)anilina
211	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-*N*-[2-(dimetilamino)etil]-4-metilbenzamida
212	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-*N*-(1,1-dimetiletil)-4-metil-5-[(2-pirrolidin-1-iletil)amino]benzamida
213	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-4-metil-*N*-piridin-3-il-5-[(2-pirrolidin-1-iletil)amino]benzamida
214	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-[(2-fluoro-2-metilpropil)oxi]-2-metil-*N*-(2-pirrolidin-1-iletil)anilina
215	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-[(ciclohexilmetil)oxi]-2-metil-*N*-(2-pirrolidin-1-iletil)anilina
216	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-[(ciclopentilmetil)oxi]-2-metil-*N*-(2-pirrolidin-1-iletil)anilina
217	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-*N*-etil-4-metil-5-[(2-pirrolidin-1-iletil)amino]benzamida
218	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-5-[(1-metiletil)oxi]-*N*-(2-pirrolidin-1-iletil)anilina
219	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-[(2,2-dimetilpropil)oxi]-2-metil-*N*-(2-pirrolidin-1-iletil)anilina

Comp No.	*Nombre*
220	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-*N*-(2-pirrolidin-1-iletil)-5-[(tetrahidrofuran-2-ilmetil)oxi]anilina
221	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-5-{[2-(metiloxi)etil]oxi}-*N*-(2-pirrolidin-1-iletil)anilina
222	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-5-(propiloxi)-*N*-(2-pirrolidin-1-iletil)anilina
223	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-{[2-(dimetilamino)etil]amino}-4-metil-*N*-fenilbenzamida
224	*N*'-{3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-[(2-fluoro-2-metilpropil)oxi]-2-metilfenil}-*N*,*N*-dimetiletano-1,2-diamina
225	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-{[2-(dimetilamino)etil]amino}-4-metil-*N*-(1-metiletil)benzamida
226	1-{3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-4-metil-5-[(2-pirrolidin-1-iletil)amino]fenil}pentan-1-ona
227	*N*'-(3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-{[2,3-difluoro-2-(fluorometil)propil]oxi}-2-metilfenil)-*N*,*N*-dimetiletano-1,2-diamina
228	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-{[2,3-difluoro-2-(fluorometil)propil]oxi}-2-metil-*N*-(2-pirrolidin-1-iletil)anilina
229	5-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-4-metil-*N*-(2-pirrolidin-1-iletil)bifenil-3-amina

Comp No.	*Nombre*
230	1-(3-{5-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-4-metilbifenil-3-il}propil)piridinio
231	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-*N*-(2-pirrolidin-1-iletil)-5-(1,3-tiazol-2-il)anilina
232	Ácido 3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-4-metil-5-[(2-pirrolidin-1-iletil)amino]benzoico
233	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-5-(feniletinil)-*N*-(2-pirrolidin-1-iletil)anilina
234	{3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-4-metil-5-[(2-pirrolidin-1-iletil)amino]fenil}(fenil)metanona
235	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-etinil-2-metil-*N*-(2-pirrolidin-1-iletil)anilina
236	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-(3,3-dimetilbut-1-in-1-il)-2-metil-*N*-(2-pirrolidin-1-iletil)anilina
237	3-bromo-4-{4-[5-{[2,3-difluoro-2-(fluorometil)propil]oxi}-2-metil-3-(3-pirrolidin-1-ilpropil)fenil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
238	3-bromo-4-{4-[2-metil-5-[(2-metilpropil)oxi]-3-(3-pirrolidin-1-ilpropil)fenil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
239	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-5-(3-fenilo-1,2,4-oxadiazol-5-il)-*N*-(2-pirrolidin-1-iletil)anilina

Comp No.	*Nombre*
240	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-5-(3-metil-1,2,4-oxadiazol-5-il)-*N*-(2-pirrolidin-1-iletil)anilina
241	1-{3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-4-metil-5-[(2-pirrolidin-1-iletil)amino]fenil}propan-1-ona
242	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-(3,3-dimetilbutil)-2-metil-*N*-(2-pirrolidin-1-iletil)anilina
243	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-etil-2-metil-*N*-(2-pirrolidin-1-iletil)anilina
244	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-*N*-(2-pirrolidin-1-iletil)-5-[2-(trimetilsilil)etil]anilina
245	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-5-(2-feniletil)-*N*-(2-pirrolidin-1-iletil)anilina
246	1-{3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-4-metil-5-[(2-pirrolidin-1-iletil)amino]fenil}butan-1-ona
247	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-*N*,4-dimetil-*N*-(metiloxi)-5-[(2-pirrolidin-1-iletil)amino]benzamida
248	3-bromo-4-[4-(3-bromo-5-{[2,3-difluoro-2-(fluorometil)propil]oxi}-2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
249	4-[4-(3-bromo-5-{[2,3-difluoro-2-(fluorometil)propil]oxi}-2-metilfenil)piperazin-1-il]-3-etil-1*H*-pirazolo[3,4-d]pirimidina

Comp No.	*Nombre*
250	1-{3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-4-metil-5-[(2-pirrolidin-1-iletil)amino]fenil}etanona
251	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-[(difluorometil)oxi]-2-metil-*N*-(2-pirrolidin-1-iletil)anilina
252	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-{[(difluorometil)oxi]metil}-2-metil-*N*-(2-pirrolidin-1-iletil)anilina
253	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-5-(metiloxi)-*N*-(2-pirrolidin-1-iletil)anilina
254	5-{[2,3-difluoro-2-(fluorometil)propil]oxi}-3-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-*N*-(2-pirrolidin-1-iletil)anilina
255	2-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-3,5,6-trifluoro-*N*-(3-metilbutil)piridin-4-amina
256	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-*N*-[(ciclopropilmetil)oxi]-4-metil-5-[(2-pirrolidin-1-iletil)amino]benzamida
257	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-5-(5-metil-1,2,4-oxadiazol-3-il)-*N*-(2-pirrolidin-1-iletil)anilina
258	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-(etilsulfonil)-2-metil-*N*-(2-pirrolidin-1-iletil)anilina
259	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-5-(metilsulfonil)-*N*-(2-pirrolidin-1-iletil)anilina

Comp No.	*Nombre*
260	1-{3-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-4-metil-5-[(2-pirrolidin-1-iletil)amino]fenil}pentan-1-ona
261	3-bromo-4-[4-(5-{[2,3-difluoro-2-(fluorometil)propil]oxi}-2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
262	6-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-3,5-difluoro-*N*~4~-(3-metilbutil)-*N*~2~-(2-pirrolidin-1-iletil)piridino-2,4-diamina
263	3-bromo-5-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-*N*-(2-pirrolidin-1-iletil)anilina
264	3-bromo-4-[4-(3',4',6-trifluoro-4-metilbifenil-3-il)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
265	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-cloro-*N*-(2-pirrolidin-1-iletil)anilina
266	{3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-4-metil-5-[(2-pirrolidin-1-iletil)amino]fenil}metanol
267	3-bromo-4-(4-{4-metil-2'-[(2-pirrolidin-1-iletil)oxi]bifenil-3-il}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
268	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-{[(2,2-difluorociclopropil)metil]oxi}-2-metil-*N*-(2-pirrolidin-1-iletil)anilina
269	5-bromo-3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-*N*-(2-pirrolidin-1-iletil)anilina

Comp No.	*Nombre*
270	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-[(etiloxi)metil]-2-metil-*N*-(2-pirrolidin-1-iletil)anilina
271	3-[4-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-1-metil-6-(trifluorometil)-1*H*-bencimidazol-2-il]propan-1-ol
272	1-{3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-4-metil-5-[(2-pirrolidin-1-iletil)amino]fenil}-4,4,4-trifluorobutan-1-ona
273	{3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-4-metil-5-[(2-pirrolidin-1-iletil)amino]fenil}(ciclopropil)metanona
274	3-({3'-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-4'-metilbifenil-2-il}oxi)-*N*,*N*-dimetilpropan-1-amina
275	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-(1,1-difluorobutil)-2-metil-*N*-(2-pirrolidin-1-iletil)anilina
276	3-bromo-4-(4-{4-metil-2'-[(3-morfolin-4-ilpropil)oxi]bifenil-3-il}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
277	3-bromo-4-(4-{4-metil-2'-[(2-morfolin-4-iletil)oxi]bifenil-3-il}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
278	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-*N*-(2-pirrolidin-1-iletil)-5-{[(2,2,2-trifluoroetil)oxi]metil}anilina
279	1-[2-({3'-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-4'-metilbifenil-2-il}oxi)etil]pirrolidine-2,5-diona

Comp No.	*Nombre*
280	3-bromo-4-(4-{3'-fluoro-4-metil-2'-[(2-pirrolidin-1-iletil)oxi]bifenil-3-il}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
281	1-{3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-[(2-pirrolidin-1-iletil)amino]fenil}butan-1-ona
282	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-*N*-(2-pirrolidin-1-iletil)-5-[(3,3,3-trifluoropropil)oxi]anilina
283	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-*N*-(2-pirrolidin-1-iletil)-5-[(2,2,2-trifluoroetil)oxi]anilina
284	1-{3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-4-metil-5-[(2-pirrolidin-1-iletil)amino]fenil}butan-1-ol
285	3-bromo-4-(4-{4-cloro-2'-[(2-pirrolidin-1-iletil)oxi]bifenil-3-il}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
286	3-[4-(4-{5-{[2,3-difluoro-2-(fluorometil)propil]oxi}-2-metil-3-[(2-pirrolidin-1-iletil)amino]fenil}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidin-3-il]prop-2-in-1-ol
287	3-bromo-4-(4-{4-cloro-4'-fluoro-2'-[(2-pirrolidin-1-iletil)oxi]bifenil-3-il}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
288	3-bromo-4-(4-{4-metil-3'-[(2-pirrolidin-1-iletil)oxi]bifenil-3-il}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
289	Ácido (2E)-3-[4-(4-{5-{[2,3-difluoro-2-(fluorometil)propil]oxi}-2-metil-3-[(2-pirrolidin-1-iletil)amino]fenil}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidin-3-il]prop-2-enoico

Comp No.	*Nombre*
290	3-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metil-*N*-(2-pirrolidin-1-iletil)-5-[4,4,4-trifluoro-1,1-bis(metiloxi)butil]anilina
291	6-(4-fenilpiperazin-1-il)-9*H*-purina
292	6-[4-(3-clorofenil)piperazin-1-il]-9*H*-purina
293	4-(4-fenilpiperazin-1-il)-7*H*-pirrolo[2,3-d]pirimidina
294	4-[4-(3-clorofenil)piperazin-1-il]-7*H*-pirrolo[2,3-d]pirimidina
295	4-(4-fenilpiperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
296	4-[4-(3-clorofenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
297	6-[4-(2-clorofenil)piperazin-1-il]-9*H*-purina
298	6-[4-(2-fluorofenil)piperazin-1-il]-9*H*-purina
299	4-[4-(2-metilfenil)piperazin-1-il]-7*H*-pirrolo[2,3-d]pirimidina
300	4-{4-[2-(metiloxi)fenil]piperazin-1-il}-7*H*-pirrolo[2,3-d]pirimidina
301	4-{4-[3-(metiloxi)fenil]piperazin-1-il}-7*H*-pirrolo[2,3-d]pirimidina
302	4-{4-[4-(metiloxi)fenil]piperazin-1-il}-7*H*-pirrolo[2,3-d]pirimidina
303	4-{4-[3-(trifluorometil)fenil]piperazin-1-il}-7*H*-pirrolo[2,3-d]pirimidina
304	6-{4-[4-(metiloxi)fenil]piperazin-1-il}-9*H*-purina
305	6-{4-[2-(metiloxi)fenil]piperazin-1-il}-9*H*-purina
306	6-[4-(4-clorofenil)piperazin-1-il]-9*H*-purina
307	6-[4-(4-fluorofenil)piperazin-1-il]-9*H*-purina
308	4-[4-(4-clorofenil)piperazin-1-il]-7*H*-pirrolo[2,3-d]pirimidina

Comp No.	*Nombre*
309	4-[4-(2-clorofenil)piperazin-1-il]-7*H*-pirrolo[2,3-d]pirimidina
310	4-[4-(4-fluorofenil)piperazin-1-il]-7*H*-pirrolo[2,3-d]pirimidina
311	4-[4-(2-fluorofenil)piperazin-1-il]-7*H*-pirrolo[2,3-d]pirimidina
312	6-{4-[3-(trifluorometil)fenil]piperazin-1-il}-9*H*-purina
313	6-[4-(2-metilfenil)piperazin-1-il]-9*H*-purina
314	4-{4-[3-(trifluorometil)fenil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
315	4-[4-(2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
316	4-[4-(3-clorofenil)piperazin-1-il]-3-metil-1*H*-pirazolo[3,4-d]pirimidina
317	3-metil-4-[4-(2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
318	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
319	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-metil-1*H*-pirazolo[3,4-d]pirimidina
320	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-metil-6-fenilo-1*H*-pirazolo[3,4-d]pirimidina
321	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-etil-1*H*-pirazolo[3,4-d]pirimidina
322	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-6-metil-1*H*-pirazolo[3,4-d]pirimidina
323	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-6-etil-1*H*-pirazolo[3,4-d]pirimidina
324	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-6-(1-metiletil)-1*H*-pirazolo[3,4-d]pirimidina

Comp No.	*Nombre*
325	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-fenilo-1*H*-pirazolo[3,4-d]pirimidina
326	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-({[2-(metiloxi)etil]oxi}metil)-1*H*-pirazolo[3,4-d]pirimidina
327	3-bromo-4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
328	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-propil-1*H*-pirazolo[3,4-d]pirimidina
329	4-{4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidin-3-il}fenol
330	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-*N*-fenilo-1*H*-pirazolo[3,4-d]pirimidin-3-amina
331	4-[4-(3-clorofenil)piperazin-1-il]-3-etil-1*H*-pirazolo[3,4-d]pirimidina
332	4-{4-[5-cloro-2-(metiloxi)fenil]piperazin-1-il}-3-etil-1*H*-pirazolo[3,4-d]pirimidina
333	3-{4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidin-3-il}fenol
334	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-{3-[(fenilmetil)oxi]fenil}-1*H*-pirazolo[3,4-d]pirimidina
335	3-(1,3-benzodioxol-5-il)-4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
336	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-(2-tienil)-1*H*-pirazolo[3,4-d]pirimidina
337	3-{4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidin-3-il}anilina
338	Ácido 3-{4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidin-3-il}benzoico
339	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-(4-metilfenil)-1*H*-pirazolo[3,4-d]pirimidina

Comp No.	*Nombre*
340	*N*-(4-{4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidin-3-il}fenil)acetamida
341	4-[4-(3-clorofenil)-1,4-diazepan-1-il]-3-etil-1*H*-pirazolo[3,4-d]pirimidina
342	4-[5-(3-clorofenil)-2,5-diazabiciclo[2,2,1]hept-2-il]-3-etil-1*H*-pirazolo[3,4-d]pirimidina
343	4-(4-{3-cloro-4-[(2-morfolin-4-iletil)oxi]fenil}piperazin-1-il)-3-etil-1*H*-pirazolo[3,4-d]pirimidina
344	1-(3-clorofenil)-4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazine-2-carboxilato de metilo
345	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-(3-metilbut-2-en-1-il)-1*H*-pirazolo[3,4-d]pirimidina
346	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-(trifluorometil)-1*H*-pirazolo[3,4-d]pirimidina
347	4-(3-clorofenil)-1-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazino-2- carboxilato de metilo
348	4-(4-{3-cloro-4-[(2-piperidin-1-iletil)oxi]fenil}piperazin-1-il)-3-etil-1*H*-pirazolo[3,4-d]pirimidina
349	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-(1-metiletil)-1*H*-pirazolo[3,4-d]pirimidina
350	Ácido 1-(3-clorofenil)-4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazino-2-carboxílico
351	1-(3-clorofenil)-4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)-*N*-metilpiperazino-2-carboxamida
352	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-(fenilmetil)-1*H*-pirazolo[3,4-d]pirimidina
353	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-(2-metilpropil)-1*H*-pirazolo[3,4-d]pirimidina

Comp No.	*Nombre*
354	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-[4-(metiloxi)fenil]-1*H*-pirazolo[3,4-d]pirimidina
355	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-(4-fluorofenil)-1*H*-pirazolo[3,4-d]pirimidina
356	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-[4-(feniloxi)fenil]-1*H*-pirazolo[3,4-d]pirimidina
357	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-{4-[(piperidin-4-ilmetil)oxi]fenil}-1*H*-pirazolo[3,4-d]pirimidina
358	1-(3-clorofenil)-*N*-[2-(dimetilamino)etil]-4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazino-2-carboxamida
359	4-[4-(5-cloro-2-metil-3-morfolin-4-ilfenil)piperazin-1-il]-3-etil-1*H*-pirazolo[3,4-d]pirimidina
360	4-(3-clorofenil)-1-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)-*N*-metilpiperazino-2-carboxamida
361	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-[2-(metiloxi)fenil]-1*H*-pirazolo[3,4-d]pirimidina
362	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-piridin-4-il-1*H*-pirazolo[3,4-d]pirimidina
363	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-[3-(metiloxi)fenil]-1*H*-pirazolo[3,4-d]pirimidina
364	4-{4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidin-3-il}benzonitrilo
365	[5-cloro-3-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-(metiloxi)fenil]metanol
366	5-cloro-3-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-(metiloxi)benzoato de metilo
367	Ácido (2E)-3-{4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidin-3-il}prop-2-enoico
368	Ácido 3-{4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidin-3-il}propanoico

Comp No.	*Nombre*
369	3-{4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidin-3-il}propan-1-ol
370	metil (2E)-3-{4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidin-3-il}prop-2-enoate
371	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-{4-[(2-morfolin-4-iletil)oxi]fenil}-1*H*-pirazolo[3,4-d]pirimidina
372	5-cloro-*N*-[2-(dimetilamino)etil]-3-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-(metiloxi)benzamida
373	4-(4-{5-cloro-2-(metiloxi)-3-[(4-metilpiperazin-1-il)carbonil]fenil}piperazin-1-il)-3-etil-1*H*-pirazolo[3,4-d]pirimidina
374	5-cloro-3-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-(metiloxi)benzoato de 2-(dimetilamino)etilo
375	1-[5-cloro-3-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-(metiloxi)fenil]-*N*,*N*-dimetilmetanamina
376	*N*'-{[5-cloro-3-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-(metiloxi)fenil]metil}-*N*,*N*-dimetiletano-1,2-diamina
377	[1-(3-clorofenil)-4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-2-il]metanol
378	3-[(4-{4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidin-3-il}fenil)oxi]-*N*,*N*-dimetilpropan-1-amina
379	2-cloro-4-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-metilfenol
380	1-(3-clorofenil)-4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)-*N*-(1-metilpiperidin-4-il)piperazino-2-carboxamida

Comp No.	*Nombre*
381	1-(3-clorofenil)-4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)-*N*-(2-morfolin-4-iletil)piperazino-2-carboxamida
382	2-{[5-cloro-3-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-(metiloxi)fenil]oxi}-*N*,*N*-dimetiletanamina
383	3-{5-cloro-3-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metilfenil}-*N*,*N*-dimetilprop-2-in-1-amina
384	*N*'-{5-cloro-3-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metilfenil}-*N*,*N*-dimetiletano-1,2-diamina
385	(2E)-3-{4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidin-3-il}prop-2-enoato de 1,1-dimetiletilo
386	3-({2-cloro-4-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-metilfenil}oxi)-*N*,*N*-dimetilpropan-1-amina
387	2-({2-cloro-4-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-5-metilfenil}oxi)-*N*,*N*-dimetiletanamina
388	4-{4-[5-cloro-2-metil-4-(metiloxi)fenil]piperazin-1-il}-3-etil-1*H*-pirazolo[3,4-d]pirimidina
389	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-(4-metilpiperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
390	3-{4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidin-3-il}-*N*,*N*-dietilprop-2-in-1-amina
391	3-{4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidin-3-il}prop-2-in-1-ol
392	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-(piperidin-4-ilmetil)-1*H*-pirazolo[3,4-d]pirimidina

Comp No.	*Nombre*
393	(3aR,6aS)-5-({4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidin-3-il}metiliden)hexahidrociclopenta[c]pirrol-2(1*H*)-carboxilato de fenilmetilo
394	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-[(E)-(3aR,6aS)-hexahidrociclopenta[c]pirrol-5(1*H*)-ilidenmetil]-1*H*-pirazolo[3,4-d]pirimidina
395	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-(3-pirrolidin-1-ilprop-1-in-1-il)-1*H*-pirazolo[3,4-d]pirimidina
396	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-[3-(4-metilpiperazin-1-il)prop-1-in-1-il]-1*H*-pirazolo[3,4-d]pirimidina
397	3-{4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidin-3-il}-*N*,*N*-dietilpropan-1-amina
398	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-(3-pirrolidin-1-ilpropil)-1*H*-pirazolo[3,4-d]pirimidina
399	4-[4-(5-cloro-2-metilfenil)piperazin-1-il]-3-(1,2,3,6-tetrahidropiridin-4-il)-1*H*-pirazolo[3,4-d]pirimidina
400	3-{5-cloro-3-[4-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-metilfenil}-*N*,*N*-dietilpropan-1-amina
401	4-{4-[5-cloro-2-metil-3-(3-pirrolidin-1-ilpropil)fenil]piperazin-1-il}-3-etil-1*H*-pirazolo[3,4-d]pirimidina

Tabla 2b.

Inhibidores representativos de AKT adicionales

[00216] Los Compuestos de la Tabla 2b se pueden preparar como sales, solvatos, hidratos y/o isómeros farmacéuticamente aceptables de estos. Todas las

combinaciones de sales, solvatos, hidratos e isómeros de los Compuestos de la Tabla 2b se pueden usar para practicar la la invención.

Entrada	Nombre
1	[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il](4-clorofenil)metanol
2	2-{[[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il](4-clorofenil)metil]oxi}-*N*,*N*-dimetiletanamina
3	3-{[[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il](4-clorofenil)metil]oxi}-*N*,*N*-dimetilpropan-1-amina
4	3-bromo-4-{4-[(4-bromofenil)metil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
5	{4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)-1-[(4-clorofenil)metil]piperazin-2-il}metanol
6	*N*'-[[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il](4-clorofenil)metil]-*N*,*N*-dietiletano-1,2-diamina
7	3-bromo-4-(4-{[4-(1,1-dimetiletil)fenil]metil}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
8	4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)-1-[(4-clorofenil)metil]piperazin-2-ona
9	2-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-2-(4-clorofenil)-*N*-[2-(dimetilamino)etil]acetamida
10	*N*-[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il]-*N*-(4-clorofenil)-*N*',*N*'-dietilpropane-1,3-diamina
11	3-bromo-4-(4-{[4-(trifluorometil)fenil]metil}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina

Entrada	Nombre
12	*N*-[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il]-*N*-(4-clorofenil)-*N*'-[2-(dimetilamino)etil]urea
13	*N*-[[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il](4-clorofenil)metil]-*N*'-[2-(dimetilamino)etil]urea
14	2-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)-2-oxopiperazin-1-il]-2-(4-clorofenil)-*N*-[2-(dimetilamino)etil]acetamida
15	2-(dimetilamino)etil [1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il](4-clorofenil)carbamate
16	3-bromo-4-{4-[(4-cloro-3-fluorofenil)metil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
17	3-bromo-4-{4-[(4-cloro-2-fluorofenil)metil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
18	*N*-[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il]-*N*-(4-clorofenil)-*N*',*N*'-dietiletano-1,2-diamina
19	3-bromo-4-{4-[(4-clorofenil)metil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
20	[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il](4-fluorofenil)metanona
21	*N*-[[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il](4-clorofenil)metil]-*N*',*N*'-dietil-*N*-metiletano-1,2-diamina
22	[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il](4-fluorofenil)metanol
23	3-bromo-4-(4-{[2-fluoro-4-(trifluorometil)fenil]metil}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina

Entrada	Nombre
24	*N*-[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il]-*N*-(4-clorofenil)-*N*~3~,*N*~3~-dietil-beta-alaninamida
25	2-{[[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il](4-fluorofenil)metil]oxi}-*N*,*N*-dimetiletanamina
26	*N*-[[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il](4-clorofenil)metil]-*N*~3~,*N*~3~-dietil-beta-alaninamida
27	3-bromo-4-{4-[(3,4-diclorofenil)metil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
28	*N*-[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il]-*N*-(4-clorofenil)-*N*'-[2-(dimetilamino)etil]etandiamida
29	*N*-[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il]-*N*-(4-clorofenil)-2-(dietilamino)etansulfonamida
30	4-[4-(bifenil-4-ilmetil)piperazin-1-il]-3-bromo-1*H*-pirazolo[3,4-d]pirimidina
31	3-bromo-4-{(3S)-4-[(4-clorofenil)metil]-3-metilpiperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
32	3-bromo-4-(4-{[4-(metiloxi)fenil]metil}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
33	4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)-*N*-[3-(trifluorometil)fenil]piperazino-1-carboxamida
34	3-bromo-4-{4-[(4-fluorofenil)metil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
35	*N*-[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il]-*N*-(4-clorofenil)pent-4-enamida
36	3-bromo-4-[4-(2,3-dihidro-1,4-benzodioxin-6-ilmetil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
37	4-[4-(1,3-benzodioxol-5-ilmetil)piperazin-1-il]-3-bromo-1*H*-pirazolo[3,4-d]pirimidina

Entrada	Nombre
38	[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il](4-clorofenil)metanona
39	3-bromo-4-(4-{[4-(feniloxi)fenil]metil}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
40	3-bromo-4-{4-[(3,4-diclorofenil)metil]piperidin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
41	4-{[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]metil}-*N*,*N*-dimetilanilina
42	4-{[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]metil}benzoato de metilo
43	3-bromo-4-{4-[(2E)-3-fenilprop-2-enoil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
44	1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)-4-[(4-clorofenil)metil]-*N*-[3-(dietilamino)propil]piperidino-4-carboxamida
45	3-bromo-4-{4-[(2-bromofenil)metil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
46	3-bromo-4-{4-[(2-clorofenil)metil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
47	3-bromo-4-{4-[(2,4-diclorofenil)metil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
48	3-bromo-4-{4-[(2-cloro-4-fluorofenil)metil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
49	1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)-4-(4-clorofenil)-*N*-[3-(dietilamino)propil]piperidino-4-carboxamida
50	3-bromo-4-[4-(fenilmetil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
51	2-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-*N*-piridin-2-ilacetamida
52	3-bromo-4-[4-(1*H*-imidazol-2-ilmetil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
53	3-bromo-4-(4-{[3-(feniloxi)fenil]metil}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina

Entrada	Nombre
54	3-bromo-4-{4-[(3-metilfenil)metil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
55	3-{[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]metil}benzonitrilo
56	3-bromo-4-{4-[(2-cloro-6-fluorofenil)metil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
57	3-bromo-4-[4-(1-feniletil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
58	3-bromo-4-[4-(piridin-4-ilmetil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
59	1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)-*N*-(4-clorofenil)piperidin-4-amina
60	3-bromo-4-[4-(piridin-3-ilmetil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
61	3-bromo-4-(4-{[2,3,4-tris(metiloxi)fenil]metil}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
62	3-bromo-4-[4-({3-[(fenilmetil)oxi]fenil}metil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
63	3-bromo-4-[4-(naftalen-1-ilmetil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
64	3-bromo-4-(4-{[5-(4-clorofenil)furan-2-il]metil}piperazin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
65	3-bromo-4-[4-({4-[(4-fluorofenil)oxi]-3-nitrofenil}metil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
66	3-bromo-4-[4-(furan-2-ilcarbonil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
67	3-bromo-4-[4-(1*H*-indol-6-ilcarbonil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
68	3-bromo-4-{4-[2-(2-tienil)etil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina

Entrada	Nombre
69	3-bromo-4-[4-(3-pirrolidin-1-ilpropil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
70	3-bromo-4-[4-(ciclohexilmetil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
71	3-bromo-4-{4-[(10-cloroanthracen-9-il)metil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
72	3-bromo-4-[4-(1-metilpropil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
73	4-(4-{[4,6-bis(metiloxi)pirimidin-2-il]metil}piperazin-1-il)-3-bromo-1*H*-pirazolo[3,4-d]pirimidina
74	3-bromo-4-{4-[2-(metiloxi)etil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
75	3-bromo-4-[4-(2-morfolin-4-il-2-oxoetil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
76	3-bromo-4-{4-[3-(metiloxi)propil]piperazin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
77	4-{4-[[4,6-bis(metiloxi)pirimidin-2-il](fenil)metil]piperazin-1-il}-3-bromo-1*H*-pirazolo[3,4-d]pirimidina
78	3-bromo-4-[4-(6,7,8,9-tetrahidro-5*H*-benzociclohepten-5-il)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
79	3-bromo-4-[4-({4-[(fenilmetil)oxi]fenil}metil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
80	3-bromo-4-[4-({3-cloro-4-[(fenilmetil)oxi]fenil}metil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
81	4-{[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]metil}-*N*-(3-morfolin-4-ilpropil)benzamida
82	4-{[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]metil}-*N*-[3-(metiloxi)propil]benzamida

Entrada	Nombre
83	2-[({4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)-1-[(4-clorofenil)metil]piperazin-2-il}metil)oxi]-*N*,*N*-dimetiletanamina
84	3-bromo-4-[4-({4-[(4-clorofenil)oxi]-3-nitrofenil}metil)piperazin-1-il]-1*H*-pirazolo[3,4-d]pirimidina
85	2-[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il]-*N*,*N*-dimetilacetamida
86	2-{[(R)-[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il](4-clorofenil)metil]oxi}-*N*,*N*-dimetiletanamina
87	*N*-(4-bromo-3-fluorofenil)-*N*-[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il]-*N*'-[2-(dimetilamino)etil]urea
88	2-({(R)-(4-clorofenil)[1-(3-etil-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il]metil}oxi)-*N*,*N*-dimetiletanamina
89	2-{[(S)-[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il](4-clorofenil)metil]oxi}-*N*,*N*-dimetiletanamina
90	3-bromo-4-(4-{(R)-(4-clorofenil)[(2-pirrolidin-1-iletil)oxi]metil}piperidin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
91	1-[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il]-1-(4-clorofenil)-4-(dimetilamino)butan-1-ol
92	2-{[(R)-[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il](4-cloro-3-fluorofenil)metil]oxi}-*N*,*N*-dimetiletanamina
93	3-bromo-4-(4-{(R)-(4-clorofenil)[(2-piperidin-1-iletil)oxi]metil}piperidin-1-il)-1*H*-pirazolo[3,4-d]pirimidina

Entrada	Nombre
94	4-[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il]-4-(4-clorofenil)-*N*,*N*-dimetilbutan-1-amina
95	3-bromo-4-(4-{(R)-(4-clorofenil)[(2-morfolin-4-iletil)oxi]metil}piperidin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
96	1-[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il]-1-(4-fluorofenil)-*N*-(furan-2-ilmetil)-*N*-metilmetanamina
97	1-[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il]-1-(4-fluorofenil)-*N*-metil-*N*-(piridin-2-ilmetil)metanamina
98	4-{{{[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il](4-fluorofenil)metil}(metil)amino]metil}-*N*,*N*-dimetilanilina
99	[4-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperazin-1-il](1*H*-indol-6-il)metanol
100	3-bromo-4-(4-{(R)-(4-cloro-3-fluorofenil)[(2-pirrolidin-1-iletil)oxi]metil}piperidin-1-il)-1*H*-pirazolo[3,4-d]pirimidina
101	3-bromo-4-{4-[(4-clorofenil)oxi]piperidin-1-il}-1*H*-pirazolo[3,4-d]pirimidina
102	2-{[(R)-[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il](4-clorofenil)metil]oxi}-*N*,*N*-dietiletanamina
103	2-{[1-(3-bromo-1*H*-pirazolo[3,4-d]pirimidin-4-il)piperidin-4-il]oxi}-5-cloro-*N*-(2-pirrolidin-1-iletil)anilina

Tabla 3a.

Inhibidores representativos de c-MET y/o Flt-3

[00217] Los Compuestos de la Tabla 3a se pueden preparar como sales, solvatos, hidratos y/o isómeros

farmacéuticamente aceptables de estos. Todas las combinaciones de sales, solvatos, hidratos e isómeros de los Compuestos de la Tabla 3a se pueden usar para practicar la la invención.

Comp No.	Nombre
1	*N*-(4-fluorofenil)-*N*'-[3-fluoro-4-(7*H*-pirrolo[2,3-d]pirimidin-4-iloxi)fenil]propandiamida
2	*N*-(4-fluorofenil)-*N*'-[3-fluoro-4-(7*H*-pirrolo[2,3-d]pirimidin-4-iloxi)fenil]ciclopropano-1,1-dicarboxamida
3	*N*-({[3-fluoro-4-(7*H*-pirrolo[2,3-d]pirimidin-4-iloxi)fenil]amino}carbonotioil)-2-fenilacetamida
4	*N*-(4-fluorofenil)-*N*'-(4-{[1-(tetrahidro-2*H*-piran-2-il)-1*H*-pirazolo[3,4-d]pirimidin-4-il]oxi}fenil)ciclopropano-1,1-dicarboxamida
5	2-fenilo-*N*-{[(4-{[1-(tetrahidro-2*H*-piran-2-il)-1*H*-pirazolo[3,4-d]pirimidin-4-il]oxi}fenil)amino]carbonotioil}acetamida
6	*N*-(4-fluorofenil)-*N*'-[4-(1*H*-pirazolo[3,4-d]pirimidin-4-iloxi)fenil]ciclopropano-1,1-dicarboxamida
7	2-fenilo-*N*-({[4-(1*H*-pirazolo[3,4-d]pirimidin-4-iloxi)fenil]amino}carbonotioil)acetamida
8	*N*-(4-fluorofenil)-*N*'-(4-{[9-(tetrahidro-2*H*-piran-2-il)-9*H*-purin-6-il]oxi}fenil)ciclopropano-1,1-dicarboxamida
9	2-fenilo-*N*-{[(4-{[9-(tetrahidro-2*H*-piran-2-il)-9*H*-purin-6-il]oxi}fenil)amino]carbonotioil}acetamida
10	*N*-(4-fluorofenil)-*N*'-[4-(9*H*-purin-6-iloxi)fenil]ciclopropano-1,1-dicarboxamida

Comp No.	Nombre
11	2-fenilo-*N*-({[4-(9*H*-purin-6-iloxi)fenil]amino}carbonotioil)acetamida
12	*N*-{3-fluoro-4-[(6-{[(2-morfolin-4-iletil)amino]carbonil}-7*H*-pirrolo[2,3-d]pirimidin-4-il)oxi]fenil}-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida

Tabla 3b.

Inhibidores representativos adicionales de c-MET, c-KIT, y/o Flt-3

[00218] Los Compuestos de la Tabla 3b se pueden preparar como sales, solvatos, hidratos y/o isómeros farmacéuticamente aceptables de estos. Todas las combinaciones de sales, solvatos, hidratos e isómeros de los Compuestos de la Tabla 3b se pueden usar para practicar la invención.

Entrada	Nombre
1	*N*-[({3-fluoro-4-[(6-(metiloxi)-7-{[(3aR,6aS)-octahidrociclopenta[c]pirrol-5-ilmetil]oxi}quinazolin-4-il)oxi]fenil}amino)carbonotioil]-2-fenilacetamida
2	*N*-{[(3-fluoro-4-{[7-({[(3aR,6aS)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-il]oxi}fenil)amino]carbonotioil}-2-fenilacetamida
3	*N*-{[(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)(metil)amino]carbonotioil}-2-fenilacetamida
4	1-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)imidazolidin-2-ona

Entrada	Nombre
5	1-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-3-(fenilmetil)imidazolidin-2-ona
6	1-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-3-(fenilacetil)imidazolidin-2-ona
7	[(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)amino](oxo)acetato de etilo
8	*N*-{[(4-{[6,7-bis(metiloxi)quinazolin-4-il]amino}-3-fluorofenil)amino]carbonotioil}-2-fenilacetamida
9	*N*'-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*-metil-*N*-(2-feniletil)sulfamida
10	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-3-(fenilmetil)-1,2,4-oxadiazol-5-amina
11	1-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)piperidin-2-ona
12	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(fenilmetil)etandiamida
13	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-4-fenilo-1,3-tiazol-2-amina
14	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(2-feniletil)etandiamida
15	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-1-fenilmetansulfonamida
16	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-2-feniletansulfonamida
17	4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluoro-*N*-(fenilmetil)bencensulfonamida
18	4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluoro-*N*-metil-*N*-(fenilmetil)bencensulfonamida
19	4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluoro-*N*-(2-feniletil)bencensulfonamida

Entrada	Nombre
20	4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluoro-*N*-metil-*N*-(2-feniletil)bencensulfonamida
21	4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluoro-*N*-(3-fenilpropil)bencensulfonamida
22	1-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)pirrolidin-2-ona
23	(fenilmetil)carbamato de 4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}fenilo
24	(2-feniletil)carbamato de 4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}fenilo
25	4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluoro-*N*-metil-*N*-(3-fenilpropil)bencensulfonamida
26	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-feniletandiamida
27	*N*-{[(3-fluoro-4-{[7-{[(2-metiloctahidrociclopenta[c]pirrol-5-il)metil]oxi}-6-(metiloxi)quinolin-4-il]oxi}fenil)amino]carbonotioil}-2-fenilacetamida
28	*N*-[(Z)-[(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)amino](imino)metil]-2-fenilacetamida
29	4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluoro-*N*-[2-(feniloxi)etil]bencensulfonamida
30	*N*,*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-bis-(3-fenilpropano-1-sulfonamida)
31	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-3-fenilpropano-1-sulfonamida
32	*N*2-[(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)sulfonil]-*N*1-fenilglicinamida
33	*N*-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}piridin-3-il)-2-fenilacetamida
34	*N*-{[(6-{[6,7-bis(metiloxi)quinolin-4-

Entrada	Nombre
	il]oxi}piridin-3-il)amino]carbonotioil}-2-fenilacetamida
35	6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-1,3-benzotiazol-2-amina
36	6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-fluoro-1,3-benzotiazol-2-amina
37	*N*-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-fluoro-1,3-benzotiazol-2-il)-2-fenilacetamida
38	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N'*-(2-morfolin-4-iletil)etandiamida
39	ter-butil éster del ácido bencil-{[4-(6,7-dimetoxi-quinolin-4-iloxi)-3-fluoro-fenilcarbamoil]-metil}-carbámico
40	*N*1-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*2-(fenilmetil)glicinamida
41	*N*2-acetil-*N*1-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*2-(fenilmetil)glicinamida
42	*N*-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-1,3-benzotiazol-2-il)-2-fenilacetamida
43	ter-butil éster del ácido bencil-{[6-(6,7-dimetoxi-quinolin-4-iloxi)-piridin-3-ilcarbamoil]-metil}-carbámico
44	*N*1-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}piridin-3-il)-*N*2-(fenilmetil)glicinamida
45	*N*2-acetil-*N*1-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}piridin-3-il)-*N*2-(fenilmetil)glicinamida
46	*N*-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}piridin-3-il)-3-fenilpropanamida
47	*N*-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}piridin-3-il)-4-fenilbutanamida
48	*N*1-(6-{[6,7-bis(metiloxi)quinolin-4-

Entrada	Nombre
	il]oxi}piridin-3-il)-*N*2-metil-*N*2-(fenilmetil)glicinamida
49	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-{2-[4-(metiloxi)fenil]etil}etandiamida
50	*N*1-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*2-metil-*N*2-(fenilmetil)glicinamida
51	4-[(2-amino-1,3-benzotiazol-6-il)oxi]-6,7-bis(metiloxi)-1-(2-oxo-2-feniletil)quinolinio
52	*N*-{[(4-{[6,7-bis(metiloxi)quinolin-4-il]amino}fenil)amino]carbonotioil}-2-fenilacetamida
53	*N*-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-fluoro-1,3-benzotiazol-2-il)-3-fenilpropanamida
54	*N*-{[(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-cloropiridin-3-il)amino]carbonotioil}-2-fenilacetamida
55	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(2,3-dihidro-1*H*-inden-1-il)etandiamida
56	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(2,3-dihidro-1*H*-inden-2-il)etandiamida
57	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(1,2,3,4-tetrahidronaftalen-1-il)etandiamida
58	*N*'-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*-(2-feniletil)-*N*-(fenilmetil)sulfamida
59	*N*1-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*2-(trifluoroacetil)glicinamida

Entrada	Nombre
60	*N*-{[4-(6,7-dimetoxi-quinolin-4-iloxi)-3-fluoro-fenilcarbamoil]-metil}-benzamida
61	*N*-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}piridin-3-il)-*N*'-(4-fluorofenil)propandiamida
62	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-[(2S)-1,2,3,4-tetrahidronaftalen-2-il]etandiamida
63	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-[2-(4-metilfenil)etil]etandiamida
64	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(2-fenilpropil)etandiamida
65	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-[2-(4-clorofenil)etil]etandiamida
66	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*,*N*'-bis(fenilmetil)sulfamida
67	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*,*N*'-bis(2-feniletil)sulfamida
68	[(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-cloropiridin-3-il)amino](oxo)acetato de etilo
69	*N*-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-cloropiridin-3-il)-*N*'-(2-feniletil)etandiamida
70	*N*-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-cloropiridin-3-il)-*N*'-(4-fluorofenil)propandiamida
71	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(1,2,3,4-tetrahidronaftalen-2-il)etandiamida
72	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-[2-(1-metilpirrolidin-2-il)etil]etandiamida
73	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-[2-(feniloxi)etil]etandiamida

Entrada	Nombre
74	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-[2-hidroxi-1-(fenilmetil)etil]urea
75	1-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-3-[(4-metilfenil)sulfonil]-4-(fenilmetil)imidazolidin-2-ona
76	*N*'-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*-metil-*N*-(2-feniletil)etandiamida
77	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-{[3-(trifluorometil)fenil]metil}etandiamida
78	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-{2-[3-(trifluorometil)fenil]etil}etandiamida
79	*N*-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-cloropiridin-3-il)-3-oxo-4-fenilbutanamida
80	*N*-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-cloropiridin-3-il)-2-[3-(trifluorometil)fenil]acetamida
81	6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-fluoro-*N*-[2-(feniloxi)etil]-1,3-benzotiazol-2-amina
82	6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-fluoro-*N*-(2-piperidin-1-iletil)-1,3-benzotiazol-2-amina
83	6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-fluoro-*N*-metil-*N*-(2-feniletil)-1,3-benzotiazol-2-amina
84	6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-fluoro-*N*-(2-pirrolidin-1-iletil)-1,3-benzotiazol-2-amina
85	6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-fluoro-*N*-{[3-(trifluorometil)fenil]metil}-1,3-benzotiazol-2-amina
86	6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-fluoro-*N*-{2-[3-(trifluorometil)fenil]etil}-1,3-

Entrada	Nombre
	benzotiazol-2-amina
87	*N*-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-cloropiridin-3-il)-*N*'-[3-(trifluorometil)fenil]propandiamida
88	*N*-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-fluoro-1,3-benzotiazol-2-il)-2-[3-(trifluorometil)fenil]acetamida
89	*N*1-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*2-{[3-(trifluorometil)fenil]metil}glicinamida
90	*N*1-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*2-(2-feniletil)glicinamida
91	*N*1-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*2-{2-[3-(trifluorometil)fenil]etil}glicinamida
92	ter-butil éster del ácido bencil-{[5-cloro-6-(6,7-dimetoxi-quinolin-4-iloxi)-piridin-3-ilcarbamoil]-metil}-carbámico
93	*N*1-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-cloropiridin-3-il)-*N*2-(fenilmetil)glicinamida
94	*N*-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-fluoro-1,3-benzotiazol-2-il)-2-[3,5-bis(trifluorometil)fenil]acetamida
95	*N*-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-fluoro-1,3-benzotiazol-2-il)-2-[2-cloro-5-(trifluorometil)fenil]acetamida
96	*N*-{3-fluoro-4-[(6-(metiloxi)-7-{[(1-metilpiperidin-4-il)metil]oxi}quinolin-4-il)oxi]fenil}-*N*'-(2-feniletil)etandiamida
97	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(1,2,3,4-tetrahidroisoquinolin-1-

Entrada	Nombre
	ilmetil)etandiamida
98	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-[(2-metil-1,2,3,4-tetrahidroisoquinolin-1-il)metil]etandiamida
99	*N*1-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*2-metil-*N*2-{[3-(trifluorometil)fenil]metil}glicinamida
100	*N*1-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*2-metil-*N*2-{2-[3-(trifluorometil)fenil]etil}glicinamida
101	*N*1-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*2-metil-*N*2-(2-feniletil)glicinamida
102	1-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-4-(fenilmetil)imidazolidin-2-ona
103	*N*-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}piridazin-3-il)-*N*'-(4-fluorofenil)propandiamida
104	*N*-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-cloropiridin-3-il)-*N*'-(2-clorofenil)propandiamida
105	*N*-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-cloropiridin-3-il)-*N*'-(3-clorofenil)propandiamida
106	*N*1-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-cloropiridin-3-il)-*N*2-metil-*N*2-(fenilmetil)glicinamida
107	*N*-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-cloropiridin-3-il)-*N*'-(4-clorofenil)propandiamida
108	(2E)-*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}fenil)-2-[(metiloxi)imino]propanamida
109	(2E)-*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}fenil)-2-[(etiloxi)imino]propanamida
110	(2E)-*N*-(4-{[6,7-bis(metiloxi)quinolin-4-

Entrada	Nombre
	il]oxi}fenil)-2-{[(fenilmetil)oxi]imino}propanamida
111	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}fenil)-1-(fenilmetil)prolinamida
112	1-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}fenil)-3-[(4-metilfenil)sulfonil]-4-(fenilmetil)imidazolidin-2-ona
113	1-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}fenil)-4-(fenilmetil)imidazolidin-2-ona
114	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}fenil)-4-(fenilmetil)-4,5-dihidro-1,3-oxazol-2-amina
115	6,7-bis(metiloxi)-4-({4-[4-(fenilmetil)piperazin-1-il]fenil}oxi)quinolina
116	1-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}fenil)-4-(fenilmetil)piperazin-2-ona
117	*N*1-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}fenil)-*N*2-(fenilmetil)alaninamida
118	*N*1-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}fenil)-*N*2-metil-*N*2-(fenilmetil)alaninamida
119	*N*1-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}fenil)-*N*2-(fenilmetil)leucinamida
120	*N*1-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}fenil)-*N*2-metil-*N*2-(fenilmetil)leucinamida
121	*N*1-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}fenil)-*N*2-(fenilmetil)valinamida
122	4-(6,7-dimetoxi-quinolin-4-ilamino)-*N*-(3-fenilo-propil)-benzamida
123	4-bencil-1-[4-(6,7-dimetoxi-quinolin-4-iloxi)-fenil]-tetrahidro-pirimidin-2-ona
124	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-phenetil-oxalamida

Entrada	Nombre
125	2-(Bencil-metil-amino)-*N*-[4-(6,7-dimetoxi-quinolin-4-iloxi)-fenil]-3-metil-butiramida (nota: Orden alfabético de prefijos ignorado mientras se selecciona la cadena original)
126	*N*-[4-(6,7-Dimetoxi-quinolin-4-iloxi)-fenil]-2-fenoxiimino-propionamida
127	2-Benciloxiimino-*N*-[4-(6,7-dimetoxi-quinolin-4-iloxi)-fenil]-2-fenilo-acetamida
128	4-[4-(4-Bencil-piperidin-1-il)-fenoxi]-6,7-dimetoxi-quinolina
129	*N*-[4-(6,7-Dimetoxi-quinolin-4-iloxi)-3-fluoro-fenil]-*N*'-(2-isopropil-1,2,3,4-tetrahidro-isoquinolin-1-ilmetil)-oxalamida
130	*N*-[4-(6,7-Dimetoxi-quinolin-4-iloxi)-3-fluoro-fenil]-*N*'-(2-etil-1,2,3,4-tetrahidro-isoquinolin-1-ilmetil)-oxalamida
131	ter-butil éster del ácido 4-(4-{3-cloro-5-[2-(4-fluoro-fenilcarbamoil)-acetilamino]-piridin-2-iloxi}-6-metoxi-quinolin-7-iloximetil)-piperidino-1-carboxílico
132	*N*-{5-cloro-6-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-piridin-3-il}-*N*'-(4-fluoro-fenil)-malonamida
133	*N*-{5-Cloro-6-[6-metoxi-7-(1-metil-piperidin-4-ilmetoxi)-quinolin-4-iloxi]-piridin-3-il}-*N*'-(4-fluoro-fenil)-malonamida
134	*N*-{4-[7-(3-Dietilamino-propoxi)-6-metoxi-quinolin-4-iloxi]-3-fluoro-fenil}-*N*'-phenetil-oxalamida
135	*N*-{3-Fluoro-4-[6-metoxi-7-(3-morfolin-4-il-propoxi)-quinolin-4-iloxi]-fenil}-*N*'-fenetil-oxalamida

Entrada	Nombre
136	*N*-{3-Fluoro-4-[6-metoxi-7-(3-piperidin-1-il-propoxi)-quinolin-4-iloxi]-fenil}-*N*'-fenetil-oxalamida
137	*N*-{4-[7-(2-Dietilamino-etoxi)-6-metoxi-quinolin-4-iloxi]-3-fluoro-fenil}-*N*'-fenetil-oxalamida
138	*N*-{3-Fluoro-4-[6-metoxi-7-(1-metil-piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-metil-*N*'-fenetil-oxalamida
139	*N*-{3-Fluoro-4-[6-metoxi-7-(2-metil-octahidro-ciclopenta[c]pirrol-5-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-fenetil-oxalamida
140	*N*-{3-Fluoro-4-[6-metoxi-7-(2-metil-octahidro-ciclopenta[c]pirrol-5-ilmetoxi)-quinazolin-4-iloxi]-fenil}-*N*'-fenetil-oxalamida
141	2-(3,4-Dihidro-1*H*-isoquinolin-2-il)-*N*-{3-fluoro-4-[6-metoxi-7-(1-metil-piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-2-oxo-acetamida
142	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-2-oxo-2-(3-fenilo-pirrolidin-1-il)-acetamida
143	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-2-oxo-2-(2-fenilo-morfolin-4-il)-acetamida
144	*N*-(2-Dimetilamino-2-fenilo-etil)-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
145	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(2-oxo-2-fenilo-etil)-oxalamida
146	*N*-[5-Cloro-6-(6,7-dimetoxi-quinolin-4-iloxi)-piridin-3-il]-2,2-difluoro-*N*'-(4-fluoro-fenil)-

Entrada	Nombre
	malonamida
147	*N*-Bencil-*N*'-{3-fluoro-4-[6-metoxi-7-(1-metil-piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
148	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-[2-(2-fluoro-fenil)-etil]-oxalamida
149	*N*-[2-(3-Cloro-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
150	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-[2-(2-metoxi-fenil)-etil]-oxalamida
151	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(2-piridin-3-il-etil)-oxalamida
152	*N*-Bencil-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
153	*N*-[2-(2,5-Dimetoxi-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
154	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-[2-(2-trifluorometil-fenil)-etil]-oxalamida
155	*N*-[2-(2-Etoxi-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
156	*N*-[2-(2,4-Dimetil-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
157	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-

Entrada	Nombre
	quinolin-4-iloxi]-fenil}-*N*'-(1*S* -fenilo-2-p-tolil-etil)-oxalamida
158	*N*-[2-(4-Cloro-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
159	Ácido *N*-{3-Fluoro-4-[6-metoxi-7-(1-metil-piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalámico
160	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-[2-(3-fluoro-fenil)-etil]-oxalamida
161	*N*-[2-(2-Cloro-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
162	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-[2-(3-metoxi-fenil)-etil]-oxalamida
163	*N*-(1,2-Difenil-etil)-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
164	*N*-[2-(2,4-Dicloro-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
165	*N*-[2-(3,4-Dimetoxi-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
166	*N*-[2-(4-Etil-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
167	*N*-[2-(4-Etoxi-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-

Entrada	Nombre
	fenil}-oxalamida
168	*N*-[2-(4-Etoxi-3-metoxi-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
169	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-[2-(4-fenoxi-fenil)-etil]-oxalamida
170	*N*-[2-(3-Etoxi-4-metoxi-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
171	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(2-piridin-2-il-etil)-oxalamida
172	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(2-piridin-4-il-etil)-oxalamida
173	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-[2-(4-fluoro-fenil)-etil]-oxalamida
174	*N*-[2-(2-Bromo-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
175	*N*-[2-(2-Cloro-6-fluoro-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
176	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(2*R*-fenilo-propil)-oxalamida
177	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-indan-1-il-oxalamida
178	*N*-{3-Fluoro-4-[6-metoxi-7-(1-metil-piperidin-4-

Entrada	Nombre
	ilmetoxi)-quinolin-4-iloxi]-fenil}-*N'*-isobutil-oxalamida
179	*N*-{3-Fluoro-4-[6-metoxi-7-(1-metil-piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N'*-(3-metil-butil)-oxalamida
180	*N*-{3-Fluoro-4-[6-metoxi-7-(1-metil-piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N'*-(2*R*-fenilo-propil)-oxalamida
181	*N*-{3-Fluoro-4-[6-metoxi-7-(1-metil-piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N'*-(2-fenilo-propil)-oxalamida
182	*N*-{3-Fluoro-4-[6-metoxi-7-(1-metil-piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N'*-indan-2-il-oxalamida
183	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N'*-(1*R*-fenilo-etil)-oxalamida
184	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N'*-(1*S*-fenilo-etil)-oxalamida
185	*N*-[2-(3-Bromo-fenil)-etil]-*N'*-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
186	*N*-[2-(2,6-Dicloro-fenil)-etil]-*N'*-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
187	*N*-[2-(2,4-Dicloro-fenil)-etil]-*N'*-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
188	*N*-(2-Benzo[1,3]dioxol-5-il-etil)-*N'*-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-

Entrada	Nombre
	iloxi]-fenil}-oxalamida
189	*N*-[2-(3-Bromo-4-metoxi-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
190	*N*-[2-(3,5-Dimetoxi-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
191	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(2-o-tolil-etil)-oxalamida
192	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(2-m-tolil-etil)-oxalamida
193	*N*-[2-(3-Etoxi-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
194	*N*-[2-(3,4-Dimetil-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
195	*N*-[2-(2,5-Dimetil-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
196	*N*-[2-(3-Cloro-4-propoxi-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
197	*N*-[2-(4-Butoxi-3-cloro-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
198	*N*-[2-(4-tert-Butil-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida

Entrada	Nombre
199	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N'*-[2-(4-sulfamoil-fenil)-etil]-oxalamida
200	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N'*-[2-(4-hidroxi-3-metoxi-fenil)-etil]-oxalamida
201	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N'*-[2-(3-hidroxi-4-metoxi-fenil)-etil]-oxalamida
202	*N*-(2,4-Dicloro-bencil)-*N'*-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
203	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N'*-(4-fluoro-2-trifluorometil-bencil)-oxalamida
204	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N'*-(1-p-tolil-etil)-oxalamida
205	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N'*-(3-fluoro-4-trifluorometil-bencil)-oxalamida
206	*N*-(3-Cloro-4-fluoro-bencil)-*N'*-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
207	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N'*-[1-(3-metoxi-fenil)-etil]-oxalamida
208	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N'*-(1-naftalen-2-il-etil)-oxalamida
209	*N*-(4-Cloro-3-trifluorometil-bencil)-*N'*-{3-fluoro-

Entrada	Nombre
	4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
210	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(1-p-tolil-etil)-oxalamida
211	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(6-trifluorometil-piridin-3-ilmetil)-oxalamida
212	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(2-metil-bencil)-oxalamida
213	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(3-metil-bencil)-oxalamida
214	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(4-fluoro-3-trifluorometil-bencil)-oxalamida
215	*N*-(3,5-Dicloro-bencil)-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
216	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(1R,2,3,4-tetrahidro-naftalen-1-il)-oxalamida
217	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(1S,2,3,4-tetrahidro-naftalen-1-il)-oxalamida
218	*N*-Ciclopentil-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
219	*N*-[1-(4-Bromo-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-

Entrada	Nombre
	fenil}-oxalamida
220	*N*-(2-Fluoro-bencil)-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
221	*N*-[2-(3,4-Dicloro-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
222	*N*-(4-Fluoro-bencil)-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
223	*N*-(2,3-Difluoro-bencil)-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
224	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(2-fenoxi-etil)-oxalamida
225	*N*-(2,2-Difenil-etil)-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
226	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-[2-(4-metoxi-fenil)-etil]-oxalamida
227	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(2-fenilo-propil)-oxalamida
228	*N*-[2-(4-Bromo-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
229	*N*-{4-[7-(1-Etil-piperidin-4-ilmetoxi)-6-metoxi-quinolin-4-iloxi]-3-fluoro-fenil}-2-oxo-2-(2-fenilo-morfolin-4-il)-acetamida

Entrada	Nombre
230	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(3-fluoro-5-trifluorometil-bencil)-oxalamida
231	*N*-(3,5-Difluoro-bencil)-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
232	*N*-(2-Cloro-5-trifluorometil-bencil)-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
233	*N*-[4-(6,7-Dimetoxi-quinolin-4-iloxi)-3-fluoro-fenil]-*N*'-(2-dimetilamino-2-fenilo-etil)-oxalamida
234	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(4-metoxi-bencil)-oxalamida
235	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(4-trifluorometil-bencil)-oxalamida
236	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(3-metoxi-bencil)-oxalamida
237	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(3-trifluorometil-bencil)-oxalamida
238	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(3-trifluorometoxi-bencil)-oxalamida
239	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(2-metoxi-bencil)-oxalamida

Entrada	Nombre
240	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(2-trifluorometil-bencil)-oxalamida
241	*N*-(3-Cloro-bencil)-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
242	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(2-trifluorometoxi-bencil)-oxalamida
243	*N*-(2-Cloro-bencil)-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
244	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(4-trifluorometoxi-bencil)-oxalamida
245	*N*-{3-Fluoro-4-[6-metoxi-7-(1-metil-piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(4-metoxi-bencil)-oxalamida
246	*N*-{3-Fluoro-4-[6-metoxi-7-(1-metil-piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(4-trifluorometil-bencil)-oxalamida
247	*N*-{4-[7-(Azetidin-3-ilmetoxi)-6-metoxi-quinolin-4-iloxi]-3-fluoro-fenil}-*N*'-fenetil-oxalamida
248	*N*-{3-Fluoro-4-[6-metoxi-7-(1-metil-azetidin-3-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-fenetil-oxalamida
249	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(2-hidroxi-2-fenilo-etil)-oxalamida
250	*N*-[5-Cloro-6-(6,7-dimetoxi-quinolin-4-iloxi)-piridin-3-il]-*N*'-(2,4-difluoro-fenil)-malonamida

Entrada	Nombre
251	*N*-[5-Cloro-6-(6,7-dimetoxi-quinolin-4-iloxi)-piridin-3-il]-*N*'-(4-fluoro-fenil)-*N*'-metil-malonamida
252	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(1R-fenilo-propil)-oxalamida
253	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(1R-fenilo-propil)-oxalamida
254	*N*-(3,4-Difluoro-bencil)-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
255	*N*-(2,6-Difluoro-bencil)-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
256	*N*-{3-Fluoro-4-[6-metoxi-7-(1-metil-piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-[2-(4-fluoro-fenil)-etil]-oxalamida
257	*N*-{3-Fluoro-4-[6-metoxi-7-(1-metil-piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-fenil-oxalamida
258	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(3-fluoro-fenil)-oxalamida
259	*N*-(4-Cloro-3-fluoro-fenil)-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
260	*N*-(3,4-Dimetoxi-fenil)-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
261	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-

Entrada	Nombre
	quinolin-4-iloxi]-fenil}-*N*'-(3-metil-butil)-oxalamida
262	*N*-(3,3-Dimetil-butil)-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
263	*N*-{5-Cloro-6-[6-metoxi-7-(3-piperidin-1-il-propoxi)-quinolin-4-iloxi]-piridin-3-il}-*N*'-(4-fluoro-fenil)-malonamida
264	*N*-{5-Cloro-6-[6-metoxi-7-(3-morfolin-4-il-propoxi)-quinolin-4-iloxi]-piridin-3-il}-*N*'-(4-fluoro-fenil)-malonamida
265	*N*-{5-Cloro-6-[7-(3-dietilamino-propoxi)-6-metoxi-quinolin-4-iloxi]-piridin-3-il}-*N*'-(4-fluoro-fenil)-malonamida
266	*N*-(4-Cloro-bencil)-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
267	*N*-(3,5-Dimetoxi-bencil)-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
268	*N*-(4-Butil-bencil)-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
269	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(2-p-tolil-etil)-oxalamida
270	*N*-(3,5-Bis-trifluorometil-bencil)-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
271	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-pirazin-2-ilmetil-

Entrada	Nombre
	oxalamida
272	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-piridin-2-ilmetil-oxalamida
273	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinazolin-4-iloxi]-fenil}-*N*'-fenetil-oxalamida
274	*N*-{3-Fluoro-4-[6-metoxi-7-(1-metil-piperidin-4-ilmetoxi)-quinazolin-4-iloxi]-fenil}-*N*'-fenetil-oxalamida
275	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(2-fluoro-3-trifluorometil-bencil)-oxalamida
276	*N*-[2-(2-Bromo-6-metoxi-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
277	*N*-[2-(3,4-Dimetoxi-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*-metil-oxalamida
278	*N*-[2-(5-Bromo-2-metoxi-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
279	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(2-fluoro-5-trifluorometil-bencil)-oxalamida
280	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-[1-(4-fluoro-fenil)-etil]-oxalamida
281	*N*-(1S-Bencil-2-oxo-2-pirrolidin-1-il-etil)-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
282	*N*-{3-Fluoro-4-[6-metoxi-7-(octahidro-

Entrada	Nombre
	ciclopenta[c]pirrol-5-ilmetoxi)-quinazolin-4-iloxi]-fenil}-*N*'-fenetil-oxalamida
283	*N*-[2-(4-Amino-fenil)-etil]-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
284	2-(4-Bencil-piperidin-1-il)-*N*-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-2-oxo-acetamida
285	*N*-[4-(6,7-Dimetoxi-quinolin-4-iloxi)-fenil]-*N*'-(4-fluoro-fenil)-malonamida
286	*N*-[5-Cloro-6-(6,7-dimetoxi-quinolin-4-iloxi)-piridin-3-il]-*N*'-(3-fluoro-fenil)-malonamida
287	*N*-[5-Cloro-6-(6,7-dimetoxi-quinolin-4-iloxi)-piridin-3-il]-*N*'-fenilo-malonamida
288	*N*-[5-Cloro-6-(6,7-dimetoxi-quinolin-4-iloxi)-piridin-3-il]-*N*'-(4-fluoro-fenil)-2,2-dimetil-malonamida
289	*N*-Etil-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
290	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-isopropil-oxalamida
291	*N*-Butil-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
292	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(2-metoxi-etil)-oxalamida
293	*N*-Ciclopropilmetil-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-oxalamida
294	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*'-(2-morfolin-4-il-

Entrada	Nombre
	etil)-oxalamida
295	*N*-{3-Fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-2-oxo-2-pirrolidin-1-il-acetamida
296	*N*-Etil-*N*'-{3-fluoro-4-[6-metoxi-7-(piperidin-4-ilmetoxi)-quinolin-4-iloxi]-fenil}-*N*-metil-oxalamida

Tabla 3c.

Inhibidores representativos adicionales de c-MET, c-KIT, y/o Flt-3

[00219] Los Compuestos de la Tabla 3c se pueden preparar como sales, solvatos, hidratos y/o isómeros farmacéuticamente aceptables de estos. Todas las combinaciones de sales, solvatos, hidratos e isómeros de los Compuestos de la Tabla 3c se pueden usar para practicar la la invención.

Entrada	Nombre
1	*N*-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-cloropiridin-3-il)-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
2	*N*-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-cloropiridin-3-il)-*N*'-(4-fluorofenil)ciclobutano-1,1-dicarboxamida
3	*N*-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-cloropiridin-3-il)-*N*'-(fenilmetil)ciclopropano-1,1-dicarboxamida
4	*N*-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-cloropiridin-3-il)-*N*'-fenilciclopropano-1,1-dicarboxamida

Entrada	Nombre
5	*N*-[3-fluoro-4-({6-(metiloxi)-7-[(3-morfolin-4-ilpropil)oxi]quinolin-4-il}oxi)fenil]-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
6	*N*-[3-fluoro-4-({6-(metiloxi)-7-[(3-piperidin-1-ilpropil)oxi]quinolin-4-il}oxi)fenil]-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
7	*N*-[3-fluoro-4-({6-(metiloxi)-7-[(3-piperidin-1-ilpropil)oxi]quinolin-4-il}oxi)fenil]-*N*'-(4-fluorofenil)ciclobutano-1,1-dicarboxamida
8	*N*-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-cloropiridin-3-il)-*N*'-(2-feniletil)ciclopropano-1,1-dicarboxamida
9	*N*-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-2-metilpiridin-3-il)-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
10	*N*-{4-[(7-cloroquinolin-4-il)oxi]-3-fluorofenil}-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
11	*N*-{4-[(7-cloroquinolin-4-il)oxi]fenil}-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
12	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}fenil)-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
13	*N*-(4-{[6,7-bis(metiloxi)quinazolin-4-il]oxi}fenil)-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
14	*N*-(4-{[6,7-bis(metiloxi)quinazolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
15	*N*-[3-fluoro-4-({6-(metiloxi)-7-[(3-morfolin-4-ilpropil)oxi]quinazolin-4-il}oxi)fenil]-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
16	*N*-{5-cloro-6-[(6-(metiloxi)-7-{[(1-metilpiperidin-4-

Entrada	Nombre
	il)metil]oxi}quinolin-4-il)oxi]piridin-3-il}-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
17	*N*-[5-cloro-6-({6-(metiloxi)-7-[(piperidin-4-ilmetil)oxi]quinolin-4-il}oxi)piridin-3-il]-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
18	*N*-[5-cloro-6-({6-(metiloxi)-7-[(fenilmetil)oxi]quinolin-4-il}oxi)piridin-3-il]-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
19	*N*-(4-{[7-{[2-(dietilamino)etil]oxi}-6-(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
20	*N*-(4-{[7-{[2-(dietilamino)etil]oxi}-6-(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)ciclobutano-1,1-dicarboxamida
21	*N*-{3-fluoro-4-[(6-(metiloxi)-7-{[(1-metilpiperidin-4-il)metil]oxi}quinazolin-4-il)oxi]fenil}-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
22	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-2-metilfenil)-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
23	*N*-(4-fluorofenil)-*N*'-[2-metil-6-({6-(metiloxi)-7-[(3-morfolin-4-ilpropil)oxi]quinolin-4-il}oxi)piridin-3-il]ciclopropano-1,1-dicarboxamida
24	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
25	*N*-(6-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-cloro-2-metilpiridin-3-il)-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
26	*N*-[3-fluoro-4-({7-(metiloxi)-6-[(3-morfolin-4-

Entrada	Nombre
	ilpropil)oxi]quinazolin-4-il}oxi)fenil]-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
27	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-3,5-difluorofenil)-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
28	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-2,5-difluorofenil)-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
29	*N*-[3-fluoro-4-({7-(metiloxi)-6-[(3-morfolin-4-ilpropil)oxi]quinolin-4-il}oxi)fenil]-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
30	*N*-{3-fluoro-4-[(6-(metiloxi)-7-(2-metil octahidrociclo-penta[c]pirrol-5-ilmetoxi)quinazolin-4-il)oxi]fenil}-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
31	*N*-{3-fluoro-4-[(7-(metiloxi)-6-{[(1-metilpiperidin-4-il)metil]oxi}quinazolin-4-il)oxi]fenil}-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
32	*N*-[5-fluoro-2-metil-4-({6-(metiloxi)-7-[(3-morfolin-4-ilpropil)oxi]quinolin-4-il}oxi)fenil]-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
33	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-2,3,5-trifluorofenil)-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
34	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-5-fluoro-2-metilfenil)-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
35	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-2-cloro-5-metilfenil)-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida

Entrada	Nombre
36	*N*-(3-fluoro-4-{[6-hidroxi-7-(metiloxi)quinolin-4-il]oxi}fenil)-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
37	*N*-(4-fluorofenil)-*N*'-[2-metil-4-({6-(metiloxi)-7-[(3-morfolin-4-ilpropil)oxi]quinolin-4-il}oxi)fenil]ciclopropano-1,1-dicarboxamida
38	*N*-[3-fluoro-4-({6-(metiloxi)-7-[(3-piperazin-1-ilpropil)oxi]quinolin-4-il}oxi)fenil]-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
39	*N*-{3-fluoro-4-[(6-(metiloxi)-7-{[3-(4-metilpiperazin-1-il)propil]oxi}quinolin-4-il)oxi]fenil}-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
40	*N*-{3-fluoro-4-[(6-(metiloxi)-7-{[(1-metilpiperidin-4-il)metil]oxi}quinolin-4-il)oxi]fenil}-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
41	*N*-(4-fluorofenil)-*N*'-[4-({6-(metiloxi)-7-[(3-morfolin-4-ilpropil)oxi]quinolin-4-il}oxi)fenil]ciclopropano-1,1-dicarboxamida
42	*N*-(4-{[7-{[3-(dietilamino)propil]oxi}-6-(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
43	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}-2-cloro-5-fluorofenil)-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
44	*N*-(4-{[6,7-bis(metiloxi)-2-(metiltio)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
45	*N*-(4-fluorofenil)-*N*'-(4-{[2-metil-6,7-bis(metiloxi)quinazolin-4-il]oxi}fenil)ciclopropano-1,1-dicarboxamida

Entrada	Nombre
46	*N*-(4-{[2-amino-6,7-bis(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
47	*N*-(3-fluoro-4-{[2-(metilamino)-6,7-bis(metiloxi)quinolin-4-il]oxi}fenil)-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
48	(1S,2R)-*N*-[3-fluoro-4-({6-(metiloxi)-7-[(3-morfolin-4-ilpropil)oxi]quinolin-4-il}oxi)fenil]-*N*'-(4-fluorofenil)-2-metilciclopropano-1,1-dicarboxamida
49	(1R,2R)-*N*-[3-fluoro-4-({6-(metiloxi)-7-[(3-morfolin-4-ilpropil)oxi]quinolin-4-il}oxi)fenil]-*N*'-(4-fluorofenil)-2-metilciclopropano-1,1-dicarboxamida
50	*N*-(4-{[6-{[3-(dietilamino)propil]oxi}-7-(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
51	*N*-(4-{[6-{[2-(dietilamino)etil]oxi}-7-(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
52	4-(3-{[4-[(2-fluoro-4-{[(1-{[(4-fluorofenil)amino]carbonil}ciclopropil)carbonil]amino}fenil)oxi]-6-(metiloxi)quinolin-7-il]oxi}propil)piperazino-1-carboxilato de 1,1-dimetiletilo
53	(1R,2R)-*N*-[3-fluoro-4-({6-(metiloxi)-7-[(3-morfolin-4-ilpropil)oxi]quinazolin-4-il}oxi)fenil]-*N*'-(4-fluorofenil)-2-metilciclopropano-1,1-dicarboxamida
54	(1R,2R)-*N*-(4-{[7-{[2-(dietilamino)etil]oxi}-6-(metiloxi)quinazolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)-2-metilciclopropano-1,1-dicarboxamida
55	*N*-(4-{[7-{[3-(dietilamino)propil]oxi}-6-

Entrada	Nombre
	(metiloxi)quinazolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
56	*N*-(4-{[7-{[3-(4-acetilpiperazin-1-il)propil]oxi}-6-(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
57	4-(3-{[4-[(2-fluoro-4-{[((1R,2R)-1-{[(4-fluorofenil)amino]carbonil}-2-metilciclopropil)carbonil]amino}fenil)oxi]-6-(metiloxi)quinolin-7-il]oxi}propil)piperazino-1-carboxilato de 1,1-dimetiletilo
58	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}fenil)-*N*'-(4-fluorofenil)-1-(fenilmetil)azetidin-3,3-dicarboxamida
59	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}fenil)-*N*'-(4-fluorofenil)azetidin-3,3-dicarboxamida
60	(1R,2S)-*N*-{3-fluoro-4-[(6-(metiloxi)-7-{[3-(4-metilpiperazin-1-il)propil]oxi}quinolin-4-il)oxi]fenil}-*N*'-(4-fluorofenil)-2-metilciclopropano-1,1-dicarboxamida
61	(1R,2R)-*N*-{3-fluoro-4-[(6-(metiloxi)-7-{[3-(4-metilpiperazin-1-il)propil]oxi}quinolin-4-il)oxi]fenil}-*N*'-(4-fluorofenil)-2-metilciclopropano-1,1-dicarboxamida
62	(1R,2R)-*N*-[3-fluoro-4-({6-(metiloxi)-7-[(3-piperazin-1-ilpropil)oxi]quinolin-4-il}oxi)fenil]-*N*'-(4-fluorofenil)-2-metilciclopropano-1,1-dicarboxamida
63	*N*-(3-fluoro-4-{[7-({3-[4-(1-metiletil)piperazin-1-il]propil}oxi)-6-(metiloxi)quinolin-4-il]oxi}fenil)-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
64	*N*-(4-{[7-{[3-(dietilamino)propil]oxi}-6-

Entrada	Nombre
	(metiloxi)quinazolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)ciclopropano-1,1-dicarboxamida
65	(1R,2R)-*N*-(4-{[7-{[3-(dietilamino)propil]oxi}-6-(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)-2-metilciclopropano-1,1-dicarboxamida
66	(1R,2R)-*N*-(4-{[7-{[2-(dietilamino)etil]oxi}-6-(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)-2-metilciclopropano-1,1-dicarboxamida
67	(1R,2S)-*N*-(4-{[7-{[3-(dietilamino)propil]oxi}-6-(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)-2-metilciclopropano-1,1-dicarboxamida
68	(1R,2S)-*N*-(4-{[7-{[2-(dietilamino)etil]oxi}-6-(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)-2-metilciclopropano-1,1-dicarboxamida
69	*N*-(4-{[7-{[2-(dietilamino)etil]oxi}-6-(metiloxi)quinazolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)ciclobutano-1,1-dicarboxamida
70	(1R,2S)-*N*-[3-fluoro-4-({6-(metiloxi)-7-[(3-piperazin-1-ilpropil)oxi]quinolin-4-il}oxi)fenil]-*N*'-(4-fluorofenil)-2-metilciclopropano-1,1-dicarboxamida
71	(1R,2R,3S)-*N*-[3-fluoro-4-({6-(metiloxi)-7-[(3-morfolin-4-ilpropil)oxi]quinolin-4-il}oxi)fenil]-*N*'-(4-fluorofenil)-2,3-dimetilciclopropano-1,1-dicarboxamida
72	(1R,2R,3S)-*N*-{3-fluoro-4-[(6-(metiloxi)-7-{[3-(4-metilpiperazin-1-il)propil]oxi}quinolin-4-il)oxi]fenil}-*N*'-(4-fluorofenil)-2,3-dimetilciclopropano-1,1-dicarboxamida
73	(1R,2R,3S)-*N*-[3-fluoro-4-({6-(metiloxi)-7-[(3-morfolin-4-ilpropil)oxi]quinazolin-4-il}oxi)fenil]-

Entrada	Nombre
	N'-(4-fluorofenil)-2,3-dimetilciclopropano-1,1-dicarboxamida
74	(1R,2R,3S)-*N*-{3-fluoro-4-[(6-(metiloxi)-7-{[3-(4-metilpiperazin-1-il)propil]oxi}quinazolin-4-il)oxi]fenil}-*N*'-(4-fluorofenil)-2,3-dimetilciclopropano-1,1-dicarboxamida
75	*N*-[3-fluoro-4-({6-(metiloxi)-7-[(3-morfolin-4-ilpropil)oxi]quinazolin-4-il}oxi)fenil]-*N*'-(4-fluorofenil)ciclobutano-1,1-dicarboxamida
76	(2R,3R)-*N*-[3-fluoro-4-({6-(metiloxi)-7-[(3-morfolin-4-ilpropil)oxi]quinolin-4-il}oxi)fenil]-*N*'-(4-fluorofenil)-2,3-dimetilciclopropano-1,1-dicarboxamida
77	(2R,3R)-*N*-(4-{[7-{[3-(dietilamino)propil]oxi}-6-(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)-2,3-dimetilciclopropano-1,1-dicarboxamida
78	*N*-(4-{[7-{[3-(dietilamino)propil]oxi}-6-(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)-2,2-dimetilciclopropano-1,1-dicarboxamida
79	*N*-[3-fluoro-4-({6-(metiloxi)-7-[(3-morfolin-4-ilpropil)oxi]quinazolin-4-il}oxi)fenil]-*N*'-(4-fluorofenil)-2,2-dimetilciclopropano-1,1-dicarboxamida
80	(1R,2R,3S)-*N*-(4-{[7-{[3-(dietilamino)propil]oxi}-6-(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)-2,3-dimetilciclopropano-1,1-dicarboxamida

Entrada	Nombre
81	*N*-(4-{[7-{[2-(dietilamino)etil]oxi}-6-(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)-2,2-dimetilciclopropano-1,1-dicarboxamida
82	(1R,2R,3S)-*N*-(4-{[7-{[2-(dietilamino)etil]oxi}-6-(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)-2,3-dimetilciclopropano-1,1-dicarboxamida
83	*N*-[3-fluoro-4-({6-(metiloxi)-7-[(3-morfolin-4-ilpropil)oxi]quinolin-4-il}oxi)fenil]-*N*'-(4-fluorofenil)-2,2-dimetilciclopropano-1,1-dicarboxamida
84	*N*-(4-{[7-{[2-(dietilamino)etil]oxi}-6-(metiloxi)quinazolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)-2,2-dimetilciclopropano-1,1-dicarboxamida
85	*N*-(4-{[7-{[3-(dietilamino)propil]oxi}-6-(metiloxi)quinazolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)-2,2-dimetilciclopropano-1,1-dicarboxamida
86	*N*-(4-{[7-{[3-(dietilamino)propil]oxi}-6-(metiloxi)quinazolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)ciclobutano-1,1-dicarboxamida
87	*N*-{3-fluoro-4-[(6-(metiloxi)-7-{[3-(4-metilpiperazin-1-il)propil]oxi}quinazolin-4-il)oxi]fenil}-*N*'-(4-fluorofenil)ciclobutano-1,1-dicarboxamida
88	*N*-[3-fluoro-4-({6-(metiloxi)-7-[(3-piperazin-1-ilpropil)oxi]quinazolin-4-il}oxi)fenil]-*N*'-(4-fluorofenil)ciclobutano-1,1-dicarboxamida
89	(2R,3R)-*N*-[3-fluoro-4-({6-(metiloxi)-7-[(3-morfolin-

Entrada	Nombre
	4-ilpropil)oxi]quinazolin-4-il}oxi)fenil]-*N*'-(4-fluorofenil)-2,3-dimetilciclopropano-1,1-dicarboxamida
90	*N*-(4-{[7-{[3-(dietilamino)propil]oxi}-6-(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)ciclobutano-1,1-dicarboxamida
91	*N*-{3-fluoro-4-[(6-(metiloxi)-7-{[3-(4-metilpiperazin-1-il)propil]oxi}quinolin-4-il)oxi]fenil}-*N*'-(4-fluorofenil)ciclobutano-1,1-dicarboxamida
92	(1R,2R)-*N*-(4-{[7-{[3-(dietilamino)propil]oxi}-6-(metiloxi)quinazolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)-2-metilciclopropano-1,1-dicarboxamida
93	(1R,2R)-*N*-{3-fluoro-4-[(6-(metiloxi)-7-{[3-(4-metilpiperazin-1-il)propil]oxi}quinazolin-4-il)oxi]fenil}-*N*'-(4-fluorofenil)-2-metilciclopropano-1,1-dicarboxamida
94	(2R,3R)-*N*-(4-{[7-{[2-(dietilamino)etil]oxi}-6-(metiloxi)quinazolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)-2,3-dimetilciclopropano-1,1-dicarboxamida
95	(2R,3R)-*N*-(4-{[7-{[3-(dietilamino)propil]oxi}-6-(metiloxi)quinazolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)-2,3-dimetilciclopropano-1,1-dicarboxamida
96	(1R,2R)-*N*-[3-fluoro-4-({6-(metiloxi)-7-[(3-piperazin-1-ilpropil)oxi]quinazolin-4-il}oxi)fenil]-*N*'-(4-fluorofenil)-2-metilciclopropano-1,1-dicarboxamida
97	(2R,3R)-*N*-(4-{[7-{[2-(dietilamino)etil]oxi}-6-(metiloxi)quinolin-4-il]oxi}-3-fluorofenil)-*N*'-(4-fluorofenil)-2,3-dimetilciclopropano-1,1-

Entrada	Nombre
	dicarboxamida
98	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}fenil)-*N*'-[(4-fluorofenil)metil]ciclopropano-1,1-dicarboxamida
99	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}fenil)-*N*'-(2-morfolin-4-iletil)ciclopropano-1,1-dicarboxamida
100	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}fenil)-*N*'-[2-(piperidin-1-ilmetil)fenil]ciclopropano-1,1-dicarboxamida
101	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}fenil)-*N*'-[2-(pirrolidin-1-ilmetil)fenil]ciclopropano-1,1-dicarboxamida
102	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}fenil)-*N*'-[3-(morfolin-4-ilmetil)fenil]ciclopropano-1,1-dicarboxamida
103	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}fenil)-*N*'-[2-(morfolin-4-ilmetil)fenil]ciclopropano-1,1-dicarboxamida
104	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}fenil)-*N*'-fenilciclopropano-1,1-dicarboxamida
105	*N*-[3-(aminometil)fenil]-*N*'-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}fenil)ciclopropano-1,1-dicarboxamida
106	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}fenil)-*N*'-[3-(piperidin-1-ilmetil)fenil]ciclopropano-1,1-dicarboxamida
107	*N*-(4-{[6,7-bis(metiloxi)quinolin-4-il]oxi}fenil)-*N*'-[3-(pirrolidin-1-ilmetil)fenil]ciclopropano-1,1-dicarboxamida

Tabla 4.

Inhibidores representativos de EGFR, ErbB2 y/o VEGFR

[00220] Los Compuestos de la Tabla 4 se pueden preparar como sales, solvatos, hidratos y/o isómeros farmacéuticamente aceptables de estos. Todas las combinaciones de sales, solvatos, hidratos e isómeros de los Compuestos de la Tabla 4 se pueden usar para practicar la invención. En particular, la invención se puede practicar con una o dos sales farmacéuticamente aceptables de un Compuesto de Tabla 4, dichas sales se forman con uno o dos ácidos seleccionados de modo independiente de ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico, ácido fosfórico, 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 metansulfónico, ácido etansulfónico, ácido 1,2-etandisulfónico, ácido 2-hidroxietansulfónico, ácido bencensulfónico, ácido 4-clorobencensulfónico, ácido 2-naftalenosulfónico, ácido 4-toluensulfónico, ácido canforsulfónico, ácido glucoheptónico, ácido 4,4'-metilenbis-(3-hidroxi-2-ene-1-carboxílico), ácido 3-fenilpropiónico, ácido trimetilacético, ácido ter-butilacético, ácido lauril sulfúrico, ácido glucónico, ácido glutámico, ácido hidroxinaftoico, ácido salicílico, ácido esteárico, ácido mucónico ácido p-toluensulfónico y ácido salicílico.

Entrada	Nombre

Entrada	Nombre
1	*N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5r,6a*S*)-2-(1-metiletil)octahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
2	*N*-(4-bromo-3-cloro-2-fluorofenil)-7-({[(3a*R*,5r,6a*S*)-2-(1-metiletil)octahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
3	7-({[(3a*R*,5r,6a*S*)-2-acetiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-*N*-(4-bromo-3-cloro-2-fluorofenil)-6-(metiloxi)quinazolin-4-amina
4	*N*-(4-bromo-3-cloro-2-fluorofenil)-6-(metiloxi)-7-{[(3a*R*,5r,6a*S*)-octahidrociclopenta[c]pirrol-5-ilmetil]oxi}quinazolin-4-amina
5	(3a*R*,6a*S*)-5-({[4-[(4-bromo-3-cloro-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)hexahidrociclopenta[c]pirrol-2(1*H*)-carboxilato de etilo
6	*N*-(4-bromo-3-cloro-2-fluorofenil)-6-(metiloxi)-7-({[(3a*R*,5r,6a*S*)-2-(metilsulfonil)octahidrociclopenta[c]pirrol-5-il]metil}oxi)quinazolin-4-amina
7	*N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5r,6a*S*)-2-etiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
8	*N*-(3,4-dicloro-2-fluorofenil)-6-(metiloxi)-7-({[(3a*R*,5r,6a*S*)-2-(2-metilpropil)octahidrociclopenta[c]pirrol-5-il]metil}oxi)quinazolin-4-amina
9	*N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5s,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
10	*N*-(4-bromo-3-cloro-2-fluorofenil)-7-({[(3a*R*,5s,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina

Entrada	Nombre
11	*N*-(3-cloro-2,4-difluorofenil)-7-({[(3a*R*,5s,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
12	*N*-(4,5-dicloro-2-fluorofenil)-7-({[(3a*R*,5s,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
13	*N*-(4-bromo-5-cloro-2-fluorofenil)-7-({[(3a*R*,5s,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
14	*N*-(4-bromo-2,3-diclorofenil)-7-({[(3a*R*,5s,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
15	*N*-(3,4-diclorofenil)-7-({[(3a*R*,5s,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
16	*N*-(4-bromo-3-cloro-2-fluorofenil)-7-({[(3a*R*,5r,6a*S*)-2-etiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
17	*N*-(4-bromo-3-cloro-2-fluorofenil)-6-(metiloxi)-7-({[(3a*R*,5r,6a*S*)-2-(2-metilpropil)octahidrociclopenta[c]pirrol-5-il]metil}oxi)quinazolin-4-amina
18	*N*-(4-bromo-2,3-diclorofenil)-7-{[(3*R*,9a*S*)-hexahidro-1*H*-[1,4]oxazino[3,4-c][1,4]oxazin-3-ilmetil]oxi}-6-(metiloxi)quinazolin-4-amina
19	*N*-(4,5-dicloro-2-fluorofenil)-7-{[(3*R*,9a*S*)-hexahidro-1*H*-[1,4]oxazino[3,4-c][1,4]oxazin-3-ilmetil]oxi}-6-(metiloxi)quinazolin-4-amina
20	*N*-(4-bromo-5-cloro-2-fluorofenil)-7-{[(3*R*,9a*S*)-hexahidro-1*H*-[1,4]oxazino[3,4-c][1,4]oxazin-3-ilmetil]oxi}-6-(metiloxi)quinazolin-4-amina
21	*N*-(3-cloro-2,4-difluorofenil)-7-{[(3*R*,9a*S*)-hexahidro-1*H*-[1,4]oxazino[3,4-c][1,4]oxazin-3-ilmetil]oxi}-6-

Entrada	Nombre
	(metiloxi)quinazolin-4-amina
22	*N*-(3,4-dicloro-2-fluorofenil)-7-{[(3*S*,9a*S*)-hexahidro-1*H*-[1,4]oxazino[3,4-c][1,4]oxazin-3-ilmetil]oxi}-6-(metiloxi)quinazolin-4-amina
23	*N*-(4-bromo-3-cloro-2-fluorofenil)-7-{[(3*S*,9a*S*)-hexahidro-1*H*-[1,4]oxazino[3,4-c][1,4]oxazin-3-ilmetil]oxi}-6-(metiloxi)quinazolin-4-amina
24	*N*-(3-cloro-2,4-difluorofenil)-7-{[(3*S*,9a*S*)-hexahidro-1*H*-[1,4]oxazino[3,4-c][1,4]oxazin-3-ilmetil]oxi}-6-(metiloxi)quinazolin-4-amina
25	*N*-(3,4-diclorofenil)-7-[(hexahidro-1*H*-[1,4]oxazino[3,4-c][1,4]oxazin-3-ilmetil)oxi]-6-(metiloxi)quinazolin-4-amina
26	*N*-(4,5-dicloro-2-fluorofenil)-7-{[(3*S*,9a*S*)-hexahidro-1*H*-[1,4]oxazino[3,4-c][1,4]oxazin-3-ilmetil]oxi}-6-(metiloxi)quinazolin-4-amina
27	*N*-(4-bromo-2,3-diclorofenil)-7-{[(3*S*,9a*S*)-hexahidro-1*H*-[1,4]oxazino[3,4-c][1,4]oxazin-3-ilmetil]oxi}-6-(metiloxi)quinazolin-4-amina
28	*N*-(4-bromo-5-cloro-2-fluorofenil)-7-{[(3*S*,9a*S*)-hexahidro-1*H*-[1,4]oxazino[3,4-c][1,4]oxazin-3-ilmetil]oxi}-6-(metiloxi)quinazolin-4-amina
29	*N*-(3,4-dicloro-2-fluorofenil)-7-{[(3*R*,9a*S*)-hexahidro-1*H*-[1,4]oxazino[3,4-c][1,4]oxazin-3-ilmetil]oxi}-6-(metiloxi)quinazolin-4-amina
30	*N*-(4-bromo-3-cloro-2-fluorofenil)-7-{[(3*R*,9a*S*)-hexahidro-1*H*-[1,4]oxazino[3,4-c][1,4]oxazin-3-ilmetil]oxi}-6-(metiloxi)quinazolin-4-amina
31	*N*-(3,4-diclorofenil)-7-{[(3*R*,8a*R*)-hexahidro-1*H*-pirrolo[2,1-c][1,4]oxazin-3-ilmetil]oxi}-6-(metiloxi)quinazolin-4-amina
32	*N*-(4-bromo-5-cloro-2-fluorofenil)-7-{[(3*S*,8a*S*)-hexahidro-1*H*-pirrolo[2,1-c][1,4]oxazin-3-ilmetil]oxi}-

Entrada	Nombre
	6-(metiloxi)quinazolin-4-amina
33	*N*-(3,4-diclorofenil)-7-{[(3*S*,8a*R*)-hexahidro-1*H*-pirrolo[2,1-c][1,4]oxazin-3-ilmetil]oxi}-6-(metiloxi)quinazolin-4-amina
34	*N*-(3,4-diclorofenil)-7-{[(3*S*,8a*S*)-hexahidro-1*H*-pirrolo[2,1-c][1,4]oxazin-3-ilmetil]oxi}-6-(metiloxi)quinazolin-4-amina
35	*N*-(3,4-diclorofenil)-7-{[(3*R*,8a*S*)-hexahidro-1*H*-pirrolo[2,1-c][1,4]oxazin-3-ilmetil]oxi}-6-(metiloxi)quinazolin-4-amina
36	*N*-(3,4-dicloro-2-fluorofenil)-7-{[(3*S*,8a*S*)-hexahidro-1*H*-pirrolo[2,1-c][1,4]oxazin-3-ilmetil]oxi}-6-(metiloxi)quinazolin-4-amina
37	*N*-(4-bromo-3-cloro-2-fluorofenil)-7-{[(3*S*,8a*S*)-hexahidro-1*H*-pirrolo[2,1-c][1,4]oxazin-3-ilmetil]oxi}-6-(metiloxi)quinazolin-4-amina
38	*N*-(3-cloro-2,4-difluorofenil)-7-{[(3*S*,8a*S*)-hexahidro-1*H*-pirrolo[2,1-c][1,4]oxazin-3-ilmetil]oxi}-6-(metiloxi)quinazolin-4-amina
39	*N*-(4-bromo-2,3-diclorofenil)-7-{[(3*S*,8a*S*)-hexahidro-1*H*-pirrolo[2,1-c][1,4]oxazin-3-ilmetil]oxi}-6-(metiloxi)quinazolin-4-amina
40	*N*-(4,5-dicloro-2-fluorofenil)-7-{[(3*S*,8a*S*)-hexahidro-1*H*-pirrolo[2,1-c][1,4]oxazin-3-ilmetil]oxi}-6-(metiloxi)quinazolin-4-amina
41	1,4:3,6-dianhidro-5-({[4-[(4-bromo-5-cloro-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)-5-deoxi-2-O-metil-D-xilo-hexitol
42	1,4:3,6-dianhidro-5-deoxi-5-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)-2-O-metil-D-glucitol
43	1,4:3,6-dianhidro-5-deoxi-5-({[4-[(3,4-dicloro-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-

Entrada	Nombre
	il]oxi}metil)-2-O-metil-D-xilo-hexitol
44	1,4:3,6-dianhidro-5-({[4-[(4-bromo-3-cloro-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)-5-deoxi-2-O-metil-D-xilo-hexitol
45	1,4:3,6-dianhidro-5-({[4-[(3-cloro-2,4-difluorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)-5-deoxi-2-O-metil-D-xilo-hexitol
46	1,4:3,6-dianhidro-5-({[4-[(4-bromo-2,3-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)-5-deoxi-2-O-metil-D-glucitol
47	1,4:3,6-dianhidro-2-deoxi-2-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)-5-O-metil-D-treo-hexitol
48	1,4:3,6-dianhidro-5-deoxi-5-({[4-[(4,5-dicloro-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)-2-O-metil-D-glucitol
49	(3*S*,9a*S*)-3-({[4-[(3,4-dicloro-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)hexahidro-2*H*-pirido[1,2-a]pirazin-1(6*H*)-ona
50	(3*S*,9a*R*)-3-({[4-[(3,4-dicloro-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)hexahidro-2*H*-pirido[1,2-a]pirazin-1(6*H*)-ona
51	(3*S*,8a*S*)-3-({[4-[(3,4-dicloro-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)hexahidropirrolo[1,2-a]pirazin-1(2*H*)-ona
52	(3*S*,8a*R*)-3-({[4-[(3,4-dicloro-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)hexahidropirrolo[1,2-a]pirazin-1(2*H*)-ona
53	(3*S*,8a*S*)-3-({[4-[(4-bromo-3-cloro-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)hexahidropirrolo[1,2-a]pirazin-1(2*H*)-ona
54	(3*S*,8a*S*)-3-({[4-[(3,4-dicloro-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)-2-

Entrada	Nombre
	metilhexahidropirrolo[1,2-a]pirazin-1(2*H*)-ona
55	*N*-(3,4-diclorofenil)-7-({2-[(8-metil-8-azabiciclo[3,2,1]oct-3-il)amino]etil}oxi)-6-(metiloxi)quinazolin-4-amina
56	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(8a*R*)-tetrahidro-1*H*-[1,3]tiazolo[4,3-c][1,4]oxazin-6-ilmetil]oxi}quinazolin-4-amina
57	*N*-(3,4-diclorofenil)-7-{[2-(8-metil-8-azabiciclo[3,2,1]oct-3-il)etil]oxi}-6-(metiloxi)quinazolin-4-amina
58	*N*-(3,4-diclorofenil)-7-{[(8-metil-8-azabiciclo[3,2,1]oct-3-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
59	*N*-(3,4-diclorofenil)-7-{[(3a*R*,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]oxi}-6-(metiloxi)quinazolin-4-amina
60	*N*-(3,4-diclorofenil)-7-[(8-metil-8-azabiciclo[3,2,1]oct-3-il)oxi]-6-(metiloxi)quinazolin-4-amina
61	1,4:3,6-dianhidro-2-O-[4-[(4-bromo-5-cloro-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-5-O-metil-L-iditol
62	1,4:3,6-dianhidro-2-O-[4-[(3,4-dicloro-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-5-O-metil-L-iditol
63	1,4:3,6-dianhidro-2-O-[4-[(4-bromo-3-cloro-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-5-O-metil-L-iditol
64	1,4:3,6-dianhidro-2-O-metil-5-O-{6-(metiloxi)-4-[(2,3,4-triclorofenil)amino]quinazolin-7-il}-L-iditol
65	1,4:3,6-dianhidro-5-O-[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-O-metil-D-xilo-hexitol
66	1,4:3,6-dianhidro-2-O-[4-[(4-bromo-2,3-

Entrada	Nombre
	diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]-5-O-metil-L-iditol
67	1,4:3,6-dianhidro-5-*O*-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-L-sorbose etilene glicol acetal
68	1,4:3,6-dianhidro-2-O-[4-[(3-cloro-2,4-difluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-5-O-metil-L-iditol
69	1,4:3,6-dianhidro-2-O-[4-[(4,5-dicloro-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-5-O-metil-L-iditol
70	1,4:3,6-dianhidro-2-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-5-O-(difluorometil)-L-iditol
71	1,4:3,6-dianhidro-2-O-[4-[(3-cloro-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-5-O-metil-L-iditol
72	1,4:3,6-dianhidro-2-O-[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]-5-O-metil-L-iditol
73	1,4:3,6-dianhidro-2-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-5-O-metil-L-iditol
74	1,4:3,6-dianhidro-2-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-5-O-etil-L-iditol
75	1,4:3,6-dianhidro-2-O-[4-[(3-bromo-2-metilfenil)amino]-6-(metiloxi)quinazolin-7-il]-5-O-metil-L-iditol
76	1,4:3,6-dianhidro-2-O-[4-[(3-cloro-2-metilfenil)amino]-6-(metiloxi)quinazolin-7-il]-5-O-metil-L-iditol
77	1,4:3,6-dianhidro-2-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-5-deoxi-D-xilo-hexitol
78	1,4:3,6-dianhidro-2-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-5-O-metil-D-glucitol
79	metil 3,6-anhidro-5-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-O-metil-alfa-L-

Entrada	Nombre
	idofuranoside
80	3,6-anhidro-5-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-1,2-O-(1-metiletiliden)-beta-L-xilo-hexofuranose
81	1,4:3,6-dianhidro-2-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-5-deoxi-5-metiliden-D-xilo-hexitol
82	metil 3,6-anhidro-5-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-O-metil-beta-L-idofuranósido
83	*N*-(3,4-dicloro-2-fluorofenil)-6-(metiloxi)-7-[(octahidro-2*H*-quinolizin-3-ilmetil)oxi]quinazolin-4-amina
84	1,4:3,6-dianhidro-2-deoxi-2-fluoro-5-O-{6-(metiloxi)-4-[(2,3,4-trifluorofenil)amino]quinazolin-7-il}-D-iditol
85	1,4:3,6-dianhidro-5-O-[4-[(2-cloro-4-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
86	1,4:3,6-dianhidro-5-O-[4-[(2-bromo-4-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
87	1,4:3,6-dianhidro-2-deoxi-5-O-[4-[(2,6-difluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-fluoro-D-iditol
88	1,4:3,6-dianhidro-5-O-[4-[(3-cloro-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
89	1,4:3,6-dianhidro-2-deoxi-2-fluoro-5-O-[4-{[4-fluoro-3-(trifluorometil)fenil]amino}-6-(metiloxi)quinazolin-7-il]-D-iditol
90	1,4:3,6-dianhidro-2-deoxi-5-O-[4-[(2,4-difluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-fluoro-D-iditol

Entrada	Nombre
91	1,4:3,6-dianhidro-2-deoxi-5-O-[4-[(2,5-difluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-fluoro-D-iditol
92	1,4:3,6-dianhidro-2-deoxi-5-O-[4-[(2,3-difluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-fluoro-D-iditol
93	1,4:3,6-dianhidro-5-O-[4-[(5-cloro-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
94	1,4:3,6-dianhidro-2-deoxi-5-O-[4-[(3,5-difluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-fluoro-D-iditol
95	1,4:3,6-dianhidro-5-O-[4-[(3-cloro-4-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
96	1,4:3,6-dianhidro-5-O-[4-[(4-bromo-2-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
97	1,4:3,6-dianhidro-2-deoxi-5-O-[4-[(3,4-dicloro-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-fluoro-D-iditol
98	1,4:3,6-dianhidro-5-O-[4-[(4-bromo-5-cloro-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
99	1,4:3,6-dianhidro-2-deoxi-2-fluoro-5-O-{6-(metiloxi)-4-[(2,4,5-trifluorofenil)amino]quinazolin-7-il}-D-iditol
100	1,4:3,6-dianhidro-2-deoxi-2-fluoro-5-O-{6-(metiloxi)-4-[(2,4,6-trifluorofenil)amino]quinazolin-7-il}-D-iditol
101	1,4:3,6-dianhidro-5-O-[4-({4-[(4-clorofenil)oxi]-3,5-difluorofenil}amino)-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
102	1,4:3,6-dianhidro-5-O-[4-[(4-bromo-3-cloro-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol

Entrada	Nombre
103	1,4:3,6-dianhidro-5-O-[4-[(4-bromo-2,3-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
104	1,4:3,6-dianhidro-5-O-[4-[(4-bromo-3-cloro-5-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
105	1,4:3,6-dianhidro-2-deoxi-5-O-[4-[(4,5-dicloro-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-fluoro-D-iditol
106	1,4:3,6-dianhidro-2-deoxi-2-fluoro-5-O-{6-(metiloxi)-4-[(2,3,4-triclorofenil)amino]quinazolin-7-il}-D-iditol
107	1,4:3,6-dianhidro-2-deoxi-2-fluoro-5-O-{6-(metiloxi)-4-[(3,4,5-triclorofenil)amino]quinazolin-7-il}-D-iditol
108	1,4:3,6-dianhidro-5-O-[4-[(4-bromo-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
109	1,4:3,6-dianhidro-5-O-[4-[(4-cloro-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
110	1,4:3,6-dianhidro-5-O-[4-[(3-cloro-2-metilfenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
111	1,4:3,6-dianhidro-2-deoxi-5-O-[4-[(3,4-difluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-fluoro-D-iditol
112	1,4:3,6-dianhidro-5-O-[4-[(2-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
113	1,4:3,6-dianhidro-2-deoxi-2-fluoro-5-O-[4-[(2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-D-iditol
114	1,4:3,6-dianhidro-5-O-[4-[(3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
115	1,4:3,6-dianhidro-2-deoxi-2-fluoro-5-O-[4-[(4-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-D-

Entrada	Nombre
	iditol
116	1,4:3,6-dianhidro-5-O-[4-[(4-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
117	1,4:3,6-dianhidro-2-deoxi-5-O-[4-[(2,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-fluoro-D-iditol
118	1,4:3,6-dianhidro-2-deoxi-5-O-[4-[(2,5-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-fluoro-D-iditol
119	1,4:3,6-dianhidro-2-deoxi-5-O-[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-fluoro-D-iditol
120	1,4:3,6-dianhidro-5-O-[4-[(2-bromo-4,6-difluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
121	1,4:3,6-dianhidro-5-O-[4-{[4-cloro-3-(trifluorometil)fenil]amino}-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
122	1,4:3,6-dianhidro-5-O-[4-{[2-cloro-5-(trifluorometil)fenil]amino}-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
123	1,4:3,6-dianhidro-2-deoxi-2-fluoro-5-O-[4-{[2-fluoro-3-(trifluorometil)fenil]amino}-6-(metiloxi)quinazolin-7-il]-D-iditol
124	1,4:3,6-dianhidro-5-O-[4-{[2-bromo-5-(trifluorometil)fenil]amino}-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
125	1,4:3,6-dianhidro-5-O-[4-{[2-bromo-4-(trifluorometil)fenil]amino}-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
126	1,4:3,6-dianhidro-2-deoxi-2-fluoro-5-O-[4-{[4-fluoro-2-(trifluorometil)fenil]amino}-6-(metiloxi)quinazolin-7-il]-D-iditol

Entrada	Nombre
127	1,4:3,6-dianhidro-5-O-[4-{[3-bromo-5-(trifluorometil)fenil]amino}-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
128	1,4:3,6-dianhidro-5-O-[4-[(2-bromofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
129	1,4:3,6-dianhidro-5-O-[4-[(3-bromofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
130	1,4:3,6-dianhidro-5-O-[4-[(4-bromofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
131	1,4:3,6-dianhidro-5-O-[4-[(3-bromo-4-metilfenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
132	1,4:3,6-dianhidro-5-O-[4-[(5-cloro-2-metilfenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
133	1,4:3,6-dianhidro-2-deoxi-5-O-[4-[(3,5-dimetilfenil)amino]-6-(metiloxi)quinazolin-7-il]-2-fluoro-D-iditol
134	1,4:3,6-dianhidro-5-O-[4-{[2,5-bis(metiloxi)fenil]amino}-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
135	1,4:3,6-dianhidro-5-O-[4-{[5-cloro-2,4-bis(metiloxi)fenil]amino}-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
136	1,4:3,6-dianhidro-5-O-[4-{[4-cloro-2,5-bis(metiloxi)fenil]amino}-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
137	1,4:3,6-dianhidro-5-O-[4-[(3-cloro-2,4-difluorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-fluoro-D-iditol
138	*N*-(3,4-diclorofenil)-7-[({5-[(dimetilamino)metil]-1,2,4-oxadiazol-3-il}metil)oxi]-6-(metiloxi)quinazolin-4-amina
139	*N*-(3,4-diclorofenil)-7-[({3-[(dimetilamino)metil]-1,2,4-oxadiazol-5-il}metil)oxi]-6-(metiloxi)quinazolin-

Entrada	Nombre
	4-amina
140	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[({3-[(4-metilpiperazin-1-il)metil]-1,2,4-oxadiazol-5-il}metil)oxi]quinazolin-4-amina
141	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(5-piperidin-4-il-1,2,4-oxadiazol-3-il)metil]oxi}quinazolin-4-amina
142	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[5-(1-metilpiperidin-4-il)-1,2,4-oxadiazol-3-il]metil}oxi)quinazolin-4-amina
143	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[3-(morfolin-4-ilmetil)-1,2,4-oxadiazol-5-il]metil}oxi)quinazolin-4-amina
144	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[(morfolin-2-ilmetil)oxi]quinazolin-4-amina
145	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(5-piperidin-2-il-1,2,4-oxadiazol-3-il)metil]oxi}quinazolin-4-amina
146	*N*-(3,4-diclorofenil)-7-[({2-[(dimetilamino)metil]-1,3-tiazol-4-il}metil)oxi]-6-(metiloxi)quinazolin-4-amina
147	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[4-(fenilmetil)morfolin-2-il]metil}oxi)quinazolin-4-amina
148	1,1-dimetiletil 2-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)morfolino-4-carboxilate
149	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[2-(morfolin-4-ilmetil)-1,3-tiazol-4-il]metil}oxi)quinazolin-4-amina
150	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[({2-[(4-metilpiperazin-1-il)metil]-1,3-tiazol-4-il}metil)oxi]quinazolin-4-amina
151	*N*-(3,4-diclorofenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
152	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[(1,4-oxazepan-2-ilmetil)oxi]quinazolin-4-amina
153	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(5-piperidin-3-

Entrada	Nombre
	il-1,2,4-oxadiazol-3-il)metil]oxi}quinazolin-4-amina
154	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[5-(1-metilpiperidin-2-il)-1,2,4-oxadiazol-3-il]metil}oxi)quinazolin-4-amina
155	*N*-(3,4-diclorofenil)-7-{[(4-metil-1,4-oxazepan-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
156	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[5-(1-metilpiperidin-3-il)-1,2,4-oxadiazol-3-il]metil}oxi)quinazolin-4-amina
157	*N*-(3,4-diclorofenil)-7-({[5-(1,1-dimetiletil)-1,2,4-oxadiazol-3-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
158	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(2-fenilo-1,3-tiazol-4-il)metil]oxi}quinazolin-4-amina
159	7-[(2,1,3-benzotiadiazol-4-ilmetil)oxi]-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
160	*N*-(3,4-diclorofenil)-7-{[(5-metilisoxazol-3-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
161	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(5-metil-4-fenilisoxazol-3-il)metil]oxi}quinazolin-4-amina
162	7-[(1,3-benzotiazol-2-ilmetil)oxi]-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
163	7-[(2,1,3-benzoxadiazol-5-ilmetil)oxi]-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
164	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[2-(2-tienil)-1,3-tiazol-4-il]metil}oxi)quinazolin-4-amina
165	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(1-fenilo-1*H*-pirazol-4-il)metil]oxi}quinazolin-4-amina
166	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[({5-[3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}metil)oxi]quinazolin-4-amina
167	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[({5-[4-(trifluorometil)fenil]-1,2,4-oxadiazol-3-

Entrada	Nombre
	il}metil)oxi]quinazolin-4-amina
168	7-({[3-(4-clorofenil)-1,2,4-oxadiazol-5-il]metil}oxi)-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
169	7-({[6-bromo-2-(metiloxi)naftalen-1-il]metil}oxi)-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
170	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[(1,3-tiazol-4-ilmetil)oxi]quinazolin-4-amina
171	7-{[(6-cloropiridin-3-il)metil]oxi}-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
172	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[(piridin-4-ilmetil)oxi]quinazolin-4-amina
173	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(2-metil-1,3-tiazol-4-il)metil]oxi}quinazolin-4-amina
174	7-{[(6-cloro-4*H*-1,3-benzodioxin-8-il)metil]oxi}-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
175	7-{[(5-cloro-1-metil-3-fenilo-1*H*-pirazol-4-il)metil]oxi}-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
176	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[1-metil-3-(trifluorometil)-1*H*-tieno[2,3-c]pirazol-5-il]metil}oxi)quinazolin-4-amina
177	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(3-fenilisoxazol-5-il)metil]oxi}quinazolin-4-amina
178	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(2,4,6-trimetilfenil)metil]oxi}quinazolin-4-amina
179	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[(piridin-3-ilmetil)oxi]quinazolin-4-amina
180	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[({3-[4-(metiloxi)fenil]isoxazol-5-il}metil)oxi]quinazolin-4-amina
181	*N*-(3,4-diclorofenil)-7-({[5-[(2,4-diclorofenil)oxi]-1-metil-3-(trifluorometil)-1*H*-pirazol-4-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina

Entrada	Nombre
182	7-[(ciclopropilmetil)oxi]-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
183	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[(tetrahidrofuran-2-ilmetil)oxi]quinazolin-4-amina
184	7-(ciclopentiloxi)-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
185	7-[(2-ciclohexiletil)oxi]-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
186	7-[(ciclohexilmetil)oxi]-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
187	7-[(ciclobutilmetil)oxi]-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
188	*N*-(3,4-diclorofenil)-7-{[2-(1,3-dioxolan-2-il)etil]oxi}-6-(metiloxi)quinazolin-4-amina
189	*N*-(3,4-diclorofenil)-7-{[2-(1,3-dioxan-2-il)etil]oxi}-6-(metiloxi)quinazolin-4-amina
190	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[(2-morfolin-4-iletil)oxi]quinazolin-4-amina
191	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[(2-pirrolidin-1-iletil)oxi]quinazolin-4-amina
192	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[(2-piperidin-1-iletil)oxi]quinazolin-4-amina
193	2-(2-{[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}etil)-1*H*-isoindole-1,3(2*H*)-diona
194	metil 6-O-[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]-alfa-D-glucopiranósido
195	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[(2-morfolin-4-il-2-oxoetil)oxi]quinazolin-4-amina
196	2-[3-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)-1,2,4-oxadiazol-5-il]piperidino-1-carboxilato de 1,1-dimetiletilo
197	4-[3-({[4-[(3,4-diclorofenil)amino]-6-

Entrada	Nombre
	(metiloxi)quinazolin-7-il]oxi}metil)-1,2,4-oxadiazol-5-il]piperidino-1-carboxilato de 1,1-dimetiletilo
198	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[4-(4-pirrolidin-1-ilfenil)-1,3-tiazol-2-il]metil}oxi)quinazolin-4-amina
199	*N*-(3,4-diclorofenil)-7-[({4-[4-(dietilamino)fenil]-1,3-tiazol-2-il}metil)oxi]-6-(metiloxi)quinazolin-4-amina
200	5-[2-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)-1,3-tiazol-4-il]-2-hidroxibenzamida
201	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(4-piridin-3-il-1,3-tiazol-2-il)metil]oxi}quinazolin-4-amina
202	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(4-piridin-2-il-1,3-tiazol-2-il)metil]oxi}quinazolin-4-amina
203	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(4-piridin-4-il-1,3-tiazol-2-il)metil]oxi}quinazolin-4-amina
204	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(2-morfolin-4-il-1,3-tiazol-4-il)metil]oxi}quinazolin-4-amina
205	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(3-morfolin-4-il-1,2,4-oxadiazol-5-il)metil]oxi}quinazolin-4-amina
206	*N*-(3,4-diclorofenil)-7-({[3-(dimetilamino)-1,2,4-oxadiazol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
207	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[({4-[(4-metilpiperazin-1-il)metil]-1,3-tiazol-2-il}metil)oxi]quinazolin-4-amina
208	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[(4,5,6,7-tetrahidro[1,3]tiazolo[5,4-c]piridin-2-ilmetil)oxi]quinazolin-4-amina
209	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[4-(morfolin-4-ilmetil)-1,3-tiazol-2-il]metil}oxi)quinazolin-4-amina
210	*N*-(3,4-diclorofenil)-7-[({4-[(4-metil-1,4-diazepan-1-il)metil]-1,3-tiazol-2-il}metil)oxi]-6-(metiloxi)quinazolin-4-amina

Entrada	Nombre
211	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(5-{[(fenilmetil)oxi]metil}-1,2,4-oxadiazol-3-il)metil]oxi}quinazolin-4-amina
212	*N*-(3,4-diclorofenil)-7-{[(4-etilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
213	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(2-piperidin-4-il-1,3-tiazol-4-il)metil]oxi}quinazolin-4-amina
214	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[2-(1-metilpiperidin-4-il)-1,3-tiazol-4-il]metil}oxi)quinazolin-4-amina
215	4-[5-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)-1,2,4-oxadiazol-3-il]piperazino-1-carboxilato de 1,1-dimetiletilo
217	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(3-piperazin-1-il-1,2,4-oxadiazol-5-il)metil]oxi}quinazolin-4-amina
218	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[3-(4-metilpiperazin-1-il)-1,2,4-oxadiazol-5-il]metil}oxi)quinazolin-4-amina
219	*N*-(3,4-diclorofenil)-7-({[5-(1-etilpiperidin-2-il)-1,2,4-oxadiazol-3-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
220	*N*-(3,4-diclorofenil)-7-({[3-(4-etilpiperazin-1-il)-1,2,4-oxadiazol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
221	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[({5-[4-(metiloxi)fenil]-1,2,4-oxadiazol-3-il}metil)oxi]quinazolin-4-amina
222	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[({2-[4-(trifluorometil)fenil]-1,3-tiazol-4-il}metil)oxi]quinazolin-4-amina
223	7-({[2-(4-clorofenil)-1,3-tiazol-4-il]metil}oxi)-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
224	*N*-(3,4-diclorofenil)-7-({[5-(3,5-dimetilisoxazol-4-il)-

Entrada	Nombre
	1,2,4-oxadiazol-3-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
225	7-{[(5-cloro-1-benzotien-3-il)metil]oxi}-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
226	*N*-(3,4-diclorofenil)-7-[({3-[4-(1,1-dimetiletil)fenil]-1,2,4-oxadiazol-5-il}metil)oxi]-6-(metiloxi)quinazolin-4-amina
227	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[({5-[2-(metiloxi)fenil]-1,2,4-oxadiazol-3-il}metil)oxi]quinazolin-4-amina
228	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[5-(4-metilfenil)-1,3,4-oxadiazol-2-il]metil}oxi)quinazolin-4-amina
229	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[1-(fenilmetil)-1*H*-imidazol-2-il]metil}oxi)quinazolin-4-amina
230	*N*-(3,4-diclorofenil)-7-({[3-(2,6-diclorofenil)-5-metilisoxazol-4-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
231	*N*-(3,4-diclorofenil)-7-{[(6-fluoro-4*H*-1,3-benzodioxin-8-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
232	7-{[(3,5-dibromofenil)metil]oxi}-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
233	*N*-(3,4-diclorofenil)-7-{[(2,6-difluorofenil)metil]oxi}-6-(metiloxi)quinazolin-4-amina
234	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[({3-[(piridin-2-ilsulfonil)metil]-1,2,4-oxadiazol-5-il}metil)oxi]quinazolin-4-amina
235	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(5-fenilo-1,2,4-oxadiazol-3-il)metil]oxi}quinazolin-4-amina
236	7-({[4-cloro-2-(trifluorometil)quinolin-6-il]metil}oxi)-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
237	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[2-(1-

Entrada	Nombre
	metilpirrolidin-2-il)etil]oxi}quinazolin-4-amina
238	*N*-(3,4-diclorofenil)-7-({[5-(1-etilpiperidin-4-il)-1,2,4-oxadiazol-3-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
239	*N*-(3,4-diclorofenil)-7-({[5-(1-etilpiperidin-3-il)-1,2,4-oxadiazol-3-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
240	*N*-(3,4-diclorofenil)-7-({[2-(dimetilamino)-1,3-tiazol-4-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
241	*N*-(3,4-diclorofenil)-7-{[(4-etil-1,4-oxazepan-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
242	*N*-(3,4-diclorofenil)-7-({[2-(1-etilpiperidin-4-il)-1,3-tiazol-4-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
243	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[({3-[(2*S*)-pirrolidin-2-il]-1,2,4-oxadiazol-5-il}metil)oxi]quinazolin-4-amina
244	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[({2-[(2*S*)-pirrolidin-2-il]-1,3-tiazol-4-il}metil)oxi]quinazolin-4-amina
245	Benzoato de [4-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)-1,3-tiazol-2-il]metilo
246	[4-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)-1,3-tiazol-2-il]metanol
247	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(5-metil-4,5,6,7-tetrahidro[1,3]tiazolo[5,4-c]piridin-2-il)metil]oxi}quinazolin-4-amina
248	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[({2-[(4*S*)-1,3-tiazolidin-4-il]-1,3-tiazol-4-il}metil)oxi]quinazolin-4-amina
249	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(2-piperidin-2-il-1,3-tiazol-4-il)metil]oxi}quinazolin-4-amina

Entrada	Nombre
250	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[2-(1-metilpiperidin-2-il)-1,3-tiazol-4-il]metil}oxi)quinazolin-4-amina
251	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(2-piperidin-3-il-1,3-tiazol-4-il)metil]oxi}quinazolin-4-amina
252	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[2-(1-metilpiperidin-3-il)-1,3-tiazol-4-il]metil}oxi)quinazolin-4-amina
253	*N*-(3,4-diclorofenil)-7-({[2-(1-etilpiperidin-2-il)-1,3-tiazol-4-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
254	*N*-(3,4-diclorofenil)-7-({[2-(1-etilpiperidin-3-il)-1,3-tiazol-4-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
255	*N*-(3,4-diclorofenil)-7-[({3-[(2*S*)-1-etilpirrolidin-2-il]-1,2,4-oxadiazol-5-il}metil)oxi]-6-(metiloxi)quinazolin-4-amina
256	*N*-(3,4-diclorofenil)-7-[({2-[(2*S*)-1-etilpirrolidin-2-il]-1,3-tiazol-4-il}metil)oxi]-6-(metiloxi)quinazolin-4-amina
257	*N*-(3,4-diclorofenil)-7-{[(5-etil-4,5,6,7-tetrahidro[1,3]tiazolo[5,4-c]piridin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
258	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(4-propil-1,4-oxazepan-2-il)metil]oxi}quinazolin-4-amina
259	7-({[4-(ciclopropilmetil)-1,4-oxazepan-2-il]metil}oxi)-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
260	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[({4-[2-(metiloxi)etil]-1,4-oxazepan-2-il}metil)oxi]quinazolin-4-amina
261	*N*-(3,4-diclorofenil)-7-({[4-(1-metiletil)-1,4-oxazepan-2-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
262	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(2-piperazin-1-il-1,3-tiazol-4-il)metil]oxi}quinazolin-4-amina
263	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(5-pirrolidin-2-

Entrada	Nombre
	il-1,2,4-oxadiazol-3-il)metil]oxi}quinazolin-4-amina
264	*N*-(3,4-diclorofenil)-7-({[5-(1-etilpirrolidin-2-il)-1,2,4-oxadiazol-3-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
265	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[({3-[(2*S*)-1-metilpirrolidin-2-il]-1,2,4-oxadiazol-5-il}metil)oxi]quinazolin-4-amina
266	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[({2-[(2*S*)-1-metilpirrolidin-2-il]-1,3-tiazol-4-il}metil)oxi]quinazolin-4-amina
267	*N*-(3,4-diclorofenil)-7-({[2-(4-etilpiperazin-1-il)-1,3-tiazol-4-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
268	*N*-(3,4-diclorofenil)-7-{[(1,4-dimetilpiperazin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
269	7-{[(4-ciclopentilmorfolin-2-il)metil]oxi}-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
270	*N*-(3,4-diclorofenil)-7-({[4-(1-metiletil)morfolin-2-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
271	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[4-(3-fenilpropil)morfolin-2-il]metil}oxi)quinazolin-4-amina
272	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[({4-[2-(metiloxi)etil]morfolin-2-il}metil)oxi]quinazolin-4-amina
273	2-[2-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)morfolin-4-il]propanoato de etilo
274	*N*-(3,4-diclorofenil)-7-{[(4-hex-5-en-1-ilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
275	2-({2-[2-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)morfolin-4-il]etil}oxi)etanol
276	3-[2-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)morfolin-4-

Entrada	Nombre
	il]propanoato de metilo
277	6-[2-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)morfolin-4-il]hexanonitrilo
278	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[4-(tetrahidro-2*H*-piran-2-ilmetil)morfolin-2-il]metil}oxi)quinazolin-4-amina
279	4-[2-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)morfolin-4-il]butanenitrilo
280	*N*-(3,4-diclorofenil)-7-[({4-[(4-fluorofenil)metil]morfolin-2-il}metil)oxi]-6-(metiloxi)quinazolin-4-amina
281	5-[2-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)morfolin-4-il]pentanoato de metilo
282	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(4-oct-7-en-1-ilmorfolin-2-il)metil]oxi}quinazolin-4-amina
283	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(4-propilmorfolin-2-il)metil]oxi}quinazolin-4-amina
284	6-[2-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)morfolin-4-il]hexan-1-ol
285	7-{[(4-acetilmorfolin-2-il)metil]oxi}-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
286	7-({[4-(ciclopropilmetil)morfolin-2-il]metil}oxi)-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
287	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(4-prop-2-in-1-ilmorfolin-2-il)metil]oxi}quinazolin-4-amina
288	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(4-piridin-4-ilmorfolin-2-il)metil]oxi}quinazolin-4-amina
289	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[4-(piridin-2-ilmetil)morfolin-2-il]metil}oxi)quinazolin-4-amina

Entrada	Nombre
290	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(4-pent-2-in-1-ilmorfolin-2-il)metil]oxi}quinazolin-4-amina
291	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[2-(4-metilpiperazin-1-il)-1,3-tiazol-4-il]metil}oxi)quinazolin-4-amina
292	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[5-(1-metilpirrolidin-2-il)-1,2,4-oxadiazol-3-il]metil}oxi)quinazolin-4-amina
293	*N*-(3-cloro-4-fluorofenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
294	7-{[(4-butil-1,4-oxazepan-2-il)metil]oxi}-*N*-(3,4-diclorofenil)-6-(metiloxi) quinazolin-4-amina
295	(3,4-diclorofenil)[7-(metiloxi)-6-({[4-(2-metilpropil)-1,4-oxazepan-2-il]metil}oxi) quinazolin-4-amina
296	7-{[(4-acetil-1-etilpiperazin-2-il)metil]oxi}-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
297	(3,4-diclorofenil)(6-(metiloxi)-7-{[(4-pentil-1,4-oxazepan-2-il)metil]oxi} quinazolin-4-amina
298	(3,4-diclorofenil)[6-(metiloxi)-7-({[4-(tetrahidro-2*H*-piran-2-ilmetil)-1,4-oxazepan-2-il]metil}oxi)quinazolin-4-amina
299	(3,4-diclorofenil)[6-(metiloxi)-7-({[4-(3-tienilmetil)-1,4-oxazepan-2-il]metil}oxi) quinazolin-4-amina
300	*N*-[4-cloro-2,5-bis(metiloxi)fenil]-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
301	*N*-(3-bromo-2-metilfenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
302	7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)-*N*-(3,4,5-triclorofenil)quinazolin-4-amina
303	*N*-(3-cloro-2-metilfenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
304	*N*-(3,4-diclorofenil)-7-{[(4-etanimidoil-1,4-oxazepan-2-

Entrada	Nombre
	il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
305	*N*-(4-bromo-2-fluorofenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
306	*N*-(5-cloro-2-fluorofenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
307	*N*-(4-cloro-2-fluorofenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
308	*N*-(2,4-diclorofenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
309	*N*-(2,4-dibromofenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
310	7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)-*N*-(2,3,4-triclorofenil)quinazolin-4-amina
311	*N*-(3,4-diclorofenil)-7-{[(1-etil-4-metilpiperazin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
312	*N'*-ciano-2-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)morfolino-4-carboximidamida
313	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[2-(pirrolidin-1-ilmetil)-1,3-tiazol-4-il]metil}oxi)quinazolin-4-amina
314	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[4-(tetrahidro-2*H*-piran-4-il)morfolin-2-il]metil}oxi)quinazolin-4-amina
315	*N*-(3,4-diclorofenil)-7-({[4-(2-etilbutil)morfolin-2-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
316	7-({[4-(ciclohexilmetil)morfolin-2-il]metil}oxi)-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
317	2-[2-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)morfolin-4-il]etanol
318	7-{[(4-but-2-in-1-ilmorfolin-2-il)metil]oxi}-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
319	7-{[(4-ciclobutilmorfolin-2-il)metil]oxi}-*N*-(3,4-

Entrada	Nombre
	diclorofenil)-6-(metiloxi)quinazolin-4-amina
320	*N*-(3,4-diclorofenil)-7-[({4-[2-(1,3-dioxolan-2-il)etil]morfolin-2-il}metil)oxi]-6-(metiloxi)quinazolin-4-amina
321	7-({[4-(2-ciclohexiletil)morfolin-2-il]metil}oxi)-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
322	*N*-(3,4-diclorofenil)-7-[({4-[2-(1,3-dioxan-2-il)etil]morfolin-2-il}metil)oxi]-6-(metiloxi)quinazolin-4-amina
323	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(4-pent-4-en-1-ilmorfolin-2-il)metil]oxi}quinazolin-4-amina
324	*N*-(3,4-diclorofenil)-7-[({4-[(2*R*)-2-metilbutil]morfolin-2-il}metil)oxi]-6-(metiloxi)quinazolin-4-amina
325	*N*-(3,4-diclorofenil)-7-({[4-(4-fluorobutil)morfolin-2-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
326	3-[2-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)morfolin-4-il]butan-2-ona
327	1-[2-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)morfolin-4-il]butan-2-ona
328	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(4-pentilmorfolin-2-il)metil]oxi}quinazolin-4-amina
329	*N*-(3,4-diclorofenil)-7-{[(4-hexilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
330	*N*-(3,4-diclorofenil)-7-{[(4-heptilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
331	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(4-octilmorfolin-2-il)metil]oxi}quinazolin-4-amina
332	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[4-(2-feniletil)morfolin-2-il]metil}oxi)quinazolin-4-amina
333	7-{[(4-butilmorfolin-2-il)metil]oxi}-*N*-(3,4-

Entrada	Nombre
	diclorofenil)-6-(metiloxi)quinazolin-4-amina
334	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(4-prop-2-en-1-ilmorfolin-2-il)metil]oxi}quinazolin-4-amina
335	2-[2-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)morfolin-4-il]-1-feniletanona
336	*N*-(3,4-diclorofenil)-7-({[4-(2-fluoroetil)morfolin-2-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
337	*N*-(3,4-diclorofenil)-7-({[4-(3-metilbut-2-en-1-il)morfolin-2-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
338	7-[({4-[(2E)-3-bromoprop-2-en-1-il]morfolin-2-il}metil)oxi]-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
339	2-[2-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)morfolin-4-il]acetamida
340	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[({4-[3-(tetrahidro-2*H*-piran-2-iloxi)propil]-1,4-oxazepan-2-il}metil)oxi]quinazolin-4-amina
341	*N*-(3,4-diclorofenil)-7-({[4-(3-metilbutil)-1,4-oxazepan-2-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
342	7-({[4-(ciclohexilmetil)-1,4-oxazepan-2-il]metil}oxi)-4-[(3,4-diclorofenil)metil]-6-(metiloxi)quinazoline
343	7-({[4-(2-ciclohexiletil)-1,4-oxazepan-2-il]metil}oxi)-4-[(3,4-diclorofenil)metil]-6-(metiloxi)quinazoline
345	*N*-(3,4-diclorofenil)-7-({[4-(2-etilbutil)-1,4-oxazepan-2-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
346	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[4-(metilsulfonil)-1,4-oxazepan-2-il]metil}oxi)quinazolin-4-amina

Entrada	Nombre
347	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[4-(1-metilpiperidin-4-il)morfolin-2-il]metil}oxi)quinazolin-4-amina
348	*N*-(3-cloro-2-fluorofenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
349	*N*'-ciano-2-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)-1,4-oxazepano-4-carboximidamida
350	*N*-(3-bromo-4-metilfenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
351	*N*-(3,4-diclorofenil)-7-{[(1,4-dietilpiperazin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
352	4-({[4-[(4-bromo-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)-*N*'-cianopiperidino-1-carboximidamida
353	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[4-(metilsulfonil)morfolin-2-il]metil}oxi)quinazolin-4-amina
354	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[({4-[(fenilmetil)sulfonil]morfolin-2-il}metil)oxi]quinazolin-4-amina
355	*N*-(3,4-diclorofenil)-7-[({4-[(4-fluorofenil)sulfonil]morfolin-2-il}metil)oxi]-6-(metiloxi)quinazolin-4-amina
356	*N*-(3,4-diclorofenil)-7-({[4-(etilsulfonil)morfolin-2-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
357	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[4-(fenilsulfonil)morfolin-2-il]metil}oxi)quinazolin-4-amina
358	7-[({4-[(3-cloropropil)sulfonil]morfolin-2-il}metil)oxi]-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
359	7-({[4-(butilsulfonil)morfolin-2-il]metil}oxi)-*N*-(3,4-

Entrada	Nombre
	diclorofenil)-6-(metiloxi)quinazolin-4-amina
360	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[({4-[(4-metilfenil)sulfonil]morfolin-2-il}metil)oxi]quinazolin-4-amina
361	*N*-(3,4-diclorofenil)-7-[({4-[(3,5-dimetilisoxazol-4-il)carbonil]morfolin-2-il}metil)oxi]-6-(metiloxi)quinazolin-4-amina
362	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(4-{[3-(metiloxi)fenil]acetil}morfolin-2-il)metil]oxi}quinazolin-4-amina
363	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[4-(2-metilpentanoil)morfolin-2-il]metil}oxi)quinazolin-4-amina
364	7-[({4-[(4-butilfenil)carbonil]morfolin-2-il}metil)oxi]-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
365	7-[({4-[(4-clorofenil)acetil]morfolin-2-il}metil)oxi]-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
366	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[4-(2-propilpentanoil)morfolin-2-il]metil}oxi)quinazolin-4-amina
367	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[4-(4-metilpentanoil)morfolin-2-il]metil}oxi)quinazolin-4-amina
368	*N*-(3,4-diclorofenil)-7-[({4-[(2,5-difluorofenil)carbonil]morfolin-2-il}metil)oxi]-6-(metiloxi)quinazolin-4-amina
369	7-({[4-(ciclopentilcarbonil)morfolin-2-il]metil}oxi)-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
370	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[4-(2-fenilbutanoil)morfolin-2-il]metil}oxi)quinazolin-4-amina
371	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-[({4-[(2,3,6-

Entrada	Nombre
	trifluorofenil)carbonil]morfolin-2-il}metil)oxi]quinazolin-4-amina
372	*N*-(3,4-diclorofenil)-7-({[4-(furan-3-ilcarbonil)morfolin-2-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
373	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(4-propanoilmorfolin-2-il)metil]oxi}quinazolin-4-amina
374	*N*-(3,4-diclorofenil)-7-{[(4-hexanoilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
375	*N*-(3,4-diclorofenil)-7-({[4-(2-etilhexanoil)morfolin-2-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
376	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[4-(3-fenilpropanoil)morfolin-2-il]metil}oxi)quinazolin-4-amina
377	*N*-(3,4-diclorofenil)-7-({[4-(2,2-dimetilpropanoil)morfolin-2-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
378	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[4-(naftalen-1-ilcarbonil)morfolin-2-il]metil}oxi)quinazolin-4-amina
379	7-[({4-[(2-cloropiridin-3-il)carbonil]morfolin-2-il}metil)oxi]-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
380	7-[({4-[(6-cloropiridin-3-il)carbonil]morfolin-2-il}metil)oxi]-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
381	7-({[4-(1,3-benzodioxol-5-ilcarbonil)morfolin-2-il]metil}oxi)-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
382	*N*-(3,4-diclorofenil)-6-[(1-metiletil)oxi]-7-[(morfolin-2-ilmetil)oxi]quinazolin-4-amina
383	*N*-(3,4-diclorofenil)-6-{[2-(metiloxi)etil]oxi}-7-[(morfolin-2-ilmetil)oxi]quinazolin-4-amina
384	*N*-(3,4-diclorofenil)-6-(etiloxi)-7-[(morfolin-2-

Entrada	Nombre
	ilmetil)oxi]quinazolin-4-amina
385	*N*-(3,4-diclorofenil)-6-(etiloxi)-7-{[(4-metilmorfolin-2-il)metil]oxi}quinazolin-4-amina
386	*N*-(4-bromo-2-metilfenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
387	*N*-(4-cloro-3-metilfenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
388	*N'*-ciano-2-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)-*N*-metilmorfolino-4-carboximidamida
389	*N*-(4-bromo-3-clorofenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
390	*N*-(3,4-diclorofenil)-6-[(1-metiletil)oxi]-7-{[(4-metilmorfolin-2-il)metil]oxi}quinazolin-4-amina
391	*N*-(3,4-diclorofenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-{[2-(metiloxi)etil]oxi}quinazolin-4-amina
392	*N*-(4-bromo-2-clorofenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
393	7-{[(4-acetil-1,4-oxazepan-2-il)metil]oxi}-*N*-(3,4-diclorofenil)-6-(metiloxi)quinazolin-4-amina
394	4-[(3,4-diclorofenil)amino]-7-{[(4-metilmorfolin-2-il)metil]oxi}quinazolin-6-ol
395	*N*-(3-bromo-4-clorofenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
396	Ácido 3-[2-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)morfolin-4-il]-3-oxopropanoico
397	4-[2-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)morfolin-4-il]-4-oxobutanoato de metilo
398	*N*-(3,4-diclorofenil)-7-{[(4-metilmorfolin-3-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina

Entrada	Nombre
399	*N*-(3-bromo-2-clorofenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
400	*N'*-ciano-2-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)-*N*-[2-(metiloxi)etil]morfolino-4-carboximidamida
401	*N'*-ciano-2-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)-*N*-etilmorfolino-4-carboximidamida
402	[(1E)-[2-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)morfolin-4-il](piperidin-1-il)metiliden]cianamida
403	[(1E)-[2-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)morfolin-4-il](pirrolidin-1-il)metiliden]cianamida
404	[(1E)-[2-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)morfolin-4-il](4-metilpiperazin-1-il)metiliden]cianamida
405	*N*-(3,4-diclorofenil)-7-{[(6-etil-4,6-dimetilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
406	*N*-(4-bromo-3-metilfenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
407	*N*-(3,4-diclorofenil)-7-{[(6,6-dimetilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
408	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(4,6,6-trimetilmorfolin-2-il)metil]oxi}quinazolin-4-amina
409	*N*-(3,4-diclorofenil)-7-{[2-(5,5-dimetilmorfolin-2-il)etil]oxi}-6-(metiloxi)quinazolin-4-amina
410	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[2-(4,5,5-trimetilmorfolin-2-il)etil]oxi}quinazolin-4-amina
411	2-(2-{[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}etil)-5,5-dimetilmorfolino-4-carboxilato de 1,1-dimetiletilo
412	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[(4,5,5-

Entrada	Nombre
	trimetilmorfolin-2-il)metil]oxi}quinazolin-4-amina
413	*N*-(4-bromo-2,3-diclorofenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
414	*N*-(4,5-dicloro-2-fluorofenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
415	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-{[2-(4,6,6-trimetilmorfolin-2-il)etil]oxi}quinazolin-4-amina
416	*N*-(4-bromo-2,3-difluorofenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
417	*N*-(4-bromo-2,5-difluorofenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
418	*N*-(4-bromo-3,5-difluorofenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
419	*N*-(3,4-dicloro-2-metilfenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
420	*N*-(3,4-diclorofenil)-7-({[(2*R*,5*S*,6*S*)-5,6-dimetilmorfolin-2-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
421	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[(2*R*,5*S*,6*S*)-4,5,6-trimetilmorfolin-2-il]metil}oxi)quinazolin-4-amina
422	*N*-(3,4-diclorofenil)-6-(metiloxi)-7-({[(2*S*,5*S*,6*S*)-4,5,6-trimetilmorfolin-2-il]metil}oxi)quinazolin-4-amina
423	*N*-(4-bromo-3-cloro-2-metilfenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
424	*N*-(4-bromo-5-cloro-2-fluorofenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
425	*N*-(4-bromo-3-cloro-2-fluorofenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
426	*N*-(3,4-dicloro-2-fluorofenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina

Entrada	Nombre
427	*N*-(3-cloro-2,4-difluorofenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
428	*N*-(2,3-dicloro-4-metilfenil)-7-{[(4-metilmorfolin-2-il)metil]oxi}-6-(metiloxi)quinazolin-4-amina
429	6-({[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)-3,3,4-trimetilmorfolin-2-ona
430	*N*-(4-bromo-2,3-diclorofenil)-6-(metiloxi)-7-{[(4,5,5-trimetilmorfolin-2-il)metil]oxi}quinazolin-4-amina
431	*N*-(4-bromo-5-cloro-2-fluorofenil)-6-(metiloxi)-7-{[(4,5,5-trimetilmorfolin-2-il)metil]oxi}quinazolin-4-amina
432	*N*-(4,5-dicloro-2-fluorofenil)-6-(metiloxi)-7-{[(4,5,5-trimetilmorfolin-2-il)metil]oxi}quinazolin-4-amina
433	*N*-(3,4-dicloro-2-fluorofenil)-6-(metiloxi)-7-{[(4,5,5-trimetilmorfolin-2-il)metil]oxi}quinazolin-4-amina
434	*N*-(4-bromo-3-cloro-2-fluorofenil)-6-(metiloxi)-7-{[(4,5,5-trimetilmorfolin-2-il)metil]oxi}quinazolin-4-amina
435	*N*-(3-cloro-2,4-difluorofenil)-6-(metiloxi)-7-{[(4,5,5-trimetilmorfolin-2-il)metil]oxi}quinazolin-4-amina
436	(6*S*)-6-({[4-[(4-bromo-3-cloro-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)-4-metilpiperazin-2-ona
437	(6*S*)-6-({[4-[(3,4-dicloro-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)-4-metilpiperazin-2-ona
438	(6*S*)-6-({[4-[(4-bromo-3-cloro-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)-1,4-dimetilpiperazin-2-ona
439	(6*S*)-6-({[4-[(3,4-dicloro-2-fluorofenil)amino]-6-(metiloxi)quinazolin-7-il]oxi}metil)-1,4-dimetilpiperazin-2-ona

Entrada	Nombre
440	*N*-(4-bromo-3-clorofenil)-7-{[(3a'*S*,4*R*,6'*S*,6a'*R*)-2,2-dimetiltetrahidrospiro[1,3-dioxolane-4,3'-furo[3,2-b]furan]-6'-il]oxi}-6-(metiloxi)quinazolin-4-amina
441	1,4:3,6-dianhidro-2-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-5-O-metil-5-C-[(metiloxi)metil]-L-glucitol
442	1,4:3,6-dianhidro-2-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-5-O-(metilsulfonil)-L-glucitol
443	1,4:3,6-dianhidro-2-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-L-glucitol
444	1,4:3,6-dianhidro-2-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-5-*S*-metil-5-tio-D-iditol
445	1,4:3,6-dianhidro-5-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-morfolin-4-il-D-iditol
446	1,4:3,6-dianhidro-5-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-(4-metilpiperazin-1-il)-D-iditol
447	1,4:3,6-dianhidro-5-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-pirrolidin-1-il-D-iditol
448	2-O-acetil-1,4:3,6-dianhidro-5-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-D-iditol
449	1,4:3,6-dianhidro-2-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-D-iditol
450	1,4:3,6-dianhidro-5-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-(metilsulfonil)-D-iditol
451	2-amino-1,4:3,6-dianhidro-5-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-D-iditol
452	1,4:3,6-dianhidro-5-O-[4-[(4-bromo-3-clorofenil)amino]-

Entrada	Nombre
	6-(metiloxi)quinazolin-7-il]-2-deoxi-2-(dimetilamino)-D-iditol
453	1,4:3,6-dianhidro-5-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-(dietilamino)-D-iditol
454	1,4:3,6-dianhidro-5-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-piperidin-1-il-D-iditol
455	2-(acetilamino)-1,4:3,6-dianhidro-5-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-D-iditol
456	1,4:3,6-dianhidro-2-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-5-O-metil-5-C-(trifluorometil)-L-glucitol
457	1,4:3,6-dianhidro-5-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-[(metilsulfonil)amino]-D-iditol
458	*N*-(4-bromo-3-clorofenil)-6-(metiloxi)-7-[(1-metilpirrolidin-3-il)oxi]quinazolin-4-amina
459	*N*-(4-bromo-3-clorofenil)-6-(metiloxi)-7-[(3*R*)-tetrahidrofuran-3-iloxi]quinazolin-4-amina
460	*N*-(4-bromo-3-clorofenil)-6-(metiloxi)-7-{[(3*S*,4*R*)-4-(metiloxi)tetrahidrofuran-3-il]oxi}quinazolin-4-amina
461	1,4:3,6-dianhidro-2-deoxi-2-fluoro-5-O-(6-(metiloxi)-4-{[4-(4-metilpiperazin-1-il)fenil]amino}quinazolin-7-il)-D-iditol
462	1,4:3,6-dianhidro-2-deoxi-2-fluoro-5-O-[4-{[3-fluoro-4-(4-metilpiperazin-1-il)fenil]amino}-6-(metiloxi)quinazolin-7-il]-D-iditol
463	1,4:3,6-dianhidro-2-deoxi-5-O-[4-{[2,3-dicloro-4-(4-metilpiperazin-1-il)fenil]amino}-6-(metiloxi)quinazolin-7-il]-2-fluoro-D-iditol
464	1,4:3,6-dianhidro-2-deoxi-5-O-[4-{[3,4-dicloro-2-(4-

Entrada	Nombre
	metilpiperazin-1-il)fenil]amino}-6-(metiloxi)quinazolin-7-il]-2-fluoro-D-iditol
465	1,4:3,6-dianhidro-2-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-5-C-(trifluorometil)-D-glucitol
466	(3,4-diclorofenil)[6-(metiloxi)-7-({[4-(tetrahidrofuran-2-ilmetil)-1,4-oxazepan-2-il]metil}oxi)quinazolin -4-amina
467	*N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5*r*,6a*S*)-2-metiloctahidrociclopenta-[*c*]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
468	*N*-(4-bromo-3-cloro-2-fluorofenil)-7-({[(3a*R*,5*r*,6a*S*)-2-metiloctahidrociclo-penta[*c*]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
469	*N*-(3-cloro-2,4-difluorofenil)-7-({[(3a*R*,5*r*,6a*S*)-2-metiloctahidrociclopenta-[*c*]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
470	*N*-(4,5-dicloro-2-fluorofenil)-7-({[(3a*R*,5*r*,6a*S*)-2-metiloctahidrociclo-penta[*c*]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
471	*N*-(4-bromo-5-cloro-2-fluorofenil)-7-({[(3a*R*,5*r*,6a*S*)-2-metiloctahidrociclo-penta[*c*]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
472	*N*-(4-bromo-2,3-diclorofenil)-7-({[(3a*R*,5*r*,6a*S*)-2-metiloctahidrociclo-penta[*c*]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
473	*N*-(3,4-diclorofenil)-7-({[(3a*R*,5*r*,6a*S*)-2-metiloctahidrociclopenta[*c*]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
474	*N*-(3,4-diclorofenil)-7-[(2-{[(3-*endo*)-8-metil-8-azabiciclo[3,2,1]oct-3-il]amino}etil)oxi]-6-(metiloxi)quinazolin-4-amina
475	*N*-(3,4-diclorofenil)-7-({2-[(3-*endo*)-8-metil-8-

Entrada	Nombre
	azabiciclo[3,2,1]oct-3-il]etil}oxi)-6-(metiloxi)quinazolin-4-amina
476	*N*-(3,4-diclorofenil)-7-({[(3-*endo*)-8-metil-8-azabiciclo[3,2,1]oct-3-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina
477	*N*-(3,4-diclorofenil)-7-{[(3-*exo*)-8-metil-8-azabiciclo[3,2,1]oct-3-il]oxi}-6-(metiloxi)quinazolin-4-amina
478	1,4:3,6-Dianhidro-5-*O*-[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-*O*-metil-D-glucitol
479	1,4:3,6-dianhidro-5-*O*-{4-[(3-cloro-2-fluorofenil)amino]-6-(metiloxi)quin-azolin-7-il}-2-deoxi-2-fluoro-L-iditol
480	1,4:3,6-dianhidro-2-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-5-O-(metilsulfonil)-D-glucitol
481	1,4:3,6-dianhidro-2-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-D-glucitol
482	1,4:3,6-dianhidro-2-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-5-S-metil-5-tio-L-iditol
483	1,4:3,6-dianhidro-5-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-morfolin-4-il-L-iditol
484	1,4:3,6-dianhidro-5-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-(4-metilpiperazin-1-il)-L-iditol
485	1,4:3,6-dianhidro-5-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-pirrolidin-1-il-L-iditol
486	2-O-acetil-1,4:3,6-dianhidro-5-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-L-iditol
487	1,4:3,6-dianhidro-2-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-L-iditol

Entrada	Nombre
488	1,4:3,6-dianhidro-5-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-(metilsulfonil)-L-iditol
489	2-amino-1,4:3,6-dianhidro-5-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-L-iditol
490	1,4:3,6-dianhidro-5-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-(dimetilamino)-L-iditol
491	1,4:3,6-dianhidro-5-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-(dietilamino)-L-iditol
492	1,4:3,6-dianhidro-5-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-piperidin-1-il-L-iditol
493	2-(acetilamino)-1,4:3,6-dianhidro-5-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-L-iditol
494	1,4:3,6-dianhidro-2-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-5-O-metil-5-C-(trifluorometil)-D-glucitol
495	1,4:3,6-dianhidro-5-O-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-deoxi-2-[(metilsulfonil)amino]-L-iditol
496	1,4:3,6-dianhidro-2-deoxi-2-fluoro-5-O-(6-(metiloxi)-4-{[4-(4-metilpiperazin-1-il)fenil]amino}quinazolin-7-il)-L-iditol
497	1,4:3,6-dianhidro-2-deoxi-2-fluoro-5-O-[4-{[3-fluoro-4-(4-metilpiperazin-1-il)fenil]amino}-6-(metiloxi)quinazolin-7-il]-L-iditol
498	1,4:3,6-dianhidro-2-deoxi-5-O-[4-{[2,3-dicloro-4-(4-metilpiperazin-1-il)fenil]amino}-6-(metiloxi)quinazolin-7-il]-2-fluoro-L-iditol

Entrada	Nombre
499	1,4:3,6-dianhidro-2-deoxi-5-O-[4-{[3,4-dicloro-2-(4-metilpiperazin-1-il)fenil]amino}-6-(metiloxi)quinazolin-7-il]-2-fluoro-L-iditol
500	1,4:3,6-Dianhidro-5-*O*-[4-[(3,4-diclorofenil)amino]-6-(metiloxi)quinazolin-7-il]-2-*O*-metil-D-glucitol
501	1,4:3,6-Dianhidro-2-*O*-[4-[(4-bromo-3-clorofenil)amino]-6-(metiloxi)quinazolin-7-il]-5-*O*-metil-L-glucitol

Tabla 5a.

Inhibidores representativos de IGF-1R

[00221] Los Compuestos de la Tabla 5a se pueden preparar como sales, solvatos, hidratos y/o isómeros farmacéuticamente aceptables de estos. Todas las combinaciones de sales, solvatos, hidratos e isómeros de los Compuestos de la Tabla 5a se pueden usar para practicar la invención.

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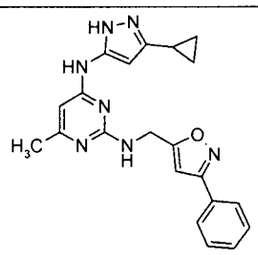
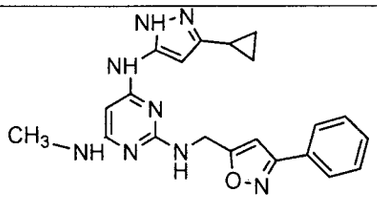
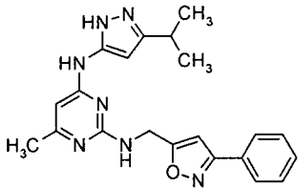
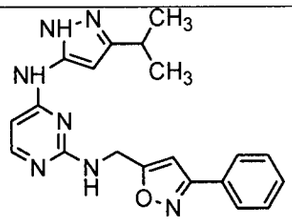
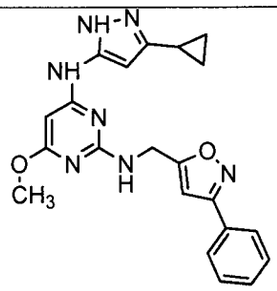
1	
2	
3	
4	
5	

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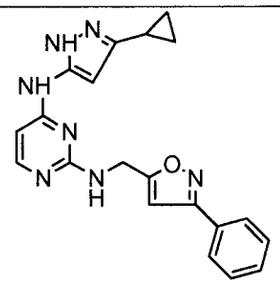
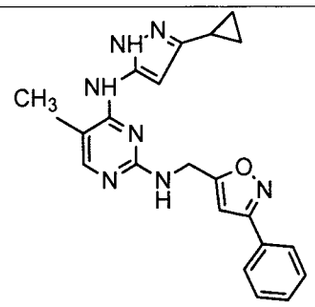
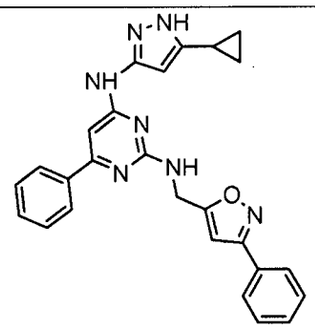
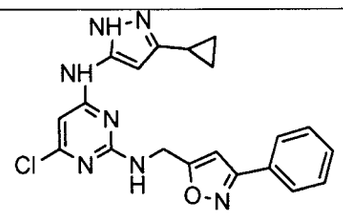
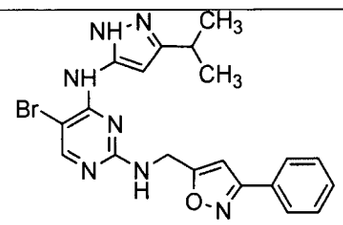
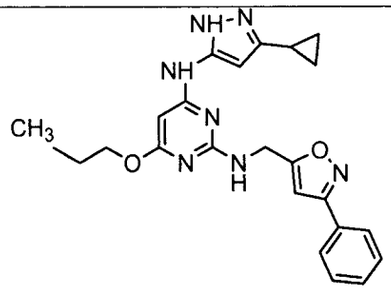
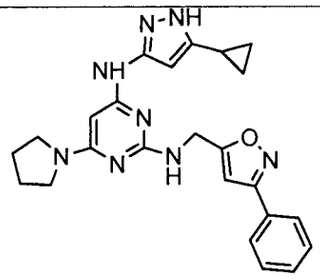
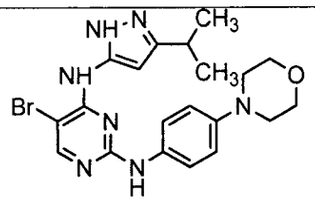
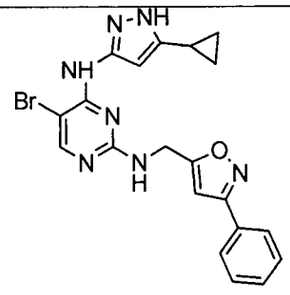
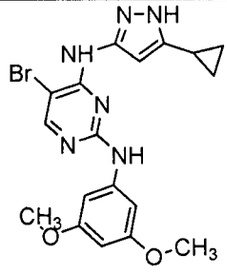
6	
7	
8	
9	
10	

Entrada	Estructura
11	
12	
13	
14	
15	

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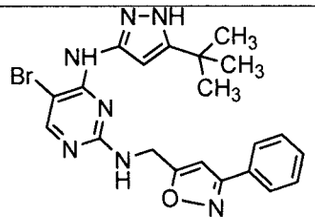
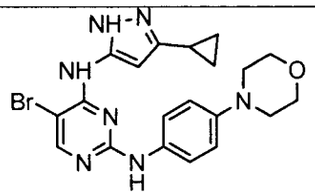
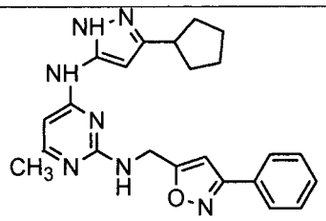
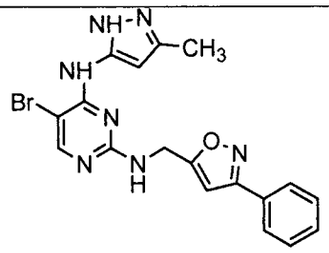
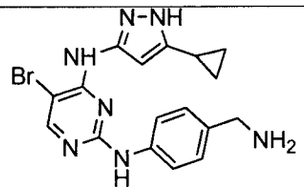
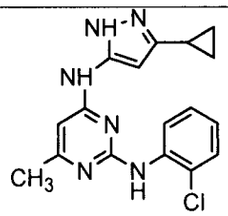
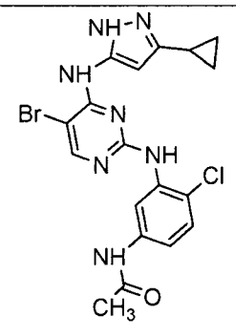
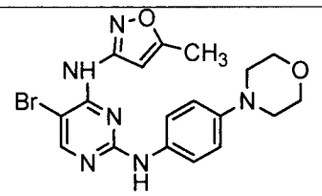
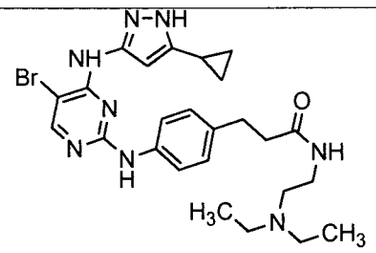
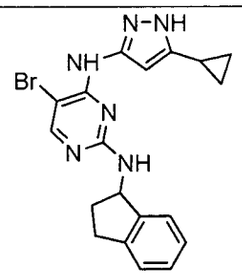
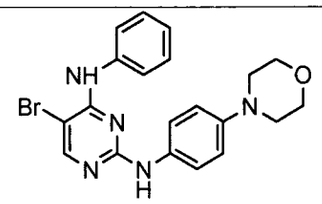
16	
17	
18	
19	
20	
21	

Entrada	Estructura
22	
23	
24	
25	
26	

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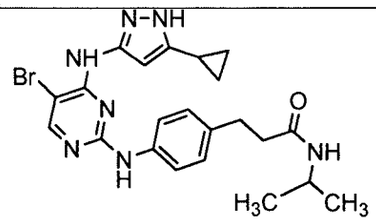
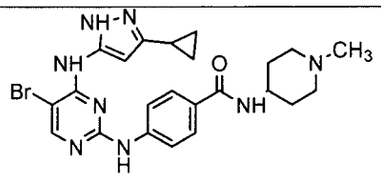
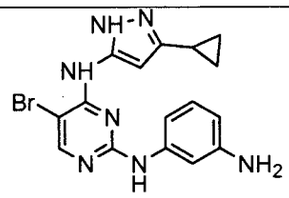
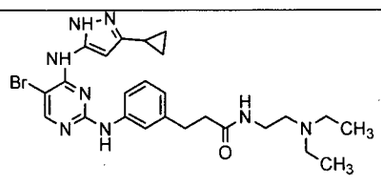
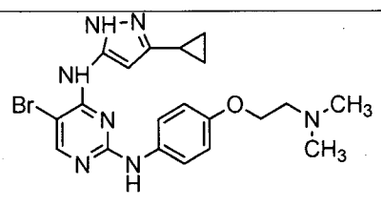
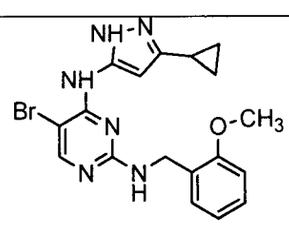
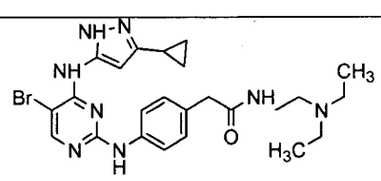
27	
28	
29	
30	
31	
32	
33	

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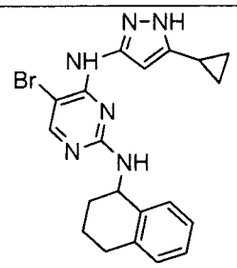
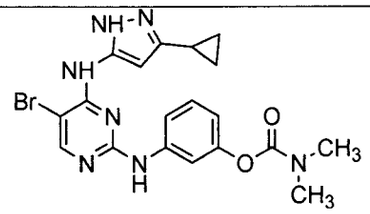
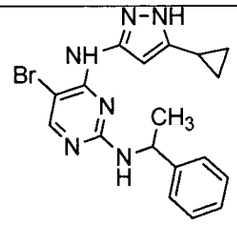
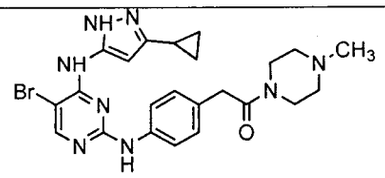
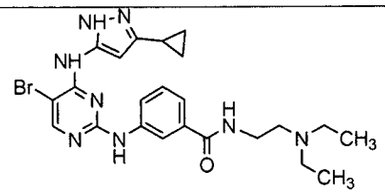
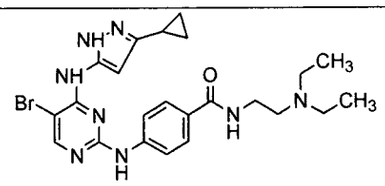
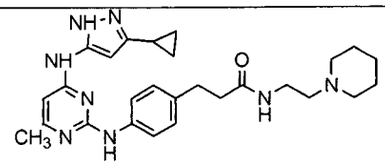
34	
35	
36	
37	
38	
39	
40	

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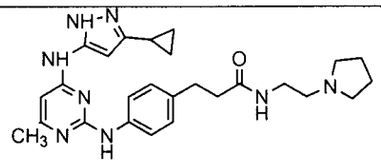
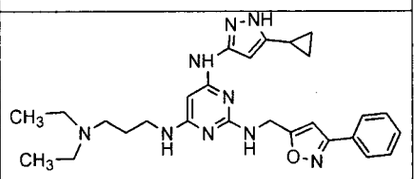
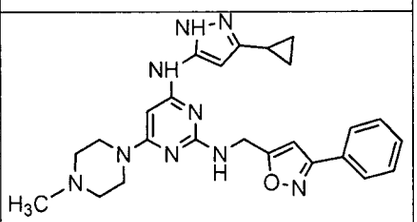
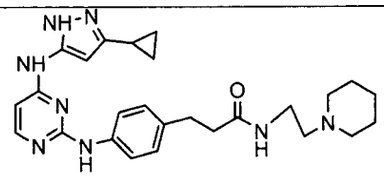
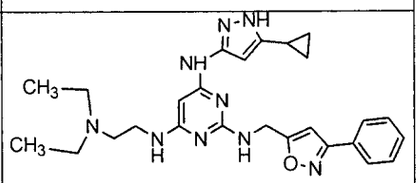
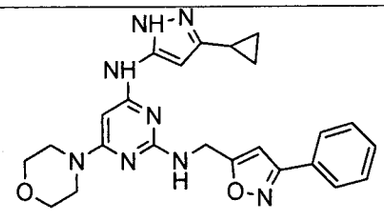
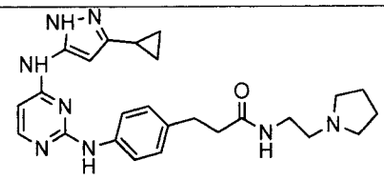
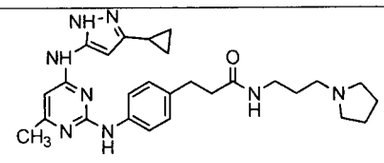
41	
42	
43	
44	
45	
46	
47	
48	

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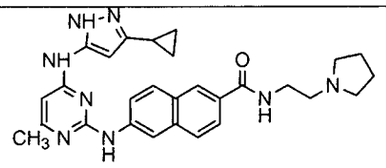
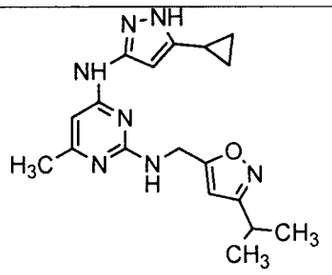
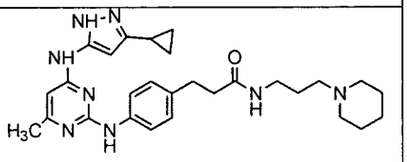
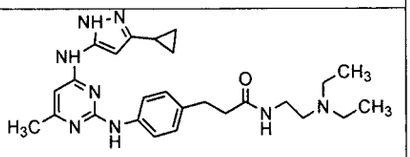
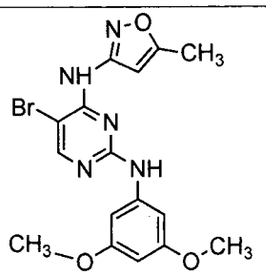
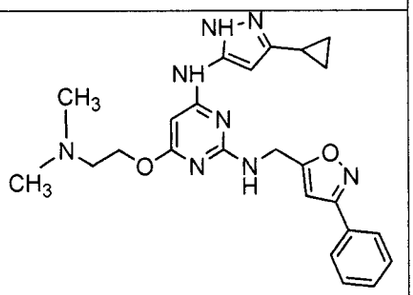
49	
50	
51	
52	
53	
54	

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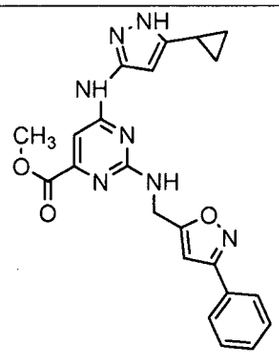
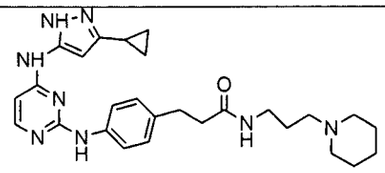
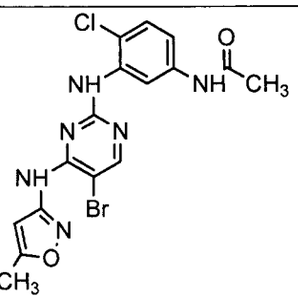
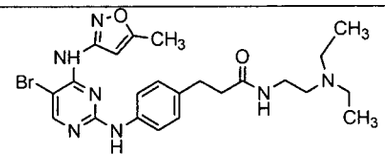
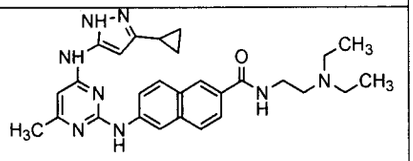
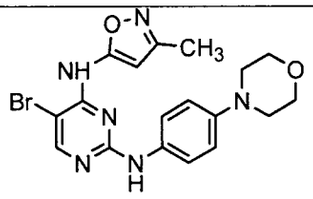
55	
56	
57	
58	
59	
60	

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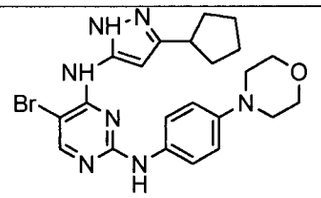
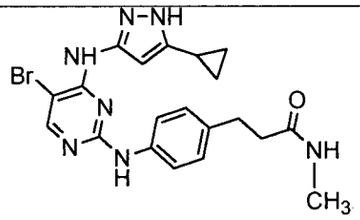
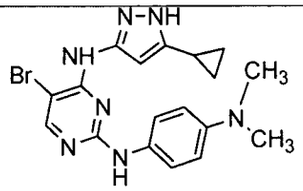
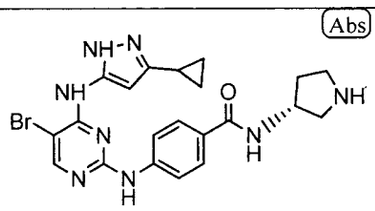
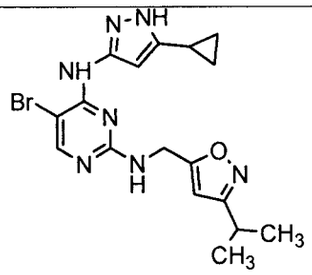
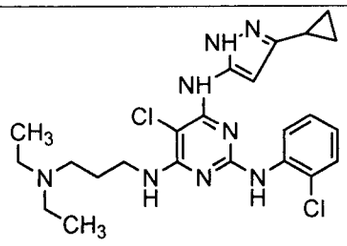
61	
62	
63	
64	
65	
66	

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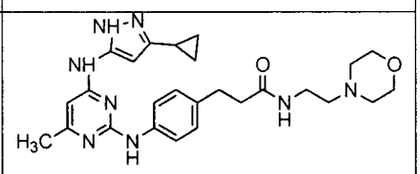
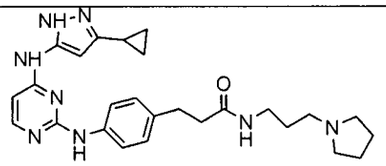
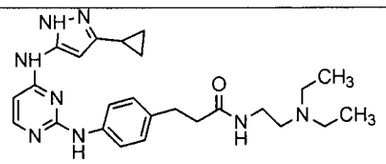
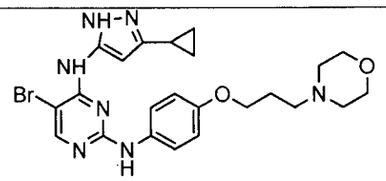
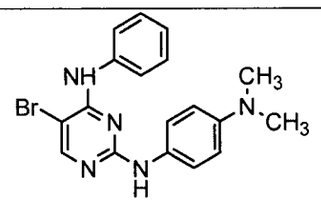
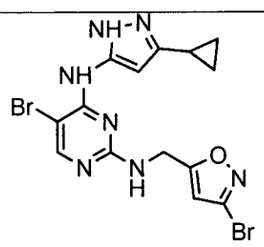
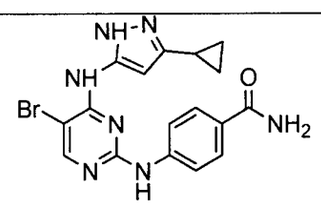
67	
68	
69	
70	
71	
72	
73	

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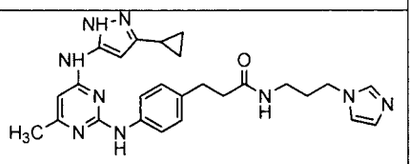
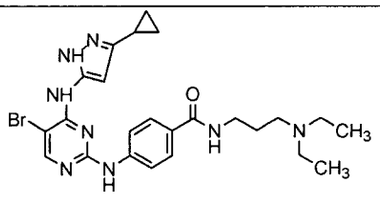
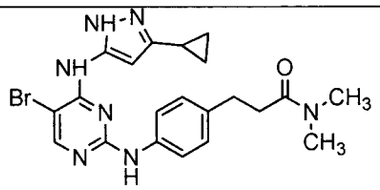
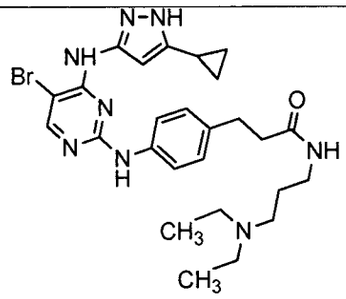
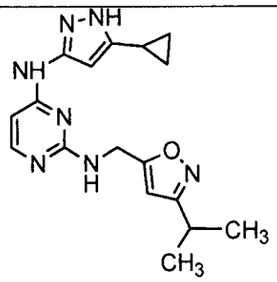
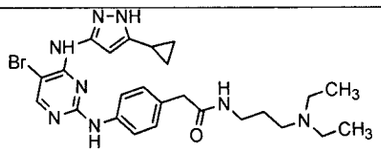
74	
75	
76	
77	
78	
79	

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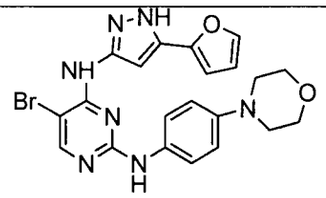
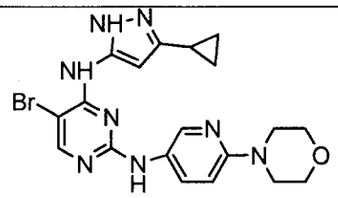
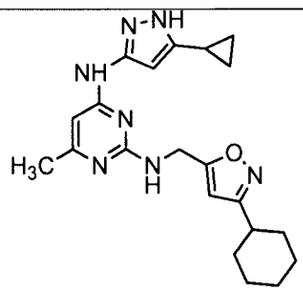
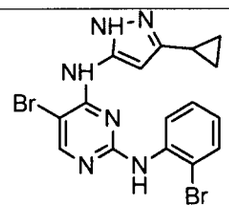
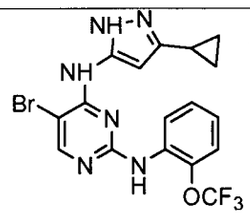
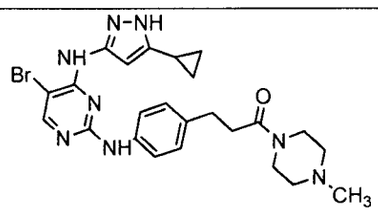
80	
81	
82	
83	
84	
85	

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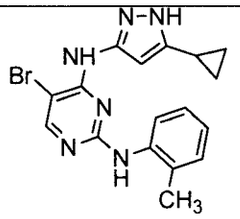
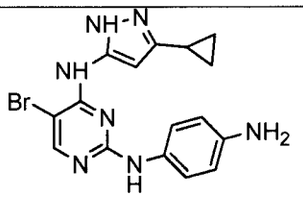
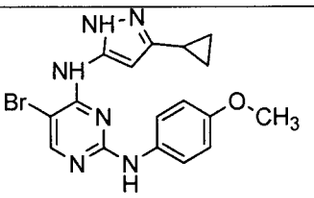
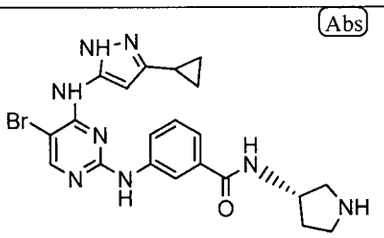
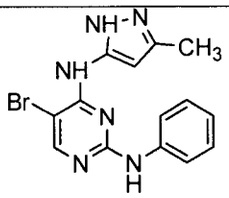
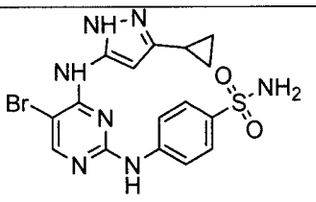
86	
87	
88	
89	 Abs
90	
91	

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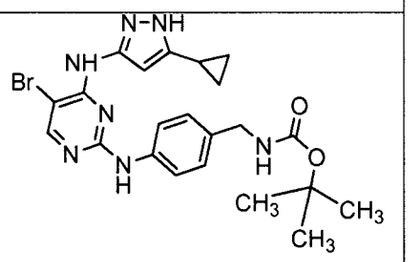
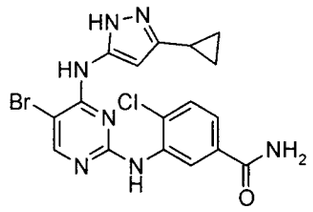
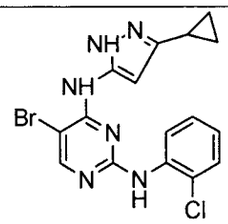
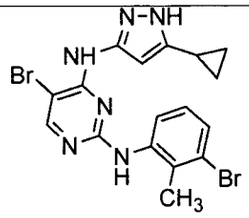
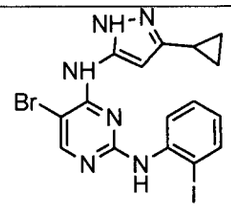
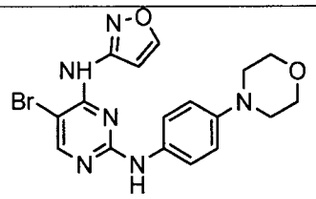
92	
93	
94	
95	
96	
97	

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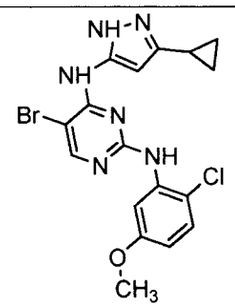
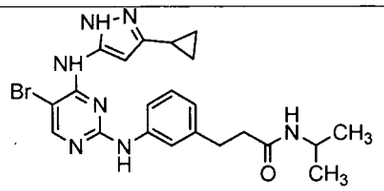
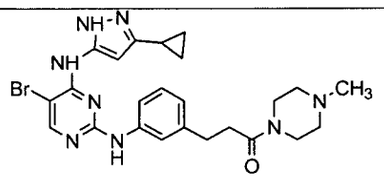
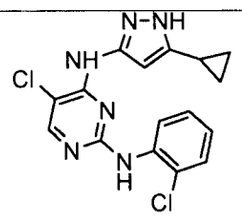
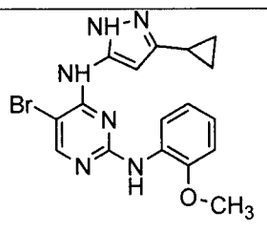
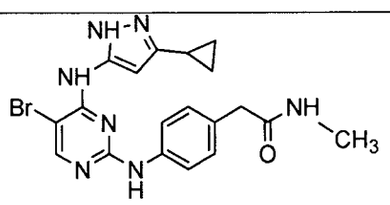
98	
99	
100	
101	
102	
103	

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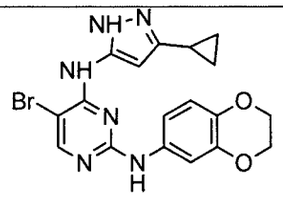
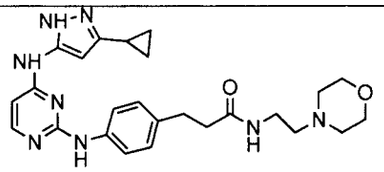
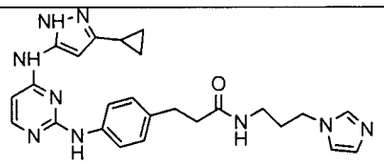
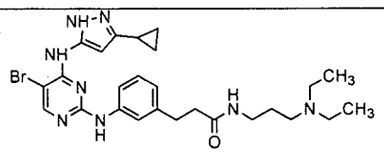
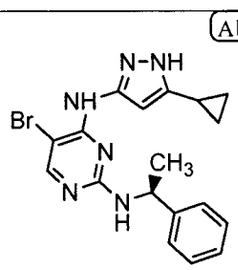
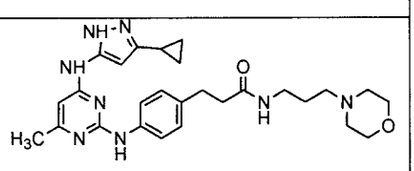
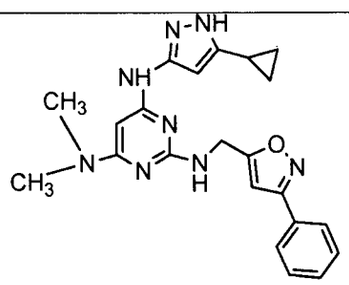
104	
105	
106	
107	
108	
109	
110	

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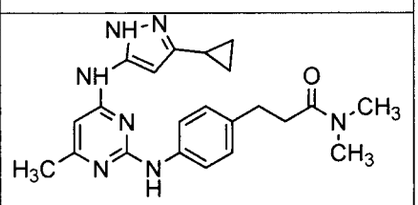
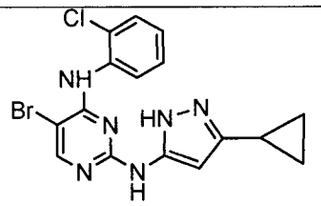
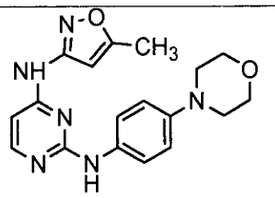
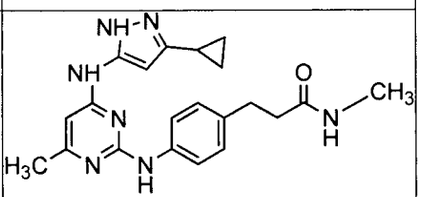
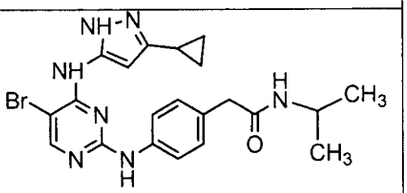
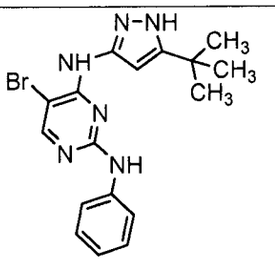
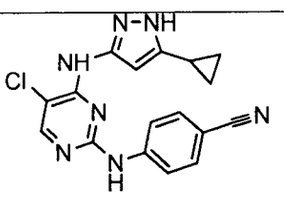
111	
112	
113	
114	
115	
116	
117	

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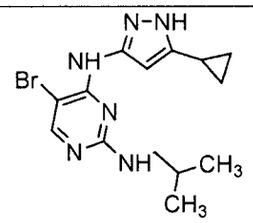
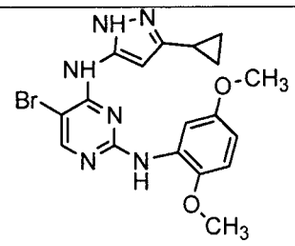
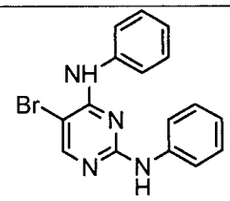
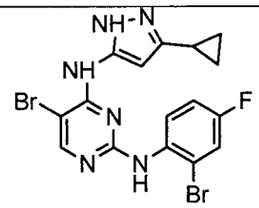
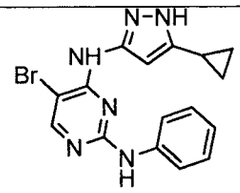
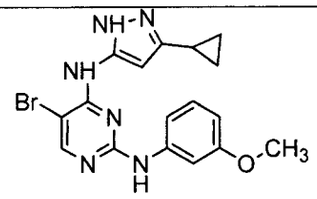
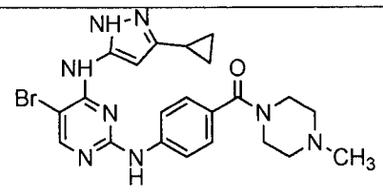
118	
119	
120	
121	
122	
123	
124	

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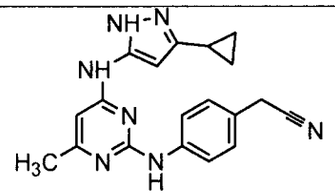
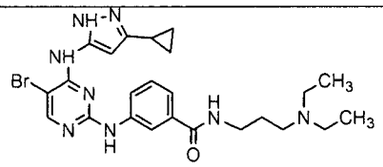
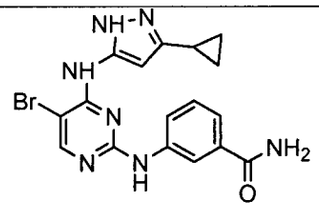
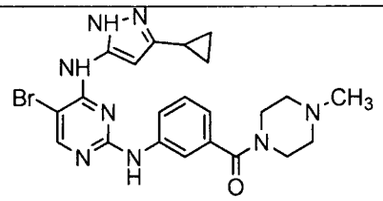
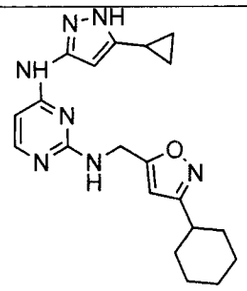
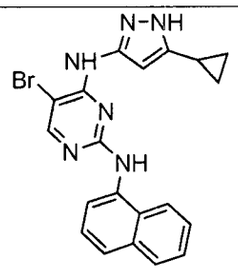
125	
126	
127	
128	
129	
130	

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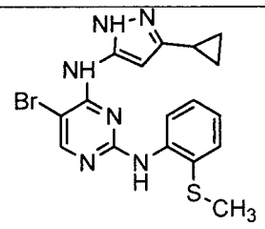
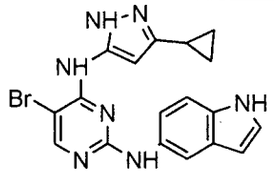
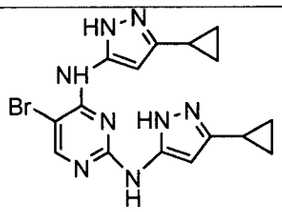
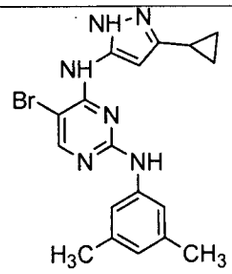
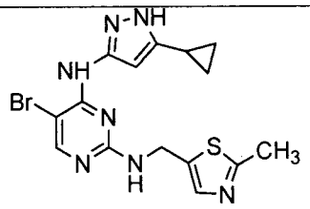
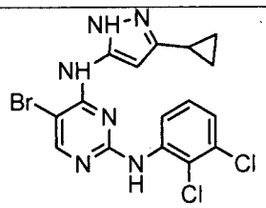
131	
132	
133	
134	
135	
136	

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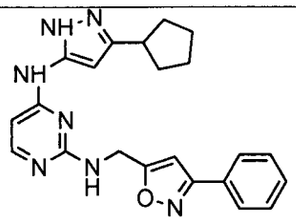
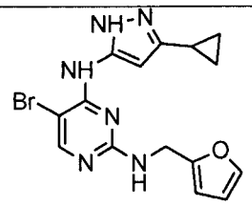
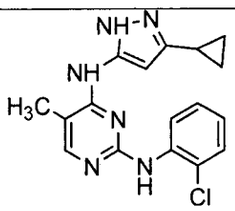
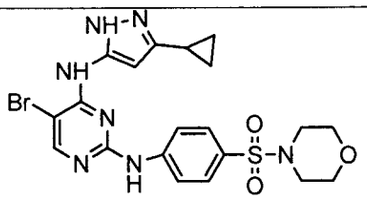
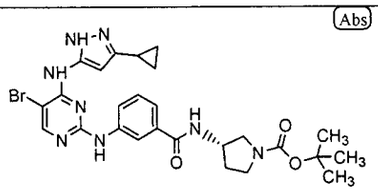
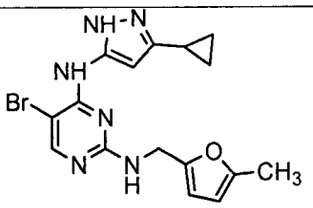
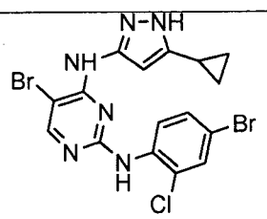
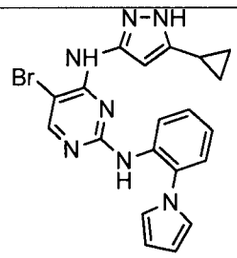
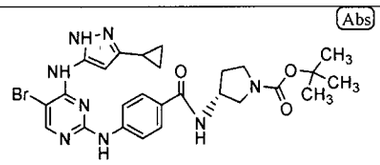
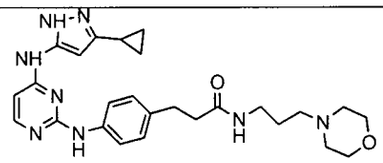
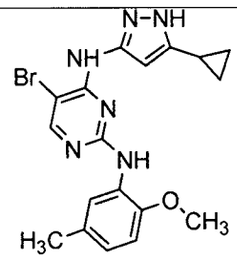
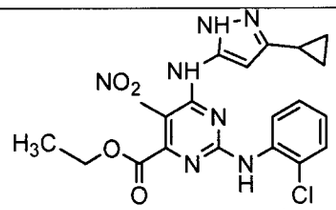
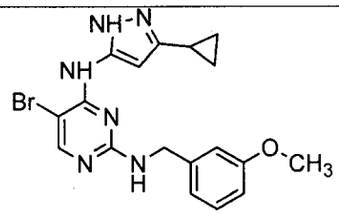
137	
138	
139	
140	
141	
142	
143	

Entrada	Estructura
144	
145	
146	
147	
148	
149	

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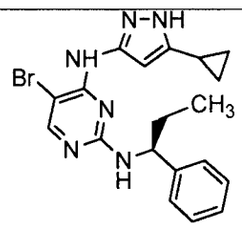
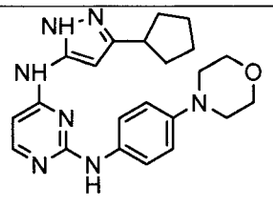
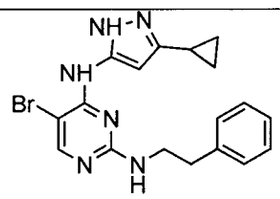
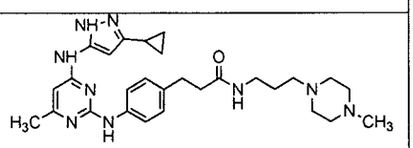
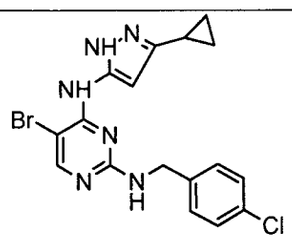
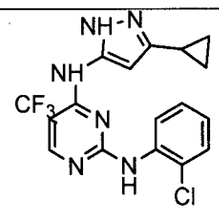
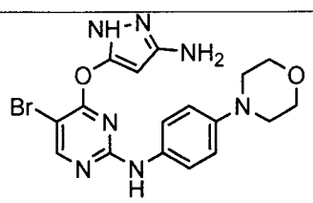
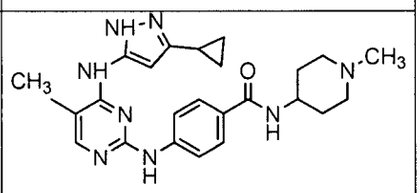
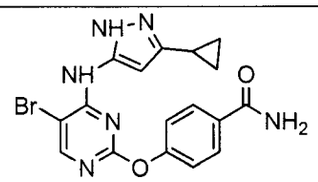
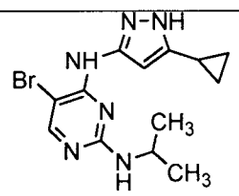
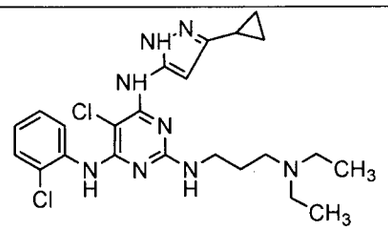
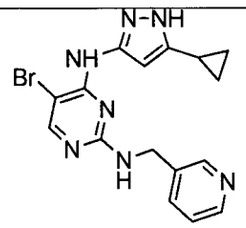
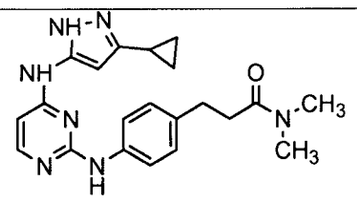
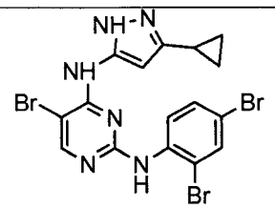
150	
151	
152	
153	
154	
155	
156	

Entrada	Estructura
157	
158	
159	
160	
161	
162	
163	

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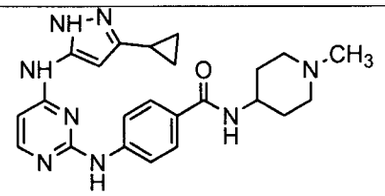
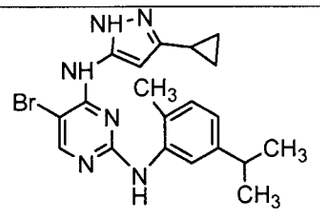
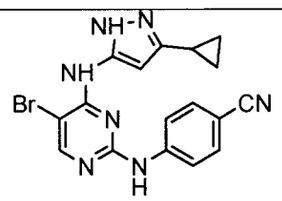
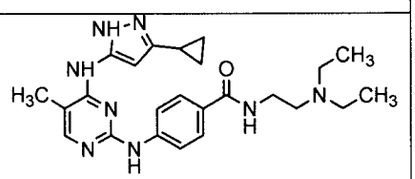
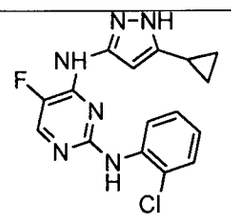
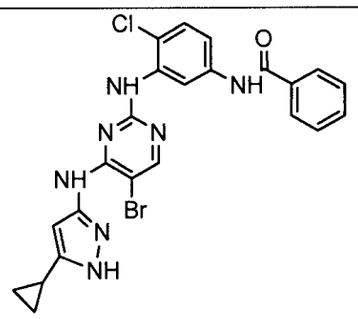
164	
165	
166	
167	
168	
169	

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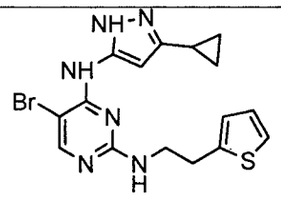
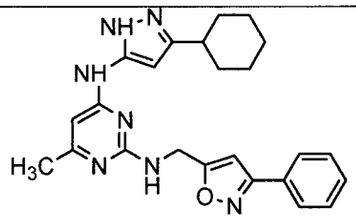
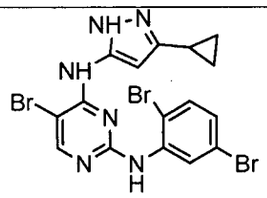
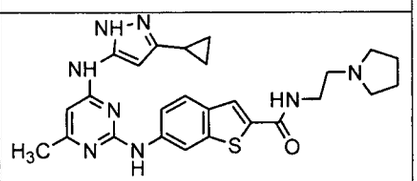
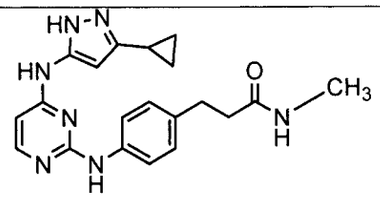
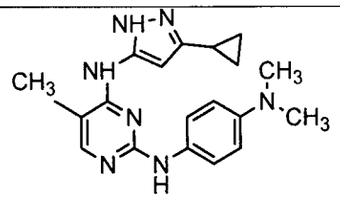
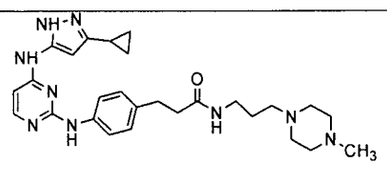
170	
171	
172	
173	
174	
175	
176	

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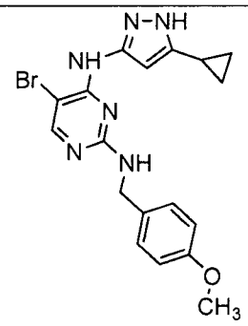
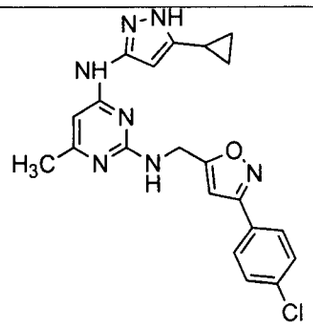
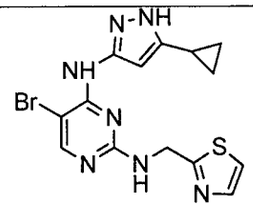
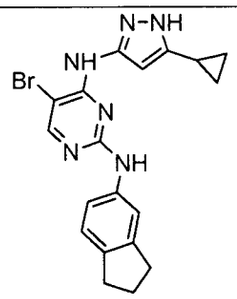
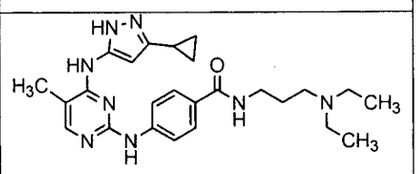
177	
178	
179	
180	
181	

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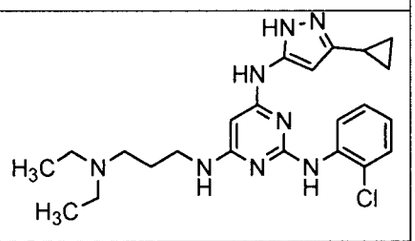
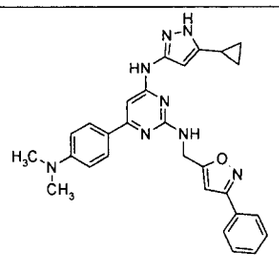
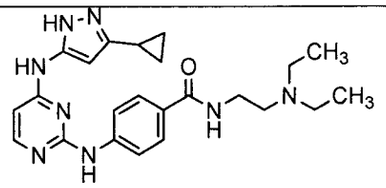
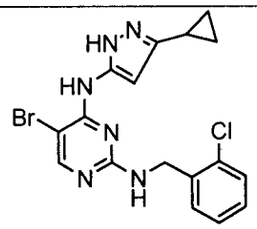
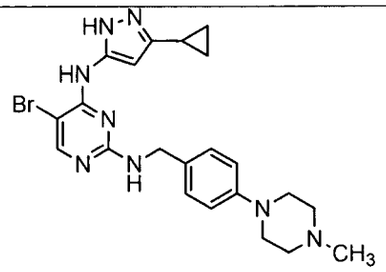
182	
183	
184	
185	
186	

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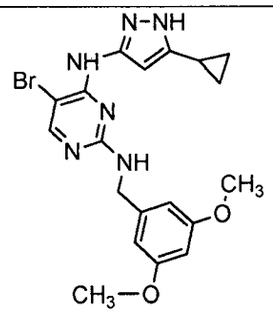
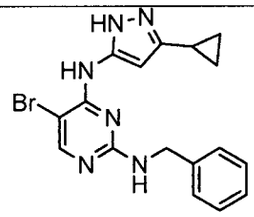
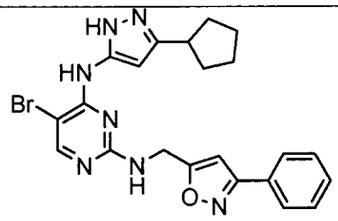
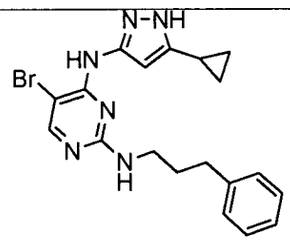
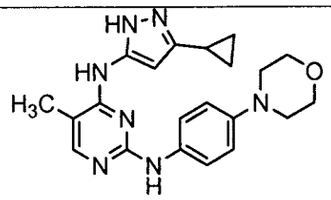
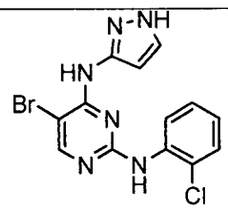
187	
188	
189	
190	
191	
192	

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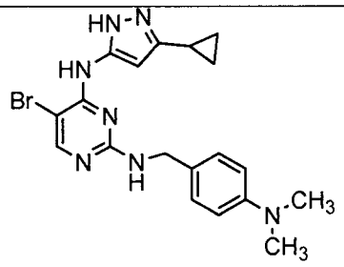
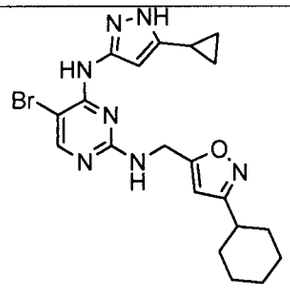
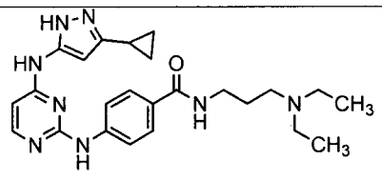
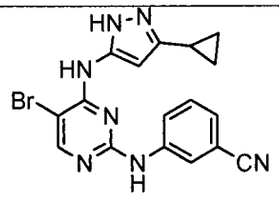
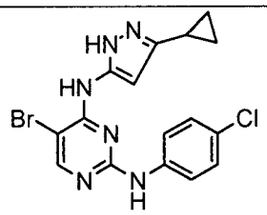
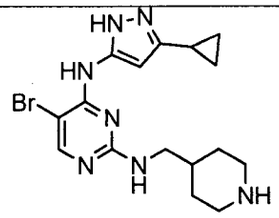
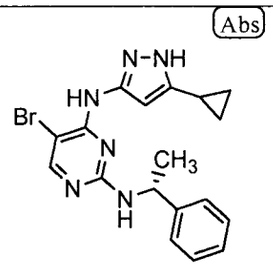
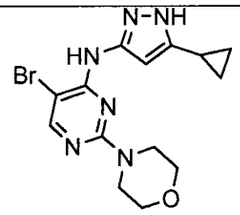
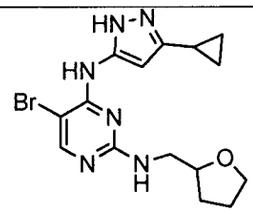
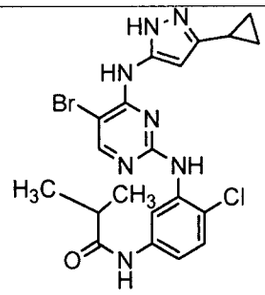
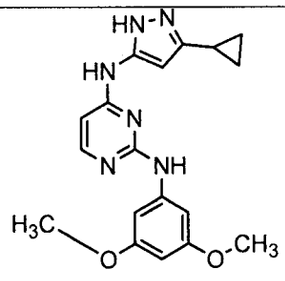
193	
194	
195	
196	
197	
198	

Entrada	Estructura
199	
200	
201	
202	
203	

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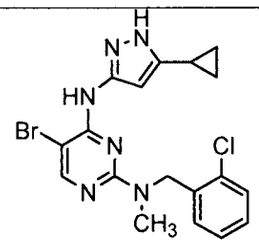
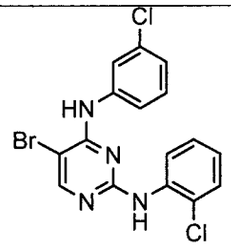
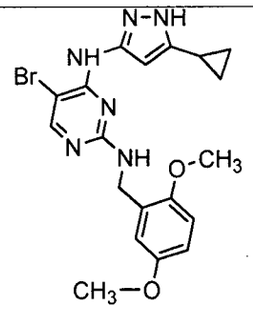
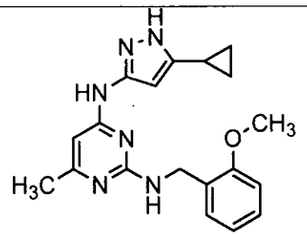
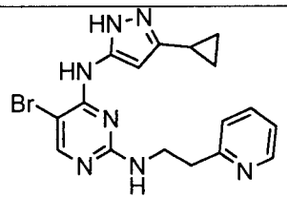
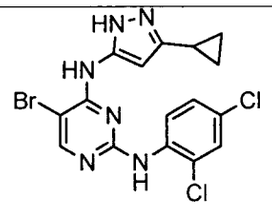
204	
205	
206	
207	
208	
209	

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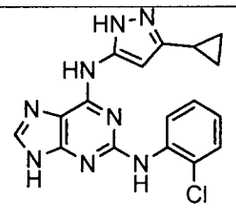
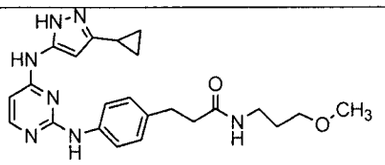
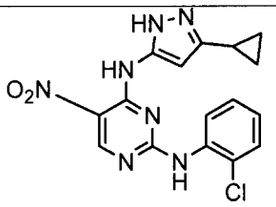
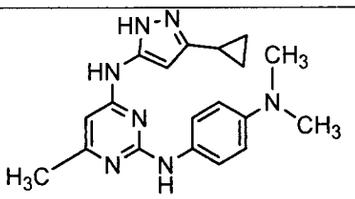
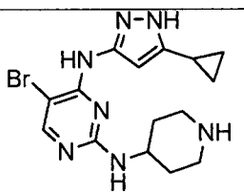
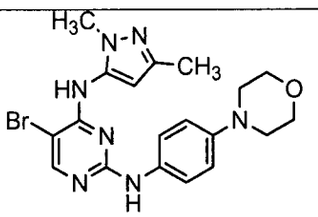
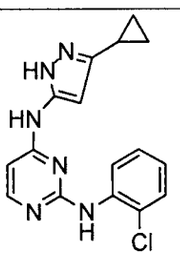
210	
211	
212	
213	
214	
215	
216	

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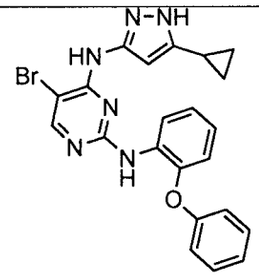
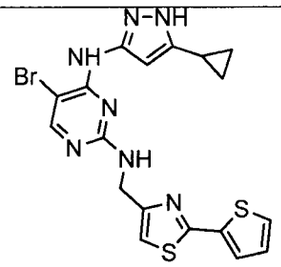
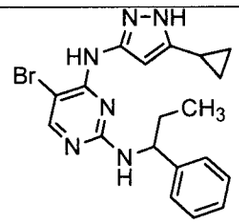
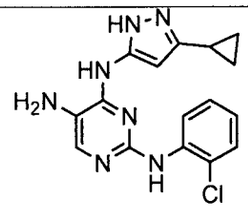
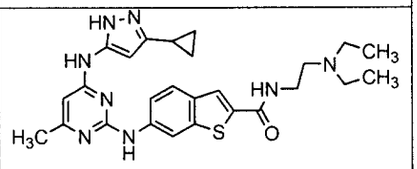
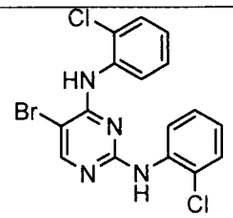
217	
218	
219	
220	
221	
222	

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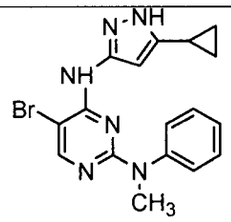
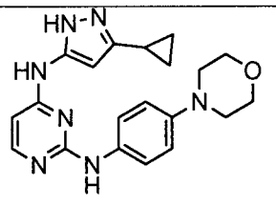
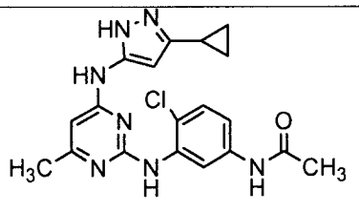
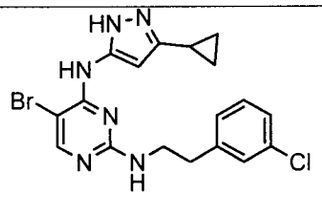
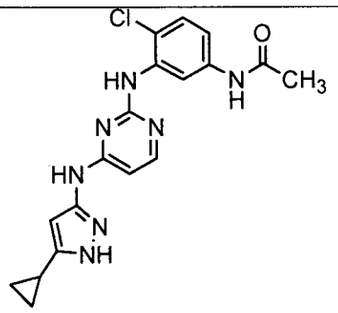
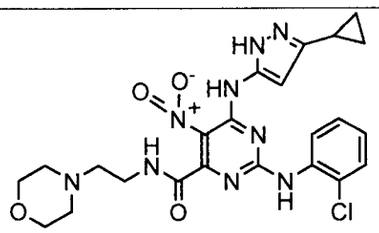
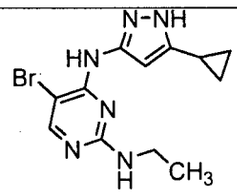
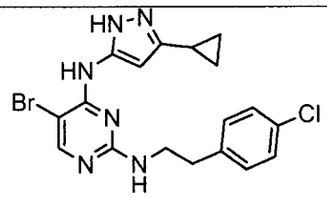
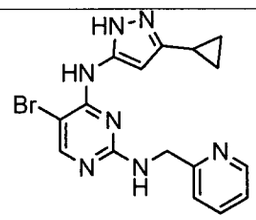
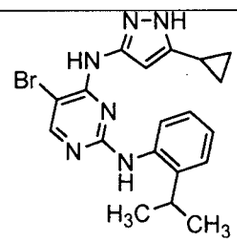
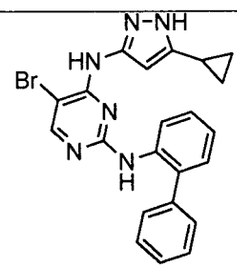
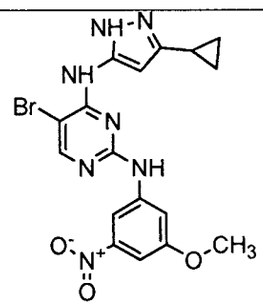
223	
224	
225	
226	
227	
228	

Entrada	Estructura
229	
230	
231	
232	
233	
234	

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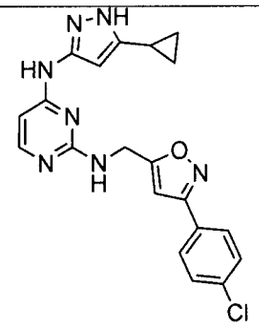
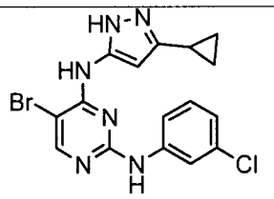
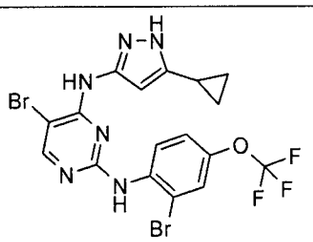
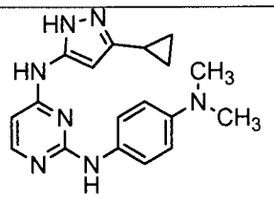
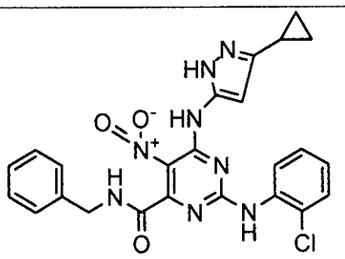
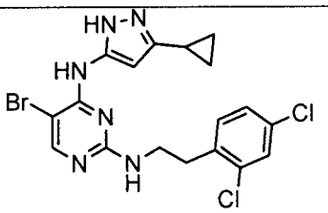
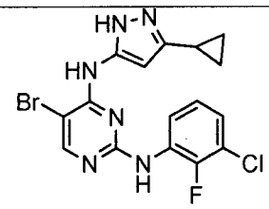
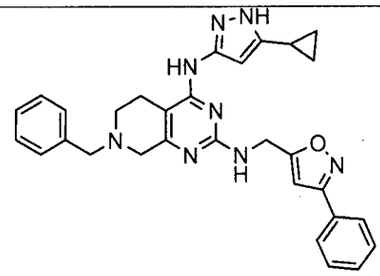
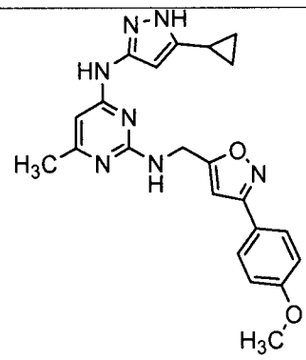
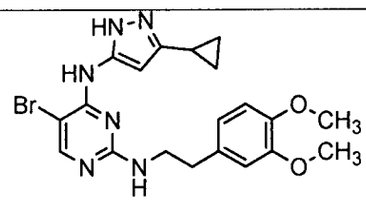
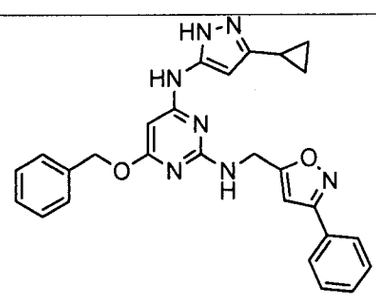
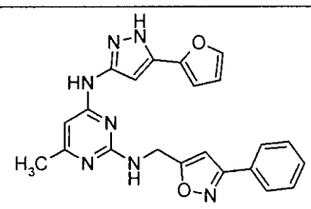
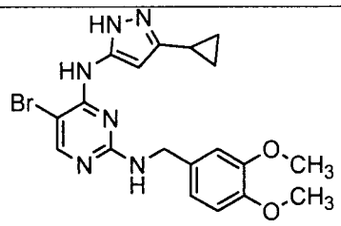
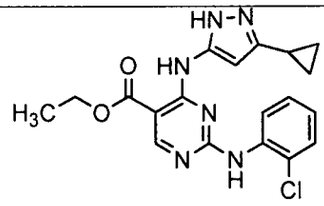
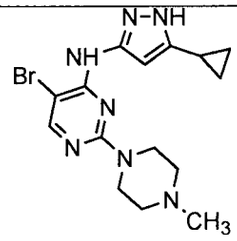
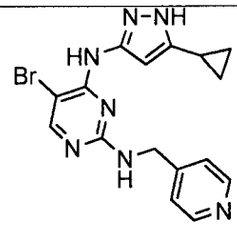
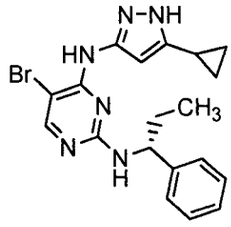
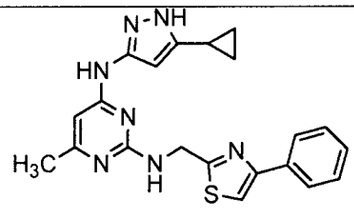
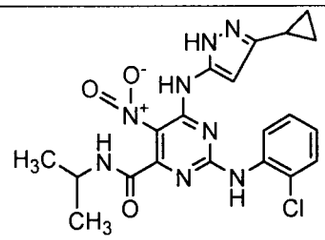
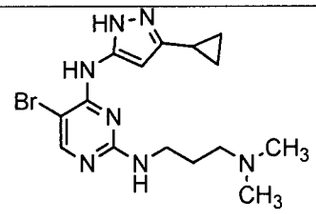
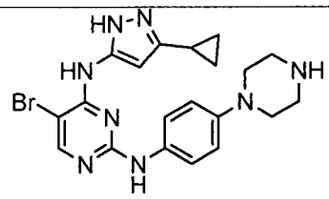
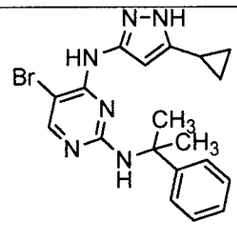
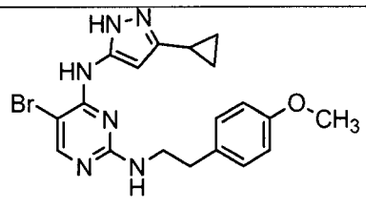
235	
236	
237	
238	
239	
240	

Entrada	Estructura
241	
242	
243	
244	
245	

Entrada	Estructura
246	
247	
248	
249	
250	
251	Abs 

Entrada	Estructura
252	
253	
254	
255	
256	
257	

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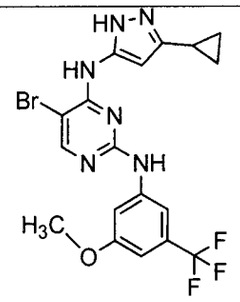
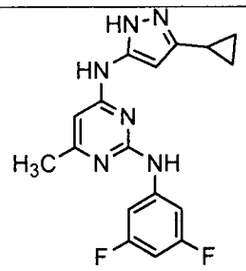
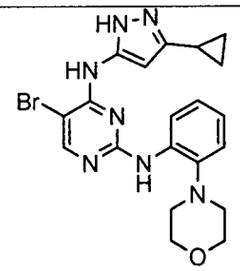
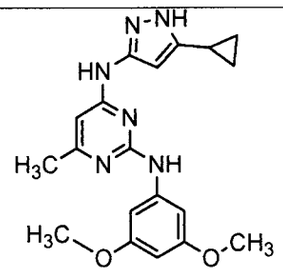
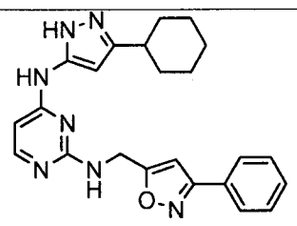
258	
259	
260	
261	
262	

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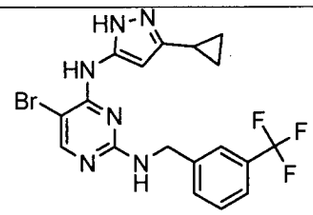
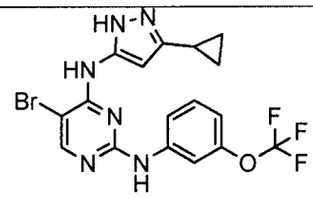
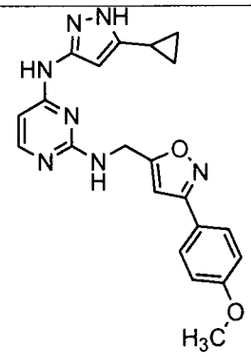
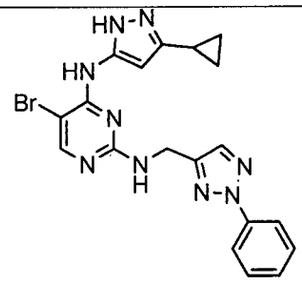
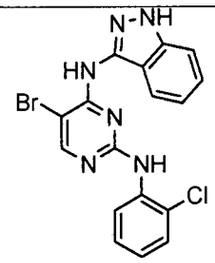
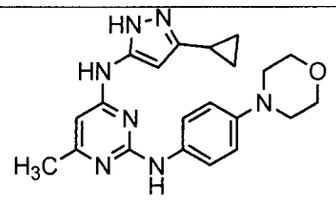
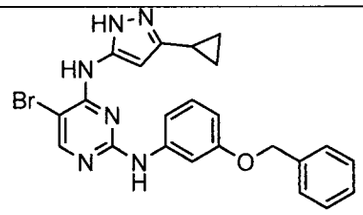
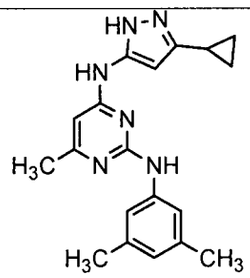
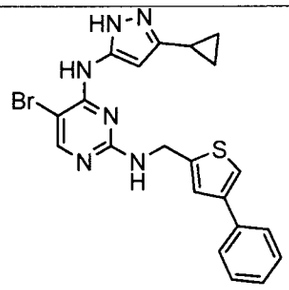
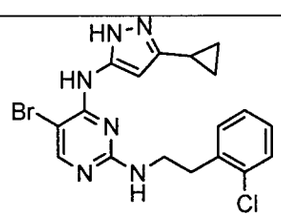
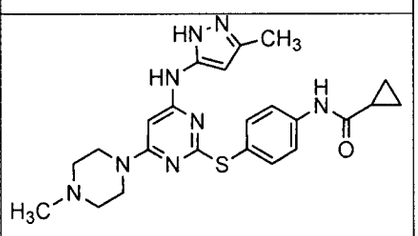
263	
264	
265	
266	
267	

Entrada	Estructura
268	
269	
270	
271	
272	
273	

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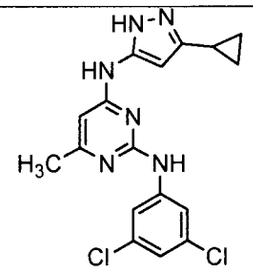
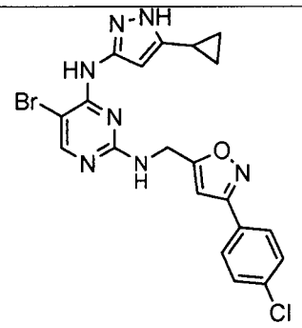
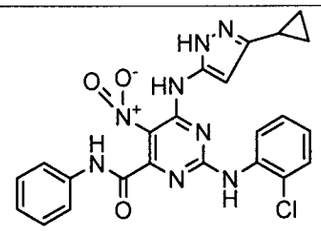
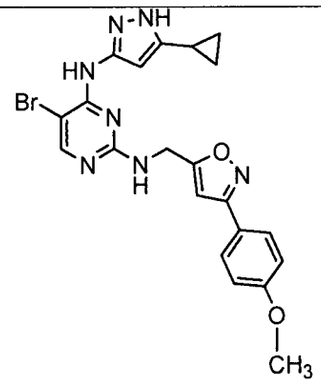
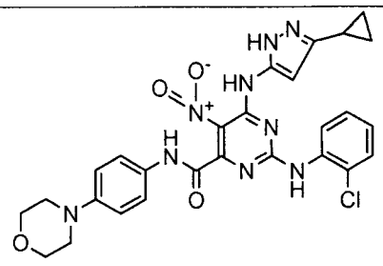
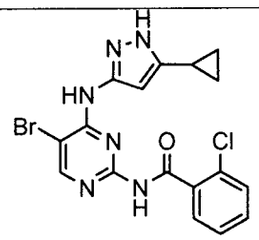
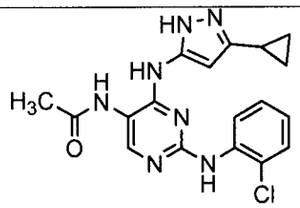
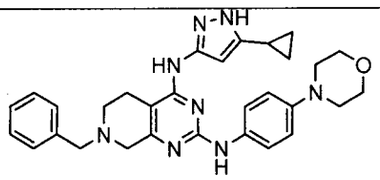
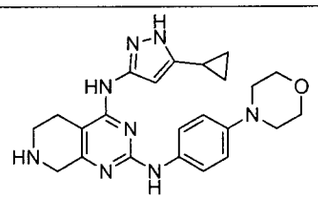
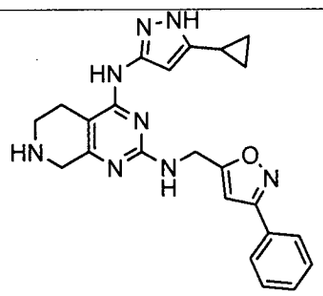
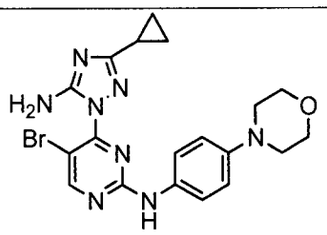
274	
275	
276	
277	
278	

Entrada	Estructura
279	
280	
281	
282	
283	
284	

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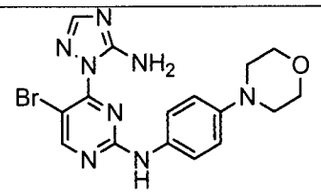
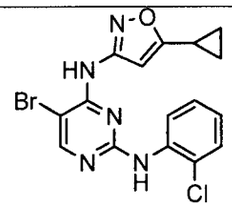
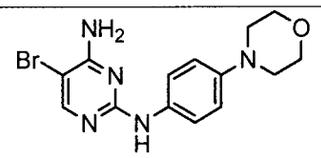
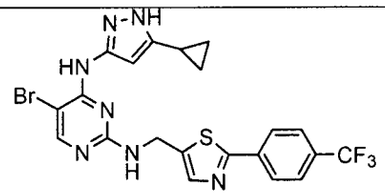
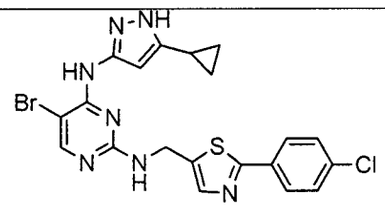
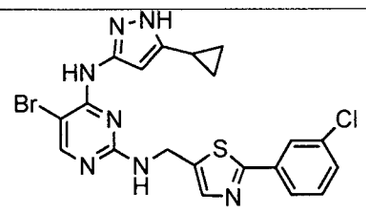
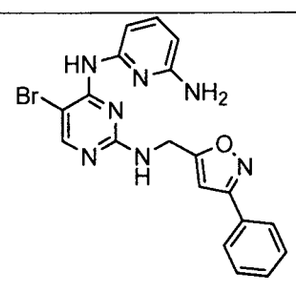
285	
286	
287	
288	
289	
290	
291	

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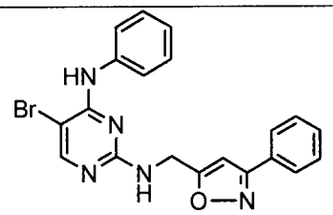
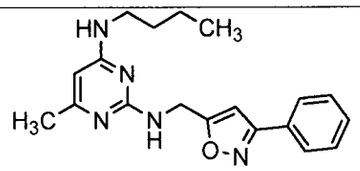
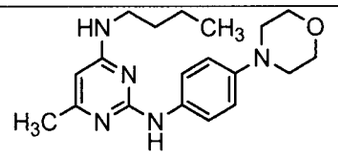
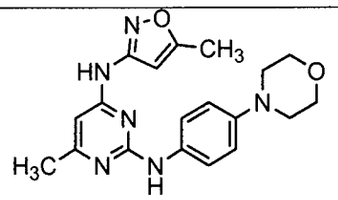
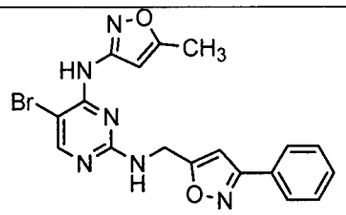
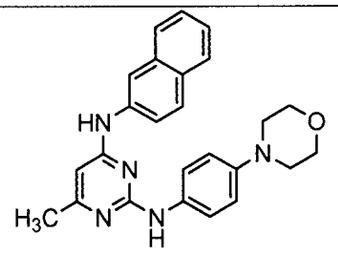
292	
293	
294	
295	
296	
297	

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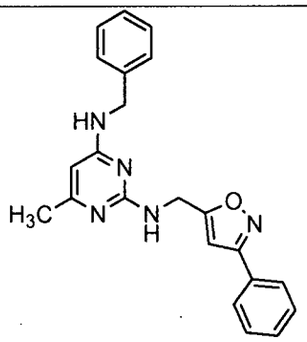
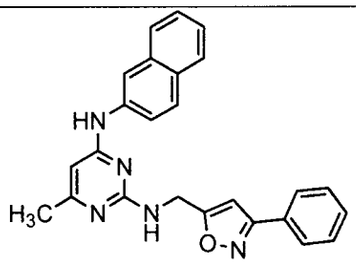
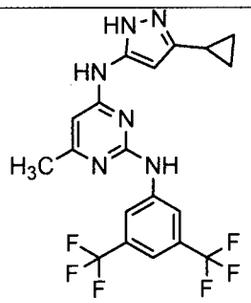
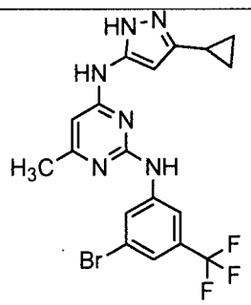
298	
299	
300	
301	

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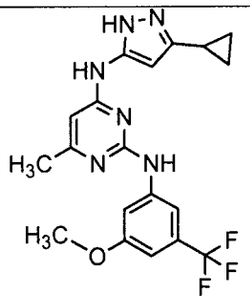
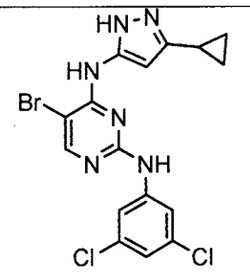
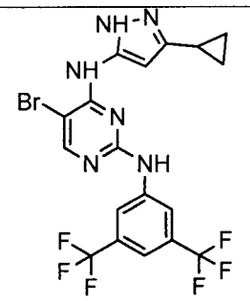
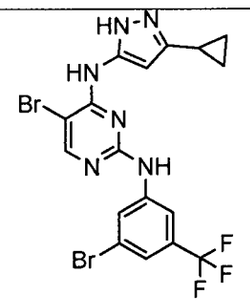
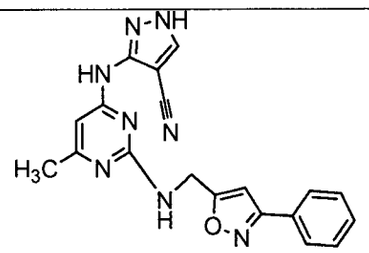
302	
303	
304	
305	
306	

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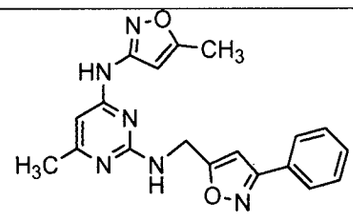
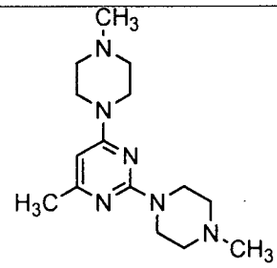
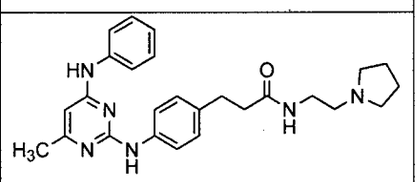
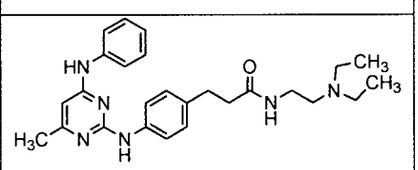
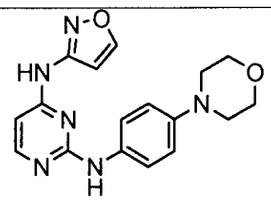
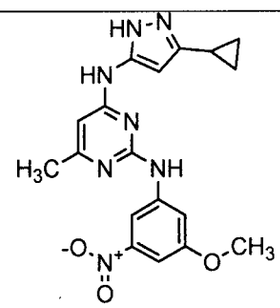
307	
308	
309	
310	
311	
312	

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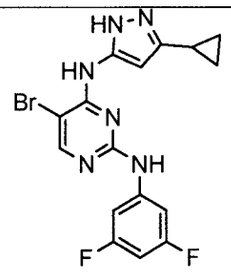
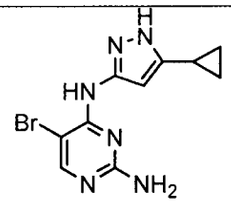
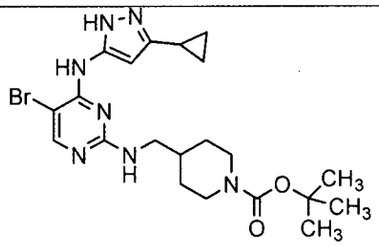
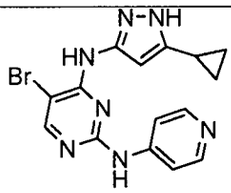
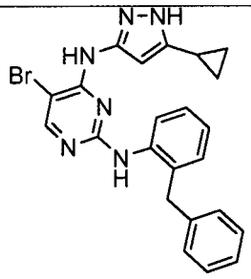
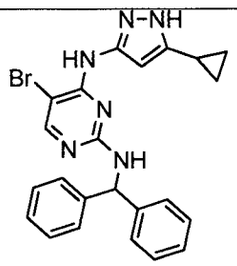
313	
314	
315	
316	
317	
318	

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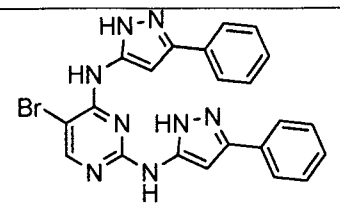
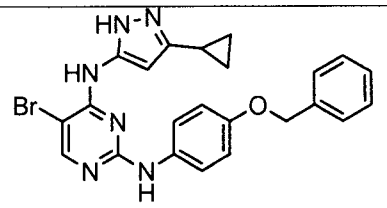
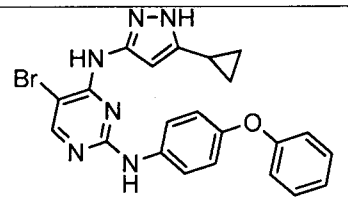
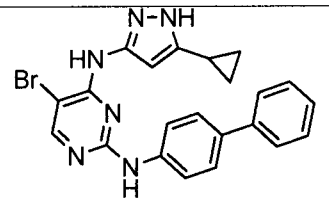
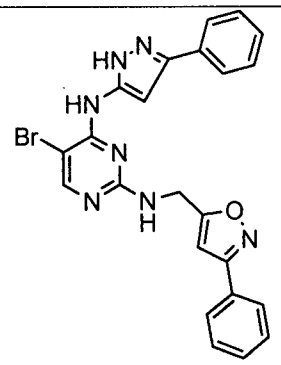
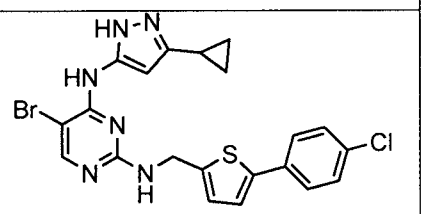
319	
320	
321	
322	
323	
324	

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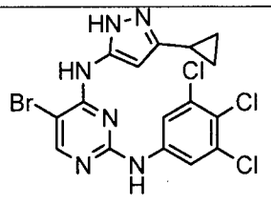
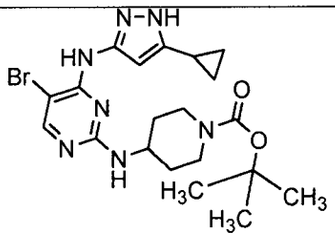
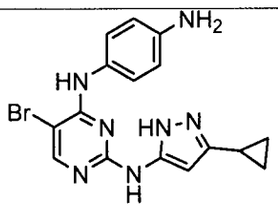
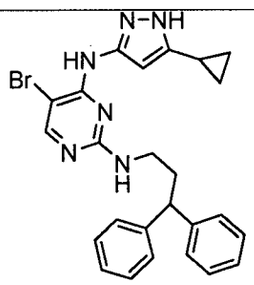
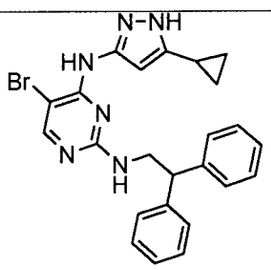
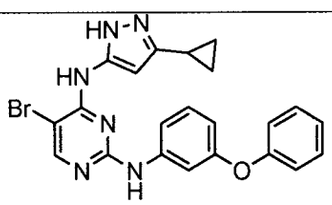
325	
326	
327	
328	
329	
330	

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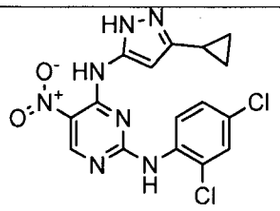
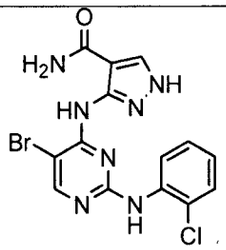
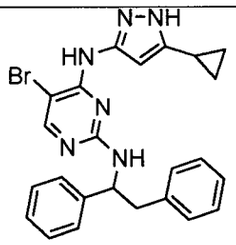
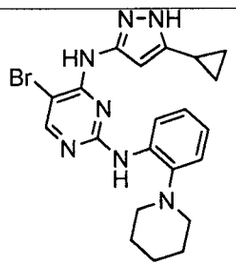
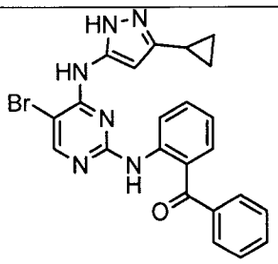
331	
332	
333	
334	
335	

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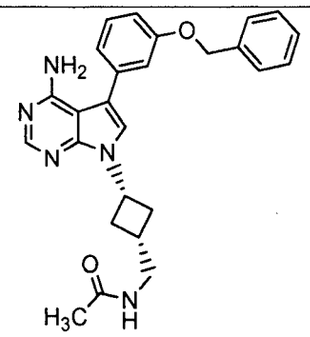
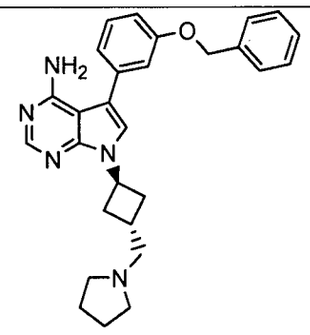
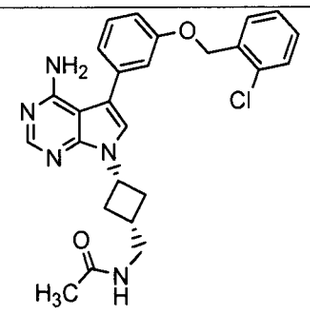
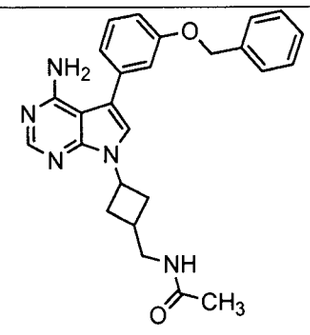
336	
337	
338	
339	

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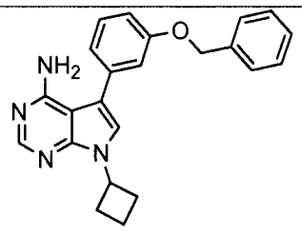
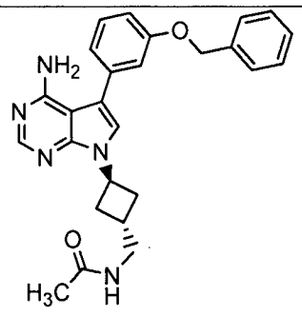
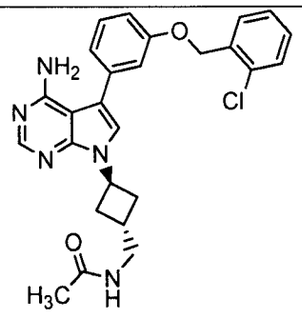
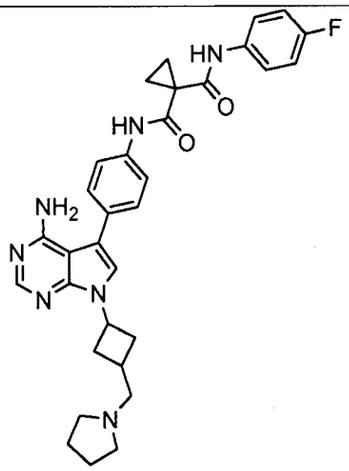
340	
341	
342	
343	

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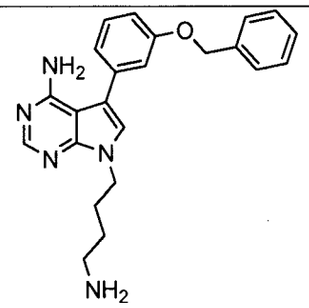
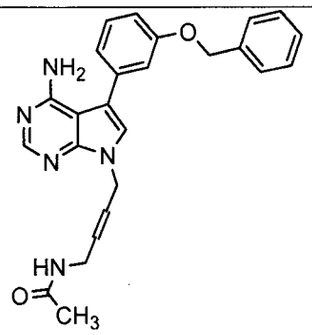
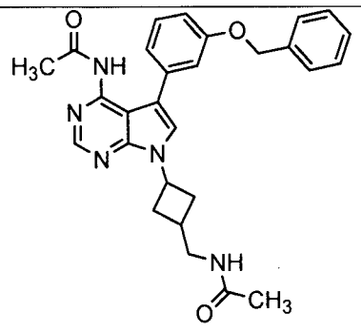
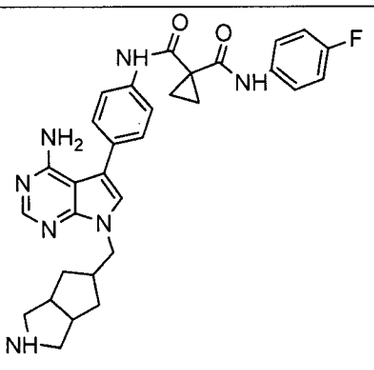
344	
345	
346	
347	

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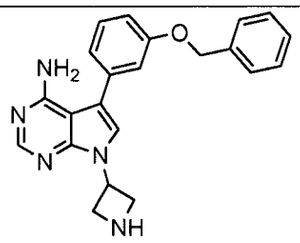
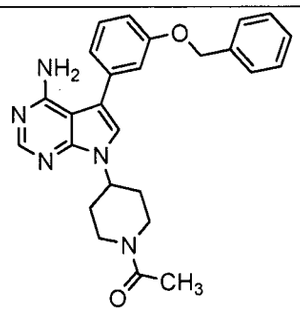
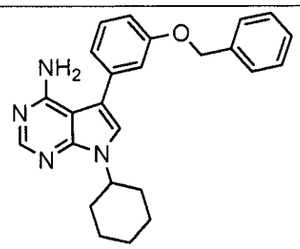
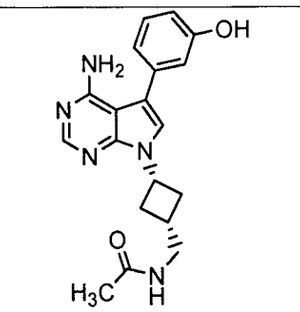
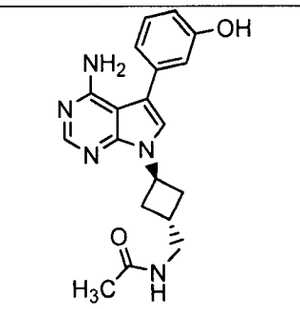
348	
349	
350	
351	
352	

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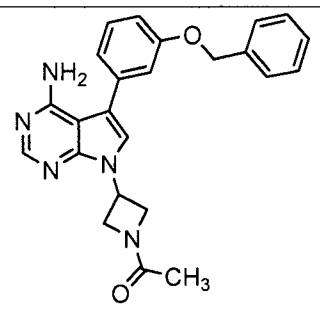
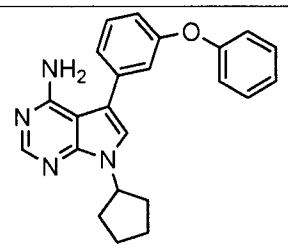
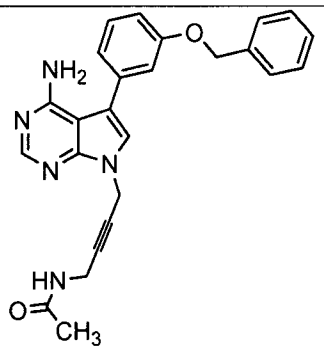
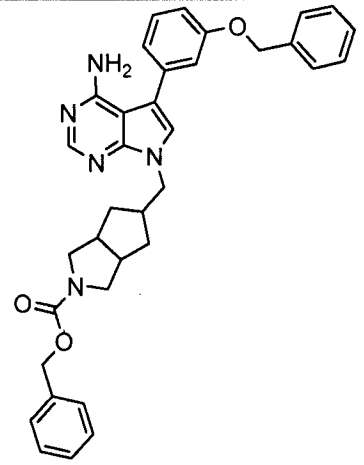
353	
354	
355	
356	

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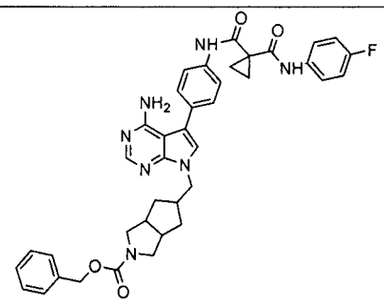
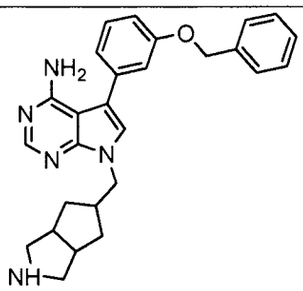
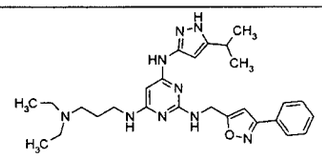
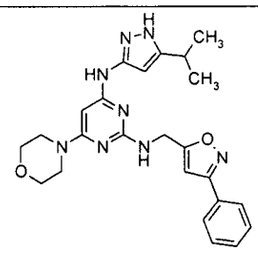
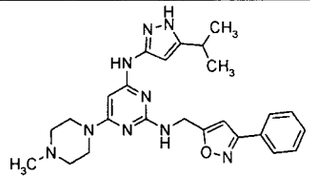
357	
358	
495	
496	
497	

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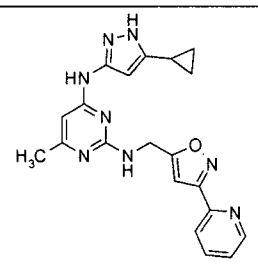
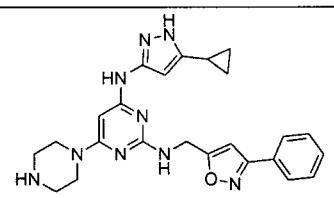
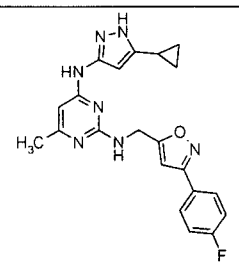
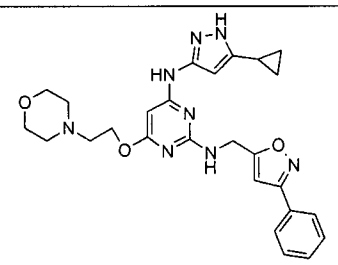
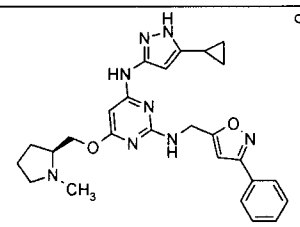
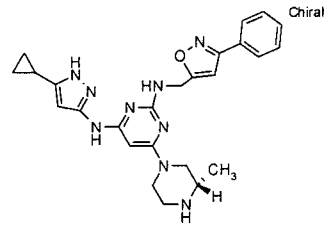
498	
499	
500	
501	
502	Chiral 
503	Chiral 

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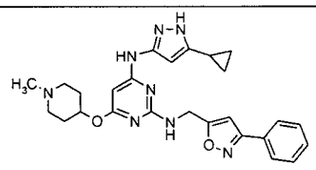
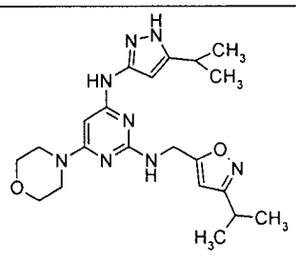
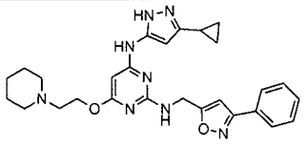
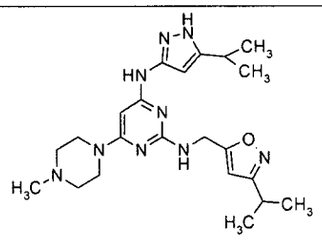
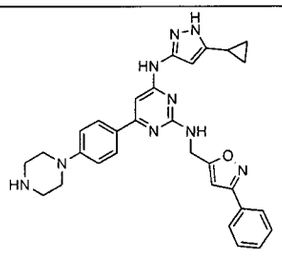
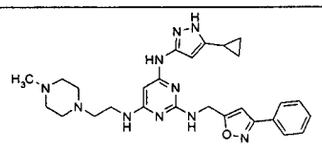
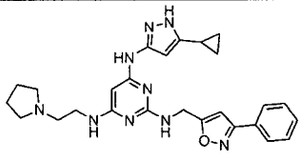
504	
505	
506	
507	
508	
509	
510	

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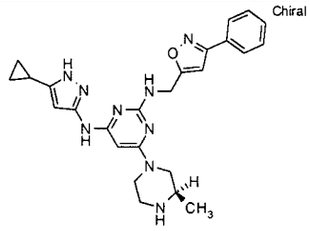
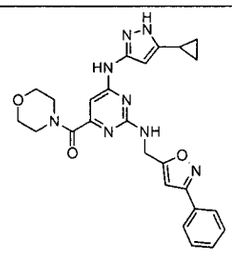
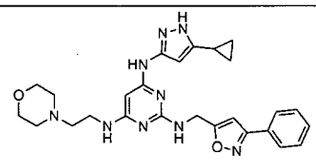
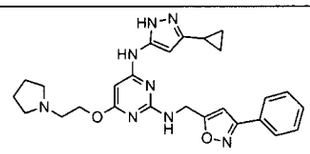
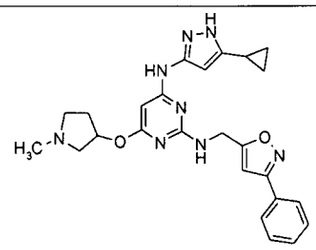
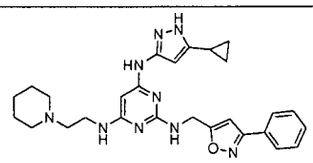
511	
512	
513	
514	
515	
516	

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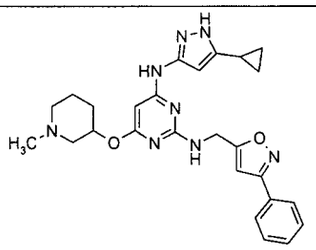
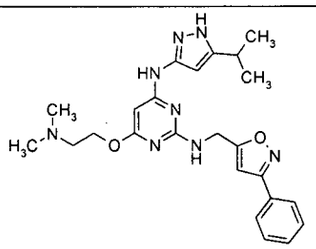
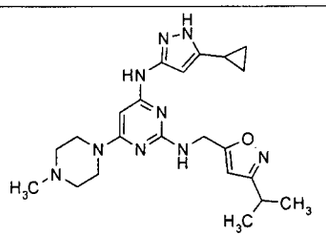
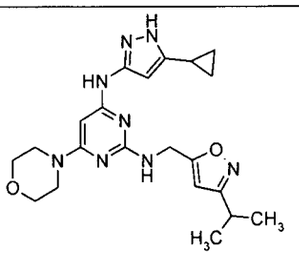
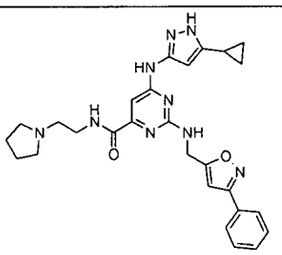
517	
518	
519	
520	
521	

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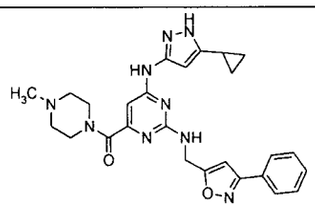
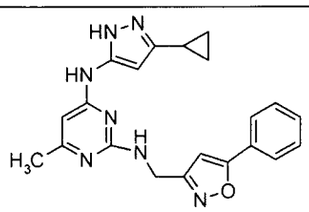
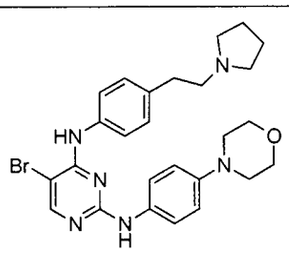
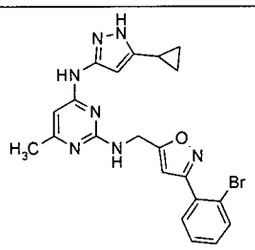
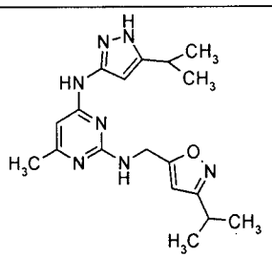
522	
523	
524	
525	
526	

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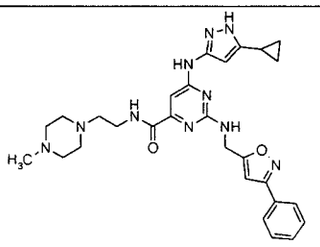
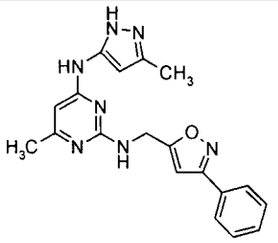
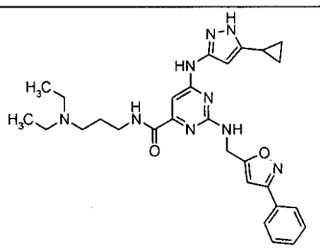
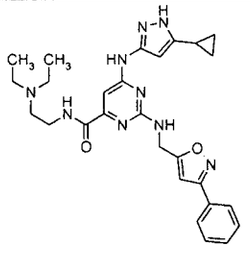
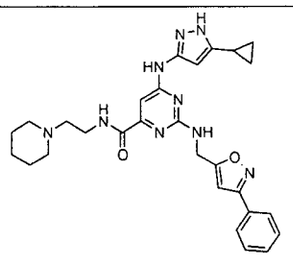
527	
528	
529	
530	
531	

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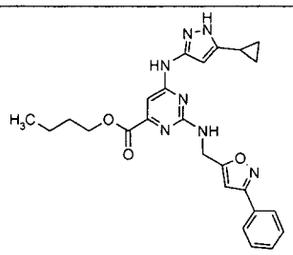
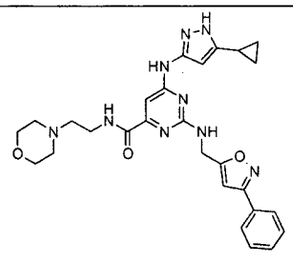
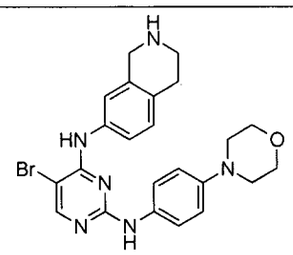
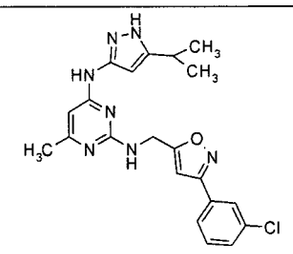
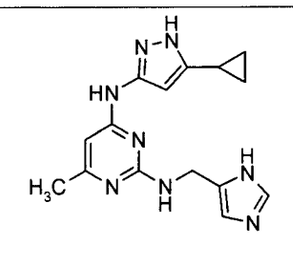
532	
533	
534	
535	
536	

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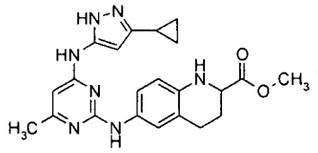
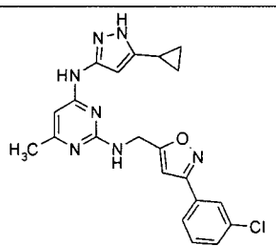
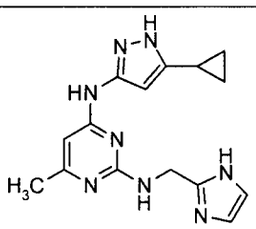
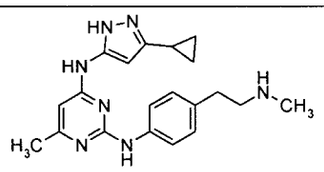
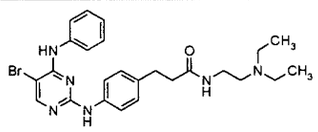
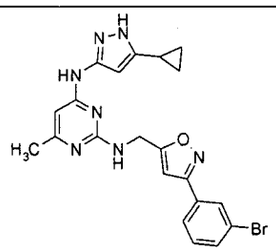
537	
538	
539	
540	
541	
542	

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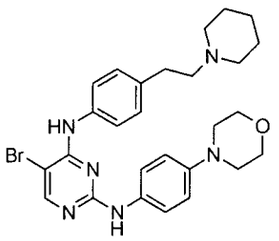
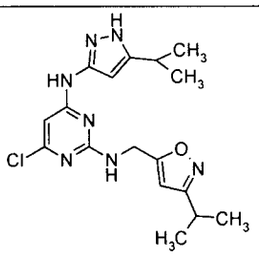
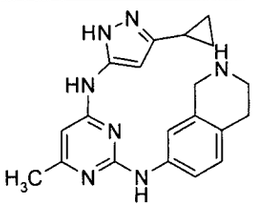
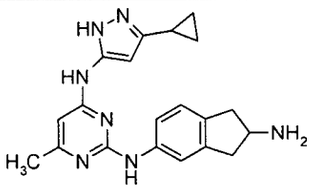
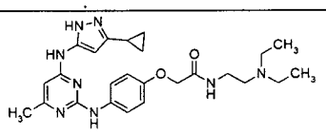
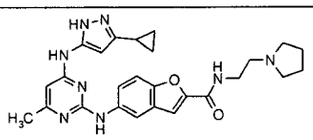
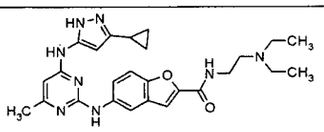
543	
544	
545	
546	
547	
548	
549	

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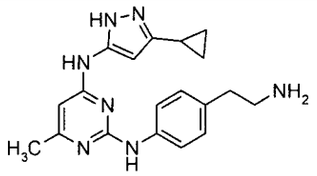
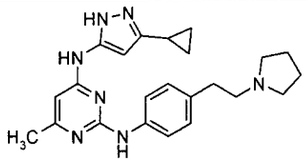
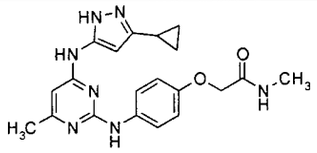
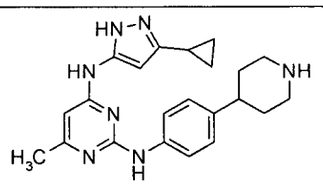
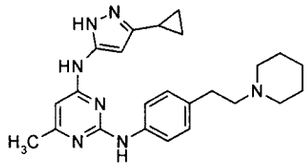
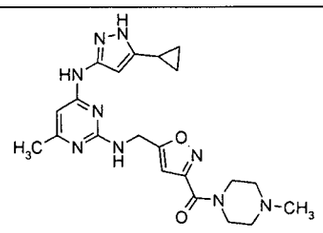
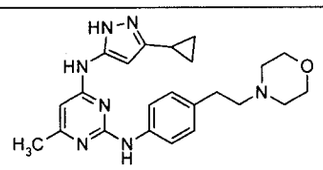
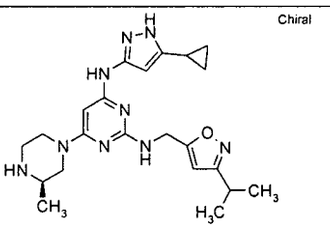
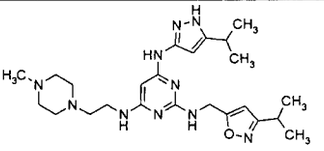
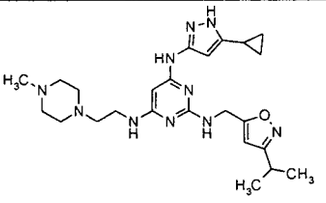
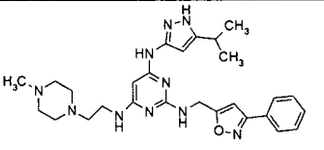
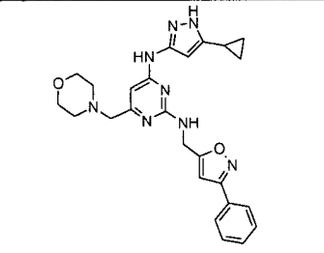
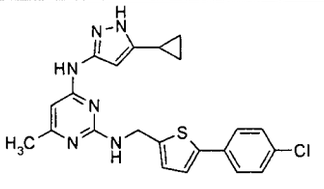
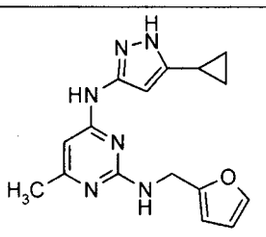
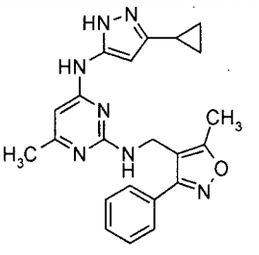
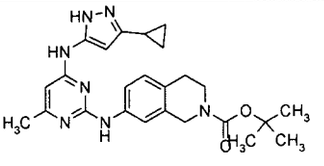
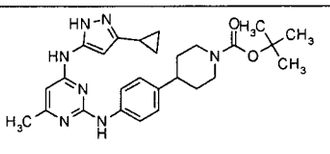
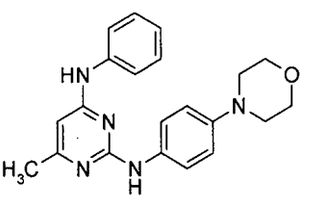
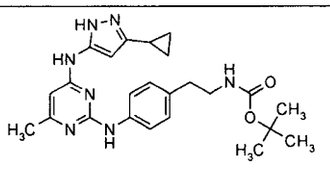
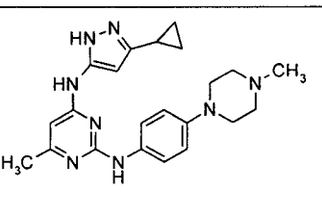
550	
551	
552	
553	
554	
555	
556	

Entrada	Estructura
557	 Chiral
558	
559	
560	
561	
562	

Entrada	Estructura
563	
564	
565	
566	
567	
568	
569	

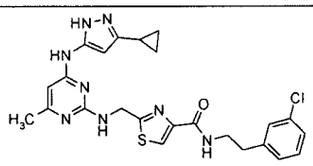
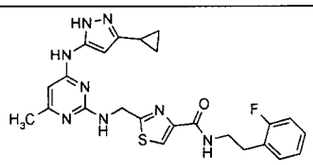
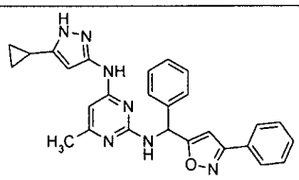
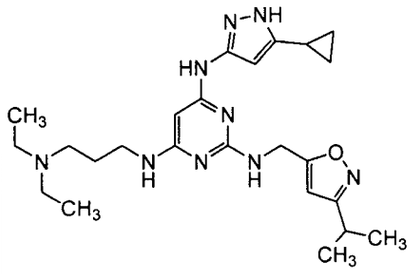
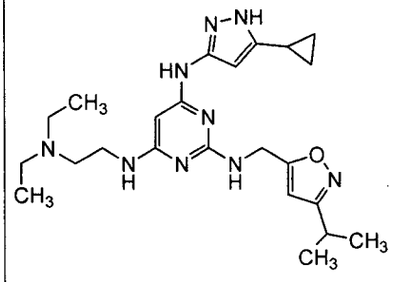
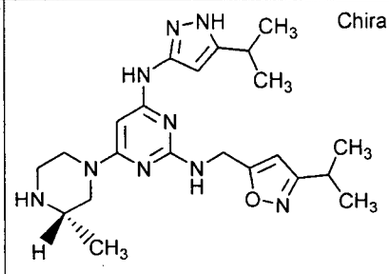
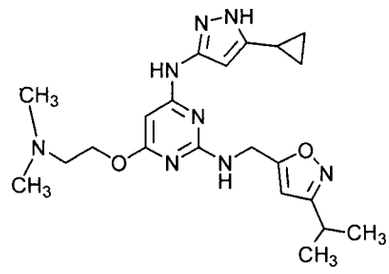
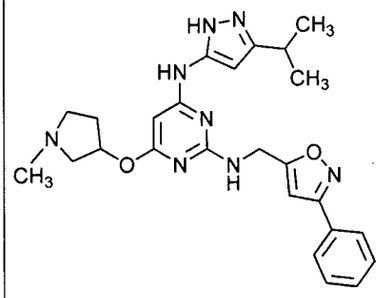
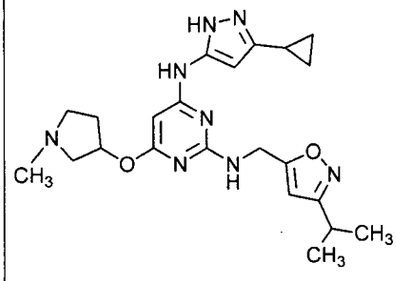
Entrada	Estructura
570	
571	
572	

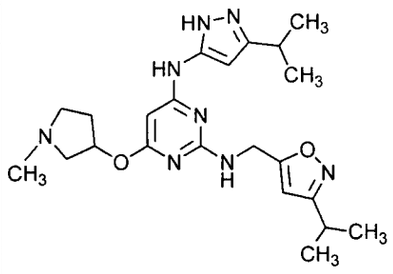
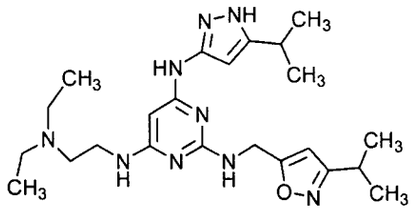
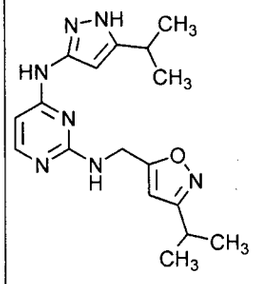
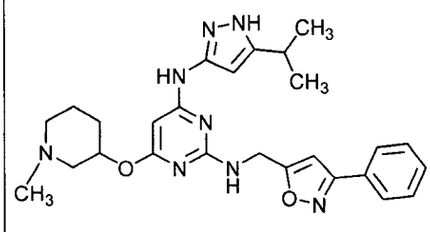
Tabla 5b.

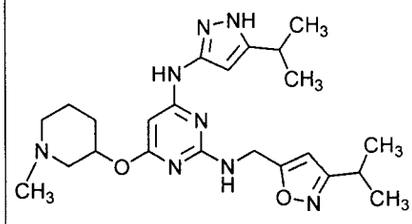
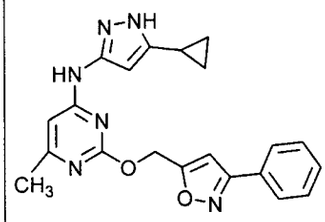
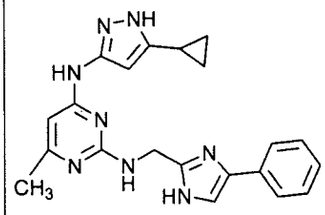
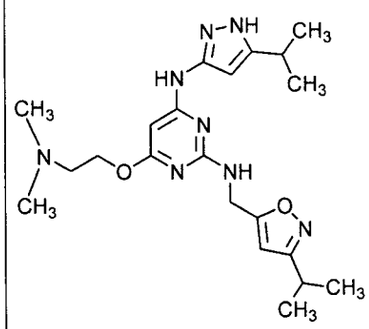
Inhibidores representativos adicionales de IGF1R

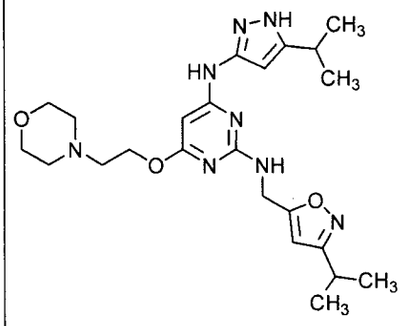
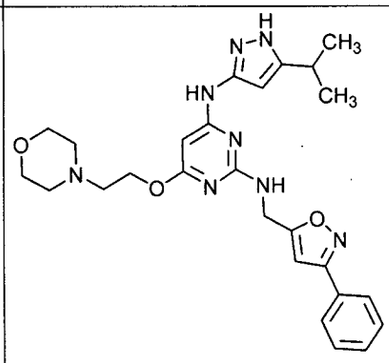
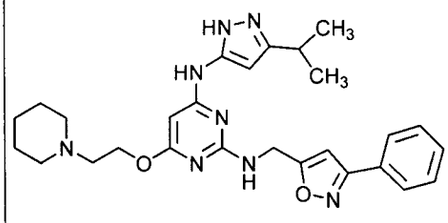
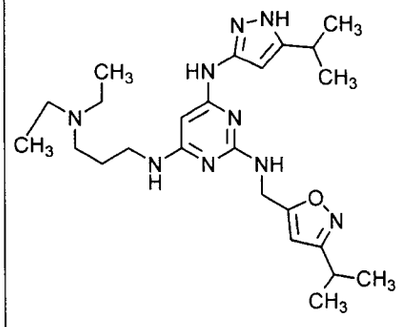
[00222] Los Compuestos de la Tabla 5b se pueden preparar como sales, solvatos, hidratos y/o isómeros farmacéuticamente aceptables de estos. Todas las combinaciones de sales, solvatos, hidratos e isómeros de los Compuestos de la Tabla 5b se pueden usar para practicar la invención.

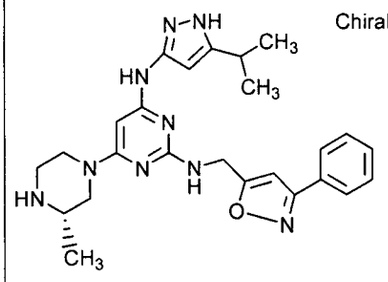
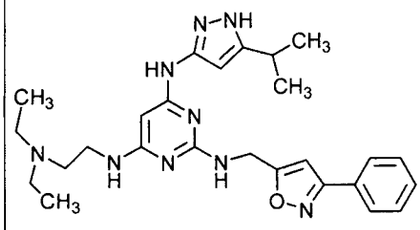
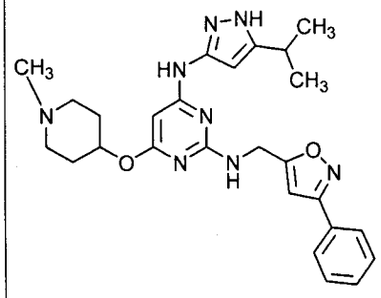
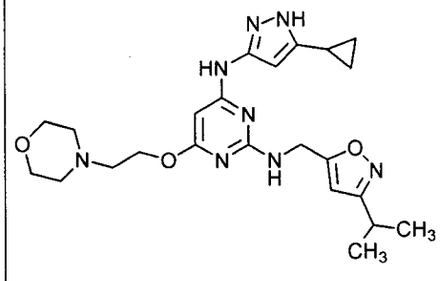
Entrada	Estructura	Nombre
573		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-N^6-[3-(dietilamino)propil]-N^2-{[3-(1-metiletil)isoxazol-5-il]metil}pirimidino-2,4,6-triamina
574		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-N^6-[2-(dietilamino)etil]-N^2-{[3-(1-metiletil)isoxazol-5-il]metil}pirimidino-2,4,6-triamina
575	 Chiral	N^2-{[3-(1-metiletil)isoxazol-5-il]metil}-N^4-[5-(1-metiletil)-1*H*-pirazol-3-il]-6-[(3S)-3-metilpiperazin-1-

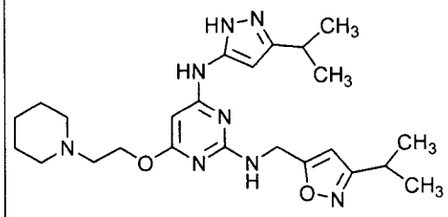
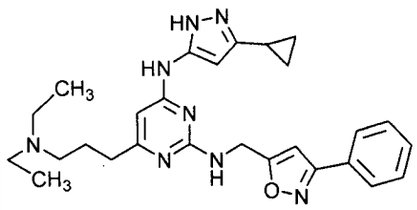
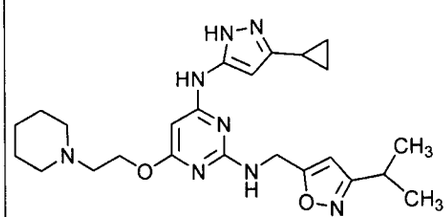
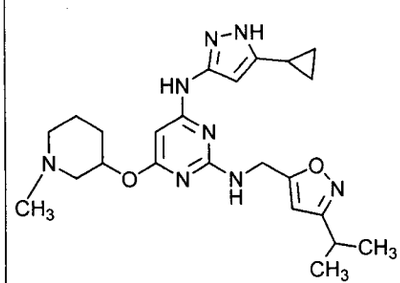
Entrada	Estructura	Nombre
		il]pirimidino-2,4-diamina
576		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-6-{[2-(dimetilamino)etil]oxi}-N^2-{[3-(1-metiletil)isoxazol-5-il]metil}pirimidino-2,4-diamina
577		N^4-[3-(1-metiletil)-1*H*-pirazol-5-il]-6-[(1-metilpirrolidin-3-il)oxi]-N^2-[(3-fenilisoxazol-5-il)metil]pirimidino-2,4-diamina
578		N^4-(3-ciclopropil-1*H*-pirazol-5-il)-N^2-{[3-(1-metiletil)isoxazol-5-il]metil}-6-[(1-metilpirrolidin-3-il)oxi]pirimidino-2,4-diamina

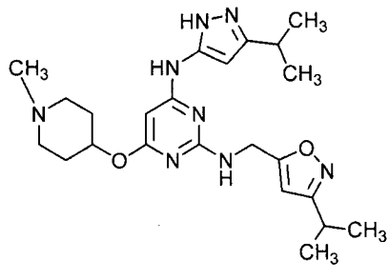
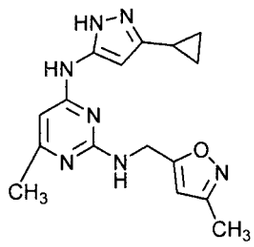
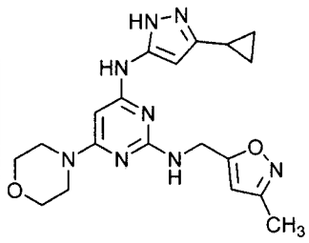
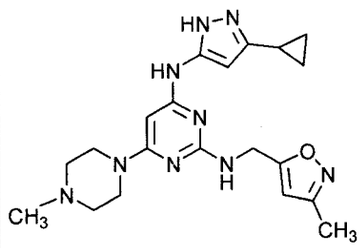
Entrada	Estructura	Nombre
579		N^2-{[3-(1-metiletil)isoxazol-5-il]metil}-N^4-[3-(1-metiletil)-1*H*-pirazol-5-il]-6-[(1-metilpirrolidin-3-il)oxi]pirimidino-2,4-diamina
580		N^4-[2-(dietilamino)etil]-N^2-{[3-(1-metiletil)isoxazol-5-il]metil}-N^6-[5-(1-metiletil)-1*H*-pirazol-3-il]pirimidino-2,4,6-triamina
581		N^2-{[3-(1-metiletil)isoxazol-5-il]metil}-N^4-[5-(1-metiletil)-1*H*-pirazol-3-il]pirimidino-2,4-diamina
582		N^4-[5-(1-metiletil)-1*H*-pirazol-3-il]-6-[(1-metilpiperidin-3-il)oxi]-N^2-[(3-fenilisoxazol-5-il)metil]pirimidino-2,4-diamina

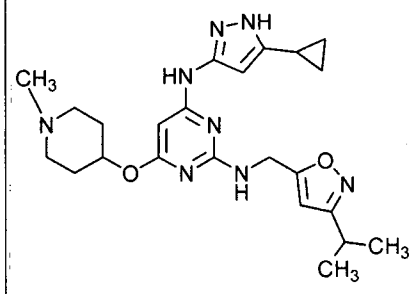
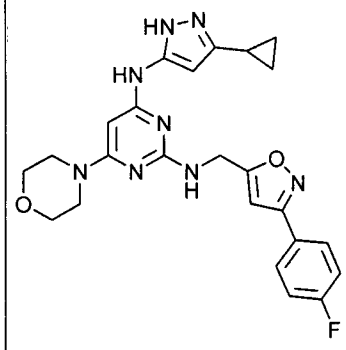
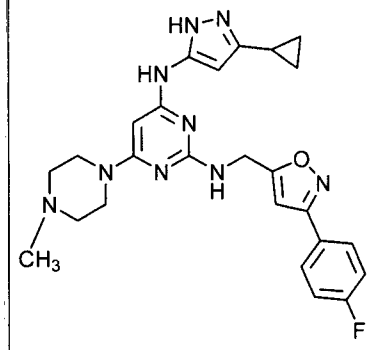
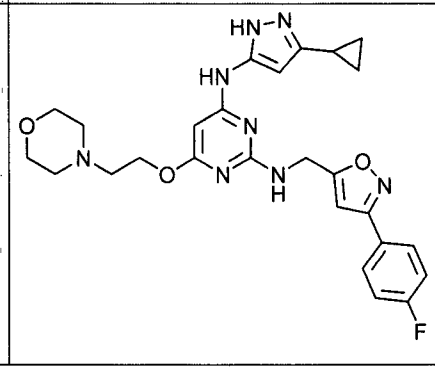
Entrada	Estructura	Nombre
583		N^2-{[3-(1-metiletil)isoxazol-5-il]metil}-N^4-[5-(1-metiletil)-1*H*-pirazol-3-il]-6-[(1-metilpiperidin-3-il)oxi]pirimidino-2,4-diamina
584		*N*-(5-ciclopropil-1*H*-pirazol-3-il)-6-metil-2-{[(3-fenilisoxazol-5-il)metil]oxi}pirimidin-4-amina
585		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-6-metil-N^2-[(4-fenilo-1*H*-imidazol-2-il)metil]pirimidino-2,4-diamina
586		6-{[2-(dimetilamino)etil]oxi}-N^2-{[3-(1-metiletil)isoxazol-5-il]metil}-N^4-[5-(1-metiletil)-1*H*-pirazol-3-il]pirimidino-2,4-diamina

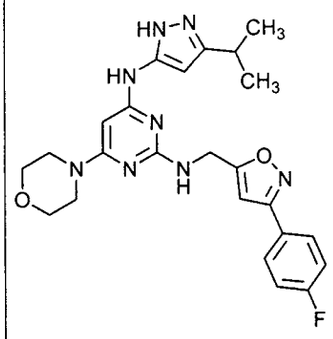
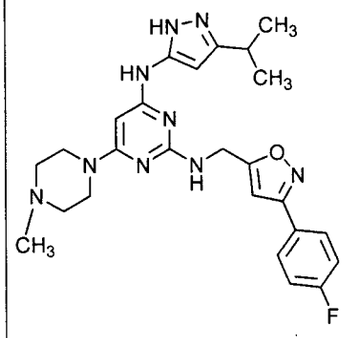
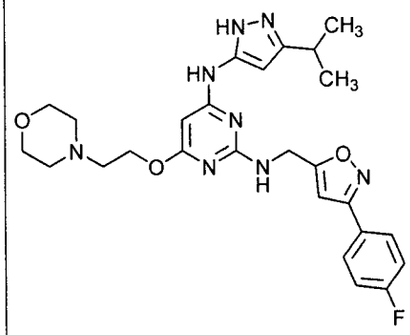
Entrada	Estructura	Nombre
587		N^2-{[3-(1-metiletil)isoxazol-5-il]metil}-N^4-[5-(1-metiletil)-1*H*-pirazol-3-il]-6-[(2-morfolin-4-iletil)oxi]pirimidino-2,4-diamina
588		N^4-[5-(1-metiletil)-1*H*-pirazol-3-il]-6-[(2-morfolin-4-iletil)oxi]-N^2-[(3-fenilisoxazol-5-il)metil]pirimidino-2,4-diamina
589		N^4-[3-(1-metiletil)-1*H*-pirazol-5-il]-N^2-[(3-fenilisoxazol-5-il)metil]-6-[(2-piperidin-1-iletil)oxi]pirimidino-2,4-diamina
590		N^4-[3-(dietilamino)propil]-N^2-{[3-(1-metiletil)isoxazol-5-il]metil}-N^6-[5-(1-metiletil)-1*H*-pirazol-3-il]pirimidino-2,4,6-triamina

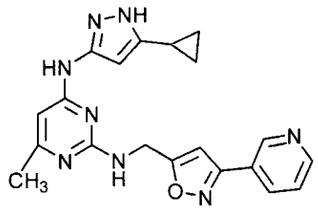
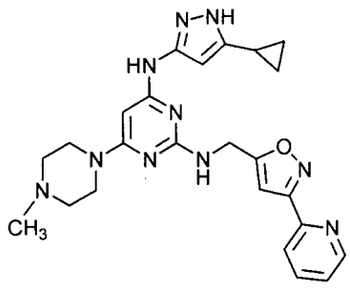
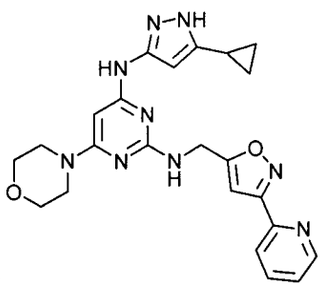
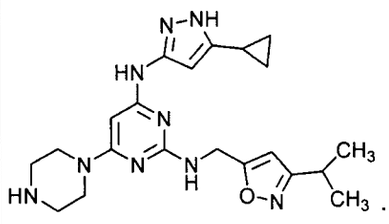
Entrada	Estructura	Nombre
591		N^4-[5-(1-metiletil)-1*H*-pirazol-3-il]-6-[(3S)-3-metilpiperazin-1-il]-N^2-[(3-fenilisoxazol-5-il)metil]pirimidino-2,4-diamina
592		N^4-[2-(dietilamino)etil]-N^6-[5-(1-metiletil)-1*H*-pirazol-3-il]-N^2-[(3-fenilisoxazol-5-il)metil]pirimidino-2,4,6-triamina
593		N^4-[5-(1-metiletil)-1*H*-pirazol-3-il]-6-[(1-metilpiperidin-4-il)oxi]-N^2-[(3-fenilisoxazol-5-il)metil]pirimidino-2,4-diamina
594		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-N^2-{[3-(1-metiletil)isoxazol-5-il]metil}-6-[(2-morfolin-4-iletil)oxi]pirimidino-2,4-diamina

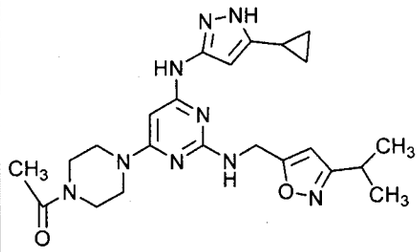
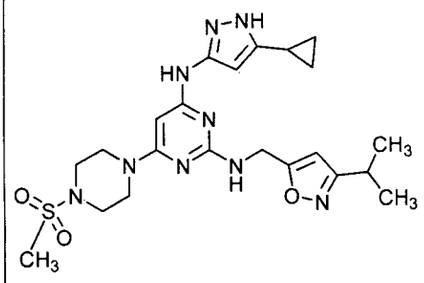
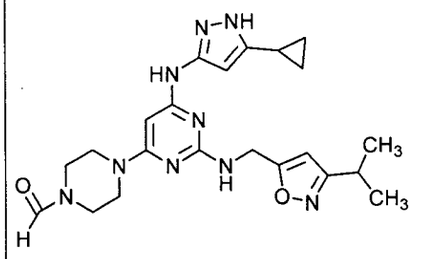
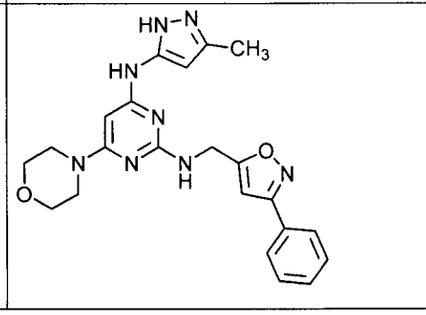
Entrada	Estructura	Nombre
595		N^2-{[3-(1-metiletil)isoxazol-5-il]metil}-N^4-[3-(1-metiletil)-1*H*-pirazol-5-il]-6-[(2-piperidin-1-iletil)oxi]pirimidino-2,4-diamina
596		N^4-(3-ciclopropil-1*H*-pirazol-5-il)-6-[3-(dietilamino)propil]-N^2-[(3-fenilisoxazol-5-il)metil]pirimidino-2,4-diamina
597		N^4-(3-ciclopropil-1*H*-pirazol-5-il)-N^2-{[3-(1-metiletil)isoxazol-5-il]metil}-6-[(2-piperidin-1-iletil)oxi]pirimidino-2,4-diamina
598		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-N^2-{[3-(1-metiletil)isoxazol-5-il]metil}-6-[(1-metilpiperidin-3-il)oxi]pirimidino-2,4-diamina

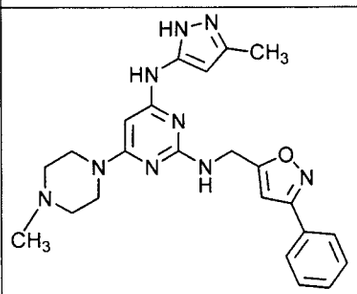
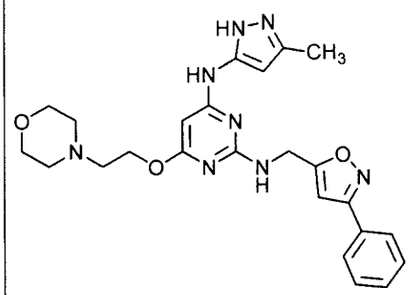
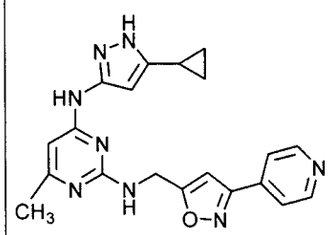
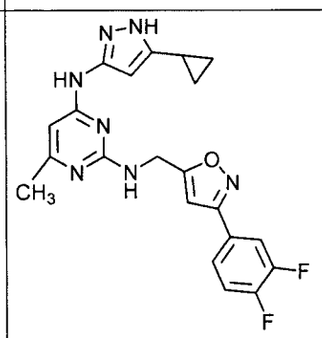
Entrada	Estructura	Nombre
599		N^2-{[3-(1-metiletil)isoxazol-5-il]metil}-N^4-[3-(1-metiletil)-1*H*-pirazol-5-il]-6-[(1-metilpiperidin-4-il)oxi]pirimidino-2,4-diamina
600		N^4-(3-ciclopropil-1*H*-pirazol-5-il)-6-metil-N^2-[(3-metilisoxazol-5-il)metil]pirimidino-2,4-diamina
601		N^4-(3-ciclopropil-1*H*-pirazol-5-il)-N^2-[(3-metilisoxazol-5-il)metil]-6-morfolin-4-ilpirimidino-2,4-diamina
602		N^4-(3-ciclopropil-1*H*-pirazol-5-il)-N^2-[(3-metilisoxazol-5-il)metil]-6-(4-metilpiperazin-1-il)pirimidino-2,4-diamina

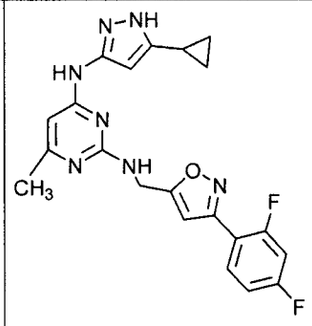
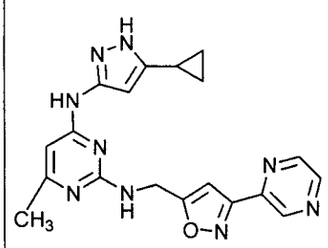
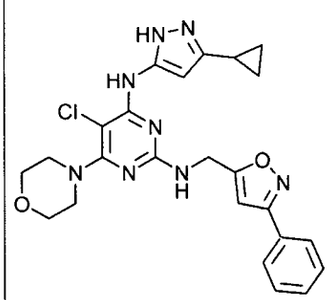
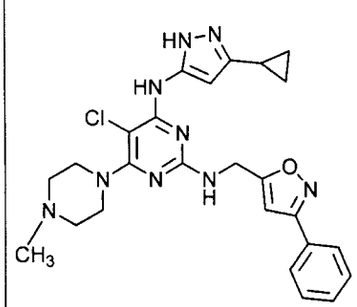
Entrada	Estructura	Nombre
603		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-N^2-{[3-(1-metiletil)isoxazol-5-il]metil}-6-[(1-metilpiperidin-4-il)oxi]pirimidino-2,4-diamina
604		N^4-(3-ciclopropil-1*H*-pirazol-5-il)-N^2-{[3-(4-fluorofenil)isoxazol-5-il]metil}-6-morfolin-4-ilpirimidino-2,4-diamina
605		N^4-(3-ciclopropil-1*H*-pirazol-5-il)-N^2-{[3-(4-fluorofenil)isoxazol-5-il]metil}-6-(4-metilpiperazin-1-il)pirimidino-2,4-diamina
606		N^4-(3-ciclopropil-1*H*-pirazol-5-il)-N^2-{[3-(4-fluorofenil)isoxazol-5-il]metil}-6-[(2-morfolin-4-iletil)oxi]pirimidino

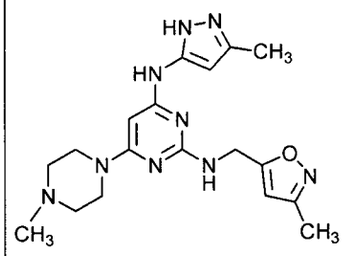
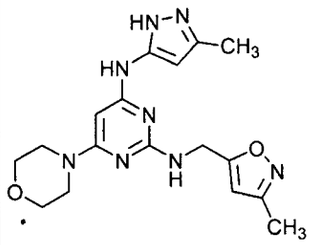
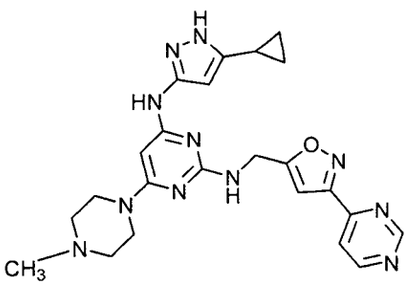
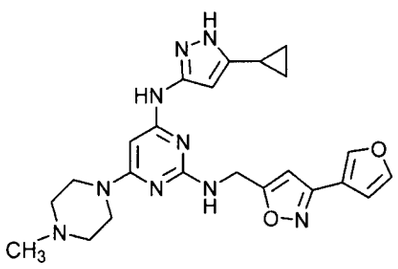
Entrada	Estructura	Nombre
		-2,4-diamina
607		N^2-{[3-(4-fluorofenil)isoxazol-5-il]metil}-N^4-[3-(1-metiletil)-1*H*-pirazol-5-il]-6-morfolin-4-ilpirimidino-2,4-diamina
608		N^2-{[3-(4-fluorofenil)isoxazol-5-il]metil}-N^4-[3-(1-metiletil)-1*H*-pirazol-5-il]-6-(4-metilpiperazin-1-il)pirimidino-2,4-diamina
609		N^2-{[3-(4-fluorofenil)isoxazol-5-il]metil}-N^4-[3-(1-metiletil)-1*H*-pirazol-5-il]-6-[(2-morfolin-4-iletil)oxi]pirimidino-2,4-diamina

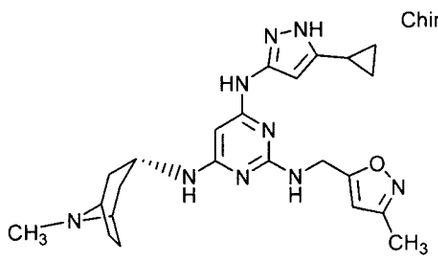
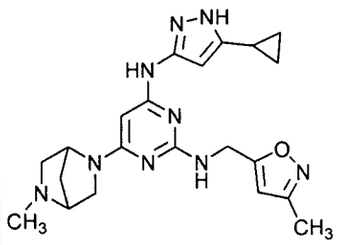
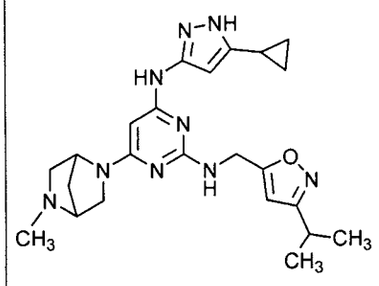
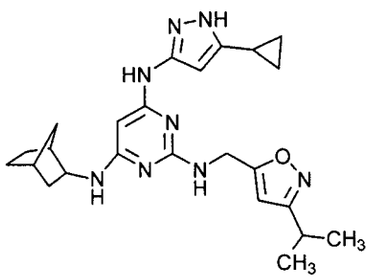
Entrada	Estructura	Nombre
610		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-6-metil-N^2-[(3-piridin-3-ilisoxazol-5-il)metil]pirimidino-2,4-diamina
611		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-6-(4-metilpiperazin-1-il)-N^2-[(3-piridin-2-ilisoxazol-5-il)metil]pirimidino-2,4-diamina
612		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-6-morfolin-4-il-N^2-[(3-piridin-2-ilisoxazol-5-il)metil]pirimidino-2,4-diamina
613		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-N^2-{[3-(1-metiletil)isoxazol-5-il]metil}-6-piperazin-1-ilpirimidino-2,4-diamina

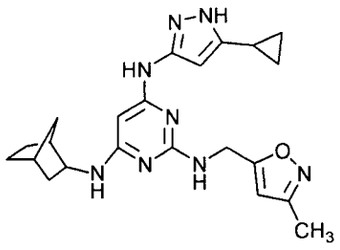
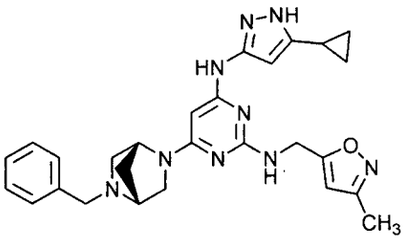
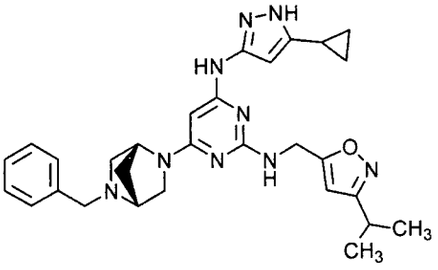
Entrada	Estructura	Nombre
614		6-(4-acetilpiperazin-1-il)-N^4-(5-ciclopropil-1*H*-pirazol-3-il)-N^2-{[3-(1-metiletil)isoxazol-5-il]metil}pirimidino-2,4-diamina
615		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-N^2-{[3-(1-metiletil)isoxazol-5-il]metil}-6-[4-(metilsulfonil)piperazin-1-il]pirimidino-2,4-diamina
616		4-{6-[(5-ciclopropil-1*H*-pirazol-3-il)amino]-2-({[3-(1-metiletil)isoxazol-5-il]metil}amino)pirimidin-4-il}piperazino-1-carbaldehído
617		N^4-(3-metil-1*H*-pirazol-5-il)-6-morfolin-4-il-N^2-[(3-fenilisoxazol-5-il)metil]pirimidino-2,4-diamina

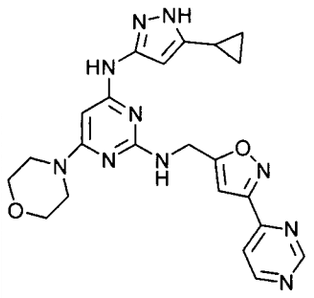
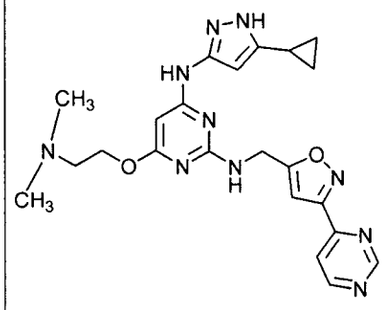
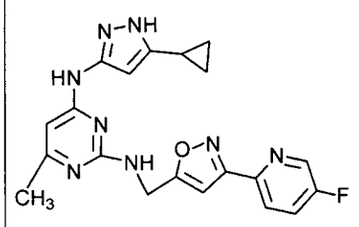
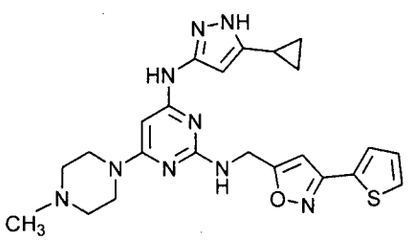
Entrada	Estructura	Nombre
618		6-(4-metilpiperazin-1-il)-N^4-(3-metil-1*H*-pirazol-5-il)-N^2-[(3-fenilisoxazol-5-il)metil]pirimidino-2,4-diamina
619		N^4-(3-metil-1*H*-pirazol-5-il)-6-[(2-morfolin-4-iletil)oxi]-N^2-[(3-fenilisoxazol-5-il)metil]pirimidino-2,4-diamina
620		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-6-metil-N^2-[(3-piridin-4-ilisoxazol-5-il)metil]pirimidino-2,4-diamina
621		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-N^2-{[3-(3,4-difluorofenil)isoxazol-5-il]metil}-6-metilpirimidino-2,4-diamina

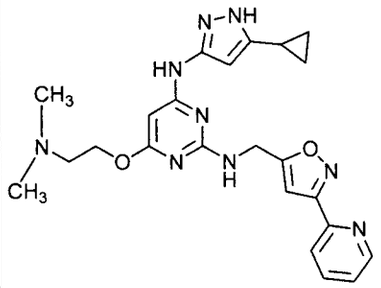
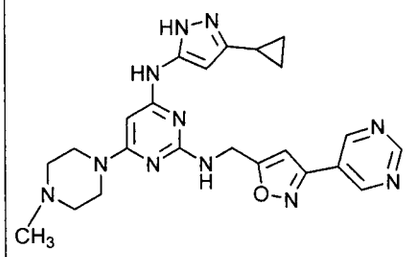
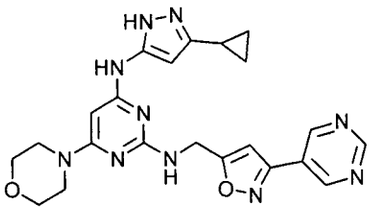
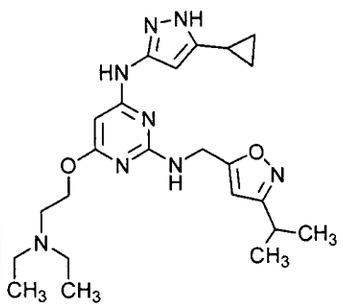
Entrada	Estructura	Nombre
622		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-N^2-{[3-(2,4-difluorofenil)isoxazol-5-il]metil}-6-metilpirimidino-2,4-diamina
623		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-6-metil-N^2-[(3-pirazin-2-ilisoxazol-5-il)metil]pirimidino-2,4-diamina
624		5-cloro-N^4-(3-ciclopropil-1*H*-pirazol-5-il)-6-morfolin-4-il-N^2-[(3-fenilisoxazol-5-il)metil]pirimidino-2,4-diamina
625		5-cloro-N^4-(3-ciclopropil-1*H*-pirazol-5-il)-6-(4-metilpiperazin-1-il)-N^2-[(3-fenilisoxazol-5-il)metil]pirimidino-2,4-diamina

Entrada	Estructura	Nombre
626		N^2-[(3-metilisoxazol-5-il)metil]-6-(4-metilpiperazin-1-il)-N^4-(3-metil-1*H*-pirazol-5-il)pirimidino-2,4-diamina
627		N^2-[(3-metilisoxazol-5-il)metil]-N^4-(3-metil-1*H*-pirazol-5-il)-6-morfolin-4-ilpirimidino-2,4-diamina
628		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-6-(4-metilpiperazin-1-il)-N^2-[(3-pirimidin-4-ilisoxazol-5-il)metil]pirimidino-2,4-diamina
629		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-N^2-[(3-furan-3-ilisoxazol-5-il)metil]-6-(4-metilpiperazin-1-il)pirimidino-2,4-diamina

Entrada	Estructura	Nombre
630		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-N^6-(8-metil-8-azabiciclo[3,2,1]oct-3-il)-N^2-[(3-metilisoxazol-5-il)metil]pirimidino-2,4,6-triamina
631		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-6-(5-metil-2,5-diazabiciclo[2,2,1]hept-2-il)-N^2-[(3-metilisoxazol-5-il)metil]pirimidino-2,4-diamina
632		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-6-(5-metil-2,5-diazabiciclo[2,2,1]hept-2-il)-N^2-{[3-(1-metiletil)isoxazol-5-il]metil}pirimidino-2,4-diamina
633		N^4-biciclo[2,2,1]hept-2-il-N^6-(5-ciclopropil-1*H*-pirazol-3-il)-N^2-{[3-(1-metiletil)isoxazol-5-il]metil}pirimidino-

Entrada	Estructura	Nombre
		2,4,6-triamina
634		N^4-biciclo[2,2,1]hept-2-il-N^6-(5-ciclopropil-1*H*-pirazol-3-il)-N^2-[(3-metilisoxazol-5-il)metil]pirimidino-2,4,6-triamina
635		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-N^2-[(3-metilisoxazol-5-il)metil]-6-[(1R,4R)-5-(fenilmetil)-2,5-diazabiciclo[2,2,1]hept-2-il]pirimidino-2,4-diamina
636		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-N^2-{[3-(1-metiletil)isoxazol-5-il]metil}-6-[(1R,4R)-5-(fenilmetil)-2,5-diazabiciclo[2,2,1]hept-2-il]pirimidino-2,4-diamina

Entrada	Estructura	Nombre
637		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-6-morfolin-4-il-N^2-[(3-pirimidin-4-ilisoxazol-5-il)metil]pirimidino-2,4-diamina
638		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-6-{[2-(dimetilamino)etil]oxi}-N^2-[(3-pirimidin-4-ilisoxazol-5-il)metil]pirimidino-2,4-diamina
639		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-N^2-{[3-(5-fluoropiridin-2-il)isoxazol-5-il]metil}-6-metilpirimidino-2,4-diamina
640		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-6-(4-metilpiperazin-1-il)-N^2-{[3-(2-tienil)isoxazol-5-il]metil}pirimidino-2,4-diamina

Entrada	Estructura	Nombre
641		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-6-{[2-(dimetilamino)etil]oxi}-N^2-[(3-piridin-2-ilisoxazol-5-il)metil]pirimidino-2,4-diamina
642		N^4-(3-ciclopropil-1*H*-pirazol-5-il)-6-(4-metilpiperazin-1-il)-N^2-[(3-pirimidin-5-ilisoxazol-5-il)metil]pirimidino-2,4-diamina
643		N^4-(3-ciclopropil-1*H*-pirazol-5-il)-6-morfolin-4-il-N^2-[(3-pirimidin-5-ilisoxazol-5-il)metil]pirimidino-2,4-diamina
644		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-6-{[2-(dietilamino)etil]oxi}-N^2-{[3-(1-metiletil)isoxazol-5-il]metil}pirimidino-2,4-diamina

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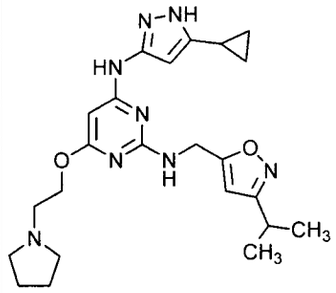
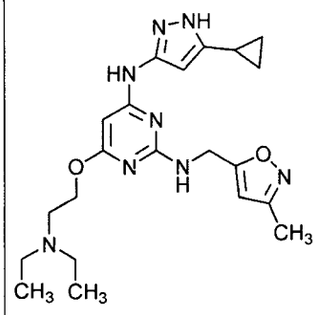
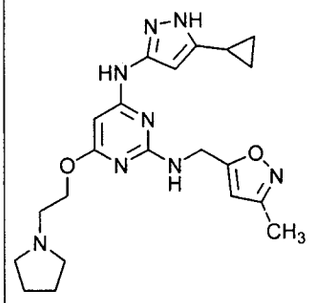
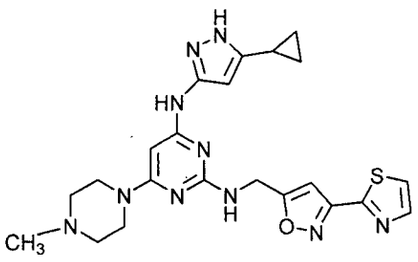
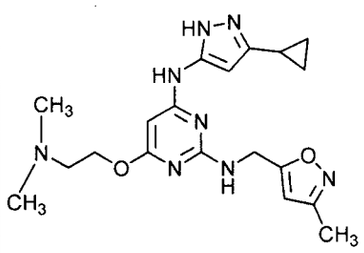
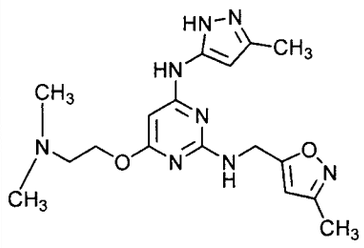
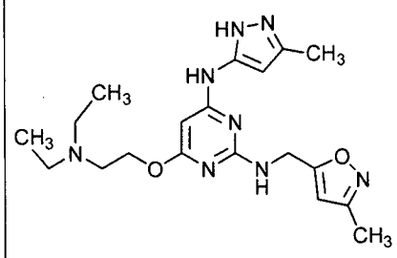
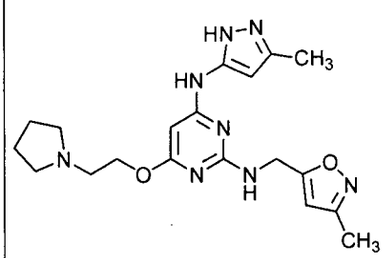
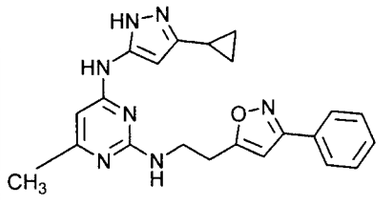
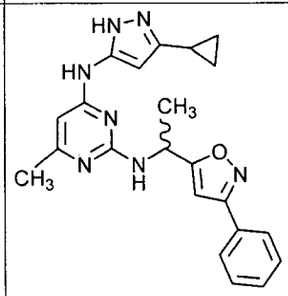
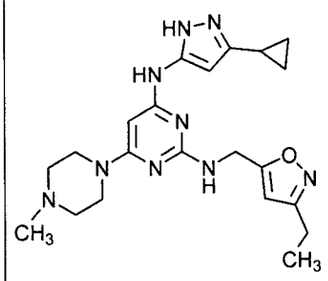
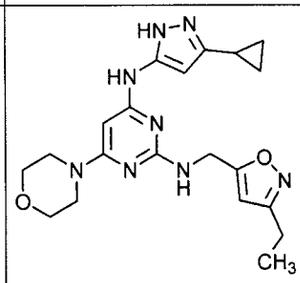
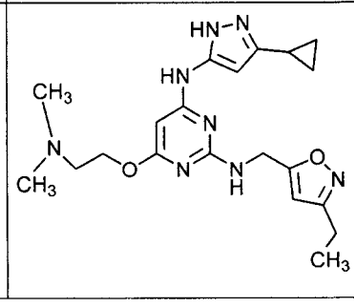
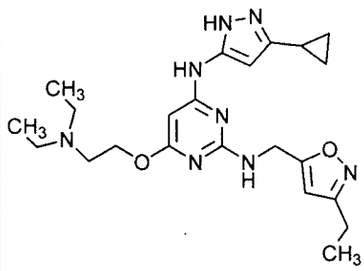
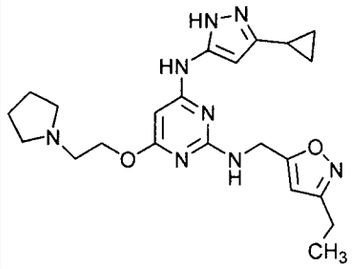
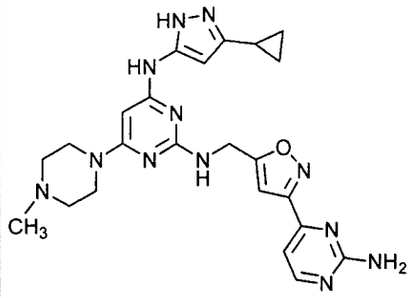
Entrada	Estructura	Nombre
645		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-N^2-{[3-(1-metiletil)isoxazol-5-il]metil}-6-[(2-pirrolidin-1-iletil)oxi]pirimidino-2,4-diamina
646		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-6-{[2-(dietilamino)etil]oxi}-N^2-[(3-metilisoxazol-5-il)metil]pirimidino-2,4-diamina
647		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-N^2-[(3-metilisoxazol-5-il)metil]-6-[(2-pirrolidin-1-iletil)oxi]pirimidino-2,4-diamina
648		N^4-(5-ciclopropil-1*H*-pirazol-3-il)-6-(4-metilpiperazin-1-il)-N^2-{[3-(1,3-tiazol-2-il)isoxazol-5-il]metil}pirimidino-2,4-diamina

Entrada	Estructura	Nombre
649		N^4-(3-ciclopropil-1*H*-pirazol-5-il)-6-[2-(dimetilamino)etoxi]-N^2-[(3-metilisoxazol-5-il)metil]pirimidino-2,4-diamina
650		6-{[2-(dimetilamino)etil]oxi}-N^2-[(3-metilisoxazol-5-il)metil]-N^4-(3-metil-1*H*-pirazol-5-il)pirimidino-2,4-diamina
651		6-{[2-(dietilamino)etil]oxi}-N^2-[(3-metilisoxazol-5-il)metil]-N^4-(3-metil-1*H*-pirazol-5-il)pirimidino-2,4-diamina
652		N^2-[(3-metilisoxazol-5-il)metil]-N^4-(3-metil-1*H*-pirazol-5-il)-6-[(2-pirrolidin-1-iletil)oxi]pirimidino-2,4-diamina

Entrada	Estructura	Nombre
653		N^4-(3-ciclopropil-1*H*-pirazol-5-il)-6-metil-N^2-[2-(3-fenilisoxazol-5-il)etil]pirimidino-2,4-diamina
654		N^4-(3-ciclopropil-1*H*-pirazol-5-il)-6-metil-N^2-[1-(3-fenilisoxazol-5-il)etil]pirimidino-2,4-diamina
655		N^4-(3-ciclopropil-1*H*-pirazol-5-il)-N^2-[(3-etilisoxazol-5-il)metil]-6-(4-metilpiperazin-1-il)pirimidino-2,4-diamina
656		N^4-(3-ciclopropil-1*H*-pirazol-5-il)-N^2-[(3-etilisoxazol-5-il)metil]-6-morfolin-4-ilpirimidino-2,4-diamina
657		N^4-(3-ciclopropil-1*H*-pirazol-5-il)-6-{[2-(dimetilamino)etil]oxi}-N^2-[(3-etilisoxazol-5-il)metil]pirimidino-

Entrada	Estructura	Nombre
		2,4-diamina
658		N^4-(3-ciclopropil-1*H*-pirazol-5-il)-6-{[2-(dietilamino)etil]oxi}-N^2-[(3-etilisoxazol-5-il)metil]pirimidino-2,4-diamina
659		N^4-(3-ciclopropil-1*H*-pirazol-5-il)-N^2-[(3-etilisoxazol-5-il)metil]-6-[(2-pirrolidin-1-iletil)oxi]pirimidino-2,4-diamina
660		N^2-{[3-(2-aminopirimidin-4-il)isoxazol-5-il]metil}-N^4-(3-ciclopropil-1*H*-pirazol-5-il)-6-(4-metilpiperazin-1-il)pirimidino-2,4-diamina

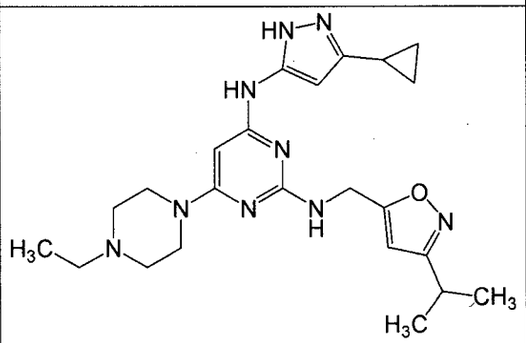
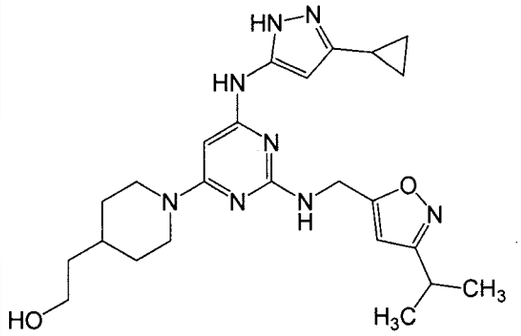
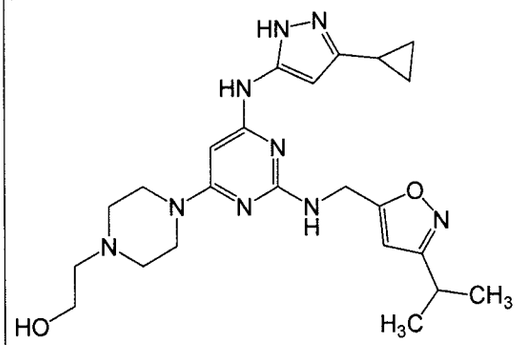
Entrada	Estructura	Nombre
661		N^4-(3-ciclopropil-1*H*-pirazol-5-il)-6-(4-etilpiperazin-1-il)-N^2-{[3-(1-metiletil)isoxazol-5-il]metil}pirimidino-2,4-diamina
662		2-(1-{6-[(3-ciclopropil-1*H*-pirazol-5-il)amino]-2-({[3-(1-metiletil)isoxazol-5-il]metil}amino)pirimidin-4-il}piperidin-4-il)etanol
663		2-(4-{6-[(3-ciclopropil-1*H*-pirazol-5-il)amino]-2-({[3-(1-metiletil)isoxazol-5-il]metil}amino)pirimidin-4-il}piperazin-1-il)etanol

Tabla 6.

Inhibidores representativos de Raf

[00223] Los Compuestos de la Tabla 6 se pueden preparar como sales, solvatos, hidratos y/o isómeros farmacéuticamente aceptables de estos. Todas las combinaciones de sales, solvatos, hidratos e isómeros

de los Compuestos de la Tabla 6 se pueden usar para practicar la invención.

Entrada	Nombre
1	6-(2-butil-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il)-2*H*-1,4-benzoxazin-3(4*H*)-ona
2	6-[1-hidroxi-3-oxo-2-(2-feniletil)-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona
3	6-(1-hidroxi-2-{[4-(metiloxi)fenil]metil}-3-oxo-2,3-dihidro-1*H*-isoindol-1-il)-2*H*-1,4-benzoxazin-3(4*H*)-ona
4	6-(1-hidroxi-2-{[3-(metiloxi)fenil]metil}-3-oxo-2,3-dihidro-1*H*-isoindol-1-il)-2*H*-1,4-benzoxazin-3(4*H*)-ona
5	6-{2-[(4-fluorofenil)metil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-2*H*-1,4-benzoxazin-3(4*H*)-ona
6	6-(1-hidroxi-3-oxo-2-fenilo-2,3-dihidro-1*H*-isoindol-1-il)-2*H*-1,4-benzoxazin-3(4*H*)-ona
7	6-{2-[(3-bromofenil)metil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-2*H*-1,4-benzoxazin-3(4*H*)-ona
8	6-{2-[(4-bromofenil)metil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-2*H*-1,4-benzoxazin-3(4*H*)-ona
9	6-[1-hidroxi-3-oxo-2-(3-fenilpropil)-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona
10	6-{2-[(3,4-diclorofenil)metil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-2*H*-1,4-benzoxazin-3(4*H*)-ona
11	6-{1-hidroxi-2-[(4-metilfenil)metil]-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-2*H*-1,4-benzoxazin-3(4*H*)-ona

Entrada	Nombre
12	6-{2-[(4-clorofenil)metil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-2*H*-1,4-benzoxazin-3(4*H*)-ona
13	6-[1-hidroxi-2-(1-metiletil)-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona
14	{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
15	6-{2-[(3,4-dimetilfenil)metil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-2*H*-1,4-benzoxazin-3(4*H*)-ona
16	6-(2-{[4-cloro-3-(trifluorometil)fenil]metil}-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il)-2*H*-1,4-benzoxazin-3(4*H*)-ona
17	6-(2-{[4-(dimetilamino)fenil]metil}-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il)-2*H*-1,4-benzoxazin-3(4*H*)-ona
18	6-[2-(3-clorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona
19	6-[2-(4-clorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona
20	6-[2-(3,4-diclorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona
21	6-[1-hidroxi-2-(4-metilfenil)-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona
22	3-(2-{[3,5-bis(metiloxi)fenil]amino}-1*H*-bencimidazol-5-il)-3-(metiloxi)-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-ona

Entrada	Nombre
23	3-(2-{[3,5-bis(metiloxi)fenil]amino}-1*H*-bencimidazol-5-il)-2-(1-metiletil)-3-(metiloxi)-2,3-dihidro-1*H*-isoindol-1-ona
24	3-(2-{[3,5-bis(metiloxi)fenil]amino}-1*H*-bencimidazol-5-il)-3-hidroxi-2-fenilo-2,3-dihidro-1*H*-isoindol-1-ona
25	3-(2-{[3,5-bis(metiloxi)fenil]amino}-1*H*-bencimidazol-5-il)-3-hidroxi-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-ona
26	{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1-metil-1*H*-bencimidazol-2-il}carbamate
27	3-(1*H*-bencimidazol-5-il)-3-hidroxi-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-ona
28	5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-*N*-metil-1*H*-bencimidazol-2-carboxamida
29	3-hidroxi-3-(2-metil-1*H*-bencimidazol-5-il)-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-ona
30	7-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-3,4-dihidroquinoxalin-2(1*H*)-ona
31	7-[2-(3-clorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-3,4-dihidroquinoxalin-2(1*H*)-ona
32	1,1-dimetiletil 4-{[1-hidroxi-3-oxo-1-(3-oxo-3,4-dihidro-2*H*-1,4-benzoxazin-6-il)-1,3-dihidro-2*H*-isoindol-2-il]metil}piperidino-1-carboxilate
33	6-(1-hidroxi-2-{[2-(metiloxi)fenil]metil}-3-oxo-2,3-dihidro-1*H*-isoindol-1-il)-2*H*-1,4-benzoxazin-3(4*H*)-ona

Entrada	Nombre
34	6-{2-[(3-clorofenil)metil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-2*H*-1,4-benzoxazin-3(4*H*)-ona
35	6-{2-[(2-clorofenil)metil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-2*H*-1,4-benzoxazin-3(4*H*)-ona
36	6-{2-[(3-fluorofenil)metil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-2*H*-1,4-benzoxazin-3(4*H*)-ona
37	6-{2-[(2-bromofenil)metil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-2*H*-1,4-benzoxazin-3(4*H*)-ona
38	6-{2-[(2-fluorofenil)metil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-2*H*-1,4-benzoxazin-3(4*H*)-ona
39	6-[2-(3-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona
40	6-[1-hidroxi-2-(3-yodofenil)-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona
41	6-[2-(3-bromofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona
42	6-[1-hidroxi-2-(3-nitrofenil)-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona
43	6-{1-hidroxi-2-[3-(metiloxi)fenil]-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-2*H*-1,4-benzoxazin-3(4*H*)-ona
44	6-[1-hidroxi-2-(3-metilfenil)-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona
45	3-hidroxi-3-(1*H*-indol-5-il)-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-ona

Entrada	Nombre
46	[6-(1-hidroxi-3-oxo-2-fenilo-2,3-dihidro-1*H*-isoindol-1-il)-1*H*-bencimidazol-2-il]carbamate
47	6-[2-(2-aminofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona
48	6-{[2-(3-fenilo-1,2,4-oxadiazol-5-il)fenil]carbonil}-2*H*-1,4-benzoxazin-3(4*H*)-ona
49	6-{[2-(1*H*-bencimidazol-2-il)fenil]carbonil}-2*H*-1,4-benzoxazin-3(4*H*)-ona
50	6-(1-hidroxi-3-oxo-2-{[2-(trifluorometil)fenil]metil}-2,3-dihidro-1*H*-isoindol-1-il)-2*H*-1,4-benzoxazin-3(4*H*)-ona
51	6-{2-[(5-bromo-2-fluorofenil)metil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-2*H*-1,4-benzoxazin-3(4*H*)-ona
52	6-{1-hidroxi-2-[(3-nitrofenil)metil]-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-2*H*-1,4-benzoxazin-3(4*H*)-ona
53	6-(1-hidroxi-3-oxo-2-{[3-(trifluorometil)fenil]metil}-2,3-dihidro-1*H*-isoindol-1-il)-2*H*-1,4-benzoxazin-3(4*H*)-ona
54	6-(2-{[2,3-bis(metiloxi)fenil]metil}-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il)-2*H*-1,4-benzoxazin-3(4*H*)-ona
55	6-{1-hidroxi-2-[(3-yodofenil)metil]-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-2*H*-1,4-benzoxazin-3(4*H*)-ona
56	6-[1-hidroxi-3-oxo-2-({3-[(trifluorometil)oxi]fenil}metil)-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona

Entrada	Nombre
57	6-(1-hidroxi-2-{[2-(metiltio)fenil]metil}-3-oxo-2,3-dihidro-1*H*-isoindol-1-il)-2*H*-1,4-benzoxazin-3(4*H*)-ona
58	6-[2-(3,4-difluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona
59	6-{1-hidroxi-2-[3-(1-metiletil)fenil]-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-2*H*-1,4-benzoxazin-3(4*H*)-ona
60	6-(1-hidroxi-3-oxo-2-{3-[(trifluorometil)oxi]fenil}-2,3-dihidro-1*H*-isoindol-1-il)-2*H*-1,4-benzoxazin-3(4*H*)-ona
61	6-{1-hidroxi-3-oxo-2-[3-(trifluorometil)fenil]-2,3-dihidro-1*H*-isoindol-1-il}-2*H*-1,4-benzoxazin-3(4*H*)-ona
62	3-[1-hidroxi-3-oxo-1-(3-oxo-3,4-dihidro-2*H*-1,4-benzoxazin-6-il)-1,3-dihidro-2*H*-isoindol-2-il]bencensulfonamida
63	6-{2-[5-cloro-2-(metiloxi)fenil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-2*H*-1,4-benzoxazin-3(4*H*)-ona
64	6-{2-[4-fluoro-3-(trifluorometil)fenil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-2*H*-1,4-benzoxazin-3(4*H*)-ona
65	3-hidroxi-3-(1*H*-indol-6-il)-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-ona
66	6-[2-(3-fluoro-5-yodofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona
67	6-[2-(3-aminofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona

Entrada	Nombre
68	6-[2-(3,5-difluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona
69	6-{1-hidroxi-2-[3-(metilsulfonil)fenil]-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-2*H*-1,4-benzoxazin-3(4*H*)-ona
70	etil 3-[1-hidroxi-3-oxo-1-(3-oxo-3,4-dihidro-2*H*-1,4-benzoxazin-6-il)-1,3-dihidro-2*H*-isoindol-2-il]benzoate
71	3-[1-hidroxi-3-oxo-1-(3-oxo-3,4-dihidro-2*H*-1,4-benzoxazin-6-il)-1,3-dihidro-2*H*-isoindol-2-il]benzonitrilo
72	6-[2-(2-clorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona
73	6-[2-(3-amino-5-clorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona
74	6-[2-(5-cloro-2-metilfenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona
75	6-[2-(3-cloro-2-metilfenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona
76	6-[2-(3-etilfenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona
77	6-[2-(3-etinilfenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona
78	6-[1-hidroxi-2-(3-hidroxifenil)-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona

Entrada	Nombre
79	6-{1-hidroxi-3-oxo-2-[3-(feniloxi)fenil]-2,3-dihidro-1*H*-isoindol-1-il}-2*H*-1,4-benzoxazin-3(4*H*)-ona
80	6-(1-hidroxi-3-oxo-2-{3-[(fenilmetil)oxi]fenil}-2,3-dihidro-1*H*-isoindol-1-il)-2*H*-1,4-benzoxazin-3(4*H*)-ona
81	3-[1-hidroxi-3-oxo-1-(3-oxo-3,4-dihidro-2*H*-1,4-benzoxazin-6-il)-1,3-dihidro-2*H*-isoindol-2-il]benzamida
82	6-{1-hidroxi-2-[3-(hidroximetil)fenil]-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-2*H*-1,4-benzoxazin-3(4*H*)-ona
83	6-[2-(2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona
84	3-hidroxi-3-[2-(metilamino)-1*H*-bencimidazol-5-il]-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-ona
85	6-(2-bifenil-3-il-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il)-2*H*-1,4-benzoxazin-3(4*H*)-ona
86	6-(2-{3-[(dimetilamino)metil]fenil}-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il)-2*H*-1,4-benzoxazin-3(4*H*)-ona
87	6-[2-(3,5-diclorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona
88	6-(1-hidroxi-3-oxo-2-piperidin-4-il-2,3-dihidro-1*H*-isoindol-1-il)-2*H*-1,4-benzoxazin-3(4*H*)-ona
89	6-[2-(3-{[2-(dimetilamino)etil]oxi}fenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona
90	6-[1-hidroxi-2-(2-metilfenil)-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-2*H*-1,4-benzoxazin-3(4*H*)-ona

Entrada	Nombre
91	*N*-metil-2-[(3-oxo-3,4-dihidro-2*H*-1,4-benzoxazin-6-il)carbonil]-*N*-fenilbenzamida
92	{5-[1-(etiloxi)-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
93	fenilmetil 2-[(2-{[(metiloxi)carbonil]amino}-1*H*-bencimidazol-5-il)carbonil]benzoate
94	3-hidroxi-3-(1*H*-indazol-5-il)-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-ona
95	3-hidroxi-3-(1*H*-indazol-6-il)-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-ona
96	{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de etilo
97	{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 2-metilpropilo
98	{5-[1-hidroxi-3-oxo-2-(2-tienilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
99	{5-[1-hidroxi-3-oxo-2-(2-feniletil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il} carbamato de metilo
100	3-[2-amino-1-(1,1-dimetiletil)-1*H*-bencimidazol-5-il]-3-hidroxi-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-ona
101	3-(2-amino-1*H*-bencimidazol-5-il)-3-hidroxi-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-ona
102	[5-(1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il)-1*H*-bencimidazol-2-il]carbamato de metilo

Entrada	Nombre
103	{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 3-(metiloxi)butilo
104	(5-{1-hidroxi-3-oxo-2-[(1*R*)-1-feniletil]-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il) carbamato de metilo
105	(5-{1-hidroxi-3-oxo-2-[(1*S*)-1-feniletil]-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il) carbamato de metilo
106	{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 2-(metiloxi)etilo
107	{6-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1-metil-1*H*-bencimidazol-2-il} carbamato de metilo
108	{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de prop-2-in-1-ilo
109	{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de but-2-in-1-ilo
110	{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 1-metiletilo
111	{5-[2-(2,3-dihidro-1*H*-inden-2-il)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
112	{5-[1-hidroxi-3-oxo-2-(piridin-4-ilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il} carbamato de metilo

Entrada	Nombre
113	{5-[1-hidroxi-3-oxo-2-(piridin-3-ilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il} carbamato de metilo
114	(6-{2-[(3-fluorofenil)metil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il) carbamato de metilo
115	{5-[1-hidroxi-2-(3-metilfenil)-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
116	[5-(1-hidroxi-2-{[2-(metiloxi)fenil]metil}-3-oxo-2,3-dihidro-1*H*-isoindol-1-il)-1*H*-bencimidazol-2-il]carbamato de metilo
117	[5-(1-hidroxi-2-{[3-(metiloxi)fenil]metil}-3-oxo-2,3-dihidro-1*H*-isoindol-1-il)-1*H*-bencimidazol-2-il]carbamato de metilo
118	[5-(1-hidroxi-2-{[4-(metiloxi)fenil]metil}-3-oxo-2,3-dihidro-1*H*-isoindol-1-il)-1*H*-bencimidazol-2-il]carbamato de metilo
119	(6-{2-[(4-fluorofenil)metil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
120	(6-{2-[(3-bromofenil)metil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il) carbamato de metilo
121	(5-{1-hidroxi-2-[(3-yodofenil)metil]-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il) carbamato de metilo
122	(5-{2-[(3-clorofenil)metil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo

Entrada	Nombre
123	(5-{2-[(2-fluorofenil)metil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il) carbamato de metilo
124	{5-[1-hidroxi-3-oxo-2-(piridin-2-ilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
125	{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de fenilmetilo
126	{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 2-fluoroetilo
127	{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de propilo
128	(5-{1-hidroxi-2-[4-(metiloxi)fenil]-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
129	(5-{2-[(2-clorofenil)metil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
130	(5-{2-[(2-bromofenil)metil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il) carbamato de metilo
131	(5-{1-hidroxi-2-[(3-metilfenil)metil]-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
132	(5-{1-hidroxi-2-[(4-metilfenil)metil]-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il) carbamato de metilo

Entrada	Nombre
133	(5-{1-hidroxi-2-[(2-metilfenil)metil]-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il) carbamato de metilo
134	{5-[2-(3-bromofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
135	{5-[2-(3-clorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
136	{5-[2-(3-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
137	(5-{1-hidroxi-2-[3-(metiloxi)fenil]-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
138	{5-[2-(4-bromofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
139	{5-[2-(4-clorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
140	{5-[2-(4-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
141	{5-[2-(3,5-dimetilfenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
142	{5-[2-(2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo

Entrada	Nombre
143	{5-[2-(2-clorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
144	{5-[1-hidroxi-2-(2-metilfenil)-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
145	(5-{1-hidroxi-2-[2-(metiloxi)fenil]-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
146	{5-[1-hidroxi-2-(4-metilfenil)-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
147	(5-{1-hidroxi-3-oxo-2-[3-(trifluorometil)fenil]-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
148	(5-{1-hidroxi-3-oxo-2-[(1*R*)-1-feniletil]-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de but-2-in-1-ilo
149	*N*-etil-*N*'-{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}urea
150	(5-{1-hidroxi-3-oxo-2-[(1*R*)-1-feniletil]-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de fenilmetilo
151	{6-[2-(3-amino-5-clorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
152	{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de piperidin-4-ilmetilo

Entrada	Nombre
153	{5-[2-(ciclopropilmetil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
154	{5-[2-(2,2-dimetilpropil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
155	{5-[2-(3,5-diclorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
156	{5-[2-(3,5-difluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
157	*N*-etil-*N*'-(5-{1-hidroxi-3-oxo-2-[(1*R*)-1-feniletil]-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)urea
158	*N*'-{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}-*N*,*N*-dimetilurea
159	{5-[2-(3-{[2-(dimetilamino)etil]oxi}fenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
160	{6-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 3-(4-metilpiperazin-1-il)propilo
161	{5-[2-(ciclohexilmetil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
162	{5-[1-hidroxi-2-(2-metilpropil)-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo

Entrada	Nombre
163	{5-[1-hidroxi-3-oxo-2-(1,3-tiazol-2-ilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
164	{5-[2-(3,4-difluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
165	(5-{2-[1-(3,5-difluorofenil)etil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
166	(5-{2-[1-(3-fluorofenil)etil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
167	[5-(2-ciclohexil-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il)-1*H*-bencimidazol-2-il]carbamato de metilo
168	{5-[2-(2,5-difluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
169	*N*-{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}-*N*'-(fenilmetil)urea
170	{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de piperidin-4-ilo
171	*N*-{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}-*N*'-metilurea
172	(5-{2-[1-(2-fluorofenil)etil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo

Entrada	Nombre
173	(5-{1-hidroxi-3-oxo-2-[1-(2-tienil)etil]-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
174	(5-{2-[1-(3-clorofenil)etil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
175	(5-{1-hidroxi-2-[3-metil-5-(trifluorometil)fenil]-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
176	*N*-{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}propanamida
177	{5-[2-(3,4-diclorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
178	{5-[2-(3-etilfenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
179	{5-[2-(3-etinilfenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
180	{5-[2-(4-cloro-3-metilfenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
181	[5-(1-hidroxi-3-oxo-2-{1-[3-(trifluorometil)fenil]etil}-2,3-dihidro-1*H*-isoindol-1-il)-1*H*-bencimidazol-2-il]carbamato de metilo
182	(5-{1-hidroxi-3-oxo-2-[(1*R*)-1-fenilpropil]-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo

Entrada	Nombre
183	[5-(1-hidroxi-3-oxo-2-{2-[(trifluorometil)oxi]fenil}-2,3-dihidro-1*H*-isoindol-1-il)-1*H*-bencimidazol-2-il]carbamato de metilo
184	{5-[2-(2,3-difluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
185	{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de ciclohexilo
186	{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de tetrahidrofuran-2-ilmetilo
187	{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de m ciclopropilmetilo
188	*N*-{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}morfolino-4-carboxamida
189	{5-[2-(ciclopentilmetil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
190	{5-[2-(2,3-dimetilfenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
191	{5-[2-(2,3-dihidro-1*H*-inden-1-il)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo

Entrada	Nombre
192	(2*S*)-ciclohexil[1-hidroxi-1-(2-{[(metiloxi)carbonil]amino}-1*H*-bencimidazol-5-il)-3-oxo-1,3-dihidro-2*H*-isoindol-2-il]etanoato de metilo
193	{5-[2-(2,6-difluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
194	{5-[2-(3-cloro-4-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
195	{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de but-3-en-1-ilo
196	{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 2,2,2-trifluoroetilo
197	{5-[2-(5-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
198	(5-{2-[1-(5-cloro-2-metilfenil)etil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
199	(5-{1-hidroxi-3-oxo-2-[(1*S*)-1-fenilpropil]-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
200	(5-{2-[1-(3-cloro-2-metilfenil)etil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
201	(5-{1-hidroxi-2-[1-(5-metil-2-tienil)etil]-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo

Entrada	Nombre
202	(5-{2-[1-(5-cloro-2-tienil)etil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
203	{5-[1-hidroxi-2-(3-yodofenil)-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
204	(5-{1-hidroxi-2-[3-(1-metiletil)fenil]-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
205	{5-[2-(furan-2-ilmetil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
206	{5-[1-hidroxi-3-oxo-2-(3-tienilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
207	{5-[2-(ciclobutilmetil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
208	3,3,3-trifluoro-2-hidroxi-*N*-{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}-2-(trifluorometil)propanamida
209	(5-{1-hidroxi-2-[1-(4-metil-2-tienil)etil]-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
210	(5-{2-[1-(4-bromo-2-tienil)etil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
211	{5-[1-hidroxi-2-(3-{[2-(metiloxi)etil]oxi}fenil)-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo

Entrada	Nombre
212	{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de tetrahidrofuran-3-ilmetilo
213	*N*-{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}piperidino-1-carboxamida
214	{5-[2-(3-bromo-4-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
215	{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 2,3-dihidroxipropilo
216	{5-[1-hidroxi-3-oxo-2-(tetrahidrofuran-2-ilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
217	(5-{2-[3-(aminocarbonil)fenil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
218	4,4,4-trifluoro-3-hidroxi-*N*-{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}-3-(trifluorometil)butanamida
219	(5-{1-hidroxi-2-[3-(metilsulfonil)fenil]-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
220	(5-{1-hidroxi-3-oxo-2-[3-(feniloxi)fenil]-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
221	[5-(1-hidroxi-3-oxo-2-{3-[(fenilmetil)oxi]fenil}-2,3-dihidro-1*H*-isoindol-1-il)-1*H*-bencimidazol-2-il]carbamato de metilo

Entrada	Nombre
222	[5-(2-bifenil-3-il-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il)-1*H*-bencimidazol-2-il]carbamato de metilo
223	{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 2,2-dimetil-3-[(fenilmetil)oxi]propilo
224	{5-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
225	{5-[2-(3-cianofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
226	{5-[2-(3-etinil-4-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
227	{5-[2-(4-fluoro-3-metilfenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
228	{6-[2-(3,4-dicloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
229	{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de [(4*S*)-2,2-dimetil-1,3-dioxolan-4-il]metilo
230	{5-[2-(5-bromo-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
231	(5-{2-[3-(acetilamino)fenil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo

Entrada	Nombre
232	(5-{1-hidroxi-3-oxo-2-[3-(fenilmetil)fenil]-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
233	(5-{2-[1-(4-cloro-2-tienil)etil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
234	(5-{1-hidroxi-3-oxo-2-[3-(fenilcarbonil)fenil]-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
235	[5-(2-{3-[(dimetilamino)metil]fenil}-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il)-1*H*-bencimidazol-2-il]carbamato de metilo
236	(5-{2-[3-(aminosulfonil)fenil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
237	{5-[2-(3-acetilfenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
238	{5-[2-(3-etil-4-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
239	{5-[2-(3-cloro-5-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
240	*N*-{6-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}-2-metilpropanamida
241	(5-{2-[1-(3-cloro-2-tienil)etil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo

Entrada	Nombre
242	[5-(1-hidroxi-3-oxo-2-piridin-3-il-2,3-dihidro-1*H*-isoindol-1-il)-1*H*-bencimidazol-2-il]carbamato de metilo
243	(5-{1-hidroxi-3-oxo-2-[3-(fenilamino)fenil]-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
244	{5-[2-(5-bromo-2,4-difluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
245	{5-[2-(5-cloro-2,4-difluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
246	{5-[2-(3,5-dicloro-4-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
247	{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 2,2-dimetil-3-(metiloxi)propilo
248	3-hidroxi-2,2-dimetilpropil {5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
249	(5-{2-[1-(5-bromo-2-tienil)etil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
250	{5-[2-(4,5-dicloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
251	{5-[2-(3-bromo-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo

Entrada	Nombre
252	{5-[2-(3-cloro-2,4-difluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
253	*N*-{6-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}pent-4-ynamida
254	(6-{1-metil-3-oxo-2-[3-(trifluorometil)fenil]-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
255	[5-(1-hidroxi-3-oxo-2-{3-[(1,1,2,2-tetrafluoroetil)oxi]fenil}-2,3-dihidro-1*H*-isoindol-1-il)-1*H*-bencimidazol-2-il]carbamato de metilo
256	{5-[1-hidroxi-3-oxo-2-(3-piperidin-4-ilfenil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
257	{5-[2-(3-etenilfenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
258	(5-{2-[3-(dimetilamino)fenil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
259	2,2-difluoro-*N*-{6-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}ciclopropanocarboxamida
260	*N*-etil-*N*'-{6-[2-(4-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}urea
261	{5-[2-(3-aminofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo

Entrada	Nombre
262	*N*-{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}-4-[(fenilmetil)oxi]butanamida
263	*N*-{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}-4-piperidin-1-ilbutanamida
264	*N*-{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}-4-(4-metilpiperazin-1-il)butanamida
265	*N*-{6-[2-(4-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}butanamida
266	{6-[2-(3-bromofenil)-5,6-dicloro-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
267	[5-(1-hidroxi-2-{3-[metil(fenil)amino]fenil}-3-oxo-2,3-dihidro-1*H*-isoindol-1-il)-1*H*-bencimidazol-2-il]carbamato de metilo
268	{5-[1-hidroxi-3-oxo-2-(fenilsulfonil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
269	{5-[(2-{[(fenilamino)carbonil]amino}fenil)carbonil]-1*H*-bencimidazol-2-il}carbamato de metilo
270	(5-{[2-({[(fenilmetil)oxi]carbonil}amino)fenil]carbonil}-1*H*-bencimidazol-2-il)carbamato de metilo
271	[5-({2-[(2-fenilhidrazino)carbonil]fenil}carbonil)-1*H*-bencimidazol-2-il]carbamato de metilo
272	{5-[(2-{[(feniloxi)amino]carbonil}fenil)carbonil]-1*H*-bencimidazol-2-il}carbamato de metilo

Entrada	Nombre
273	{5-[2-(4-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de but-2-in-1-ilo
274	*N*-{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}-3-piperidin-1-ilpropanamida
275	*N*-{6-[2-(4-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}propanamida
276	*N*-(4-fluorofenil)-2-{[2-(pent-4-ynoilamino)-1*H*-bencimidazol-6-il]carbonil}benzamida
277	4-(dietilamino)-*N*-{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}butanamida
278	*N*-{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}-4-pirrolidin-1-ilbutanamida
279	{6-[2-(4-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 3-piperidin-1-ilpropilo
280	{6-[2-(4-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de -(4-metilpiperazin-1-il)propilo
281	{5-[2-(3-bromofenil)-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
282	{5-[2-(3-etinil-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
283	{5-[2-(4-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 2-piperidin-1-iletilo

Entrada	Nombre
284	{5-[2-(3-cloro-2-metilfenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
285	{5-[2-(5-cloro-2-metilfenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
286	*N*-{6-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}-2,2-dimetil-3-piperidin-1-ilpropanamida
287	*N*-{5-[2-(4-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}-4-piperidin-1-ilbutanamida
288	*N*-{5-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}-4-piperidin-1-ilbutanamida
289	[6-({2-[(fenilcarbonil)amino]fenil}carbonil)-1*H*-bencimidazol-2-il]carbamato de metilo
290	{5-[1-hidroxi-2-(3-morfolin-4-ilfenil)-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
291	{6-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 2-(dimetilamino)etilo
292	{5-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 2-(dietilamino)etilo
293	{5-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 2-piperidin-1-iletilo

Entrada	Nombre
294	{6-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 3-piperidin-1-ilpropilo
295	{6-[2-(3-bromofenil)-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
296	{6-[2-(3-bromofenil)-4,7-difluoro-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 2-piperidin-1-iletilo
297	{5-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 2-[metil(fenilmetil)amino]etilo
298	{5-[1-hidroxi-3-oxo-2-(3-pirrolidin-1-ilfenil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
299	{5-[2-(5-cloro-2,3-difluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
300	{5-[1-hidroxi-3-oxo-2-(pirrolidin-2-ilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
301	{5-[1-hidroxi-3-oxo-2-(pirrolidin-3-ilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
302	{6-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de (1-metilpiperidin-2-il)metilo
303	{6-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de [(2*S*)-1-metilpirrolidin-2-il]metilo

Entrada	Nombre
304	{6-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de octahidro-2*H*-quinolizin-1-ilmetilo
305	{5-[2-(5-bromo-2-metilfenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
306	5-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1,3-dihidro-2*H*-bencimidazol-2-ona
307	{5-[2-(3-bromo-2,5-difluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
308	{6-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 2-morfolin-4-iletilo
309	{6-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de (1-metilpiperidin-3-il)metilo
310	(5-{2-[5-cloro-2-(metiloxi)fenil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
311	[5-(2-{3-[ciclohexil(metil)amino]fenil}-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il)-1*H*-bencimidazol-2-il]carbamato de metilo
312	{6-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 8-azabiciclo[3,2,1]oct-3-ilmetilo
313	{6-[1-(3-bromofenil)-5-oxopirrolidin-2-il]-1*H*-bencimidazol-2-il}carbamato de metilo

Entrada	Nombre
314	{5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de (1-metilpiperidin-4-il)metilo
315	4-({[({5-[1-hidroxi-3-oxo-2-(fenilmetil)-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}amino)carbonil]oxi}metil)piperidino-1-carboxilato de 1,1-dimetiletilo
316	{5-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de (1-metilpiperidin-4-il)metilo
317	{5-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 2-(1-metilpiperidin-4-il)etilo
318	({6-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}amino)(oxo)acetato de metilo
319	*N*-(5-{1-hidroxi-3-oxo-2-[3-(feniloxi)fenil]-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)-4-piperidin-1-ilbutanamida
320	{6-[2-(3-bromofenil)-1-metil-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
321	{6-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 4-(dietilamino)but-2-in-1-ilo
322	{5-[2-(3-cloro-2,6-difluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
323	{6-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 2-(2-oxopirrolidin-1-il)etilo

Entrada	Nombre
324	{6-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 2-(2,5-dioxopirrolidin-1-il)etilo
325	{5-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 2,2,3,3-tetrafluorociclobutilo
326	1-acetil-*N*-{5-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}piperidino-4-carboxamida
327	*N*-{5-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}ciclobutanocarboxamida
328	[5-(2-{3-[etil(fenil)amino]fenil}-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il)-1*H*-bencimidazol-2-il]carbamato de metilo
329	*N*-{6-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}-2,2-difluorociclopropanocarboxamida
330	{6-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de ciclobutilo
331	{6-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 2,2-difluoroetilo
332	2-(3-cloro-2-fluorofenil)-3-hidroxi-3-[2-(piridin-2-ilamino)-1*H*-bencimidazol-5-il]-2,3-dihidro-1*H*-isoindol-1-ona
333	{6-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 1-metiletilo

Entrada	Nombre
334	{6-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de ciclopropilmetilo
335	*N*-{5-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}ciclopropanocarboxamida
336	{5-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 2-(metiloxi)etilo
337	{6-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de tetrahidrofuran-2-ilmetilo
338	*N*-{5-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}-2-(2-tienil)acetamida
339	{6-[2-(3-cloro-2-fluorofenil)-4,7-difluoro-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
340	{6-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de etilo
341	{6-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 2-fluoroetilo
342	(5-{1-hidroxi-3-oxo-2-[2-(feniloxi)fenil]-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
343	*N*'-{5-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}-*N*,*N*-dietilpentanediamida

Entrada	Nombre
344	{6-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de ciclobutilmetilo
345	{6-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de 2,2,2-trifluoroetilo
346	(5-{2-[3-(1,1-dimetiletil)fenil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
347	{6-[2-(3-cloro-2-fluorofenil)-7-fluoro-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
348	2-(3-cloro-2-fluorofenil)-3-hidroxi-3-[2-(fenilamino)-1*H*-bencimidazol-5-il]-2,3-dihidro-1*H*-isoindol-1-ona
349	{6-[4,7-dicloro-2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
350	2-[(2-{[(etiloxi)carbonil]amino}-1,3-benzoxazol-5-il)carbonil]benzoato de fenilmetilo
351	{5-[2-(5-cloro-3-etinil-2-metilfenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
352	{5-[2-(5-etinil-2,4-difluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
353	{5-[2-(3-etinil-2,4-difluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo

Entrada	Nombre
354	2-(3-cloro-2-fluorofenil)-3-hidroxi-3-[2-(pirimidin-2-ilamino)-1*H*-bencimidazol-5-il]-2,3-dihidro-1*H*-isoindol-1-ona
355	{5-[2-(3-etinil-2-fluorofenil)-4,7-difluoro-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
356	2-(3-cloro-2-fluorofenil)-3-hidroxi-3-[2-(1,3-tiazol-2-ilamino)-1*H*-bencimidazol-5-il]-2,3-dihidro-1*H*-isoindol-1-ona
357	{5-[2-(3-cloro-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1,3-benzoxazol-2-il}carbamato de etilo
358	{5-[2-(5-cloro-3-yodo-2-metilfenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
359	{5-[2-(3-etil-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
360	{5-[2-(5-etinil-2-metilfenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
361	2-(3-cloro-2-fluorofenil)-3-hidroxi-3-[2-(pirazin-2-ilamino)-1*H*-bencimidazol-5-il]-2,3-dihidro-1*H*-isoindol-1-ona
362	{5-[2-(2-fluoro-3-yodofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
363	{6-[2-(5-etinil-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo

Entrada	Nombre
364	2-(3-etinil-2-fluorofenil)-3-hidroxi-3-[2-(pirimidin-2-ilamino)-1*H*-bencimidazol-5-il]-2,3-dihidro-1*H*-isoindol-1-ona
365	{5-[2-(2,5-dimetilfenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
366	{5-[2-(3-etenil-2-fluorofenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
367	(6-{2-[2-fluoro-3-(metiloxi)fenil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
368	(5-{1-hidroxi-2-[2-metil-5-(metiloxi)fenil]-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
369	{5-[2-(3-etinil-2-fluorofenil)-7-fluoro-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
370	{5-[2-(2-fluoro-3-prop-1-in-1-ilfenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
371	{5-[2-(5-cloro-2-metilfenil)-7-fluoro-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
372	{5-[2-(3-etinil-2-metilfenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
373	3-hidroxi-2-[3-(metiloxi)fenil]-3-[2-(pirimidin-2-ilamino)-1*H*-bencimidazol-6-il]-2,3-dihidro-1*H*-isoindol-1-ona

Entrada	Nombre
374	3-hidroxi-2-(3-metilfenil)-3-[2-(pirimidin-2-ilamino)-1*H*-bencimidazol-6-il]-2,3-dihidro-1*H*-isoindol-1-ona
375	2-(5-cloro-2-metilfenil)-3-hidroxi-3-[2-(pirimidin-2-ilamino)-1*H*-bencimidazol-6-il]-2,3-dihidro-1*H*-isoindol-1-ona
376	{6-[2-(5-cloro-2-metilfenil)-4,7-difluoro-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
377	{5-[2-(3-etinil-2-fluorofenil)-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
378	2-(3-cloro-2-fluorofenil)-3-{2-[(6-cloropiridazin-3-il)amino]-1*H*-bencimidazol-5-il}-3-hidroxi-2,3-dihidro-1*H*-isoindol-1-ona
379	2-(3-cloro-2-fluorofenil)-4,7-difluoro-3-hidroxi-3-[2-(pirimidin-2-ilamino)-1*H*-bencimidazol-5-il]-2,3-dihidro-1*H*-isoindol-1-ona
380	{5-[2-(2-fluoro-5-metilfenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
381	(5-{2-[2-fluoro-5-(metiloxi)fenil]-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
382	(5-{1-hidroxi-2-[5-metil-2-(metiloxi)fenil]-3-oxo-2,3-dihidro-1*H*-isoindol-1-il}-1*H*-bencimidazol-2-il)carbamato de metilo
383	{5-[2-(3-etinil-5-metilfenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo

Entrada	Nombre
384	2-(3-cloro-2-fluorofenil)-3-{2-[(5-cloropirimidin-2-il)amino]-1*H*-bencimidazol-5-il}-3-hidroxi-2,3-dihidro-1*H*-isoindol-1-ona
385	2-(3-cloro-2-fluorofenil)-3-hidroxi-3-{2-[(4-metilpirimidin-2-il)amino]-1*H*-bencimidazol-5-il}-2,3-dihidro-1*H*-isoindol-1-ona
386	3-(2-{[4,6-bis(metiloxi)pirimidin-2-il]amino}-1*H*-bencimidazol-5-il)-2-(3-cloro-2-fluorofenil)-3-hidroxi-2,3-dihidro-1*H*-isoindol-1-ona
387	2-(3-cloro-2-fluorofenil)-3-hidroxi-3-(2-{[4-metil-6-(metiloxi)pirimidin-2-il]amino}-1*H*-bencimidazol-5-il)-2,3-dihidro-1*H*-isoindol-1-ona
388	3-hidroxi-2-(3-metilfenil)-3-[2-(pirazin-2-ilamino)-1*H*-bencimidazol-6-il]-2,3-dihidro-1*H*-isoindol-1-ona
389	2-(5-cloro-2-metilfenil)-3-hidroxi-3-[2-(pirazin-2-ilamino)-1*H*-bencimidazol-6-il]-2,3-dihidro-1*H*-isoindol-1-ona
390	{6-[2-(2-fluoro-3-metilfenil)-1-hidroxi-3-oxo-2,3-dihidro-1*H*-isoindol-1-il]-1*H*-bencimidazol-2-il}carbamato de metilo
391	3-hidroxi-2-[3-(metiloxi)fenil]-3-[2-(pirazin-2-ilamino)-1*H*-bencimidazol-5-il]-2,3-dihidro-1*H*-isoindol-1-ona
392	{6-[(2-{[(2-tienilmetil)amino]carbonil}fenil)carbonil]-1*H*-bencimidazol-2-il}carbamato de metilo
393	{6-[(2-{[(3-metilfenil)amino]carbonil}fenil)carbonil]-1*H*-bencimidazol-2-il}carbamato de metilo

Entrada	Nombre
394	{6-[(2-{[(3-bromofenil)amino]carbonil}fenil)carbonil]-1*H*-bencimidazol-2-il}carbamato de metilo
395	{6-[(2-{[(3-clorofenil)amino]carbonil}fenil)carbonil]-1*H*-bencimidazol-2-il}carbamato de metilo
396	{6-[(2-{[(3-fluorofenil)amino]carbonil}fenil)carbonil]-1*H*-bencimidazol-2-il}carbamato de metilo
397	(6-{[2-({[3-(metiloxi)fenil]amino}carbonil)fenil]carbonil}-1*H*-bencimidazol-2-il)carbamato de metilo
398	(6-{[2-({[3-(trifluorometil)fenil]amino}carbonil)fenil]carbonil}-1*H*-bencimidazol-2-il)carbamato de metilo
399	{6-[(2-{[(3-etilfenil)amino]carbonil}fenil)carbonil]-1*H*-bencimidazol-2-il}carbamato de metilo
400	{6-[(2-{[(3-etinilfenil)amino]carbonil}fenil)carbonil]-1*H*-bencimidazol-2-il}carbamato de metilo
401	{6-[(2-{[(3-cloro-4-fluorofenil)amino]carbonil}fenil)carbonil]-1*H*-bencimidazol-2-il}carbamato de metilo
402	{6-[(2-{[(5-cloro-2-fluorofenil)amino]carbonil}fenil)carbonil]-1*H*-bencimidazol-2-il}carbamato de metilo
403	{6-[(2-{[(3-yodofenil)amino]carbonil}fenil)carbonil]-1*H*-bencimidazol-2-il}carbamato de metilo

Entrada	Nombre
404	(6-{[2-({[3-(1-metiletil)fenil]amino}carbonil)fenil]carbonil}-1*H*-bencimidazol-2-il)carbamato de metilo
405	{6-[(2-{[(3-tienilmetil)amino]carbonil}fenil)carbonil]-1*H*-bencimidazol-2-il}carbamato de metilo
406	{6-[(2-{[(3-bromo-4-fluorofenil)amino]carbonil}fenil)carbonil]-1*H*-bencimidazol-2-il}carbamato de metilo
407	{6-[(2-{[(3-cloro-2-fluorofenil)amino]carbonil}fenil)carbonil]-1*H*-bencimidazol-2-il}carbamato de metilo
408	{6-[(2-{[(4-fluoro-3-metilfenil)amino]carbonil}fenil)carbonil]-1*H*-bencimidazol-2-il}carbamato de metilo
409	{6-[(2-{[(5-bromo-2-fluorofenil)amino]carbonil}fenil)carbonil]-1*H*-bencimidazol-2-il}carbamato de metilo
410	{6-[(2-{[(5-bromo-2,4-difluorofenil)amino]carbonil}fenil)carbonil]-1*H*-bencimidazol-2-il}carbamato de metilo
411	{6-[(2-{[(5-cloro-2,4-difluorofenil)amino]carbonil}fenil)carbonil]-1*H*-bencimidazol-2-il}carbamato de metilo
412	{6-[(2-{[(3-bromo-2-fluorofenil)amino]carbonil}fenil)carbonil]-1*H*-bencimidazol-2-il}carbamato de metilo
413	{6-[(2-{[(3-etenilfenil)amino]carbonil}fenil)carbonil]-1*H*-bencimidazol-2-il}carbamato de metilo

Entrada	Nombre
414	{6-[(2-{[(3-etinil-2-fluorofenil)amino]carbonil}fenil)carbonil]-1*H*-bencimidazol-2-il}carbamato de metilo
415	{6-[(2-{[(5-cloro-2-metilfenil)amino]carbonil}fenil)carbonil]-1*H*-bencimidazol-2-il}carbamato de metilo
416	{6-[(2-{[(5-bromo-2-metilfenil)amino]carbonil}fenil)carbonil]-1*H*-bencimidazol-2-il}carbamato de metilo
417	{6-[(2-{[(2-fluoro-3-yodofenil)amino]carbonil}fenil)carbonil]-1*H*-bencimidazol-2-il}carbamato de metilo
418	{6-[(2-{[(3-etenil-2-fluorofenil)amino]carbonil}fenil)carbonil]-1*H*-bencimidazol-2-il}carbamato de metilo
419	{6-[(2-{[(2-fluoro-5-metilfenil)amino]carbonil}fenil)carbonil]-1*H*-bencimidazol-2-il}carbamato de metilo

Tabla 7.

Inhibidores representativos de EGFR y/o VEGFR

[00224] Los Compuestos de la Tabla 7 se pueden preparar como sales, solvatos, hidratos y/o isómeros farmacéuticamente aceptables de estos. Todas las combinaciones de sales, solvatos, hidratos e isómeros de los Compuestos de la Tabla 7 se pueden usar para practicar la invención.

Entrada	Nombre
1	(3*Z*)-3-[[5-(metiloxi)-1*H*-bencimidazol-2-il](fenil)metiliden]-5-{[1-(fenilmetil)pirrolidin-3-il]amino}-1,3-dihidro-2*H*-indol-2-ona

Entrada	Nombre
2	(3*Z*)-5-[(1-etilpiperidin-3-il)amino]-3-[[5-(metiloxi)-1*H*-bencimidazol-2-il](fenil)metiliden]-1,3-dihidro-2*H*-indol-2-ona
3	(3*Z*)-5-[(1-etilpiperidin-4-il)amino]-3-[[5-(metiloxi)-1*H*-bencimidazol-2-il](fenil)metiliden]-1,3-dihidro-2*H*-indol-2-ona
4	(3*Z*)-5-[(1-etilpiperidin-4-il)amino]-3-[1*H*-imidazol-2-il(fenil)metiliden]-1,3-dihidro-2*H*-indol-2-ona
5	(3*Z*)-5-[(1-etilpiperidin-4-il)amino]-3-{[5-(metiloxi)-1*H*-bencimidazol-2-il][4-(metiloxi)fenil]metiliden}-1,3-dihidro-2*H*-indol-2-ona
6	(3*Z*)-5-[(1-etilpiperidin-4-il)amino]-3-[[5-(metiloxi)-1*H*-bencimidazol-2-il](4-metilfenil)metiliden]-1,3-dihidro-2*H*-indol-2-ona
7	(3*Z*)-3-[1*H*-bencimidazol-2-il(4-nitrofenil)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
8	(3*Z*)-3-{1*H*-bencimidazol-2-il[4-(metiloxi)fenil]metiliden}-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
9	(3*Z*)-3-[1*H*-bencimidazol-2-il(fenil)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
10	(3*Z*)-3-[[5-(metiloxi)-1*H*-bencimidazol-2-il](fenil)metiliden]-5-[(2,2,6,6-tetrametilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
11	(3*Z*)-3-[(4-aminofenil)(1*H*-bencimidazol-2-il)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
12	(3*Z*)-3-[1*H*-bencimidazol-2-il(4-metilfenil)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
13	(3*Z*)-5-[(1-etilpiperidin-4-il)amino]-3-[1*H*-imidazol-2-il(4-metilfenil)metiliden]-1,3-dihidro-2*H*-indol-2-ona
14	(3*Z*)-5-[(1-etilpiperidin-4-il)oxi]-3-[[5-(metiloxi)-1*H*-bencimidazol-2-il](fenil)metiliden]-1,3-dihidro-2*H*-indol-2-ona
15	(3*Z*)-5-[(1-etilpiperidin-4-il)amino]-3-{1*H*-imidazol-2-il[4-(metiloxi)fenil]metiliden}-1,3-dihidro-2*H*-indol-2-ona

Entrada	Nombre
16	(3*Z*)-3-[1*H*-bencimidazol-2-il(4-fluorofenil)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
17	(3*Z*)-3-[1*H*-bencimidazol-2-il(3,5-difluorofenil)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
18	(3*Z*)-3-[1*H*-bencimidazol-2-il(3-fluorofenil)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
19	(3*Z*)-3-[1*H*-bencimidazol-2-il(3-nitrofenil)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
20	3-((*Z*)-1*H*-bencimidazol-2-il{5-[(1-etilpiperidin-4-il)amino]-2-oxo-1,2-dihidro-3*H*-indol-3-iliden}metil)benzonitrilo
21	(3*Z*)-3-[(3-aminofenil)(1*H*-bencimidazol-2-il)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
22	(3*Z*)-3-[1*H*-bencimidazol-2-il(fenil)metiliden]-5-(piperidin-4-ilamino)-1,3-dihidro-2*H*-indol-2-ona
23	3-((*Z*)-1*H*-bencimidazol-2-il{5-[(1-etilpiperidin-4-il)amino]-2-oxo-1,2-dihidro-3*H*-indol-3-iliden}metil)bencenocarboximidamida
24	(3*Z*)-3-[1*H*-bencimidazol-2-il(fenil)metiliden]-5-({1-[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
25	(3*Z*)-3-[1*H*-bencimidazol-2-il(fenil)metiliden]-5-[(2,2,6,6-tetrametilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
26	(3*Z*)-3-{1*H*-bencimidazol-2-il[3-(metiloxi)fenil]metiliden}-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
27	(3*Z*)-3-[1*H*-bencimidazol-2-il(3-clorofenil)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
28	2-(2-{2-[(*Z*)-{5-[(1-etilpiperidin-4-il)amino]-2-oxo-1,2-dihidro-3*H*-indol-3-iliden}(fenil)metil]-1*H*-imidazol-4-il}etil)-1*H*-isoindole-1,3(2*H*)-diona
29	(3*Z*)-3-[1*H*-bencimidazol-2-il(fenil)metiliden]-5-({1-[2-(dimetilamino)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
30	(3*Z*)-3-[1*H*-bencimidazol-2-il(fenil)metiliden]-5-{[1-

Entrada	Nombre
	(metilsulfonil)piperidin-4-il]amino}-1,3-dihidro-2*H*-indol-2-ona
31	(3*Z*)-5-(8-azabiciclo[3,2,1]oct-3-ilamino)-3-[1*H*-bencimidazol-2-il(fenil)metiliden]-1,3-dihidro-2*H*-indol-2-ona
32	(3*Z*)-3-{1*H*-bencimidazol-2-il[3-(metiloxi)fenil]metiliden}-5-[(1-etilpiperidin-4-il)oxi]-1,3-dihidro-2*H*-indol-2-ona
33	(3*Z*)-3-[1*H*-bencimidazol-2-il(3,5-difluorofenil)metiliden]-5-[(1-etilpiperidin-4-il)oxi]-1,3-dihidro-2*H*-indol-2-ona
34	(3*Z*)-3-[1*H*-bencimidazol-2-il(fenil)metiliden]-5-{[1-(fenilmetil)piperidin-4-il]oxi}-1,3-dihidro-2*H*-indol-2-ona
35	(3*Z*)-3-[1*H*-bencimidazol-2-il(3-clorofenil)metiliden]-5-[(1-etilpiperidin-4-il)oxi]-1,3-dihidro-2*H*-indol-2-ona
36	(3*Z*)-3-[1*H*-bencimidazol-2-il(3,5-difluorofenil)metiliden]-5-({1-[2-(metiloxi)etil]piperidin-4-il}oxi)-1,3-dihidro-2*H*-indol-2-ona
37	(3*Z*)-3-[1*H*-bencimidazol-2-il(3-clorofenil)metiliden]-5-({1-[2-(metiloxi)etil]piperidin-4-il}oxi)-1,3-dihidro-2*H*-indol-2-ona
38	(3*Z*)-3-[1*H*-bencimidazol-2-il(3-clorofenil)metiliden]-5-({1-[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
39	(3*Z*)-3-{1*H*-bencimidazol-2-il[3-(metiloxi)fenil]metiliden}-5-({1-[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
40	(3*Z*)-3-[(3-clorofenil)(1*H*-imidazol-2-il)metiliden]-5-({1-[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
41	(3*Z*)-3-[(3-fluorofenil)(1*H*-imidazol-2-il)metiliden]-5-({1-[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
42	(3*Z*)-3-[1*H*-bencimidazol-2-il(3,5-difluorofenil)metiliden]-5-({1-[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona

Entrada	Nombre
43	(3*Z*)-3-[1*H*-bencimidazol-2-il(3-clorofenil)metiliden]-5-[(1-etilpiperidin-4-il)(metil)amino]-1,3-dihidro-2*H*-indol-2-ona
44	(3*Z*)-3-[(3-clorofenil)(1*H*-imidazol-2-il)metiliden]-5-[(1-etilpiperidin-4-il)oxi]-1,3-dihidro-2*H*-indol-2-ona
45	(3*Z*)-3-[1*H*-bencimidazol-2-il(4-clorofenil)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
46	(3*Z*)-3-[1*H*-bencimidazol-2-il(3-fluorofenil)metiliden]-5-({1-[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
47	(3*Z*)-3-[1*H*-bencimidazol-2-il(4-fluorofenil)metiliden]-5-({1-[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
48	(3*Z*)-3-[(3-clorofenil)(1*H*-imidazol-2-il)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
49	(3*Z*)-5-[(1-etilpiperidin-4-il)amino]-3-[(3-fluorofenil)(1*H*-imidazol-2-il)metiliden]-1,3-dihidro-2*H*-indol-2-ona
50	(3*Z*)-3-[1*H*-bencimidazol-2-il(3-fluoro-4-metilfenil)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
51	(3*Z*)-5-[(1-etilpiperidin-4-il)amino]-3-[(3-fluorofenil)(4-metil-1*H*-imidazol-2-il)metiliden]-1,3-dihidro-2*H*-indol-2-ona
52	(3*Z*)-3-[1*H*-bencimidazol-2-il(4-fluoro-3-metilfenil)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
53	(3*Z*)-3-[(3-cloro-4-fluorofenil)(1*H*-imidazol-2-il)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
54	(3*Z*)-3-[(3,4-difluorofenil)(1*H*-imidazol-2-il)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
55	(3*Z*)-3-[(5-cloro-1*H*-bencimidazol-2-il)(fenil)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona

Entrada	Nombre
56	(3*Z*)-3-[(5-cloro-1*H*-bencimidazol-2-il)(3,5-difluorofenil)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
57	(3*Z*)-5-[(1-etilpiperidin-4-il)amino]-3-[(3-fluoro-4-metilfenil)(1*H*-imidazol-2-il)metiliden]-1,3-dihidro-2*H*-indol-2-ona
58	(3*Z*)-5-[(1-etilpiperidin-4-il)amino]-3-[(4-fluorofenil)(1*H*-imidazol-2-il)metiliden]-1,3-dihidro-2*H*-indol-2-ona
59	(3*Z*)-5-[(1-etilpiperidin-4-il)amino]-3-[1*H*-imidazol-2-il(4-propilfenil)metiliden]-1,3-dihidro-2*H*-indol-2-ona
60	(3*Z*)-5-[(1-etilpiperidin-4-il)amino]-3-{1*H*-imidazol-2-il[4-(trifluorometil)fenil]metiliden}-1,3-dihidro-2*H*-indol-2-ona
61	(3*E*)-3-[(3,5-difluorofenil)(5-fluoro-1*H*-bencimidazol-2-il)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
62	(3*Z*)-3-[(3,5-difluorofenil)(5-fluoro-1*H*-bencimidazol-2-il)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
63	(3*Z*)-3-[(3-fluoro-4-metilfenil)(1*H*-imidazol-2-il)metiliden]-5-({1-[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
64	(3*Z*)-5-[(1-etilpiperidin-4-il)amino]-3-[(4-metil-1*H*-imidazol-2-il)(4-metilfenil)metiliden]-1,3-dihidro-2*H*-indol-2-ona
65	(3*Z*)-5-[(1-etilpiperidin-4-il)amino]-3-[[3-fluoro-4-(trifluorometil)fenil](1*H*-imidazol-2-il)metiliden]-1,3-dihidro-2*H*-indol-2-ona
66	(3*Z*)-3-[(4-clorofenil)(1*H*-imidazol-2-il)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
67	(3*Z*)-5-[(1-etilpiperidin-4-il)amino]-3-[(3-fluoro-4-metilfenil)(4-metil-1*H*-imidazol-2-il)metiliden]-1,3-dihidro-2*H*-indol-2-ona

Entrada	Nombre
68	(3*Z*)-5-[(1-etilpiperidin-4-il)amino]-3-{1*H*-imidazol-2-il[6-(trifluorometil)piridin-3-il]metiliden}-1,3-dihidro-2*H*-indol-2-ona
69	(3*Z*)-3-[1*H*-imidazol-2-il(4-metilfenil)metiliden]-5-({1-[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
70	(3*Z*)-3-[(3-fluorofenil)(4-metil-1*H*-imidazol-2-il)metiliden]-5-({1-[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
71	(3*Z*)-3-{1*H*-imidazol-2-il[4-(trifluorometil)fenil]metiliden}-5-({1-[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
72	(3*Z*)-3-[(5-cloro-1*H*-bencimidazol-2-il)(fenil)metiliden]-5-({1-[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
73	(3*Z*)-3-[(3,5-difluorofenil)(1*H*-imidazol-2-il)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
74	(3*Z*)-3-[(3,5-difluorofenil)(4-metil-1*H*-imidazol-2-il)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
75	(3*Z*)-3-[(3,5-difluorofenil)(1*H*-imidazol-2-il)metiliden]-5-({1-[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
76	(3*Z*)-3-[(3,5-difluorofenil)(4-metil-1*H*-imidazol-2-il)metiliden]-5-({1-[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
77	(3*Z*)-3-[(4-metil-1*H*-imidazol-2-il)(4-metilfenil)metiliden]-5-({1-[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
78	(3*Z*)-3-[(4-fluorofenil)(1*H*-imidazol-2-il)metiliden]-5-({1-[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
79	(3*Z*)-3-[(3,4-difluorofenil)(1*H*-imidazol-2-il)metiliden]-5-

Entrada	Nombre
	({1-[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
80	(3*Z*)-3-[(3-cloro-4-fluorofenil)(1*H*-imidazol-2-il)metiliden]-5-({1-[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
81	(3*Z*)-3-[(3-fluorofenil)(1*H*-imidazol-2-il)metiliden]-5-(piperidin-4-ilamino)-1,3-dihidro-2*H*-indol-2-ona
82	(3*Z*)-3-[(3-fluorofenil)(1*H*-imidazol-2-il)metiliden]-5-{[1-(2-piperidin-1-iletil)piperidin-4-il]amino}-1,3-dihidro-2*H*-indol-2-ona
83	(3*Z*)-3-[(3-fluorofenil)(1*H*-imidazol-2-il)metiliden]-5-{[1-(2-morfolin-4-iletil)piperidin-4-il]amino}-1,3-dihidro-2*H*-indol-2-ona
84	(3*Z*)-5-({1-[2-(dietilamino)etil]piperidin-4-il}amino)-3-[(3-fluorofenil)(1*H*-imidazol-2-il)metiliden]-1,3-dihidro-2*H*-indol-2-ona
85	(3*Z*)-3-[(3-fluorofenil)(1*H*-imidazol-2-il)metiliden]-5-{[1-(2-pirrolidin-1-iletil)piperidin-4-il]amino}-1,3-dihidro-2*H*-indol-2-ona
86	(3*Z*)-3-[1*H*-imidazol-2-il(4-metilfenil)metiliden]-5-[(1-metilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
87	(3*Z*)-3-[(3-fluorofenil)(1*H*-1,2,4-triazol-5-il)metiliden]-5-({1-[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
88	2-{(*Z*)-(3-fluorofenil)[5-({1-[2-(metiloxi)etil]piperidin-4-il}amino)-2-oxo-1,2-dihidro-3*H*-indol-3-iliden]metil}-4-metil-1*H*-imidazol-5-carboxilato de etilo
89	(3*Z*)-3-[1*H*-imidazol-2-il(fenil)metiliden]-5-({1-[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
90	(3*Z*)-3-{1*H*-imidazol-2-il[4-(metiloxi)fenil]metiliden}-5-({1-[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
91	(3*Z*)-3-[(4-clorofenil)(1*H*-imidazol-2-il)metiliden]-5-({1-

Entrada	Nombre
	[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
92	(3*Z*)-3-[[3-fluoro-4-(trifluorometil)fenil](1*H*-imidazol-2-il)metiliden]-5-({1-[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
93	(3*Z*)-3-[(3-fluorofenil)(1*H*-imidazol-2-il)metiliden]-5-{[1-(metilsulfonil)piperidin-4-il]amino}-1,3-dihidro-2*H*-indol-2-ona
94	(3*Z*)-3-[1*H*-imidazol-2-il(4-propilfenil)metiliden]-5-({1-[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
95	(3*Z*)-5-[(1-etilpiperidin-4-il)amino]-3-[(3-fluorofenil)(4-fenilo-1*H*-imidazol-2-il)metiliden]-1,3-dihidro-2*H*-indol-2-ona
96	(3*Z*)-3-[(3-fluorofenil)(4-fenilo-1*H*-imidazol-2-il)metiliden]-5-({1-[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
97	(3*Z*)-3-[(3-fluoro-4-metilfenil)(4-metil-1*H*-imidazol-2-il)metiliden]-5-({1-[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
98	(3*Z*)-3-{1*H*-imidazol-2-il[6-(trifluorometil)piridin-3-il]metiliden}-5-({1-[2-(metiloxi)etil]piperidin-4-il}amino)-1,3-dihidro-2*H*-indol-2-ona
99	(3*Z*)-5-[(1-etilpiperidin-4-il)amino]-3-[(3-fluorofenil)(1*H*-1,2,4-triazol-5-il)metiliden]-1,3-dihidro-2*H*-indol-2-ona
100	(3*Z*)-5-[(1-etilpiperidin-4-il)amino]-3-[[2-fluoro-4-(trifluorometil)fenil](1*H*-imidazol-2-il)metiliden]-1,3-dihidro-2*H*-indol-2-ona
101	(3*Z*)-5-[(1-etilpiperidin-4-il)amino]-3-{(4-metil-1*H*-imidazol-2-il)[4-(trifluorometil)fenil]metiliden}-1,3-dihidro-2*H*-indol-2-ona
102	(3*Z*)-3-[(4-clorofenil)(4-metil-1*H*-imidazol-2-il)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-

Entrada	Nombre
	2*H*-indol-2-ona
103	(3*Z*)-5-[(1-etilpiperidin-4-il)amino]-3-[[3-fluoro-4-(trifluorometil)fenil](4-metil-1*H*-imidazol-2-il)metiliden]-1,3-dihidro-2*H*-indol-2-ona
104	(3*Z*)-3-[(3,4-difluorofenil)(4-metil-1*H*-imidazol-2-il)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
105	(3*Z*)-3-[(3-cloro-4-fluorofenil)(4-metil-1*H*-imidazol-2-il)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
106	(3*Z*)-5-[(1-etilpiperidin-4-il)amino]-3-[(4-fluorofenil)(4-metil-1*H*-imidazol-2-il)metiliden]-1,3-dihidro-2*H*-indol-2-ona
107	(3*Z*)-5-[(1-etilpiperidin-4-il)amino]-3-[(2-fluorofenil)(1*H*-imidazol-2-il)metiliden]-1,3-dihidro-2*H*-indol-2-ona
108	(3*Z*)-5-[(1-etilpiperidin-4-il)amino]-3-[[2-fluoro-4-(trifluorometil)fenil](4-metil-1*H*-imidazol-2-il)metiliden]-1,3-dihidro-2*H*-indol-2-ona
109	(3*Z*)-3-[(2,3-difluorofenil)(1*H*-imidazol-2-il)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
110	(3*Z*)-3-[(2,3-difluorofenil)(4-metil-1*H*-imidazol-2-il)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
111	(3*Z*)-3-[(2,4-difluorofenil)(4-metil-1*H*-imidazol-2-il)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
112	(3*Z*)-3-[(2,4-difluorofenil)(1*H*-imidazol-2-il)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
113	(3*Z*)-3-[(2-fluorofenil)(4-metil-1*H*-imidazol-2-il)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
114	(3*Z*)-3-[(3-trifluorometilfenil)(1*H*-imidazol-2-il)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-

Entrada	Nombre
	2*H*-indol-2-ona
115	(3*Z*)-3-[(3-trifluorometilfenil)(4-metil-1*H*-imidazol-2-il)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
116	(3*Z*)-3-[(2,4-dicloro-5-fluorofenil)(1*H*-imidazol-2-il)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
117	(3*Z*)-3-[(2,4-dicloro-5-fluorofenil)(4-metil-1*H*-imidazol-2-il)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona
118	(3*Z*)-3-[(4-cloro-2-fluorofenil)(4-metil-1*H*-imidazol-2-il)metiliden]-5-[(1-etilpiperidin-4-il)amino]-1,3-dihidro-2*H*-indol-2-ona

Tabla 8. Inhibidores de c-KIT

[00225] Los Compuestos de la Tabla 8 se pueden preparar como sales, solvatos, hidratos y/o isómeros farmacéuticamente aceptables de estos. Todas las combinaciones de sales, solvatos, hidratos e isómeros de los Compuestos de la Tabla 8 se pueden usar para practicar la invención.

Entrada	Nombre
1	*N*-[5-cloro-2-(metiloxi)fenil]-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
2	*N*-fenilo-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
3	*N*-(2-metilfenil)-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
4	*N*-(2-clorofenil)-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
5	*N*-[4-cloro-3-(trifluorometil)fenil]-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida

Entrada	Nombre
6	2-[({[3-(1*H*-tetrazol-1-il)fenil]oxi}acetil)amino]-4,5,6,7-tetrahidro-1-benzotiofeno-3-carboxilato de etilo
7	*N*-(3-cloro-2-metilfenil)-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
8	*N*-(3-fluorofenil)-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
9	*N*-[4-cloro-3-(trifluorometil)fenil]-2-{[3-(2*H*-tetrazol-5-il)fenil]oxi}acetamida
10	*N*-(4-cloro-2-fluorofenil)-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
11	*N*-(4-bromo-3-metilfenil)-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
12	*N*-(4-morfolin-4-ilfenil)-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
13	*N*-[4-fluoro-3-(trifluorometil)fenil]-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
14	*N*-[4-bromo-3-(trifluorometil)fenil]-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
15	*N*-[4-cloro-3-(trifluorometil)fenil]-2-{[4-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
16	*N*-[4-cloro-3-(trifluorometil)fenil]-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}propanamida
17	*N*-[4-cloro-3-(trifluorometil)fenil]-2-{[3-(5-metil-1*H*-tetrazol-1-il)fenil]oxi}acetamida
18	*N*-[4-cloro-3-(trifluorometil)fenil]-2-{[2-metil-5-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
19	*N*-(4-clorofenil)-*N*-metil-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
20	*N*-[4-cloro-2-(trifluorometil)fenil]-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida

Entrada	Nombre
21	*N*-[4-cloro-3-(trifluorometil)fenil]-2-{[3-(2,5-dioxopirrolidin-1-il)fenil]oxi}acetamida
22	(2E)-*N*-[4-cloro-3-(trifluorometil)fenil]-3-[3-(1*H*-tetrazol-1-il)fenil]prop-2-enamida
23	*N*-[4-fluoro-3-(trifluorometil)fenil]-2-{[4-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
24	*N*-[4-cloro-3-(trifluorometil)fenil]-2-{[3-(2-metil-2*H*-tetrazol-5-il)fenil]oxi}acetamida
25	*N*-[4-cloro-3-(trifluorometil)fenil]-2-{[2,4-dicloro-5-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
26	*N*-[4-cloro-3-(trifluorometil)fenil]-2-{[3-(1*H*-tetrazol-1-il)fenil]tio}acetamida
27	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*~2~-[3-(1*H*-tetrazol-1-il)fenil]glicinamida
28	*N*-[4-cloro-3-(trifluorometil)fenil]-2-{[2-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
29	1-{3-[(2-{[4-cloro-3-(trifluorometil)fenil]amino}-2-oxoetil)oxi]fenil}-1*H*-1,2,3-triazol-4-carboxilato de metilo
30	{4-[({[3-(1*H*-tetrazol-1-il)fenil]oxi}acetil)amino]fenil}carbamato de 1,1-dimetiletilo
31	{4-[({[4-(1*H*-tetrazol-1-il)fenil]oxi}acetil)amino]fenil}carbamato de 1,1-dimetiletilo
32	*N*-{4-[(1-etilpiperidin-4-il)amino]fenil}-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
33	*N*-{4-[(1-etilpiperidin-3-il)amino]fenil}-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida

Entrada	Nombre
34	*N*-(4-aminofenil)-2-{[4-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
35	*N*-{4-[(1-etilpiperidin-4-il)amino]fenil}-2-{[4-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
36	*N*-{4-[(1-etilpiperidin-3-il)amino]fenil}-2-{[4-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
37	*N*-[4-cloro-3-(trifluorometil)fenil]-2-[(3-piridin-4-ilfenil)oxi]acetamida
38	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*~2~-metil-*N*~2~-[3-(1*H*-tetrazol-1-il)fenil]glicinamida
39	*N*-1,3-benzotiazol-2-il-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
40	*N*-quinolin-8-il-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
41	*N*-(2,3-dihidro-1,4-benzodioxin-6-il)-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
42	*N*-isoquinolin-5-il-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
43	*N*-{3-[(fenilmetil)oxi]fenil}-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
44	*N*-[5-metil-2-(metiloxi)fenil]-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
45	*N*-[2,5-bis(metiloxi)fenil]-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
46	*N*-(6-fluoro-1,3-benzotiazol-2-il)-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
47	3-[({[3-(1*H*-tetrazol-1-il)fenil]oxi}acetil)amino]benzoato de metilo
48	5-cloro-2-[({[3-(1*H*-tetrazol-1-il)fenil]oxi}acetil)amino]benzamida

Entrada	Nombre
49	*N*-[5-cloro-2,4-bis(metiloxi)fenil]-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
50	*N*-[2-(feniloxi)fenil]-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
51	*N*-[3-(aminosulfonil)fenil]-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
52	*N*-[2-(metiloxi)-5-(trifluorometil)fenil]-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
53	*N*-(4-{[(4-metilfenil)sulfonil]amino}fenil)-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
54	*N*-(5-fenilo-1*H*-pirazol-3-il)-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
55	*N*-1,3-benzotiazol-2-il-2-{[4-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
56	*N*-quinolin-8-il-2-{[4-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
57	2-{3-[(2-{[4-cloro-3-(trifluorometil)fenil]amino}-2-oxoetil)oxi]fenil}-1*H*-pirrol-1-carboxilato de 1,1-dimetiletilo
58	*N*-[4-cloro-3-(trifluorometil)fenil]-2-{[3-(1*H*-pirrol-2-il)fenil]oxi}acetamida
59	*N*-[4-cloro-3-(trifluorometil)fenil]-2-[(3-pirimidin-5-ilfenil)oxi]acetamida
60	*N*-[4-cloro-3-(trifluorometil)fenil]-2-{[3-(1*H*-1,2,3-triazol-1-il)fenil]oxi}acetamida
61	4-cloro-*N*-(2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}etil)-3-(trifluorometil)anilina
62	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*-(2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}etil)formamida

Entrada	Nombre
63	*N*-[4-cloro-3-(trifluorometil)fenil]-2-[(3-piridin-3-ilfenil)oxi]acetamida
64	*N*-[4-cloro-3-(trifluorometil)fenil]-2-[(3-furan-3-ilfenil)oxi]acetamida
65	(2E)-*N*-[4-fluoro-3-(trifluorometil)fenil]-3-[3-(1*H*-tetrazol-1-il)fenil]prop-2-enamida
66	*N*-[4-fluoro-3-(trifluorometil)fenil]-3-[3-(1*H*-tetrazol-1-il)fenil]propanamida
67	*N*-[4-cloro-3-(trifluorometil)fenil]-2-{[6-(1*H*-tetrazol-1-il)pirimidin-4-il]oxi}acetamida
68	*N*-[4-cloro-3-(trifluorometil)fenil]-2-{[3-(3,5-dimetilisoxazol-4-il)fenil]oxi}acetamida
69	*N*-[4-cloro-3-(trifluorometil)fenil]-2-[(3-quinolin-7-ilfenil)oxi]acetamida
70	*N*-[4-cloro-3-(trifluorometil)fenil]-2-[(3-furan-2-ilfenil)oxi]acetamida
71	*N*-[4-cloro-3-(trifluorometil)fenil]-2-[3-(1*H*-tetrazol-1-il)fenil]hidrazinocarboxamida
72	*N*-[4-cloro-3-(trifluorometil)fenil]-2-[(3-dibenzo[b,d]furan-4-ilfenil)oxi]acetamida
73	*N*-[4-cloro-3-(trifluorometil)fenil]-2-[(4-pirimidin-5-ilfenil)oxi]acetamida
74	*N*-metil-*N*-[4-(metiloxi)fenil]-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
75	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-{[3-(1*H*-tetrazol-1-il)fenil]metil}urea
76	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*-metil-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
77	*N*-[4-fluoro-3-(trifluorometil)fenil]-*N*~2~-[3-(1*H*-tetrazol-1-il)fenil]glicinamida

Entrada	Nombre
78	*N*-[4-fluoro-3-(trifluorometil)fenil]-2-{[3-(piridin-2-ilamino)fenil]oxi}acetamida
79	*N*-[2-fluoro-5-(trifluorometil)fenil]-2-[3-(1*H*-tetrazol-1-il)fenil]hidrazinocarboxamida
80	*N*-[4-cloro-3-(trifluorometil)fenil]-2-[(4-piridin-3-ilfenil)oxi]acetamida
81	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-[(3-pirimidin-5-ilfenil)metil]urea
82	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-[(4-pirimidin-5-ilfenil)metil]urea
83	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-[(4-piridin-3-ilfenil)metil]urea
84	[4-cloro-3-(trifluorometil)fenil]carbamato de [3-(1*H*-tetrazol-1-il)fenil]metilo
85	*N*-[4-fluoro-3-(trifluorometil)fenil]-2-[(4-pirimidin-5-ilfenil)oxi]acetamida
86	*N*~2~-[4-cloro-3-(trifluorometil)fenil]-*N*-[3-(1*H*-tetrazol-1-il)fenil]glicinamida
87	2-{[4-cloro-3-(trifluorometil)fenil]oxi}-*N*-[3-(1*H*-tetrazol-1-il)fenil]acetamida
88	*N*-[4-cloro-3-(trifluorometil)fenil]-2-{[3-metil-4-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
89	*N*-[4-cloro-3-(trifluorometil)fenil]-2-{[4-(1*H*-1,2,3-triazol-1-il)fenil]oxi}acetamida
90	*N*-[4-cloro-3-(trifluorometil)fenil]-2-{[3-fluoro-4-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
91	*N*-[4-cloro-3-(trifluorometil)fenil]-2-{[2-fluoro-4-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
92	*N*-({[4-cloro-3-(trifluorometil)fenil]amino}carbonil)-3-(1*H*-tetrazol-1-il)bencensulfonamida

Entrada	Nombre
93	*N*-({[4-cloro-3-(trifluorometil)fenil]amino}carbonil)-*N*-metil-3-(1*H*-tetrazol-1-il)bencensulfonamida
94	*N*-[4-fluoro-3-(trifluorometil)fenil]-2-[(4-piridin-3-ilfenil)oxi]acetamida
95	2-({4-[2,4-bis(metiloxi)pirimidin-5-il]fenil}oxi)-*N*-[4-fluoro-3-(trifluorometil)fenil]acetamida
96	2-({4-[2,4-bis(metiloxi)pirimidin-5-il]fenil}oxi)-*N*-[4-cloro-3-(trifluorometil)fenil]acetamida
97	*N*-[4-cloro-3-(trifluorometil)fenil]-2-[(4-piridin-4-ilfenil)oxi]acetamida
98	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*~2~-[3-(metiloxi)-4-(1*H*-tetrazol-1-il)fenil]glicinamida
99	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*~2~-[4-(metiloxi)-3-(1*H*-tetrazol-1-il)fenil]glicinamida
100	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*~2~-[4-(1*H*-tetrazol-1-il)fenil]glicinamida
101	*N*-[4-cloro-3-(trifluorometil)fenil]-2-(2,3,5,6-tetrafluoro-4-pirimidin-5-ilfenil)hidrazinocarboxamida
102	*N*-[4-cloro-3-(trifluorometil)fenil]-*N'*-{[4-(1*H*-tetrazol-1-il)fenil]metil}urea
103	*N*-[4-cloro-3-(trifluorometil)fenil]-2-(4-pirimidin-5-ilfenil)hidrazinocarboxamida
104	*N*-[4-cloro-3-(trifluorometil)fenil]-*N'*-[(3-piridin-3-ilfenil)metil]urea

Entrada	Nombre
105	*N*-[4-cloro-3-(trifluorometil)fenil]-2-metil-2-{[3-(1*H*-tetrazol-1-il)fenil]oxi}propanamida
106	*N*-[4-cloro-3-(trifluorometil)fenil]-2-{[4-(1*H*-tetrazol-1-il)fenil]oxi}propanamida
107	*N*-({4-[2,4-bis(metiloxi)pirimidin-5-il]fenil}metil)-*N*'-[4-cloro-3-(trifluorometil)fenil]urea
108	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-({3-[2-(metiloxi)pirimidin-5-il]fenil}metil)urea
109	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-({3-[6-(metiloxi)piridin-3-il]fenil}metil)urea
110	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-({4-[2-(metiloxi)pirimidin-5-il]fenil}metil)urea
111	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-({4-[6-(metiloxi)piridin-3-il]fenil}metil)urea
112	2-{4-[(2-{[4-cloro-3-(trifluorometil)fenil]amino}-2-oxoetil)oxi]fenil}-1*H*-indole-1-carboxilato de 1,1-dimetiletilo
113	*N*-({[4-cloro-3-(trifluorometil)fenil]amino}carbonil)-4-(1*H*-tetrazol-1-il)bencensulfonamida
114	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*~2~-[3-(2*H*-tetrazol-5-il)fenil]glicinamida
115	*N*-[4-cloro-3-(trifluorometil)fenil]-2-{[2,6-difluoro-4-(1*H*-tetrazol-1-il)fenil]oxi}acetamida
116	[4-cloro-3-(trifluorometil)fenil]carbamato de (3-piridin-3-ilfenil)metilo
117	[4-cloro-3-(trifluorometil)fenil]carbamato de (3-pirimidin-5-ilfenil)metilo

Entrada	Nombre
118	[4-cloro-3-(trifluorometil)fenil]carbamato de (3-piridin-4-ilfenil)metil
119	*N*-[4-cloro-3-(trifluorometil)fenil]-2-[4-(1*H*-tetrazol-1-il)fenil]hidrazinocarboxamida
120	*N*-[4-cloro-3-(trifluorometil)fenil]-2-(4-piridin-3-ilfenil)hidrazinocarboxamida
121	[4-cloro-3-(trifluorometil)fenil]carbamato de (4-piridin-3-ilfenil)metilo
122	([4-cloro-3-(trifluorometil)fenil]carbamato de 4-piridin-4-ilfenil)metilo
123	[4-cloro-3-(trifluorometil)fenil]carbamato de (4-pirimidin-5-ilfenil)metilo
124	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-[(4-piridin-4-ilfenil)metil]urea
125	*N*-[4-cloro-3-(trifluorometil)fenil]-2-(3-piridin-3-ilfenil)hidrazinocarboxamida
126	*N*-[4-cloro-3-(trifluorometil)fenil]-2-(3-pirimidin-5-ilfenil)hidrazinocarboxamida
127	*N*-[5-cloro-2,4-bis(metiloxi)fenil]-*N*'-[(4-pirimidin-5-ilfenil)metil]urea
128	*N*-[5-cloro-2,4-bis(metiloxi)fenil]-*N*'-[(4-piridin-3-ilfenil)metil]urea
129	[5-cloro-2,4-bis(metiloxi)fenil]carbamato de (4-pirimidin-5-ilfenilo)
130	[5-cloro-2,4-bis(metiloxi)fenil]carbamato de (4-piridin-3-ilfenilo)
131	[4-cloro-3-(trifluorometil)fenil]carbamato de 1-(4-piridin-3-ilfenil)etilo
132	[4-cloro-3-(trifluorometil)fenil]carbamato de 1-(4-pirimidin-5-ilfenil)etilo

Entrada	Nombre
133	*N*-[5-cloro-2,4-bis(metiloxi)fenil]-*N*'-[(3-piridin-3-ilfenil)metil]urea
134	*N*-[5-cloro-2,4-bis(metiloxi)fenil]-*N*'-[(3-pirimidin-5-ilfenil)metil]urea
135	[5-cloro-2,4-bis(metiloxi)fenil]carbamato de (3-piridin-3-ilfenilo)
136	[5-cloro-2,4-bis(metiloxi)fenil]carbamato de (3-pirimidin-5-ilfenilo)
137	*N*-[4-cloro-3-(trifluorometil)fenil]-2-metil-2-(3-pirimidin-5-ilfenil)hidrazinocarboxamida
138	*N*-[4-fluoro-3-(trifluorometil)fenil]-*N*'-[(4-piridin-3-ilfenil)metil]urea
139	*N*-{[3-(6-aminopiridin-3-il)fenil]metil}-*N*'-[4-cloro-3-(trifluorometil)fenil]urea
140	*N*-{[4-(6-aminopiridin-3-il)fenil]metil}-*N*'-[4-cloro-3-(trifluorometil)fenil]urea
141	*N*-{[3-(2-aminopirimidin-5-il)fenil]metil}-*N*'-[4-cloro-3-(trifluorometil)fenil]urea
142	*N*-{[4-(2-aminopirimidin-5-il)fenil]metil}-*N*'-[4-cloro-3-(trifluorometil)fenil]urea
143	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-[1-(4-piridin-3-ilfenil)etil]urea
144	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-[1-(4-pirimidin-5-ilfenil)etil]urea
145	*N*-[4-cloro-3-(trifluorometil)fenil]-2-{[4-(1*H*-indol-2-il)fenil]oxi}acetamida
146	*N*-[4-cloro-3-(trifluorometil)fenil]-2-(isoquinolin-7-iloxi)acetamida
147	*N*-[4-cloro-3-(trifluorometil)fenil]-2-(4-piridin-4-ilfenil)hidrazinocarboxamida

Entrada	Nombre
148	*N*-[4-cloro-3-(trifluorometil)fenil]-2-(3-piridin-4-ilfenil)hidrazinocarboxamida
149	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-[(3-piridin-4-ilfenil)metil]urea
150	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-[(3-quinoxalin-6-ilfenil)metil]urea
151	3-amino-6-(3-{[({[4-cloro-3-(trifluorometil)fenil]amino}carbonil)amino]metil}fenil)pirazino-2-carboxilato de metilo
152	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-[(4-quinoxalin-6-ilfenil)metil]urea
153	*N*-{[3-(2-amino-5-metilpiridin-3-il)fenil]metil}-*N*'-[4-cloro-3-(trifluorometil)fenil]urea
154	3-amino-6-(4-{[({[4-cloro-3-(trifluorometil)fenil]amino}carbonil)amino]metil}fenil)pirazino-2-carboxilato de metilo
155	[3-cloro-4-(metiloxi)fenil]carbamato de [3-(1*H*-tetrazol-1-il)fenil]metilo
156	*N*-[3-cloro-4-(metiloxi)fenil]-*N*'-{[3-(1*H*-tetrazol-1-il)fenil]metil}urea
157	*N*-[4-cloro-3-(trifluorometil)fenil]-2-{[4-(5-hidroxi-1*H*-tetrazol-1-il)fenil]oxi}acetamida
158	*N*-{[3-(2-amino-5-cloropiridin-3-il)fenil]metil}-*N*'-[4-cloro-3-(trifluorometil)fenil]urea
159	*N*-{[4-(2-amino-5-cloropiridin-3-il)fenil]metil}-*N*'-[4-cloro-3-(trifluorometil)fenil]urea
160	*N*-{[3-(6-cloropiridin-3-il)fenil]metil}-*N*'-[4-cloro-3-(trifluorometil)fenil]urea

Entrada	Nombre
161	*N*-{[4-(6-cloropiridin-3-il)fenil]metil}-*N*'-[4-cloro-3-(trifluorometil)fenil]urea
162	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-{[4-(pirimidin-2-iloxi)fenil]metil}urea
163	*N*-({[4-cloro-3-(trifluorometil)fenil]amino}carbonil)-3-(1*H*-tetrazol-1-il)benzamida
164	3-amino-6-(3-{[({[4-cloro-3-(trifluorometil)fenil]amino}carbonil)amino]metil}fenil)-*N*-[2-(dimetilamino)etil]pirazino-2-carboxamida
165	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-{[3-(6-fluoropiridin-3-il)fenil]metil}urea
166	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-({3-[2-(metiloxi)piridin-3-il]fenil}metil)urea
167	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-{[4-(6-fluoropiridin-3-il)fenil]metil}urea
168	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-({4-[2-(metiloxi)piridin-3-il]fenil}metil)urea
169	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-{[4-(6-metilpiridin-3-il)fenil]metil}urea
170	*N*-{[4-(2-amino-5-fluoropiridin-3-il)fenil]metil}-*N*'-[4-cloro-3-(trifluorometil)fenil]urea
171	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-{[3-(6-metilpiridin-3-il)fenil]metil}urea
172	*N*-{[4-(2-aminopiridin-3-il)fenil]metil}-*N*'-[4-cloro-3-(trifluorometil)fenil]urea
173	*N*-{[3-(2-aminopiridin-3-il)fenil]metil}-*N*'-[4-cloro-3-(trifluorometil)fenil]urea

Entrada	Nombre
174	[4-cloro-3-(trifluorometil)fenil]carbamato de [3-(6-metilpiridin-3-il)fenil]metilo
175	[4-cloro-3-(trifluorometil)fenil]carbamato de [3-(2-amino-5-fluoropiridin-3-il)fenil]metilo
176	[4-cloro-3-(trifluorometil)fenil]carbamato de [3-(2-aminopiridin-3-il)fenil]metilo
177	[4-cloro-3-(trifluorometil)fenil]carbamato de (3-pirazin-2-ilfenil)metilo
178	*N*-[4-cloro-3-(trifluorometil)fenil]-*N'*-({3-[6-(hidroximetil)piridin-3-il]fenil}metil)urea
179	*N*-{[3-(6-acetilpiridin-3-il)fenil]metil}-*N'*-[4-cloro-3-(trifluorometil)fenil]urea
180	*N*-[4-cloro-3-(trifluorometil)fenil]-*N'*-{[3-(6-cianopiridin-3-il)fenil]metil}urea
181	(3S)-3-({[3-amino-6-(3-{[({[4-cloro-3-(trifluorometil)fenil]amino}carbonil)amino]metil}fenil)pirazin-2-il]carbonil}amino)piperidino-1-carboxilato de 1,1-dimetiletilo
182	3-amino-6-(3-{[({[4-cloro-3-(trifluorometil)fenil]amino}carbonil)amino]metil}fenil)-*N*-[(3S)-piperidin-3-il]pirazino-2-carboxamida
183	(3S)-3-({[3-amino-6-(4-{[({[4-cloro-3-(trifluorometil)fenil]amino}carbonil)amino]metil}fenil)pirazin-2-il]carbonil}amino)piperidino-1-carboxilato de 1,1-dimetiletilo
184	3-amino-6-(4-{[({[4-cloro-3-(trifluorometil)fenil]amino}carbonil)amino]metil}fenil)-*N*-[(3S)-piperidin-3-il]pirazino-2-carboxamida

Entrada	Nombre
185	[4-cloro-3-(trifluorometil)fenil]carbamato de [3-(7*H*-pirrolo[2,3-d]pirimidin-4-il)fenil]metilo
186	*N*-{[3-(2-amino-5-fluoropiridin-3-il)fenil]metil}-*N'*-[4-cloro-3-(trifluorometil)fenil]urea
187	[4-cloro-3-(trifluorometil)fenil]carbamato de [6-(1*H*-tetrazol-1-il)piridin-2-il]metilo
188	[4-cloro-3-(trifluorometil)fenil]carbamato de [3-(1*H*-bencimidazol-2-il)fenil]metilo
189	[4-cloro-3-(trifluorometil)fenil]carbamato de [3-(6-amino-2-metilpiridin-3-il)fenil]metilo
190	*N*-[4-cloro-3-(trifluorometil)fenil]-*N'*-({3-[5-(metiltio)piridin-3-il]fenil}metil)urea
191	[4-(6-metilpiridin-3-il)fenil]metil [4-cloro-3-(trifluorometil)fenil]carbamato de metilo
192	[4-cloro-3-(trifluorometil)fenil]carbamato de [4-(2-amino-5-fluoropiridin-3-il)fenil]metilo
193	[4-cloro-3-(trifluorometil)fenil]carbamato de [4-(2-aminopiridin-3-il)fenil]metilo
194	[4-cloro-3-(trifluorometil)fenil]carbamato de (4-pirazin-2-ilfenil)metilo
195	[4-cloro-3-(trifluorometil)fenil]carbamato de [4-(7*H*-pirrolo[2,3-d]pirimidin-4-il)fenil]metilo
196	[4-cloro-3-(trifluorometil)fenil]carbamato de [4-(6-amino-2-metilpiridin-3-il)fenil]metilo
197	1,3-benzotiazol-2-ilcarbamato de [3-(1*H*-tetrazol-1-il)fenil]metilo
198	(5-bromopiridin-2-il)carbamato de [3-(1*H*-tetrazol-1-il)fenilo]

Entrada	Nombre
199	(3,5-dimetilfenil)carbamato de (3-piridin-3-ilfenil)metilo
200	[5-cloro-2-(metiloxi)fenil]carbamato de (3-piridin-3-ilfenilo)
201	[4-cloro-3-(trifluorometil)fenil]carbamato de [4-(1*H*-tetrazol-1-il)fenil]metilo
202	[5-cloro-2-(metiloxi)fenil]carbamato de (3-pirimidin-5-ilfenilo)
203	(3,4-dimetilfenil)carbamato de (4-pirimidin-5-ilfenil)metilo
204	(3,4-dimetilfenil)carbamato de (3-piridin-3-ilfenil)metilo
205	3-({[3-amino-6-(3-{[({[4-cloro-3-(trifluorometil)fenil]amino}carbonil)amino]metil}fenil)pirazin-2-il]carbonil}amino)piperidino-1-carboxilato de 1,1-dimetiletilo
206	3-({[3-amino-6-(4-{[({[4-cloro-3-(trifluorometil)fenil]amino}carbonil)amino]metil}fenil)pirazin-2-il]carbonil}amino)piperidino-1-carboxilato de 1,1-dimetiletilo
207	3-amino-6-(3-{[({[4-cloro-3-(trifluorometil)fenil]amino}carbonil)amino]metil}fenil)-*N*-piperidin-3-ilpirazino-2-carboxamida
208	3-amino-6-(4-{[({[4-cloro-3-(trifluorometil)fenil]amino}carbonil)amino]metil}fenil)-*N*-piperidin-3-ilpirazino-2-carboxamida
209	4-{[3-amino-6-(3-{[({[4-cloro-3-(trifluorometil)fenil]amino}carbonil)amino]metil}fenil)pirazin-2-il]carbonil}piperazino-1-carboxilato de 1,1-dimetiletilo

Entrada	Nombre
210	4-{[3-amino-6-(4-{[({[4-cloro-3-(trifluorometil)fenil]amino}carbonil)amino]metil}fenil)pirazin-2-il]carbonil}piperazino-1-carboxilato de 1,1-dimetiletilo
211	*N*-({3-[5-amino-6-(piperazin-1-ilcarbonil)pirazin-2-il]fenil}metil)-*N*'-[4-cloro-3-(trifluorometil)fenil]urea
212	*N*-({4-[5-amino-6-(piperazin-1-ilcarbonil)pirazin-2-il]fenil}metil)-*N*'-[4-cloro-3-(trifluorometil)fenil]urea
213	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-{[3-(1*H*-pirazol-4-il)fenil]metil}urea
214	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-{[4-(1*H*-pirazol-4-il)fenil]metil}urea
215	[4-cloro-3-(trifluorometil)fenil]carbamato de [3-(2-piperazin-1-ilpirimidin-5-il)fenil]metilo
216	[4-cloro-3-(trifluorometil)fenil]carbamato de [4-(2-piperazin-1-ilpirimidin-5-il)fenil]metilo
217	*N*-{[3-(2-cloropiridin-3-il)fenil]metil}-*N*'-[4-cloro-3-(trifluorometil)fenil]urea
218	*N*-{[4-(2-cloropiridin-3-il)fenil]metil}-*N*'-[4-cloro-3-(trifluorometil)fenil]urea
219	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-{[3-(2-fluoropiridin-3-il)fenil]metil}urea
220	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-{[4-(2-fluoropiridin-3-il)fenil]metil}urea
221	[3-(trifluorometil)fenil]carbamato de [3-(1*H*-tetrazol-1-il)fenil]metilo
222	[6-(trifluorometil)piridin-2-il]carbamato de [3-(1*H*-tetrazol-1-il)fenilo]

Entrada	Nombre
223	[4-(trifluorometil)piridin-2-il]carbamato de [3-(1*H*-tetrazol-1-il)fenil]metilo
224	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-({3-[5-(metiltio)piridin-2-il]fenil}metil)urea
225	[4-cloro-3-(trifluorometil)fenil]carbamato de [3-(2,6-dimetilpiridin-3-il)fenil]metilo
226	[4-cloro-3-(trifluorometil)fenil]carbamato de {3-[5-(metiloxi)piridin-3-il]fenil}metilo
227	[4-cloro-3-(trifluorometil)fenil]carbamato de 2,3'-bipiridin-6-ilmetilo
228	[4-cloro-3-(trifluorometil)fenil]carbamato de (6-pirimidin-5-ilpiridin-2-il)metilo
229	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-[(3-isoquinolin-4-ilfenil)metil]urea
230	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-[(4-isoquinolin-4-ilfenil)metil]urea
231	[4-(trifluorometil)piridin-2-il]carbamato de [6-(1*H*-tetrazol-1-il)piridin-2-il]metilo
232	[4-cloro-3-(trifluorometil)fenil]carbamato de [3-(1*H*-pirazol-4-il)fenil]metilo
233	[4-cloro-3-(trifluorometil)fenil]carbamato de [4-(1*H*-pirazol-4-il)fenil]metilo

Tabla 9. Inhibidores de c-KIT y/o Flt-3

[00226] Los Compuestos de la Tabla 9 se pueden preparar como sales, solvatos, hidratos y/o isómeros farmacéuticamente aceptables de estos. Todas las combinaciones de sales, solvatos, hidratos e isómeros de los Compuestos de la Tabla 9 se pueden usar para practicar la invención.

Entrada	Nombre

Entrada	Nombre
1	4-((*E*)-2-{3-[6-(4-metilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}etenil)fenol
2	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-(4-{3-[5-(4-etilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)urea
3	*N*-(3-etilfenil)-*N*'-(4-{3-[5-(4-etilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)urea
4	*N*-(4-{3-[5-(4-etilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)-*N*'-[3-(trifluorometil)fenil]urea
5	*N*-(3-acetilfenil)-*N*'-(4-{3-[5-(4-metilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)urea
6	*N*-(3,4-diclorofenil)-*N*'-(4-{3-[5-(4-metilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)urea
7	*N*-(3-bromofenil)-*N*'-(4-{3-[6-(4-metilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)urea
8	*N*-[4-fluoro-3-(trifluorometil)fenil]-*N*'-(4-{3-[5-(4-metilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)urea
9	*N*-(4-{3-[5-(4-metilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)-*N*'-[4-(feniloxi)fenil]urea
10	*N*-(3-clorofenil)-*N*'-(4-{3-[5-(4-metilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)urea
11	*N*-[3,5-bis(metiloxi)fenil]-*N*'-(4-{3-[6-(4-metilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)urea
12	*N*-(4-{3-[5-(4-metilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)-*N*'-{4-[(trifluorometil)oxi]fenil}urea

Entrada	Nombre
13	*N*-(4-{3-[6-(4-metilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)-*N*'-[4-(trifluorometil)fenil]urea
14	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-(4-{3-[5-(4-metilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)urea
15	*N*-(4-{3-[5-(4-metilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)-*N*'-[3-(trifluorometil)fenil]urea
16	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-(4-{3-[4-(4-metilpiperazin-1-il)fenil]-1*H*-pirazol-5-il}fenil)urea
17	*N*-(3,4-dimetilfenil)-*N*'-(4-{5-[4-(4-metilpiperazin-1-il)fenil]-1*H*-pirazol-3-il}fenil)urea
18	*N*-(4-clorofenil)-*N*'-(4-{3-[5-(4-metilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)urea
19	*N*-(3,5-difluorofenil)-*N*'-(4-{3-[5-(4-metilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)urea
20	*N*-[3-(metiloxi)fenil]-*N*'-(4-{3-[5-(4-metilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)urea
21	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-(4-{3-[4-(4-etilpiperazin-1-il)fenil]-1*H*-pirazol-5-il}fenil)urea
22	*N*-(3-fluorofenil)-*N*'-(4-{3-[5-(4-metilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)urea
23	*N*-(4-fluorofenil)-*N*'-(4-{3-[5-(4-metilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)urea
24	*N*-(3-cianofenil)-*N*'-(4-{3-[6-(4-metilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)urea
25	*N*-(3,4-difluorofenil)-*N*'-(4-{3-[5-(4-metilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)urea

Entrada	Nombre
26	*N*-[3,4-bis(metiloxi)fenil]-*N*'-(4-{3-[5-(4-metilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)urea
27	*N*-[5-cloro-2-(metiloxi)fenil]-*N*'-(4-{5-[4-(4-metilpiperazin-1-il)fenil]-1*H*-pirazol-3-il}fenil)urea
28	*N*-(4-{5-[4-(4-metilpiperazin-1-il)fenil]-1*H*-pirazol-3-il}fenil)-*N*'-[4-(feniloxi)fenil]urea
29	*N*-(2,4-difluorofenil)-*N*'-(4-{3-[6-(4-etilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)urea
30	*N*-{4-[3-(1*H*-bencimidazol-2-il)-1*H*-pirazol-5-il]fenil}-*N*'-[4-cloro-3-(trifluorometil)fenil]urea
31	*N*-{4-[3-(1*H*-bencimidazol-2-il)-1*H*-pirazol-5-il]fenil}-*N*'-[2-fluoro-5-(trifluorometil)fenil]urea
32	*N*-(2,4-difluorofenil)-*N*'-(4-{3-[5-(4-metilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)urea
33	*N*-{4-[3-(1*H*-bencimidazol-2-il)-1*H*-pirazol-5-il]fenil}-*N*'-fenilurea
34	*N*-[3,5-bis(trifluorometil)fenil]-*N*'-(4-{3-[5-(4-metilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)urea
35	*N*-(2-fluorofenil)-*N*'-(4-{3-[5-(4-metilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)urea
36	4-((*E*)-2-{5-[(*E*)-2-feniletenil]-1*H*-pirazol-3-il}etenil)fenol
37	2-(metiloxi)-4-((*E*)-2-{5-[(*E*)-2-feniletenil]-1*H*-pirazol-3-il}etenil)fenol
38	*N*-(5-fluoro-2-metilfenil)-*N*'-(4-{3-[6-(4-metilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)urea
39	*N*-(4-{3-[5-(4-metilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)-*N*'-fenilurea

Entrada	Nombre
40	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-(4-{3-[3-(4-metilpiperazin-1-il)fenil]-1*H*-pirazol-5-il}fenil)urea
41	*N*-(2,4-difluorofenil)-*N*'-(4-{3-[4-(4-metilpiperazin-1-il)fenil]-1*H*-pirazol-5-il}fenil)urea
42	*N*-(2,3-dihidro-1,4-benzodioxin-6-il)-*N*'-(4-{5-[4-(4-metilpiperazin-1-il)fenil]-1*H*-pirazol-3-il}fenil)urea
43	*N*-[2,4-bis(metiloxi)fenil]-*N*'-(4-{5-[4-(4-metilpiperazin-1-il)fenil]-1*H*-pirazol-3-il}fenil)urea
44	4-((*E*)-2-{3-[(*E*)-2-(4-fluorofenil)etenil]-1*H*-pirazol-5-il}etenil)-2-(metiloxi)fenol
45	4-{(*E*)-2-[3-(1-benzofuran-2-il)-1*H*-pirazol-5-il]etenil}fenol
46	*N*-(4-{3-[4-(4-metilpiperazin-1-il)fenil]-1*H*-pirazol-5-il}fenil)-*N*'-(2-feniletil)etandiamida
47	4-{(*E*)-2-[3-(1*H*-bencimidazol-2-il)-1*H*-pirazol-5-il]etenil}fenol
48	4-((*E*)-2-{3-[(*E*)-2-(4-clorofenil)etenil]-1*H*-pirazol-5-il}etenil)-2-(metiloxi)fenol
49	4-{(*E*)-2-[3-(1-benzotien-2-il)-1*H*-pirazol-5-il]etenil}fenol
50	*N*-[4-cloro-3-(trifluorometil)fenil]-*N*'-[4-(3-fenilo-1*H*-pirazol-5-il)fenil]urea
51	4-((*E*)-2-{3-[4-(4-metilpiperazin-1-il)fenil]-1*H*-pirazol-5-il}etenil)fenol
52	{4-[3-(1*H*-bencimidazol-2-il)-1*H*-pirazol-5-il]fenil}carbamato de 1,1-dimetiletilo
53	*N*-(5-fluoro-2-metilfenil)-*N*'-(4-{5-[4-(4-metilpiperazin-1-il)fenil]-1*H*-pirazol-3-il}fenil)urea
54	4-[(*E*)-2-(3-fenilo-1*H*-pirazol-5-il)etenil]fenol
55	2-(metiloxi)-4-[(*E*)-2-(5-fenilo-1*H*-pirazol-3-il)etenil]fenol

Entrada	Nombre
56	4-[(*E*)-2-(5-naftalen-2-il-1*H*-pirazol-3-il)etenil]fenol
57	4-{(*E*)-2-[5-(2-fluorofenil)-1*H*-pirazol-3-il]etenil}fenol
58	4-((*E*)-2-{3-[3-(4-metilpiperazin-1-il)fenil]-1*H*-pirazol-5-il}etenil)fenol
59	4-((*E*)-2-{3-[(*E*)-2-(2,4-difluorofenil)etenil]-1*H*-pirazol-5-il}etenil)-2-(metiloxi)fenol
60	4-{(*E*)-2-[5-(4-fluorofenil)-1*H*-pirazol-3-il]etenil}fenol
61	4-{(*E*)-2-[3-(4-clorofenil)-1*H*-pirazol-5-il]etenil}fenol
62	4-[(*E*)-2-(5-piridin-2-il-1*H*-pirazol-3-il)etenil]fenol
63	4-{(*E*)-2-[3-(5-cloro-1-benzofuran-2-il)-1*H*-pirazol-5-il]etenil}fenol
64	*N*-(1,1-dimetiletil)-*N*'-(4-{3-[5-(4-etilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-5-il}fenil)urea
65	4-[(*E*)-2-(3-piridin-4-il-1*H*-pirazol-5-il)etenil]fenol
66	4-{(*E*)-2-[3-(3-clorofenil)-1*H*-pirazol-5-il]etenil}fenol
67	4-((*E*)-2-{5-[2-(metiloxi)fenil]-1*H*-pirazol-3-il}etenil)fenol
68	4-{(*E*)-2-[3-(2-clorofenil)-1*H*-pirazol-5-il]etenil}fenol
69	4-[(*E*)-2-(3-piridin-3-il-1*H*-pirazol-5-il)etenil]fenol
70	4-((*E*)-2-{5-[3-(metiloxi)fenil]-1*H*-pirazol-3-il}etenil)fenol
71	(4-{3-[(*E*)-2-feniletenil]-1*H*-pirazol-5-il}fenil)carbamato de 1,1-dimetiletil
72	4-{(*E*)-2-[3-(3,4-diclorofenil)-1*H*-pirazol-5-il]etenil}fenol

Entrada	Nombre
73	2-{5-[(*E*)-2-feniletenil]-1*H*-pirazol-3-il}-1-benzofuran-6-ol
74	4-{(*E*)-2-[5-(3-fluorofenil)-1*H*-pirazol-3-il]etenil}fenol
75	2-(5-fenilo-1*H*-pirazol-3-il)-1*H*-bencimidazol
76	*N*-fenilo-*N'*-[4-(3-fenilo-1*H*-pirazol-5-il)fenil]urea
77	4-[3-(1*H*-bencimidazol-2-il)-1*H*-pirazol-5-il]anilina
78	4-[(*E*)-2-(5-bifenil-3-il-1*H*-pirazol-3-il)etenil]fenol
79	4-((*E*)-2-{5-[5-(4-metilpiperazin-1-il)-1*H*-bencimidazol-2-il]-1*H*-pirazol-3-il}etenil)fenol

Administración general

[00227] En un aspecto, la invención proporciona composiciones farmacéuticas que comprende un inhibidor de PI3K de acuerdo con la invención y un portador, excipiente o diluyente farmacéuticamente aceptable. En otras formas de realización específicas, la administración es 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 por cualquiera de los modos aceptados de administración o agentes para cumplir utilidades similares. En consecuencia, la administración puede ser, por ejemplo, oral, nasal, parenteral (intravenosa, intramuscular, o subcutánea), tópica, transdérmica, intravaginal, intravesical, intracisternal, o rectal, en formas de dosificación en forma sólida, semisólida, polvo liofilizado o líquido, tal como por ejemplo, comprimidos, supositorios, pastillas, cápsulas de gelatina

elástica blanda y dura, polvos, soluciones, suspensiones, o aerosoles, o similares, con preferencia en formas de dosificación unitaria adecuadas para la administración simple de dosis exactas.

[00228] Las composiciones incluirán un portador o excipiente farmacéutico convencional y un compuesto de la invención como un agente activo, además puede incluir portadores y adyuvantes.

[00229] Los adyuvantes incluyen agentes conservantes, humectantes, de suspensión, edulcorantes, saborizantes, perfumantes, emulsionantes y de dispensado. La prevención de la acción de los microorganismos se puede asegurar con varios agentes antibacterianos y antifúngicos, por ejemplo, parabenos, clorobutanol, fenol, ácido sórbico y similares. También puede ser conveniente incluir agentes isotónicos, por ejemplo, azúcares, cloruro de sodio y similares. La absorción prolongada de la forma farmacéutica inyectable se puede producir por el uso de agentes que retardan la absorción, por ejemplo, monoestearato de aluminio y gelatina.

[00230] Si se desea, una composición farmacéutica de la invención también puede contener cantidades menores de sustancias auxiliares tales como agentes humectantes o emulsionantes, agentes tamponantes de pH, antioxidantes, y similares, tales como, por ejemplo, ácido cítrico, monolaurato de sorbitano, oleato de trietanolamina, hidroxitolueno butilado, etc.

[00231] La elección de la formulación depende de varios factores tales como el modo de administración del fármaco (por ejemplo, para administración oral,

formulaciones en forma de comprimidos, pastillas o cápsulas) y biodisponibilidad de la sustancia fármaco. Recientemente, se han desarrollado formulaciones farmacéuticas especialmente para fármacos que muestran baja biodisponibilidad sobre la base del principio de que la biodisponibilidad se puede aumentar por incremento del área de superficie, es decir, disminuyendo el tamaño de partícula. Por ejemplo, la patente estadounidense No. 4.107.288 describe una formulación farmacéutica que tiene partículas en el rango de tamaño de 10 a 1,000 nm en el que el material activo está soportado en una matriz de macromoléculas entrecruzadas. La patente estadounidense No. 5.145.684 describe la producción de una formulación farmacéutica en que la sustancia fármaco se pulveriza a nanopartículas (tamaño de partículas promedio de 400 nm) en presencia de un modificador de matriz y luego se dispersa en un medio líquido para dar una formulación farmacéutica que exhibe biodisponibilidad muy marcada.

[00232] Las composiciones adecuadas para la inyección parenteral pueden comprender soluciones, dispersiones, suspensiones o emulsiones acuosas o no acuosas estériles y fisiológicamente aceptables y polvos estériles para la reconstitución en soluciones o dispersiones inyectables estériles. Los ejemplos de portadores, diluyentes, solventes o vehículos acuosos o no acuosos adecuados incluyen agua, etanol, polioles (propilenglicol, polietilenglicol, glicerol, y similares), sus mezclas adecuadas, aceites vegetales (tales como, aceite de oliva) y ésteres orgánicos inyectables tales como oleato de etilo. La fluidez apropiada se puede mantener, por ejemplo, por

el uso de una cubierta tal como lecitina, por el mantenimiento del tamaño de partícula requerido en el caso de las dispersiones y por el uso de tensioactivos.

[00233] Una vía de administración específica es la oral, mediante un régimen de dosis diario conveniente que se puede ajustar de acuerdo con el grado de gravedad del estado de enfermedad tratado.

[00234] Las formas de dosis sólidas para la administración oral incluyen cápsulas, comprimidos, pastillas, polvos y gránulos. En dichas formas de dosis sólidas, el compuesto activo se mezcla con al menos un excipiente (o portador) inerte, tal como citrato de sodio o fosfato dicálcico o (a) rellenos o expansores tales como almidones, lactosa, sacarosa, glucosa, manitol, y ácido silícico, (b) aglutinantes tales como, por ejemplo, derivados de celulosa, almidón, alginatos, gelatina, polivinilpirrolidinona, sacarosa, y goma de acacia, (c) humectantes como por ejemplo, glicerol, (d) agentes desintegrantes como por ejemplo, agar-agar, carbonato de calcio, almidón de papa o mandioca, ácido algínico, croscarmelosa sódica, silicatos complejos y carbonato de sodio, (e) agentes retardadores de solución como por ejemplo, parafina, (f) aceleradores de absorción como por ejemplo, compuestos de amonio cuaternario, (g) agentes humectantes como por ejemplo, alcohol cetílico y monoestearato de glicerol, estearato de magnesio y similares (h) adsorbentes como por ejemplo, caolín y bentonita, e i) lubricantes como por ejemplo, talco, estearato de calcio, estearato de magnesio, polietilenglicoles sólidos, laurilsulfato de sodio o sus mezclas. En el caso de cápsulas,

comprimidos y pastillas, la forma de dosis también puede comprender agentes amortiguadores.

[00235] Las formas de dosis sólidas descriptas anteriormente se pueden preparar con cubiertas y cáscaras tales como cubiertas entéricas y otras cubiertas bien conocidas en la técnica. Estas pueden comprender agentes opacificantes y también pueden ser de una composición tal que solo liberen el compuesto o compuestos activos en una parte determinada del aparato intestinal en una forma retardada. Los ejemplos de composiciones incluidas que se pueden usar son sustancias y ceras poliméricas. Los compuestos activos también pueden estar en forma microencapsulada, según corresponda con uno o más excipientes mencionados anteriormente.

[00236] Las formas de dosis líquidas para administración oral y parenteral incluyen, emulsiones, soluciones, suspensiones, jarabes y elixires farmacéuticamente aceptables. Dichas formas de dosis se preparan, por ejemplo, por disolución, dispersión, etc., un compuesto(s) de la invención, o una de sus sales farmacéuticamente aceptables y adyuvantes farmacéuticos opcionales en un portador tal como, por ejemplo, agua, solución salina, dextrosa acuosa, glicerol, etanol y similares; agentes solubilizantes y emulsionantes 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, aceites de semilla de algodón, aceite de maní, aceite de germen de maíz, aceite de oliva, aceite de ricino y aceite de sésamo), glicerol,

alcohol tetrahidrofurfurílico, polietilenglicoles y ésteres de ácido graso de sorbitanos; o mezcla de estas sustancias, y similares, para formar de este modo una solución o suspensión.

[00237] Las suspensiones, además de los compuestos activos, pueden contener agentes de suspensión, como por ejemplo, alcoholes isotearílicos etoxilados, polioxietilen sorbitol y ésteres de sorbitano, celulosa microcristalina, metahidróxido de aluminio, bentonita, agar-agar y tragacanto, o mezclas de estas sustancias, y similares.

[00238] Las composiciones para administración rectal o vaginal son por ejemplo, supositorios que se pueden preparar por la mezcla de los compuestos de la presente invención con por ejemplo excipientes o portadores no irritantes adecuados tales como manteca de cacao, polietilenglicol o una cera de supositorio que son sólidos a temperaturas ordinarias pero líquidos a temperatura corporal y en consecuencia se funden en una cavidad adecuada y liberan allí el componente activo-

[00239] Las formas de dosis para administración tópica de un compuesto de esta invención incluye ungüentos, polvos, spray e inhalantes. El componente activo se mezcla en condiciones estériles con un portador farmacéuticamente aceptable y/o cualquiera de los conservantes, amortiguadores o propelentes, según sea necesario. Las formulaciones oftálmicas, ungüentos, polvos y soluciones oculares también están contempladas en el alcance de esta invención.

[00240] Los gases comprimidos se pueden usar para dispersar un compuesto de esta invención en forma de

aerosol. Los gases inertes adecuados para este fin son nitrógeno, dióxido de carbono, etc.

[00241] Generalmente, de acuerdo con el modo de administración deseado, las composiciones farmacéuticamente aceptables contendrán aproximadamente 1% a aproximadamente 99% en peso de un compuesto(s) de la invención, o una de sus sales farmacéuticamente aceptables, y 99% a 1% en peso de un excipiente farmacéutico adecuado. En un ejemplo, la composición estará entre aproximadamente 5% y aproximadamente 75% en peso de un compuesto(s) de la invención, o a una de sus sales farmacéuticamente aceptables, con el resto de excipientes farmacéuticos adecuados.

[00242] Los métodos reales de preparación de dichas formas de dosis son conocidas, o serán evidentes para los expertos en esta técnica; por ejemplo, ver Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). La composición que se administra, en cualquier caso, contendrá una cantidad terapéuticamente efectiva de un compuesto de la invención, o a una de sus sales o solvatos farmacéuticamente aceptables, para el tratamiento de un estado de enfermedad de acuerdo con las enseñanzas de esta invención.

[00243] Los compuestos de la invención, o sus sales farmacéuticamente aceptables o solvatos, se administran en una cantidad terapéuticamente efectiva que variará de acuerdo con una variedad de factores que incluye la actividad del compuesto específico empleado, la estabilidad metabólica y la duración de acción del compuesto, la edad, peso corporal, salud general, sexo, dieta, modo y tiempo de

administración, tasa de excreción, combinación farmacológica, la gravedad de los estados de enfermedad particulares, y la terapia a la se somete el huésped. Los compuestos de la presente invención se pueden administrar a un paciente a niveles de dosis en el rango de aproximadamente 0,1 a aproximadamente 1,000 mg por día. Para un adulto humano normal que tiene un peso corporal de aproximadamente 70 kilogramos, un ejemplo es una dosis en el rango de aproximadamente 0,01 a aproximadamente 100 mg por kilo de peso corporal por día. La dosis específica usada, sin embargo, puede variar. Por ejemplo, la dosis puede depender de numerosos factores que incluyen las necesidades del paciente, la gravedad de la enfermedad tratada, y la actividad farmacológica del compuesto usado. La determinación de las dosis óptimas para un paciente particular es bien conocida para los expertos en la técnica.

[00244] Si se formula en forma de dosis fija, dichos productos de combinación emplean los compuestos de esta invención dentro del rango de dosis descripto anteriormente y otros agentes farmacéuticamente activos dentro de su rango de dosis aprobado. Los compuestos de la presente invención en forma alternativa se pueden usar secuencialmente con agentes farmacéuticamente aceptables conocidos cuando una formulación combinada es inapropiada.

[00245] Las formulaciones farmacéuticas representativas que contienen un compuesto de Fórmula I se describen a continuación en los Ejemplos de la composición farmacéutica.

UTILIDAD

[00246] Ciertos compuestos de Fórmula I se han analizado usando el ensayo descripto en el Ejemplo biológico 1 y se han determinado como inhibidores de PI3K. Como tal, los compuestos de Fórmula I son útiles para tratar enfermedades, en particular cáncer en el que la actividad de PI3K contribuye a la patología y/o sintomatología de la enfermedad. Por ejemplo, el cáncer en que la actividad de PI3K contribuye a su patología y/o sintomatología incluye cáncer de mamas, cáncer de colon, cáncer rectal, cáncer de endometrio, carcinoma gástrico, glioblastoma, carcinoma hepatocelular, cáncer pulmonar de células pequeñas, cáncer pulmonar de células no pequeñas, melanoma, cáncer ovárico, cáncer pancreático, carcinoma prostático, leucemia mielógena aguda (AML), leucemia mielógena crónica (CML), y carcinoma tiroideo, y similares.

[00247] Los ensayos *in vitro* adecuados para medir la actividad de PI3K y su inhibición por los compuestos son conocidos en la técnica. Normalmente, el ensayo medirá el consumo de ART inducido por PI3K. Para mayores detalles de un ensayo *in vitro* para medir la actividad de PI3K ver Ejemplos biológicos, Ejemplo 1 *infra*. La actividad celular se puede determinar usando los ensayos descriptos en los Ejemplos biológicos 2, 3, y 4 *infra*. Los modelos *in vivo* adecuados para el cáncer son conocidos para los expertos en la técnica. Para mayores detalles de ensayos *in vivo* para adenocarcinoma de próstata, glioblastoma, carcinoma de pulmón y ver los Ejemplos biológicos 5-10, *infra*. Los ejemplos que describen la administración de un compuesto de Fórmula I en combinación con agentes anticáncer se describen en

los Ejemplos Biológicos 11-14, *infra*. . Siguiendo los ejemplos descriptos en la presente, así como los descriptos en la técnica, los expertos en la técnica pueden determinar que combinaciones de un compuesto de Fórmula I y agentes anticáncer deben ser efectivos para tratar cáncer.

SÍNTESIS GENERAL

[00248] Los compuestos de esta invención se pueden obtener por los procedimientos de síntesis que se describen a continuación. Los materiales de partida y reactivos usados para preparar estos compuestos están disponibles en proveedores comerciales tales como Aldrich Chemical Co. (Milwaukee, Wis.), o Bachem (Torrance, Calif.), o se preparan por métodos conocidos por los expertos en la técnica siguiendo los procedimientos expuestos en referencias tales como como Fieser y Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley y Sons, 1991); Rodd's Chemistry de Carbon Compounds, Volumes 1-5 y Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley y Sons, 1991), March's Advanced Organic Chemistry, (John Wiley y Sons, 4th Edition) y Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989). Estos esquemas son simplemente ilustrativos de algunos métodos por los que se pueden sintetizar los compuestos de esta invención, y se pueden realizar diversas modificaciones a estos esquemas y serán sugeridas por los expertos en la técnica con referencia a esta descripción. Los materiales de partida y los intermediarios de la reacción se pueden aislar y purificar si se desea usando técnicas convencionales, que incluye pero sin limitación

filtración, destilación, cristalización, cromatografía y similares. Dichos materiales se pueden caracterizar usando medios convencionales, que incluyen constantes físicas y datos de espectros.

[00249] A menos que se especifique lo contrario, las reacciones descriptas en la presente ocurren a presión atmosféricas y en un rango de temperatura de aproximadamente -78 °C a aproximadamente 150 °C, en otra forma de realización de aproximadamente a 0 °C a aproximadamente 125 °C y en otra forma de realización a aproximadamente temperatura ambiente (o ambiente), por ejemplo, aproximadamente 20 °C. A menos que indique de otro modo (como en el caso de una hidrogenación), todas las reacciones se realizan bajo una atmósfera de nitrógeno.

[00250] Los profármacos se pueden preparar por técnicas conocidas por los expertos en la técnica. Estas técnicas generalmente modifican grupos funcionales apropiados en un compuesto dado. Estos grupos funcionales modificados regeneran grupos funcionales originales por manipulación de rutina o *in vivo*. Las amidas y los ésteres de los compuestos de la presente invención se pueden preparar de acuerdo con métodos convencionales. Una descripción completa de profármacos se proporciona en T. Higuchi y V. Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 del A.C.S. Symposio Series, y en Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, los cuales se incorporan en la presente por referencia para todos los propósitos.

[00251] Los compuestos de la invención, o sus sales farmacéuticamente aceptables, puede tener átomos de

carbono asimétricos o átomos de nitrógeno cuaternizados en su estructura. Los compuestos de Fórmula I que se pueden preparar mediante la síntesis descripta en la presente pueden existir como estereoisómeros simples, racematos y como mezclas de enantiómeros y diastereómeros. Los compuestos también pueden existir como isómeros geométricos. Todos estos estereoisómeros simples, racematos y sus mezclas, y los isómeros geométricos se consideran dentro del alcance de esta invención. Algunos de los compuestos de la invención pueden existir como tautómeros. Por ejemplo, cuando está presente una cetona o aldehído, la molécula puede existir en la forma enol; cuando una amida está presente, la molécula puede existir como ácido imídico; y cuando está presente una enamina, la molécula puede existir como una imina. Todos estos tautómeros están dentro del alcance de la invención. En particular, imidazol-5-ilo y pirazol-5-ilo también pueden existir en sus respectivas foras tautoméricas imidazol-4-ilo y pirazol-3-ilo. Independientemente de que estructura o terminología se use, cada tautómero está incluido dentro del alcance de la invención.

[00252] La presente invención también incluye derivados de N-óxidos y derivados protegidos de los compuestos de Fórmula I. Por ejemplo, cuando los compuestos de Fórmula I contienen un átomo de nitrógeno oxidable, el átomo de nitrógeno se puede convertir a un N-óxido por métodos bien conocidos en la técnica. Cuando los compuestos de Fórmula I contienen grupos tales como hidroxi, carboxi, tiol o cualquier grupo que contiene un átomo de nitrógeno, estos grupos pueden estar protegidos con un "grupo protector" o "grupo que

protege". Una lista exhaustiva de grupos protectores adecuados se puede hallar en T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1991, cuya descripción se incorpora en la presente por referencia en su totalidad. Los derivados protegidos de los compuestos de Fórmula I se pueden preparar por métodos conocidos en la técnica.

[00253] Los métodos para la preparación y/o separación y aislamiento de estereoisómeros de las mezclas racémicas o mezclas no racémicas de estereoisómeros son bien conocidos en la técnica. Por ejemplo, los isómeros (R)- y (S)- óptimamente activos se pueden preparar usando sintones de síntesis quiral o reactivos quirales o resueltos usando técnicas convencionales. Los enantiómeros (R- y S-isómeros) se pueden resolver por métodos conocidos por los expertos en la técnica, por ejemplo por: formación de sales o complejos diastereoisoméricos que se pueden separar, por ejemplo, por cristalización; por medio de la formación de derivados diastereoisoméricas que se pueden separar, por ejemplo, por cristalización, reacción selectiva de un enantiómero con un reactivo específico de enantiómero, por ejemplo oxidación o reducción enzimática, seguido por la separación de enantiómeros modificados o no modificados; o cromatografía gas-líquido o líquida en un ambiente quiral, por ejemplo en un soporte quiral, tal como sílice con un ligando quiral unido o en presencia de un solvente quiral. Se apreciará que cuando un enantiómero deseado se convierte en otra entidad química por uno de los procedimientos de separación descriptos anteriormente, se puede requerir una etapa adicional para liberar la forma enantiomérica

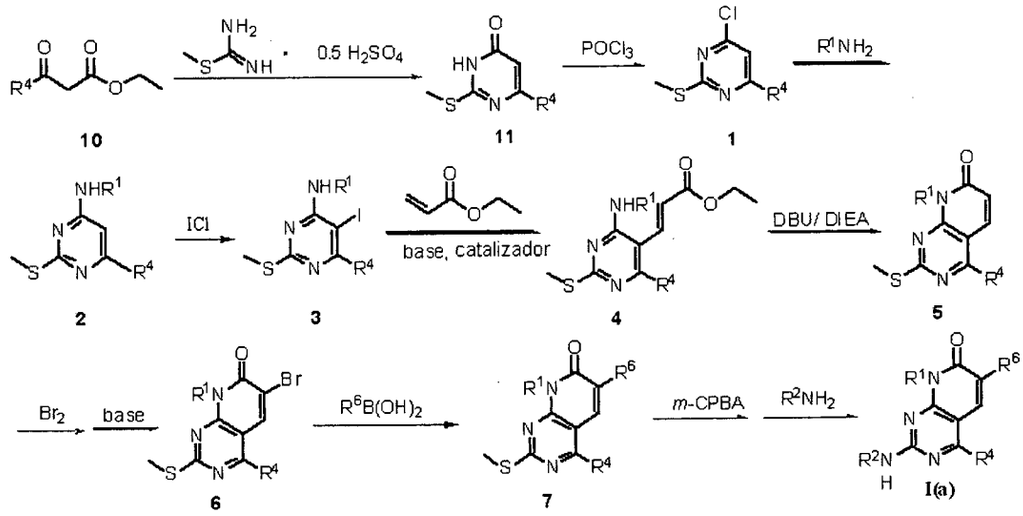
deseada. Alternativamente, el enantiómero específico se puede sintetizar por síntesis asimétrica usando reactivos, sustratos, catalizadores o solventes ópticamente activos o por la conversión de enantiómero al otro por transformación asimétrica. Para una mezcla de enantiómeros, enriquecida en un enantiómero particular, el mayor componente enantiómero se puede enriquecer adicionalmente (con pérdida concomitante de rendimiento) por recristalización.

[00254] Además, los compuestos de la presente invención pueden existir en forma no solvatada así como solvatada 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 fines de la presente invención.

[00255] Las reacciones químicas para la preparación de los compuestos de esta invención son conocidas por los expertos en la técnica. En efecto, puede haber más de un proceso para preparar los compuestos de la invención. Para ejemplos específicos, ver M. Barvian et al. J. Med. Chem. 2000, 43, 4606-4616; S. N. VanderWei et al. J. Med. Chem. 2005, 48, 2371-2387; P. L. Toogood et al. J. Med. Chem. 2005, 48, 2388-2406; J. Kasparec et al. Tetrahedron Letters 2003, 44, 4567-4570; y references cited terein. Ver también publicación U.S. Pre-grant US2004/0009993 A1 (M. Angiolini et al.), que se incorpora en la presente por referencia, y las referencias mencionadas en ella. Los siguientes ejemplos ilustran pero no limitan la invención. Todas las referencias mencionadas en la presente se incorporan por referencia en su totalidad.

[00256] Un compuesto de la invención donde R^1 es alquilo opcionalmente sustituido, R^2 es hidrógeno o alquilo opcionalmente sustituido, R^4 es metilo o etilo, R^6 es fenilo o heteroarilo cada uno de los cuales está opcionalmente sustituido con 1, 2, 3, 4, o 5 grupos R^9 (como se define en la Síntesis de la invención), y R^2 es hidrógeno se puede preparar de acuerdo con el Esquema 1.

Esquema 1



[00257] A una solución de sulfato de 2-metil-2-tiopseudourea disponible en el comercio en un solvente tal como agua se añade a base tal como carbonato de sodio y un intermediario de fórmula **10** a temperatura ambiente. La mezcla de reacción se agita durante toda la noche o menos. Después de neutralizar, **11** se recolecta a través de filtración y seguido por secado al vacío. **11** luego se trata con $POCl_3$ y la reacción se calienta a reflujo durante aproximadamente 2 h y luego se concentra al vacío a sequedad. **1** se puede usar directamente en la próxima reacción sin purificación adicional.

[00258] Un intermediario de fórmula **2** se prepara por la reacción de un intermediario de fórmula 1 con una amina

primaria R^1NH_2 en un solvente tal como agua y con calentamiento. **2** luego se trata con monocloruro de yodo en un solvente tal como metanol a aproximadamente 0 °C y se deja reaccionar durante aproximadamente toda la noche o menos según sea necesario para completar la reacción para formar **3**. Después de la finalización el residuo se tritura con acetona. El intermediario **3** luego se hace reaccionar en un solvente, tal como DMA, con acrilato de etilo en presencia de una base, tal como trietilamina, y en presencia de un catalizador, tal como $Pd(OAc)_2$, y (+)BINAP. La reacción se calienta a aproximadamente 100 °C y se deja reaccionar durante aproximadamente toda la noche o menos según sea necesario para completar la reacción para formar **4**.Luego **4** se purifica opcionalmente por cromatografía en columna.

[00259] **5** se prepara por el tratamiento de **4** con DBU en presencia de una base tal como DIPEA a temperatura ambiente. Ten la mezcla de reacción se calienta a reflujo y se hace reaccionar durante aproximadamente 15 h. Después de la evaporación del solvente, el residuo se tritura con acetona y se recolecta por filtración para producir **5**.

[00260] **6** se prepara por la reacción **5** con un agente bromante tal como Br_2 en un solvente tal como DCM a temperatura ambiente. Luego la mezcla de reacción se agita durante aproximadamente toda la noche. El producto resultante se filtra y luego se suspende en un solvente tal como DCM y se trata con una base tal como trietilamina. La mezcla luego se lava con agua y se seca con un agente desecante tal como Na_2SO_4 para producir **6**.

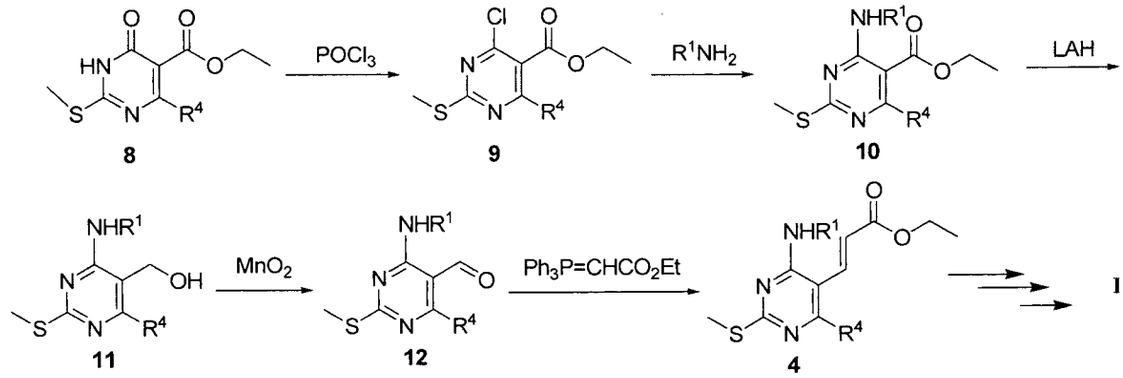
[00261] Luego se realiza un acoplamiento Suzuki mediante la reacción de **6** con un ácido borónico (o éster) de fórmula $R^6B(OH)_2$ en un solvente tal como una mezcla de

DME-H_2O, en presencia de un catalizador tal como Pd(dpppf) y una base tal como trietilamina a temperatura ambiente. La mezcla de reacción se calienta a reflujo durante aproximadamente 4 h. Después de enfriar a temperatura ambiente, la mezcla de reacción se divide en agua y acetato de etilo. Después de la separación, la fase orgánica se seca con un agente desecante tal como Na_2SO_4 para producir **7**.

[00262] El grupo metilito de **7** luego se oxida con *m*-CPBA en un solvente tal como DCM a temperatura ambiente dejando agitar durante aproximadamente 4 h. Después de extraer el solvente presión reducida, el producto se trata con una amina de fórmula R^2NH_2 en un solvente tal como dioxano y se agita a temperatura ambiente durante aproximadamente toda la noche para producir un compuesto de fórmula I.

[00263] En forma alternativa, un compuesto de la invención donde R^1 es alquilo opcionalmente sustituido, R^4 es metilo o etilo, R^6 es fenilo o heteroarilo cada uno de los cuales está opcionalmente sustituido con 1, 2, 3, 4, o 5 grupos R^9 (como se define en la Síntesis de la invención), y R^2 es hidrógeno se puede preparar de acuerdo con el Esquema 2.

Esquema 2

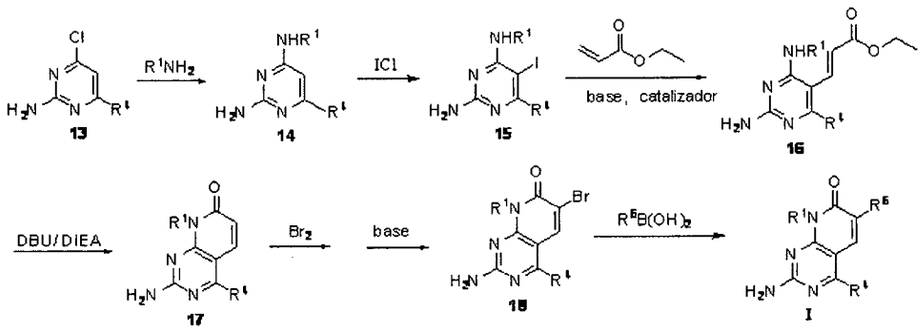


[00264] Un intermediario de fórmula **9** se prepara por la reacción de un intermediario de fórmula **8** con $POCl_3$ puro y calentamiento. **9** luego se trata con una amina primaria R^1NH_2 en un solvente tal como agua o TF y trietilamina a 0 °C para formar **10**. Después de extraer el solvente presión reducida, el intermediario **10** luego se hace reaccionar con hidruro de litio y aluminio en un solvente tal como TF a 0 °C. Después de la inactivación y el desarrollo acuoso, la extracción del solvente proporcionó **11** cristalino sin purificación adicional. El tratamiento de **11** con dióxido de manganeso (II) en un solvente tal como cloruro de metileno o cloroformo a temperatura ambiente proporcionó aldehído **12** después de la filtración y la extracción del solvente. Se puede emplear una reacción de Wittig con aldehído **12** con (carbetoximetilen)trifenilfosforano en reflujo TF para proporcionar el intermediario común **4**. **4** se puede usar para preparar el Compuesto de Fórmula I usando los procedimientos descriptos en el Esquema 1.

[00265] Un compuesto de la invención donde R^1 es alquilo opcionalmente sustituido, R^4 es metilo o etilo, R^6 es fenilo o heteroarilo cada uno de los cuales está opcionalmente sustituido con 1, 2, 3, 4, o 5 grupos R^9

(como se define en la Síntesis de la invención), y R^2 es hidrógeno se puede preparar de acuerdo con el Esquema 3.

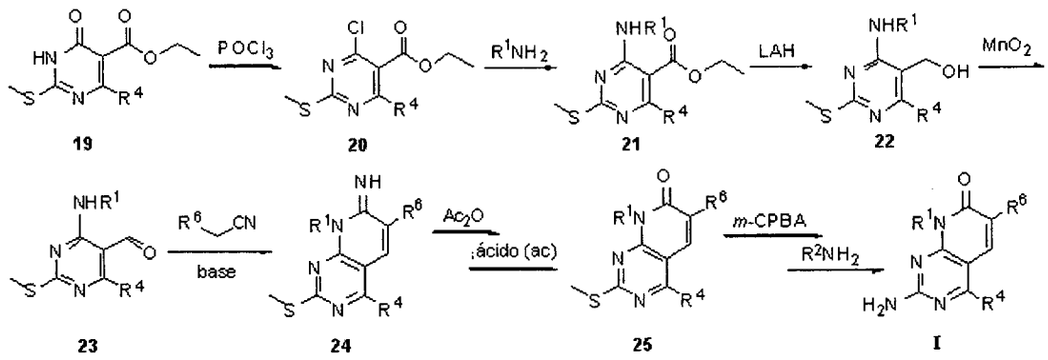
Esquema 3



[00266] Un intermediario de fórmula **14** se prepara por la reacción de un intermediario de fórmula **13** con una amina primaria R^1NH_2 en un solvente tal como agua y con calentamiento. **14** luego se trata con monocloruro de yodo en un solvente tal como metanol a aproximadamente 0 °C y se deja reaccionar durante aproximadamente toda la noche o menos según sea necesario para completar la reacción para formar **15**. Después de la finalización el residuo se tritura con acetona. El intermediario **15** luego se hace reaccionar en un solvente, tal como DMA, con acrilato de etilo en presencia de una base, tal como trietilamina, y en presencia de un catalizador, tal como $Pd(OAc)_2$, y (+)BINAP. La reacción se calienta a aproximadamente 100 °C y se deja reaccionar durante aproximadamente toda la noche o menos según sea necesario para completar la reacción para formar **16**. **16** luego se purifica opcionalmente por cromatografía en columna. Un compuesto de fórmula I luego se puede preparar a partir de **16** usando la mismas condiciones de reacción que se describen en el Esquema 1 (a partir del punto de la preparación de **5** desde **4**).

[00267] Un compuesto de la invención donde R^1 es alquilo opcionalmente sustituido, R^4 es metilo o etilo, R^6 es fenilo o heteroarilo cada uno de los cuales está opcionalmente sustituido con 1, 2, 3, 4, o 5 grupos R^9 (como se define en la Síntesis de la invención), y R^2 es hidrógeno en forma alternativa se pueden preparar de acuerdo con el Esquema 4.

Esquema 4



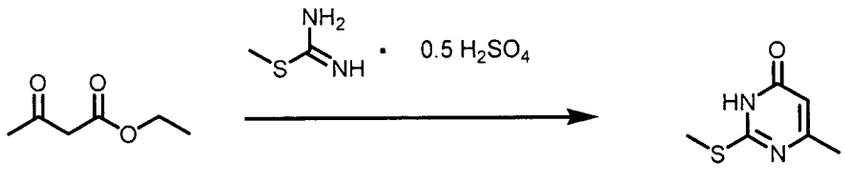
[00268] Un intermediario de fórmula **20** se prepara por la reacción de un intermediario de fórmula **19** con $POCl_3$ solo y calentamiento. **20** luego se trata con una amina primaria R^1NH_2 en un solvente tal como agua o TF y trietilamina a 0 °C para formar **21**.después de extraer el solvente presión reducida, el intermediario **21** luego se hace reaccionar con hidruro de litio y aluminio en un solvente tal como TF a 0 °C. Después de la inactivación y el desarrollo acuoso, la extracción del solvente proporcionó **22** cristalino sin purificación adicional. El tratamiento de **22** con dióxido de manganeso (II) en un solvente tal como cloruro de metileno o cloroformo a temperatura ambiente proporcionó aldehído **23** después de la filtración y la extracción del solvente. Una condensación tipo Knovenegal con **23** y un arilacetonitrilo en presencia de una base tal como carbonato de potasio o hidróxido de

sodio en un solvente prótico proporciona la imiba ciclada **24**. La acetilación de la imina con anhídrido acético se requiere antes de ocurra la hidrólisis en presencia de ácido acuoso y calentamiento para proporcionar **25**. Posteriormente, **25** se puede oxidar a la correspondiente sulfona con *m*-CPBA a temperatura ambiente y se desplazó con amonio para proporcionar **I**.

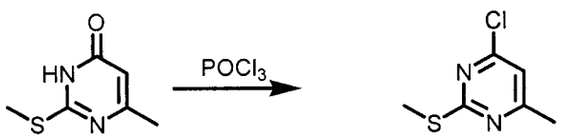
Ejemplos de síntesis

Ejemplo 1

2-amino-8-etil-4-metil-6-(1*H*-pirazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona

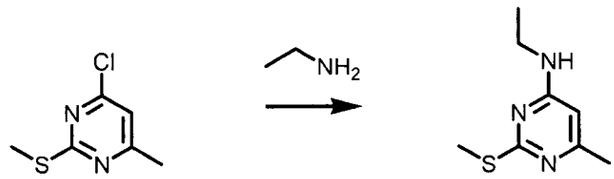


[00269] A una solución de sulfato de 2-metil-2-tiopseudourea (Aldrich, 58,74 g, 0,422 mol) en agua (1000 mL) se añadieron carbonato de sodio (81,44 g, 0,768 mol) y acetoacetato de etilo (50 g, 0,384 mol) a temperatura ambiente. La mezcla de reacción se agitó toda la noche. Después de neutralizar a pH = 8, el sólido se recolectó mediante filtración seguido por secado al vacío toda la noche para proporcionar 6-metil-2-(metiltio)pirimidin-4(3*H*)-ona (57,2 g, 95% de rendimiento) de producto. ^{1}H RMN (400 MHz, DMSO-d6): δ 12,47 (bs, 1H), 5,96 (bs, 1H), 2,47(s, 3H), 2,17 (s, 3H).

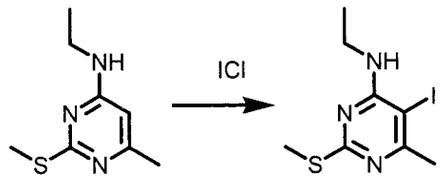


[00270] Al balón que contiene 6-metil-2-(metiltio)pirimidin-4(3*H*)-ona (19 g, 121,6 mmol) se

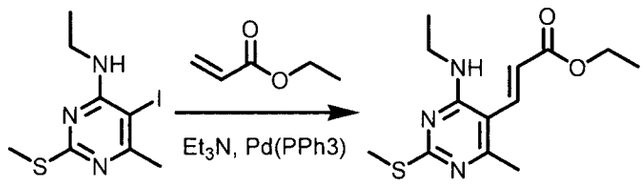
añadió $POCl_3$ (30 mL). La mezcla de reacción se calentó a reflujo durante 2 h y luego se concentró en un evaporador giratorio a sequedad. La 4-cloro-6-metil-2-(metiltio)pirimidina bruta se usó directamente en la próxima reacción sin purificación adicional.



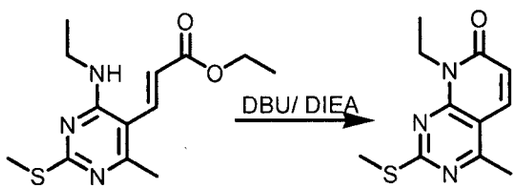
[00271] A la 4-cloro-6-metil-2-(metiltio)pirimidina anterior se añadieron 30 mL de una solución de 70% de etilamina en agua. La mezcla de reacción se calentó a 50 °C durante 3 h. Después de la finalización, el exceso de etilamina se evaporó en un evaporador giratorio al vacío. El sólido se filtró y secó al vacío para proporcionar *N*-etil-6-metil-2-(metiltio)pirimidin-4-amina (20 g, 90% de rendimiento).



[00272] A la solución de *N*-etil-6-metil-2-(metiltio)pirimidin-4-amina (20 g, 121,6 mmol) en metanol se añadió monocloruro de yodo (26,58 g, 163,7 mmol) en pequeñas porciones a 0 °C. Luego la mezcla de reacción se agitó toda la noche. Después de la evaporación del solvente, el residuo se trituró con acetona. El producto *N*-etil-5-iodo-6-metil-2-(metiltio)pirimin-4-amina (25,2 g, 75% de rendimiento) se recolectó por filtración. ^1H RMN (400 MHz, $CDCl_3$): δ 5,37 (bs, 1H), 3,52 (q, J = 7,2 Hz, 1H), 2,50 (s, 3H), 1,26 (t, J = 7,2 Hz, 3H).

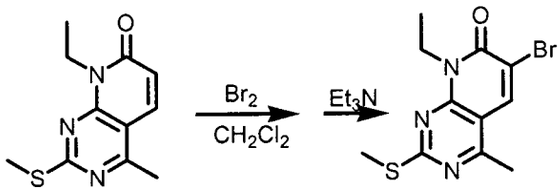


[00273] A la solución de *N*-etil-5-yodo-6-metil-2-(metiltio)pirimin-4-amina (25,2 g, 81,48 mmol) en DMA (260 mL) se añadieron acrilato de etilo (12,23 g, 122,2 mmol), $Pd(OAc)_2$ (3,65 g, 16,25 mmol), (+)BINAP y trietilamina (24,68 g, 244,4 mmol). Luego la mezcla de reacción se calentó a 100 °C y se hizó reaccionar toda la noche. Después de la evaporación del solvente, el residuo se diluyó con agua y la fase acuosa se extrajo con acetato de etilo. El producto (*E*)-etil-3-(4-(etilamino)-6-metil-2-(metiltio)pirimidin-5-il)acrilato (16,8 g, 73% de rendimiento) se aisló por cromatografía en columna de gel de sílice con 6-8% acetato de etilo en hexano como eluyente. ^1H RMN (400 MHz, $CDCl_3$): δ 7,65 (d, J = 16,4Hz, 1H), 6,20 (d, J = 16,4Hz, 1H), 5,15 (bs, 1H), 4,28(q, J = 7,2 Hz, 2H), 3,54 (q, J = 7,2 Hz, 2H), 2,53 (s, 3H), 2,37 (s, 3H), 1,35 (t, J = 7,2 Hz, 3H), 1,24 (t, J = 7,2 Hz, 3H).

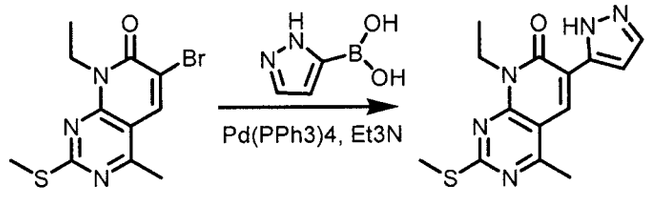


[00274] A una solución de (E)-etil-3-(4-(etilamino)-6-metil-2-(metiltio)pirimidin-5-il)acrilato (16,8 g, 59,8 mmol) en DIPEA se añadió 1,8-diazabiciclo[5,4,0]undec-7-ene (DBU, 18,21 g, 119,6 mmol) a temperatura ambiente. Luego la mezcla de reacción se calentó a reflujo y se hizo reaccionar durante 15 h. Después de la evaporación

del solvente, el residuo se trituró con acetona. El producto 8-etil-4-metil-2-(metiltio)pirido[2,3-d]pirimidin-7(8*H*)-ona (10,77 g, 77% de rendimiento) se recolectó por filtración. ^{1}H RMN (400 MHz, $CDCl_3$): δ 7,78 (d, J = 9,6 Hz, 1H), 6,63 (d, J = 9,6 Hz, 1H), 4,5(q, J = 7,2 Hz, 2H), 2,67 (s, 3H), 2,62 (s, 3H), 1,33 (t, J = 7,2 Hz, 3H).

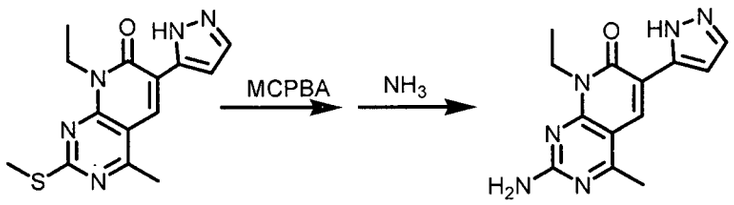


[00275] A una solución de 8-etil-4-metil-2-(metiltio)pirido[2,3-d]pirimidin-7(8*H*)-ona (6,31 g, 26,84 mmol) en DCM se añadió Br_2 (4,79 g, 29,52 mmol) gota a gota a temperatura ambiente. Luego la mezcla de reacción se agitó a temperatura ambiente toda la noche. Después de la filtración el sólido se suspendió en DCM (100 mL), y trietilamina (20 mL) se añadió. La mezcla se lavó con agua y secó con Na_2SO_4, y el producto 6-bromo-8-etil-4-metil-2-(metiltio)pirido[2,3-d]pirimidin-7(8*H*)-ona (6,96 g, 83 % de rendimiento) se obtuvo después de la evaporación DCM. ^{1}H RMN (400 MHz, $CDCl_3$): δ 8,22 (s, 1H), 4,56 (q, J = 7,2 Hz, 2H), 2,68 (s, 3H), 2,62 (s, 3H), 1,34 (t, J = 7,2Hz, 3H).



[00276] A una solución de 6-bromo-8-etil-4-metil-2-(metiltio)pirido[2,3-d]pirimidin-7(8*H*)-ona (0,765 g, 2,43 mmol) en DME-H_2O (10:1 11 mL) se añadió ácido 1H-

pirazol-5-ilborónico (Frontier, 0,408 g, 3,65 mmol), [1,1'-complejo de bis(difenilfosfino)ferroceno]dicloropaladio(II) con CH_2Cl_2 (Pd(dpppf),0,198 g, 0,243 mmol) y trietilamina (0,736 g, 7,29 mmol) a temperatura ambiente. Luego la mezcla de reacción se calentó a reflujo y se hizo reaccionar for 4 h. Después de enfriar a temperatura ambiente, la mezcla de reacción se dividió en agua y acetato de etilo. Después de la separación, la fase orgánica se secó con Na_2SO_4, y el producto 8-etil-4-metil-2-(metiltio)-6-(1*H*-pirazol-5-il)pirido[2,3-d]pirimidin-7(8*H*)-ona (0,567 g, 77% de rendimiento) se obtuvo por cromatografía en columna de gel de sílice. ^{1}H RMN (400 MHz, $CDCl_3$): δ 13,3 (bs, 1H), 8,54 (s, 1H), 7,82-7,07 (m, 2H), 4,45 (q, J = 7,2 Hz, 2H), 2,71 (s, 3H), 2,60 (s, 3H), 1,26 (t, J = 7,2Hz, 3H).



[00277] A la solución de 8-etil-4-metil-2-(metiltio)-6-(1*H*-pirazol-5-il)pirido[2,3-d]pirimidin-7(8*H*)-ona (0,123 g, 0,41mmol) in DCM (2 mL) se añadió MCPBA (0,176 g, 77%, 0,785 mmol) en una pequeña porción a temperatura ambiente. Luego la mezcla de reacción se agitó durante 4 h. Después de la evaporación DCM, se introdujeron dioxano (1 mL) y amoníaco líquido (1 mL). La reacción se agitó a temperatura ambiente toda la noche. El producto 2-amino-8-etil-4-metil-6-(1*H*-pirazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona (50,4 mg) se obtuvo por cromatografía en columna de gel de sílice. ^{1}H RMN (400 MHz, CD_3OD): δ

8,41 (s, 1H), 7,62 (d, J = 2,0 Hz, 1H), 6,96 (d, J = 2,0Hz, 1H), 4,51 (q, J = 7,2Hz, 2H), 2,64 (s, 3H), 1,29 (t, J = 7,2Hz, 3H); EM (EI) para $C_{13}H_{14}N_6O$: 271,3 (MH^+).

[00278] Usando técnicas de síntesis iguales o análogas y sustituyendo con los reactivos apropiados, se prepararon los siguientes compuestos:

Ejemplo 1a. 2-(amino)-8-etil-4-etil-6-(1H-pirazol-5-il)pirido[2,3-d]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, DMSO-D6): δ 8,40 (s, 1H), 7,27 (bs, 1H), 7,00 (s, 1H), 4,40 (q, J = 7,2 Hz, 2H), 2,95 (d, J = 7,20 Hz, 2H), 1,14 (t, J = 7,2 Hz, 3H), 1,08 (t, J = 7,2Hz, 3H), 0,89 (m, 1H), 0,24 (m, 2H), 0,01 (m, 2H); EM (EI) para $C_{14}H_{16}N_6O$: 285,2 (MH^+).

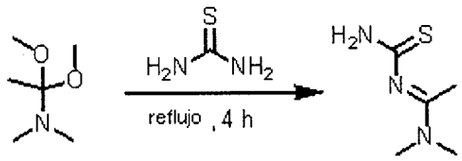
Ejemplo 1b. **8-etil-4-metil-2-(metilamino)-6-(1H-pirazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, CH_3OH-d_4): δ 8,39 (s, 1H), 7,60 (bs, 1H), 6,93 (bs, 1H), 4,53 (bs, 2H), 3,02 (s, 3H), 2,84 (bs, 3H), 1,33 (bs, 3H); EM (EI) para $C_{14}H_{16}N_6O$: 285,3 (MH^+).**

Ejemplo 1c. **8-Etil-2-[(2-fluoroetil)amino]-4-metil-6-(1*H*-pirazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, CH_3OH-d_4): δ 8,34 (bs, 1H), 7,25 (bs, 1H), 6,90 (bs, 1H), 4,60 (dt, *J* = 5,2, 2,2 Hz, 2H), 4,49 (q, *J* = 7,20 Hz, 2H), 3,78 (dt, *J* = 5,2, 2,2 Hz, 2H), 2,64 (s, 3H), 1,30 (t, *J* = 7,2 Hz, 3H); EM (EI) para $C_{15}H_{17}FN_6O$: 317,3 (MH^+).**

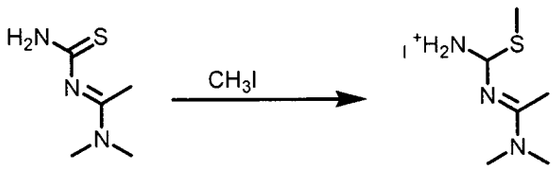
Ejemplo 1d. 2-Amino-8-ciclopentil-4-metil-6-(1*H*-pirazol-3-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, DMSO-d_6): δ 13,10 (s, 1H), 8,42 (d, 1H), 7,70 (s, 1H), 7,20 (bs, 2H), 6,01 (m, 1H), 2,61 (s, 3H), 2,30 (m, 2H), 2,10 (m, 2H), 1,80 (m, 2H), 1,60 (m, 2H); EM (EI) para $C_{16}H_{18}N_6O$: 311,8 (M+H).

Intermediario 1

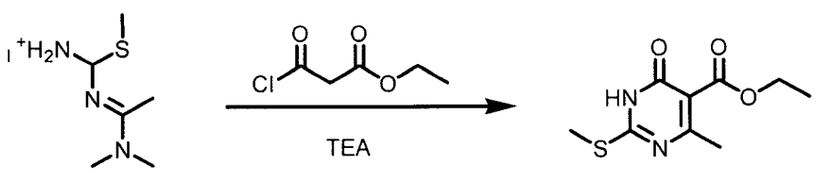
Ruta alternativa a (E)-etil-3-(4-(etilamino)-6-metil-2-(metiltio)pirimidin-5-il)acrilato



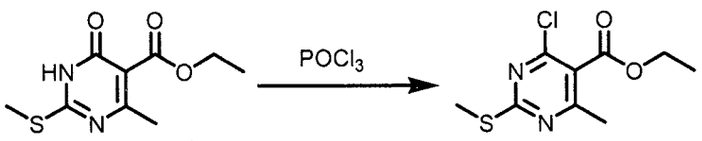
[00279] *N,N*-Dimetil acetamida dimetil acetal (75 g, 0,56 mol) se añadió a una suspensión de tiourea (33,0 g, 0,43 mol) en cloruro de metileno. La mezcla se calentó bajo reflujo durante 4 h. Se extrajo el solvente y el residuo se cristalizó en 5% de MeOH y éter dietílico proporcionando (1E)-*N'*-(aminocarbonotioil)-*N,N*-dimetiletanimidamida (47,8 g, 76% de rendimiento).



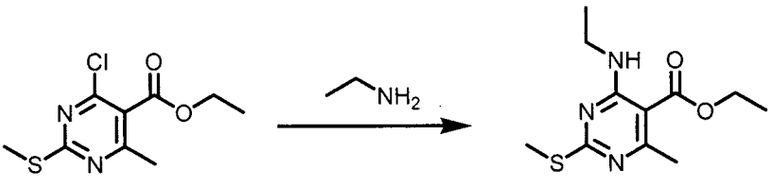
[00280] Una suspensión de (1E)-*N'*-(aminocarbonotioil)-*N,N*-dimetiletanimidamida (47,8 g, 0,33 mol) en yoduro de metilo (150 mL) y TF (350 mL) se agitó durante 18 h a temperatura ambiente. La mezcla se evaporó a presión reducida. Después de la adición de 5% de MeOH y éter dietílico, el compuesto precipitó y se recolectó por filtración proporcionando (1*E*)-*N'*-sal de yoduro de hidrógeno de [amino(metiltio)metil]-*N,N*-dimetiletanimidamida (91,0 g, 96% de rendimiento).



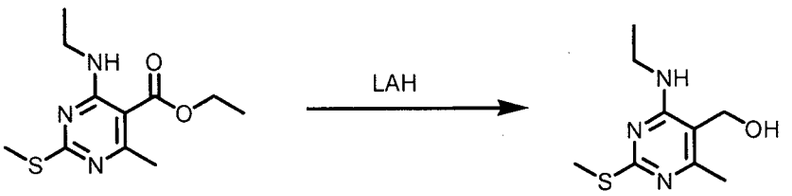
[00281] A una solución de sal de yoduro de hidrógeno de (1E)-*N'*-[amino(metiltio)metil]-*N,N*-dimetiletanimidamida (73,0 g, 0,26 mole) en diclorometano seco (900 mL), se añadió 3-cloro-3-oxopropanoato de etilo (44 mL, 95% Lancaster, 0,34 mole) se añadió bajo atmósfera de nitrógeno. La mezcla se agitó durante 4 h a temperatura ambiente, se enfrió a 0 °C luego se añadió trietilamina (107 mL, 0,78 mol). La mezcla de reacción se agitó toda la noche. Se extrajo el solvente y se añadió H_2O. El pH se ajustó a pH = 5,0 con ácido acético y se extrajo con acetato de etilo luego se evaporó y cristalizó en el solvente apropiado (mezcla de solventes acetato de etilo-Hexanos, aproximadamente 20% acetato de etilo-Hexanos). Esto proporcionó 4-metil-2-(metiltio)-6-oxo-1,6-dihidropirimidin-5-carboxilato de etilo (36,5 g, 62% de rendimiento) después del secado al vacío.



[00282] Una solución de 4-metil-2-(metiltio)-6-oxo-1,6-dihidropirimidin-5-carboxilato de etilo (60 g, 0,26 mol) y oxicloruro de fósforo ($POCl_3$, 320 mL) se calentó bajo reflujo durante 4 a 5 h (reacción controlada por TLC usando 30% de acetato de etilo y hexanos). Después de la finalización de la reacción, el oxicloruro de fósforo se extrajo en un evaporador giratorio. El residuo se vertió en agua helada y se extrajo con acetato de etilo varias veces. Las fases orgánicas combinadas se evaporaron, en un evaporador giratorio, para dar 4-cloro-6-metil-2-(metiltio)pirimidin-5-carboxilato de etilo bruto (65 g). Este compuesto se usó sin purificación.

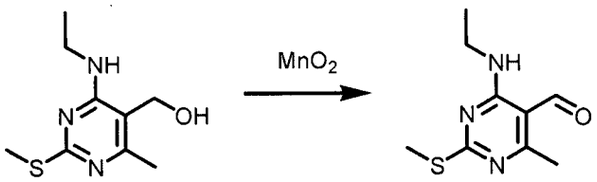


[00283] A una solución de 4-cloro-6-metil-2-(metiltio)pirimidin-5-carboxilato de etilo (65 g) en TF (1000 mL) y trietilamina (110 mL, 0,81 mol) se añadió etilamina (2,0 M en TF, 0,81 mol) a 0 °C. Esta mezcla de reacción se agitó a temperatura ambiente toda la noche y luego los solventes se extrajeron en un evaporador giratorio. Se añadió H_2O y la mezcla se extrajo con acetato de etilo varias veces. Los solventes de las fases orgánicas combinadas se extrajeron en un evaporador giratorio proporcionando 58 g (86% de rendimiento) de 4-(etilamino)-6-metil-2-(metiltio)pirimidin-5-carboxilato de etilo. Este material se usó como tal sin purificación adicional.

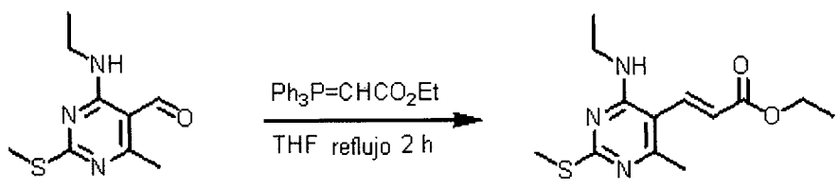


[00284] A una solución de hidruro de litio y aluminio (LAH, solución 1,0 M en TF, Aldrich, 450 mL) se añadió una solución de 4-(etilamino)-6-metil-2-(metiltio)pirimidin-5-carboxilato de etilo (57 g) en TF (1000 mL). La mezcla de reacción se agitó toda la noche. Después de enfriar a 0 °C, la mezcla de reacción se inactivó con cuidado con una mezcla 1:9 de H_2O/TF hasta que cesó el desarrollo de gas, luego se diluyó con H_2O (500 mL) y se agitó bien durante 2 h. La suspensión resultante se extrajo con acetato de etilo varias veces.

La fase acuosa luego se filtró a través de Celite y se lavó otra vez con acetato de etilo. Las fases orgánicas combinadas se lavaron con salmuera, secaron y se concentraron a presión reducida para dar 41,0 g (85% de rendimiento) de [4-(etilamino)-6-metil-2-(metiltio)pirimidin-5-il]metanol en forma de cristal amarillo claro, que se usó sin purificación en la próxima etapa



[00285] A una solución de [4-(etilamino)-6-metil-2-(metiltio)pirimidin-5-il]metanol (41,0 g) in cloroformo (4000 mL) se añadió óxido de manganeso (125 g, 1,4 mol) y se agitó durante 4 h a temperatura ambiente. Se añadió más óxido de manganeso hasta que se observó la desaparición del compuesto. La mezcla de reacción se filtró a través de celite y se lavó con algo de cloroformo y se evaporaron todos los solventes orgánicos para dar 38 g (92 % de rendimiento) de 4-(etilamino)-6-metil-2-(metiltio)pirimidin-5-carbaldehído como un sólido incoloro, que se usó sin purificación en la próxima etapa

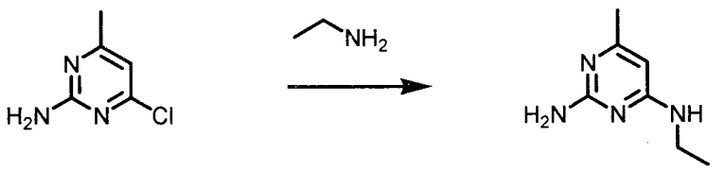


[00286] A una solución de 4-(etilamino)-6-metil-2-(metiltio)pirimidin-5-carbaldehído (38 g, 180 mmol) en TF

(500 mL) se añadió (Carbetoximetilen)trifenilfosforano (95%, Aldrich, 85,18 g, 244 mmol). La mezcla de reacción se calentó a reflujo durante 1,5 h y se controló por TLC (4:1 hexanos/acetato de etilo). La reacción se enfrió a temperatura ambiente y se concentró en un evaporador giratorio. Se sometió directamente a cromatografía en columna (4:1 hexanos/acetato de etilo) para dar (E)-etil-3-(4-(etilamino)-6-metil-2-(metiltio)pirimidin-5-il)acrilato en forma de un cristal blanco, 46,14 g (91% de rendimiento).

Ejemplo 2

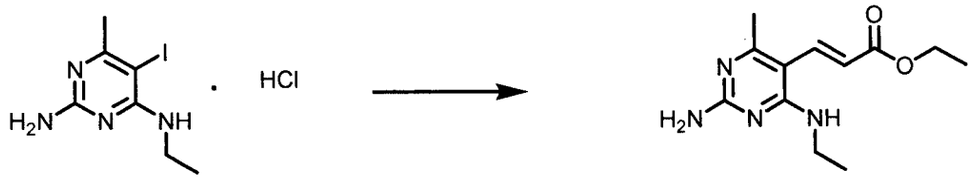
2-Amino-6-bromo-8-etil-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona



[00287] A un matraz de tres bocas de 3 L, que estaba equipado con un agitador superior, se añadió en orden 2-amino-4-cloro-6-metilpirimidina (Aldrich, 100 g, 0,696 mol, 1 equiv.), etilamina (70% etilamina in agua, Lancaster, 625 mL), 625 mL H_2O, y 125 mL TEA (0,889 mol, 1,28 equiv.). La mezcla se agitó y calentó a reflujo durante 20 h, durante este tiempo la reacción se tornó homogénea. La reacción se dejó enfriar a temperatura ambiente. La etilamina volátil se extrajo en un evaporador giratorio. Se formó un precipitado. La mezcla acuosa que contiene el precipitado se dejó decantar a temperatura ambiente durante 2 h y luego se filtró. Después del secado al vacío, se obtuvieron 106 g (100% de rendimiento) de 2-amino-6-etilaminopirimidina en forma de

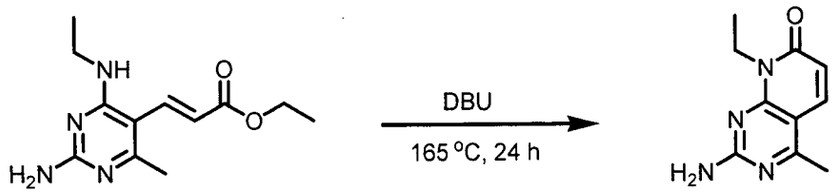
un sólido incoloro. Este material se usó como tal en la siguiente reacción.

[00288] A una solución de 2-amino-6-etilaminopirimidina (98 g, 0,64 mol) en metanol (1,6 L) se añadió ICl (115,0 g, 0,71 mol) en una pequeña porción a 15 °C. Luego la mezcla de reacción se agitó a temperatura ambiente durante 3 h (controlado por LC/EM). Después de la evaporación del solvente por evaporador giratorio, el residuo se trituró con acetona. Se obtuvo cloridrato de 2-amino-6-etilamino-4-yodopirimidina (188,5 g, 93% de rendimiento aislado) por filtración al vacío y secado. ^{1}H RMN (400 MHz, CD_3OD) δ 3,58 (q, 2H), 2,14 (s, 3H), 1,11 (t, 3H); EM (EI) para $C_7H_{11}N_4ClI$: 279,1 (MH^+).

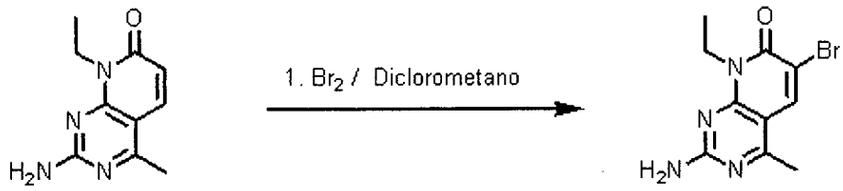


[00289] A un balón de tres bocas equipado con agitador mecánico superior se añadieron clorhidrato de 2-amino-6-etilamino-4-yodopirimidina (188,5 g, 0,60 mol), acrilato de etilo (221 mL, 2,0 mol), trietilamina (285 mL, 2,0 mol), DMF (1,3 L), y tetrakis(trifenilfosfina)paladio(0) ($Pd(PF_3)_4$, 31,3 g, 0,027 mol). La mezcla de reacción se calentó a 95 °C y se agitó durante 3 h (monitoreado por LC/MC). Después de finalizar la reacción, la mezcla de reacción se evaporó a aproximadamente el 1/10 del volumen original y se dividió en 500 mL de acetato de etilo y

1000 mL de agua. La fase acuosa se extrajo con acetato de etilo 5 veces. Se obtuvo (E) 3-(2-amino-4-(etilamino)-6-metilpirimidin-5-il)acrilato de etilo (100 g, 67% de rendimiento) se obtuvo por recristalización en acetona después de la evaporación acetato de etilo. ^{1}H RMN (400 MHz, CD_3OD) δ 7,48 (dd, *J1* = 16,0 Hz, *J2* = 4,0 Hz, 1H), 6,20 (dd, *J1* = 16 Hz, *J2* = 4 Hz, 1H), 4,25 (q, *J* = 7,2 Hz, 2H), 3,51 (q, *J* = 7,6 Hz, 2H), 2,39 (s, 3H), 1,3 (t, *J* = 7,2 Hz, 3H), 1,2 (t, *J* = 7,6 Hz, 3H). EM (EI) para $C_{12}H_{18}N_4O_2$: 251,3 (MH^+).



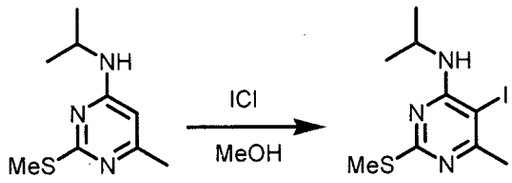
[00290] (E)-3-(2-amino-4-(etilamino)-6-metilpirimidin-5-il)acrilato de etilo (4,50 g, 18,0 mmol) se añadió a DBU (10,95 g, 4,0 equiv.) y la mezcla se calentó a 165 °C y se agitó durante 24 h. Después de esto, la mezcla se enfrió a 70 °C seguido por la adición de H_2O (20 mL) para precipitar el cristal y se agitó durante 1 h a temperatura ambiente. El cristal se recolectó y lavó con H_2O y acetona y se secó al vacío para proporcionar 2,70 g (73,5% de rendimiento de 2-amino-8-etil-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona en forma de un sólido marrón amarillento claro. LC/EM: Calculado para $C_{10}H_{12}N_4O$ (204,2). Found: 205,31 (M+1); Pureza analítica de HPLC: 98,5%. ^{1}H RMN (400 MHz, DMSO-d_6): δ 7,9 (d, 1H), 7,20 (bs, 2H), 6,20 (m, 1H), 4,20 (q, 2H), 2,50 (s, 3H), 1,20 (t, 3H); EM (EI) para $C_{10}H_{12}N_4O$: 205,11 (MH^+).



[00291] 2-Amino-8-etil-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona (2,70 g, 13,2 mmol) se añadió a diclorometano (100 mL), y luego se agregó lentamente bromo (0,75 mL, 1,10 equiv.). Esta mezcla de reacción se agitó durante 3 h a temperatura ambiente. Después de esto, el solvente se evaporó a casi 80% del volumen de la mezcla de reacción al vacío, y luego se añadió acetona para dar 3,54 g 2-Amino-6-bromo-8-etil-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona en forma de un sólido canela. LC/EM: Calculado para $C_{10}H_{11}BrN_4O$ (283,12). Experimental: 285,15 (M+2). Pureza analítica de HPLC: 97,7%.

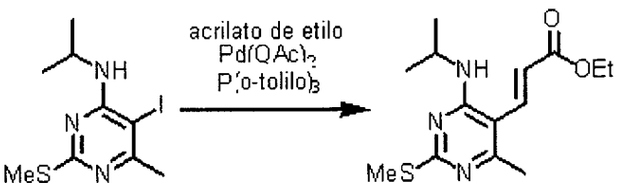
Ejemplo 3

2-Amino-4-metil-8-(metiletil)-6-(1*H*-pirazol-3-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona

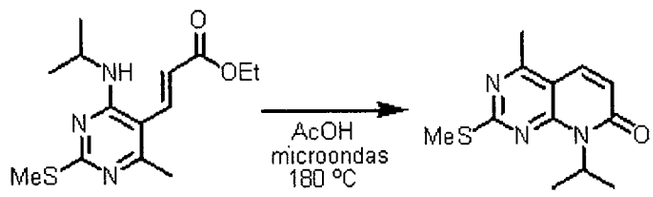


[00292] A una solución de *N*-isopropil-6-metil-2-(metiltio)pirimidin-4-amina bruta (44,6 g, 224 mmol), que se preparó usando procedimientos análogos a los descriptos en el Ejemplo 1, en 400 mL de metanol se añadió ICl (40,0 g, 246 mmol) en pequeñas porciones a temperatura ambiente. La mezcla de reacción luego se agito durante 3 h controlando con LC/EM. Después de la evaporación del solvente por evaporador giratorio, el

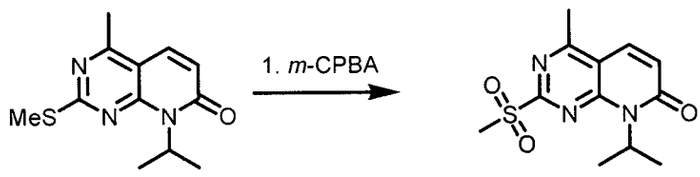
residuo se trituró con acetona para producir 5-yodo-*N*-isopropil-6-metil-2-(metiltio)pirimidin-4-amina. ^{1}H RMN (400 MHz, $CDCl_3$) δ 6,37 (br m, 1H), 4,47 (m, 1H), 2,78 (s, 3H), 2,67 (s, 3H), 1,41 (d, J = 6,4, 6H).



[00293] 5-Yodo-*N*-isopropil-6-metil-2-(metiltio)pirimidin-4-amina (8,1 g, 26,2 mmol), acrilato de etilo (5,24 g, 52,4 mmol), trietilamina (10,6 g, 105 mmol), acetato de paladio (II) (1,17 g, 5,23 mmol), y tri-o-tolil fosfina (1,59 g, 5,23 mmol) se añadieron en este orden a 10,8 mL de DMA en un tubo de presión y se selló. La mezcla de reacción se calentó a 100 °C y se dejó agitar toda la noche. La reacción se inactivó por filtración a través de una bolsa de sílice corta lavando con ACN. El solvente se evaporó y diluyó con acetato de etilo luego se extrajo con 10% de LiCl acuoso, seguido por agua y salmuera. NOTA: La extracción es necesaria para eliminar todo DMA que da resolución en la cromatografía. La muestra se purificó por cromatografía en columna de gel de sílice usando 20% de acetato de etilo/hexano como eluyente. Las fracciones deseadas se combinaron y redujeron para proporcionar 2,5 g (34 % de rendimiento) de (2E)-3-[4-(isopropilamino)-6-metil-2-(metiltio)pirimidin-5-il]acrilato de etilo en forma de aceite amarillo/anaranjado.

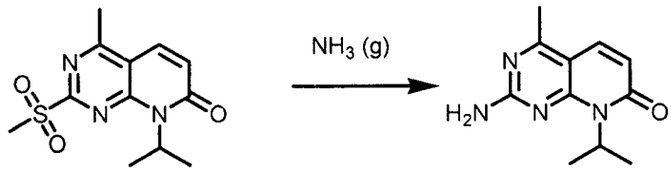


[00294] Se disolvió (E)-3-(4-(isopropilamino)-6-metil-2-(metiltio)pirimidin-5-il)acrilato de etilo (2,5 g, 8,46 mmol) en ácido acético por calentamiento suave. La muestra se colocó en un reactor de microondas durante 6 h a 180 °C, 300 W, y 200 PSI. El producto se purificó por cromatografía en columna de gel de sílice eluyendo con 20 % acetato de etilo/hexano. Las fracciones deseadas se combinaron y redujeron en 8-isopropil-4-metil-2-(metiltio)pirido[2,3-d]pirimidin-7(8*H*)-ona en forma d de un polvo amarillo (1,20 g, 57 % de rendimiento) que luego se secó a alto vacío toda la noche. ^{1}H RMN (400MHz, $CDCl_3$) δ 7,74 (d, *J* = 9,6, 1H), 6,58 (d, *J* = 9,6, 1H), 5,84 (br s, 1H), 2,65 (s, 3H), 2,63 (s, 3H), 1,63 (d, *J* = 6,8, 6H).

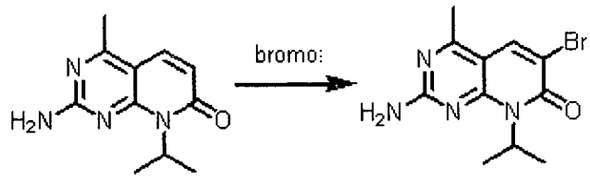


[00295] 8-Isopropil-4-metil-2-(metiltio)pirido[2,3-d]pirimidin-7(8*H*)-ona (5,38 g, 21,59 mmol) se disolvió en 100 mL DCM. A la solución agitada, se añadió m-CPBA (13,97 g, 64,78 mmol). La reacción se dejó agitar durante 2,5 h a temperatura ambiente. LCMS indicó que la reacción había terminado. La muestra se diluyó con 300 mL de DCM y 300 mL de K_2CO_3, después de la adición de una base se formó un precipitado blanco que se disolvió en exceso de H_2O. La fase orgánica se extrajo también con H_2O y

salmuera, y luego secó en Na_2CO_3. El solvente se evaporó a para proporcionar el producto 8-isopropil-4-metil-2-(metilsulfonil)pirido[2,3-d]pirimidin-7(8*H*)-ona (6,0 g, 99 % de rendimiento) en forma de un aceite amarillo claro que se usó inmediatamente en la próxima reacción.

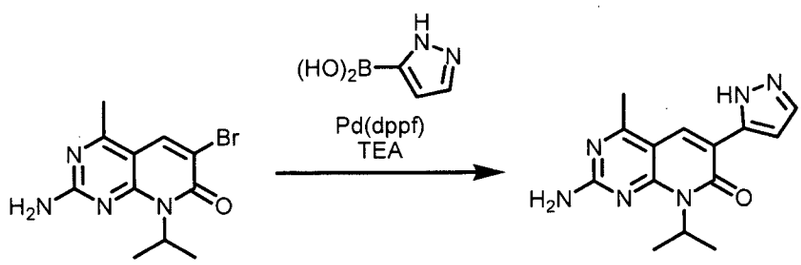


[00296] Se disolvió 8-isopropil-4-metil-2-(metilsulfonil)pirido[2,3-d]pirimidin-7(8*H*)-ona (aproximadamente 3,0 g) en 50 mL TF, en un tubo de presión de 350 mL. Mientras se agita, se burubujeó NH_3 (g) a través de la solución durante 1,5 minutes. Se observó un cambio de color desde amarillo claro a verde oliva en aproximadamente 120 segundos. El tubo se selló y agitó a temperatura ambiente toda la noche. Se formó un precipitado. La mezcla de reacción, que incluye el precipitado, se redujo a casi sequedad, se filtró y lavó con un volumen mínimo de TF frío, proporcionando 2,88 g de 2-amino-8-isopropil-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona.



[00297] A una solución de 2-amino-8-isopropil-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona (2,88 g, 13,19 mmol) disuelta en 80 mL de DCM a 0 °C, (4,21 g, 26,39 mmol) se añadió bromo. El recipiente de reacción se retiró del baño de hielo y se deja reaccionar a temperatura ambiente toda la noche. LCMS indicó la

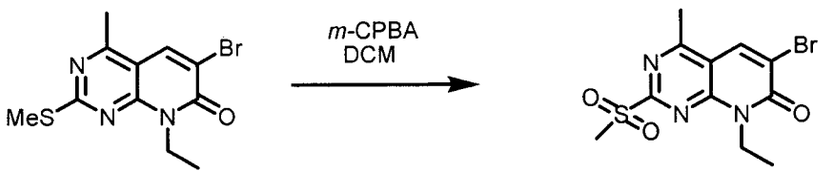
conversión completa del material inicial al producto. La muestra se evaporó para eliminar DCM y exceso de bromo. El sólido anaranjado se diluyó en acetato de etilo y se extrajo con 10% de $NaHSO_3$, H_2O, y salmuera. La fase orgánica se secó en Na_2SO_4, se filtró, y redujo a sequedad dando 2-amino-6-bromo-8-isopropil-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona en forma de polvo amarillo claro (2,2 g, 56% de rendimiento). ^1H RMN (400MHz, $CDCl_3$) δ 8,08 (s, 1H), 5,83 (m, 1H), 5,69 (br s, 2H), 2,60 (s, 3H), 1,58 (d, J = 6,8, 6H).



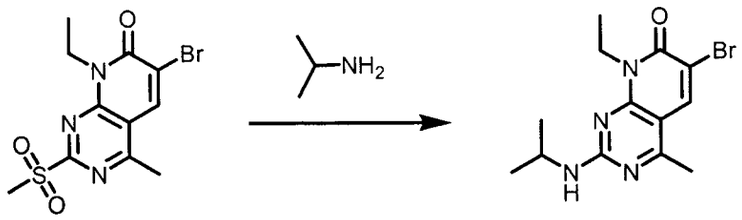
[00298] En un tubo de presión de 350 ml 2-amino-6-bromo-8-isopropil-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona (1,50 g, 5,05 mmol), ácido 1H-pirazol-3-ilborónico (1,12 g, 10,09 mmol), K_2CO_3 (336 mg, 15,1 mmol), y tetrakis(trifenilfosfina)paladio (0) (583 mg, 0,0504 mmol) se disolvieron en 50 mL de dioxano y 5 mL H_2O. El tubo se selló, se calentó a 100 °C y se deja reaccionar toda la noche. Se observó cambio de color. LCMS indicó no presencia de material inicial. La muestra se filtró a través de filtro de jeringar y se evaporó a sequedad. El compuesto se e disolvió en acetato de etilo y se trituró en hexano. Se halló que el polvo amarillo claro de 2-amino-8-isopropil-4-metil-6-(1H-pirazol-5-il)pirido[2,3-d]pirimidin-7(8*H*)-ona (195 mg, 13,7% de rendimiento) es 98% puro por HPLC. ^1H RMN (400MHz, $CDCl_3$) δ 12,97 (br s, 1H), 8,35 (s, 1H), 7,60 (br s, 1H), 7,21 (s, 2H), 6,94

(s, 1H), 5,86 (br s, 1H), 2,50 (m, 6H), 1,54 (s, 3H), EM (EI) para $C_{14}H_{16}N_6O$: 285,0 (MH^+).

Ejemplo 4



[00299] Se añadió ácido 3-cloroperbenzoico (0,565 g, 3,27 mmol) a una solución de 6-bromo-8-etil-4-metil-2-(metiltio)pirido[2,3-*d*]pirimidin-7(8*H*)-ona (0,308 g, 0,980 mmol) en diclorometano (5,0 mL) a temperatura ambiente. Después de 30 minutos, la reacción se diluyó con diclorometano (50 mL) y se lavó dos veces con $NaHCO_3$ saturado, seguido por salmuera. La fase orgánica se separó y secó en Na_2SO_4, se filtró, y concentrated in vacuo. El residuo se precipitó con acetato de etilo para proporcionar 8-etil-4-metil-2-(metilsulfonil)pirido[2,3-d]pirimidin-7(8*H*)-ona (302 mg, 89 % de rendimiento) en forma de un sólido amarillo.



[00300] A una solución agitada de (76,5 mg, 0,221 mmol) en 1,5 mL de CH_2Cl_2 se añadió isopropilamina (709,9 mg, 12,0 mmol, 54 eq.) La reacción se agitó durante 15 h a temperatura ambiente. La reacción se diluyó con CH_2Cl_2 y se extrajo con NaOH 2 N, H_2O, y salmuera. La fase orgánica se secó en Na_2SO_4, se filtró y concentró. El material bruto se purificó usando HPLC preparativa. La

liofilización del producto que contiene las fracciones proporcionó 19,9 mg (27,6 % de rendimiento) de 6-bromo-8-etil-2-(isopropilamino)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 8,08 (s, 1H), 5,30 (bs, 1H), 4,48 (bd, 2H), 4,18 (bs, 1H), 2,52 (s, 3H), 1,62 (bs, 3H), 1,29 (m, 9H), EM (EI) para $C_{13}H_{17}BrN_4O$: 325,2 (MH^+).

[00301] Usando técnicas de síntesis iguales o análogas y sustituyendo con los reactivos apropiados, se prepararon los siguientes compuestos:

Ejemplo 4b. 6-bromo-2-(*ter*-butilamino)-8-etil-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 8,08 (s, 1H), 5,47 (bs, 1H), 4,48 (m, 2H), 2,50 (s, 3H), 1,58 (bs, 3H), 1,49 (s, 9H), EM (EI) para $C_{14}H_{19}BrN_4O$: 339,2 (MH^+)

Ejemplo 4c. 6-Bromo-2-(ciclopentilamino)-8-etil-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 8,07 (s, 1H), 5,89 (bs, 1H), 4,49 (bd, 2H), 2,51 (s, 3H), 2,07 (m, 2H), 1,71 (m, 2H), 1,58 (m, 2H), 1,31 (t, 3H), EM (EI) para $C_{15}H_{19}BrN_4O$: 351,2 (MH^+)

Ejemplo 4d. 6-Bromo-2-(ciclohexilamino)-8-etil-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 8,07 (s, 1H), 5,41 (bs, 1H), 4,47 (bd, 2H), 3,84 (bs, 1H), 2,51 (s, 3H), 2,05 (d, J = 12,4 Hz, 2H), 1,77 (m, 2H), 1,64 (br m, 4H), 1,39 (m, 2H), 1,30 (m, 3H), EM (EI) para $C_{16}H_{21}BrN_4O$: 365,2 (MH^+)

Ejemplo 4e. 6-Bromo-8-etil-4-metil-2-(2-morfolinoetilamino)pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 8,08 (s, 1H), 6,22 (bs, 1H), 4,48 (q, J = 6,4 Hz, 2H), 3,74 (t, J = 4,4 Hz, 1H), 3,57 (q, J = 4,8 Hz, 3H), 2,98 (bs, 2H), 2,63 (t, J = 6,0 Hz, 2H), 2,53 (s, 3H), 1,30 (t, J = 6,8 Hz, 2H), EM (EI) para $C_{16}H_{22}BrN_5O$: 396,2 (MH^+)

Ejemplo 4f. 6-Bromo-8-etil-4-metil-2-[(3-morfolino-4-ilpropil)amino]pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 8,07 (s, 1H), 6,23 (bs, 1H), 4,47 (bs, 1H), 3,75 (m, 4H), 3,57 (m, 2H), 2,52 (m, 4H), 2,48 (m, 2H), 1,82 (m, 2H), 1,28 (s, 3H), EM (EI) para $C_{17}H_{24}BrN_5O$: 410,2 (MH^+)

Ejemplo 4g. 6-Bromo-2-{[3-(dimetilamino)propil]amino}-8-etil-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 8,08 (s, 1H), 7,26 (bs, 1H), 4,47 (m, 2H), 3,54 (m, 2H), 2,78 (t, *J* = 7,6 Hz, 2H), 2,52 (s, 3H), 2,50 (s, 3H), 2,04 (s, 3H), 2,00 (m, 2H), 1,29 (t, *J* = 7,2 Hz, 3H), EM (EI) para $C_{15}H_{22}BrN_5O$: 369,2 (MH^+)

Ejemplo 4h. 8-Etil-2-(etilamino)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 7,67 (d, *J* = 9,2 Hz, 1H), 6,39 (d, *J* = 9,2 Hz, 1H), 5,31 (bs, 1H), 2,54 (s, 3H), 4,32 (q, *J* = 6,8 Hz, 2H), 3,52 (q, *J* = 6,8 Hz, 2H), 2,53 (s, 3H), 1,15 (m, 6H); EM (EI) para $C_{12}H_{16}N_4O$: 233,2 (MH^+).

Ejemplo 4j. **6-Bromo-2-{[2-(dimetilamino)etilo]amino}-8-etil-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, DMSO-d_6): δ 8,37 (s, 1H), 7,83 (bt, *J* = 8,0 Hz, 1H), 4,34 (q, *J* = 8,0 Hz, 2H), 3,42 (q, *J* = 4,0 Hz, 2H), 2,51 (s, 3H), 2,45 (t, *J* = 4,0 Hz, 2H), 1,83 (s, 6H), 1,20 (t, *J* = 8,0 Hz, 3H); EM (EI) para $C_{14}H_{20}BrN_5O$: 354,3 (M^+).**

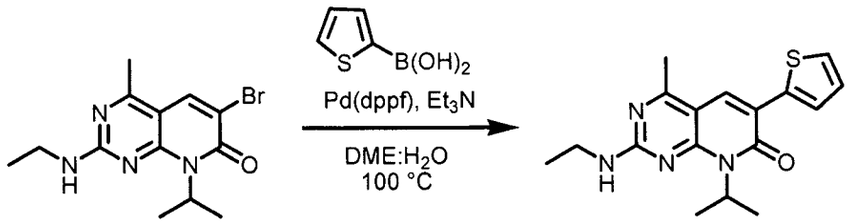
Ejemplo 4k. **6-bromo-2-(etilamino)-4-metil-8-(1-metiletil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 8,04 (s, 1H), 6,66 (bs, 1H), 5,83 (sept, *J* = 6,8 Hz, 1H), 3,54 (dq, *J* = 12,8, 7,6 Hz, 2H), 2,62 (s, 3H), 1,60 (d, *J* = 6,8 Hz, 6H), 1,34 (t, *J* = 7,2 Hz, 3H); EM (EI) para $C_{13}H_{17}BrN_4O$: 324,9 (M^+).**

Ejemplo 4m. 6-Bromo-8-etil-4-metil-2-morfoli*N*-4-ilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 8,09 (s, 1H), 4,45 (q, *J* = 6,8 Hz, 2H), 3,92 (s, 3H), 3,79 (s, 3H), 2,55 (s, 3H), 1,30 (t, *J* = 6,8 Hz, 3H); EM (EI) para $C_{14}H_{17}Br\ N_4O_2$: 355,1 ($M2H^+$).

Ejemplo 4n. **6-Bromo-8-etil-4-metil-2-[(fenilmetil)amino]pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 8,09 (s, 1H), 7,32 (m, 5H), 5,86 (bs, 1H), 4,68 (s, 2H), 4,43 (q, *J* = 7,2 Hz, 2H), 2,54 (s, 3H), 1,13 (t, *J* = 7,2 Hz, 3H); EM (EI) para $C_{17}H_{17}BrN_4O$: 375,1 ($M2H^+$).**Ejemplo 4p. **6-Bromo-8-etil-2-(etilamino)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 8,09 (s, 1H), 5,71 (bs, 1H), 4,48 (bs, 2H), 3,54 (q, *J* = 6,8 Hz, 2H), 2,53 (s, 3H), 1,16 (m, 6H); EM (EI) para $C_{12}H_{15}BrN_4O$: 311,9 (MH^+).**

Ejemplo 5

2-(Etilamino)-4-metil-8-(1-metiletil)-6-(2-tienil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona



[00302] Se añadió aducto de Pd(dppf)diclorometano (0,077 g, 0,095 mmol) a una suspensión de 6-bromo-2-(etilamino)-4-metil-8-(1-metiletil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona (0,154 g, 0,474 mmol), ácido 2-tiofenborónico (0,079 g, 0,616 mmol), y trietilamina

(165 µL, 1,19 mmol) en 10:1 DME: água (1,5 mL). La reacción se calentó a 100 °C. Después de 5 h, la reacción se enfrió a temperatura ambiente, se filtró a través de una bolsa de celite y se concentró in vacuo. El residuo se purificó en SiO_2 (3:2 hexanos: acetato de etilo) para dar 2-(etilamino)-4-metil-8-(1-metiletil)-6-(2-tienil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona (28 mg, 18 % de rendimiento) en forma de un sólido amarillo claro: ^{1}H RMN (400 MHz, $CDCl_3$): δ 8,06 (s, 1H), 7,60 (dd, *J* = 4,0, 1,2 Hz, 1H), 7,38 (dd, *J* = 5,2 , 0,8 Hz, 1H), 7,10 (dd, *J* = 4,8, 3,2 Hz, 1H), 5,93 (bsept, 1H), 5,13 (bs, 1H), 3,54 (pent, *J* = 7,2 Hz, 2H), 2,61 (s, 3H), 1,66 (d, *J* = 6,8 Hz, 6H), 1,28 (t, *J* = 7,6 Hz, 3H); EM (EI) para $C_{17}H_{20}N_4OS$: 329,0 (MH^+).

[00303] Usando técnicas de síntesis iguales o análogas y sustituyendo con los reactivos apropiados, se prepararon los siguientes compuestos:

EJEMPLO 5a. 2-(Etilamino)-6-furan-2-il-4-metil-8-(1-metiletil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHZ, $CDCL_3$): Δ 8,43 (S, 1H), 7,81 (S, 1H), 7,47 (T, *J* = 2 HZ, 1H), 6,75 (DD, *J* = 2,0 , 0,8 HZ, 1H), 5,92 (BSEPT, 1H), 5,25 (BS, 1H), 3,53 (DQ, *J* = 12,5, 7,6 HZ, 2H), 2,60 (S, 3H), 1,65 (D, *J* = 6,8 HZ, 6H), 1,29 (T, *J* = 7,2 HZ, 3H); EM (EI) PARA $C_{17}H_{20}N_4O_2$: 313,1 (MH^+).

Ejemplo 5b. **2-(Etilamino)-4-metil-8-(1-metiletil)-6-(1*H*-pirazol-3-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 8,08 (s, 1H), 7,61 (d, *J* = 2,0 Hz, 1H), 6,65 (bs, 1H), 5,93 (bs, 1H), 5,44 (bs, 1H), 3,55 (dq, *J* = 12,8, 6,4 Hz, 2H), 2,62 (s, 3H), 1,66 (d, *J* = 6,4 Hz, 6H), 1,30 (t, *J* = 7,6 Hz, 3H); EM (EI) para $C_{16}H_{20}N_6O$: 313,3 (MH^+).**

Ejemplo 5c. **2-(Etilamino)-4-metil-6-(1*H*-pirazol-3-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, MeOH-d_4:TFA-*d*, 10:1): δ 8,59 (s, 1H), 8,07 (s, 1H), 7,30 (s, 1H), 3,59 (q, *J* = 8,0 Hz, 2H), 2,88 (s, 3H), 1,28 (t, *J* = 8,0 Hz, 3H); EM (EI) para $C_{13}H_{14}N_6O$: 271,0 (MH^+).**

Ejemplo 5e. 8-Ciclopentil-2-(etilamino)-4-metil-6-(1*H*-pirazol-3-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400MHz, DMSO-d_6): δ 8,32 (s, 1H), 7,80 (s, 1H), 7,59 (s, 1H), 6,916 (s, 1H), 5,95 (m, 1H), 2,35 (bs, 2H), 1,95 (bs, 2H), 1,73 (bs, 2H), 1,61 (bs, 2H), 1,12 (t, *J* = 6,8 Hz, 3H), EM (EI) para $C_{18H22}N_6O$: 339,1 (MH^+)

Ejemplo 5f. 6-(2,4-Difluorofenil)-8-etil-2-(etilamino)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 7,78 (d, 2H), 7,52 (m, 1H), 6,85 (m, 2H), 5,38 (bs, 1H), 4,48 (m, 2H), 3,56 (m, 2H), 2,57 (s, 3H), 1,39 (m, 6H); EM (EI) para $C_{18H18}F_2N_4O$: 345,1 (MH^+).

Ejemplo 5g. 6-(3-Cloro-4-fluorofenil)-8-etil-2-(etilamino)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 7,79 (s, 2H), 7,57 (m, 1H), 7,19 (m, 1H), 5,41 (bs, 1H), 4,45 (bs, 2H), 3,58 (m, 2H), 2,59 (m, 3H), 1,36 (m, 6H); EM (EI) para $C_{18H18}ClFN_4O$: 361,0 (MH^+).

Ejemplo 5h. 6-(2,4-Diclorofenil)-8-etil-2-(etilamino)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 7,75 (s, 1H), 7,42 (d, 1H), 7,38 (m, 2H), 5,38 (bs, 1H), 4,42 (m, 2H), 3,59 (m, 2H), 2,56 (s, 3H), 1,24 (m, 6H); EM (EI) para $C_{18H18}Cl_2N_4O$: 377,0 (M^+), 379,0 (M+2)

Ejemplo 5i. 6-(3,4-Difluorofenil)-8-etil-2-(etilamino)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 7,79 (s, 1H), 7,59 (m, 1H), 7,39 (m, 1H), 7,18 (m, 1H), 5,39 (bs, 1H), 4,46 (m, 2H), 3,58 (m, 2H), 2,59

(s, 3H), 1,27 (m, 6H); EM (EI) para $C_{18}H_{18}F_2N_4O$: 345,1 (MH^+).

Ejemplo 5j. 8-Etil-2-(etilamino)-4-metil-6-[4-(feniloxi)fenilo]pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^1H RMN (400 MHz, $CDCl_3$): δ 7,78 (s, 1H), 7,63 (d, 2H), 7,39 (t, 2H), 7,16 (t, 1H), 7,04 (d, 4H), 5,38 (bs, 1H), 4,47 (m, 2H), 3,57 (m, 2H), 2,59 (s, 3H), 1,26 (m, 6H); EM (EI) para $C_{24}H_{24}N_4O_2$: 401,1 (MH^+).

Ejemplo 5k. 8-Etil-2-(etilamino)-4-metil-6-naftale*N*-1-ilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^1H RMN (400 MHz, $CDCl_3$): δ 7,84 (d, 2H), 7,80 (s, 1H), 7,73 (d, 1H), 7,48 (m, 4H), 539 (bs, 1H), 4,55 (bs, 2H), 3,59 (m, 2H), 2,54 (s, 3H), 1,37 (m, 6H); EM (EI) para $C_{22}H_{22}N_4O$: 359,1 (MH^+).

Ejemplo 5m. 8-Etil-2-(etilamino)-4-metil-6-[3-(trifluorometil)fenilo]pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^1H RMN (400 MHz, $CDCl_3$): δ 7,82 (m, 3H), 7,56 (m, 2H), 5,59 (bs, 1H), 4,47 (d, 2H), 3,51 (m, 2H), 2,58 (s, 3H), 1,30 (m, 6H); EM (EI) para $C_{19}H_{19}F_3N_4O$: 377,1 (MH^+).

Ejemplo 5n. 8-Etil-2-(etilamino)-4-metil-6-(2-tienil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^1H RMN (400 MHz, $CDCl_3$): δ 8,09 (s, 1H), 7,64 (dd, *J* = 3,60, 1,20 Hz, 1H), 7,38 (dd, *J* = 5,20, 1,20 Hz, 1H), 7,10 (dd, *J* = 4,78, 3,60 Hz, 2H), 3,54 (qn, 2H), 2,62 (s, 3H), 1,30 (m, 6H); EM (EI) para $C_{16}H_{18}N_4OS$: 315,0 (MH^+).

Ejemplo 5p. 6-(3-Clorofenil)-8-etil-2-(etilamino)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^1H RMN (400 MHz, $CDCl_3$): δ 7,78 (s, 1H), 7,65 (s, 1H), 7,56 (dd, 1H), 7,34 (m, 2H), 5,39 (bs, 1H), 4,43 (m, 2H0, 3,57 (m, 2H), 2,59 (s, 3H), 1,32 (m, 6H); EM (EI) para $C_{18}H_{19}ClN_4O$: 343,0 (MH^+).

Ejemplo 5q. 6-(4-Clorofenil)-8-etil-2-(etilamino)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^1H RMN (400 MHz, $CDCl_3$): δ 7,77 (s, 1H), 7,62 (dd, 2H0, 7,40 (dd, 2H),

5,38 (bs, 1H), 4,47 (m, 2H), 3,58 (m, 2H), 2,59 (s, 3H), 1,39 (m, 6H); EM (EI) para $C_{18}H_{19}ClN_4O$: 343,0 (MH^+).

Ejemplo 5r. 8-Etil-2-(etilamino)-4-metil-6-[4-(trifluorometil)fenilo]pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^1H RMN (400 MHz, $CDCl_3$): δ 7,80 (m, 3H), 7,63 (dd, 2H), 5,39 (bs, 1H), 4,51 (m, 2H), 3,58 (m, 2H), 2,58 (s, 3H), 1,33 (m, 6H); EM (EI) para $C_{19}H_{19}F_3N_4O$: 343,0 (MH^+).

Ejemplo 5s. 8-Etil-2-(etilamino)-4-metil-6-(3-tienil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^1H RMN (400 MHz, $CDCl_3$): δ 8,11 (dd, *J* = 2,10, 0,90 Hz, 1H), 7,94 (s, 1H), 7,52 (dd, *J* = 3,90, 1,20 Hz, 1H), 7,35 (qr, 1H), 5,33 (bs, 1H), 4,52 (qr, 2H), 3,54 (m, 2H), 2,58 (s, 3H), 1,28 (m, 6H); EM (EI) para $C_{16}H_{18}N_4OS$: 315,0 (MH^+).

Ejemplo 5t. 8-Etil-2-(etilamino)-4-metil-6-(4-metil-2-tienil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^1H RMN (400 MHz, $CDCl_3$): δ 8,01 (s, 1H), 7,52 (s, 1H), 6,93 (s, 1H), 5,38 (bs, 1H), 4,58 (qr, 2H), 3,57 (m, 2H), 2,61 (s, 1H), 2,33 (s, 1H), 1,60 (s, 3H); EM (EI) para $C_{17}H_{20}N_4OS$: 329,0 (MH^+).

Ejemplo 5u. 8-Etil-2-(etilamino)-4-metil-6-(4-metil-3-tienil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^1H RMN (400 MHz, $CDCl_3$): δ 7,69 (s, 1H), 7,38 (d, 1H), 6,99 (m, 1H), 5,35 (bs, 1H), 4,51 (qr, 2H), 3,57 (m, 2H), 2,58 (s, 3H), 2,22 (s, 3H), 1,32 (m, 6H); EM (EI) para $C_{17}H_{20}N_4OS$: 329,0 (MH^+).

Ejemplo 5v. 1,1-Dimetiletil 2-[8-etil-2-(etilamino)-4-metil-7-oxo-7,8-dihidropirido[2,3-*d*]pirimidin-6-il]-1*H*-pirrol-1-carboxilate: ^1H RMN (400 MHz, $CDCl_3$): δ 7,65 (s, 1H), 7,38 (d, 1H), 6,22 (m, 2H), 5,29 (bs, 1H), 4,41 (m, 2H), 3,57 (m, 2H), 2,56 (s, 3H), 1,41 (s, 9H), 1,22 (m, 6H); EM (EI) para $C_{21}H_{27}N_5O_3$: 398,0 (MH^+).

Ejemplo 5w. 8-Etil-2-(etilamino)-4-metil-6-(1H-pirrol-2-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^1H RMN (400 MHz,

$CDCl_3$): δ 11,1 (bs, 1H), 7,99 (s, 1H), 6,85 (d, 1H), 6,62 (d, 1H), 6,29 (d, 1H), 5,28 (bs, 1H), 4,57 (m, 2H), 3,56 (m, 2H), 2,61 (s, 3H), 1,35 (m, 6H); EM (EI) para $C_{16}H_{19}N_5O$: 298,1 (MH^+).

Ejemplo 5x. 8-Etil-2-(etilamino)-6-furan-3-il-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^1H RMN (400 MHz, $CDCl_3$): δ 8,42 (s, 1H), 7,83 (s, 1H), 7,43 (s, 1H),6,76 (s, 1H), 5,37 (bs, 1H), 4,52 (m, 2H), 3,58 (m, 2H), 2,61 (s, 3H), 1,30 (m, 6H); EM (EI) para $C_{16}H_{18}N_4O_2$: 299,1 (MH^+).

Ejemplo 5y. 8-Etil-2-(etilamino)-4-metil-6-[1-(fenilmetil)-1*H*-pirazol-4-il]pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^1H RMN (400 MHz, $CDCl_3$): δ 8,39 (s, 1H), 7,98 (d, 1H), 7,96 (d, 1H), 7,35 (m, 5H), 5,39 (s, 2H), 5,35 (bs, 1H), 4,52 (m, 2H), 3,58 (m, 2H), 2,62 (s, 3H), 1,35 (m, 6H) ; EM (EI) para $C_{22}H_{24}N_6O$: 389,3 (MH^+).

Ejemplo 5z. 6-(3,5-Dimetilisoxazol-4-il)-8-etil-2-(etilamino)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^1H RMN (400 MHz, $CDCl_3$): δ 7,59 (s, 1H), 7,24 (s, 1H), 5,43 (bs, 1H), 4,47 (bs, 2H), 3,56 (m, 2H), 2,58 (s, 3H), 2,39 (s, 3H), 2,25 (s, 3H), 1,29 (m, 6H) ; EM (EI) para $C_{17}H_{21}N_5O_2$: 328,1 (MH^+).

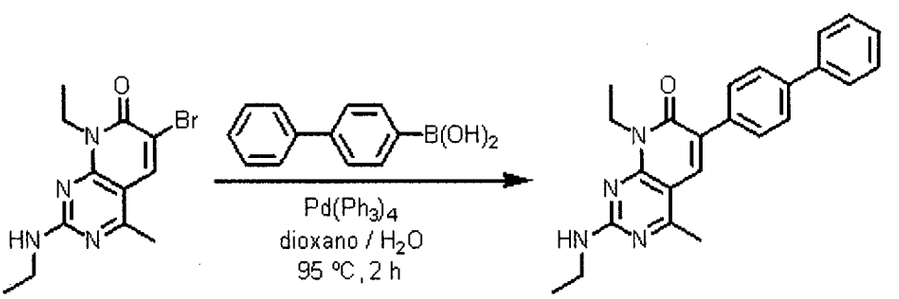
Ejemplo 5aa. 8-Etil-2-(etilamino)-4-metil-6-(1*H*-pirazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^1H RMN (400 MHz, $CDCl_3$): δ 8,11 (s, 1H), 7,62 (s, 1H), 6,65 (d, 1H), 5,43 (bs, 1H), 4,58 (m, 2H), 3,59 (m, 2H), 2,62 (s, 3H), 1,38 (m, 6H); EM (EI) para $C_{15}H_{18}N_6O$: 299,1 (MH^+).

Ejemplo 5bb. 8-Etil-4-metil-6-(1*H*-pirazol-5-il)-2-[(2,2,2-trifluoroetil)amino]pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^1H RMN (400 MHz, $CDCl_3$): δ 8,18 (s, 1H), 7,63 (d, 1H), 6,73 (d, 1H), 5,62 (bs, 1H), 4,58 (m, 2H), 4,30 (m, 2H), 2,74 (s, 3H), 1,35 (t, 3H); EM (EI) para $C_{15}H_{15}F_3N_6O$: 353,0 (MH^+).

Ejemplo 5cc. 8-Etil-2-(etilamino)-4-metil-6-(1,3-tiazol-2-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 8,87 (s, 1H), 7,98 (s, 1H), 7,43 (s, 1H), 7,22 (s, 1H), 5,56 (bs, 1H), 4,58 (bs, 2H), 2,72 (s, 3H0, 1,36 (m, 6H); EM (EI) para $C_{15}H_{17}N_5OS$: 316,0 (MH^+).

Ejemplo 6

6-Bifenil-4-il-8-etil-2-(etilamino)-4-metilpirido[2,3-*d*]piridimidi*N*-7(8*H*)-ona



[00304] 2-Etilamino-6-bromo-8-etil-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona (60 mg, 0,194 mmol), K_2CO_3 (81,0 mg, 3,0 equiv.), ácido bifenilborónico (17,8 mg, 1,5 equiv.) y $Pd(PF_3)_4$ (10 mol %, 225 mg) se añadieron a dioxano / H_2O (10 mL / 3 mL). La reacción se calentó a 95 °C y se agitó durante 2 h. La mezcla de reacción se dividió entre las fases orgánicas y acuosas con acetato de etilo (20 mL) y H_2O (10 mL) y NaCl acuoso saturado (5 mL). La fase orgánica se secó en sulfato de magnesio anhidro, se filtró y evaporó para dar 6-Bifenil-4-il-8-etil-2-(etilamino)-4-metilpirido[2,3-*d*]piridimidi*N*-7(8*H*)-ona (48,42 mg, 65 % de rendimiento): ^{1}H RMN (400 MHz, $CDCl_3$): δ 7,81 (s, 1H), 7,74 (m, 2H), 7,60 (m, 4H), 7,42 (m, 2H), 7,38 (m, 1H), 4,50 (q, 2H), 3,60 (q, 2H), 2,60 (s, 3H), 1,30 (m, 6H); EM (EI) para $C_{24}H_{24}N_4O$: 385,1 (MH^+).

[00305] Usando técnicas de síntesis iguales o análogas y sustituyendo con los reactivos apropiados, se prepararon los siguientes compuestos:

Ejemplo 6a. 8-Etil-2-(etilamino)-4-metil-6-[4-(metiloxi)fenilo]pirido[2,3-*d*]piridimidi*N*-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 7,81 (s, 1H), 7,60 (d, 2H), 6,96 (d, 2H), 4,50 (q, 2H), 3,82 (s, 3H), 3,58 (q, 2H), 2,58 (s, 3H), 1,30 (m, 6H); EM (EI) para $C_{19}H_{22}N_4O_2$: 339,1 (MH^+).

Ejemplo 6b. 8-Etil-2-(etilamino)-4-metil-6-[2-(metiloxi)fenilo]pirido[2,3-*d*]piridimidi*N*-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 7,81 (s, 1H), 7,60 (d, 2H), 6,96 (d, 2H), 4,50 (q, 2H), 3,80 (s, 3H), 3,58 (q, 2H), 2,50 (s, 3H), 1,30 (m, 6H); EM (EI) para $C_{19}H_{22}N_4O_2$: 339,1 (MH^+).

Ejemplo 6c. 6-[2,4-Bis(metiloxi)fenilo]-8-etil-2-(etilamino)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 7,70 (s, 1H), 7,30 (s, 1H), 6,60 (m, 2H), 4,50 (q, 2H), 3,82 (s, 3H), 3,80 (s, 3H), 3,45 (q, 2H), 2,50 (s, 3H), 1,30 (m, 6H); EM (EI) para $C_{20}H_{24}N_4O_3$: 369,1 (MH^+).

Ejemplo 6d. 8-Etil-2-(etilamino)-4-metil-6-[3-(metiloxi)fenilo]pirido[2,3-*d*]piridimidi*N*-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 7,81 (s, 1H), 7,60 (d, 2H), 6,96 (d, 2H), 4,50 (q, 2H), 3,80 (s, 3H), 3,58 (q, 2H), 2,50 (s, 3H), 1,30 (m, 6H); EM (EI) para $C_{19}H_{22}N_4O_2$: 339,1 (MH^+).

Ejemplo 6e. 8-(5-Cloro-2-tienil)-8-etil-2-(etilamino)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 8,00 (s, 1H), 7,38 (d, 2H), 6,96 (d, 2H), 4,50 (q, 2H), 3,58 (q, 2H), 2,60 (s, 3H), 1,30 (m, 6H); EM (EI) para $C_{16}H_{17}ClN_4OS$: 349,2 (MH^+).

Ejemplo 6f. 8-Etil-2-(etilamino)-4-metil-6-pirimidin-5-ilpirido[2,3-*d*]piridimidi*N*-7(8*H*)-ona: ^{1}H RMN (400 MHz, DMSO-d_6): δ 9,19 (s, 1H), 9,16 (s, 1H), 8,23 (s, 1H), 8,00 (m, 1H), 4,38 (q, 2H), 3,40 (q, 2H), 2,50 (s, 3H), 1,30 (m, 6H); EM (EI) para $C_{16}H_{18}N_6O$: 311,3 (MH^+).

Ejemplo 6g. 8-Etil-2-(etilamino)-6-(3-fluoropiridi*N*-4-il)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 8,58 (s, 1H), 8,42 (d, 1H), 7,98 (s, 1H), 7,60 (t, 1H), 4,50 (q, 2H), 3,58 (q, 2H), 2,60 (s, 3H), 1,30 (m, 6H); EM (EI) para $C_{17}H_{18}FN_5O$: 328,3 (MH^+).

Ejemplo 6h. 8-Etil-2-(etilamino)-6-(1*H*-indole-6-il)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, DMSO-d_6): δ 11,2 (s, 1H), 7,90 (s, 1H), 7,88 (s, 1H), 7,42 (s, 2H), 7,38 (s, 1H), 6,50 (s, 1H), 4,40 (q, 2H), 3,40 (q, 2H), 2,42 (s, 3H), 1,30 (m, 6H); EM (EI) para $C_{20}H_{21}N_5O$: 348,3 (MH^+).

Ejemplo 6i. 8-Etil-2-(etilamino)-4-metil-6-(5-fenilo-2-tienil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, DMSO-d_6): δ 8,40 (s, 1H), 7,81 (d, 1H), 7,70 (d, 2H), 7,50 (d, 1H), 7,42 (m, 2H), 7,30 (m, 1H), 4,40 (q, 2H), 3,40 (q, 2H), 2,42 (s, 3H), 1,30 (m, 6H); EM (EI) para $C_{22}H_{22}N_4OS$: 391,3 (MH^+).

Ejemplo 6j. **8-Etil-2-(etilamino)-4-metil-6-fenilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 7,78 (s, 1H), 7,46 (m, 5H), 5,41 (bs, 1H), 4,50 (q, *J* = 6,8 Hz, 2H), 3,60 (m, 2H), 2,57 (s, 3H), 1,30 (m, 6H); EM (EI) para C_{18H20} N_4O: 309,2 (MH^+).**

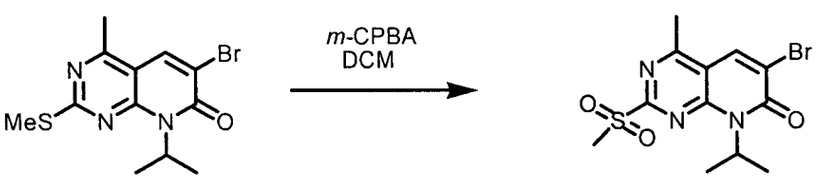
Ejemplo 6k. **8-Etil-2-(etilamino)-6-(3-fluorofenil)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 7,79 (s, 1H), 7,46-7,02 (m, 4H), 5,41 (bs, 1H), 4,51 (q, *J* = 6,4 Hz, 2H), 3,55 (q, *J* = 6,8 Hz, 2H), 2,58**

(s, 3H), 1,34 (t, *J* = 6,80 Hz, 3H), 1,29 (t, *J* = 6,40 Hz, 3H); EM (EI) para $C_{18}H_{19}FN_4O$: 327,3 (MH^+).

Ejemplo 6m. **8-etil-2-(etilamino)-6-(2-fluorofenil)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^1H RMN (400 MHz, $CDCl_3$): δ 7,80 (s, 1H), 7,52-7,12 (m, 4H), 5,33 (bs, 1H), 4,49 (q, *J* = 6,8 Hz, 2H), 3,53 (q, *J* = 7,2 Hz, 2H), 2,55 (s, 3H), 1,34 (t, *J* = 7,20 Hz, 3H), 1,28 (t, *J* = 6,80 Hz, 3H); EM (EI) para $C_{18}H_{19}FN_4O$: 327,3 (MH^+).**

Ejemplo 6n. **8-etil-2-(etilamino)-6-(4-fluorofenil)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^1H RMN (400 MHz, $CDCl_3$): δ 7,75 (s, 1H), 7,66-7,08 (m, 4H), 5,30 (bs, 1H), 4,52 (q, *J* = 6,4 Hz, 2H), 3,54 (q, *J* = 6,8 Hz, 2H), 2,58 (s, 3H), 1,34 (t, *J* = 6,80 Hz, 3H), 1,29 (t, *J* = 6,40 Hz, 3H); EM (EI) para $C_{18}H_{19}FN_4O$: 327,3 (MH^+).**

Intermediario 2

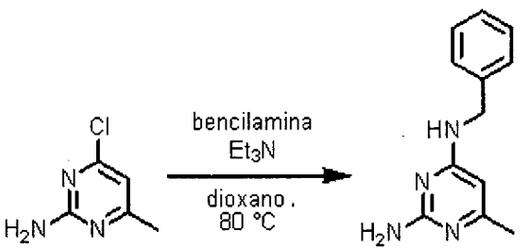


[00306] Se añadió ácido 3-cloroperbenzoico (1,78 g, 10,4 mmol) a una solución de 6-bromo-4-metil-8-(1-metiletil)-2-(metiltio)pirido[2,3-*d*]pirimidin-7(8*H*)-ona (1,33 g, 4,14 mmol), preparada usando procedimientos similares a los descriptos en el Ejemplo 1, en diclorometano (30,0 mL) a temperatura ambiente. Después de 1, la reacción se diluyó con diclorometano (50 mL) y se lavó dos veces con $NaHCO_3$ saturado, seguido por salmuera. La fase orgánica se separó y secó en Na_2SO_4, se filtró, y se concentró in

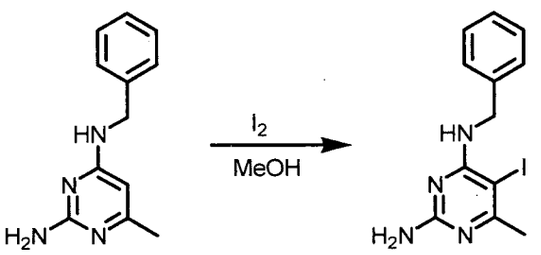
vacuo. El residuo se precipitó con acetato de etilo/hexanos para proporcionar la correspondiente sulfona (1,31 g, 93 % de rendimiento) en forma de un s´olido blancuzco.

Ejemplo 8

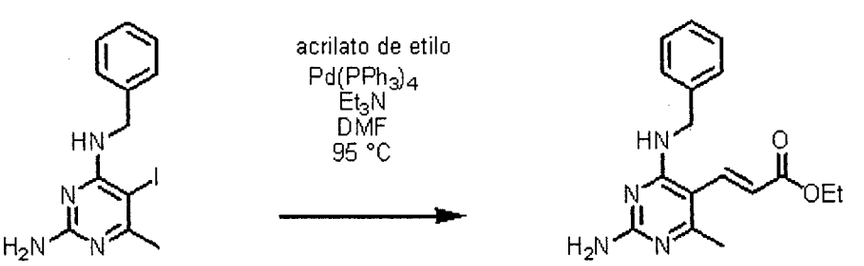
2-Amino-4-metil-8-(fenilmetil)-6-(1*H*-pirazol-3-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona



[00307] Se añadió trietilamina (3,4 mL, 24,6 mmol)a una suspensión de 2-amino-4-cloro-6-metilpirimidina (Aldrich, 1,77 g, 12,3 mmol) y bencilamina (1,98 g, 18,5 mmol) en dioxano anhidro (20 mL). La reacción se calentó a 80 °C y se dejó corree durante 12 h. Después de enfriar a temperatura ambiente, se formó un precipitado blanco que se recolectó por filtración al vacío. El sólido se recristalizó en acetona: hexanos para proporcionar N^4-benzil-6-metilpirimidin-2,4-diamina (2,33 g, 89 % de rendimiento) en forma un de un sólido blanco.

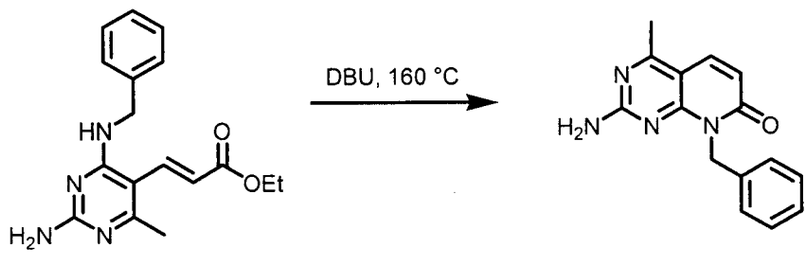


[00308] Se añadió yodo (3,04 g, 12,0 mmol) a una solución de N^4-bencil-6-metilpirimidin-2,4-diamina (2,33 g, 10,9 mmol) en s MeOH anhidro (50 mL) a 0 °C. La reacción se dejó calentar a temperatura ambiente toda la noche. Después de 12 horas, se añadieron 0,5 equiv adicionales de yodo, y la reacción se calentó a 50 °C. Después de cuatro horas, la reacción se enfrió a temperatura ambiente y se concentró in vacuo. El residuo se diluyó con acetato de etilo (200 mL) y lavó con 10% $NaHSO_3$ (200 mL). La fase acuosa se separó y lavó una vez más con acetato de etilo (200 mL). Las fases orgánicas se combinaron, lavaron con salmuera, separaron y se secaron en Na_2SO_4, El filtrado se concentró in vacuo para proporcionar el producto N^4-benzil-5-yodo-6-metilpirimidin-2,4-diamina (3,14 g, 85 % de rendimiento).

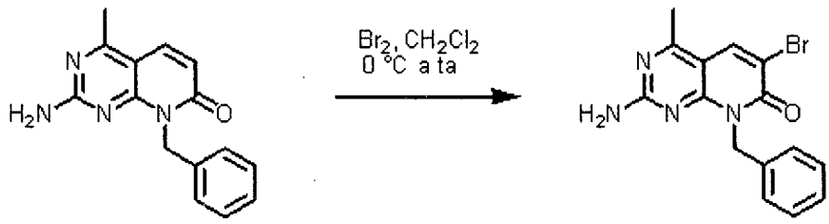


[00309] Se añadió trietilamina (7,60 mL, 54,5 mmol) a una suspensión de N^4-benzil-5-yodo-6-metilpirimidin-2,4-diamina (3,14 g, 10,9 mmol), acrilato de etilo (3,55 mL, 32,7 mmol) y $Pd(PF_3)_4$ (629 mg, 0,545 mmol) en DMF anhidro (20 mL). La reacción se calentó a 95 °C bajo nitrógeno. Después de 24 h, la reacción se dejó enfriar a temperatura ambiente y se concentró in

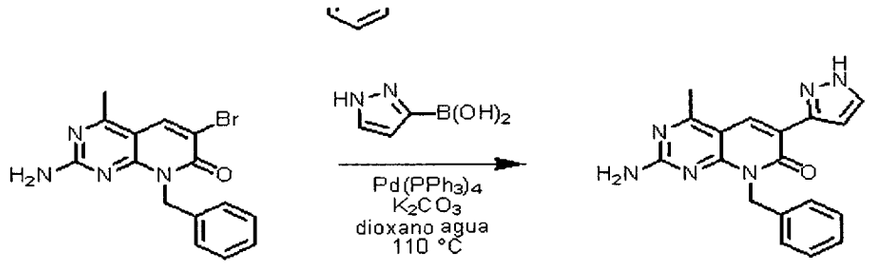
vacuo. El residuo se vertió en a 10% solución de LiCl y se lavó con acetato de etilo (100 mL). La fase orgánica se separó y lavó con salmuera, se separó y secó en Na_2SO_4. El filtrado se concentró in vacuo y se purificó en SiO_2 (3:2 cloruro de metileno: acetato de etilo) para proporcionar (*E*)-etil-3-(2-amino-4-(benzilamino)-6-metilpirimidin-5-il)acrilato (0,954 g, 28 % de rendimiento) en forma de sólido amarillo claro.



[00310] 2-amino-4-metil-8-(fenilmetil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona Diazabiciclo[5,4,0]undec-7-en (DBU) (1,83 mL, 12,2 mmol) se añadió a n matraz cargado con (*E*)-etil-3-(2-amino-4-(benzilamino)-6-metilpirimidin-5-il)acrilato (0,954 g, 3,05 mmol) y la reacción se sometió a reflujo a 160 °C bajo atmósfera de nitrógeno. Después de 20 horas, la reacción se enfrió a temperatura ambiente y se concentró in vacuo. La purificación en SiO_2 (1:1 cloruro de metileno: acetato de etilo) proporcionó el producto (0,508 g, 62 % de rendimiento) en forma de sólido blancuzco.



[00311] Se añadió bromo (72 µL, 1,40 mmol) a una suspensión de 2-amino-4-metil-8-(fenilmetil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona (0,340 g, 1,27 mmol) en cloruro de metileno (20 mL) a 0 °C. La reacción se dejó calentar a temperatura ambiente durante una hora y el precipitado resultante se recolectó por filtración al vacío para proporcionar 2-amino-6-bromo-4-metil-(8-fenilmetil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona (0,435 g, 99 % de rendimiento) después del secado. El sólido amarillo se usó en la etapa siguiente sin purificación adicional.

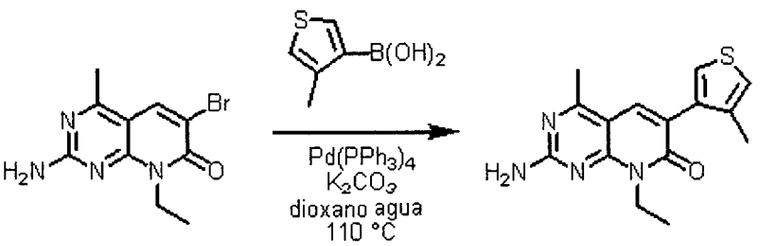


[00312] Una solución de dioxano y agua 10:1 (11 mL) se añadió a un matraz cargado con 2-amino-6-bromo-4-metil-(8-fenilmetil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona (0,435 g, 1,27 mmol), ácido 1*H*-pirazol-5-borónico (0,284 g, 2,54 mmol), $Pd(PF_3)_4$ (0,073 mg, 0,063 mmol), y K_2CO_3 (0,527 g, 3,81 mmol). El matraz se lavó con nitrógeno y estaba equipado con un condensador de reflujo y se calentó a 110 °C. Después de 12 h la reacción se enfrió a temperatura ambiente y se diluyó con acetato de etilo (100 mL) y se lavó con agua. La

fase acuosa se acidificó a pH 1,0 y se lavó con acetato de etilo (100 mL). Las fases orgánicas se combinaron y lavaron con salmuera, se separaron y secaron en Na_2SO_4, se filtraron y se concentraron in vacuo. El residuo se precipitó con acetato de etilo para dar 2-Amino-4-metil-8-(fenilmetil)-6-(1*H*-pirazol-3-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona (0,062 g, 15 % de rendimiento) as a iellow solid: ^{1}H RMN (400 MHz, DMSO-d_6): δ 13,10 (bs, 1H), 12,93 (bs, 1H), 8,47 (s, 1H), 7,76 (bs, 1H), 7,51 (bs, 1H), 7,28 (m, 5H), 6,97 (s, 1H), 5,55 (s, 2H), 2,55 (bs, 3H); EM (EI) para $C_{18}H_{16}N_6O$: 333,1 (MH^+).

Ejemplo 9

2-Amino-8-etil-4-metil-6-(4-metil-3-tienil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona



[00313] Una solución de dioxano y agua 3:1 (4 mL) se añadió a un matraz cargado con 2-amino-6-bromo-8-etil-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona (0,140 g, 0,495 mmol) del anterior, ácido 4-metiltiofeno-3-borónico (0,140 g, 0,989 mmol), $Pd(PF_3)_4$ (0,057 mg, 0,050 mmol), y K_2CO_3 (0,205 g, 1,48 mmol). El matraz se lavó con nitrógeno y estaba equipado con un condensador de reflujo y se calentó a 100 °C. Después

de 12 horas la reacción se enfrió a temperatura ambiente y se diluyó con acetato de etilo (70 mL) y lavó con agua. La fase acuosa se separó y lavó con una cantidad adicional de acetato de etilo (70 mL). Las fases orgánicas se combinaron y lavaron con salmuera, se separaron y secaron en Na_2SO_4, se filtraron y se concentraron in vacuo. El residuo se purificó en SiO_2 (1:1 cloruro de metileno: acetato de etilo) para dar 2-Amino-8-etil-4-metil-6-(4-metil-3-tienil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona (0,081 g, 55 % de rendimiento) en forma de sólido blancuzco: ^{1}H RMN (400 MHz, DMSO-d_6): δ 7,84 (s, 1H), 7,46 (d, *J* = 4,0 Hz, 1H), 7,19 (m, 3H), 4,32 (q, *J* = 8,0 Hz, 2H), 2,52 (s, 3H), 2,11 (bs, 3H), 1,19 (t, *J* = 8,0 Hz, 3H); EM (EI) para $C_{15}H_{16}N_4OS$: 301,1 (MH^+).

[00314] Usando técnicas de síntesis iguales o análogas y sustituyendo con los reactivos apropiados, se prepararon los siguientes compuestos:

Ejemplo 9a. **2-Amino-8-etil-4-metil-6-(3-tienil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 8,11 (dd, *J* = 2,8, 1,2 Hz, 1H), 7,95 (s, 1H), 7,51 (dd, *J* = 5,2, 1,2 Hz, 1H), 7,37 (dd, *J* = 4,8, 3,2 Hz, 1H), 5,21, (bs, 2H), 4,48 (q, *J* = 6,8 Hz, 2H), 2,63 (s, 3H), 1,32 (t, *J* = 7,2 Hz, 3H); EM (EI) para $C_{14}H_{14}N_4OS$: 287,0 (MH^+).**

Ejemplo 9b. 2-Amino-8-etil-6-furan-3-il-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 8,47 (bs, 1H), 7,85 (s, 1H), 7,49 (t, *J* = 1,6 Hz, 1H), 6,77 (dd, *J* = 2,0, 0,8 Hz, 1H), 5,19, (bs, 2H), 4,48 (q, *J* = 6,8 Hz, 2H), 2,64 (s, 3H), 1,31 (t, *J* = 7,2 Hz, 3H); EM (EI) para $C_{14}H_{14}N_4O_2$: 271,1 (MH^+).

Ejemplo 9c. 2-Amino-6-(3,5-dimetilisoxazol-4-il)-8-etil-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 7,62 (s, 1H), 5,27, (bs, 2H), 4,44 (q, *J* = 7,2 Hz, 2H), 2,59 (s, 3H), 2,38 (s, 3H), 2,25 (s, 3H), 1,31 (t, *J* = 6,8 Hz, 3H); EM (EI) para $C_{15}H_{17}N_5O_2$: 300,1 (MH^+).

Ejemplo 9d. 2-Amino-8-etil-6-isoxazol-4-il-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 9,36 (s, 1H), 8,71 (s, 1H), 7,91 (s, 1H), 5,30, (bs, 2H), 4,48 (q, *J* = 7,2 Hz, 2H), 2,67 (s, 3H), 1,32 (t, *J* = 6,8 Hz, 3H); EM (EI) para $C_{13}H_{13}N_5O_2$: 272,0 (MH^+).

Ejemplo 9e. 2-Amino-8-etil-6-furan-2-il-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 8,19 (s, 1H), 7,48 (d, *J* = 0,8 Hz, 1H), 7,37 (d, *J* = 3,6 Hz, 1H), 6,53 (dd, *J* = 3,6, 2,0 Hz 1H), 5,21, (bs, 2H), 4,48 (q, *J* = 7,2 Hz, 2H), 2,66 (s, 3H), 1,32 (t, *J* = 6,8 Hz, 3H); EM (EI) para $C_{14}H_{14}N_4O_2$: 271,0 (MH^+).

Ejemplo 9f. 5-(2-Amino-8-etil-4-metil-7-oxo-7,8-dihidropirido[2,3-*d*]pirimidin-6-il)tiofeno-2-carbonitrilo: ^{1}H RMN (400 MHz, $CDCl_3$): δ 8,24 (s, 1H), 7,61 (d, *J* = 4,4 Hz, 1H), 7,55 (d, *J* = 4,4 Hz, 1H), 5,33, (bs, 2H), 4,48 (q, *J* = 7,2 Hz, 2H), 2,68 (s, 3H), 1,33 (t, *J* = 6,8 Hz, 3H); EM (EI) para $C_{15}H_{13}N_5OS$: 312,0 (MH^+).

Ejemplo 9g. 2-Amino-8-etil-4-metil-6-(1*H*-pirazol-4-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, DMSO-d_6): δ 12,88 (s, 1H), 8,38 (s, 1H), 8,17 (s, 2H), 7,10 (bs, 2H), 4,35 (q, *J* = 7,2 Hz, 2H), 2,59 (s, 3H), 1,20 (t, *J* = 7,2 Hz, 3H); EM (EI) para $C_{13}H_{14}N_6O$: 271,0 (MH^+).

Ejemplo 9h. 2-Amino-8-etil-4-metil-6-(1,3-tiazol-2-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$): δ 8,94 (s, 1H), 7,94 (d, *J* = 3,2 Hz, 1H), 7,46

(d, *J* = 3,2 Hz, 1H), 5,34 (bs, 2H), 4,54 (q, *J* = 7,2 Hz, 2H), 2,73 (s, 3H), 1,35 (t, *J* = 7,2 Hz, 3H); EM (EI) para $C_{13}H_{13}N_5OS$: 288,0 (MH^+).

Ejemplo 9i. 2-Amino-8-etil-4-metil-6-(1-metil-1*H*-pirrol-2-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^1H RMN (400 MHz, DMSO-d_6): δ 7,81 (s, 1H), 7,20 (bs, 2H), 6,81 6,11 (dd, *J* = 3,6, 2 ,0Hz, 1H), 6,02 (t, *J* = 3,2 Hz, 1H), 4,32 (q, *J* = 7,2 Hz, 2H), 3,49 (s, 3H), 2,52 (s, 3H), 1,19 (t, *J* = 7,2 Hz, 3H); EM (EI) para $C_{15}H_{17}N_5O$: 284,1 (MH^+).

Ejemplo 9j. 2-Amino-8-etil-4-metil-6-fenilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^1H RMN (400MHz, $CDCl_3$): δ 7,79 (s, 1H), 7,65 (d, *J* = 6,8 Hz, 2H), 7,43 (d, *J* = 7,2 Hz, 2H), 7,36 (d, *J* = 7,2 Hz, 1H), 5,24 (bs, 2H), 4,47 (q, *J* = 7,2 Hz, 2H), 2,60 (s, 3H), 1,31 (d, *J* = 7,2 Hz, 3H), EM (EI) para $C_{16}H_{16}N_4O$: 281,2 (MH^+)

Ejemplo 9k 2-Amino-8-etil-6-(4-metoxifenil)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^1H RMN (400MHz, $CDCl_3$): δ 7,75 (s, 1H), 7,62 (d, *J* = 8,8 Hz, 2H), 6,96 (d, *J* = 8,8 Hz, 2H), 5,17 (bs, 2H), 4,47 (q, *J* = 6,8 Hz, 2H), 3,85 (s, 3H), 2,60 (s, 3H), 1,31 (d, *J* = 7,2 Hz, 3H), EM (EI) para $C_{17}H_{18}N_4O_2$: 311,2 (MH^+)

Ejemplo 9m 2-Amino-8-etil-6-(2-metoxifenil)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^1H RMN (400MHz, $CDCl_3$): δ 7,75 (m, 1H), 7,36 (m, 2H), 7,01 (m, 2H), 5,20 (bs, 2H), 4,45 (m, 2H), 3,82 (s, 3H), 2,56 (s, 3H), 1,31 (m, 3H), EM (EI) para $C_{17}H_{18}N_4O_2$: 311,2 (MH^+)

Ejemplo 9n 2-Amino-6-(4-clorofenil)-8-etil-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^1H RMN (400MHz, $CDCl_3$): δ 7,78 (s, 1H), 7,61 (d, *J* = 8,8 Hz, 2H), 7,39 (d, *J* = 8,8 Hz, 2H), 5,23 (bs, 2H), 4,46 (q, *J* = 7,2 Hz, 2H), 2,61 (s, 3H), 1,31 (d, *J* = 6,8 Hz, 3H), EM (EI) para $C_{16}H_{15}ClN_4O$: 315,1 (MH^+)

Ejemplo 9p 2-Amino-6-(3-clorofenil)-8-etil-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400MHz, $CDCl_3$): δ 7,79 (s, 1H), 7,66 (m, 1H), 7,56 (m, 1H), 7,35 (m, 2H), 5,25 (bs, 2H), 4,46 (q, *J* = 5,6 Hz, 2H), 2,61 (s, 3H), 1,31 (d, *J* = 7,2 Hz, 3H), EM (EI) para $C_{16}H_{15}ClN_4O$: 315,1 (MH^+)

Ejemplo 9q 2-Amino-6-(2-clorofenil)-8-etil-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400MHz, $CDCl_3$): δ 7,75 (s, 1H), 7,67 (m, 1H), 7,54 (m, 2H), 7,38 (m, 1H), 7,333 (m, 1H), 5,22 (bs, 2H), 4,46 (q, *J* = 6,8 Hz, 2H), 2,57 (s, 3H), 1,31 (d, *J* = 6,8 Hz, 3H), EM (EI) para $C_{16}H_{15}ClN_4O$: 315,1 (MH^+)

Ejemplo 9r 2-Amino-6-(2,4-diclorofenil)-8-etil-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400MHz, $CDCl_3$): δ 7,77 (s, 1H), 7,67 (m, 1H), 7,49 (m, 1H), 7,32 (m, 1H), 5,24 (bs, 2H), 4,45 (q, *J* = 6,8 Hz, 2H), 2,58 (s, 3H), 1,30 (d, *J* = 7,2 Hz, 3H), EM (EI) para $C_{16}H_{14}Cl_2N_4O$: 349,1 (MH^+)

Ejemplo 9t 2-Amino-8-etil-4-metil-6-(2-tienil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, DMSO-d_6): δ 8,39 (s, 1H), 7,85-7,13 (m, 5H), 4,37 (q, *J* = 7,2 Hz, 2H), 2,62 (s, 3H), 1,18 (t, *J* = 7,2 Hz, 3H); EM (EI) para $C_{14}H_{14}N_4OS$: 287,1 (MH^+).

Ejemplo 9u **2-Amino-8-etil-6-(4-fluorofenil)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, DMSO-d_6): δ 7,99 (s, 1H), 7,76-7,22 (m, 6H), 4,34 (q, *J* = 7,2Hz, 2H), 2,56 (s, 3H), 1,20 (t, *J* = 7,2 Hz, 3H); EM (EI) para $C_{16}H_{15}FN_4O$: 299,2 (MH^+).**

Ejemplo 9v **2-Amino-8-etil-6-(3-fluorofenil)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, DMSO-d_6): δ 8,06 (s, 1H), 7,61-7,44 (m, 3H), 7,29 (bs, 2H), 7,20-7,15 (m, 1H), 4,34 (q, *J* = 7,2Hz, 2H), 2,58 (s,**

3H), 1,20 (t, *J* = 7,2 Hz, 3H); EM (EI) para $C_{16}H_{15}FN_4O$: 299,2 (MH^+).

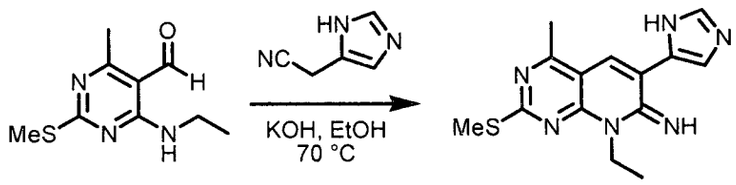
Ejemplo 9w **2-Amino-8-etil-6-(2-fluorofenil)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, DMSO-d_6): δ 7,96 (s, 1H), 7,50-7,23 (m, 6H), 4,32 (q, *J* = 6,8 Hz, 2H), 2,52 (s, 3H), 1,19 (t, *J* = 6,8 Hz, 3H); EM (EI) para $C_{16}H_{15}FN_4O$: 299,2 (MH^+).**

Ejemplo 9x **Metil 3-(2-amino-8-etil-4-metil-7-oxo-7,8-dihidropirido[2,3-*d*]pirimidin-6-il)benzoate: ^{1}H RMN (400 MHz, DMSO-d_6): δ 8,34 (s, 1H), 8,06 (s, 1H), 7,95-7,55 (m, 3H), 7,28 (bs, 1H), 4,35 (q, *J* = 6,8 Hz, 2H), 3,89 (s, 3H), 2,58 (s, 3H), 1,21 (t, *J* = 6,8 Hz, 3H); EM (EI) para $C_{18H18}N_4O_3$: 339,2 (MH^+).**

Ejemplo 9y 2-Amino-8-etil-4-metil-6-pirimidin-5-ilpirido[2,3-*d*]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, DMSO-d_6): δ 8,39 (s, 1H), 7,65-7,30 (m, 5H), 4,31 (q, *J* = 7,2 Hz, 2H), 2,50 (s, 3H), 1,17 (t, *J* = 7,2 Hz, 3H); EM (EI) para $C_{14}H_{14}N_6O$: 283,2 (MH^+).

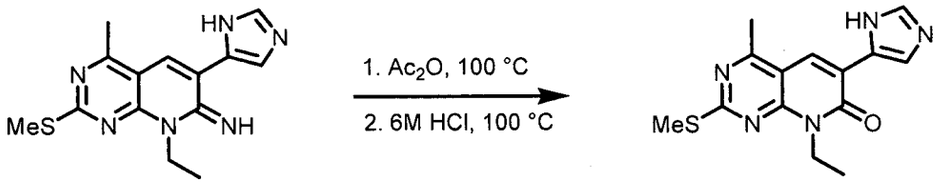
Ejemplo 10

2-Amino-8-etil-6-(1*H*-imidazol-5-il)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona



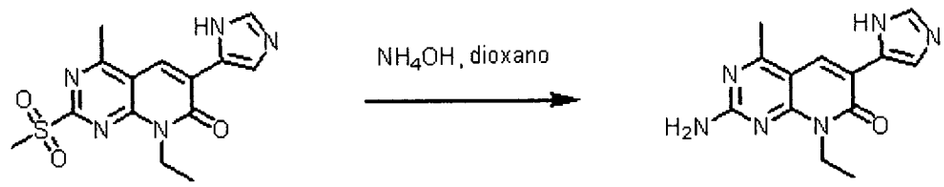
[00315] Una solución de hidróxido de potasio (0,139 g, 2,48 mmol) en etanol absoluto (3,0 mL) se añadió a un tubo de presión cargado con 4-(etilamino)-6-metil-2-(metiltio)pirimidin-5-carbaldehído (0,229 g, 1,08 mmol), preparado mediante procedimientos similares a los que se describen para el Intermediario 1, y 2-

(1*H*-imidazol-5-il)acetonitrilo (0,174 g, 162 mmol) y se calientan a 70 °C. Después de 12 h, la reacción se dejó enfriar a temperatura ambiente y se concentró in vacuo proporcionando 8-etil-6-(1*H*-imidazol-5-il)-4-metil-2-(metiltio)pirido[2,3-*d*]pirimidin-7(8*H*)-imina en forma de un sólido. El producto se usó en la etapa posterior sin purificación adicional.



[00316] Se añadió anhídrido acético (15,0 mL) a un matraz cargado con 8-etil-6-(1*H*-imidazol-5-il)-4-metil-2-(metiltio)pirido[2,3-*d*]pirimidin-7(8*H*)-imina bruta y se calentó a 100 °C. Después de 30 minutos, la reacción se dejó enfriar a temperatura ambiente y se concentró in vacuo. El residuo acetilado luego se trató con HCl 6 N (16 mL) y se calentó a 95 °C durante 30 minutos luego se transfirió a un matraz grande. Una solución de $NaHCO_3$ saturado (150 mL) se añadió a 0 °C a aproximadamente pH = 8,0. La fase acuosa se lavó tres veces con acetato de etilo (100 mL) y las fase orgánicas se combinaron, luego lavó con salmuera y se secó en Na_2SO_4. El agente de secado se filtró y las fases orgánicas se concentraron in vacuo para proporcionar 8-etil-6-(1*H*-imidazol-5-il)-4-metil-2-(metiltio)pirido[2,3-*d*]pirimidin-7(8*H*)-ona bruta que se usó en la etapa posterior sin purificación adicional.

[00317] Se añadió ácido 3-cloroperbenzoico (0,299 g, 1,73 mmol) a una solución de 8-etil-6-(1*H*-imidazol-5-il)-4-metil-2-(metiltio)pirido[2,3-*d*]pirimidin-7(8*H*)-ona bruta (0,260 g, 0,866 mmol) en diclorometano (10,0 mL) a temperatura ambiente. Después de 1,5 h, la reacción se diluyó con diclorometano (50 mL) y se lavó dos veces con $NaHCO_3$ saturado, seguido por salmuera. La fase orgánica se separó y secó en Na_2SO_4, se filtró, y se concentró in vacuo. La correspondiente sulfona se usó en la etapa posterior sin purificación adicional.

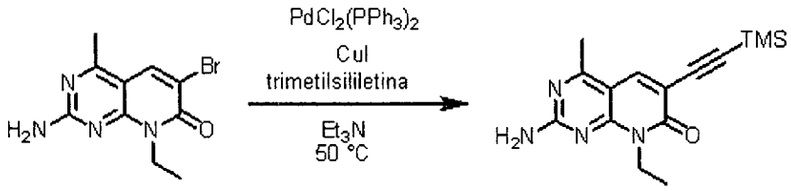


[00318] Se añadió hidróxido de amonio acuoso concentrado (400 µL) a una solución de la sulfona en dioxano (10 mL) a 0 °C. El matraz de reacción se selló, y se dejó calentar a temperatura ambiente después de decantar toda la noche. La reacción se concentró in vacuo y se purificó en HPLC de fase inversa (acetonitrilo: agua 0,1% de TFA, 20-60% de gradiente). Las fracciones que contienen el producto se recolectaron y concentraron a la mitad de volumen y se vertieron en $NaHCO_3$ saturado (50 mL). La fase

acuosa se lavó treces veces con acetato de etilo (50 mL) y se secó en Na_2SO_4, se filtró, y se concentró in vacuo. El residuo se trituró con cloruro de metileno y acetato de etilo para proporcionar 2-amino-8-etil-6-(1*H*-imidazol-5-il)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona (29 mg, 12 % de rendimiento) en forma de sólido amarillo claro: ^{1}H RMN (400 MHz, CH_3OH-d_4): δ 8,52 (bs, 1H), 7,88 (bs, 1H), 7,76 (s, 1H), 4,30 (q, *J* = 6,8 Hz, 2H), 2,65 (s, 3H), 1,29 (t, *J* = 6,8 Hz, 3H); EM (EI) para $C_{13}H_{14}N_6O$: 271,0 (MH^+).

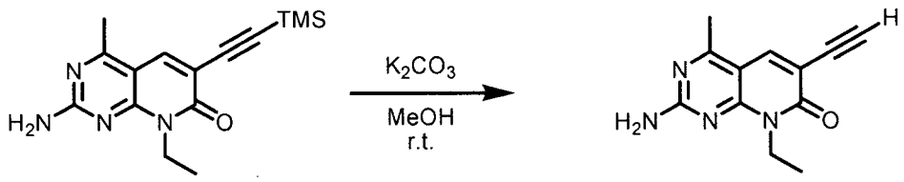
Ejemplo 11

2-Amino-8-etil-4-metil-6-(1*H*-1,2,3-triazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona

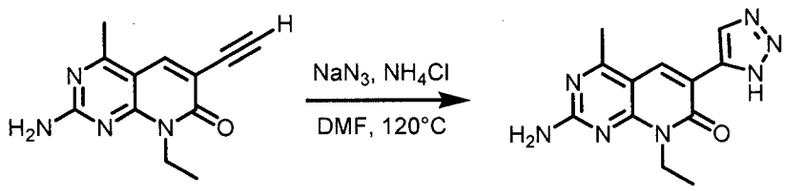


[00319] Se añadió trimetilsililetina (1,44 mL, 10,2 mmol) a un tubo de presión cargado con 2-amino-6-bromo-8-etil-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona (1,58 g, 5,59 mmol) del anterior, CuI (0,053 g, 0,279 mmol), y $PdCl_2(PF_3)_2$ (0,211 g, 0,279 mmol) en trietilamina (20 mL). El tubo de presión se selló bajo nitrógeno y se calentó a 50 °C 96 h. La reacción se enfrió a temperatura ambiente y se vertió en una solución saturada de $NaHCO_3$ (150 mL), luego se lavó cuatro veces con acetato de etilo (50 mL). Las fases orgánicas se mezclaron y secaron en Na_2SO_4, se

filtraron y concentraron in vacuo. El residuo se purificó en SiO_2 (2:1, cloruro de metileno: acetato de etilo) para proporcionar 2-amino-8-etil-4-metil-6-((trimetilsilil)etinil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona (1,09 g, 65 % de rendimiento) en forma de sólido blancuzco.



[00320] Se añadió carbonato de potasio (1,00 g, 7,28 mmol) a un matraz cargado con 2-amino-8-etil-4-metil-6-((trimetilsilil)etinil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona (1,09 g, 3,64 mmol) en metanol anhidro (15 mL). La reacción se agitó a temperatura ambiente bajo nitrógeno durante 16 h. La reacción se concentró a la mitad de volumen y se recolectó el precipitado amarillo por filtración al vacío para proporcionar 2-amino-8-etilo -6-etinil-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona.

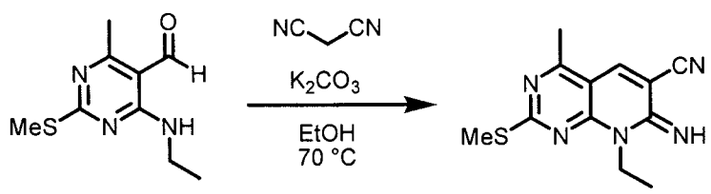


[00321] Se añadió DMF anhidro (5,0 mL) a un matraz cargado con 2-amino-8-etilo-6-etinil-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona (0,204 g, 0,894 mmol), azida sódica (0,070 g, 1,07 mmol), y cloruro de amonio (0,057 g, 1,07 mmol). La reacción se terminó bajo nitrógeno y se calentó a 120 °C. Después de 48 h, la reacción se enfrió a temperatura ambiente

y se concentró in vacuo. El residuo se purificó en HPLC de fase inversa (acetonitrilo: agua 0,1% de TFA, gradiente de 20-60%). Las fracciones que contienen el producto se recolectaron y concentraron a la mitad de volumen y se vertieron en $NaHCO_3$ saturado (50 mL). La fase acuosa se lavó tres veces con acetato de etilo (50 mL) y se secó en Na_2SO_4, se filtró, y concentró in vacuo. El residuo se trituró con cloruro de metileno y acetato de etilo para proporcionar 2-amino-8-etil-4-metil-6-(1*H*-1,2,3-triazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona (14 mg, 6 % de rendimiento) en forma de sólido amarillo claro: ^{1}H RMN (400 MHz, DMSO-d_6): δ 8,55 (bs, 1H), 8,41 (bs, 1H), 7,32 (bs, 2H), 4,37 (q, *J* = 7,2 Hz, 2H), 2,60 (s, 3H), 1,21 (t, *J* = 7,2 Hz, 3H); EM (EI) para $C_{12}H_{13}N_7O$: 272,0 (MH^+).

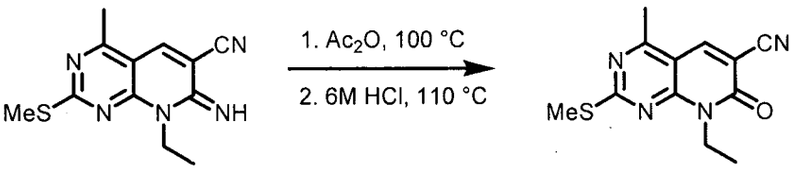
Ejemplo 12

2-Amino-8-etil-4-metil-6-(1*H*-tetrazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona

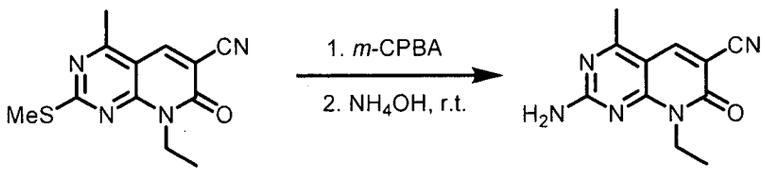


[00322] Se añadió carbonato de potasio (0,539 g, 3,90 mmol) a una suspensión de 4-(etilamino)-6-metil-2-(metiltio)pirimidin-5-carbaldehído (0,413 g, 1,95 mmol) del anterior, y malononitrilo (0,194 g, 2,93 mmol) en etanol absoluto (15,0 mL) y se calentó a 70 °C. Después de una h, la reacción se dejó enfriar a temperatura ambiente y se concentró in vacuo. El residuo se diluyó con acetato de etilo (50 mL) y lavó

con $NaHCO_3$ saturado (50 mL), y salmuera. La fase orgánica se separó y se concentró in vacuo. El residuo se precipitó con acetato de etilo y hexanos para dar 8-etil-7-imino-4-metil-2-(metiltio)-7,8-dihidropirido[2,3-*d*]pirimidin-6-carbonitrilo en forma de sólido canela que se usó en la etapa posterior sin purificación adicional.

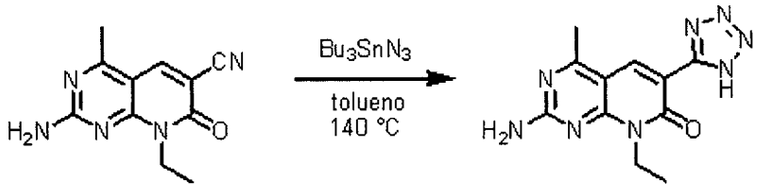


[00323] Se añadió anhídrido acético (10,0 mL) a un matraz cargado con 8-etil-7-imino-4-metil-2-(metiltio)-7,8-dihidropirido[2,3-*d*]pirimidin-6-carbonitrilo (0,506 g, 1,95 mmol) y se calentó a 100 °C. Después de una h, la reacción se dejó enfriar a temperatura ambiente y se concentró in vacuo. El residuo acetilado luego se trató con HCl 6 N (40 mL) y se calentó a 95 °C durante una hora luego se transfirió a un matraz grande. Se añadió una solución saturada de $NaHCO_3$ (500 mL) lentamente a 0 °C hasta obtener ~pH 8,0. La fase acuosa se lavó tres veces con acetato de etilo (100 mL) y las fases orgánicas se combinaron, luego se lavaron con salmuera y secaron en Na_2SO_4. El agente de secado se filtró y se concentró in vacuo para proporcionar 8-etil-4-metil-2-(metiltio)-7-oxo-7,8-dihidropirido[2,3-*d*]pirimidin-6-carbonitrilo bruto que se usó en la etapa posterior sin purificación adicional.



[00324] Se añadió ácido 3-cloroperbenzoico (1,00 g, 5,85 mmol) a una solución de 8-etil-4-metil-2-(metiltio)-7-oxo-7,8-dihidropirido[2,3-*d*]pirimidin-6-carbonitrilo bruto (0,507 g, 1,95 mmol) en diclorometano (30,0 mL) a temperatura ambiente. Después de 2,5 horas, la reacción se diluyó con diclorometano (50 mL) y se lavó dos veces con $NaHCO_3$ saturado, seguido por salmuera. La fase orgánica se separó y secó en Na_2SO_4, se filtró, y se concentró in vacuo. 2-Amino-8-etil-4-metil-7-oxo-7,8-dihidropirido[2,3-*d*]pirimidin-6-carbonitrilo se usó en la etapa posterior sin purificación adicional.

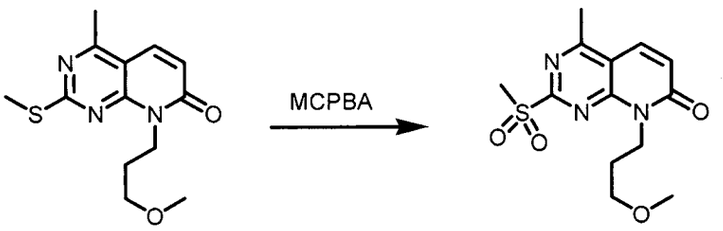
[00325] Se añadió hidróxido de amonio (500 µL) a una solución de la sulfona anterior en dioxano (10 mL) a 0 °C. El recipiente de reacción se selló, y se dejó calentar a temperatura ambiente después de decantar toda la noche. La reacción se concentró in vacuo y se trituró con acetato de etilo para proporcionar el producto que se usó en la etapa posterior sin purificación adicional.



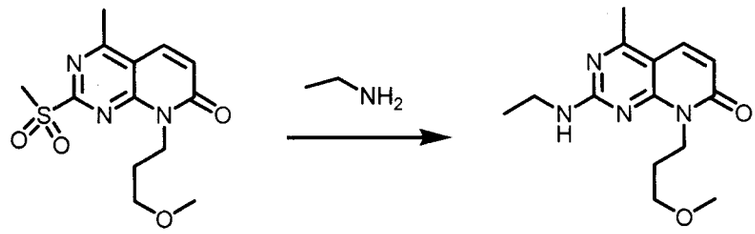
[00326] Se añadió azida de tributilestaño (660 µL, 2,41 mmol) a un matraz cargado con 2-amino-8-etil-4-metil-7-oxo-7,8-dihidropirido[2,3-*d*]pirimidin-6-carbonitrilo

(0,184 g, 0,803 mmol) en tolueno anhidro (5,0 mL). La reacción se sometió a un condensador de reflujo y se calentó a 140 °C bajo atmósfera de nitrógeno. Después de 20 h, la reacción se enfrió a temperatura ambiente y se recolectó el precipitado por filtración al vacío y se lavó con etanol absoluto para dar 2-amino-8-etil-4-metil-6-(1*H*-tetrazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona (98 mg, 45 % de rendimiento) as a light brown solid: ^{1}H RMN (400 MHz, 20 % DCl in D_2O)δ 6,97 (s, 1H), 2,42 (q, *J* = 7,2 Hz, 2H), 0,953 (s, 3H), -0,73 (t, *J* = 7,2 Hz, 3H); EM (EI) para $C_{11}H_{11}N_8O$: 271,0 (MH^+).

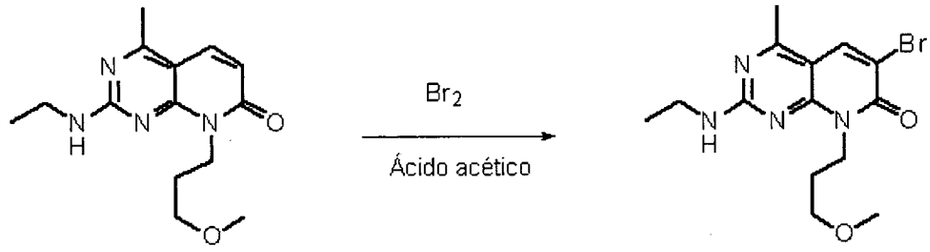
Ejemplo 13



[00327] Una mezcla de 8-(3-metoxipropil)-4-metil-2-(metiltio)pirido[2,3-d]pirimidin-7(8*H*)-ona (0,36 g, 1,29 mmol), preparada usando procedimientos similares a los que se describen en el Ejemplo 1, diclorometano (10 mL), y 77% de ácido 3-cloroperbenzoico con agua (0,723 g, 3,23 mmol) se agitó durante 1 h. La mezcla se diluyó con diclorometano, se lavó con bicarbonato de sodio saturado (3 veces), salmuera, se secó en sulfato de sodio, y se extrajo DCM a presión reducida. La e 8-(3-metoxipropil)-4-metil-2-(metilsulfonil)pirido[2,3-d]pirimidin-7(8*H*)-ona bruta se usó sin purificación adicional en la etapa subsiguiente.



[00328] 8-(3-metoxipropil)-4-metil-2-(metilsulfonil)pirido[2,3-d]pirimidin-7(8*H*)-ona, y una solución de etilamina 2 M en TF (20 mL) se agitó durante 2 h. TF se extrajo a presión reducida y el producto bruto se purificó por cromatografía en columna flash para dar 2-(etilamino)-8-(3-metoxipropil)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona (0,18 g, 50% de rendimiento en las 2 etapas).



[00329] A una solución de 2-(etilamino)-8-(3-metoxipropil)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona (0,18 g, 0,65 mmol), ácido acético (5 mL) y diclorometano (3 mL) se añadió bromo (36 ul, 0,7 mmol). La mezcla se agitó durante 5 minutos, y luego se diluyó con DCM y agua. La fase orgánica se lavó con bicarbonato de sodio saturado (3 veces), salmuera, secó en sulfato de sodio, se filtró y se concentró a presión reducida. El producto bruto se purificó por cromatografía en columna flash para dar 0,13 g (56% de rendimiento) de 6-bromo-2-(etilamino)-8-(3-metoxipropil)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona. ^{1}H RMN (400MHz, $CDCl_3$) δ 8,09 (s, 1H), 5,44 (Br. s, 1H), 4,55 (m, 2H), 3,54-3,47 (m, 4H), 3,33 (s, 3H), 2,53

(s, 3H), 2,05-2,00 (m, 2H), 1,30- 1,23 (m, 3H); EM (EI) para $C_{14}H_{19}BrN_4O_2$: 355 (MH+).

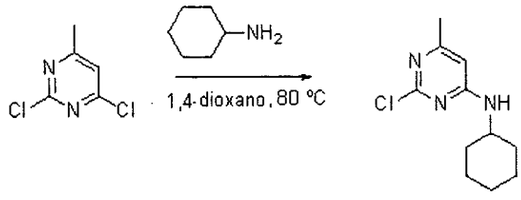
[00330] Usando técnicas de síntesis iguales o análogas y sustituyendo con los reactivos apropiados, se prepararon los siguientes compuestos:

Ejemplo 13a. 6-bromo-8-(2-etoxietil)-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona: ^{1}H RMN (400MHz, $CDCl_3$) δ 8,09 (s, 1H), 5,37 (Br. s, 1H), 4,67 (m, 2H), 3,74 (m, 2H), 3,61-3,56 (t, 2H), 3,51 (m, 2H), 2,53 (s, 3H), 1,29-1,25 (t, 3H), 1,19-1,15 (t, 3H); EM (EI) para $C_{14}H_{19}BrN_4O_2$: 355 (MH+).

Ejemplo 13b. 6-bromo-8-(3-etoxipropil)-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona: ^{1}H RMN (400MHz, $CDCl_3$) δ 8,09 (s, 1H), 5,37 (Br. s, 1H), 4,53 (m, 2H), 3,52 (m, 4H), 3,48-3,43 (m, 2H), 2,53 (s, 3H), 2,04-2,00 (m, 2H), 1,29-1,25 (t, 3H), 1,19-1,15 (t, 3H); EM (EI) para $C_{15}H_{21}BrN_4O_2$: 369 (MH+).

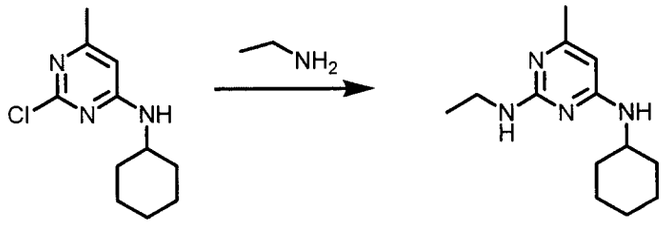
Ejemplo 13c. 6-bromo-2-(etilamino)-8-(3-isopropoxipropil)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona: ^{1}H RMN (400MHz, $CDCl_3$) δ 8,09 (s, 1H), 5,37 (Br. s, 1H), 4,53 (m, 2H), 3,59-3,49 (m, 5H), 2,52 (s, 3H), 2,01-1,98 (m, 2H), 1,28-1,25 (t, 3H), 1,13-1,11 (t, 6H); EM (EI) para $C_{16}H_{23}BrN_4O_2$: 383 (MH+).

Ejemplo 14

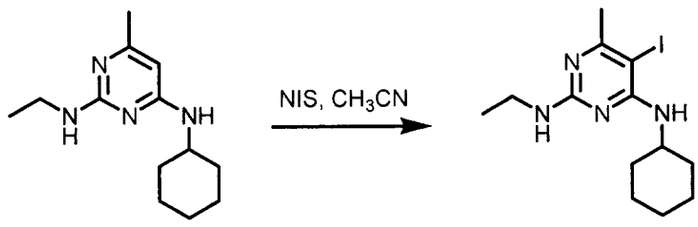


[00331] Una mezcla de 2,4-dicloro-6-metilpirimidina (Aldrich, 5 g, 30 mmol), ciclohexilamina (3 g, 30 mmol) y DIEA (10 mL) se agitó a 80 °C durante 12 h. El material volátil se extrajo a presión reducida. El residuo se

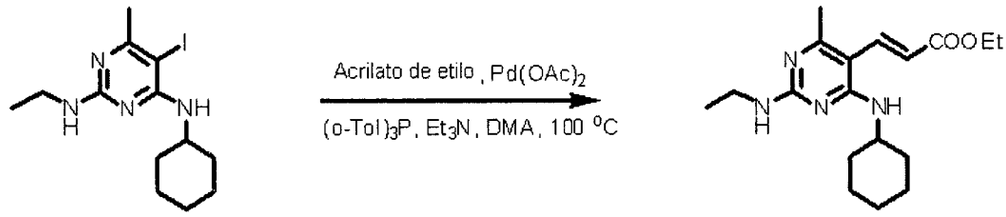
cargó en una columna de gel de sílice y se eluyó con hexanos/acetato de etilo (3:1). 8-ciclohexil-2-(etilamino)-4-metil-6-(tiofe*N*-2-il)pirido[2,3-d]pirimidin-7(8*H*)-ona se obtuvo como aceite incoloro (2,8 g, 41% de rendimiento).



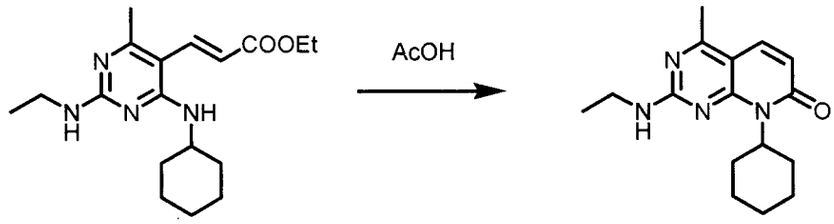
[00332] El producto se hizo reaccionar con una solución de etilamina (10 equiv.) en TF a 100 °C durante 12 h. La 2-etilamino-4-ciclohexilamino-6-metilpirimidina bruta se obtuvo a partir de un desarrollo estándar y se usó en la etapa siguiente.



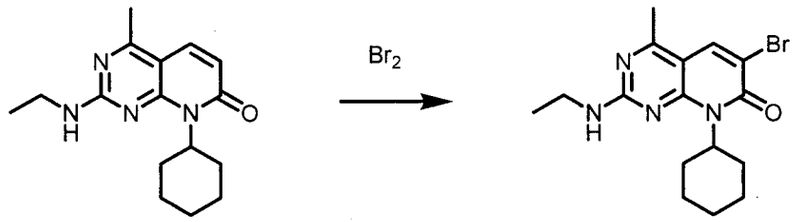
[00333] A una solución de 2-etilamino-4-ciclohexilamino-6-metilpirimidina (600 mg, 2,56 mmol) en CH_3CN (10 mL) se añadió *N*-yodosuccinimida (NIS, 658 mg, 2,92 mmol). La reacción se agitó durante 2 h a temperatura ambiente. después de extraer el solvente, el residuo se disolvió en EtOAc. La fase orgánica luego se lavó con bisulfito de sodio, salmuera, y se secó en Na_2SO_4. La purificación por cromatografía en columna flash proporcionó 660 mg (73% de rendimiento) de 2-etilamino-4-ciclohexilamino-5-yodo-6-metilpirimidina.



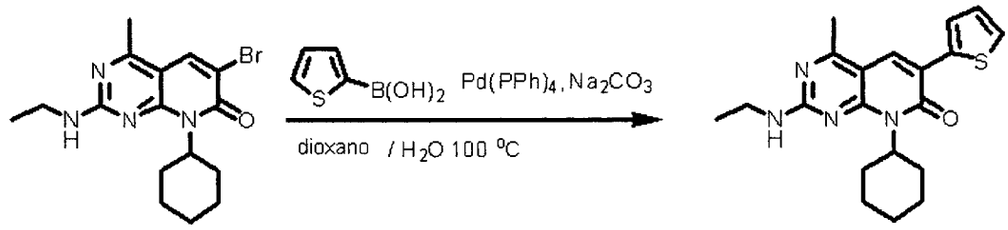
[00334] A una solución de 2-etilamino-4-ciclohexilamino-5-yodo-6-metilpirimidina (660 mg, 1,83 mmol) en DMA (7 mL) se añadió acrilato de etilo (458 mg, 4,58 mmol), $Pd(OAc)_2$ (121 mg, 0,18 mmol), $(o\text{-}Tol)_3P$ (110 mg, 0,37 mmol), y Et_3N (740 mg, 7,32 mmol). La mezcla luego se agitó a 100 °C durante 12 h bajo N_2. El desarrollo estándar y la purificación por cromatografía en columna proporcionaron 411 mg (67% de rendimiento) de (*E*)-(4-(ciclohexilamino)-2-(etilamino)-6-metilpirimidin-5-il)acrilato de etilo.



[00335] Se disolvió (E)-3-(4-(ciclohexilamino)-2-(etilamino)-6-metilpirimidin-5-il)acrilato de etilo (200 mg, 0,6 mmol) en AcOH (2 mL). Esta solución se calentó en un tubo sellado a 186 °C durante 17 h. El desarrollo estándar y la purificación por cromatografía en columna proporcionaron 65 mg (38% de rendimiento) de 8-ciclohexil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona.



[00336] A 8-ciclohexil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona en AcOH y CH_2Cl_2 se añadió Br_2 (22 uL, 0,42 mmol) a 80 °C. El desarrollo estándar y la purificación por cromatografía en columna proporcionaron 65 mg (0,17 mmol, 80 % de rendimiento) de 6-bromo-8-ciclohexil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona.

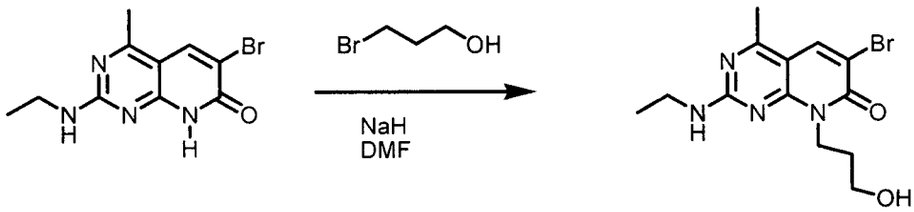


[00337] El bromuro (65 mg, 0,17 mmol) obtenido antes se hizo reaccionar con ácido 2-tiofenoborónico (45 mg, 0,36 mmol) en presencia de $Pd(PF_3)_4$ (20 mg, 0,018 mmol) y Na_2CO_3 (38 mg, 0,36 mmol) en 1,4-dioxano/H2O (1:1) a 100 °C durante 2 h. La extracción de solventes y la purificación por cromatografía en columna proporcionaron 33 mg (50% de rendimiento) de 8-ciclohexil-2-(etilamino)-4-metil-6-(tiofe*N*-2-il)pirido[2,3-d]pirimidin-7(8*H*)-ona. ^{1}H RMN (400 MHz, DMSO-d6) δ8,01 (br s, 1 H), 7,60 (m, 1 H), 7,37 (m, 1 H), 7,10 (m, 1H), 5,60-5,40 (m, 1 H), 3,55 (m, 2 H), 2,85 (m, 1 H), 2,61 (s, 3 H), 1,90 (m, 2 H), 1,71 (m, 4 H), 1,43 (m, 2 H), 1,30-1,2 (m, 2 H),1,30 (t, 3 H); EM (EI) para $C_{20}H_{24}N_4OS$: 369 (MH+).

[00338] Usando técnicas de síntesis iguales o análogas y sustituyendo con los reactivos apropiados, se prepararon los siguientes compuestos:

Ejemplo 14a. 6-bromo-8-ciclopropil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,06 (s, 1 H), 5,37 (br s, 1 H), 3,54 (m, 2 H), 2,94 (br s, 1H), 2,51 (s, 3 H), 1,31-1,25 (m, 5 H), 0,91 (br s, 2 H); EM (EI) para $C_{13}H_{15}BrN_4O$: 323 (MH+).

Ejemplo 15



[00339] A una solución de 6-bromo-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona (100 mg, 0,35 mmol) in DMF (2 mL), preparada mediante procedimientos análogos a los descriptos en el Ejemplo 14, se añadió NaH (30 mg, 60%, 0,7 mmol). La mezcla se agitó durante 30 min a temperatura ambiente y se calentó a 70 °C. Luego se agregó 3-bromopropanol (48 mg, 0,35 mmol). La agitación continuó durante 12 h. . El desarrollo estándar y la purificación por cromatografía en columna proporcionaron 33 mg (27% de rendimiento) de 6-bromo-2-(etilamino)-8-(3-hidroxipropil)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona. ^{1}H RMN (400 MHz, CDCl3) δ ,13 (s, 1 H), 5,42 (br s, 1 H), 4,59 (br s, 2 H), 3,50-3,47 (m, 5 H), 2,55 (s, 3 H), 2,02 (br s, 2 H), 1,28 (t, 3 H); EM (EI) para $C_{13}H_{17}BrN_4O_2$: 341 (MH+).

[00340] Usando técnicas de síntesis iguales o análogas y sustituyendo con los reactivos apropiados, se prepararon los siguientes compuestos:

Ejemplo 15a. 6-bromo-2-(etilamino)-8-(2-hidroxietil)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, DMSO-d6) δ 8,38 (s, 1 H), 4,82 (br s, 1 H), 4,40 (br s, 2 H), 3,62-3,55 (m, 2 H), 3,40-3,20 (m, 3 H), 2,55 (s, 3 H), 1,15 (t, 3 H); EM (EI) para $C_{12}H_{15}BrN_4O_2$: 327 (MH+).

Ejemplo 15b. 6-bromo-2-(etilamino)-4-metil-8-(2-(piperidin-1-il)etilo)pirido[2,3-d]pirimidin-7(8*H*)-ona: ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,08 (s, 1 H), 5,39 (br s, 1 H), 4,59 (br s, 2 H), 3,55-3,40 (m, 2 H), 2,70-2,50 (m, 6 H), 2,52 (s, 3 H), 1,62-1,58 (m, 4 H), 1,46-1,40 (m, 2 H), 1,27 (t, 3 H); EM (EI) para $C_{17}H_{24}BrN_5O$: 394 (MH+).

Ejemplo biológicos

Ejemplo biológico 1

Ensayo de quimioluminiscencia acoplada a PI3Kalfa luciferasa

[00341] La actividad de PI3Kα se midió como el porcentaje de ATP consumido después de la reacción de quinasa usando quimioluminiscencia acoplada a luciferasa-luciferi*N*. Las reacciones se realizaron en placas blancas de microtitulación de unión al medio de 384 pocillos (Greiner). Las reacciones de quinasa se iniciaron por la combinación de compuestos de ensayo, ATP, sustrato (PIP2), y quinasa en un volumen de 20 µL en una solución buffer. El buffer de ensayo de PI3Kalpha estándar esta compuesto de Tris 50 mM, pH 7,5, 1 mM de EGTA, 10 mM de MgCl, 1 mM de DTT y 0,03% de CHAPS. Las concentraciones de ensayo estándares para la enzima, ATP y sustrato eran 0,5-1,1 nM, 1 µM y 7,5 µM, respectivamente. La mezcla de reacción se incubó a temperatura ambiente durante aproximadamente 2 horas. Después de la reacción de quinasa, se añadió una alícuota de 10 µL de mezcla de

luciferasa-luciferina (Promega Kinase-Glo) y se midió la señal de quimioluminiscencia usando un lector de placa Victor2 (Perkin Elmer). El consumo de ATP total se limitó a 40-60% y los valores de IC50 de los compuestos control se correlacionan bien con las referencias de la bibliografía.

[00342] Ciertos compuestos de la invención se analizaron en este ensayo y demostraron capacidad de unirse al PI3K cuando. Las siguientes formas de realización se refiere a los compuestos por sí mismos así como a su uso un método de tratamiento. Por ejemplo, en una forma de realización de la invención, el inhibidor de PI3K se selecciona de los compuestos de la Tabla 1 que tienen una Afinidad de unión a PI3K de aproximadamente 9 μM o menos. En otra forma de realización, el inhibidor de PI3K se selecciona de los compuestos de la Tabla 1 que tienen una afinidad de unión a PI3K de aproximadamente 5 μM o menos. En otra forma de realización, el inhibidor de PI3K se selecciona de los compuestos de la Tabla 1 que tienen una afinidad de unión a PI3K de aproximadamente 3 μM o menos. En otra forma de realización, el inhibidor de PI3K se selecciona de los compuestos de la Tabla 1 que tienen una afinidad de unión a PI3K de aproximadamente 1,5 μM o menos. En otra forma de realización, el inhibidor de PI3K se selecciona de los compuestos de la Tabla 1 que tienen una afinidad de unión a PI3K de aproximadamente 1 μM o menos. En otra forma de realización, el inhibidor de PI3K se selecciona de los compuestos de la Tabla 1 que tienen una afinidad de unión a PI3K de aproximadamente 0,6 μM o menos. En otra forma de realización, el inhibidor de PI3K se selecciona de los compuestos de

la Tabla 1 que tienen una afinidad de unión a PI3K de aproximadamente 0,3 µM o menos. En otra forma de realización, el inhibidor de PI3K se selecciona de los compuestos de la Tabla 1 que tienen una afinidad de unión a PI3K de aproximadamente 0,2 µM o menos. En otra forma de realización, el inhibidor de PI3K se selecciona de los compuestos de la Tabla 1 que tienen una afinidad de unión a PI3K de aproximadamente 0,1 µM o menos. En otra forma de realización, el inhibidor de PI3K se selecciona de los compuestos de la Tabla 1 que tienen una afinidad de unión a PI3K de aproximadamente 0,04 µM o menos. En otra forma de realización, el inhibidor de PI3K se selecciona de los compuestos de la Tabla 1 que tienen una afinidad de unión a PI3K de aproximadamente 0,020 µM o menos.

Ejemplo biológico 2

Ensayo de fosfo AKT

[00343] Su sembraron células PC-3 en placas de 6 pocillos a razón de 150.000 células/pocillo. Las células se cultivaron durante 3 días, luego se trataron con compuestos en medio libre de suero durante 3 horas. Se añadió EGF (100 ng/mL) durante los últimos 10 min. Las células se lisaron en buffer TENN. Las Akt fosfo T308 y Akt1 total se cuantificaron por ELISA realizado de acuerdo con el protocolo de ensayo de Biosource. Las lecturas de fosfo Akt se normalizaron a las lecturas de Akt total.

Ejemplo biológico 2

Ensayo de fosfo S6

[00344] Las células PC3 se sembraron en placas de 96 pocillos a razón de 8.000 células/pocillo. Para cada experimento, se sembraron células y se trataron en placas duplicadas: una placa para fosfo S6 CellELISA, y una placa para S6 CellELISA total. Las células se cultivaron en las placas durante 3 días, luego se trató con compuestos en medio libre de suero durante 3 horas por triplicado. Las células se fijaron con 4% formaldehído, se inactivaron con 0,6% de H_2O, se bloqueron con 5% de BSA, se incubaron con anticuerpo fosfo S6 o anticuerpo S6 total toda la noche, se incubó con IgG-HRP de conejo anti cabra durante 1 hora, y se desarrolló en sustrato quimioluminiscente.

Ejemplo biológico 4

Ensayo de PIP_3

[00345] Las células MCF-7 cultivadas en placas de 10 cm se privaron de nutrientes durante 3 horas en DMEM, y luego se trataron con compuestos durante 20 minutos. En los últimos 2 minutos de la incubación con los compuestos, se añadió EGF (100 ng/mL) para estimular la producción de PIP3. El medio se aspiró y las células se eliminaron con 10% de ácido tricloroacético. Los lípidos se extrajeron del pellet después de centrifugar los lisados celulares. Se cuantificó PIP3 en la extracción de lípidos celulares con el ensayo AlphaScreen en el que se usa Grp1-PH como sonda específica de PIP3. La cantidad de PIP3 celular se calcula a partir de la curva estándar de diC PI (3,4,5) P3.

Ejemplo biológico 5-10

Modelos in vivo

[00346] El compuesto A es un compuesto de Fórmula I. El compuesto B es *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5*r*,6a*S*)-2-metiloctahidrociclopenta-[*c*]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina.

[00347] Se usan ratones desnudos atímicos hembra y macho (NCr) de 5-8 semanas y de peso aproximado de 20-25 g en el siguiente modelo. Antes de la iniciación de un estudio, los animales se dejan aclimatar durante un mínimo de 48 horas. Durante estos estudios, se proveyó a los animales alimento y agua ad libitum y se alojaron en una habitación acondicionada a 70-75°F y 60% de humedad relativa. Un ciclo de 12 horas de luz y 12 horas de oscuridad se mantiene con temporizadores automáticos. Todos los animales se examinan diariamente en cuanto a muertes inducidas por el compuesto o relacionadas con el tumor.

[00348] Las células de adenocarcinoma de próstata humano PC-3 se cultivaron in vitro en DMEM (Mediatech) suplementado con 20% de suero fetal bovino (Hyclone), penicilina-estreptomicina y aminoácidos no esenciales a 37°C en una atmósfera de 5% de CO humidificado. En el día 0, las células se recolectaron por tripsinización y $3x10^6$ células (pasaje 13, 99% de viabilidad) en 0,1 mL de solución salina equilibrada de Hank enfriada en hielo se implantaron en forma subcutánea en el flanco trasero de ratones desnudos machos de 5-8 semanas. Se implantó un transmisor en cada ratón para la identificación, y los animales se controlaron diariamente para determinar síntomas clínicos y

supervivencia. Los pesos corporales se registraron diariamente. Los experimentos se realizaron con el Compuesto A como un agente simple así como el Compuesto A en combinación con taxol y el Compuesto A en combinación con rapamicina. Este modelo se puede usar para evaluar la conveniencia de tratar con el Compuesto A en combinación con otros agentes anti-cáncer.

[00349] Las células de glioblastoma humano U-87 MG se cultivaron in vitro en DMEM (Mediatech) suplementado con 10% de suero fetal bovino (Hyclone), penicilina-estreptomicina y aminoácidos no esenciales a 37°C en una atmósfera de 5% de CO humidificado. En el día 0, las células se recolectaron por tripsinización y $2x10^6$ células (pasaje 5, 96% de viabilidad) en 0,1 mL de solución salina equilibrada de Hank enfriada en hielo se implantaron en forma intradérmica en el flanco trasero de ratones desnudos machos de 5 8 semanas. Se implantó un transmisor en cada ratón para la identificación, y los animales se controlaron diariamente para determinar síntomas clínicos y supervivencia. Los pesos corporales se registraron diariamente. Los experimentos se realizaron con el Compuesto A como único agente y los resultados no están incluidos. Este modelo se puede usar para evaluar la conveniencia de tratar con el Compuesto A en combinación con con otros agentes anti-cáncer.

[00350] Las células de carcinoma de pulmón humano A549 se cultivaron in vitro en DMEM (Mediatech) suplementado con 10% de suero fetal bovino (Hyclone), penicilina-estreptomicina y aminoácidos no esenciales a 37°C en una atmósfera de 5% de CO humidificado. En el día 0, las células se recolectaron por

tripsinización y $10x10^6$ de células (pasaje 12, 99% de viabilidad) en 0,1 mL de solución salina equilibrada de Hank enfriada en hielo se implantaron en forma intradérmica en el flanco trasero de ratones desnudos machos de 5 8 semanas. Se implantó un transmisor en cada ratón para la identificación, y los animales se controlaron diariamente para determinar síntomas clínicos y supervivencia. Los pesos corporales se registraron diariamente. Los experimentos se realizaron con el Compuesto A como agente único así como el Compuesto A en combinación con el Compuesto B. Este modelo se puede usar para evaluar la conveniencia de tratar con el Compuesto A en combinación con otros agentes anti-cáncer.

[00351] Células de adenocarcinoma de mamas humano MDA-MB-468, pasaje número <6, se mantienen y propagan en crecimiento en fase logarítmica en medio Eagle modificado por Dulbecco (DMEM; Mediatech) que contiene L-glutamina suplementada con 10% de suero fetal bovino (Hyclone), penicilina-estreptomicina y aminoácidos no esenciales a 37 °C en una atmósfera de 5% de CO humidificado. En el día 0, las células se recolectaron por tripsinización y $10x10^6$ de células (pasaje 12, 99% de viabilidad) en 0,1 mL de solución salina equilibrada de Hank enfriada en hielo se implantaron en forma intradérmica en el flanco trasero de ratones desnudos machos de 5 8 semanas. en 50% solución salina equilibrada de Hank enfriada/50% Matrigel (100 µL de volumen total por ratón) se implantaron en forma subcutánea en tejido adiposo mamario de los ratones desnudos hembra. Los experimentos se realizaron con el Compuesto A como agente único así como el Compuesto A en combinación

con erlotinib. Este modelo se puede usar para evaluar la conveniencia de tratar con el Compuesto A en combinación con otros agentes anti-cáncer.

[00352] Las células de carcinoma anaplásico de pulmón Calu-6 humanas se cultivaron *in vitro* en DMEM (Mediatech) suplementado con 10% de suero fetal bovino (Hyclone), penicilina-estreptomicina y aminoácidos no esenciales a 37 °C en una atmósfera de 5% de CO humidificado. En el día 0, las células se recolectaron por tripsinización, y $5x10^6$ células (pasaje #8, 96% de viabilidad) en 0,1 mL de solución salina equilibrada de Hank enfriada en hielo se implantaron en forma intradérmica en el flanco trasero de ratones desnudos hembra de 5 8 semanas. Se implantó un transmisor en cada ratón para la identificación, y los animales se controlaron diariamente para determinar síntomas clínicos y supervivencia. Los pesos corporales se registraron diariamente. Los experimentos se realizaron con el Compuesto A como agente único así como el Compuesto A en combinación con carboplatino. Este modelo se puede usar para evaluar la conveniencia de tratar con el Compuesto A en combinación con con otros agentes anti-cáncer.

[00353] Células de adenocarcinoma humano MCF7 se cultivaron in vitro en DMEM (Cellgro) suplementado con 10% de suero fetal bovino (Cellgro), penicilina-estreptomicina y aminoácidos no esenciales a 37 °C en una atmósfera de 5% de CO humidificado. En el día 0, las células se recolectaron por tripsinización, y $5x10^6$ células (pasaje #10 y 95% de viabilidad para el Estudio 1, pasaje 9 y 90% de viabilidad para el Estudio 2)) en 100 µL de solución preparada de

solución salina equilibrada de Hank con 50% de factor de crecimiento reducido matrigel (R&D Systems para el Estudio 1 y Becton Dickinson para el Estudio 2) se implantaron en forma subcutánea en el flanco trasero de los ratones desnudos hembra. Se implantó un transmisor en cada ratón para la identificación y rastreo de datos y los animales se monitorearon diariamente en cuanto a síntomas clínicos y supervivencia. Durante el período de dosificación, se determinó el peso del tumor de cada animal dos veces por semana y se midió diariamente el peso corporal de cada animal. Los experimentos se realizaron con el Compuesto A como agente único así como el Compuesto A en combinación con el Compuesto B. Este modelo se usó para evaluar la conveniencia de tratar con el Compuesto A en combinación con otros agentes anticáncer.

[00354] En los tumores subcutáneos o intradérmicos, se determinó dos veces por semana el peso del tumor medio de cada animal en los respectivos grupos control y tratamiento durante el estudio. Se determinó el peso tumoral (TW) por la medición de los diámetros perpendiculares con un calibre, usando la siguiente fórmula:

[00355]

Peso del tumor (mg) = [volumen de tumor = longitud (mm) x ancho^2 (mm^2)]/2

Estos datos se registran y representan en un gráfico lineal de pesos de tumor versus días posimplantación y se presentan gráficamente como una indicación de las tasas de crecimiento del tumor. Se determina el porcentaje de inhibición del crecimiento tumoral (TGI) 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 al día del grupo

X_f = TW de grupo tratado en el día f

Y_f = TW de grupo control con vehículo en el día f

Si los tumores regresan por debajo de sus tamaños iniciales, luego se determina el porcentaje de regresión del tumor con la siguiente fórmula:

$$\frac{(X_0 - X_f)}{X_0} * 100$$

El tamaño del tumor se calcula individualmente para cada tumor para obtener un valor de media ± para cada grupo experimental. Se determina la significación estadística usando la prueba t de Student de dos colas (significancia definida como $P<0,05$).

Ejemplos biológicos 11-14

[00356] El Compuesto A es un compuesto de Fórmula I y es un inhibidor de las I PI3-quinasas de Clase I. El Compuesto B es *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5*r*,6a*S*)-2-metiloctahidrociclopenta-[*c*]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina.

Modelo de xenoinjerto de cáncer de próstata - Un compuesto de Fórmula I en combinación con Taxol

[00357] El Compuesto A se analizó solo y en combinación con taxol en un modelo de tumor de carcinoma prostático. PC-3 es una línea celular de carcinoma prostático humano que alberga una mutación por supresión homocigota en PTEN, que produce una activación constitutiva de la vía

de PI3K. En experimentos farmacodinámicos de dosis única, la administración oral del Compuesto A produce una reduccion dependiente de la dosis de la fosforilación de AKT, p70S6K, y S6 en tumores PC-3 que crecen en forma extópica en los ratones. La administración de una dosis repetida del Compuesto A también inhibe el crecimiento de estos tumores, pero no induce regresiones.

[00358] La administración oral del Compuesto A a 100 mg/kg qd o 30 mg/kg dos veces por semana (biw) produjo una substancial inhibición de crecimiento tumoral en los ratones. Ver Figura 1. La inhibición de crecimiento tumoral comparable se obtuvo con 7,5 mg/kg de taxol administrado i.v. dos veces por semana. Si bien el crecimiento tumoral fue inhibido sustancialmente con el Compuesto A solo, la combinación de la dosis del Compuesto A con taxol fue superior al agente solo e indujo una significativa regresión de los tumores. La pérdida de peso corporal y el salteo de dosis fueron mínimos en todos los grupos y no se exacerbó en el grupo de combinación lo que indica que la combinación fue bien tolerada. Estos resultados respaldan el uso de un compuesto de Fórmula I en combinación con taxol en tumores con señalización de PI3K activada en forma constitutiva.

Modelo de xenoinjerto de cáncer de próstata – Un compuesto de Fórmula I en combinación con Rapamicina

[00359] El Compuesto A se analizó solo y en combinación con rapamicina en un modelo de tumor de carcinoma prostático (línea celular PC-3). La administración oral del Compuesto A a 100 mg/kg q2d produjo una inhibición de crecimiento tumoral significativa. Ver Figura 2. También se observó inhibición de crecimiento tumoral

significativo se obtuvo con 5 mg/kg rapamicina administrada i.p. en forma diaria. Si bien el crecimiento tumoral fue inhibido sustancialmente con el Compuesto A solo, la combinación de la dosis del Compuesto A con rapamicina fue transitoriamente superior al agente solo e indujo regresión de los tumores, si bien los pesos tumorales finales fueron similares. La pérdida de peso corporal y el salteo de dosis fue mínimo con cada agente solo, pero la pérdida de peso corporal se exacerbó en el grupo de combinación que necesitan saltear la dosis. El hecho de que se observó regresión del tumor a pesar del salteo de dosis sugiere que usar un esquema de dosis intermitente debería mantener la eficacia y mejorar la tolerabilidad.

[00360] Al final del estudio de eficacia, se resecaron los tumores y procesaron para análisis histológico de los marcadores de proliferación (Ki67) y apoptosis (TUNEL). La administración del compuesto A como monoterapia (100 mg/kg q2d) se asoció con una reducción significativa de 44% de la fracción de células proliferantes. La administración de rapamicina como monoterpia también se asoció con una reducción (77%) de la fracción de células proliferantes. La administración combinada de Compuesto A y rapamicina produjo un fuerte efecto anti-proliferativo (96% de reducción) que estaba aumentado significativamente respecto del observado con la monoterapia (Fig. 6). La administración del Compuesto A como monoterapia se asoció con una inducción significativa de 3,6 veces de la fracción de células apoptóticas, mientras que la rapamicina administrada como monoterapia no ejerció efectos pro-apoptóticos. La administración combinada del Compuesto A y rapamicina produjo una inducción de 7 veces de la fracción de

células apoptóticas, que estaba significativamente aumentada respecto de la observada con la monoterapia (Fig. 7). En conjunto, estos datos indican que la coadministración de Compuesto A y rapamicina lleva a una reducción significativa de la proliferación de células tumorales y un aumento significativo de la apoptosis de células tumorales en comparación con cualquier agente administrado como monoterapia. Estos resultados respaldan el uso de un compuesto de Fórmula I en combinación con rapamicina en tumores con señalización de PI3K activada en forma constitutiva.

Modelo de xenoijerto de cáncer pulmonar de células no pequeñas - Un compuesto de Fórmula I en combinación con Carboplatino

[00361] El Compuesto A se analizó como agente único y en combinación con carboplatino en un modelo de tumor NSCLC. Calu-6 es es una línea celular humana de NSCLC que alberga una mutación activadora heterocigota en K-Ras (Q61K).

[00362] La administración oral del Compuesto A a 100 mg/kg q2d o 30 mg/kg bid a los ratones portadores de los tumores de Calu-6 produjo sustancial inhibición de crecimiento tumoral. Ver Figura 3. Ambos esquemas de dosis produjeron una similar inhibición de crecimiento tumoral. También se observó significativa inhibición de crecimiento tumoral con 50 mg/kg de carboplatino administrado i.v. q4d, pero no fue tan pronunciado como con el Compuesto A. La combinación del Compuesto A 100 mg/kg q2d y carboplatino fue superior al cualquiera de los agentes solo, sin embargo, la combinación del Compuesto A 30 mg/kg bid con carboplatino no fue significativamente diferente del Compuesto A 30 mg/kg bid

solo. La pérdida de peso corporal y el salteo de dosis fueron mínimos en todos los grupos y no se exacerbó en el grupo de combinación lo que indica que la combinación fue bien tolerada. Estos resultados respaldan el uso de un compuesto de Fórmula I tanto como agente único y en combinación con platinos en los tumores con mutaciones activadoras en K-Ras.

Modelo de xenoijerto de cáncer pulmonar de células no pequeñas - Un compuesto de Fórmula I en combinación con el Compuesto B

[00363] El Compuesto A se analizó tanto como agente único como en combinación con el Compuesto B, un inhibidor de EGFR en un modelo de tumor NSCLC. La línea celular de carcinoma de pulmón de células no pequeñas A549 humanoas alberga una mutacíon de detención homocigota en el gen que codifica LKB1, y una mutación activadora G12S en K-Ras, que promueve la activación de PI3K y mTOR. Las células A549 también expresan EGFR de tipo salvaje.

[00364] La administracion de agente único oral del Compuesto B a 30 mg/kg qd durante 18 días causó una inhibición significativa del crecimiento del tumor de 80%. Ver Fig. 4a. El Compuesto A administrado como agente único a 30 mg/kg causó una inhibición significativa del crecimiento del tumor de 80%. La aadministración oral del Compuesto B a 30 mg/kg qd seguida por la administración del Compuesto A a 30 mg/kg qd después de aproximadamente seis horas llevó a un TGI significativa de 93%, con una tendencia a un incremento de la eficacia antitumoral en comparación con la eficacia del tratamiento único, si bien no alcanzó significancia estadística en estos estudios. Una posible explicación para el modesto efecto de la combinación es la corta duración del período de

dosificación (14 días), que puede ser demasiado corto para observar al beneficio completa de la combinación. Los regimenes de dosificación más largos pueden producir diferencias más significativas, ya que el efecto previsto de inhibición dual de PI3K/mTOR y EGFR sobre el crecimiento y supervivencia celular es más evidente.

[00365] Como agente único del Compuesto B dosificado a 30 mg/kg qd fue en general bien tolerado, con un peso corporal de 1,5 a 7% sin omisión de dosis. El Compuesto A con una dosis de 30 mg/kg qd también fue tolerado sin salteo de dosis y no se observó pérdida de peso corporal significativa. La coadministración del Compuesto B a 30 mg/kg qd con el Compuesto A a 30 mg/kg qd se asoció con una pérdida de peso corporal de 3 a 12%, que necesitó salteo de dosis mínimo (2 dosis) sin salteo de dosis durante los últimos 8 días.

Modelo de xenoinjerto de cáncer de mamas - Un compuesto de Fórmula I en combinación con el Compuesto B

[00366] El Compuesto A, un inhibidor de PI3K, se analizó tanto como agente único y en combinación con el Compuesto B, un inhibidor de EGFR, en un modelo de tumor de cáncer mamario. L La línea celular de adenocarcinoma mamario humano MCF7 alberga una mutación activadora heterocigota en PI3K (PI3KCA/E545K) y expresa EGFR tipo salvaje.

[00367] El Compuesto B se administró por vía oral una vez por día (qd) a 30 mg/kg, y el Compuesto A se administró por vía oral una vez por día a 30 mg/kg. Las terapias de combinación consistían en la administración del Compuesto B a 30 mg/kg qd seguido por administración del Compuesto A a 30 mg/kg qd dentro de aproximadamente 6-7 horas. La administración de Compuesto B como agente único a una dosis de 30 mg/kg qd durante 14 días causó una inhibición del crecimiento del tumor de 38 a 61%. Ver Figuras 4b-1 y

4b-2. La inhibición del crecimiento del tumor de 53-76% se observó con el Compuesto A con una dosis de 30 mg/kg qd. La combinación del Compuesto B con una dosis de 30 mg/kg qd con Compuesto A con una dosis de 30 mg/kg qd produjo una inhibición significativa del crecimiento del tumor de 83-87%, con una tendencia al incremento de la eficacia antitumoral en comparación con la eficacia de los tratamientos simples, si bien esto no alcanzó significancia estadística en estos estudios. Una posible explicación para el modesto efecto de la combinación es la corta duración del período de dosificación (14 días), que puede ser demasiado corto para observar el beneficio completo de la combinación. Los regimenes de dosis más largos producen diferencias más significativas, ya que el efecto previsto de la inhibición dual de PI3K y EGFR sobre el crecimiento y superveniencia celular es más evidente. En ambos estudios (Fig 4b-1 y 4b-2) el tamaño del tumor promedio en los grupos de combinación está aún disminuyendo en el último punto de medición.

[00368] Al final del estudio de eficacia, se resecaron los tumores y procesaron para análisis de las células proliferantes (tinción con Ki67), determinación de densidad de microvasos (MVD) después de la inmunotinción para CD31, y para análisis TUNEL (células apoptóticas) (ver Tablas 8 y 9). La administración del Compuesto B con una dosis de 30 mg/kg qd produjo una reducción significativa de 14 a 19% de la cantidsad de células tumorales proliferantes positivas a Ki67 viables en comparación con el grupo control tratado con vehículo culo. El Compuesto A con una dosis de 30 mg/kg qd produjo una reducción significativa de 13% de las células positivas Ki67 solo en el Estudio 2. La combinación del Compuesto B con el Compuesto A produjo una reducción

significativa de 23 a 37% de las células tumorales positivas Ki67, que fue significativamente más eficaz en este modelo que los tratamientos con agente único (sin embargo no mejor que la rama de Compuesto B único del Estudio 1). El tratamiento con el Compuesto B con una dosis de 30 mg/kg qd produjo una inducción significativa de las células positivas a TUNEL (apoptóticas) en comparación con el grupo tratado con control de vehículo. La administración del Compuesto A con una dosis de 30 mg/kg qd no produjo una inducción significativa de las células tumorales apoptóticas. La combinación del Compuesto B con el Compuesto A no produjo una inducción significativa de apoptosis en comparación con el grupo control tratado con vehículo. La administración del Compuesto B con una dosis de 30 mg/kg qd y el Compuesto A con una dosis de 30 mg/kg qd produjo una reducción significativa de 31% y 32%, respectivamente, en los vasos tumorales positivos a CD31. La combinación del Compuesto B con Compuesto A produjo una reducción de 22% del MVD, que no fue significativamente diferente del tratamiento de agente único con el Compuesto B o Compuesto A. Los análisis inmunohistoquímicos del final del estudio sugieren que la co-administración del Compuesto B y Compuesto A puede proporcionar un beneficio adicional sobre la efecto anti-proliferativo, pero no sobre el efecto anti-angiogénico de los agentes únicos en los tumores MCF-7.

[00369] Como agente único el Compuesto B con una dosis de 30 mg/kg qd fue en general bien tolerado, con una pérdida de peso corporal de 4,5 a 6,1% (no significativamente diferente del grupo control tratado con vehículo) y 7 a 13 omisiones de dosis. La mayoría de las dosis salteadas (11 de 13) del Estudio 1 provino de un ratón

que mantiene un bajo peso corporal a lo largo del estudio desde la dosis del día 3. La administración del Compuesto A con una dosis de 30 mg/kg qd también fue bien tolerada con 3 a 9 dosis salteadas y pérdida o aumento de peso corporal no significativos. La coadministración del Compuesto B a 30 mg/kg qd con el Compuesto A a 30 mg/kg qd se asoció con una pérdida de peso corporal de 0,3 a 10% a lo largo del estudio y salteo de dosis mínimo (6 a 11 dosis). Al fin del perdió de dosificación no hubo pérdida de peso significativo de 0,3 a 6,2% de peso corporal.

Modelo de xenoijerto de cáncer de mamas – Un compuesto de Fórmula I en combinación con Erlotinib

[00370] El Compuesto A se analizó como agente único y en combinación con erlotinib, en un modelo de tumor resistente a erolitinib con señalización de PI3K. MDA-MB-468 es una línea celular de carcinoma de mamas humano que tiene un aumento del número de copias del gen EGFR y una supresión homocigota de PTEN. El tratamiento in vitro de estas células con los inhibidores de EGFR tales como erlotinib inhiben la actividad de EGFR pero no puede regular por disminución la vía de PI3K.

[00371] La administración oral de erlotinib a 100 mg/kg qd a los ratones que portan los tumores de MDA-MB-468 produjeron una inhibicion significativa pero incompleta del crecimiento tumoral. Ver Figura 5. La administración oral del Compuesto A a 100 mg/kg q2d también produjo inhibición de crecimiento tumoral. La combinación de los dos agentes fue levemente superior a cualquiera de los agentes solos. El incremento relativamente modesto de la eficacia del grupo de combinación podría mejorar por la alteración de la dosis y el esquema de administración del Compuesto A.

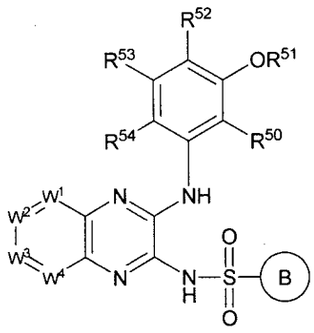
[00372] Los ratones a los que se administró el Compuesto A a 100 mg/kg q2d exhibieron una tasa de aumento de peso corporal comparable con los vehículos control. Los ratones a los que se administró erlotinib exhibieron un reducción evidente de su tasa de aumento de peso corporal con respecto a los controles con vehículo. La coadministración con erlotinib produjo una pérdida sustancial del peso corporal en los ratones tratados con el Compuesto A (10% pérdida de peso corporal desde el inicio de la dosificación). Coherente con estos datos, se requirió solo un mínimo salteo de dosis cuando el Compuesto A se administró como monoterapia (1-3 dosis salteadas), pero se requirió un sustancial salteo de dosis para el Compuesto A cuando se coadministró con erlotinib. Estos resultados respaldan el uso de un compuesto de Fórmula I en combinación con erlotinib en tumores que expresan receptores de EGF y albergan supresiones de PTEN.

[00373] La siguiente invención ha sido descripta en algún detalle a modo de ilustración y ejemplo con fines de claridad y comprensión. La invención se ha descripto con referencia a varias formas de realización y técnicas específicas. Sin embargo, se debe considerar que se pueden realizar muchas variaciones y modificaciones mientras que continúe dentro del espíritu y alcance de la invención. Será obvio para los expertos en la técnica que se pueden practicar cambios y modificaciones dentro del alcance de las reivindicaciones adjuntas. En consecuencia, se considera que la anterior descripción es ilustrativa y no restrictiva. El alcance de la invención debe, en consecuencia, ser determinado no con referencia a la anterior descripción, sino que en cambio se debe determinar con referencia a las siguientes

reivindicaciones adjuntas, junto con el alcance pleno de las equivalentes a lo que facultan dichas reivindicaciones. Todas las patentes, solicitudes de patente y publicaciones mencionadas en esta solicitud se incorporan en la presente por referencia en su totalidad para los fines en la misma medida que si cada patente, solicitud de patente y publicación individual fuera indicada individualmente de este modo.

REIVINDICACIONES

1. Un método de tratamiento del cáncer, dicho método comprende administrar a un paciente cantidad terapéuticamente efectiva de un compuesto de Fórmula I:



I

o un isómero simple de este donde el compuesto está opcionalmente como una sal farmacéuticamente aceptable y en forma adicional opcionalmente como un hidrato y en forma adicional opcionalmente como un solvato de este; o administrar una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de un compuesto de Fórmula I y al menos uno de un portador, excipiente o diluyente farmacéuticamente aceptable en combinación con uno o más y tratamientos seleccionados de modo independiente cirugía, uno o más agentes quimioterapéuticos, una o más de las terapias hormonales, uno o más anticuerpos, una o más inmunoterapias, terapia de yodo radiactivo, y radiación donde el Compuesto de Fórmula I es aquel donde:

R^1 es hidrógeno, alquilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, cicloalquilalquilo opcionalmente sustituido, arilo opcionalmente sustituido, arilalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente sustituido, heterocicloalquilalquilo opcionalmente

sustituido, heteroarilo opcionalmente sustituido o heteroarilalquilo opcionalmente sustituido;

R^2 es hidrógeno o alquilo donde el alquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 grupos R^8;

X es $-NR^3-$;

R^3 es hidrógeno;

R^4 es alquilo opcionalmente sustituido;

R^5 es hidrógeno; y

R^6 es fenilo, acilo, o heteroarilo donde el fenilo y heteroarilo están opcionalmente sustituidos con 1, 2, 3, 4, o 5 grupos R^9;

cada R^8, cuando está presente, es de modo independiente hidroxi, halo, alcoxi, haloalcoxi, amino, alquilamino, dialquilaminoalquilo, o alcoxialquilamino; y

cada R^9, cuando está presente, es de modo independiente halo, alquilo, haloalquilo, alcoxi, haloalcoxi, ciano, amino, alquilamino, dialquilamino, alcoxialquilo, carboxialquilo, alcoxicarbonilo, aminoalquilo, cicloalquilo, arilo, arilalquilo, ariloxi, heterocicloalquilo, o heteroarilo y donde el cicloalquilo, arilo, heterocicloalquilo, y heteroarilo, cada uno solo o como parte de otro grupo de R^9, están opcionalmente sustituidos de modo independiente con 1, 2, 3, o 4 grupos seleccionados de halo, alquilo, haloalquilo, hidroxi, alcoxi, haloalcoxi, amino, alquilamino, y dialquilamino.

2. El método de acuerdo con la reivindicación 1 donde el cáncer se selecciona de cáncer de mamas, cáncer de colon, cáncer rectal, cáncer de endometrio, tumores carcinoides gastrointestinales, tumores estromales

gastrointestinales, glioblastoma, carcinoma hepatocelular, cáncer pulmonar de células pequeñas, cáncer pulmonar de células no pequeñas, melanoma, cáncer ovárico, cáncer cervical, cáncer pancreático, carcinoma prostático, leucemia mielógena aguda, leucemia mielógena crónica, linfoma no Hodgkin, y carcinoma tiroideo.

3. El método de acuerdo con la reivindicación 1 o 2 donde el tratamiento es uno o dos agentes quimioterapéuticos.

4. El método de acuerdo con las reivindicaciones 1 o 2 donde el tratamiento es un anticuerpo seleccionado de un anticuerpo EGFR y un anticuerpo ErbB2, o el tratamiento es uno o dos agentes quimioterapéuticos seleccionados de modo independiente rapamicina, un análogo de rapamicina, un agente alquilante, un taxano, un platino, un inhibidor de EGFR, y un inhibidor de ErbB2.

5. El método de acuerdo con la reivindicación 4 donde el tratamiento es uno o dos agentes quimioterapéuticos seleccionados de modo independiente rapamicina, paclitaxel, carboplatino, lapatinib, erlotinib, y *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5*r*,6a*S*)-2-metiloctahidrociclopenta-[*c*]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, opcionalmente en forma de sal farmacéuticamente aceptable y en forma adicional opcionalmente como un hidrato y en forma adicional opcionalmente como un solvato de este.

6. El método de acuerdo con la reivindicación 3 donde el tratamiento es un agente quimioterapéutico y el agente quimioterapéutico es un inhibidor de EGFR.

7. El método de acuerdo con la reivindicación 3 donde el tratamiento es un agente quimioterapéutico y el agente quimioterapéutico es un platino.

8. El método de acuerdo con la reivindicación 3 donde el tratamiento es un agente quimioterapéutico y el agente quimioterapéutico es un taxano.

9. El método de acuerdo con la reivindicación 3 donde el tratamiento es un agente quimioterapéutico y el agente quimioterapéutico es rapamicina o un análogo de rapamicina.

10. El método de acuerdo con la reivindicación 3 donde el tratamiento es un agente quimioterapéutico y el agente quimioterapéutico es *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5r,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, *N*-(4-bromo-3-cloro-2-fluorofenil)-7-({[(3a*R*,5r,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5s,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, o *N*-(4-bromo-3-cloro-2-fluorofenil)-7-({[(3a*R*,5s,6a*S*)-2-metiloctahidrociclopenta[c]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina; cada una de las cuales está opcionalmente en forma de sal farmacéuticamente aceptable y en forma adicional opcionalmente como un hidrato y en forma adicional opcionalmente como un solvato de este.

11. El método de acuerdo con la reivindicación 1 donde el cáncer es cáncer de próstata y el tratamiento es uno o dos agentes quimioterapéuticos seleccionado de modo independiente de rapamicina, paclitaxel, y docetaxel.

12. El método de acuerdo con la reivindicación 1 donde el cáncer es cáncer de mamas y el tratamiento es un agente quimioterapéutico y el agente quimioterapéutico es lapatinib.

13. El método de acuerdo con la reivindicación 1 donde el cáncer es cáncer de mamas y el tratamiento es un agente quimioterapéutico y el agente quimioterapéutico es erlotinib.

14. El método de acuerdo con la reivindicación 1 donde el cáncer es cáncer de mamas y el tratamiento es un agente quimioterapéutico y el agente quimioterapéutico es *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5*r*,6a*S*)-2-metiloctahidrociclopenta-[*c*]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, opcionalmente en forma de sal farmacéuticamente aceptable y en forma adicional opcionalmente como un hidrato y en forma adicional opcionalmente como un solvato de este.

15. El método de acuerdo con la reivindicación 1 donde el cáncer es cáncer pulmonar de células no pequeñas y el tratamiento es un agente quimioterapéutico donde el agente quimioterapéutico es carboplatino.

16. El método de acuerdo con la reivindicación 1 donde el cáncer es cáncer pulmonar de células no pequeñas y el tratamiento es un agente quimioterapéutico donde el

agente quimioterapéutico es *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5*r*,6a*S*)-2-metiloctahidrociclopenta-[*c*]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, opcionalmente en forma de sal farmacéuticamente aceptable y en forma adicional opcionalmente como un hidrato y en forma adicional opcionalmente como un solvato de este.

17. El método de la reivindicación 1 o 2 donde el compuesto de fórmula I se selecciona de:

8-etil-2-(etilamino)-4-metil-6-fenilpirido[2,3-d]pirimidin-7(8*H*)-ona;
6-bifenil-4-il-8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
6-(2,4-difluorofenil)-8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
6-(3-cloro-4-fluorofenil)-8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-[4-(metiloxi)fenilo]pirido[2,3-d]pirimidin-7(8*H*)-ona;
6-(2,4-diclorofenil)-8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
6-(3,4-difluorofenil)-8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-[2-(metiloxi)fenilo]pirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-[4-(feniloxi)fenilo]pirido[2,3-d]pirimidin-7(8*H*)-ona;
6-[2,4-bis(metiloxi)fenilo]-8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-6-(3-fluorofenil)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-6-(2-fluorofenil)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-[3-(trifluorometil)fenilo]pirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-6-(4-fluorofenil)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-(2-tienil)pirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-[3-(metiloxi)fenilo]pirido[2,3-d]pirimidin-7(8*H*)-ona;
6-(3-clorofenil)-8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;

6-(4-clorofenil)-8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-(3-tienil)pirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-(4-metil-2-tienil)pirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-(4-metil-3-tienil)pirido[2,3-d]pirimidin-7(8*H*)-ona;
1,1-dimetiletil 2-[8-etil-2-(etilamino)-4-metil-7-oxo-7,8-dihidropirido[2,3-d]pirimidin-6-il]-1*H*-pirrole-1-carboxilate
8-etil-2-(etilamino)-4-metil-6-(1*H*-pirrol-2-il)pirido[2,3-d]pirimidin-7(8*H*)-ona;
6-(5-cloro-2-tienil)-8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-pirimidin-5-ilpirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-6-(3-fluoropiridi*N*-4-il)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-6-furan-3-il-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-[1-(fenilmetil)-1*H*-pirazol-4-il]pirido[2,3-d]pirimidin-7(8*H*)-ona;
2-(etilamino)-4-metil-8-(1-metiletil)-6-(2-tienil)pirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-6-(1*H*-indol-6-il)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-(5-fenilo-2-tienil)pirido[2,3-d]pirimidin-7(8*H*)-ona;
2-(etilamino)-6-furan-3-il-4-metil-8-(1-metiletil)pirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-(1*H*-pirazol-5-il)pirido[2,3-d]pirimidin-7(8*H*)-ona;
8-ciclohexil-2-(etilamino)-4-metil-6-(2-tienil)pirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-(1,3-tiazol-2-il)pirido[2,3-d]pirimidin-7(8*H*)-ona;
8-ciclopentil-2-(etilamino)-4-metil-6-(1*H*-pirazol-3-il)pirido[2,3-d]pirimidin-7(8*H*)-ona;
2-(etilamino)-4-metil-8-(1-metiletil)-6-(1*H*-pirazol-5-il)pirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-(1*H*-pirazol-1-il)pirido[2,3-d]pirimidin-7(8*H*)-ona;
2-(etilamino)-4-metil-8-(1-metiletil)-6-(1*H*-pirazol-1-il)pirido[2,3-d]pirimidin-7(8*H*)-ona;
8-ciclopentil-2-(etilamino)-4-metil-6-(1*H*-pirazol-1-il)pirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-4-metil-6-(1*H*-pirazol-5-il)-2-[(2,2,2-trifluoroetil)amino]pirido[2,3-*d*]pirimidin-7(8*H*)-ona;

2-amino-8-etil-4-metil-6-(1*H*-pirazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-(etilamino)-4-metil-6-(1*H*-pirazol-3-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
8-etil-4-metil-2-(metilamino)-6-(1*H*-pirazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-ciclopentil-4-metil-6-(1*H*-pirazol-3-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
8-etil-2-[(2-fluoroetil)amino]-4-metil-6-(1*H*-pirazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-4-metil-8-(1-metiletil)-6-(1*H*-pirazol-3-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-4-metil-8-(fenilmetil)-6-(1*H*-pirazol-3-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-4-metil-6-(4-metil-3-tienil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-4-metil-6-(2-tienil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-6-(4-fluorofenil)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-6-(3-fluorofenil)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-6-(2-fluorofenil)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-4-metil-6-(3-tienil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-6-furan-3-il-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-4-metil-6-fenilpirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-4-metil-6-[4-(metiloxi)fenilo]pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-6-(4-clorofenil)-8-etil-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-6-(3-clorofenil)-8-etil-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-6-isoxazol-4-il-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-6-furan-2-il-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-6-(2,4-diclorofenil)-8-etil-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona;
5-(2-amino-8-etil-4-metil-7-oxo-7,8-dihidropirido[2,3-*d*]pirimidin-6-il)tiofeno-2-carbonitrilo
2-amino-8-etil-4-metil-6-pirimidin-5-ilpirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-6-(1*H*-imidazol-5-il)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona;

2-amino-8-etil-4-metil-6-(1*H*-1,2,3-triazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-4-metil-6-(1*H*-pirazol-4-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-4-metil-6-(1,3-tiazol-2-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-4-metil-6-(1*H*-tetrazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-4-metil-6-(1-metil-1*H*-pirrol-2-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-4,8-dietil-6-(1*H*-pirazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona; y
2-amino-8-ciclopentil-4-metil-6-(1,3-tiazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;

donde el compuesto está opcionalmente como una sal farmacéuticamente aceptable y en forma adicional y opcional como un hidrato y en forma adicional opcionalmente como un solvato de este.

18. El método de acuerdo con las reivindicaciones 1, 2, 4, o 17 donde el tratamiento es un anticuerpo seleccionado de un anticuerpo EGFR y un anticuerpo ErbB2, o el tratamiento es uno o dos agentes quimioterapéuticos seleccionados de modo independiente rapamicina, un análogo de rapamicina, un agente alquilante, un taxano, un platino, un inhibidor de EGFR, y un inhibidor de ErbB2.

19. El método de acuerdo con la reivindicación 18 donde el tratamiento es uno o dos agentes quimioterapéuticos seleccionados de modo independiente rapamicina, paclitaxel, carboplatino, lapatinib, erlotinib, y *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5*r*,6a*S*)-2-metiloctahidrociclopenta-[*c*]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, opcionalmente en forma de sal farmacéuticamente aceptable

y en forma adicional opcionalmente como un hidrato y en forma adicional opcionalmente como un solvato de este.

20. El método de acuerdo con la reivindicación 1, 2, 3, 4, o 17 donde el tratamiento es un agente quimioterapéutico donde el agente quimioterapéutico es *N*-(3,4-dicloro-2-fluorofenil)-7-({[(3a*R*,5*r*,6a*S*)-2-metiloctahidrociclopenta-[*c*]pirrol-5-il]metil}oxi)-6-(metiloxi)quinazolin-4-amina, opcionalmente en forma de sal farmacéuticamente aceptable y en forma adicional opcionalmente como un hidrato y en forma adicional opcionalmente como un solvato de este.

21. El método de acuerdo con la reivindicación 1, 2, 3, 4, o 17 donde el tratamiento es un agente quimioterapéutico donde el agente quimioterapéutico es erlotinib.

22. El método de acuerdo con la reivindicación 1, 2, 3, 4, o 17, donde el tratamiento es un agente quimioterapéutico donde el agente quimioterapéutico es lapatinib.

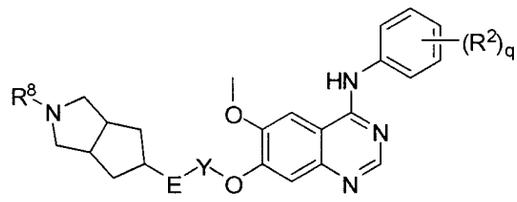
23. El método de acuerdo con la reivindicación 1, 2, 3, 4, o 17 donde el tratamiento es un agente quimioterapéutico donde el agente quimioterapéutico es carboplatino.

24. El método de acuerdo con la reivindicación 1, 2, 3, 4, o 17 donde el tratamiento es un agente quimioterapéutico donde el agente quimioterapéutico es paclitaxel.

25. El método de acuerdo con la reivindicación 1, 2, 3, 4, o 17 donde el tratamiento es un agente quimioterapéutico donde el agente quimioterapéutico es rapamicina.

26. El método de acuerdo con la reivindicación 1, 2, 3, 4, o 17 donde el tratamiento es un anticuerpo seleccionado de bevacizumab, trastuzumab, cetuximab, y panitumumab.

27. El método de acuerdo con la reivindicación 1, 2, 3, 4, o 17 donde el tratamiento es un agente quimioterapéutico donde el agente quimioterapéutico es de la fórmula 100:



100

donde q es 1, 2, o 3; E es $-NR^9-$, -O-, o ausente e Y es $-CH_2CH_2-$, $-CH_2-$, o ausente con la condición de que cuando E es $-NR^9-$ o -O-, por lo tanto Y es $-CH_2CH_2-$; R^2 se selecciona de halógeno, trihalometilo, -CN, $-NO_2$, $-OR^3$, y alquilo inferior; R^8 se selecciona de -H, alquilo inferior, $-C(O)OR^3$, $-C(O)N(R^3)R^4$, $-SO_2R^4$, y $-C(O)R^3$; R^9 es hidrógeno o alquilo inferior; R^3 es hidrógeno o R^4; R^4 se selecciona de alquilo inferior, arilo, arilalquilo inferior, heterociclilo, y heterociclilalquilo inferior; o R^3 y R^4, cuando se toman juntos con un nitrógeno común al que están unidos, forma un heterociclilo de cinco a siete miembros, dicho heterociclilo de cinco a siete miembros opcionalmente que contiene uno o más

heteroátomos adicionales seleccionados de N, O, S, y P; o uno de sus isómeros geométricos, estereoisómeros, racematos, enantiómeros o diastereómeros simples y opcionalmente en forma de sal farmacéuticamente aceptable, en forma adicional opcionalmente como un solvato y en forma adicional como un hidrato de este.

RESUMEN

La presente invención proporciona métodos de tratar cáncer por la administración de un compuesto de Fórmula I, opcionalmente en forma de sus sales farmacéuticamente aceptable, sus solvatos y/o hidratos, en combinación con otros tratamientos de cáncer.

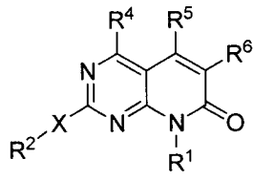


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Fig. 1. Compuesto A + Taxol en modelo de tumor de carcinoma de próstata PC-3

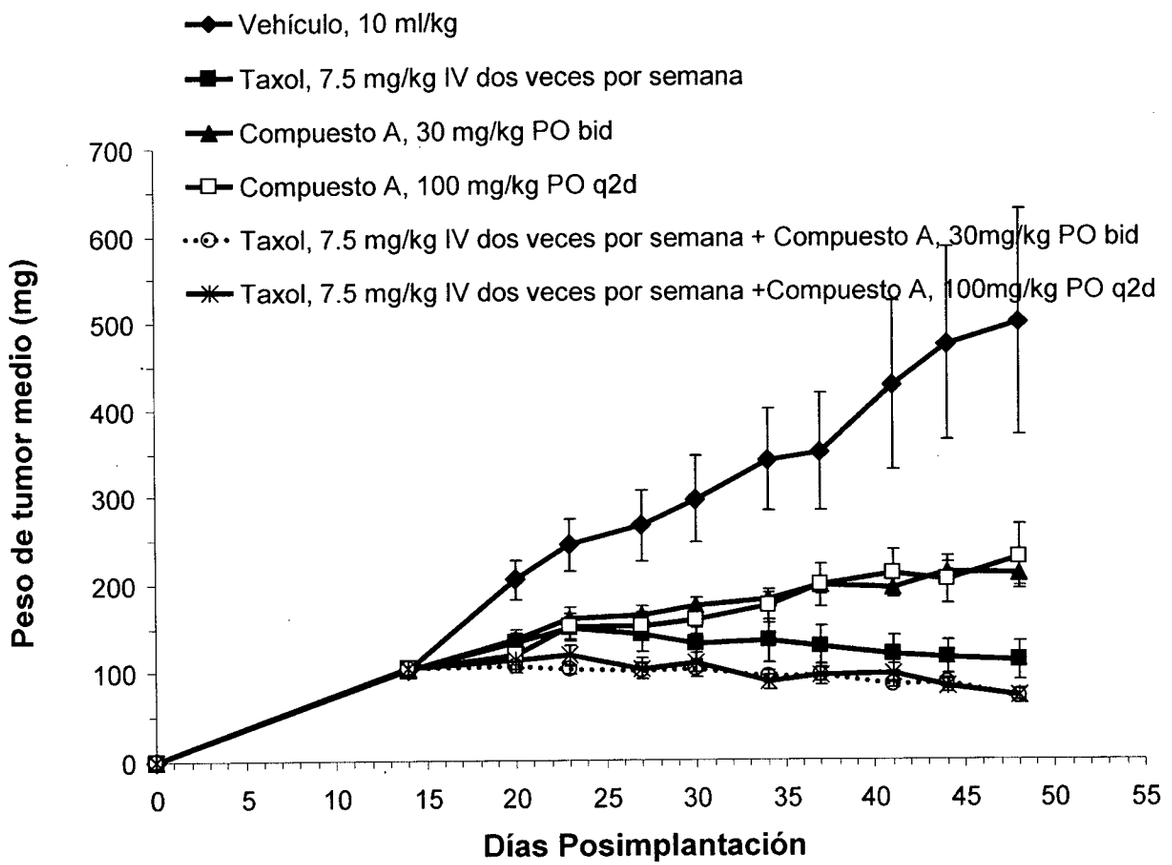

Fig. 2. Compuesto A + Rapamicina en modelo de tumor de carcinoma de próstata PC-3

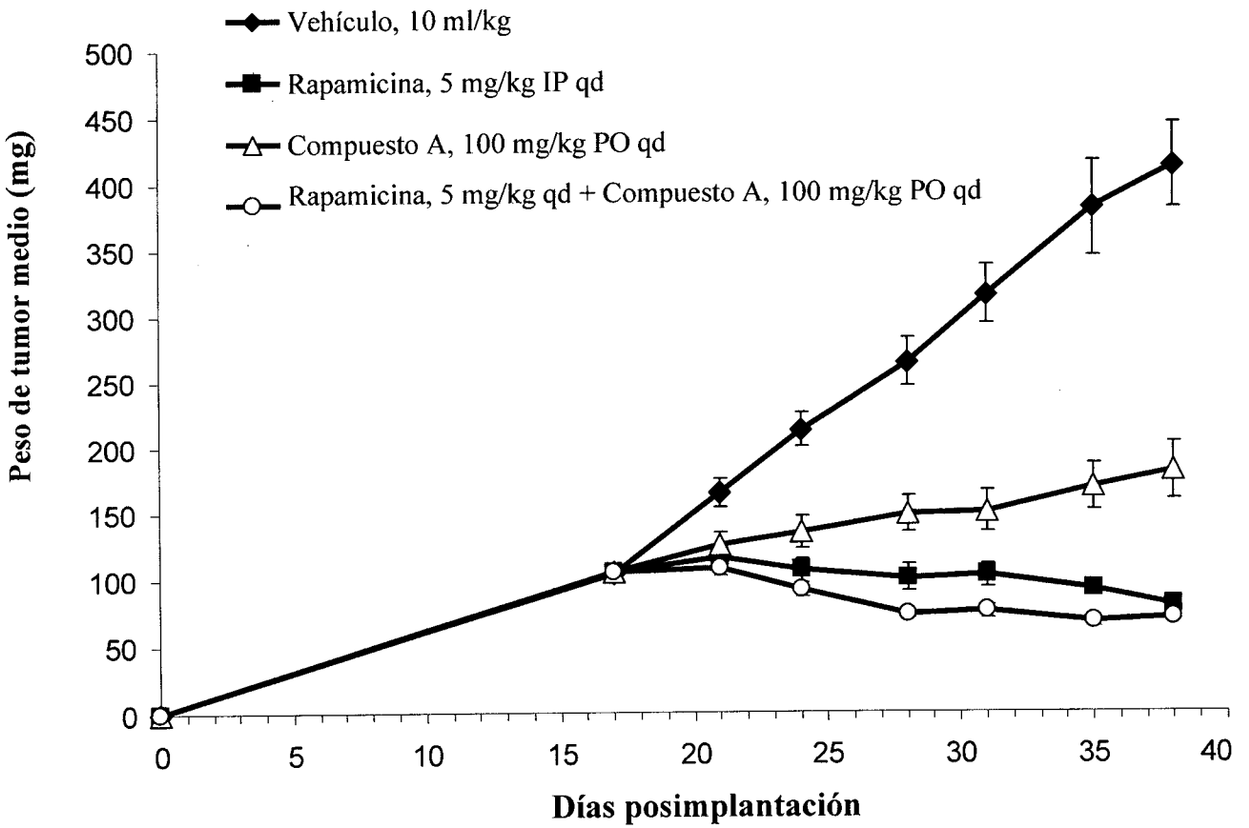

Fig. 3. Compuesto A + Carboplatino en modelo de tumor NSCLC Calu-6

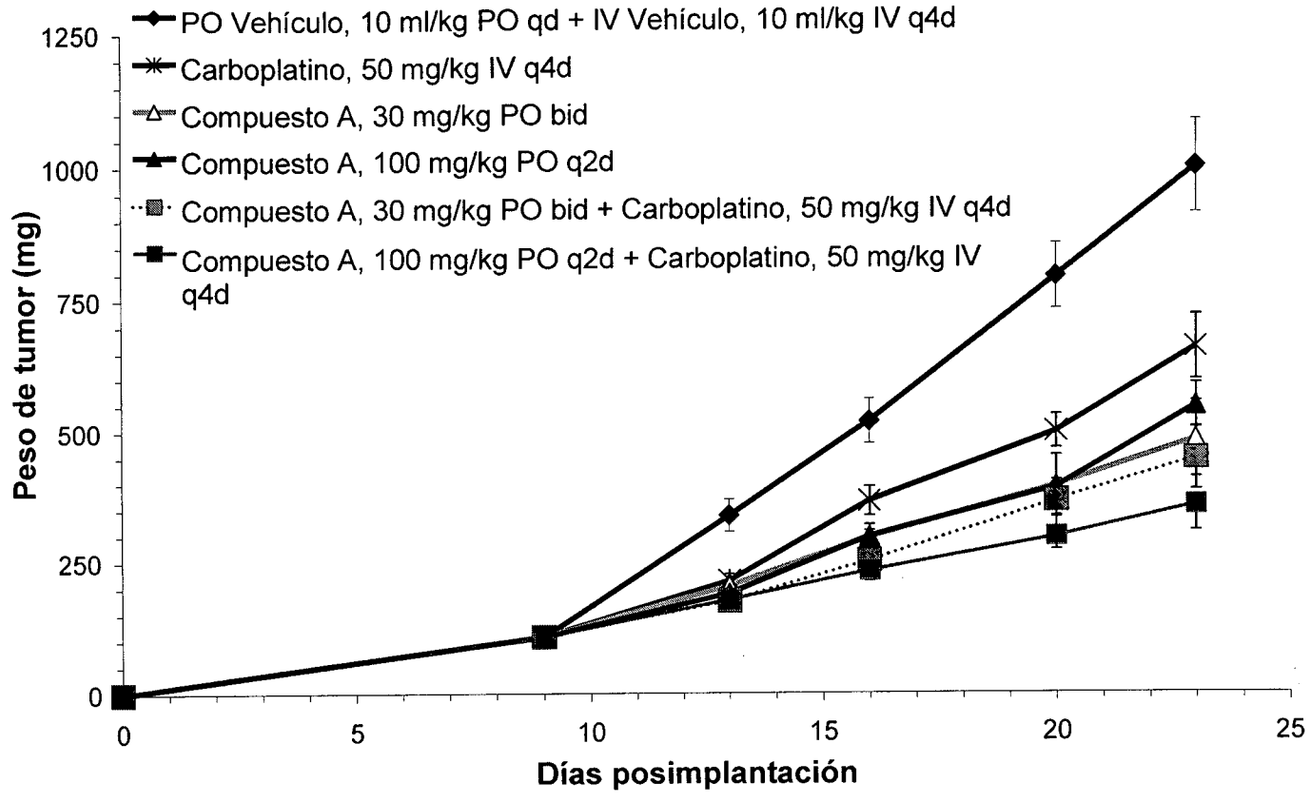

Fig. 4a. Compuesto A + Compuesto B en modelo de tumor de cáncer de pulmón de células no pequeñas A549

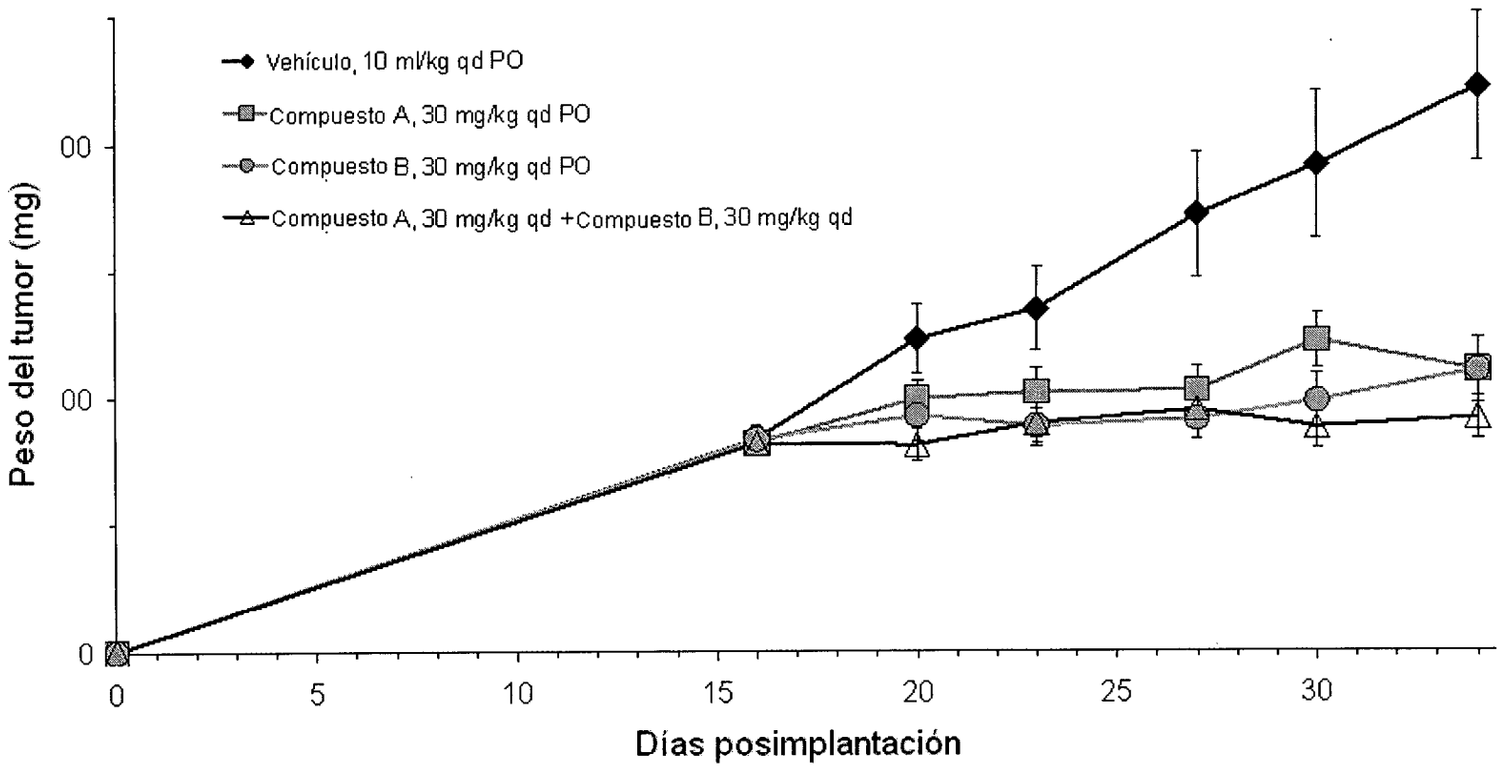

Fig. 4b-1. Compuesto A + Compuesto B en modelo de tumor de cáncer de mamas MCF7 (Estudio 1)

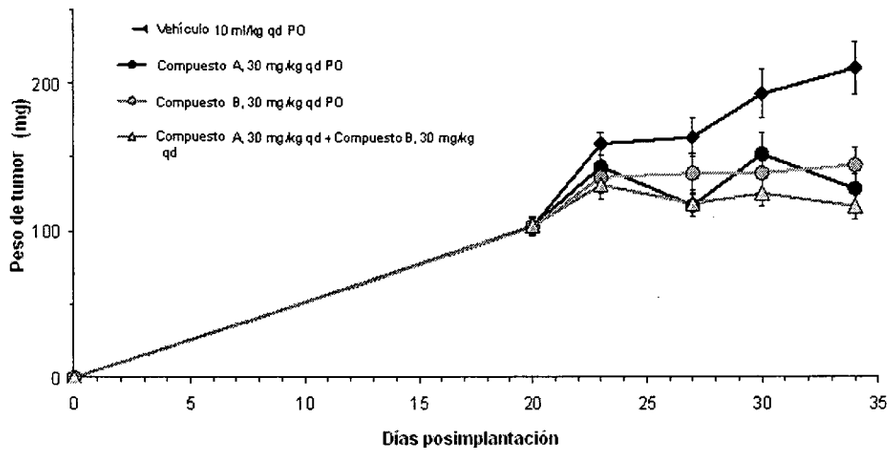

Fig. 4b-2. Compuesto A + Compuesto B en modelo de tumor de cáncer de mamas MCF7 (Estudio 2)

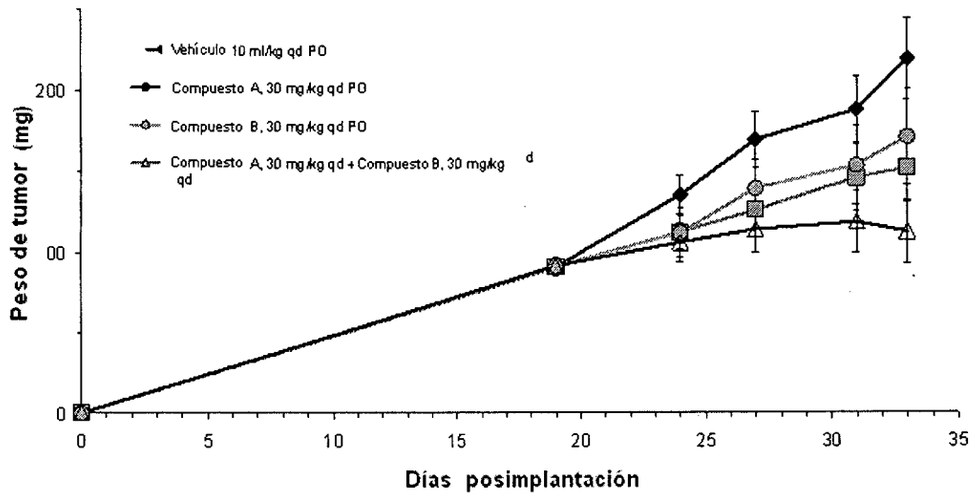

Fig. 5. Compuesto A + Erlotinib en modelo de tumor de carcinoma de mamas MDA-MB-468

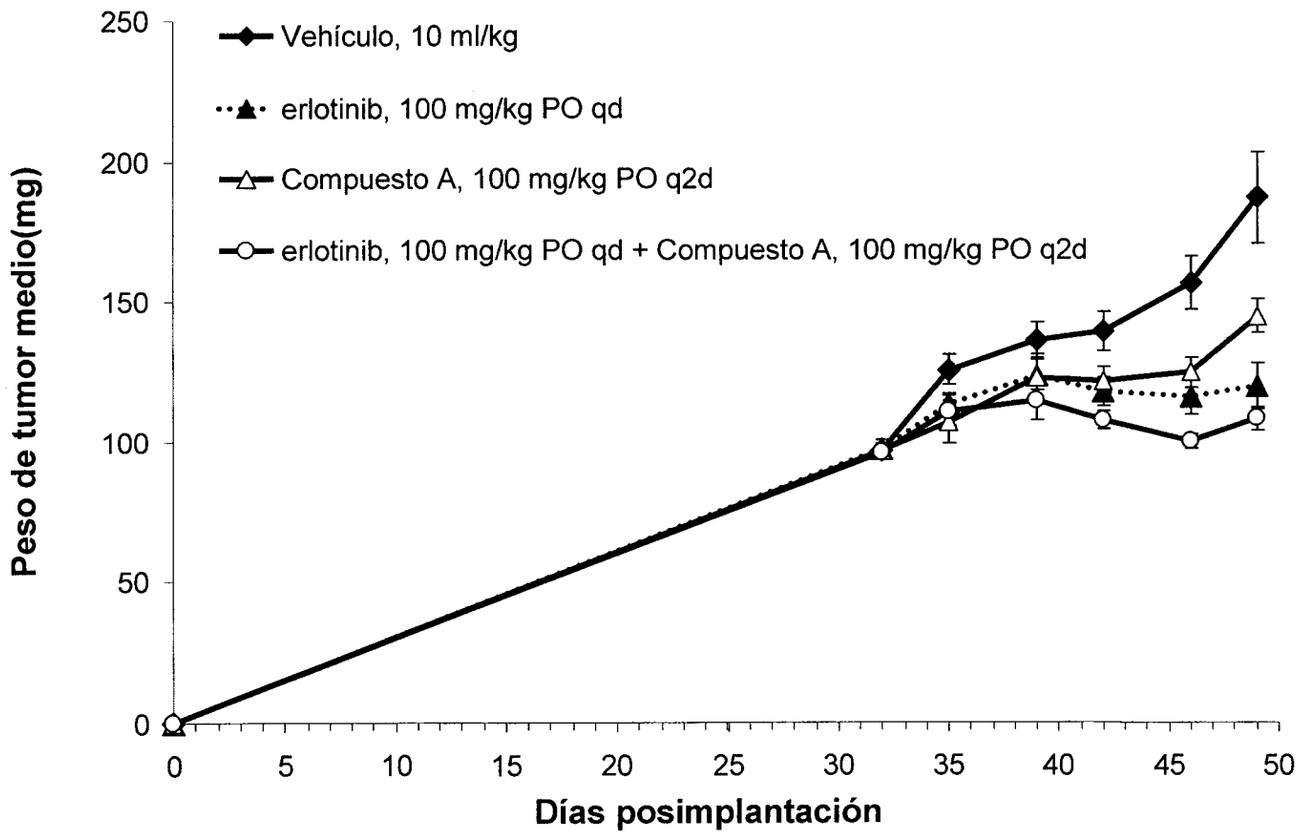

Fig. 6. Análisis histológico de marcadores de proliferación (Ki67)

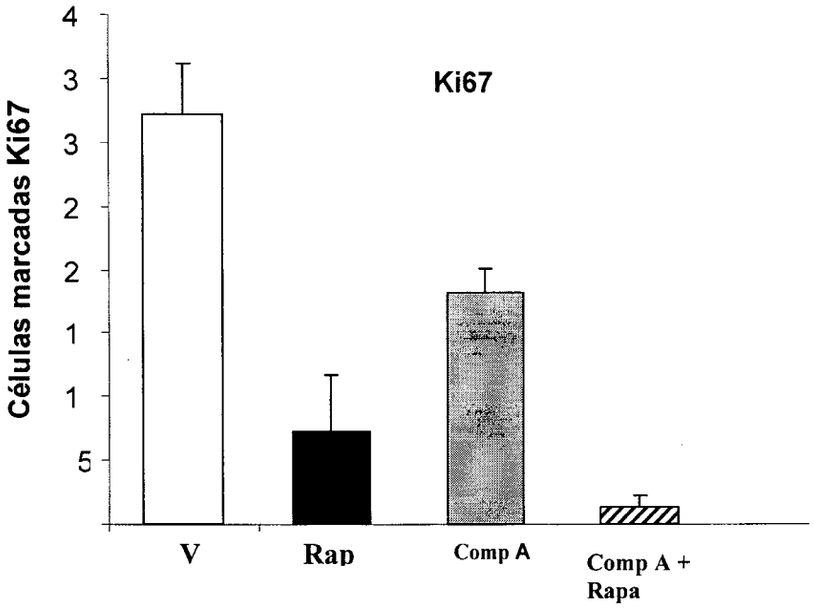

Fig. 7. Análisis histológico de marcadores de apoptosis (TUNEL)

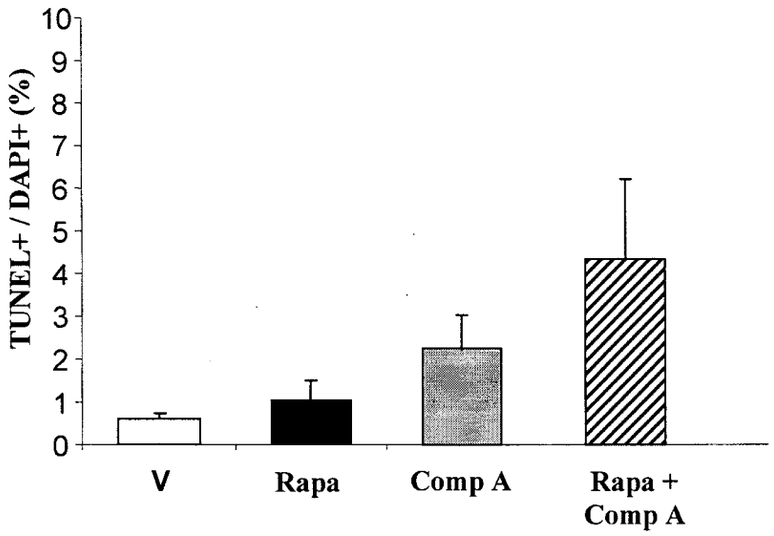

Table 8. Análisis Immunohistoquímico de proliferación, Vascularidad y apoptosis en tumores de xenoinjertos MCF7 (Estudio 1)

Grupo	Expresión de Ki67		Análisis TUNEL		Análisis CD31	
	% Células positivas[a]	% Reducción[b]	% Células positivas[a]	Veces de aumento[b]	MVD[c]	% Reducción[b]
Vehículo 1 Vehículo 2	39,4 ± 2,84	na	0,95 ± 0,45	na	43,2 ± 2,45	na
Comp B 30 mg/kg Vehículo 2	33.7 ± 4,69	14	1.52 ± 0,60	1.6 (ns)	29.7 ± 5,13	31
Vehículo 1 Comp A 30 mg/kg	36.4 ± 3,54	8 (ns)	1.35 ± 0.52	1.4 (ns)	29.3 ± 5,17	32
Comp B 30 mg/kg Comp A 30 mg/kg	30.4 ± 4,34	23	1.52± 0,49	1.6 (ns)	33.8 ± 5,70	22

[a]Valores son media ± SD

[b]Valores son relativos al control con vehículo

[c] Densidad vascular media

na: no aplicable; ns: no significativo

Tabla 9. Análisis Immunohistoquímico de proliferación, Vascularidad y apoptosis en tumores de xenoinjertos MCF7 (Estudio 2)

Grupo	Expresión de Ki67		Análisis TUNEL	
	% Células positivas[a]	% Reducción[b]	% Células positivas[a]	Veces de aumento[b]
Vehículo 1 Vehículo 2	44,5 ± 4,07	na	0,32 ± 0,19	na
Comp B 30 mg/kg Vehículo 2	35,9 ± 5,97	19	0,51 ± 0,26	1,6 (ns)
Vehículo 1 Comp A 30 mg/kg	38,7 ± 1,98	13	054 ± 0,22	1,7 (ns)
Comp B 30 mg/kg Comp A 30 mg/kg	28,0 ± 1,94	37	0,31 ± 0,04	1,0 (ns)

[a]Valores son media ± SD

[b]Valores son relativos al control con vehículo

na: no aplicable; ns: no significativo

Patente
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WO2008/124161 A1

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Act: 411 presentación Folios: 905

Industria y Comercio
SUPERINTENDENCIA

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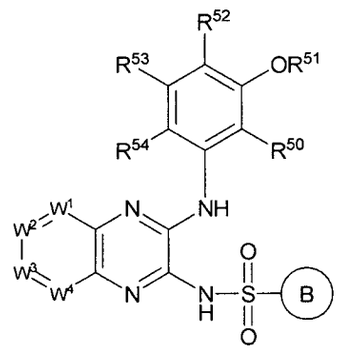
N° publicación: **WO 2008/124161 A1**

(54) Titulo: **USO DE INHIBIDORES DE PIRIDOPIRIMIDINONA DE PI3K-ALFA EN EL TRATAMIENTO DEL CÁNCER**

Reivindicación(es):

1. Uso de un compuesto de Fórmula I:



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o un isómero simple de este donde el compuesto está opcionalmente como una sal farmacéuticamente aceptable y en forma adicional opcionalmente como un hidrato y en forma adicional opcionalmente como un solvato de este, para la fabricación de un medicamento caracterizado porque dicho medicamento es para el tratamiento del cáncer y contiene el compuesto de Fórmula I y al menos uno de un portador, excipiente o diluyente farmacéuticamente aceptable en combinación con uno o más agentes quimioterapéuticos, una o más de las terapias hormonales, uno o más anticuerpos, una o más inmunoterapias, terapia de iodo radiactivo, y radiación donde el Compuesto de Fórmula I es aquel donde:

R^1 es hidrógeno, alquilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, cicloalquilalquilo opcionalmente sustituido, arilo opcionalmente sustituido, arilalquilo opcionalmente sustituido, heterocicloalquilo

opcionalmente sustituido, heterocicloalquilalquilo opcionalmente sustituido, heteroarilo opcionalmente sustituido o heteroarilalquilo opcionalmente sustituido;

R^2 es hidrógeno o alquilo donde el alquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 grupos R^8;

X es $-NR^3-$;

R^3 es hidrógeno;

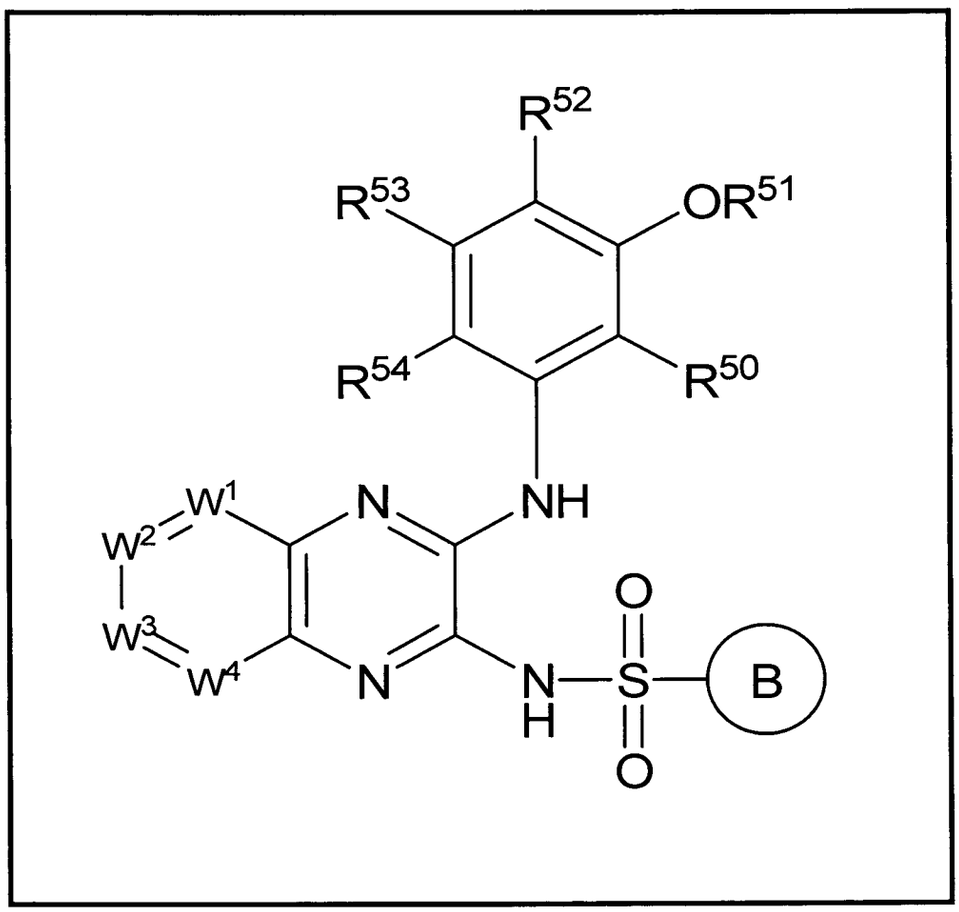
R^4 es alquilo opcionalmente sustituido;

R^5 es hidrógeno; y

R^6 es fenilo, acilo, o heteroarilo donde el fenilo y heteroarilo están opcionalmente sustituidos con 1, 2, 3, 4, o 5 grupos R^9;

cada R^8, cuando está presente, es de modo independiente hidroxi, halo, alcoxi, haloalcoxi, amino, alquilamino, dialquilaminoalquilo, o alcoxialquilamino; y

cada R^9, cuando está presente, es de modo independiente halo, alquilo, haloalquilo, alcoxi, haloalcoxi, ciano, amino, alquilamino, dialquilamino, alcoxialquilo, carboxialquilo, alcoxicarbonilo, aminoalquilo, cicloalquilo, arilo, arilalquilo, ariloxi, heterocicloalquilo, o heteroarilo y donde el cicloalquilo, arilo, heterocicloalquilo, y heteroarilo, cada uno solo o como parte de otro grupo de R^9, están opcionalmente sustituidos de modo independiente con 1, 2, 3, o 4 grupos seleccionados de halo, alquilo, haloalquilo, hidroxi, alcoxi, haloalcoxi, amino, alquilamino, y dialquilamino.


R52
R53
OR51
R54
R50
W1
N
NH
W2
W3
W4
N
N
H
S
O
O
B

For Foreign Filings – marked up

In the Specification

Please correct the heading which is located above paragraph [00356] as indicated below.

Biological Examples 11-[[14]]<u>16</u>

In the Claims

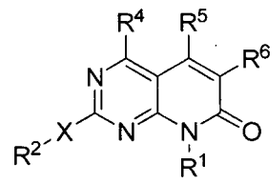
Claims 1, 2, and 17 are original.

Claims 3-6, 10-16, 20, and 27 are canceled.

Claims 7-9, 18, 19, and 21-26 are currently amended.

Claims 28 is new.

1. (**original**) A method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I:



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or a single isomer thereof where the compound is optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof, or administering to a patient a pharmaceutical composition comprising a therapeutically effective amount of a Compound of Formula I and a pharmaceutically acceptable carrier, excipient, or diluent; in combination with one or more treatments independently selected from surgery, one or more chemotherapeutic agents, one or more of the hormone therapies, one or more antibodies, one or more immunotherapies, radioactive iodine therapy, and radiation wherein the Compound of Formula I is that wherein:

R^1 is hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

R^2 is hydrogen or alkyl where the alkyl is optionally substituted with 1, 2, 3, 4, or 5 R^8 groups;

X is $-NR^3-$;

R^3 hydrogen;

R^4 is optionally substituted alkyl;

R^5 is hydrogen; and

R^6 is phenyl, acyl, or heteroaryl wherein the phenyl and heteroaryl are optionally substituted with 1, 2, 3, 4, or 5 R^9 groups;

each R^8, when present, is independently hydroxy, halo, alkoxy, haloalkoxy, amino, alkylamino, dialkylaminoalkyl, or alkoxyalkylamino; and

each R^9, when present, is independently halo, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, amino, alkylamino, dialkylamino, alkoxyalkyl, carboxyalkyl, alkoxycarbonyl, aminoalkyl, cycloalkyl, aryl, arylalkyl, aryloxy, heterocycloalkyl, or heteroaryl and where the cycloalkyl, aryl, heterocycloalkyl, and heteroaryl, each either alone or as part of another group within R^9, are independently optionally substituted with 1, 2, 3, or 4 groups selected from halo, alkyl, haloalkyl, hydroxy, alkoxy, haloalkxy, amino, alkylamino, and dialkylamino.

2. (**original**) The method of Claim 1 where the cancer is selected from breast cancer, colon cancer, rectal cancer, endometrial cancer, gastrointestinal carcinoid tumors, gastrointestinal stromal tumors, glioblastoma, hepatocellular carcinoma, small cell lung cancer, non-small cell lung cancer, melanoma, ovarian cancer, cervical cancer, pancreatic cancer, prostate carcinoma, acute myelogenous leukemia, chronic myelogenous leukemia, non-Hodgkin's lymphoma, and thyroid carcinoma.

Claims 3-6 (**canceled**)

7. (**currently amended**) The method of Claim ~~3~~ 1 or 2 where the treatment is one chemotherapeutic agent and the chemotherapeutic agent is a platin.

8. (**currently amended**) The method of Claim ~~3~~ 1 or 2 where the treatment is one chemotherapeutic agent and the chemotherapeutic agent is a taxane.

9. (**currently amended**) The method of Claim ~~3~~ 1 or 2 where the treatment is one chemotherapeutic agent and the chemotherapeutic agent is rapamycin or a rapamycin analogue.

Claims 10-16 (**canceled**)

17. (**original**) The method of Claim 1 or 2 where the Compound of Formula I is selected from:

8-ethyl-2-(ethylamino)-4-methyl-6-phenylpyrido[2,3-d]pyrimidin-7(8*H*)-one;

6-biphenyl-4-yl-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
6-(2,4-difluorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
6-(3-chloro-4-fluorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-[4-(methyloxy)phenyl]pyrido[2,3-d]pyrimidin-7(8*H*)-one;
6-(2,4-dichlorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
6-(3,4-difluorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-[2-(methyloxy)phenyl]pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-[4-(phenyloxy)phenyl]pyrido[2,3-d]pyrimidin-7(8*H*)-one;
6-[2,4-bis(methyloxy)phenyl]-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-6-(3-fluorophenyl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-6-(2-fluorophenyl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-[3-(trifluoromethyl)phenyl]pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-6-(4-fluorophenyl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-(2-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-[3-(methyloxy)phenyl]pyrido[2,3-d]pyrimidin-7(8*H*)-one;
6-(3-chlorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
6-(4-chlorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-(3-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-(4-methyl-2-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-(4-methyl-3-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
1,1-dimethylethyl 2-[8-ethyl-2-(ethylamino)-4-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl]-1*H*-pyrrole-1-carboxylate
8-ethyl-2-(ethylamino)-4-methyl-6-(1*H*-pyrrol-2-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
6-(5-chloro-2-thienyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-pyrimidin-5-ylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-6-(3-fluoropyridi*N*-4-yl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-6-furan-3-yl-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-[1-(phenylmethyl)-1*H*-pyrazol-4-yl]pyrido[2,3-d]pyrimidin-7(8*H*)-one;
2-(ethylamino)-4-methyl-8-(1-methylethyl)-6-(2-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;

8-ethyl-2-(ethylamino)-6-(1*H*-indol-6-yl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-(5-phenyl-2-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
2-(ethylamino)-6-furan-3-yl-4-methyl-8-(1-methylethyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-(1*H*-pyrazol-5-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-cyclohexyl-2-(ethylamino)-4-methyl-6-(2-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-(1,3-thiazol-2-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-cyclopentyl-2-(ethylamino)-4-methyl-6-(1*H*-pyrazol-3-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
2-(ethylamino)-4-methyl-8-(1-methylethyl)-6-(1*H*-pyrazol-5-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-(1*H*-pyrazol-1-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
2-(ethylamino)-4-methyl-8-(1-methylethyl)-6-(1*H*-pyrazol-1-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-cyclopentyl-2-(ethylamino)-4-methyl-6-(1*H*-pyrazol-1-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-4-methyl-6-(1*H*-pyrazol-5-yl)-2-[(2,2,2-trifluoroethyl)amino]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-(1*H*-pyrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-(ethylamino)-4-methyl-6-(1*H*-pyrazol-3-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
8-ethyl-4-methyl-2-(methylamino)-6-(1*H*-pyrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-cyclopentyl-4-methyl-6-(1*H*-pyrazol-3-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
8-ethyl-2-[(2-fluoroethyl)amino]-4-methyl-6-(1*H*-pyrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-4-methyl-8-(1-methylethyl)-6-(1*H*-pyrazol-3-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-4-methyl-8-(phenylmethyl)-6-(1*H*-pyrazol-3-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-(4-methyl-3-thienyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-(2-thienyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-6-(4-fluorophenyl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-6-(3-fluorophenyl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-6-(2-fluorophenyl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-(3-thienyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-6-furan-3-yl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-[4-(methyloxy)phenyl]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-6-(4-chlorophenyl)-8-ethyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-6-(3-chlorophenyl)-8-ethyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;

2-amino-8-ethyl-6-isoxazol-4-yl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-6-furan-2-yl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-6-(2,4-dichlorophenyl)-8-ethyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
5-(2-amino-8-ethyl-4-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-6-yl)thiophene-2-carbonitrile
2-amino-8-ethyl-4-methyl-6-pyrimidin-5-ylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-6-(1*H*-imidazol-5-yl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-(1*H*-1,2,3-triazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-(1*H*-pyrazol-4-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-(1,3-thiazol-2-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-(1*H*-tetrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-(1-methyl-1*H*-pyrrol-2-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-4,8-diethyl-6-(1*H*-pyrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one; and
2-amino-8-cyclopentyl-4-methyl-6-(1,3-thiazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;

where the Compound is optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof.

18. (**currently amended**) The method of Claims 1, 2, [[4,]]or 17 where the treatment is one antibody selected from an EGFR antibody and an ErbB2 antibody, or the treatment is one or two chemotherapeutic agents independently selected from rapamycin, a rapamycin analogue, an alkylating agent a taxane, a platin, an EGFR inhibitor, and an ErbB2 inhibitor.

19. (**currently amended**) The method of Claim 18 where the treatment is one or two chemotherapeutic agents independently selected from rapamycin, paclitaxel, carboplatin, lapatinib, and erlotinib~~, and *N*-(3,4-dichloro-2-fluorophenyl)-7-({[(3a*R*,5*r*,6a*S*)-2-methyloctahydrocyclopenta[*c*]pyrrol-5-yl]methyl}oxy)-6-(methyloxy)quinazolin-4-amine, optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof~~.

Claim 20 (**canceled**)

21. (**currently amended**) The method of Claim 1, 2, [[3, 4,]]or 17 where the treatment is one chemotherapeutic agent where the chemotherapeutic agent is erlotinib.

22. (**currently amended**) The method of Claim 1, 2, [[3, 4,]]or 17 where the treatment is one chemotherapeutic agent where the chemotherapeutic agent is lapatinib.

23. (**currently amended**) The method of Claim 1, 2, [[3, 4,]]or 17 where the treatment is one chemotherapeutic agent where the chemotherapeutic agent is carboplatin.

24. (**currently amended**) The method of Claim 1, 2, [[3, 4,]]or 17 where the treatment is one chemotherapeutic agent where the chemotherapeutic agent is paclitaxel.

25. (**currently amended**) The method of Claim 1, 2, [[3, 4,]]or 17 where the treatment is one chemotherapeutic agent where the chemotherapeutic agent is rapamycin.

26. (**currently amended**) The method of Claim 1, 2, [[3, 4,]]or 17 where the treatment is one antibody selected from bevacizumab, trastuzumab, cetuximab, and panitumumab.

Claim 27 (**canceled**)

28. (**new**) The method of Claim 1 or 17 where the treatment is one chemotherapeutic agent and the chemotherapeutic agent is temozolomide.

Remarks

The Specification is amended to correct a typographical error in the number of biological examples in the heading "Biological Examples 11-14."

Claims 7-9, 18, and 21-26 are amended so that they no longer depend from canceled claims. Claim 19 is amended to more distinctly claim what the Applicants regard as their Invention. Claim 28 is new and support for which can be found in paragraph [00156].

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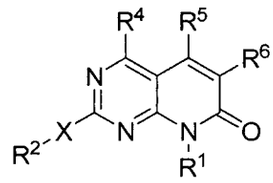
1. A method of treating cancer which method comprises administering to a patient a therapeutically effective amount of a Compound of Formula I:



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or a single isomer thereof where the compound is optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof, or administering to a patient a pharmaceutical composition comprising a therapeutically effective amount of a Compound of Formula I and a pharmaceutically acceptable carrier, excipient, or diluent; in combination with one or more treatments independently selected from surgery, one or more chemotherapeutic agents, one or more of the hormone therapies, one or more antibodies, one or more immunotherapies, radioactive iodine therapy, and radiation wherein the Compound of Formula I is that wherein:

R^1 is hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl or optionally substituted heteroarylalkyl;

R^2 is hydrogen or alkyl where the alkyl is optionally substituted with 1, 2, 3, 4, or 5 R^8 groups;

X is $-NR^3-$;

R^3 hydrogen;

R^4 is optionally substituted alkyl;

R^5 is hydrogen; and

R^6 is phenyl, acyl, or heteroaryl wherein the phenyl and heteroaryl are optionally substituted with 1, 2, 3, 4, or 5 R^9 groups;

each R^8, when present, is independently hydroxy, halo, alkoxy, haloalkoxy, amino, alkylamino, dialkylaminoalkyl, or alkoxyalkylamino; and

each R^9, when present, is independently halo, alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, amino, alkylamino, dialkylamino, alkoxyalkyl, carboxyalkyl, alkoxycarbonyl, aminoalkyl, cycloalkyl, aryl, arylalkyl, aryloxy, heterocycloalkyl, or heteroaryl and where the cycloalkyl, aryl, heterocycloalkyl, and heteroaryl, each either alone or as part of another group within R^9, are independently optionally substituted with 1, 2, 3, or 4 groups selected from halo, alkyl, haloalkyl, hydroxy, alkoxy, haloalkxy, amino, alkylamino, and dialkylamino.

2. The method of Claim 1 where the cancer is selected from breast cancer, colon cancer, rectal cancer, endometrial cancer, gastrointestinal carcinoid tumors, gastrointestinal stromal tumors, glioblastoma, hepatocellular carcinoma, small cell lung cancer, non-small cell lung cancer, melanoma, ovarian cancer, cervical cancer, pancreatic cancer, prostate carcinoma, acute myelogenous leukemia, chronic myelogenous leukemia, non-Hodgkin's lymphoma, and thyroid carcinoma.

3. The method of Claim 1 or 2 where the treatment is one chemotherapeutic agent and the chemotherapeutic agent is a platin.

4. The method of Claim 1 or 2 where the treatment is one chemotherapeutic agent and the chemotherapeutic agent is a taxane.

5. The method of Claim 1 or 2 where the treatment is one chemotherapeutic agent and the chemotherapeutic agent is rapamycin or a rapamycin analogue.

6. The method of Claim 1 or 2 where the Compound of Formula I is selected from:

8-ethyl-2-(ethylamino)-4-methyl-6-phenylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
6-biphenyl-4-yl-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
6-(2,4-difluorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
6-(3-chloro-4-fluorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-[4-(methyloxy)phenyl]pyrido[2,3-d]pyrimidin-7(8*H*)-one;
6-(2,4-dichlorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
6-(3,4-difluorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-[2-(methyloxy)phenyl]pyrido[2,3-d]pyrimidin-7(8*H*)-one;

8-ethyl-2-(ethylamino)-4-methyl-6-[4-(phenyloxy)phenyl]pyrido[2,3-d]pyrimidin-7(8*H*)-one;
6-[2,4-bis(methyloxy)phenyl]-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-6-(3-fluorophenyl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-6-(2-fluorophenyl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-[3-(trifluoromethyl)phenyl]pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-6-(4-fluorophenyl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-(2-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-[3-(methyloxy)phenyl]pyrido[2,3-d]pyrimidin-7(8*H*)-one;
6-(3-chlorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
6-(4-chlorophenyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-(3-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-(4-methyl-2-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-(4-methyl-3-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
1,1-dimethylethyl 2-[8-ethyl-2-(ethylamino)-4-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-6-yl]-1*H*-pyrrole-1-carboxylate
8-ethyl-2-(ethylamino)-4-methyl-6-(1*H*-pyrrol-2-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
6-(5-chloro-2-thienyl)-8-ethyl-2-(ethylamino)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-pyrimidin-5-ylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-6-(3-fluoropyridi*N*-4-yl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-6-furan-3-yl-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-[1-(phenylmethyl)-1*H*-pyrazol-4-yl]pyrido[2,3-d]pyrimidin-7(8*H*)-one;
2-(ethylamino)-4-methyl-8-(1-methylethyl)-6-(2-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-6-(1*H*-indol-6-yl)-4-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-(5-phenyl-2-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
2-(ethylamino)-6-furan-3-yl-4-methyl-8-(1-methylethyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-(1*H*-pyrazol-5-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-cyclohexyl-2-(ethylamino)-4-methyl-6-(2-thienyl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-2-(ethylamino)-4-methyl-6-(1,3-thiazol-2-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-cyclopentyl-2-(ethylamino)-4-methyl-6-(1*H*-pyrazol-3-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
2-(ethylamino)-4-methyl-8-(1-methylethyl)-6-(1*H*-pyrazol-5-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;

8-ethyl-2-(ethylamino)-4-methyl-6-(1*H*-pyrazol-1-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
2-(ethylamino)-4-methyl-8-(1-methylethyl)-6-(1*H*-pyrazol-1-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-cyclopentyl-2-(ethylamino)-4-methyl-6-(1*H*-pyrazol-1-yl)pyrido[2,3-d]pyrimidin-7(8*H*)-one;
8-ethyl-4-methyl-6-(1*H*-pyrazol-5-yl)-2-[(2,2,2-trifluoroethyl)amino]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-(1*H*-pyrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-(ethylamino)-4-methyl-6-(1*H*-pyrazol-3-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
8-ethyl-4-methyl-2-(methylamino)-6-(1*H*-pyrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-cyclopentyl-4-methyl-6-(1*H*-pyrazol-3-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
8-ethyl-2-[(2-fluoroethyl)amino]-4-methyl-6-(1*H*-pyrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-4-methyl-8-(1-methylethyl)-6-(1*H*-pyrazol-3-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-4-methyl-8-(phenylmethyl)-6-(1*H*-pyrazol-3-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-(4-methyl-3-thienyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-(2-thienyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-6-(4-fluorophenyl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-6-(3-fluorophenyl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-6-(2-fluorophenyl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-(3-thienyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-6-furan-3-yl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-[4-(methyloxy)phenyl]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-6-(4-chlorophenyl)-8-ethyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-6-(3-chlorophenyl)-8-ethyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-6-isoxazol-4-yl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-6-furan-2-yl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-6-(2,4-dichlorophenyl)-8-ethyl-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
5-(2-amino-8-ethyl-4-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-6-yl)thiophene-2-carbonitrile
2-amino-8-ethyl-4-methyl-6-pyrimidin-5-ylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-6-(1*H*-imidazol-5-yl)-4-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-(1*H*-1,2,3-triazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-(1*H*-pyrazol-4-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-(1,3-thiazol-2-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;

2-amino-8-ethyl-4-methyl-6-(1*H*-tetrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-8-ethyl-4-methyl-6-(1-methyl-1*H*-pyrrol-2-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;
2-amino-4,8-diethyl-6-(1*H*-pyrazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one; and
2-amino-8-cyclopentyl-4-methyl-6-(1,3-thiazol-5-yl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one;

where the Compound is optionally as a pharmaceutically acceptable salt and additionally optionally as a hydrate and additionally optionally as a solvate thereof.

7. The method of Claims 1, 2, or 6 where the treatment is one antibody selected from an EGFR antibody and an ErbB2 antibody, or the treatment is one or two chemotherapeutic agents independently selected from rapamycin, a rapamycin analogue, an alkylating agent a taxane, a platin, an EGFR inhibitor, and an ErbB2 inhibitor.

8. The method of Claim 7 where the treatment is one or two chemotherapeutic agents independently selected from rapamycin, paclitaxel, carboplatin, lapatinib, and erlotinib.

9. The method of Claim 1, 2, or 6 where the treatment is one chemotherapeutic agent where the chemotherapeutic agent is erlotinib.

10. The method of Claim 1, 2, or 6 where the treatment is one chemotherapeutic agent where the chemotherapeutic agent is lapatinib.

11. The method of Claim 1, 2, or 6 where the treatment is one chemotherapeutic agent where the chemotherapeutic agent is carboplatin.

12. The method of Claim 1, 2, or 6 where the treatment is one chemotherapeutic agent where the chemotherapeutic agent is paclitaxel.

13. The method of Claim 1, 2, or 6 where the treatment is one chemotherapeutic agent where the chemotherapeutic agent is rapamycin.

14. The method of Claim 1, 2, or 6 where the treatment is one antibody selected from bevacizumab, trastuzumab, cetuximab, and panitumumab.

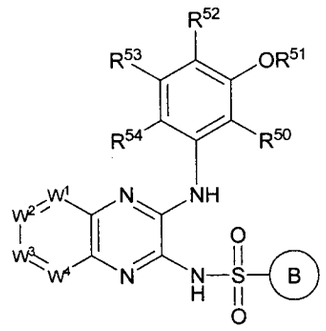
15. The method of Claim 1, 2, or 6 where the treatment is one chemotherapeutic agent and the chemotherapeutic agent is temozolomide.

Remarks

Claims 1, 2, and 6 correspond to original Claims 1, 2, and 17. New Claims 3-5, 7, and 9-14 correspond to original Claims 7-9, 18, and 21-26, repectively, which were amended so that they no longer depend from canceled claims. New Claim 8 corresponds to Claim 19 which was amended to more distinctly claim what the Applicants regard as their Invention. Claim 15 is new and support for which can be found in paragraph [00156]. No new matter is added with these amendements and new claims.

REIVINDICACIONES

1. Un método de tratamiento del cáncer, dicho método comprende administrar a un paciente cantidad terapéuticamente efectiva de un compuesto de Fórmula I:



I

o un isómero simple de este donde el compuesto está opcionalmente como una sal farmacéuticamente aceptable y en forma adicional opcionalmente como un hidrato i en forma adicional opcionalmente como un solvato de este; o administrar una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de un compuesto de Fórmula I y al menos uno de un portador, excipiente o diluiente farmacéuticamente aceptable en combinación con uno o más y tratamientos seleccionados de modo independiente cirugía, uno o más agentes quimioterapéuticos, una o más de las terapias hormonales, uno o más anticuerpos, una o más inmunoterapias, terapia de iodo radiactivo, y radiación donde el Compuesto de Fórmula I es aquel donde:

R^1 es hidrógeno, alquilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, cicloalquilalquilo opcionalmente sustituido, arilo opcionalmente sustituido, arilalquilo opcionalmente sustituido, heterocicloalquilo opcionalmente

sustituido, heterocicloalquilalquilo opcionalmente sustituido, heteroarilo opcionalmente sustituido o heteroarilalquilo opcionalmente sustituido;

R^2 es hidrógeno o alquilo donde el alquilo está opcionalmente sustituido con 1, 2, 3, 4, o 5 grupos R^8;

X es $-NR^3-$;

R^3 es hidrógeno;

R^4 es alquilo opcionalmente sustituido;

R^5 es hidrógeno; y

R^6 es fenilo, acilo, o heteroarilo donde el fenilo y heteroarilo están opcionalmente sustituidos con 1, 2, 3, 4, o 5 grupos R^9;

cada R^8, cuando está presente, es de modo independiente hidroxi, halo, alcoxi, haloalcoxi, amino, alquilamino, dialquilaminoalquilo, o alcoxialquilamino; y

cada R^9, cuando está presente, es de modo independiente halo, alquilo, haloalquilo, alcoxi, haloalcoxi, ciano, amino, alquilamino, dialquilamino, alcoxialquilo, carboxialquilo, alcoxicarbonilo, aminoalquilo, cicloalquilo, arilo, arilalquilo, ariloxi, heterocicloalquilo, o heteroarilo y donde el cicloalquilo, arilo, heterocicloalquilo, y heteroarilo, cada uno solo o como parte de otro grupo de R^9, están opcionalmente sustituidos de modo independiente con 1, 2, 3, o 4 grupos seleccionados de halo, alquilo, haloalquilo, hidroxi, alcoxi, haloalcoxi, amino, alquilamino, y dialquilamino.

2. El método de acuerdo con la reivindicación 1 donde el cáncer se selecciona de cáncer de mamas, cáncer de colon, cáncer rectal, cáncer de endometrio, tumores carcinoides

gastrointestinales, tumores estromales gastrointestinales, glioblastoma, carcinoma hepatocelular, cáncer pulmonar de células pequeñas, cáncer pulmonar de células no pequeñas, melanoma, cáncer ovárico, cáncer cervical, cáncer pancreático, carcinoma prostático, leucemia mielógena aguda, leucemia mielógena crónica, linfoma no Hodgkin, y carcinoma tiroideo

3. El método de acuerdo con la reivindicación 1 o 2 donde el tratamiento es un agente quimioterapéutico y el agente quimioterapéutico es un platino.

4. El método de acuerdo con la reivindicación 1 o 2 donde el tratamiento es un agente quimioterapéutico y el agente quimioterapéutico es un taxano.

5. El método de acuerdo con la reivindicación 1 o 2 donde el tratamiento es un agente quimioterapéutico y el agente quimioterapéutico es rapamicina o un análogo de rapamicina.

6. El método de acuerdo con la reivindicación 1 o 2 donde el Compuesto de Fórmula I se selecciona de:

8-etil-2-(etilamino)-4-metil-6-fenilpirido[2,3-d]pirimidin-7(8*H*)-ona;
6-bifenil-4-il-8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
6-(2,4-difluorofenil)-8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
6-(3-cloro-4-fluorofenil)-8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-[4-

(metiloxi)fenil]pirido[2,3-d]pirimidin-7(8*H*)-ona;
6-(2,4-diclorofenil)-8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
6-(3,4-difluorofenil)-8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-[2-(metiloxi)fenil]pirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-[4-(feniloxi)fenil]pirido[2,3-d]pirimidin-7(8*H*)-ona;
6-[2,4-bis(metiloxi)fenil]-8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-6-(3-fluorofenil)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-6-(2-fluorofenil)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-[3-(trifluorometil)fenil]pirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-6-(4-fluorofenil)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-(2-tienil)pirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-[3-(metiloxi)fenil]pirido[2,3-d]pirimidin-7(8*H*)-ona;
6-(3-clorofenil)-8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
6-(4-clorofenil)-8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-(3-tienil)pirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-(4-metil-2-tienil)pirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-(4-metil-3-tienil)pirido[2,3-

d]pirimidin-7(8*H*)-ona;
2-[8-etil-2-(etilamino)-4-metil-7-oxo-7,8-dihidropirido[2,3-d]pirimidin-6-il]-1*H*-pirrol-1-carboxilato de 1,1-dimetiletilo
8-etil-2-(etilamino)-4-metil-6-(1*H*-pirrol-2-il)pirido[2,3-d]pirimidin-7(8*H*)-ona;
6-(5-cloro-2-tienil)-8-etil-2-(etilamino)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-pirimidin-5-ilpirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-6-(3-fluoropiridi*N*-4-il)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-6-furan-3-il-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-[1-(fenilmetil)-1*H*-pirazol-4-il]pirido[2,3-d]pirimidin-7(8*H*)-ona;
2-(etilamino)-4-metil-8-(1-metiletil)-6-(2-tienil)pirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-6-(1*H*-indol-6-il)-4-metilpirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-(5-fenil-2-tienil)pirido[2,3-d]pirimidin-7(8*H*)-ona;
2-(etilamino)-6-furan-3-il-4-metil-8-(1-metiletil)pirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-(1*H*-pirazol-5-il)pirido[2,3-d]pirimidin-7(8*H*)-ona;
8-ciclohexil-2-(etilamino)-4-metil-6-(2-tienil)pirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-(1,3-tiazol-2-il)pirido[2,3-d]pirimidin-7(8*H*)-ona;
8-ciclopentil-2-(etilamino)-4-metil-6-(1*H*-pirazol-3-il)pirido[2,3-d]pirimidin-7(8*H*)-ona;

2-(etilamino)-4-metil-8-(1-metiletil)-6-(1*H*-pirazol-5-il)pirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-2-(etilamino)-4-metil-6-(1*H*-pirazol-1-il)pirido[2,3-d]pirimidin-7(8*H*)-ona;
2-(etilamino)-4-metil-8-(1-metiletil)-6-(1*H*-pirazol-1-il)pirido[2,3-d]pirimidin-7(8*H*)-ona;
8-ciclopentil-2-(etilamino)-4-metil-6-(1*H*-pirazol-1-il)pirido[2,3-d]pirimidin-7(8*H*)-ona;
8-etil-4-metil-6-(1*H*-pirazol-5-il)-2-[(2,2,2-trifluoroetil)amino]pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-4-metil-6-(1*H*-pirazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-(etilamino)-4-metil-6-(1*H*-pirazol-3-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
8-etil-4-metil-2-(metilamino)-6-(1*H*-pirazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-ciclopentil-4-metil-6-(1*H*-pirazol-3-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
8-etil-2-[(2-fluoroetil)amino]-4-metil-6-(1*H*-pirazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-4-metil-8-(1-metiletil)-6-(1*H*-pirazol-3-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-4-metil-8-(fenilmetil)-6-(1*H*-pirazol-3-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-4-metil-6-(4-metil-3-tienil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-4-metil-6-(2-tienil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-6-(4-fluorofenil)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-6-(3-fluorofenil)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona;

2-amino-8-etil-6-(2-fluorofenil)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-4-metil-6-(3-tienil)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-6-furan-3-il-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-4-metil-6-fenilpirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-4-metil-6-[4-(metiloxi)fenil]pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-6-(4-clorofenil)-8-etil-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-6-(3-clorofenil)-8-etil-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-6-isoxazol-4-il-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-6-furan-2-il-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-6-(2,4-diclorofenil)-8-etil-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona;
5-(2-amino-8-etil-4-metil-7-oxo-7,8-dihidropirido[2,3-*d*]pirimidin-6-il)tiofeno-2-carbonitrilo
2-amino-8-etil-4-metil-6-pirimidin-5-ilpirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-6-(1*H*-imidazol-5-il)-4-metilpirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-4-metil-6-(1*H*-1,2,3-triazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-4-metil-6-(1*H*-pirazol-4-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-4-metil-6-(1,3-tiazol-2-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;

2-amino-8-etil-4-metil-6-(1*H*-tetrazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-8-etil-4-metil-6-(1-metil-1*H*-pirrol-2-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;
2-amino-4,8-dietil-6-(1*H*-pirazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona; y
2-amino-8-ciclopentil-4-metil-6-(1,3-tiazol-5-il)pirido[2,3-*d*]pirimidin-7(8*H*)-ona;

donde el compuesto está opcionalmente como una sal farmacéuticamente aceptable y en forma adicional y opcional como un hidrato y en forma adicional opcionalmente como un solvato de este.

7. El método de acuerdo con la reivindicaciones 1, 2, o 6 donde el tratamiento es un anticuerpo seleccionado de un anticuerpo EGFR y un anticuerpo ErbB2, o el tratamiento es uno o dos agentes quimioterapéuticos seleccionados de modo independiente de rapamicina, un análogo de rapamicina, un agente alquilante, un taxano, un platino, un inhibidor de EGFR, y un inhibidor de ErbB2.

8. El método de acuerdo con la reivindicación 7 donde el tratamiento es uno o dos agentes quimioterapéuticos seleccionados de modo independiente de rapamicina, paclitaxel, carboplatino, lapatinib, y erlotinib.

9. El método de acuerdo con la reivindicación 1, 2, o 6 donde el tratamiento es un agente quimioterapéutico donde el agente quimioterapéutico es erlotinib.

10. El método de acuerdo con la reivindicación 1, 2, o 6 donde el tratamiento es un agente quimioterapéutico donde el agente quimioterapéutico es lapatinib.

11. El método de acuerdo con la reivindicación 1, 2, o 6 donde el tratamiento es un agente quimioterapéutico donde el agente quimioterapéutico es carboplatino.

12. El método de acuerdo con la reivindicación 1, 2, o 6 donde el tratamiento es un agente quimioterapéutico donde el agente quimioterapéutico es paclitaxel.

13. El método de acuerdo con la reivindicación 1, 2, o 6 donde el tratamiento es un agente quimioterapéutico donde el agente quimioterapéutico es rapamicina.

14. El método de acuerdo con la reivindicación 1, 2, o 6 donde el tratamiento es un anticuerpo seleccionado de bevacizumab, trastuzumab, cetuximab, y panitumumab.

15. El método de acuerdo con la reivindicación 1, 2, o 6 donde el tratamiento es un agente quimioterapéutico y el agente quimioterapéutico es temozolomida.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Act. 411 PRESENTACION Folios: 905

REQUISITOS MÍNIMOS PARA ADMISIÓN A TRAMITE PCT

PATENTE DE INVENCIÓN [ ] MODELO DE UTILIDAD [ ]

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

COMPLETA [ ] 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 [ ]

Edgar Navarro

Firma Responsable

Fecha 04-11-2009

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