SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

Industria y Comercio
SUPERINTENDENCIA

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL
DIVISIÓN DE NUEVAS CREACIONES

09-62868

SOLICITUD DE PATENTE DE
INVENCIÓN

TITULO: QUINAZOLINAS PARA LA INHIBICIÓN DE PDK1

SOLICITANTE: NOVARTIS AG

DIRECCIÓN: Lichtstrasse 35, CH- 4056 Basel, Suiza

APODERADO: CARLOS R. OLARTE

BOGOTÁ: 17 de Junio de 2009

Un Poder Escrito
Fw- 22-07-2009

P2009/000087

OLARTERAISBECK
OLARTE RAISBECK MOURE & CASTRO LTDA.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-062868- -00000-0000
Fecha: 2009-06-17 17:13:22 Dep: 2020 NUECREACION
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 933

PETITORIO - FORMULARIO Ú
PATENTE PC
ENTRADA EN FASE NACIONAL **P2009/000087**

SOLICITUD DE:

(1)

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

[X] Capítulo I. [ ] Capítulo II.

(2)

SOLICITANTE (71)

Nombre: NOVARTIS AG
Dirección: Lichtstrasse 35, CH-4056 Basel
Nacionalidad o Domicilio: Suiza
Lugar de Constitución: Suiza
Teléfono: _____ **Fax:** _____
E-mail: _____

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

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE
Dirección: World Trade Center Torre A, Calle 100 No. 8A-37 Piso 10
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN
C.C. [X] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número 79782747Bta
TP 74.295

INVENTOR (ES) (72)

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

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2007/088392 Fecha Diciembre 20,2007

Publicación Internacional No. WO 2008/079988 Fecha Julio 3, 2008

(6) **Título (54)** **QUINAZOLINAS PARA LA INHIBICIÓN DE PDK1**

Clasificación Internacional (51) C07C 239/84, C07D 403/12, C07D 401/08, C07D 411/04, C07D 401/12, C07D 413/14, C07D 401/14, C07D 417/04, C07D 403/04, A61K 31/517, C07D 403/06, A61P 35/00

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Diciembre 22, 2006	60/876.972
US	Octubre 15, 2007	60/999.170

(9) **Comprobante de pago No.** 09- 44.588 **Fecha** Junio 16 de 2009

ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 07.026.397
- [X] 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.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [X] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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

3

LISTA DE INVENTORES PCT/US2007/088392

Savithri RAMURTHY
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Nacionalidad: Estadounidense

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Estados Unidos de América
Nacionalidad: Estadounidense

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Estados Unidos de América
Nacionalidad: Estadounidense

Jeremy M. MURRAY
4560 Horton Street, Emeryville,
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Estados Unidos de América
Nacionalidad: Británica

LISTA DE INVENTORES PCT/US2007/088392

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Nacionalidad: Estadounidense

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Estados Unidos de América
Nacionalidad: Estadounidense

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Nacionalidad: China

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Nacionalidad: Estadounidense

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Nacionalidad: Estadounidense

Mina AIKAWA
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Nacionalidad: Estadounidense

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Estados Unidos de América
Nacionalidad: Estadounidense

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No. 09-062868- -00000-0000
Fecha: 2009-06-17 17:13:22 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 933

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 44,588
FECHA : JUNIO 16 DE 2009

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	105800155	16/06/2009	6,975,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	540,000.00
		TOTAL : $	540,000.00

SON: QUINIENTOS CUARENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Nota del traductor:

El documento adjunto de poder de Novartis AG a Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana Maria Frieri y/o Juan Guillermo Moure y/o Natalia Castro lleva los siguientes datos en inglés.

CERTIFICACIÓN NOTARIAL

1. En esta fecha, día 30 de Agosto de 2006, yo, el suscrito Notario Público certifico por medio del presente la autenticidad de las firmas del señor Arthur Canonica, ciudadano de Corticiasca, Suiza, residente en Wisen/SO, Suiza, y del Sr. Pascal Traub, ciudadano de Riehen, Suiza, residente en Basilea, Suiza, ambos personas mayores de edad y con dirección comercial en Lichstrasse 35, 4056, Basilea, Suiza. La autenticidad de la firmas fue establecida por medio de la comparación.
2. Además, yo, el Notario Público, certifico por el presente que las anteriores personas han ejecutado el anterior documento como apoderados de Novartis AG.
3. Además, yo, el Notario Público certifico por el presente que Novartis AG, con su principal lugar de negocios en Basilea, Suiza, está debidamente constituida, está actualmente vigente y que los propósitos para los cuales se otorgó el Documento de Poder están dentro del alcance de sus propósitos corporativos.

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JORGE E. SIERRA
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4. Además, yo, el Notario Público, certifico por el presente que las anteriores personas tienen la autoridad para ejecutar el documento de Poder y que por este instrumento, su representación es legal.

La base para mis certificaciones de los puntos 2, 3 y 4 fue la exhibición de los siguientes documentos auténticos:

- Documento de Poder de Novartis AG fechado el 19 de junio de 2006 y
- Extracto del Registro de Comercio del Cantón de la ciudad de Basilea para Novartis AG, en Basilea, fechado el 25 de enero de 2006.

Basilea, Suiza, este día 30 de Agosto de 2006.

(Firmado) Dr. Matthias Staehelin, Notario Público del Cantón de la ciudad de Basilea, Suiza.

Mi licencia vence el 11 de Marzo de 2009.

Hay una Apostilla de Suiza, firmada por Heidi Fischer, bajo el No. 8049/13584.

Traductor Ofici
JORGE E. SIERRA
Licencia 376 - 1993 A

Certificación:

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Novartis"

Fecha: 12 de Septiembre de 2006.

Traductor: Jorge Enrique Sierra Reyes.

Licencia No. 376 de 1993, del Ministerio de Justicia.

Dirección: Carrera 15 No. 99-13 Oficina 411. Bogotá, Colombia.

Teléfono: (57-1) 2182308, (57-1) 6232925.

E-mail: treseser1@yahoo.com. No. 8346

Traductor Ofic
JORGE E. SIERRA
Licencia 376 - 1993

OLARTERAISBECK

OLARTE RAISBECK & FRIERI LTDA.

Carlos R. Olarte
J. Ian Raisbeck
Ana María Frieri
Juan Guillermo Moure
Natalia Castro

Zayde Chahin
Jacqueline Chaparro
José Luis Londoño
Felipe Mendoza
Simón Salinas

Of Counsel
Guillermo Chahin
Graciela Melo

Power of Attorney

The undersigned,

domiciled in

by means of these presents hereby grants to **Carlos R. Olarte and/or J. Ian Raisbeck and/or Ana María Frieri and/or Juan Guillermo Moure and/or Natalia Castro** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents for Inventions, Utility Models, Layout-Designs (topographies) of Integrated Circuits, Industrial Designs, Trademarks, Advertising Slogans, Trade Names, Commercial Emblems, Geographical Indications, Protection of Trade Secrets, Obtainer's Certificates, Copyrights, Registration of Domain Names, Health Registrations, or any other intellectual property right** in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, recourses, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

Poder

El suscrito,

NOVARTIS AG

domiciliado en

Lichtstrasse 35, CH-4056 Basel / Switzerland

por medio del presente otorga a **Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana María Frieri y/o Juan Guillermo Moure y/o Natalia Castro** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de las **Patentes de Invención, Modelos de Utilidad, Esquemas de Trazados de Circuitos Integrados, Diseños Industriales, Marcas, Lemas Comerciales, Nombres Comerciales, Enseñas Comerciales, Denominaciones de Origen, Protección de Secretos Empresariales, Certificados de Obtentor, Derechos de Autor, Registro de Nombres de Dominio, Registros Sanitarios, o cualquier otro bien de propiedad intelectual** de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, recursos, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma:

Arthur Canonica

Pascal Haub

Date/Fecha: June 27, 2006

City,Country/Ciudad,País: Basel, Switzerland

Attestation

1 On this date, the 30th (thirtieth) day of August 2006 (two thousand and six), I, the undersigned Notary Public certify herewith the authenticity of the signatures of **Mr. Arthur Canonica**, citizen of Corticiasca, Switzerland, residing in Wisen/SO, Switzerland and of **Mr. Pascal Traub**, citizen of Riehen, Switzerland, residing in Basel, Switzerland, both of legal age and with business address at, Lichtstrasse 35, 4056 Basel, Switzerland. The authenticity of the signatures was established by means of comparison.

2 Further, I, the Notary Public certify herewith that the foregoing persons have executed the foregoing document as proxy holders for Novartis AG.

3 Further, I, the Notary Public certify herewith that Novartis AG, having its principal place of business located in Basel / Switzerland, is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

4 Further, I, the Notary Public certify herewith that the foregoing persons have the authority to execute the Power of Attorney and that for this instrument their representation is legal.

The foundation for my certifications contained in points 2 (two), 3 (three) and 4 (four) was the exhibition of the following authentic documents:

- Power of Attorney by Novartis AG dated June 19 (nineteen), 2006 (two thousand and six); and
- Extract from the Register of Commerce of the Canton of Basel-City for Novartis AG, in Basel, dated January 25 (twenty-five), 2006 (two thousand and six).

BASEL, Switzerland, this 30th (thirtieth) day of August 2006 (two thousand and six)

M. Staehelin Notar

Dr. Matthias Staehelin, Notary Public
in the Canton of Basel-City, Switzerland

My license expires on March 11 (eleven), 2009 (two thousand and nine).

Leg.Prot.Nr. 975 /2006

APOSTILLE

(Hague Convention of October 5th, 1961)

1. Country: Switzerland (Schweiz / Suisse)
   This official document
2. is signed by .....
3. in his/her function as .....
4. and certified by the seal of the .....

Certified 30. Aug. 2006

5. in Basel (Bâle) 6. on .....
7. by the State Chancery of the Canton of Basel-Stadt .....
8. no. 2'049/18'854
9. Seal/stamp: 10. Signature:

Heidi Fischer

STATE CHANCERY * BASLE-CITY *

09187

Traducción oficial de un documento que está originalmente en inglés

LOS ESTADOS UNIDOS DE AMÉRICA

A TODOS QUIENES VIEREN EL PRESENTE DOCUMENTO:

Departamento de Comercio de los Estados Unidos

Oficina de Patentes y Marcas Registradas de los Estados Unidos

5 de mayo de 2009

Se certifica que la copia anexa es una copia verdadera de los registros de esta oficina de un documento radicado el día 18 de enero de 2008.

Por autoridad del Subsecretario de Comercio para la Propiedad Intelectual y Director de la Oficina de Patentes y Marcas Registradas de los Estados Unidos.

(Firmado) T. Lawrence - Funcionario que certifica.

Sello: "Departamento de Comercio, Oficina de Patentes y Marcas Registradas de los Estados Unidos"

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

CESIÓN DE PATENTE

Versión Electrónica v1.1
Versión de hoja de estilo v1.1

Tipo de envío:	Nueva Cesión
Naturaleza de la transferencia:	Cesión

Datos de las partes que realizan la transferencia

Nombre	Fecha de ejecución
Savitthri Ramurthy	18 de enero de 2007
Xiaodong Lin	18 de enero de 2007
Sharada Subramanian	18 de enero de 2007
Alice C. Rico	18 de enero de 2007
Xiaojing M. Wang	18 de enero de 2007
Rama Jain	18 de enero de 2007
Jeremy M. Murray	18 de enero de 2007
Steven E. Basham	18 de enero de 2007
Robert L. Warne	18 de enero de 2007
Wei Shu	18 de enero de 2007
Yasheen Zhou	18 de enero de 2007
Jeffrey Dove	18 de enero de 2007
Mina Aikawa	18 de enero de 2007
Payman Amiri	18 de enero de 2007

Datos de las partes que reciben

Nombre:	Novartis Vaccines and Diagnostics, Inc
Dirección:	4560 Horton Street
Ciudad:	Emeryville
Estado/País:	California
Código postal:	94608-2916

Número total de propiedades: 1

Tipo de propiedad	Número
Número de la solicitud	60999170

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

Datos para la correspondencia:

Número de Fax: (877) 769-7945

500443218

Patente
Rollo: 020386. Marco: 0699

La correspondencia será envirada por US Mail cuando el intento de hacerlo por fax no sea exitoso.

Teléfono: 302-652-5070

E-mail: ASPI@fr.com

Nombre del correspondiente: Fish & Richardson P.C.

Dirección línea 1: P.O. Box 1022

Dirección línea 4: Minneapolis, Minnesota 55440-1022

Número del registro del Representante:	20366-161P02
Nombre del remitente:	Gwilym J.O. Attwell

Total de anexos: 4
Fuente= Assignment #page1.tif
Fuente= Assignment #page2.tif
Fuente= Assignment #page3.tif
Fuente= Assignment #page4.tif	

Patente: Rollo: 020386 Marco: 0700

Patente
Registro del Representante No. 28301.0001

CESIÓN

Puesto que nosotros, Savitthri Ramurthy, Xiaodong Lin, Sharada Subramanian, Alice C. Rico, Xiaojing M. Wang, Rama Jain, Jeremy M. Murray, Stephen Basham, Robert L. Warne, Wei Shu, Yasheen Zhou, Jeffrey Dove, Mina Aikawa y Payman Amiri, quienes de ahora en adelante serán denominados los CEDENTES, han inventado ciertas mejoras nuevas y útiles conforme se describe y presenta en la solicitud relacionada enseguida para Cartas de Patente de los Estados Unidos:

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Miniusticia

Título del Invento: QUINAZOLINES FOR PDK1 INHIBITION

Fecha de ejecución: 18 de enero, 2007. Fecha de radicación: 22 de Dic., 2006.

Serial No. 60/876,972

Puesto que NOVARTIS VACCINES AND DIAGNOSTICS INC., , 4560 Horton Street, Emeryville, California 94608-2916, una Compañía del Estado de Delaware, de ahora en adelante denominada el CESIONARIO, desea adquirir la totalidad del derecho, título e interés del anterior invento y solicitud y de cualquier Carta de Patente que pueda otorgarse sobre los mismos;

Entonces y a todos a quienes pueda interesar: sea de su conocimiento, por consideración y en consideración de la suma de un dólar (US1,00), dinero legal pagado a los CEDENTES por el CESIONARIO, recibo de lo cual se está dando acuse con el presente documento, los CEDENTES han vendido, cedido y transferido y por este documento venden ceden y transfieren a dicho CESIONARIO y a los sucesores y cesionarios del CESIONARIO la totalidad del derecho, título e interés en dicho invento y para el mismo, dicha solicitud de Carta de Patente de los Estados Unidos y cualquier Carta de Patente que se pueda otorgar sobre el mismo en los Estados Unidos y en todos los países del mundo de ahora en adelante, incluyendo cualquier división, renovación, continuación en todo o en parte, sustituciones, conversiones, (incluyendo las conversiones que reclaman prioridad según 35 U.S.C. §119(e)), reexpediciones, prolongaciones o extensiones de la misma, para que dicho interés sea poseído y disfrutado por dichos CESIONARIOS tan total y exclusivamente como hubiera sido poseído y

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Licencia 376 - 1993 Minjusticia

disfrutado por dichos CEDENTES si esta cesión y transferencia no se hubiera hecho, hasta que se complete el término de cualquier Carta de Patente.

Los CEDENTES acuerdan que el número de la solicitud de los Estados Unidos puede ser introducido en la parte anterior por el CESIONARIO o sus representantes al momento en que se designe el número de solicitud por parte de la Oficina de Patentes y Marcas Registradas de Estados Unidos.

Los CEDENTES acuerdan además que, sin cargo para dicho CESIONARIO, pero a expensas del mismo, cooperarán con el CESIONARIO en el seguimiento de dicha solicitud y/o dichas solicitudes, ejecutarán, verificarán, reconocerán y entregarán todos los papeles adicionales, incluyendo las solicitudes de Cartas de Patente y la reexpedición de las mismas, y los instrumentos de cesión y transferencia de las mismas, así como que realizarán las demás acciones que el CESIONARIO pueda requerir dentro del marco de la ley, para obtener o mantener las Cartas de Patentes para dicho invento y mejora en cualquier país y para investir el título en dicho CESIONARIO o en los sucesores y cesionarios del CESIONARIO.

En testimonio de lo anterior, los CEDENTES han firmado y puestos sus nombres en esta cesión en las fechas indicadas mas adelante.

18 de enero de 2007	(Firmado)	Savitthri Ramurthy
18 de enero de 2007	(Firmado)	Xiaodong Lin
18 de enero de 2007	(Firmado)	Sharada Subramanian
18 de enero de 2007	(Firmado)	Alice C. Rico
18 de enero de 2007	(Firmado)	Xiaojing M. Wang

Traductor Oficial
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Licencia 376 - 1993 Minjusticia

18 de enero de 2007	(Firmado)	Rama Jain
18 de enero de 2007	(Firmado)	Jeremy M. Murray
18 de enero de 2007	(Firmado)	Steven E. Basham
18 de enero de 2007	(Firmado)	Robert L. Warne
18 de enero de 2007	(Firmado)	Wei Shu
18 de enero de 2007	(Firmado)	Yasheen Zhou
18 de enero de 2007	(Firmado)	Jeffrey Dove
18 de enero de 2007	(Firmado)	Mina Aikawa
18 de enero de 2007	(Firmado)	Payman Amiri

RECONOCIMIENTO PARA TODOS LOS PROPÓSITOS CALIFORNIA

Estado de California

Condado de Alameda

El día 18 de enero de 2007, ante mí, Elissa M. Nash, Notario Público, se presentaron personalmente Savitthri Ramurthy, Xiaodong Lin, Sharada Subramanian, Alice C. Rico, Xiaojing M. Wang, Rama Jain, Jeremy M. Murray, Stephen Basham, Robert L. Warne, Wei Shu, Yasheen Zhou, Jeffrey Dove, Mina Aikawa y Payman Amiri a quienes conozco, y quienes comprobaron ante mí con evidencia satisfactoria ser las personas cuyos nombres están suscritos al documento adjunto y reconocieron ante mí que ejecutaron el mismo en su calidad de funcionarios autorizados y que por sus firmas en el instrumento, la personas o la entidad en nombre de la cual actuaron, ejecutó (aron) dicho instrumento.

En constancia de lo anterior, firmo y estampo el sello oficial.

Firma (firmado).

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

Sello: "Elissa M. Nash, comisión #1553873. Notario Público de California, Condado de Alameda. Mi nombramiento vence el 19 de febrero de 2009".

Registrado el 10 de enero de 2008. Patente. Rollo 020386. Marco: 0704

CERTIFICACIÓN

Yo, el suscrito Notario de Derecho Común de Basilea, Suiza, Dr. Matthias Staehelin, certifico por el presente documento que las firmas anteriores son las firmas genuinas de la señora Sabine Zeller, ciudadana de Ormalingen/BL, Suiza, residente en Gelterkinden/BL, Suiza y del señor Reto Halbeisen, ciudadano de Wahlen/BL, Suiza, residente en Laufen/BL, Suiza, ambos actuando en nombre de Novartis AG, en Basilea, Suiza; ambos como titulares de representación y con firma conjunta.

La autenticidad de las firmas se estableció por comparación.

Basilea, Suiza, este día 18 (dieciocho) de mayo de 2009 (dos mil nueve).

(Firmado) M. Staehelin, Notario

Sello: Dr. M. Staehelin, Notario

Protocolo de Legalización No. 1508/2009

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Miniusticia

Caso: 52100-CO-PCT

Referencia: Copia certificada de Cesión de Patente expedida por la Oficina de Patentes y Marcas Registradas de los Estados Unidos.

Para: Novartis vaccines and Diagnostics, Inc.

Solicitud de Patente de los Estados Unidos No. 60/999,170

Fecha de radicación: 15 de octubre de 2007

Título: Quinazolines for PDK1 Inhibition.

Nosotros, Sabine Zeller y Reto Halbeisen damos testimonio y confirmamos que la copia certificada adjunta de Cesión de Patente registrada el 10 de enero de 2008 fue expedida por la Oficina de Marcas Registradas de los Estados Unidos.

NOVARTIS AG

Por:	(Firmado)	(Firmado)
Nombre:	Sabine Zeller	Reto Halbeisen
Cargo:	Signatario autorizado	Signatario autorizado
Fecha:	14 de mayo de 2009.	

Apostilla:

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

APOSTILLA:

(Convention de La Haye du 5 octobre 1961)

1. País: Suiza

El presente documento público

2. Ha sido firmado por: Dr. M. Staehelin

3. Actuando en calidad de: Notario

4. Lleva el sello/estampilla de: (Ilegible).

Certificado

5. En: Basilea.

6. El: 18 de mayo de 2009

7. Por: Cancillería municipal del Cantón de la ciudad de Basilea.

8. Bajo el No.: 3440/6556

9. Sello / estampilla: Cancillería municipal · Ciudad de Basilea.

10. Firma: Hanna Lauener

2009 JUN -5 P 3:37

Jorge Sierra 9269118

FIN DE LA TRADUCCIÓN

Certificación:
Certifico que la presente es una traducción auténtica y completa del inglés al español del documento adjunto, la cual he elaborado según mi leal saber y entender.
Documento: "Novartis Vaccines – Nueva Cesion"
Fecha: 2 de junio 2009.
Traductor: Jorge Enrique Sierra Reyes (Sello y firma digital debidamente registrados ante el Ministerio de Relaciones Exteriores de Colombia)
Licencia # 376 de 1993, expedida por el Ministerio de Justicia.
Dirección: Carrera 15 # 99-13 Of. 411, Bogotá, D.C.
Teléfonos: (571) 218 2308, (571) 623 2925.
E-mail: tresser1(@)yahoo.com
Traducción # 13-257@

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

CO
646

A 1751639

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

May 05, 2009

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF A DOCUMENT RECORDED ON JANUARY 18, 2008.

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

T. Lawrence

T. LAWRENCE
Certifying Officer

PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
SAVITHRI RAMURTHY	01/18/2007
XIAODONG LIN	01/18/2007
SHARADA SUBRAMANIAN	01/18/2007
ALICE C. RICO	01/18/2007
XIAOJING M. WANG	01/18/2007
RAMA JAIN	01/18/2007
JEREMY M. MURRAY	01/18/2007
STEVEN E. BASHAM	01/18/2007
ROBERT L. WARNE	01/18/2007
WEI SHU	01/18/2007
YASHEEN ZHOU	01/18/2007
JEFFREY DOVE	01/18/2007
MINA AIKAWA	01/18/2007
PAYMAN AMIRI	01/18/2007

RECEIVING PARTY DATA

Name:	NOVARTIS VACCINES AND DIAGNOSTICS, INC.
Street Address:	4560 HORTON STREET
City:	EMERYVILLE
State/Country:	CALIFORNIA
Postal Code:	94608-2916

PROPERTY NUMBERS Total: 1

Property Type	Number
Application Number:	60999170

CORRESPONDENCE DATA

Fax Number: (877)769-7945

CH $40.00 60999170

Correspondence will be sent via US Mail when the fax attempt is unsuccessful.

Phone:	302-652-5070
Email:	ASPI@fr.com
Correspondent Name:	Fish & Richardson P.C.
Address Line 1:	P.O. Box 1022
Address Line 4:	Minneapolis, MINNESOTA 55440-1022

ATTORNEY DOCKET NUMBER:	20366-161P02
NAME OF SUBMITTER:	Gwilym J. O. Attwell

Total Attachments: 4
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source=Assignment#page4.tif

PATENT

Atty. Docket No. 28301.0001

ASSIGNMENT XIAODONG Lin Jan. 10, 2008

WHEREAS, We, Savithri Ramurthy, ~~Xiadong~~ Lin, Sharada Subramanian, Alice C. Rico, Xiaojing M. Wang, Rama Jain, Jeremy M. Murray, Stephen Basham, Robert L. Warne, Wei Shu, Yasheen Zhou, Jeffrey Dove, Mina Aikawa, and Payman Amiri, hereinafter referred to as *ASSIGNORS*, have invented certain new and useful improvements as described and set forth in the below-identified application for United States Letters Patent:

Title of Invention: QUINAZOLINES FOR PDK1 INHIBITION

Date(s) of Execution: January 18, 2007 Filing Date: December 22, 2006

Serial No: 60/876,972

WHEREAS, NOVARTIS VACCINES AND DIAGNOSTICS, INC., 4560 Horton Street, Emeryville, California 94608-2916, a corporation of the State of Delaware, hereinafter referred to as *ASSIGNEE*, is desirous of acquiring the entire right, title and interest in the above invention and application and in any Letters Patent which may be granted on the same;

NOW, THEREFORE, TO ALL WHOM IT MAY CONCERN: Be it known that, for and in consideration of the sum of One Dollar ($1.00) lawful money paid to *ASSIGNORS* by *ASSIGNEE*, receipt of which is hereby acknowledged, *ASSIGNORS* have sold, assigned and transferred, and by these presents do sell, assign and transfer unto said *ASSIGNEE*, and *ASSIGNEE'S* successors and assigns, all right, title and interest in and to the said invention, said application for United States Letters Patent, and any Letters Patent which may hereafter be granted on the same in the United States and all countries throughout the world including any divisions, renewals, continuations in whole or in part, substitutions, conversions (including conversions claiming priority under 35 U.S.C. §119(e)), reissues, prolongations or extensions thereof, the said interest to be held and enjoyed by said *ASSIGNEE* as fully and exclusively as it would have been held and enjoyed by said *ASSIGNORS* had this assignment and transfer not been made, to the full end and term of any Letters Patent.

ASSIGNORS also agree that the U.S. application number may be entered above by *ASSIGNEE* or its agents upon designation of the application number by the U.S. Patent and Trademark Office.

ASSIGNORS further agree that they will, without charge to said *ASSIGNEE*, but at *ASSIGNEE'S* expense, cooperate with *ASSIGNEE* in the prosecution of said application and/or applications, execute, verify, acknowledge and deliver all such further papers, including applications for Letters Patent and for the reissue thereof, and instruments of assignment and transfer thereof, and will perform such other acts as *ASSIGNEE* lawfully may request, to obtain or maintain Letters Patent for said invention and improvement in any and all countries, and to vest title thereto in said *ASSIGNEE*, or *ASSIGNEE'S* successors and assigns.

IN TESTIMONY WHEREOF, *ASSIGNORS* have hereunto signed their names to this assignment on the dates indicated below.

DATE 1/18/07 — Savithri Ramurthy

DATE 1/18/07 — Xiadong Lin (XIAODONG XIN) Jan. 19, 2008

DATE 1/18/07 — Sharada Subramanian

DATE 1/18/2007 — Alice C. Rico

DATE 1/18/2007 — Xiaojing M. Wang

DATE 1/18/2007 — Rama Jain

DATE 1/18/2007 — Jeremy M. Murray

DATE 1/18/2007 — Steven E. Basham

DATE 1/18/2007 — Robert L. Warne

DATE 1/18/2007 Wei Shu

DATE 1/18/07 Yasheen Zhou

DATE 1/18/2007 Jeffrey Dove

DATE 1/18/07 Mina Aikawa

DATE 1,18,07 Payman Amiri

CALIFORNIA ALL-PURPOSE ACKNOWLEDGMENT

State of California
County of Alameda } ss.

On January 18, 2007 (Date), before me, Elissa M. Nash (Name and Title of Officer (e.g., "Jane Doe, Notary Public")),

personally appeared Savithri Ramurthy, Xiadong Lin, Sharada Subramanian, Alice C. Rico, Xiaojing M. Wang, Rama Jain, Jeremy M. Murray, Stephen Basham, Robert L. Warne, Wei Shu, Yasheen Zhou, Jeffrey Dove, Mina Aikawa, and Payman Amiri (Name(s) of Signer(s))

☒ personally known to me

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

ELISSA M. NASH
Commission # 1553873
Notary Public - California
Alameda County
My Comm. Expires Feb 19, 2009

WITNESS my hand and official seal.

Place Notary Seal Above

Signature of Notary Public

OPTIONAL

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

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☐ Individual	☐ Individual
☐ Corporate Officer — Title(s): _____	☐ Corporate Officer — Title(s): _____
☐ Partner — ☐ Limited ☐ General	☐ Partner — ☐ Limited ☐ General
☐ Attorney in Fact	☐ Attorney in Fact
☐ Trustee	☐ Trustee
☐ Guardian or Conservator	☐ Guardian or Conservator
☐ Other: _____	☐ Other: _____
Signer Is Representing: _____	Signer Is Representing: _____
RIGHT THUMBPRINT OF SIGNER — Top of thumb here	RIGHT THUMBPRINT OF SIGNER — Top of thumb here

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Attestation

I, the undersigned Civil Law Notary in Basel, Switzerland, Dr. Matthias Staehelin, certify herewith that the above signatures are the genuine signatures of **Ms. Sabine Zeller**, citizen of Ormalingen/BL, Switzerland, residing in Gelterkinden/BL, Switzerland, and of **Mr. Reto Halbeisen**, citizen of Wahlen/BL, Switzerland, residing in Laufen/BL, Switzerland, both acting for **Novartis AG**, in Basel, Switzerland, both as proxy holders, both with joint signature.

The authenticity of the signatures was established by means of comparison.

BASEL, Switzerland, this 18th (eighteenth) day of May 2009 (two thousand and nine)

M. Staehelin, Notar

Dr. M. Staehelin
Notar

Leg.Prot.Nr. 1508 /2009

APOSTILLE

(Hague Convention of October 5th, 1961)

1. Country: Switzerland (Schweiz/Suisse)
   This official document
2. is signed by Dr. iur. M. Staehelin
3. in his/her function as aff. Notar
4. and certified by the seal of the Amannstelle

Certified

5. in Basel (Bâle) 6. on 18. Mai 2009
7. by the State Chancery of the Canton of Basel-Stadt
8. no. 3440/6556
9. Seal/stamp: 10. Signature:

Hanna Lauener

STATE CHANCERY * BASLE-CITY *

Case: 52100-CO-PCT

Re: Certified copy of Patent Assignment issued by the United States Patent and Trademark Office
for: Novartis Vaccines and Diagnostics, Inc.
US Patent Application N° 60/999,170
Filing Date: October 15, 2007
Title: Quinazolines for PDK1 Inhibition

We, Sabine ZELLER and Reto HALBEISEN testify and confirm that the attached certified copy of Patent Assignment recorded on 18 January 2008 was issued by the Unites States and Trademark Office.

NOVARTIS AG

By :

Name :	Sabine Zeller	Reto Halbeisen
Function :	Authorized Signatory	Authorized Signatory
Date:	14 May 2009	

09187

Traducción oficial de un documento que está originalmente en inglés

LOS ESTADOS UNIDOS DE AMÉRICA

A TODOS QUIENES VIEREN EL PRESENTE DOCUMENTO:

Departamento de Comercio de los Estados Unidos

Oficina de Patentes y Marcas Registradas de los Estados Unidos

30 de abril de 2009

Se certifica que la copia anexa es una copia verdadera de los registros de esta oficina de un documento radicado el día 10 de enero de 2008.

Por autoridad del Subsecretario de Comercio para la Propiedad Intelectual y Director de la Oficina de Patentes y Marcas Registradas de los Estados Unidos.

(Firmado) T. Wallace - Funcionario que certifica.

Sello: "Departamento de Comercio, Oficina de Patentes y Marcas Registradas de los Estados Unidos"

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Miniusticia

CESIÓN DE PATENTE

Versión Electrónica v1.1
Versión de hoja de estilo v1.1

Tipo de envío:	Cesión Correctiva
Naturaleza de la transferencia:	Cesión Correctiva para corregir la ortografía del nombre de Xiaodong Lin en la cesión y la hoja de portada. La ortografía del nombre de Steven E. Basham nombre en la hoja de portada, previamente registrada en el Rollo 018788 Marco 0488. El Cedente (los cedentes) confirma(n) la Cesión de los inventores a Novartis Vaccines y Diagnostic, Inc.

Datos de las partes que realizan la transferencia

Nombre	Fecha de ejecución
Savitthri Ramurthy	18 de enero de 2007
Xiaodong Lin	18 de enero de 2007
Sharada Subramanian	18 de enero de 2007
Alice C. Rico	18 de enero de 2007
Xiaojing M. Wang	18 de enero de 2007
Rama Jain	18 de enero de 2007
Jeremy M. Murray	18 de enero de 2007
Steven E. Basham	18 de enero de 2007
Robert L. Warne	18 de enero de 2007
Wei Shu	18 de enero de 2007
Yasheen Zhou	18 de enero de 2007
Jeffrey Dove	18 de enero de 2007
Mina Aikawa	18 de enero de 2007
Payman Amiri	18 de enero de 2007

Datos de las partes que reciben

Nombre:	Novartis Vaccines and Diagnostics, Inc

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JORGE E. SIERRA REYES
Licencia 376 - 1993 Ministerio

Dirección:	4560 Horton Street
Ciudad:	Emeryville
Estado/País:	California
Código postal:	94608-2916

Número total de propiedades: 1

Tipo de propiedad	Número
Número de la solicitud	60876972

500437029

Patente
Rollo: 020349. Marco: 0706

Datos para la correspondencia:

Número de Fax: (877) 769-7945

La correspondencia será enviada por US Mail cuando el intento de hacerlo por fax no sea exitoso.

Teléfono: 302-652-5070

E-mail: ASPI@fr.com

Nombre del correspondiente: Fish & Richardson P.C.

Dirección línea 1: P.O. Box 1022

Dirección línea 4: Minneapolis, Minnesota 55440-1022

Número del registro del Representante:	20366-161P01
Nombre del remitente:	Gwilym J.O. Attwell

Total de anexos: 6
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Fuente= Assignment #page6.tif	

Patente: Rollo: 020349 Marco: 0707

Traductor Oficial
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Formulario PTO-1595 (Rev. 03/01)

OMB No. 0651-0027 (Exp 5/31/2002)

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

Oficina de Patentes y Marcas Registradas de los Estados Unidos.

Hoja de Cubierta del Formulario de Registro

EXCLUSIVAMENTE PATENTES

Al Director de la Oficina de Patentes y Marcas Registradas de los Estados Unidos:

Por favor registrar los documentos adjuntos o las nuevas direcciones.

1. Nombre de la parte que traspasa:

Savitthri Ramurthy

Xiaodong Lin

Sharada Subramanian

Alice C. Rico

¿Hay nombres adicionales de partes que hacen el traspaso? (Si)

2. Nombre y dirección de las partes que reciben:

Nombre: Novartis Vaccines and Diagnostics, Inc.

Dirección interna: Mail Stop R-3

Dirección: 4560 Horton Street

Ciudad: Emeryville. Estado: California. Zip: 94608-2916

¿No hay nombres o direcciones adicionales adjuntas? (Si)

3. Naturaleza del traspaso: Cesión (X)

Fecha de la ejecución: 18 de enero de 2007

4. Número de la solicitud o número de la Patente:

A. Solicitud de Patente No. 60/876,972

¿Se adjuntan números adicionales? (Si).

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

5. Nombre y dirección de la parte a la cual debe enviarse la correspondencia que tiene que ver con el documento:

Nombre: Novartis Vaccines and Diagnostics, Inc.

Dirección interna: Mail Stop R-3

Dirección: 4560 Horton Street

Ciudad: Emeryville. Estado de California. Zip: 94608-2916

6. Número total de solicitudes y patentes del caso: 1

7. Tarifa total: (37 CFR 3.41) $40.00

Se autoriza cargar a cuenta de depósito (X) (cualquier deficiencia)

8. Información sobre el pago:

b. Cuenta de depósito No. 03-1664

(Adjunte duplicado de la copia de la página si cancela en cuenta de depósito)

9. Declaración y firma:

A mi real saber y entender, la anterior información es verdadera y correcta y cualquier copia adjunta es una copia verdadera del documento original.

Nombre de quien firma: Young J. Suh. Registro No. 41, 337. Firma (firmado)

Fecha: 18 de enero de 2009.

Número total de páginas incluyendo la hoja de portada, adjuntos y documentos: 6

Los documentos que van a registrarse (incluyendo la hoja de portada) deben enviarse por fax al (703)306-5995, o por correo a Mail Stop Assignment Recordation Services, Director of the USPTO. P.O.Box: 1450, Alexadria, V.A. 22313-1450

Patente

Rollo: 020349. Marco: 0708

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Ministerio

Formulario PTO-1595 (Rev. 03/01)
OMB No. 0651-0027 (Exp 5/31/2002)

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

Oficina de Patentes y Marcas Registradas de los Estados Unidos.

28301.0001

Hoja de Cubierta del Formulario de Registro

EXCLUSIVAMENTE PATENTES
(ANEXO)

Al Honorable Comisionado de Patentes y Marcas Registradas. Por favor registrar los documentos originales adjuntos o copiarlos.

1. Nombre de la partes que traspasa (continuación):

Xiaojing M. Wang

Rama Jain

Jeremy M. Murray

Stephen Basham

Robert L. Warne

Wei Shu

Yasheen Zhou

Jeffrey Dove

Mina Aikawa

Payman Amiri

Los documentos que van a registrarse con la información de la hoja de cubierta a: Comissioner of Patent & Trademarks, Box Assignments, Washington, D.C. 20231.

Patente

Rollo: 020349. Marco: 0709

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Miniusticia

Patente
Registro del Representante No. 28301.0001

CESIÓN

Puesto que nosotros, Savitthri Ramurthy, Xiaodong Lin, Sharada Subramanian, Alice C. Rico, Xiaojing M. Wang, Rama Jain, Jeremy M. Murray, Stephen Basham, Robert L. Warne, Wei Shu, Yasheen Zhou, Jeffrey Dove, Mina Aikawa y Payman Amiri, quienes de ahora en adelante serán denominados los CEDENTES, han inventado ciertas mejoras nuevas y útiles conforme se describe y presenta en la solicitud relacionada enseguida para Cartas de Patente de los Estados Unidos:

Título del Invento:	QUINAZOLINES FOR PDK1 INHIBITION
Fecha de ejecución:	18 de enero, 2007. Fecha de radicación: 22 de Dic., 2006.
Serial No.	60/876,972

Puesto que NOVARTIS VACCINES AND DIAGNOSTICS INC., , 4560 Horton Street, Emeryville, California 94608-2916, una Compañía del Estado de Delaware, de ahora en adelante denominada el CESIONARIO, desea adquirir la totalidad del derecho, título e interés del anterior invento y solicitud y de cualquier Carta de Patente que pueda otorgarse sobre los mismos;

Entonces y a todos a quienes pueda interesar: sea de su conocimiento, por consideración y en consideración de la suma de un dólar (US1,00), dinero legal pagado a los CEDENTES por el CESIONARIO, recibo de lo cual se está dando acuse con el presente documento, los CEDENTES han vendido, cedido y transferido y por este documento venden ceden y transfieren a dicho CESIONARIO y a los sucesores y cesionarios del CESIONARIO la totalidad del

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derecho, título e interés en dicho invento y para el mismo, dicha solicitud de Carta de Patente de los Estados Unidos y cualquier Carta de Patente que se pueda otorgar sobre el mismo en los Estados Unidos y en todos los países del mundo de ahora en adelante, incluyendo cualquier división, renovación, continuación en todo o en parte, sustituciones, conversiones, (incluyendo las conversiones que reclaman prioridad según 35 U.S.C. §119(e)), reexpediciones, prolongaciones o extensiones de la misma, para que dicho interés sea poseído y disfrutado por dichos CESIONARIOS tan total y exclusivamente como hubiera sido poseído y disfrutado por dichos CEDENTES si esta cesión y transferencia no se hubiera hecho, hasta que se complete el término de cualquier Carta de Patente.

Los CEDENTES acuerdan que el número de la solicitud de los Estados Unidos puede ser introducido en la parte anterior por el CESIONARIO o sus representantes al momento en que se designe el número de solicitud por parte de la Oficina de Patentes y Marcas Registradas de Estados Unidos.

Los CEDENTES acuerdan además que, sin cargo para dicho CESIONARIO, pero a expensas del mismo, cooperarán con el CESIONARIO en el seguimiento de dicha solicitud y/o dichas solicitudes, ejecutarán, verificarán, reconocerán y entregarán todos los papeles adicionales, incluyendo las solicitudes de Cartas de Patente y la reexpedición de las mismas, y los instrumentos de cesión y transferencia de las mismas, así como que realizarán las demás acciones que el CESIONARIO pueda requerir dentro del marco de la ley, para obtener o mantener las Cartas de Patentes

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para dicho invento y mejora en cualquier país y para investir el título en dicho CESIONARIO o en los sucesores y cesionarios del CESIONARIO.

En testimonio de lo anterior, los CEDENTES han firmado y puestos sus nombres en esta cesión en las fechas indicadas mas adelante.

18 de enero de 2007	(Firmado)	Savitthri Ramurthy
18 de enero de 2007	(Firmado)	Xiaodong Lin
18 de enero de 2007	(Firmado)	Sharada Subramanian
18 de enero de 2007	(Firmado)	Alice C. Rico
18 de enero de 2007	(Firmado)	Xiaojing M. Wang
18 de enero de 2007	(Firmado)	Rama Jain
18 de enero de 2007	(Firmado)	Jeremy M. Murray
18 de enero de 2007	(Firmado)	Steven E. Basham
18 de enero de 2007	(Firmado)	Robert L. Warne
18 de enero de 2007	(Firmado)	Wei Shu
18 de enero de 2007	(Firmado)	Yasheen Zhou
18 de enero de 2007	(Firmado)	Jeffrey Dove
18 de enero de 2007	(Firmado)	Mina Aikawa
18 de enero de 2007	(Firmado)	Payman Amiri

RECONOCIMIENTO PARA TODOS LOS PROPÓSITOS CALIFORNIA

Estado de California

Condado de Alameda

El día 18 de enero de 2007, ante mí, Elissa M. Nash, Notario Público, se presentaron personalmente Savitthri Ramurthy, Xiaodong Lin, Sharada Subramanian, Alice C. Rico, Xiaojing M. Wang, Rama Jain, Jeremy M. Murray, Stephen Basham, Robert L. Warne, Wei Shu, Yasheen Zhou, Jeffrey Dove, Mina Aikawa y Payman Amiri a

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

quienes conozco, y quienes comprobaron ante mí con evidencia satisfactoria ser las personas cuyos nombres están suscritos al documento adjunto y reconocieron ante mí que ejecutaron el mismo en su calidad de funcionarios autorizados y que por sus firmas en el instrumento, la personas o la entidad en nombre de la cual actuaron, ejecutó (aron) dicho instrumento.

En constancia de lo anterior, firmo y estampo el sello oficial.
Firma (firmado).

Sello: "Elissa M. Nash, comisión #1553873. Notario Público de California, Condado de Alameda. Mi nombramiento vence el 19 de febrero de 2009".

Registrado el 10 de enero de 2008. Patente. Rollo 020349. Marco: 0713

Caso: 52100-CO-PCT

Referencia: Copia certificada de Cesión de Patente expedida por la Oficina de Patentes y Marcas Registradas de los Estados Unidos.
Para: Novartis vaccines and Diagnostics, Inc.
Solicitud de Patente de los Estados Unidos No. 60/876,972
Fecha de radicación: 22 de diciembre de 2006
Título: Quinazolines for PDK1 Inhibition.

Nosotros, Sabine Zeller y Reto Halbeisen damos testimonio y confirmamos que la copia certificada adjunta de Cesión de Patente registrada el 10 de enero de 2008 fue expedida por la Oficina de Marcas Registradas de los Estados Unidos.

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Miniusticia

NOVARTIS AG

Por:	(Firmado)	(Firmado)
Nombre:	Sabine Zeller	Reto Halbeisen
Cargo:	Signatario autorizado	Signatario autorizado
Fecha:	14 de mayo de 2009.	

CERTIFICACIÓN

Yo, el suscrito Notario de Derecho Común de Basilea, Suiza, Dr. Matthias Staehelin, certifico por el presente documento que las firmas anteriores son las firmas genuinas de la señora Sabine Zeller, ciudadana de Ormalingen/BL, Suiza, residente en Gelterkinden/BL, Suiza y del señor Reto Halbeisen, ciudadano de Wahlen/BL, Suiza, residente en Laufen/BL, Suiza, ambos actuando en nombre de Novartis AG, en Basilea, Suiza; ambos como titulares de representación y con firma conjunta.

La autenticidad de las firmas se estableció por comparación.

Basilea, Suiza, este día 18 (dieciocho) de mayo de 2009 (dos mil nueve).

(Firmado) M. Staehelin, Notario

Sello: Dr. M. Staehelin, Notario

Protocolo de Legalización No. 1500/2009

Apostilla:

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

APOSTILLA:

(Convention de La Haye du 5 octobre 1961)

1. País: Suiza

El presente documento público

2. Ha sido firmado por: Dr. M. Staehelin

3. Actuando en calidad de: Notario

4. Lleva el sello/estampilla de: (Ilegible).

Certificado

5. En: Basilea.

6. El: 18 de mayo de 2009

7. Por: Cancillería municipal del Cantón de la ciudad de Basilea.

8. Bajo el No.: 3436/6538

9. Sello / estampilla: Cancillería municipal · Ciudad de Basilea.

10. Firma: Hanna Lauener

FIN DE LA TRADUCCIÓN

Certificación:
Certifico que la presente es una traducción auténtica y completa del inglés al español del documento adjunto, la cual he elaborado según mi leal saber y entender.
Documento: "Novartis Vaccines – Cesion Correctiva"
Fecha: 2 de junio 2009.
Traductor: Jorge Enrique Sierra Reyes (Sello y firma digital debidamente registrados ante el Ministerio de Relaciones Exteriores de Colombia)
Licencia # 376 de 1993, expedida por el Ministerio de Justicia.
Dirección: Carrera 15 # 99-13 Of. 411, Bogotá, D.C.
Teléfonos: (571) 218 2308, (571) 623 2925.
E-mail: trusersr1@yahoo.com
Traducción # 13-257

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

645

A 1751639

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

April 30, 2009

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF A DOCUMENT RECORDED ON January 10, 2008.

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

T. WALLACE
Certifying Officer

PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

SUBMISSION TYPE:	CORRECTIVE ASSIGNMENT
NATURE OF CONVEYANCE:	Corrective Assignment to correct the Spelling of Xiaodong Lin's name in assignment and cover sheet. Spelling of Steven E. Basham's name on coversheet. previously recorded on Reel 018788 Frame 0488. Assignor(s) hereby confirms the Assignment from inventors to Novartis Vaccines and Diagnostics, Inc..

CONVEYING PARTY DATA

Name	Execution Date
SAVITHRI RAMURTHY	01/18/2007
XIAODONG LIN	01/18/2007
SHARADA SUBRAMANIAN	01/18/2007
ALICE C. RICO	01/18/2007
XIAOJING M. WANG	01/18/2007
RAMA JAIN	01/18/2007
JEREMY M. MURRAY	01/18/2007
STEVEN E. BASHAM	01/18/2007
ROBERT L. WARNE	01/18/2007
WEI SHU	01/18/2007
YASHEEN ZHOU	01/18/2007
JEFFREY DOVE	01/18/2007
MINA AIKAWA	01/18/2007
PAYMAN AMIRI	01/18/2007

CH $40.00 60876972

RECEIVING PARTY DATA

Name:	NOVARTIS VACCINES AND DIAGNOSTICS, INC.
Street Address:	4560 HORTON STREET
City:	EMERYVILLE
State/Country:	CALIFORNIA
Postal Code:	94608-2916

PROPERTY NUMBERS Total: 1

Property Type	Number
Application Number:	60876972

CORRESPONDENCE DATA

Fax Number: (877)769-7945

Correspondence will be sent via US Mail when the fax attempt is unsuccessful.

Phone: 302-652-5070

Email: ASPI@fr.com

Correspondent Name: Fish & Richardson P.C.

Address Line 1: P.O. Box 1022

Address Line 4: Minneapolis, MINNESOTA 55440-1022

ATTORNEY DOCKET NUMBER:	20366-161P01
NAME OF SUBMITTER:	Gwilym J. O. Attwell

Total Attachments: 6
source=Assignment#page1.tif
source=Assignment#page2.tif
source=Assignment#page3.tif
source=Assignment#page4.tif
source=Assignment#page5.tif
source=Assignment#page6.tif

Form PTO-1595 (Rev. 03/01)
OMB No. 0651-0027 (exp. 5/31/2002)

RECORDATION FORM COVER SHEET
PATENTS ONLY

U.S. DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office

Atty Docket No.: 28301.0001

To the Director of the U.S. Patent and Trademark Office: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

Savithri Ramurthy

Xiadong Lin

Sharada Subramanian

Alice C. Rico

Additional name(s) of conveying party(ies) attached? ☒ Yes ☐ No

3. Nature of conveyance:

☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other

Execution Date: January 18, 2007

2. Name and address of receiving party(ies)
Name: Novartis Vaccines and Diagnostics, Inc.

Internal Address: Mail Stop R-3
Street Address: 4560 Horton Street

City: Emeryville State: California Zip: 94608-2916
☐ Other

Additional name(s) & address(es) attached? ☐ Yes ☒ No

4. Application number(s) or patent number(s):
If this document is being filed together with a new application, the execution date of the application is: _____

A. Patent Application No.

60/876,972

B. Patent Registration No.(s)

Additional number(s) attached ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: **Novartis Vaccines and Diagnostics, Inc.**

Internal Address: **Mail Stop R-3**
Street Address: **4560 Horton Street**

City: **Emeryville** State: **CA** Zip: **94608-2916**

6. Total number of applications and patents involved [1]

7. Total fee (37 CFR 3.41)..... $40.00

☐ Enclosed

☒ Authorized to be charged to deposit account (any deficiencies)

8. Deposit account number:

03-1664

(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Young J. Suh, Registration No. 41,337 _____ 18 January 2007
Name of Person Signing Signature Date

Total number of pages including cover sheet, attachments, and document: [6]

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Form PTO-1595 (Rev. 03/01)
OMB No. 0651-0027 (exp. 5/31/2002)

RECORDATION FORM COVER SHEET
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(ADDENDUM)

U.S. DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office
28301.0001

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies) continued:

Xiaojing M. Wang

Rama Jain

Jeremy M. Murray

Stephen Basham

Robert L. Warne

Wei Shu

Yasheen Zhou

Jeffrey Dove

Mina Aikawa

Payman Amiri

Mail documents to be recorded with required cover sheet information to:
Commissioner of Patent & Trademarks, Box Assignments
Washington, D.C. 20231

PATENT

Atty. Docket No. 28301.0001

ASSIGNMENT XIAODONG X Lin Jan. 10, 2008

WHEREAS, We, Savithri Ramurthy, ~~Xiadong~~ Lin, Sharada Subramanian, Alice C. Rico, Xiaojing M. Wang, Rama Jain, Jeremy M. Murray, Stephen Basham, Robert L. Warne, Wei Shu, Yasheen Zhou, Jeffrey Dove, Mina Aikawa, and Payman Amiri, hereinafter referred to as *ASSIGNORS*, have invented certain new and useful improvements as described and set forth in the below-identified application for United States Letters Patent:

Title of Invention: QUINAZOLINES FOR PDK1 INHIBITION

Date(s) of Execution: January 18, 2007 Filing Date: December 22, 2006

Serial No: 60/876,972

WHEREAS, NOVARTIS VACCINES AND DIAGNOSTICS, INC., 4560 Horton Street, Emeryville, California 94608-2916, a corporation of the State of Delaware, hereinafter referred to as ***ASSIGNEE***, is desirous of acquiring the entire right, title and interest in the above invention and application and in any Letters Patent which may be granted on the same;

NOW, THEREFORE, TO ALL WHOM IT MAY CONCERN: Be it known that, for and in consideration of the sum of One Dollar ($1.00) lawful money paid to ***ASSIGNORS*** by ***ASSIGNEE***, receipt of which is hereby acknowledged, ***ASSIGNORS*** have sold, assigned and transferred, and by these presents do sell, assign and transfer unto said ***ASSIGNEE***, and ***ASSIGNEE'S*** successors and assigns, all right, title and interest in and to the said invention, said application for United States Letters Patent, and any Letters Patent which may hereafter be granted on the same in the United States and all countries throughout the world including any divisions, renewals, continuations in whole or in part, substitutions, conversions (including conversions claiming priority under 35 U.S.C. §119(e)), reissues, prolongations or extensions thereof, the said interest to be held and enjoyed by said ***ASSIGNEE*** as fully and exclusively as it would have been held and enjoyed by said ***ASSIGNORS*** had this assignment and transfer not been made, to the full end and term of any Letters Patent.

ASSIGNORS also agree that the U.S. application number may be entered above by *ASSIGNEE* or its agents upon designation of the application number by the U.S. Patent and Trademark Office.

ASSIGNORS further agree that they will, without charge to said *ASSIGNEE*, but at *ASSIGNEE'S* expense, cooperate with *ASSIGNEE* in the prosecution of said application and/or applications, execute, verify, acknowledge and deliver all such further papers, including applications for Letters Patent and for the reissue thereof, and instruments of assignment and transfer thereof, and will perform such other acts as *ASSIGNEE* lawfully may request, to obtain or maintain Letters Patent for said invention and improvement in any and all countries, and to vest title thereto in said *ASSIGNEE*, or *ASSIGNEE'S* successors and assigns.

IN TESTIMONY WHEREOF, *ASSIGNORS* have hereunto signed their names to this assignment on the dates indicated below.

DATE 1/18/07 — Savithri Ramurthy

DATE 1/18/07 — ~~Xiadong~~ Lin XIAODONG XU Jan. 19, 2008

DATE 1/18/07 — Sharada Subramanian

DATE 1/18/2007 — Alice C. Rico

DATE 1/18/2007 — Xiaojing M. Wang

DATE 1/18/2007 — Rama Jain

DATE 1/18/2007 — Jeremy M. Murray

DATE 1/18/2007 — Steven E. Basham

DATE 1/18/2007 — Robert L. Warne

DATE 1/18/2007 Wei Shu

DATE 1/18/07 Yasheen Zhou

DATE 1/18/2007 Jeffrey Dove

DATE 1/18/07 Mina Aikawa

DATE 1/18/07 Payman Amiri

CALIFORNIA ALL-PURPOSE ACKNOWLEDGMENT

State of California
County of Alameda } ss.

On January 18, 2007 (Date), before me, Elissa M. Nash (Name and Title of Officer (e.g., "Jane Doe, Notary Public")),

personally appeared Savithri Ramurthy, Xiadong Lin, Sharada Subramanian, Alice C. Rico, Xiaojing M. Wang, Rama Jain, Jeremy M. Murray, Stephen Basham, Robert L. Warne, Wei Shu, Yasheen Zhou, Jeffrey Dove, Mina Aikawa, and Payman Amiri (Name(s) of Signer(s))

☒ personally known to me

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

ELISSA M. NASH
Commission # 1553873
Notary Public - California
Alameda County
My Comm. Expires Feb 19, 2009

WITNESS my hand and official seal.

Place Notary Seal Above

Signature of Notary Public

OPTIONAL

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

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☐ Individual	☐ Individual
☐ Corporate Officer — Title(s): _____	☐ Corporate Officer — Title(s): _____
☐ Partner — ☐ Limited ☐ General	☐ Partner — ☐ Limited ☐ General
☐ Attorney in Fact	☐ Attorney in Fact
☐ Trustee	☐ Trustee
☐ Guardian or Conservator	☐ Guardian or Conservator
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RIGHT THUMBPRINT OF SIGNER — Top of thumb here	RIGHT THUMBPRINT OF SIGNER — Top of thumb here

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Case: 52100-CO-PCT

Re: Certified copy of Patent Assignment issued by the United States Patent and Trademark Office
for: Novartis Vaccines and Diagnostics, Inc.
US Patent Application N° 60/876,972
Filing Date: December 22, 2006
Title: Quinazolines for PDK1 Inhibition

We, Sabine ZELLER and Reto HALBEISEN testify and confirm that the attached certified copy of Patent Assignment recorded on 10 January 2008 was issued by the Unites States and Trademark Office.

NOVARTIS AG

By : _____ _____

Name :	Sabine Zeller	Reto Halbeisen
Function :	Authorized Signatory	Authorized Signatory
Date:	14 May 2009	

Attestation

I, the undersigned Civil Law Notary in Basel, Switzerland, Dr. Matthias Staehelin, certify herewith that the above signatures are the genuine signatures of **Ms. Sabine Zeller**, citizen of Ormalingen/BL, Switzerland, residing in Gelterkinden/BL, Switzerland, and of **Mr. Reto Halbeisen**, citizen of Wahlen/BL, Switzerland, residing in Laufen/BL, Switzerland, both acting for **Novartis AG**, in Basel, Switzerland, both as proxy holders, both with joint signature.

The authenticity of the signatures was established by means of comparison.

BASEL, Switzerland, this 18th (eighteenth) day of May 2009 (two thousand and nine)

M. Staehelin, Note

Dr. M. Staehelin
Notar

Leg.Prot.Nr. 1500 /2009

APOSTILLE
(Hague Convention of October 5th, 1961)

1. Country: Switzerland (Schweiz / Suisse)
This official document
2. is signed by Dr. M. St. M. Staehelin
3. in his/her function as Dr. Notar
4. and certified by the seal of the Gerichtsschreiberei

Certified 18. Mai 2009
5. in Basel (Bâle) 6. on
7. by the State Chancery of the Canton of Basel-Stadt
8. no. 3436/6538
9. Seal/stamp: STATE CHANCERY * BASLE-CITY *
10. Signature: H. Lauener

Hanna Lauener

09187

Traducción oficial de un documento que está originalmente en inglés

CESIÓN

Por buena y valiosa consideración, de la cual por medio del presente documento se da acuse de recibo y adecuación, nosotros,

Novartis Vaccines and Diagnostics Inc./ PO Box: 8097

Emeryville, CA 94608 /US

por medio del presente vendemos, cedemos y transferimos a Novartis AG, una compañía organizada según las leyes de la Confederación Suiza, the Lichtstrasse 35, 4056, Basilea, Suiza, y a sus sucesores, cesionarios y representantes legales la totalidad de nuestro derecho, título e interés para todos los países del mundo (nos referiremos a Novartis AG de aquí en adelante como el "CESIONARIO") en y para (1) todos nuestros inventos y descubrimientos descritos en la solicitud de patente titulada

"QUINAZOLINES FOR PDK1 INHIBITION"

y radicados* en la Oficina de Patentes y Marcas Registradas de los Estados Unidos el __ de 20 __ y de acuerdo con la Solicitud No. __ y/o radicados en el RO/US el día 20 de diciembre de 2007 y de acuerdo con la Solicitud Internacional de Patente No. PCT/US2007/088392, (2) dichas solicitudes de patente, (3) todas las etapas nacionales de dicha solicitud de patente internacional, (4) todas las demás solicitudes en todos los países y regiones que reclamen la prioridad de la solicitud provisional de patente radicada en la Oficina de Patentes y Marcas Registradas de los Estados Unidos el 22 de diciembre de 2006 y 15 de octubre de 2007 de acuerdo con las Solicitudes No. 60/876,972 y 60/999,170 (5) todas las continuaciones y

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

divisiones de todas las aplicaciones de patentes antedichas (incluyendo las continuaciones y divisiones adicionales tales como, pero no solamente, continuaciones de continuaciones y continuaciones de divisiones), ((2) – (5) de aquí en adelante serán denominados colectivamente como "Solicitudes de Patente"), (6) todas las patentes que sean otorgadas sobre cualquiera de dichas aplicaciones de patentes, (7) todos los registros y confirmaciones y certificados de importación con base en una o más de dichas patentes y (8) todas las reexpediciones, renovaciones y extensiones de dichas patentes, certificados de reexamen expedidos para dichas patentes y certificados de protección suplementaria con base en dichas patentes (incluyendo el derecho a radicar solicitudes de patente sobre dichos inventos y descubrimientos a nombre del CESIONARIO, sus designados o en cualquiera de todos nuestros nombres, a su elección y de acuerdo con la ley aplicable en todos los países y regiones y todos los derechos de prioridad en todos los países y regiones para todas las solicitudes de patente dichas, de acuerdo con la Convención Internacional para la Protección de la Propiedad Industrial, la Convención Interamericana relacionada con Inventos, Patentes, Diseños y Modelos Industriales y todos los demás acuerdos internacionales de los cuales los Estados Unidos sea ahora o más adelante uno de los signatarios), lo anterior para ser poseído y disfrutado por dicho CESIONARIO, sus sucesores, cesionarios y representantes legales, hasta el extremo de los términos para los cuales puedan ser otorgadas todas las patentes para ello, tan completa y totalmente como si lo mismo hubiera sido nuestra propiedad y hubiera sido disfrutado por nosotros si esta venta, cesión y transferencia no se hubiera realizado.

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Ministerio

*Autorizamos por medio del presente al CESIONARIO y a sus representantes a insertar en este instrumento el número de la Solicitud y la fecha de radicación de dicha solicitud de patente cuando se notifique de la misma.

Y por el presente convenimos y acordamos que nosotros, en cualquier momento, a solicitud y a costa del CESIONARIO, ejecutaremos y enviaremos todos los documentos que puedan ser necesarios o deseables para perfeccionar el título de los anteriores inventos y descubrimientos, solicitudes de patente, patentes, registros, confirmaciones, certificados de importación, reexpediciones, renovaciones, extensiones, certificados de reexamen, y certificados de protección suplementaria en el CESIONARIO, sus sucesores, cesionarios u otros representantes legales, incluyendo la ejecución y consecución de todos los documentos adicionales que sean prueba de esta venta, cesión y transferencia, según pueda necesitarse o desearse para registrar eso en la Oficina de Patentes u otra oficina de propiedad intelectual, agencia o similar de cualquier país o región, que nosotros, en cualquier momento, a solicitud y a costas del CESIONARIO, ejecutaremos todas las solicitudes de patentes adicionales, solicitudes de registro y/o confirmación de una o más de dichas patentes, solicitudes de certificado de importación con base en una o más de dichas patentes, solicitudes de reexpedición, renovaciones y extensiones de una o más de dichas patentes y certificados de protección suplementaria con base en una o más de dichas patentes, y que haremos todas las declaraciones juradas y otras y haremos todos los actos legales que se requieran para lograr lo mismo o para ayudar en ello, sin compensación adicional,

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Licencia 376 - 1993 Minjusticia

pero a costas del CESIONARIO, los sucesores, cesionarios u otros representantes legales.

Ejecutado este día 12 de mayo de 2009.

Novartis Vaccines and Diagnostics Inc.
(Firmado) L.S.
Amy Hessler, Abogado

RECONOCIMIENTO PARA TODOS LOS PROPÓSITOS CALIFORNIA

Estado de California

Condado de Alameda

El día 12 de mayo de 2009, ante mí, Christy Snyder, Notario Público, se presentó personalmente Amy Hessler, quien comprobó ante mí sobre la base de evidencia satisfactoria ser la persona cuyo nombre está suscrito al documento adjunto y reconoció ante mí haber ejecutado el mismo en su calidad de funcionario autorizado y que por su firma en el instrumento, la persona o la entidad en nombre de la cual actuó, ejecutó dicho instrumento.

Certifico, so pena de perjurio, según las leyes del Estado de California, que el párrafo anterior es verdadero y correcto.

En constancia de lo anterior, firmo y estampo el sello oficial.
Firma (firmado).

Sello: "Christy Snyder, comisión #(ilegible). Notario Público de California, Condado de Alameda. Mi nombramiento vence el 13 de junio de 2012".

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Ministerio

Caso: 52100

56

ACEPTACIÓN DE CESIÓN

Con referencia a la Cesión hecha a NOVARTIS AG de un invento titulado "QUINAZOLINES FOR PDK1 INHIBITION" firmada por NOVARTIS VACCINES AND DIAGNOSTICS, INC., lo siguiente certificará que NOVARTIS AG acepta dicha Cesión.

NOVARTIS AG

Por:	(Firmado)	(Firmado)
Nombre:	Sabine Zeller	Reto Halbeisen
Cargo:	Signatario autorizado	Signatario autorizado
Fecha:	14 de mayo de 2009.	

CERTIFICACIÓN

Yo, el suscrito Notario de Derecho Común de Basilea, Suiza, Dr. Matthias Staehelin, certifico por el presente documento que las firmas adjuntas al presente son las correspondientes al señor Reto Halbeisen, ciudadano de Wahlen/BL Suiza, residente en Laufen/BL, y la señora Sabine Zeller, ciudadana de Ormalingen/BL, Suiza, residente en Gelterkinden/BL, Suiza, ambos actuando en nombre de Novartis AG, en Basilea, Suiza; ambos como titulares de representación y con firma conjunta.

La autenticidad de las firmas se estableció por comparación.

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Miniusti

Basilea, Suiza, este día 18 (dieciocho) de mayo de 2009 (dos mil nueve).

(Firmado) M. Staehelin, Notario

Sello: Dr. M. Staehelin, Notario

Protocolo de Legalización No. 1530/2009

PARA COPIA CERTIFICADA

Yo, el suscrito Notario de Derecho Civil, Dr. Matthias Staehelin, certifico por el presente que el documento adjunto es una fotocopia verdadera y auténtica del original.

Basilea, Suiza, este día 18 (dieciocho) de mayo de 2009 (dos mil nueve).

(Firmado) M. Staehelin, Notario

Protocolo de Legalización No. 1534/2009

Apostilla:

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

APOSTILLA:

(Convention de La Haye du 5 octobre 1961)

1. País: Suiza

El presente documento público

2. Ha sido firmado por: Dr. M. Staehelin

3. Actuando en calidad de: Notario

4. Lleva el sello/estampilla de: (Ilegible).

Certificado

5. En: Basilea.

6. El: 19 de mayo de 2009

7. Por: Cancillería municipal del Cantón de la ciudad de Basilea.

8. Bajo el No.: 3481/6635

9. Sello / estampilla: Cancillería municipal · Ciudad de Basilea.

10. Firma: Hanna Lauener

MINISTERIO DE RELACIONES EXTERIORES
2009 JUN -5 P 2:38
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REPUBLICA DE COLOMBIA
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LEGALIZACION DE DOCUMENTOS

"FIN DE LA TRADUCCIÓN"

Certificación:
Certifico que la presente es una traducción auténtica y completa del inglés al español del documento adjunto, la cual he elaborado según mi leal saber y entender.
Documento: "Novartis Vaccines – Cesion de Patente a Novartis AG"
Fecha: 2 de junio 2009.
Traductor: Jorge Enrique Sierra Reyes (Sello y firma digital debidamente registrados ante el Ministerio de Relaciones Exteriores de Colombia)
Licencia # 376 de 1993, expedida por el Ministerio de Justicia.
Dirección: Carrera 15 # 99-13 Of. 411, Bogotá, D.C.
Teléfonos: (571) 218 2308, (571) 623 2925.
E-mail: tressser1(@)yahoo.com
Traducción # 13-258

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

649 CO

Case 52100

ASSIGNMENT

For good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, we

Novartis Vaccines and Diagnostics, Inc.
P.O. Box 8097
Emeryville, CA 94608
US

do hereby sell, assign and transfer to **Novartis AG**, a company organized under the laws of the Swiss Confederation, of **Lichtstrasse 35, 4056 Basel, Switzerland**, and its successors, assigns and legal representatives, all our right, title and interest for all countries of the world (Novartis AG hereinafter referred to as the "**ASSIGNEE**") in and to (1) all of our inventions and discoveries described in the patent application(s) entitled

QUINAZOLINES FOR PDK1 INHIBITION

and filed* in the United States Patent and Trademark Office on _____, 20____ and accorded Application Number _____ and/or filed in the RO/US on **20 December 2007**, and accorded International Patent Application Number **PCT/US2007/088392**, (2) said patent application(s), (3) all national stages of said international patent application, (4) all other patent applications in all countries and regions claiming the priority of the provisional patent application filed in the United States Patent and Trademark Office on **22 December 2006** and **15 October 2007** and accorded Application Numbers **60/876,972** and **60/999,170**, (5) all continuations and divisions of all of said patent applications (including further continuations and divisions such as, but not limited to, continuations of continuations and continuations of divisions), ((2)-(5) hereinafter referred to collectively as "patent applications"), (6) all patents that are granted on any of said patent applications, (7) all registrations and confirmations of, and importation certificates based on, one or more of said patents and (8) all reissues, renewals and extensions of said patents, reexamination certificates issued for said patents and supplementary protection certificates based on said patents (including the right to file patent applications on said inventions and discoveries in the names of **ASSIGNEE**, their designees or in any or all of our names, at their election and in accordance with applicable law in all countries and regions and all rights of priority in all countries and regions for all of said patent applications under the International Convention for the Protection of Industrial Property, the Inter-American Convention relating to Inventions, Patents, Designs and Industrial Models and all other international agreements to which the United States now is or hereafter becomes a signatory), the same to be held and enjoyed by said **ASSIGNEE**, their successors, assigns and legal representatives, to the full ends of the terms for which all patents therefor may be granted, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made.

*We hereby authorize **ASSIGNEE** and their representatives to insert in this instrument the Application Number and the filing date of said patent application when notified thereof.

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Executed this 12 day of May, 20 09.

Novartis Vaccines and Diagnostics, Inc.

_____ L.S.
Amy Hessler
Attorney-In-Fact

CALIFORNIA ALL-PURPOSE ACKNOWLEDGMENT

State of California
County of Alameda }

On 5-12-09 (Date) before me, Christy Snyder, Notary Public (Here Insert Name and Title of the Officer),

personally appeared Amy Hessler (Name(s) of Signer(s)),

who 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.

I certify under PENALTY OF PERJURY under the laws of the State of California that the foregoing paragraph is true and correct.

WITNESS my hand and official seal.

Signature _____ (Signature of Notary Public)

CHRISTY SNYDER
Commission # 1831688
Notary Public - California
Alameda County
My Comm. Expires Jan 13, 2013

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ACCEPTANCE OF ASSIGNMENT

With reference to the Assignment to **NOVARTIS AG** of an invention entitled **"QUINAZOLINES FOR PDK1 INHIBITION"** signed by Novartis Vaccines and Diagnostics, Inc.; this will certify that **NOVARTIS AG** accepts such Assignment.

NOVARTIS AG

By :		
Name :	SABINE ZELLER	RETO HALBEISEN
Function :	AUTHORIZED SIGNATORY	AUTHORIZED SIGNATORY
Date:	14 MAY 2009	

Attestation

I, the undersigned Civil Law Notary of Basel, Switzerland, Dr. Matthias Staehelin, certify herewith that the signatures attached heretofore are the genuine signatures of **Mr. Reto Halbeisen,** citizen of Wahlen/BL, Switzerland, residing in Laufen/BL, Switzerland; and **Ms. Sabine Zeller**, citizen of Ormalingen/BL, Switzerland, residing in Gelterkinden/BL; Switzerland, both acting for **Novartis AG,** in Basel, Switzerland, both as proxy holders, both with joint signature.

The authenticity of the signatures was established by means of comparison.

BASEL, Switzerland, this 18th (eighteenth) day of May 2009 (two thousand and nine)

M. Staehelin, Notar

Dr. M. Staehelin
Notar in Basel

Leg.Prot.Nr. 1530/2009

FOR CERTIFIED COPY

I, the undersigned Civil Law Notary of Basel, Switzerland, Dr. Matthias Staehelin, hereby certify that the document attached heretofore is a true and authentic photocopy of the original.

BASEL, Switzerland, this 18th (eighteenth) day of May 2009 (two thousand and nine)

M. Staehelin, Notar

Dr. M. Staehelin
Notar in Basel

Leg.Prot.Nr. 1534 /2009

APOSTILLE

(Hague Convention of October 5th, 1961)

1. Country: Switzerland (Schweiz/Suisse)
   This official document
2. is signed by Dr. iur. M. Staehelin
3. in his/her function as notary public
4. and certified by the seal of the above named

Certified

5. in Basel (Bâle) 6. on 19. Mai 2009
7. by the State Chancery of the Canton of Basel-Stadt
8. no. 2481/16635
9. Seal/stamp: STATE CHANCERY * BASLE-CITY *
10. Signature: H. Lauener
    Hanna Lauener

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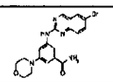
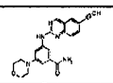
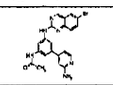
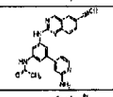
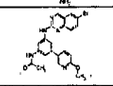
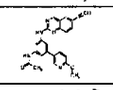
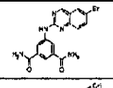
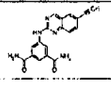
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[Continued on next page]

(54) Title: QUINAZOLINES FOR PDK1 INHIBITION

Table 2

Example	Structure	Activity	Molecular Weight	LC/MS (4.5min run) MS (M+1) m/z Rt (min)	LC/MS (1.5min run) MS (M+1) m/z Rt (min)
177		*	428.2882	428/430 3.84	
178		***	373.4141	374.1 3.51	
179		**	449.3103	249/251 3.68	
180		***	394.4362	395.1 3.39	
181		*	464.3212	464/466 4.92	
182		***	409.4471	410.1 4.57	
183		*	386.2078	386/388 3.18	
184		**	331.3337	332.1 2.88	

(57) Abstract: The invention provides novel compounds that are inhibitors of PDK1. Also provided are pharmaceutical compositions including the compounds, and methods of treating proliferative diseases, such as cancers, with the compounds or compositions.

WO 2008/079988 A2

(74) **Agents: GODDARD, Christine A.** et al.; Fish & Richardson P.C., P. O. Box 1022, Minneapolis, Minnesota 55440-1022 (US).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, 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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QUINAZOLINES FOR PDK1 INHIBITION

FIELD OF THE INVENTION

The present invention generally relates to small molecule inhibitors of 3-phosphoinositide-dependent kinase (PDK1/PDPK1). In some embodiments, the compounds can be used as therapeutics in the treatment of cellular proliferative diseases.

BACKGROUND

PDK1 (3-Phosphoinositide-dependent kinase 1) is a serine/threonine kinase belonging to the AGC kinase super family. PDK1 was first identified as the upstream kinase responsible for activating protein kinase B/AKT in the presence of phosphoinositide lipids (PIP_3). PDK1 activates AKT by phosphorylating a specific residue (threonine 308) located in the activation loop of this kinase. Subsequent research has shown that PDK1 is responsible for phosphorylating the activation-loop of many AGC kinases including p90 ribosomal S6 kinase (RSK), protein kinase C family members (PKC), p70 ribosomal S6 kinase (70S6K), and the serum and glucocorticoid-induced protein kinase (SGK). Thus, PDK1 is a central activator of multiple signaling pathways that are involved in cell proliferation, survival and control of apoptosis. Importantly, alterations in these signaling pathways are frequently observed in a variety of human cancers. For example, AKT is highly activated in a large percentage of common tumor types including melanoma, breast, lung, prostate and ovarian cancers. RSK levels are elevated in prostate cancers, and an RSK-specific inhibitor (SL0101) has recently been shown to inhibit the proliferation of multiple prostate cancer cell lines. Similarly, PKCε has been shown to play an important role in regulating apoptosis and promoting survival of glioma cells.

The human PDK1 gene encodes a 556 amino acid protein with an amino-terminal catalytic domain and a non-catalytic carboxy terminal containing a pleckstrin homology domain (PH). Recent studies suggest that PDK1 is a constitutively active kinase, and that PDK1 regulation occurs through the localization or conformational state of PDK1 target

proteins. For example, the PH domain of PDK1 is required for the binding of PIP_3 lipids produced by PI3kinase (PI3K). PDK1 binding of PIP_3 lipids results in membrane co-localization with AKT, another PH domain containing protein. Once co-localized, PDK1 activates AKT by phosphorylating threonine308. Alternatively, PDK1 can activate other AGC kinases independent of PIP_3 lipids by binding directly to a conserved motif found on these targets. Because PDK1 regulates two distinct classes of downstream signaling substrates (PI3K-dependent and independent targets), inhibitors of this enzyme could have important therapeutic value in a variety of human cancers. For instance, PDK1 inhibitors could be efficacious in tumors in which the PI3K signaling pathway is upregulated due to activating mutations, amplification of PI3K itself or its upstream receptor tyrosine kinases, or deletion of PTEN, the phosphatase the counteracts PI3K activity. The finding that mice expressing half the normal amount of PTEN are protected from developing a wide range of tumors by reducing PDK1 expression levels supports this idea. Alternatively, PDK1 inhibitors could be useful in treating cancers driven by PIP_3-independent PDK1 signaling pathways (e.g. K-ras or H-ras driven cancers).

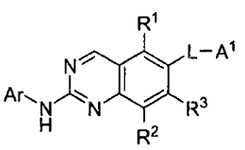
Finally, the recent identification of PDK1 mutations ($PDK1^{T354M}$, $PDK1^{D527E}$) in human colorectal cancers suggests that inhibitors of this kinase may have therapeutic value by directly inhibiting either wild-type or mutant forms of this protein. See, Parsons *et al.*, *Nature* 436, 792 (11 August 2005) "Colorectal cancer: Mutations in a signaling pathway."

In summary, PDK1 is a central activator of several signaling pathways that are frequently altered in human cancers making it an attractive target for therapeutic intervention.

SUMMARY

In one aspect, the present invention provides PDK1 inhibitors that are useful as therapeutic agents, for the treatment of diseases and disorders characterized by abnormal cellular proliferation, for example cancers of the prostate, lung, colon, breast, among others.

The present invention provides, *inter alia*, compounds of Formula I:



I

or pharmaceutically acceptable salts, ester, or tautomers thereof, wherein constituent members are provided herein.

The present invention further provides compositions comprising a compound of Formula I and at least one pharmaceutically acceptable carrier.

The present invention further provides methods of inhibiting PDK1 or a PDK1 variant in a patient comprising administering to said patient, a therapeutically effective amount of a compound of the invention, or pharmaceutically acceptable salt, ester, or tautomer thereof.

The present invention further provides methods of treating a disease characterized by abnormal cellular proliferation in a patient comprising administering to said patient a therapeutically effective amount of a compound of the invention, or pharmaceutically acceptable salt, ester, or tautomer thereof.

The present invention further provides methods of inhibiting the tumor growth in a patient, the method comprising administering to said patient a therapeutically effective amount of a compound of the invention, or pharmaceutically acceptable salt, ester, or tautomer thereof.

The present invention further provides methods of treating cancer in a patient, the method comprising administering to said patient a therapeutically effective amount of a compound of the invention, or pharmaceutically acceptable salt, ester, or tautomer thereof.

The present invention further provides a compound of the invention, or pharmaceutically acceptable salt, ester, or tautomer thereof for use in therapy.

The present invention further provides a compound of the invention, or pharmaceutically acceptable salt, ester, or tautomer thereof for use in the preparation of a medicament for use in therapy.

Other features, objects, and advantages of the invention will be apparent from the description, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 provides the chemical structures and activity data for Examples 177-681.

Figure 2 provides the chemical structures and activity data for Examples 682-1185.

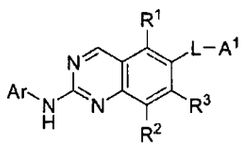
In these two Figures, the column marked "Activity" indicates the compound's activity in the PDK1 Kinase Alpha Screen Assay; the symbol "*" indicates that IC_{50} value is greater than 0.30 μM; the symbol "**" indicates that IC_{50} value is less than or equal to 0.30 μM but greater than 0.10 μM; the symbol "***" indicates that IC_{50} value is less than or equal to 0.10

μM but greater than 0.05 μM; and the symbol "****" indicates that IC_{50} value is less than or equal to 0.05 μM.

DETAILED DESCRIPTION

In accordance with the present invention, Applicants have discovered novel quinazoline PDK1 inhibitors that can provide effective treatments for disorders such as those described herein and those apparent to one skilled in the art.

In some embodiments, the invention provides compounds that have the Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

Ar is aryl, substituted aryl, heteroaryl, or substituted heteroaryl, including fused bicyclic systems;

R^1 is H, C_{1-3} alkyl, halo, cyano, nitro, CF_3, imidazolyl, thiazolyl, oxazolyl, or amino;

R^2 and R^3 are independently selected from the group consisting of H, alkoxy, substituted alkoxy, and halo;

L is a covalent bond, carbonyl, carbonylamino, aminocarbonyl, -O-, -S-, -SO-, $-SO_2-$, -NH-, C_{1-3} alkyl, substituted C_{1-3} alkyl, or an alkyl interrupted with -O-, -S-, -SO-, $-SO_2-$, -NH-, carbonyl, carbonylamino, or aminocarbonyl; and

A^1 is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, halo, hydroxy, nitro, SO_3H, sulfonyl, substituted sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, alkylthio, substituted alkylthio, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl.

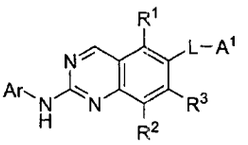
According to some embodiments, when R^1, R^2, and R^3 are each H and L is a covalent bond, then A^1 is other than aryl or substituted aryl.

According to some embodiments, when R^1, R^2, and R^3 are each H, L is a covalent bond, and A^1 is Br, substituted phenyl, or substituted pyridinyl, then Ar is other than phenyl, phenyl substituted with piperazinyl or heterocyclylalkyloxy, or pyridinyl.

According to some embodiments, when R^1, R^2, and R^3 are each H, L is a covalent bond, and A^1 is hydroxy or alkoxy, then Ar is other than phenyl substituted with one or more alkyl or halo.

According to some embodiments, when R^1, R^2, and R^3 are each H and L is O, then A^1 is other than pyridinyl or substituted pyridinyl.

In some embodiments, the invention provides compounds that have the Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

Ar is aryl, substituted aryl, heteroaryl, or substituted heteroaryl, including fused bicyclic systems;

R^1 is H, C_{1-3} alkyl, halo, cyano, nitro, CF_3, imidazolyl, thiazolyl, oxazolyl, or amino;

R^2 is selected from the group consisting of H, alkoxy, substituted alkoxy, alkyl, substituted alkyl, CN, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, and halo;

R^3 is selected from the group consisting of H, halo, CN, carboxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryloxy, substituted aryloxy, cycloalkyloxy, substituted cycloalkyloxy, heterocyclylalkyloxy, substituted heterocyclylalkyloxy, heteroaryloxy, substituted heteroaryloxy, heteroarylalkyloxy, substituted heteroarylalkyloxy, arylalkyloxy, substituted arylalkyloxy, heteroaryl, substituted heteroaryl, heterocyclyl, substituted heterocyclyl, heteroarylalkyl, substituted heteroarylalkyl, heterocyclylalkyl, substituted heterocyclylalkyl;

L is a covalent bond, carbonyl, carbonylamino, aminocarbonyl, -O-, -S-, -SO-, $-SO_2-$, -NH-, C_{1-3} alkyl, substituted C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl or an alkyl interrupted with -O-, -S-, -SO-, $-SO_2-$,

-NH-, carbonyl, carbonylamino, or aminocarbonyl; and

A^1 is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, halo, hydroxy, nitro, SO_3H, sulfonyl, substituted sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, alkylthio, substituted alkylthio, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl.

According to some embodiments, when R^1, R^2, and R^3 are each H and L is a covalent bond, then A^1 is other than aryl or substituted aryl.

According to some embodiments, when R^1, R^2, and R^3 are each H, L is a covalent bond, and A^1 is Br, substituted phenyl, or substituted pyridinyl, then Ar is other than phenyl, phenyl substituted with piperazinyl or heterocyclylalkyloxy, or pyridinyl.

According to some embodiments, when R^1, R^2, and R^3 are each H, L is a covalent bond, and A^1 is hydroxy or alkoxy, then Ar is other than phenyl substituted with one or more alkyl or halo.

According to some embodiments, when R^1, R^2, and R^3 are each H and L is O, then A^1 is other than pyridinyl or substituted pyridinyl.

According to some embodiments, L is a covalent bond. In some such embodiments, A^1 is an optionally substituted alkyne or an optionally substituted heterocyclyl or heteroaryl. Preferred alkynes include ethyne, 1-propyne, 3-hydroxypropyne, and 3-methoxypropyne, as well as other 3-alkoxypropynes. Preferred heteroaryls for these embodiments include thiazole, pyridine, imidazole, furan, 1,2,3-triazole, 1,2,4-triazole, pyrazole, isothiazole, oxazole, and isoxazole, each of which can be substituted. Specific heteroaryls for these embodiments include 2-thiazolyl; 5-hydroxymethyl-2-thiazolyl; 3-pyridyl, 5-methoxy-3-pyridyl; 6-amino-3-pyridyl; 4-thiazolyl; 3-pyrazolyl; and 4-pyrazolyl. Preferred heterocyclyl groups include pyrrolidine, morpholine, piperidine, and piperazine, each of which can be substituted.

Some specific embodiments include compounds wherein A^1 is selected from the following group:

OH, Br, methyl, ethyl, ethyne (-C≡CH), CN, CF_3, phenyl, COOH, COOMe, $CONH_2$,
1-hydroxy-1-methylethyl,
1-amino-1-methylethyl,
2-thiazolyl,

5-thiazolyl,
4-thiazolyl,
isoxazol-4-yl,
3-pyrazolyl,
4-pyrazolyl,
1-methyl-4-pyrazolyl,
1-methylpyrazol-5-yl,
2-furanyl, cyclopropyl,
4-hydroxymethyl-1,2-3-triazol-5-yl,
5-methoxypyridin-3-yl,
2-amino-3-methoxypyridin-5-yl,
3-methylpyridin-2-yl,
2-pyridyl,
3-pyridyl,
4-pyridyl,
4-methylpyridin-3-yl,
3-chloropyridin-4-yl,
1-morpholinyl,
1-pyrrolidinyl,
3-hydroxypyrrolidin-1-yl,
R-3-hydroxypyrrolidin-1-yl,
S-4-hydroxypiperidin-1-yl,
3-ketopiperazin-1-yl,
1-methylimidazol-2-yl,
5-methylthiazol-2-yl,
1-methylimidazol-5-yl,
3-hydroxy-1-propynyl,
3-methoxy-1-propynyl,
2-aminopyridin-4-yl,
3-methoxypyridin-5-yl,
2-aminopyridin-5-yl,
4-hydroxymethyl-1,2,3-triazol-5-yl,
2-amino-3-methoxypyridin-5-yl,
2-aminothiazol-5-yl,

1-(2-hydroxyethyl)pyrazol-4-yl,
1-(2-methoxyethyl)pyrazol-4-yl,
4-hydroxymethyl-thiazol-2-yl,
5-hydroxymethylthiazol-2-yl,
2-methoxypyrimidin-5-yl,
2-methoxypyridin5-yl,
2-hydroxyethylamino,
tetrahydropyran-4-yloxy,
isopropylamino,
2-pyridinylmethylamino,
2-methoxyethylamino,
3-pyridylmethylamino,
4-pyridylmethylamino,
2-pyridylamino, 3-pyridylamino,
2-(2-ketopyrrolidin-1-yl)ethylamino,
4-methylpiperazin-1-yl,
1-isopropylmethylpyrazol-4-yl,
methylamino,
1-methylpiperidin-4-ylamino,
4-isopropylpiperazin-1-yl,
isopropylamino,
pyrrolidin-1-yl,
cyclopropylamino,
2-fluoropyridin-3-yl,
2-(4-methylpiperazin-1-yl)pyridine-4-yl,
3-(benzoylamino)phenyl, and
2-amino-4-methoxypyrimidin-5-yl.

According to some embodiments, L is -O-.
According to some embodiments, L is -S-.
According to some embodiments, L is $-SO_2-$.
According to some embodiments, L is NH.
According to some embodiments, L is carbonyl.
According to some embodiments, L is aminocarbonyl or carbonylamino.

According to some embodiments, L is carbonyl amino.

According to some embodiments, L is aminocarbonyl.

According to some embodiments, L is an alkyl interrupted with -O-, -S-, -SO-, -SO_2-, -NH-, carbonyl, carbonylamino or aminocarbonyl.

According to some embodiments, L is -CH=CH- or -C≡C-.

According to some embodiments, A^1 is alkyl.

According to some embodiments, A^1 is substituted alkyl.

According to some embodiments, A^1 is alkenyl.

According to some embodiments, A^1 is substituted alkenyl.

According to some embodiments, A^1 is alkynyl.

According to some embodiments, A^1 is ethynyl, propynyl, phenylethynyl or pyridylethynyl.

According to some embodiments, A^1 is substituted alkynyl.

According to some embodiments, A^1 is alkoxy.

According to some embodiments, A^1 is substituted alkoxy.

According to some embodiments, A^1 is acyl.

According to some embodiments, A^1 is cyano.

According to some embodiments, A^1 is aryl.

According to some embodiments, A^1 is substituted aryl.

According to some embodiments, A^1 is substituted phenyl.

According to some embodiments, A^1 is heteroaryl.

According to some embodiments, A^1 is substituted heteroaryl.

According to some embodiments, the heteroaryl or substituted heteroaryl is selected from the group consisting of pyridyl, pyrazolyl, thiazolyl, pyrimidyl, pyridazinyl, oxazolyl, isoxazolyl, substituted pyridyl, substituted pyrazolyl, substituted thiazolyl, substituted pyrimidyl, substituted pyridazinyl, substituted oxazolyl and substituted isoxazolyl.

According to some embodiments, A^1 is cycloalkyl.

According to some embodiments, A^1 is substituted cycloalkyl.

According to some embodiments, A^1 is heterocyclyl.

According to some embodiments, A^1 is substituted heterocyclyl.

According to some embodiments, the heterocyclyl or substituted heterocyclyl is selected from the group consisting of piperidinyl, piperazinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, morpholinyl, thiomorpholino, substituted piperidinyl, substituted

piperazinyl, substituted pyrrolidinyl, substituted tetrahydrofuranyl, substituted tetrahydrothiophenyl, substituted morpholinyl and substituted thiomorpholino.

According to some embodiments, A^1 is hydroxy.

According to some embodiments, A^1 is halo.

According to some embodiments, A^1 is cyano.

In some embodiments, -L-A^1 is -Br, -C≡CH, -C≡N, 2-thiazolyl, or 1-methylimidazol-2-yl.

According to some embodiments, R^1 is H, C_{1-3} alkyl, halo, cyano, nitro, CF_3 or amino.

According to some embodiments, R^1 is H, C_{1-3} alkyl, halo, cyano, nitro or amino.

According to some embodiments, R^1 is H, C_{1-3} alkyl, halo, cyano, imidazolyl, thiazolyl, oxazolyl or amino.

According to some embodiments, R^1 is H, C_{1-3}alkyl, halo or cyano.

According to some embodiments, R^1 is H, C_{1-3}alkyl, or halo.

According to some embodiments, R^1 is H or halo.

According to some embodiments, R^1 is H.

According to some embodiments, R^1 is halo.

According to some embodiments, R^2 and R^3 are independently selected from the group consisting of H, alkoxy, substituted alkoxy, and halo;

According to some embodiments, R^2 and R^3 are independently selected from the group consisting of H, halo and alkoxy.

According to some embodiments, R^2 and R^3 are independently selected from the group consisting of H, and halo.

According to some embodiments, R^2 and R^3 are independently selected from the group consisting of H and alkoxy.

According to some embodiments, R^2 and R^3 are independently selected from the group consisting of H and C_{1-6} alkoxy.

According to some embodiments, R^2 and R^3 are independently selected from the group consisting of H and methoxy.

According to some embodiments, at least one of R^2 and R^3 is H.

According to some embodiments, both R^2 and R^3 are H.

According to some embodiments, R^2 is H.

According to some embodiments, R^3 is H.

In some embodiments, one of R^2 and R^3 is H and the other of R^2 and R^3 is alkoxy, substituted alkoxy, aryloxy, substituted aryloxy, cycloalkyloxy, substituted cycloalkyloxy,

heterocyclylalkyloxy, substituted heterocyclylalkyloxy, heteroaryloxy, substituted heteroaryloxy, heteroarylalkyloxy, substituted heteroarylalkyloxy, arylalkyloxy, or substituted arylalkyloxy.

In some embodiments, one of R^2 and R^3 is H and the other is arylalkoxy, alkoxy or substituted alkoxy, or a substituted or unsubstituted heteroaryloxy, heteroarylalkyloxy, heterocyclyloxy, or heterocyclylalkyloxy. In such embodiments, R^2 is often H and R^3 is substituted or unsubstituted alkoxy or heterocyclyloxy group.

In certain embodiments, R^2 is selected from H, F, Cl, Br, CN, CF_3, methoxy, ethoxy, isopropoxy, 4-piperidinyloxy, 3-azetidinyloxy, and 2-aminoethoxy.

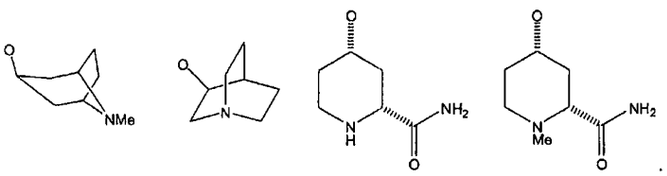
In some embodiments, R^3 is selected from:

H, Cl, CF_3, CN, COOH,
isopropoxy, methoxy, cyclopentyloxy,
2-aminoethoxy,
4-piperidinyloxy,
1-isopropyl-piperidin-4-yl,
4-piperidinylmethoxy,
1-methylpiperidin-3-ylmethoxy,
2-(4-piperidinyl)-ethoxy,
2-(1-methyl-4-piperidinyl)-ethoxy,
(1-methyl-4-piperidinyl)methoxy,
2-thiazolylmethoxy,
3-pyridylmethoxy,
4-pyridylmethoxy,
1-(4-pyridyl)-1-ethoxy,
2-pyridylmethoxy,
5-thiazolylmethoxy,
2-(4-piperidinyl)-ethoxy,
1-methyl-4-piperidinyloxy,
cyclopentyloxy,
2-(4-morpholinyl)-ethoxy,
2-methoxyethoxy,
1-aminocyclopropylmethoxy,
1-N-acetylaminocycloprop-1-ylmethoxy,
aminocarbonylmethoxy,

N-methylaminocarbonylmethoxy,
3-pyrrolidinyloxy,
R-3-pyrrolidinyloxy,
S-3-pyrrolidinyloxy,
R-(1-methylpyrrolidin-3-yl)oxy,
S-(1-methylpyrrolidin-3-yl)oxy,
pyrrolidiny-3-ylmethoxy,
piperidin-3-ylmethoxy,
R-piperidin-3-ylmethoxy,
S-piperidin-3-ylmethoxy,
2-(4-methyl-1-piperazinyl)ethyl,
1-methylpyrrolidin-3-ylmethoxy,
R-(1-methylpiperidin-3-ylmethoxy,
S-(1-methylpiperidin-3-ylmethoxy,
(3-chloro-4-pyridyl)methoxy,
2-methoxypyridyn-6-ylmethoxy,
(5-methylisoxal-3-yl)methoxy,
5-thiazolylmethoxy,
(3-fluorophenyl)methoxy,
(3-methoxyphenyl)methoxy,
phenylmethoxy,
(3-cyanophenyl)methoxy,
3-fluorophenylmethoxy,
3-methoxyphenylmethoxy,
2-pyrazinylmethoxy,
3-chloro-4-pyridinyloxy,
2-(3-pyridinyl)ethoxy,
1-isopropylpiperidin-4-yloxy,
3-azetidinyloxy,
1-methyl-3-azetidinyloxy,
1-isopropyl-3-azetidinyloxy,
1-(2,2,2-trifluoroethyl)piperidin-4-yloxy,
1-methyl-4-pyrazolyl,
3-aminopyridin-4-yl,

1-piperazinylmethyl,
1-piperazinylcarbonyl,
1-methylpiperidin-4-ylaminocarbonyl,
2-(N-morpholinyl)ethoxy,
2-methoxyethoxy,
2-chloropyridin-5-ylmethoxy,
2-chloropyridin-4-ylmethoxy,
1-acetylpiperidin-4-yloxy,
1-(2-fluoroethyl)piperidin-4-yloxy,
1-(2,2-difluorethyl)piperidin-4-yloxy,
1-(2-methoxyethyl)piperidin-4-yloxy,
1-(2-hydroxyethyl)piperidin-4-yloxy,
methylaminocarbonylmethoxy,
aminocarbonylmethoxy,
3-azetidinylmethoxy,
3-(1-methylazetidinyl)methoxy,
2-aminopyridin-4-yl,
6-methoxypyridin-2-ylmethoxy,
5-methylisoxazol-3-yl, and
2-(Pyridin-3-yl)ethoxy;

or R^3 can be one of the following heterocyclyloxy groups:



According to some embodiments, Ar is substituted aryl or substituted heteroaryl.

According to some embodiments, Ar is substituted aryl.

According to some embodiments, Ar is aryl, substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl,

aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy, cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, substituted sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, and alkylthio;

wherein the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, heterocyclyl, and heteroaryl moieties contained within any of the listed substituted aryl groups are optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of alkenyl, alkynyl, alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy, cycloalkenylthio, guanidino, guanidino, halo, hydroxy, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, alkylthio, and alkylthio.

According to some embodiments, Ar is aryl substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of aminosulfonyl, aminocarbonyl, aryl, heteroaryl, heterocyclyl, amino, substituted amino, alkyl, halo, and cyano;

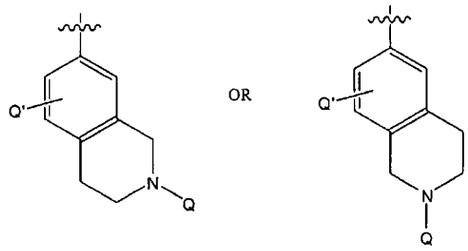
wherein the alkyl, aryl, and heteroaryl moieties contained within any of the listed substituted aryl groups are optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of alkenyl, alkynyl, alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy, cycloalkenylthio, guanidino, guanidino, halo, hydroxy, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, alkylthio, and alkylthio.

According to some embodiments, Ar is aryl selected from the group consisting of phenyl and naphthyl. Where Ar is phenyl it is often unsubstituted at one or both of the positions adjacent to the NH depicted in Formula 1 (the ortho positions).

According to some embodiments, Ar is substituted phenyl. In some embodiments, the phenyl is substituted with two or more substituents. In some such embodiments, two adjacent substituents are linked together to form a ring that is fused to the phenyl ring. The fused ring may be saturated, unsaturated or aromatic, and may itself be substituted. Preferred embodiments of these fused ring systems include phenyl fused to a 1,3-dioxolane; phenyl fused to a 1,4-dioxane; phenyl fused to a pyrazole; phenyl fused to imidazole; phenyl fused to triazole; phenyl fused to pyrazole; and phenyl fused to a pyrrolidinyl or piperidinyl ring.

In some embodiments, phenyl is substituted by 1, 2 or 3 groups that are not attached to said phenyl ortho to the NH of formula I.

In certain embodiments, Ar is of the formula:



wherein Q is an optionally substituted acyl group;

and Q' is alkyl, alkoxy, halo, aryl, heteroaryl, aryloxy, heteroaryloxy, heterocyclyloxy, arylalkyl, heteroaryl, or heterocyclyloxy, each of which can be substituted; or Q' can be H, halo, CN, COOR', $CONR'_2$, NR'_2, $S(O)_qR'$, or $S(O)_qNR'_2$, where each R' is H or C_1-C_4 alkyl.

In many such embodiments, Q' is H or halo or alkoxy.

Q in these fused systems can be, for example:

1-methylimidazol-2-ylcarbonyl,

3-methoxypropionyl,

1-methylimidazol-5-ylcarbonyl,

N,N-dimethylaminoacetyl,

Tetrahydropyran-4-ylcarbonyl,

1-methylpiperidin-4-ylcarbonyl,

1-methylpiperidin-3-ylcarbonyl,
2-pyridinoyl,
3-pyridinoyl,
4-pyridinoyl,
1-methylpyrrolidin-2-ylcarbonyl,
1-methylpyrrolidin-2S-ylcarbonyl,
(2-N-morpholino)pyridin-5-ylcarbonyl,
(2-N-morpholino)pyridin-4-ylcarbonyl,
(2-N-piperidinyl)pyridin-5-ylcarbonyl,
1-methylpyrazol-4-ylcarbonyl,
1-methylpiperidin-3-ylcarbonyl,
pyridin-3-yl-acetyl,
imidazo[1,2-a]pyridin-4-ylcarbonyl,
2-(piperazine-1-yl)pyridin-5-ylcarbonyl,
2-amino-3-hydroxybutanoyl, or
2*S*-amino-3*R*-hydroxybutanoyl.

In many embodiments, Ar is phenyl having either 1 or 2 substituents, or it is a phenyl with an additional ring fused to it. Frequently, Ar is phenyl with a non-hydrogen substituent at one or both of the 'meta' positions of the phenyl ring, i.e., it is a 3-substituted phenyl or a 3,5-disubstituted phenyl. In other embodiments, Ar is phenyl with a non-hydrogen substituent at one or both of positions 3 and 4, e.g., it is a 4-substituted phenyl or a 3,4-disubstituted phenyl.

According to some embodiments, Ar is heteroaryl.

According to some embodiments, Ar is heteroaryl selected from the group consisting of pyrrolyl, furanyl, thiophenyl (thienyl), imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, indolyl, isoindole, benzimidazolyl, benzothiophenyl, benzofuranyl, benzoxazolyl, benzothiazolyl, quinolinyl, isoquinolyl, quinazolyl, quinozalyl, cinnolyl, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, phthalazine, naphthylpyridine, phenazine, and purine.

According to some embodiments, Ar is a heteroaryl group selected from the group consisting of 2- pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, and 2-thiazolyl, 4-thiazolyl, and 5-thiazolyl.

According to some embodiments, Ar is aryl or heteroaryl, substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO_3H, substituted sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, alkylthio, and substituted alkylthio. Typically in these embodiments, Ar has one or two non-hydrogen substituents.

According to some embodiments, Ar is aryl or heteroaryl, substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy, cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, substituted sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, and alkylthio;

wherein the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, heterocyclyl, and heteroaryl moieties contained within any of the preceding "substituted aryl" groups are optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of alkenyl, alkynyl, alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy, cycloalkenylthio,

guanidino, guanidino, halo, hydroxy, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, alkylthio, and alkylthio.

According to some embodiments, Ar is heteroaryl, substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy, cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, substituted sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, and alkylthio;

wherein the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, heterocyclyl, and heteroaryl moieties contained within any of the listed substituted aryl groups are optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of alkenyl, alkynyl, alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy, cycloalkenylthio, guanidino, guanidino, halo, hydroxy, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, alkylthio, and alkylthio.

According to some embodiments, Ar is aryl or heteroaryl substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of aminosulfonyl, aminocarbonyl, aryl, heteroaryl, heteroaryl, heterocyclyl, amino, substituted amino, alkyl, alkyl, halo, and cyano;

wherein the alkyl, aryl, heterocyclyl, and heteroaryl moieties contained within any of the preceding "substituted aryl" groups are optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of alkenyl, alkynyl, alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl

ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy, cycloalkenylthio, guanidino, guanidino, halo, hydroxy, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, alkylthio, and alkylthio.

According to some embodiments, Ar is heteroaryl substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of aminosulfonyl, aminocarbonyl, aryl, heteroaryl, heterocyclyl, amino, substituted amino, alkyl, halo, and cyano;

wherein the alkyl, aryl, and heteroaryl moieties contained within any of the listed substituted aryl groups are optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of alkenyl, alkynyl, alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy, cycloalkenylthio, guanidino, guanidino, halo, hydroxy, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, alkylthio, and alkylthio.

According to some embodiments, Ar is a 5- or 6-membered heteroaryl group having 1 or 2 heteroatoms as ring members, independently selected from the group consisting of O, S and N, that is optionally substituted with 1, 2 or 3 substituents selected from the group consisting of aminosulfonyl, aminocarbonyl, aryl, heteroaryl, heterocyclyl, amino, substituted amino, alkyl, halo, and cyano.

According to some embodiments, Ar is selected from the group consisting of substituted pyridyl, substituted pyrazolyl, substituted thiazolyl, substituted pyrimidyl, substituted pyridazinyl, substituted oxazolyl and substituted isoxazolyl.

Specific examples of preferred Ar groups include the following:

Phenyl,

3-aminocarbonyl-5-N-(morpholino)phenyl,

4-aminocarbonylphenyl,

3-methanesulfonamidophenyl,

3-acetylamino-5-N-morpholinomethyl-phenyl,

3-methoxy-5-(5-methyl-1-tetrazolyl)-phenyl,

4-(N-morpholino)phenyl,
4-(N-morpholinocarbonyl)phenyl,
3-(5-oxazolyl)-phenyl,
3-(1-hydroxy-1-methyl)-1-ethylphenyl,
3-(1-hydroxyethyl)phenyl,
3-fluorophenyl,
2-fluorophenyl,
3,4,5-trifluorophenyl,
3-trifluoromethylphenyl,
2-trifluoromethylpyridin-5-yl,
3-(1-methylpyrazol-3-yl)phenyl,
3-(2-amino-4-pyridyl)-5-acetylaminophenyl,
3-pyrrolidinylcarbonylamino-5-(N-morpholino)methyl-phenyl,
3-acetylamino-5-(2-methoxy-5-pyridinyl)phenyl,
3-acetylamino-5-(4-pyrazolyl)phenyl,
3-methoxycarbonylamino-5-(pyrazol-4-yl)phenyl,
3-aminocarbonyl-5-(4-pyrazolyl)phenyl,
3-aminocarbonyl-5-(1-methyl-4-pyrazolyl)phenyl,
3,5-bis(aminocarbonyl)phenyl,
3,5-bis(acetylamino)phenyl,
3-aminocarbonyl-5-(4-methyl-1-piperazinyl)phenyl,
4-(3-pyrazolyl)phenyl,
3-aminocarbonyl-5-(2-methoxy-5-pyridinyl)phenyl,
3-aminocarbonyl-5-(6-methoxy-2-pyrazinyl)phenyl,
3-aminocarbonyl-5-(N-methylpiperidin-2-on-5-yl)phenyl,
3-(5-methyl-1-tetrazolyl)phenyl,
3-aminocarbonyl-5-(2-pyrazinyl)phenyl,
3-(methoxycarbonylamino)-5-(2-(N-morpholino)pyrimidin-5yl)phenyl,
3-(N-morpholinocarbonyl)-5-(N-morpholino)phenyl,
3-aminocarbonyl-5-(1-methyl-4-pyrazolyl)phenyl,
3-aminocarbonyl-5-(5-pyrimidinyl)phenyl,
3-(N-methylaminocarbonyl)phenyl,
4-(aminocarbonyl)phenyl,
4-(N-methylaminocarbonyl)phenyl,

3-(1,2,4-triazolyl-1-methyl)phenyl,
3-(1,2,4-triazolyl-4-methyl)phenyl,
3-(N-morpholinocarbonylmethyl)phenyl,
3-methoxyphenyl,
3-methoxy-4-fluorophenyl,
3-(1-methyl-3-pyrazolyl)phenyl,
(3-N-morpholinomethyl)phenyl,
(2-trifluoromethyl)benzimidazol-6-yl,
benzopyrazol-6-yl,
3-fluoro-4-isopropylphenyl,
3-(2-oxopyrrolidin-1-yl)phenyl,
3-methoxy-4-(5-oxazolyl)phenyl,
3-methanesulfonylphenyl,
3-methoxy-4-(isobutyrylamino)phenyl,
3-(1-pyrazolyl)phenyl,
4-(N-pyrrolidinylcarbonyl)phenyl,
benzimidazol-5-yl,
3-(4-methyl-1,2,4-triazol-3-yl)phenyl,
4-pyridyl,
3-pyridyl,
3-(N-morpholinylcarbonylmethyl)phenyl,
3-cyano-5-fluorophenyl,
4-(methylaminocarbonylmethyl)phenyl,
3-(methylaminocarbonylmethyl)phenyl,
3-(isopropylaminocarbonylmethyl)phenyl,
3-(cyclopropylaminocarbonylmethyl)phenyl,
4-(isopropylaminocarbonylmethyl)phenyl,
4-(cyclopropylaminocarbonylmethyl)phenyl,
3-(imidazol-2-yl)phenyl,
3-(2-methyl-thiazol-4-yl)phenyl,
3-(5-pyrimidinyl)phenyl,
3-(2-methoxypyrimidin-5-yl)phenyl,
3-(1,3,5-trimethylpyrazol-4-yl)phenyl,
3-(4,5-dimethyloxazol-2-yl)phenyl,

3-(5-methylfuran-2-yl)phenyl,
3-(methylaminocarbonyl-5-(1-methylpyrazol-4-yl)phenyl,
3-(methoxycarbonylamino)-5-(2-N-morpholinopyrimidin-5-yl)phenyl,
3- (4-morpholino)-5-(4-morpholinocarbonyl)phenyl,
3-(methoxycarbonylamino)-5-(pyrazol-4-yl)phenyl,
3-(methoxycarbonylamino)-5-(morpholin-4-ylmethyl)phenyl,
3-(aminocarbonyl)-5-(4-morpholinyl)phenyl,
3-methoxy-5-trifluoromethylphenyl,
3-(aminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3,5-dimethoxyphenyl,
3,5-difluorophenyl,
3,4-difluorophenyl,
3,4,5-triflurophenyl,
3-chloro-4-fluorophenyl,
3-fluoro-4-(thiazol-2-yl)phenyl,
3-ethoxyphenyl,
4-(oxazol-5-yl)phenyl,
3-fluoro-4-(morpholin-4-yl)phenyl,
4-(isopropylaminocarbonyl)phenyl,
4-(morpholin-4-ylsulfonyl)phenyl,
4-cyclohexylphenyl,
4-(pyrimidin-5-yl)phenyl,
4-(isoxazol-4-yl)phenyl,
2-fluorophenyl,
2,3-difluorophenyl,
2,4-difluorophenyl,
benzotriazol-5-yl,
4-aminosulfonylphenyl,
4-isopropylphenyl,
3-fluoro-4-isopropylphenyl,
3-methoxy-4-(oxazol-5-yl)phenyl,
4-(methylaminosulfonylmethyl)phenyl,
3-(aminosulfonyl)phenyl,
4-(1-methyl-4-pyrazolyl)phenyl,

2-methoxyphenyl,
2-trifluoropyridin-5-yl,
4-(isopropylaminosulfonyl)phenyl,
4-cyanophenyl,
4-ethoxyphenyl,
3-difluormethoxyphenyl,
3,4-dioxolanylphenyl,
3,4-dimethoxyphenyl,
3,4-dioxanylphenyl,
3-propoxyphenyl,
3-hydroxyphenyl,
4-(1-pyrazolylmethyl)phenyl,
4-(1,2,4-triazol-1-ylmethyl)phenyl,
4-(1-pyrazol-1-ylmethyl)phenyl,
4-(2-methylthiazol-4-yl)phenyl,
4-(1,2,3-thiadiazol-4-yl)phenyl,
4-(oxazolin-2-on-4-yl)phenyl,
4-(2-oxazolyl)phenyl,
3-[2-(2-hydroxypyridin-5-ylcarbonylamino)-ethoxy]-5-(1-methylpyrazol-4-yl)phenyl,
3-fluoro-4-(imidazol-2-yl)phenyl,
4-(3-methoxypyridin-5-yl)phenyl,
3-(2-methoxypyridin-5-yl)phenyl,
3-(3-pyridinyl)phenyl,
3-(dimethylaminomethyl)-5-(methanesulfonamido)phenyl,
3-(4-methylpiperazin-ylethyl)- 5-(methanesulfonamido)phenyl,
1-methylbenzimidazol-2-yl,
5,6-dimethylbenzimidazol-2-yl,
4,5-dicyanoimidazol-2-yl,
3-amino-5-aminocarbonylmethylphenyl,
imidazol-1-yl,
2-(pyridin-2-yl)ethyl,
imidazol-1-ylmethylphenyl,
3-(acetylamino)-5-(N-methyl-2-pyridon-5-yl)phenyl,
3-(acetylamino)-5-iodophenyl,

3-(acetylamino)-5-(pyridin-3-yl)phenyl,
4-(N-morpholinylsulfonyl)phenyl,
3-(acetylamino)-5-(dimethylaminomethyl)phenyl,
4-(tetrazol-5-yl)phenyl,
3-(tetrazol-5-yl)phenyl,
3-chloro-4-(N-morpholinocarbonyl)phenyl,
3-(tetrazol-1-yl)phenyl,
3-aminocarbonyl-4-(N-morpholino)phenyl,
3-acetylamino-5-(pyrrolidin-1-ylmethyl)phenyl,
6-chlorobenzopyrazol-4-yl,
6-fluorobenzopyrazol-4-yl,
3-acetylamino-5-aminomethylphenyl,
3-(acetylamino)-5-(piperazin-1-ylmethyl)phenyl,
3-(isobutyrylamino)-5-(N-morpholinomethyl)phenyl,
3-(methylsulfonamido)-5-(N-morpholinomethyl)phenyl,
3-(N-morpholinomethyl)-5-(5-tetrazolyl)phenyl,
3-acetylamino-5-(pyridin-4-yl)phenyl,
3-cyano-5-(N-morpholinomethyl)phenyl,
3-methoxy-5-(5-methyltetrazol-1-yl)phenyl,
3-methoxy-5-(tetrazol-1-yl)phenyl,
3-(4-morpholino)-5-(pyrazol-4-yl)phenyl,
3-(4-morpholino)-5-(pyridine-4-yl)phenyl,
3-(4-morpholino)-5-(3-fluoropyridine-4-yl)phenyl,
3-(4-morpholino)-5-(pyridine-3-yl)phenyl,
3-aminocarbonyl-5-(N-morpholinomethyl)phenyl,
3-(methoxycarbonylamino)-5-(morpholin-4-ylmethyl)phenyl,
3-(4-trifluoromethylpyrazol-2-yl)phenyl,
3-(cyclopropylaminocarbonyl)-5-(1-methylpyrazol-4-yl)phenyl,
3-(1-methylpyrazol-4-yl)-5-((1-methylpiperidin-4-yl)aminocarbonyl)phenyl,
3-(methylaminocarbonyl)-5-(1-methylpyrazol-4-yl)phenyl,
3-(2-methoxyethylaminocarbonyl)-5-(1-methylpyrazol-4-yl)phenyl,
3-(aminocarbonyl)-5-fluorophenyl,
3-methylaminocarbonyl-5-(pyrimidin-5-yl)phenyl,
3-methylaminocarbonyl-5-(pyridine-4-yl)phenyl,

3-methylaminocarbonyl-5-(pyridine-3-yl)phenyl,
3-amino-5-(N-morpholinomethyl)phenyl,
3-(cyanomethyl)-5-(1-methylpyrazol-4-yl)phenyl,
3-(aminocarbonyl)-5-(aminocarbonylmethoxy)phenyl,
4-(isobutyrylamino)-3-methoxyphenyl,
3-(isobutyrylamino)-5-methoxyphenyl,
3-(aminocarbonylmethyl)-5-(N-morpholinomethyl)phenyl,
3-cyano-4-(1,2,4-triazol-1-ylmethyl)phenyl,
3-(methoxycarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(hydroxycarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(cyclopropylaminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(2-(pyrrolidin-1-yl)ethylaminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(2-(methoxyethoxy)carbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(2-(2-oxopyrrolidin-1-yl)ethylaminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-((2-tetrahydrofuranyl)methylaminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-((2-tetrahydrofuranyl)methylaminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-((2-*S*-tetrahydrofuranyl)methylaminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-((2-*R*-tetrahydrofuranyl)methylaminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-((1-methylpiperidin-4-yl)aminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-((2-methylsulfonylethyl)aminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-((2-acetylaminoethyl)aminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(tetrahydropyran-4-ylaminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-((2-hydroxypropyl)aminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(pyridine-2-ylmethylaminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(cyclohexylmethylaminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(pyridine-3-ylmethylaminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(N,N-dimethylaminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(N-morpholinocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(4-methylpiperazin-1-ylcarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(3-oxopiperazin-1-ylcarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(4-dimethylaminopiperidin-1-ylcarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
4-(methylaminosulfonylmethyl)phenyl,
3-(cyclopropylaminocarbonyl)-5-(N-morpholinyl)phenyl,
3-(methylaminocarbonyl)-5-(N-morpholinyl)phenyl,
3-(3-oxomorpholin-4-ylmethyl)phenyl,
3-(2-oxopyrrolidin-1-ylmethyl)phenyl,
3-(2-oxooxazol-1-ylmethyl)phenyl,
3-(methylaminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
4-(N-morpholinomethyl)phenyl,
3-(3-methoxypropanoylaminomethyl)phenyl,
3-(isoxazol-5-ylcarbonylaminomethyl)phenyl,
3-(tetrahydrofuran-2*R*-ylcarbonylaminomethyl)phenyl,
3-(tetrahydrofuran-2*S*-ylcarbonylaminomethyl)phenyl,
3-(1-acetylpyrrolidin-2*R*-ylcarbonylaminomethyl)phenyl,
3-(1-acetylpyrrolidin-2*S*-ylcarbonylaminomethyl)phenyl,
3-(pyridin-3-ylmethylacetylaminomethyl)phenyl,
3-(pyridin-3-oylaminomethyl)phenyl,
3-(cyclopropylsulfonylaminomethyl)phenyl,
3-(ethoxycarbonylaminomethyl)phenyl,
3-hydroxy-5-(methylaminocarbonyl)phenyl,
3-ethoxy-5-(methylaminocarbonyl)phenyl,
3-(methylaminocarbonylmethyl)-5-(N-morpholinomethyl)phenyl,
3-(N,N-dimethylaminocarbonylmethyl)-5-(N-morpholinomethyl)phenyl,
3-(isopropylaminocarbonylmethyl)-5-(N-morpholinomethyl)phenyl,
3-(tetrahydropyran-4-ylaminocarbonylmethyl)-5-(N-morpholinomethyl)phenyl,
3-(t-butoxycarbonylaminomethyl)phenyl,
3-(methylaminocarbonyl)-5-(5-(4-methylpiperazin-1-yl))phenyl,
2-methoxyphenyl,
2-trifluoropyridin-5-yl,
3-(2-(pyrrolidin-1-yl)ethylaminosulfonyl)phenyl,
3-(cyclopropylaminocarbonylmethyl)phenyl,
3-(2*R*-(1-methylpyrrolidin-2-ylcarbonylamino)propoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2*S*-(1-methylpyrrolidin-2-ylcarbonylamino)propoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(1-methoxycarbonylpiperidin-4-yl)phenyl,

3-(methoxycarbonylamino)-5-(2-(morpholin-4-yl)pyrimidin-5-yl)phenyl,

3-(2-(1-pyrrolidinyl)ethylaminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-n-propoxyphenyl,

3-(N-(1-methylpiperidin-4-ylcarbonyl)piperidin-4-yl)phenyl,

3-(N-(N,N-dimethylaminoacetyl)piperidin-4-yl)phenyl,

4-(ethoxycarbonylaminomethyl)phenyl,

4-(methylsulfonylmethyl)phenyl,

4-(1-methylimidazol-5-ylcarbonylaminomethyl)phenyl,

4-(1-methylpiperidin-4-ylcarbonylaminomethyl)phenyl,

3,5-dimethoxyphenyl,

3-(1-methylpiperidin-4-ylcarbonylaminomethyl)phenyl,

4-fluoro-3-(N-morpholinocarbonylmethyl)phenyl,

3-(2-(N-morpholino)ethyloxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(*trans*-(2-dimethylamino)cyclohexylaminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(3-(dimethylamino)propoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(pyrrolidin-1-yl)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(N-morpholino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(N-piperidinyl)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(ethoxycarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(pyrrolidin-2-on-1-ylacetylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(isoxazol-2-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(N-pyrrolidinylacetylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(tetrahydrofuran-2*R*-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(tetrahydrofuran-2*S*-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(1-methylpyrazol-3-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(4-chloropyridin-2-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(piperidin-3*R*-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(piperidin-3*S*-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(piperidin-4-ylmethylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(pyrrolidin-2*R*-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(pyrrolidin-2*S*-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(2-(2R-amino-3S-hydroxybutanoylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(2-(2S-amino-3R-hydroxybutanoylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(2-(1-methylpiperidin-3*R*-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(2-(1-methylpiperidin-3*S*-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(2-(1-methylpiperidin-4-ylmethylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(2-(1-methylpyrrolidin-2*R*-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(2-(piperidin-4-ylmethylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(4-dimethylaminopiperidin-1-ylcarbonylmethyl)-5-(1-methylpyrazol-4-yl)phenyl,
3-(pyrrolidin-2*R*-ylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(pyrrolidin-2-ylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(pyrrolidin-2*S*-ylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(3-hydroxy-2-aminopropoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(2*R*-(N,N-dimethylaminoacetylamino)propoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(2*S*-(N,N-dimethylaminoacetylamino)propoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(2*R*-(N,N-dimethylaminopropoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(2*S*-(N,N-dimethylaminopropoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(2-(4-methylpiperidin-1-ylacetylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(2-aminoethylaminocarbonyl)-5-(1-methylpyrazol-4-yl)phenyl,
3-(2-(N,N-dimethylamino)ethylaminocarbonyl)-5-(1-methylpyrazol-4-yl)phenyl,
3-(2-(N,N-diethylamino)ethylaminocarbonyl)-5-(1-methylpyrazol-4-yl)phenyl,
3-(2-(acetylamino)ethylaminocarbonyl)-5-(1-methylpyrazol-4-yl)phenyl,
3-((pyrrolidin-5-on-2-yl)methylaminocarbonyl))-5-(1-methylpyrazol-4-yl)phenyl,
3-(2-(3*R*-hydroxypyrrolidin-1-yl-acetylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(2-(3*S*-hydroxypyrrolidin-1-yl-acetylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,
3-(2-(1,2*S*-dimethylpiperidin-3*S*-yl-carbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(2*S*-N,N-dimethylaminopropionyl)aminoethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2*R*-(2-pyridinoylamino)propoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2*S*-(pyrrolidin-1-ylacetylamino)propoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2*R*-(pyrrolidin-1-ylacetylamino)propoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2*R*-(1-methylimidazol-4-carbonylamino)propoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2*R*-(1-methylpiperidinyl-3-carbonylamino)propoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2*R*-(tetrahydrofuran-2*R*-ylcarbonylamino)propoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2*R*-(tetrahydrofuran-2*S*-ylcarbonylamino)propoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2*R*-(3-methoxypropionylamino)propyl)-5-(1-methylpyrazol-4-yl)phenyl,

3-(3-hydroxypropyl)-5-(1-methylpyrazol-4-yl)phenyl

3-(2-(1-t-butoxycarbonyl-2*S*-methylpiperidin-3*S*-yl-carbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(1-methyl-3*S*-methylpiperidin-4*R*-yl-carbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(3*R*-fluoropyrrolidin-1-ylacetylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(3*R*-dimethylaminopyrrolidin-1-ylacetylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(3*S*-fluoropyrrolidin-1-ylacetylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-methylthiazol-4-yl)phenyl,

3-(2-(pyridin-2-ylmethylaminoacetylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(2-aminocarbonyl)pyrrolidin-1-ylacetylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(4*S*-fluoropyrrolidin-2*S*-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(4*S*-hydroxypyrrolidin-2*S*-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(1-methyl-4*S*-fluoropyrrolidin-2*S*-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(1-methyl-4*S*-hydroxypyrrolidin-2*S*-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(4,4-difluoropyrrolidin-2*S*-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(4,4-difluoropyrrolidin-2*R*-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(1-methyl-4,4-difluoropyrrolidin-2*S*-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(1-methyl-4,4-difluoropyrrolidin-2*R*-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(4*S*-hydroxypyrrolidin-2*S*-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(4-fluoropyrrolidin-2-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(4-hydroxypyrrolidin-2-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2*R*-(2*S*-methylpiperidin-3*S*-yl-carbonylamino)propoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-aminoethoxy)-5-(thiazol-5-yl)phenyl,

3-(2-aminoethoxy)-5-(1-methylimidazol-5-yl)phenyl,

3-(2-methoxyethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(2-aminopyridin-4-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(2-hydroxypyridin-4-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-pyridylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-aminopyridin-4-ylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-((2-(4-methylpiperazin-1-yl)ethylaminocarbonyl)methoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(dimethylamino)ethoxy)-5-(pyrimidin-5-yl)phenyl,

3-(2-(3-methoxypropionylamino)ethoxy)-5-(pyrimidin-5-yl)phenyl,

3-(2-(1-methylpyrrolidin-2S-ylcarbonylamino)ethoxy)-5-(pyrimidin-5-yl)phenyl,

3-(1-methylimidazol-5-yl)-5-(N-morpholinomethyl)phenyl,

3-(1-aminocycloprop-1-ylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(3-azetidinylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2*S*-amino-3-hydroxypropyl)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2*R*-(methylaminocarbonyl)pyrrolidin-4*R*-yloxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-((imidazo[1,2-a]pyridin-4-ylcarbonyl)aminomethyl)phenyl,

3-(N-acetylpyrrolidin-2-ylcarbonylaminomethyl)phenyl,

3-(2-morpholinopyridin-5-yl)carbonylaminomethylphenyl,

3-(2-(cyclopropylsulfonylamino)ethoxy)phenyl,

3-(2-(N,N-diethylaminoethyl)-N-methylcarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-((4-N,N-dimethylaminocyclohexylamino)carbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(4-(2-methoxyethoxy)piperazin-1-ylaminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl;

3-(2-(1-methylpyrrolidin-2-yl)ethylaminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(3*S*-quinuclidylaminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(3*R*-quinuclidylaminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(N-ethylpyrrolidin-2S-ylmethylaminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(N-ethylpyrrolidin-2R-ylmethylaminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(4-methyl-1,4-diazepin-1-ylcarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(pyrrolidino[carbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(N-tetrahydropyran-4-yl-N-methylaminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(N-tetrahydropyran-3-ylaminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(N-tetrahydropyran-4-yl)methylaminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(1,2,4,-triazol-1-yl)ethylaminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-((pyrrolidin-2-on-5-ylmethyl)aminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-((pyridin-2-on-4-ylmethyl)aminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-((2R-aminocyclohex-1R-yl)aminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(4-methylpiperazin-1-yl)ethylaminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-((2R-N,N-dimethylaminocyclohex-1R-yl)aminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-((2S-N,N-dimethylaminocyclohex-1S-yl)aminocarbonylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(pyrrolidin-2-on-1-ylmethyl)carbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(ethoxycarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(N-morpholinocarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(1-methylpyrazol-4-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(isoxazol-5-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(pyrrolidin-2R-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(pyrrolidin-2S-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(piperidin-2R-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(piperidin-2S-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(piperidin-3R-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(piperidin-3S-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(1-methylpyrrolidin-2R-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(1-methylpyrrolidin-2S-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(1-methylpiperidin-2R-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(1-methylpiperidin-2S-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(1-methylpiperidin-3R-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(1-methylpiperidin-3S-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(2R-aminopropionylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(2S-aminopropionylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(2R-methylpiperidin-3S-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(2S-methylpiperidin-3R-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(4-methylpiperidin-1-ylaminomethylcarbonyl)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(2R-N,N-dimethylaminopropionylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(2S-N,N-dimethylaminopropionylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(3R-hydroxypyrrolidin-1-ylmethylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(3S- hydroxypyrrolidin-1-ylmethylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(3R-fluoropyrrolidin-1-ylmethylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(3S- fluoropyrrolidin-1-ylmethylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(3R-N,N-dimethylaminopyrrolidin-1-ylmethylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(3S- N,N-dimethylaminopyrrolidin-1-ylmethylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(4-hydroxypiperidin-1-ylaminomethylcarbonyl)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(4-fluoropiperidin-1-ylaminomethylcarbonyl)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(N-morpolino)pyridin-5-ylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(6-hydroxymethylpyridin-2-ylmethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(2S-methoxycarbonylpyrrolidin-4R-yloxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(2S-methoxycarbonylpyrrolidin-4S-yloxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(2S-carboxypyrrolidin-4R-yloxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(2S-carboxypyrrolidin-4S-yloxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(2S-N-methylaminocarbonylpyrrolidin-4R-yloxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(2S-N-methylaminocarbonylpyrrolidin-4S-yloxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(2S-N-(2-methoxyethyl)aminocarbonylpyrrolidin-4R-yloxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(2S-N-(2-methoxyethyl)aminocarbonylpyrrolidin-4S-yloxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(2-aminothiazol-4-ylmethylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(thiazol-4-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(2-aminothiazol-5-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(2-aminothiazol-4-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(2-N-acetylaminothiazol-4-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(tetrahydropyran-4-ylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-(1-methylpiperidin-4-ylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2-hydroxymethyl-3-hydroxypropoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(2R-(cyclopropylsulfonylamino)propoxy)-5-(1-methylpyrazol-4-yl)phenyl,

3-(octahydropyrrolo[1,2-a]pyrazin-2-ylcarbonylaminomethoxy)-5-(1-methylpyrazol-4-yl)phenyl,

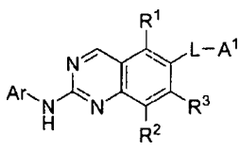
3-(aminosulfonyl)-5-(aminocarbonyl)phenyl,

3-(N-methylaminosulfonyl)-5-(N-methylaminocarbonyl)phenyl,

and

3-(2-(2-hydroxypyridin-5-ylcarbonylamino)ethoxy)-5-(1-methylpyrazol-4-yl)phenyl.

In some embodiments, the invention provides compounds that have the Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

Ar is aryl, substituted aryl, heteroaryl, or substituted heteroaryl, including fused bicyclic systems;

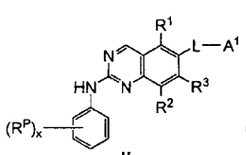
R^1 is H, C_{1-3} alkyl, halo, cyano, nitro, CF_3, imidazolyl, thiazolyl, oxazolyl, or amino;

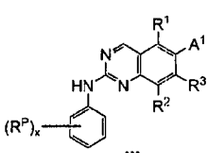
R^2 and R^3 are independently selected from the group consisting of H, alkoxy, substituted alkoxy, and halo;

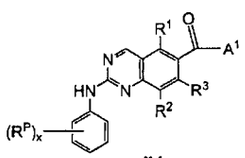
L is a covalent bond, carbonyl, carbonylamino, aminocarbonyl, -O-, -S-, -SO-, $-SO_2-$, -NH-, C_{1-3} alkyl, substituted C_{1-3} alkyl, or an alkyl interrupted with -O-, -S-, -SO-, $-SO_2-$, -NH-, carbonyl, carbonylamino, or aminocarbonyl; and

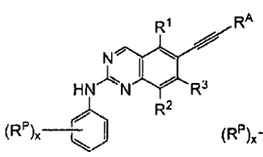
A^1 is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, halo, hydroxy, nitro, SO_3H, sulfonyl, substituted sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, alkylthio, substituted alkylthio, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl.

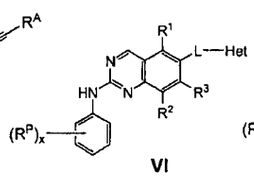
According to some embodiments, compounds of the invention have Formulae II-VII:

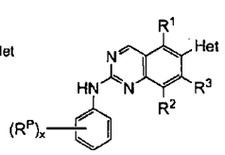

II


III


IV


V


VI


VII

wherein R^P is independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy,

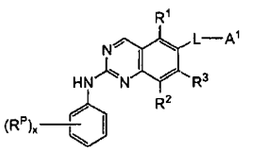
cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO_3H, substituted sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, alkylthio, and substituted alkylthio;

R^A is selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl and substituted heterocyclyl;

Het is selected from the group consisting of heteroaryl, substituted heteroaryl, heterocyclyl and substituted heterocyclyl; and

x is 1, 2, 3, 4 or 5.

According to some embodiments, compounds of the invention have Formula II:



II

wherein R^P is independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy, cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, substituted sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, and alkylthio;

wherein the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, heterocyclyl, and heteroaryl moieties contained within any of the preceding "substituted aryl" groups are optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group

consisting of alkenyl, alkynyl, alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy, cycloalkenylthio, guanidino, guanidino, halo, hydroxy, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, alkylthio, and alkylthio;

x is 1, 2, 3, 4 or 5; and

R^1, R^2, R^3, L and A^1 are as defined above.

In some embodiments of Formula II, x is 1, 2 or 3; and the isolated phenyl ring in Formula II has no substituents ortho to the NH to which it is attached. Preferred substitution patterns for this phenyl ring include mono-substitution at the 3-position ('meta' to the NH); mono-substitution at the 4-position ('para' to the NH); and disubstitution at the 3 and 4 positions or at the 3 and 5 positions.

In certain embodiments of the compounds of Formula II, R^1 is H.

In certain embodiments of the compounds of Formula II, R^2 is substituted alkoxy.

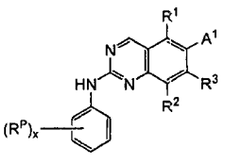
In certain embodiments of the compounds of Formula II, R^2 is substituted alkoxy, heterocyclyloxy, or heterocyclylalkoxy. In other embodiments, R^2 is H.

In some embodiments of Formula II, R^3 is substituted alkoxy such as heteroarylmethoxy. Suitable heteroaryl groups in these compounds include pyrazole, imidazole, thiazole, pyridine, and pyrazole and pyrimidine. In other such embodiments, R^3 is heterocyclyloxy or heterocyclyl-substituted alkoxy such as heterocyclylmethoxy. In other such embodiments, R^3 is heterocyclyl-substituted alkoxy such as heterocyclylmethoxy. Suitable heterocyclyl groups for these embodiments include piperidinyl, pyrrolidinyl, tetrahydrofuranyl, and the like.

In some embodiments, at least one R^P present comprises a heteroaryl or heterocyclic group. In some embodiments, it is a heteroaryl group, which may be substituted. Suitable heteroaryls include pyridinyl, imidazolyl, pyrazolyl, pyrimidinyl, thiazolyl, triazolyl, tetrazolyl, oxazolyl, thiazolyl, and thiadiazolyl. In others, R^P is a group of the formula $-O-CH_2-C(O)-NR'R''$, where R' and R'' are independently H, alkyl, or substituted alkyl, and R' and R'' can join together to form a heterocyclic ring. In other embodiments, R^P is a heterocyclyl group such as piperazinyl, piperidinyl, morpholinyl, or R^P is a heterocyclyl-substituted alkyl such as piperazinylmethyl, morpholinylmethyl, oxazolinylmethyl, and the

like. In some embodiments, R^P is a heterocyclyl or heteroaryl group linked to the phenyl ring of Formula II through –O- or $-OCH_2-$ or $-OCH_2-CH_2-$.

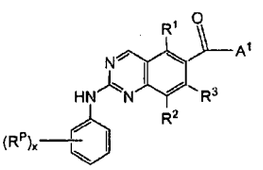
According to some embodiments, compounds of the invention have Formula III:



III

wherein R^1, R^2, R^3, A^1, R^P and x are as defined above. These correspond to compounds wherein L is a bond. Typically in these embodiments, at least one of R^1, R^2 and R^3 is a group other than H. Frequently, R^1 is H or halo, and either R^2 or R^3 is H while the other of R^2 and R^3 is a group selected from alkoxy, substituted alkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, and substituted heterocyclyloxy.

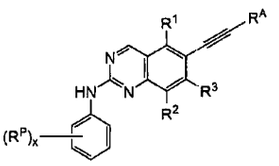
According to some embodiments, compounds of the invention have Formula IV:



IV

wherein R^1, R^2, R^3, A^1, R^P and x are as defined above.

According to some embodiments, compounds of the invention have Formula V:



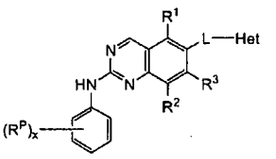
V

wherein R^1, R^2, R^3, R^P and x are as defined above; and

R^A is selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl and

substituted heterocyclyl. Frequently, $R^{\wedge}$ is selected from H, methyl, hydroxymethyl, methoxymethyl, and other alkoxymethyl groups. Often in these compounds, R^1, R^2, R^3, R^P and x are as described for the compounds of Formula II above.

According to some embodiments, compounds of the invention have Formula VI:

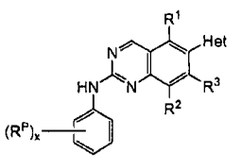


VI

wherein R^1, R^2, R^3, L, R^P and x are as defined above; and

Het is selected from the group consisting of heteroaryl, substituted heteroaryl, heterocyclyl and substituted heterocyclyl. Often in these compounds, R^1, R^2, R^3, R^P and x are as described for the compounds of Formula II above. In some of these embodiments, L is a bond, -O-, $-OCH_2-$, amino, aminocarbonyl, or carbonylamino.

According to some embodiments, compounds of the invention have Formula VII:



VII

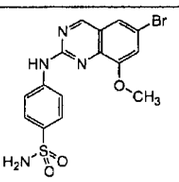
wherein R^1, R^2, R^3, R^P, x and Het are as defined above. Often in these compounds, R^1, R^2, R^3, R^P and x are as described for the compounds of Formula II above. Het in these compounds can be any heterocyclic or heteroaryl group, and sometimes it is selected from thiazole, oxazole, isothiazole, isoxazole, pyrazole, pyridine, triazole, and furan.

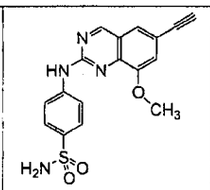
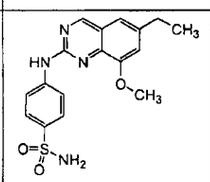
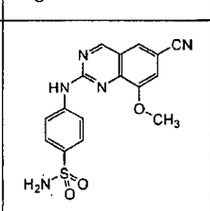
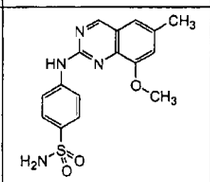
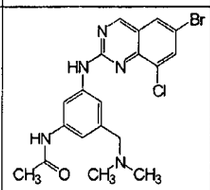
It is further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

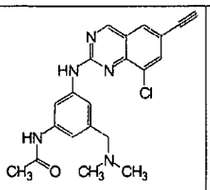
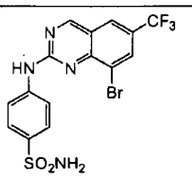
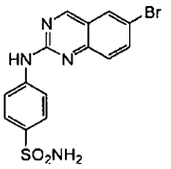
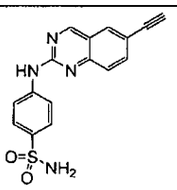
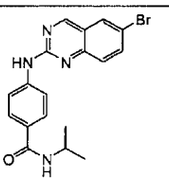
Some compounds of the invention include those of Table 1, below. The compounds in Table 1 were prepared as indicated in the column labeled "Prep. Ex. #" and the details of certain exemplary synthetic procedures are provided herein. Physical data is provided in the column marked "MS (M+1)..." for each of the compounds, as is retention time data. This physical data was acquired using one of two methods, Method A and Method B, which are provided herein in the Examples. Method B was used for the data collected for Examples 36, 19, 110, and 111, and Method A was used to collect all the remaining physical data in Table 1. Additional compounds of the invention are included in Table 2 (Figure 1) and in Table 3 (Figure 3). Methods for preparation of representative compounds from Tables 2 and 3 are provided herein, the Examples for which are numbered to correspond to the numbering of the compounds in the Tables.

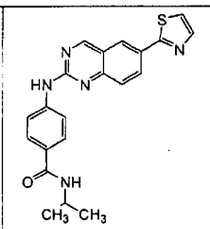
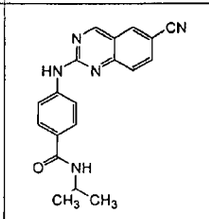
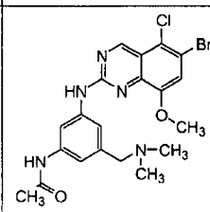
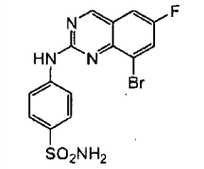
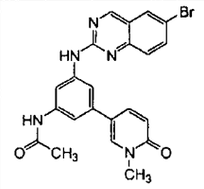
The column marked "Activity" indicates the compound's activity in the PDK1 Kinase Alpha Screen Assay described below. The symbol "+" indicates IC_{50} values of 25 μm or greater (or compounds not evaluated), the symbol "++" indicates IC_{50} values between less than 25 μm and greater than 10 μm, the symbol "+++" indicates IC_{50} values of 10 μm or less and greater than 5 μm, and the symbol "++++" indicates IC_{50} values less than 5 μm. Accordingly, as shown in Table I, 131 of the Example compounds, or about 75% of the Example compounds have been shown to demonstrate IC_{50} values of less than 5 μm.

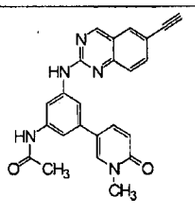
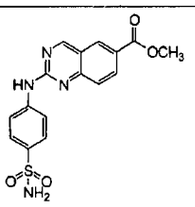
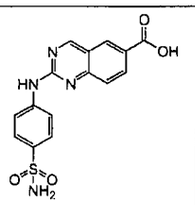
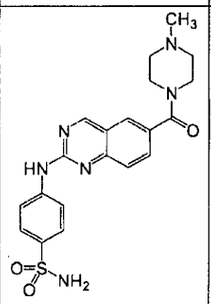
Table 1

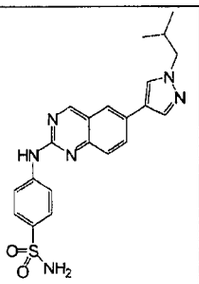
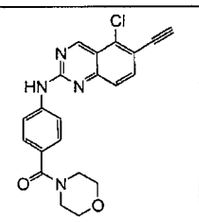
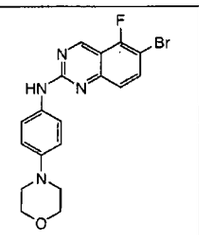
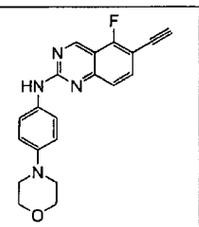
Ex. #	Structure	Name	MS (M+1) m/z Rt (min)	Activity	Prep. Ex. #
1		4-(6-bromo-8-methoxy-quinazolin-2-ylamino)-benzenesulfonamide	409/411 2.60	++++	1

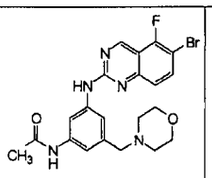
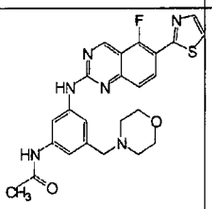
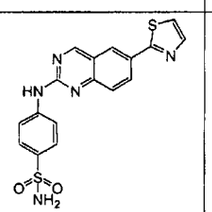
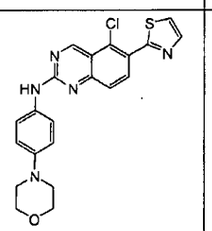
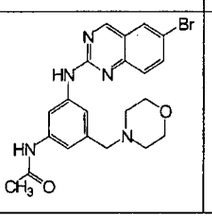
2		4-(6-ethynyl-8-methoxy-quinazolin-2-ylamino)-benzenesulfonamide	355 2.45	++++	2
3		4-(6-ethyl-8-methoxy-quinazolin-2-ylamino)-benzenesulfonamide	359 2.50	++++	3
4		4-(6-cyano-8-methoxy-quinazolin-2-ylamino)-benzenesulfonamide	356 2.20	+++	4
5		4-(8-methoxy-6-methyl-quinazolin-2-ylamino)-benzenesulfonamide	345 2.35	++++	5
6		N-(3-(6-bromo-8-chloro-quinazolin-2-ylamino)-5-((dimethylamino)methyl)-phenyl)acetamide	448/450 2.30	++++	6

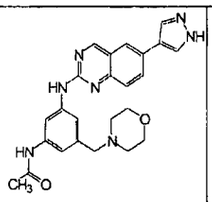
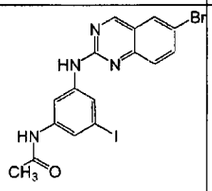
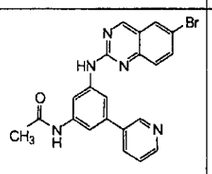
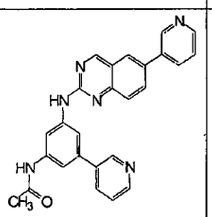
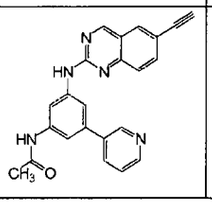
7		N-(3-(8-chloro-6-ethynyl-quinazolin-2-ylamino)-5-((dimethylamino)methyl)-phenyl)acetamide	394 2.13	++++	7
8		4-(8-bromo-6-(trifluoro-methyl)quinazolin-2-yl-amino)benzene-sulfonamide	447/449	+	8
9		4-(6-bromoquinazolin-2-ylamino)benzene-sulfonamide	379/381	+	9
10		4-(6-ethynylquinazolin-2-ylamino)benzene-sulfonamide	325.1 2.44	++++	10
11		4-(6-bromoquinazolin-2-ylamino)-N-isopropyl-benzamide	385/387	+	11

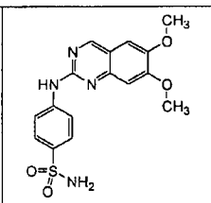
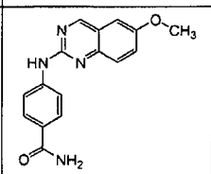
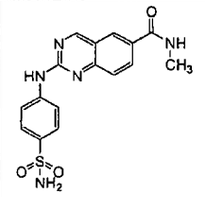
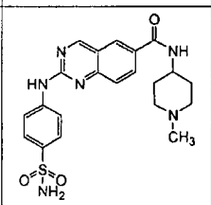
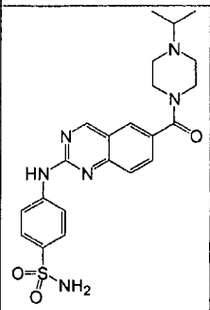
12		N-isopropyl-4-(6-(thiazol-2-yl)quinazolin-2-yl-amino)benzamide	390.1 2.71	++++	12
13		4-(6-cyanoquinazolin-2-ylamino)-N-isopropyl-benzamide	332.1 2.51	++++	13
14		N-(3-(6-bromo-5-chloro-8-methoxyquinazolin-2-yl-amino)-5-((dimethyl-amino)methyl)phenyl)-acetamide	480.0 2.36	++++	14
15		4-(8-bromo-6-fluoro-quinazolin-2-ylamino)-benzenesulfonamide	397/399	+	15
16		N-(3-(6-bromoquinazolin-2-ylamino)-5-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)acetamide	464/466 3.10	+	16

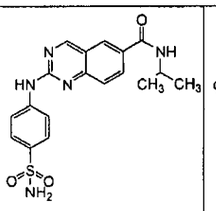
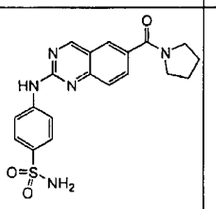
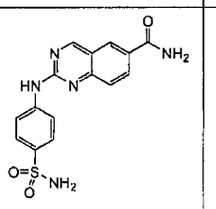
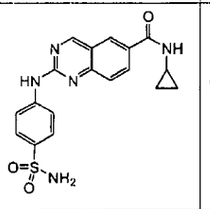
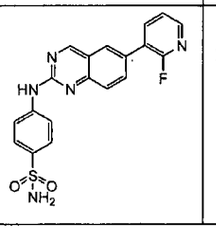
17		N-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)¬acetamide	410 2.76	+	17
18		methyl 2-(4-sulfamoyl-phenylamino)quinazoline-6-carboxylate	359	+	18
19		2-(4-sulfamoylphenyl-amino)quinazoline-6-carboxylic acid	345 2.2	++++	19
20		4-(6-(4-methylpiperazine-1-carbonyl)quinazolin-2-ylamino)benzene-sulfonamide	427.1 1.54	+	20

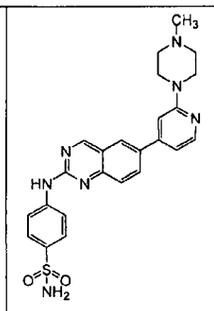
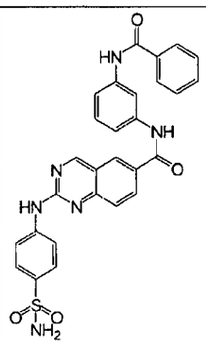
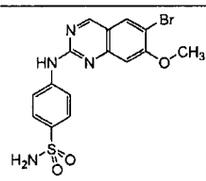
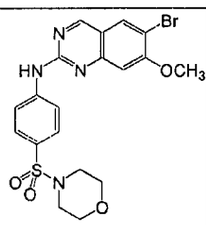
21		4-(6-(1-isobutyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)benzene-sulfonamide	423.1 3.37	+	21
22		(4-(5-chloro-6-ethynyl-quinazolin-2-ylamino)-phenyl)(morpholino)-methanone	393.1 3.7	++++	22
23		6-bromo-5-fluoro-N-(4-morpholinophenyl)-quinazolin-2-amine	403.1 3.39	++++	23
24		6-ethynyl-5-fluoro-N-(4-morpholinophenyl)-quinazolin-2-amine	349.1 2.93	++++	24

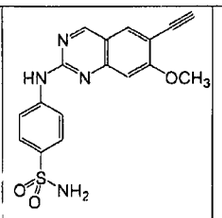
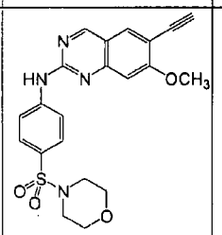
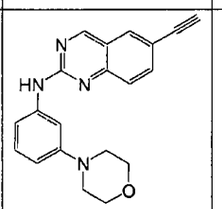
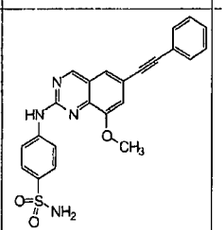
25		N-(3-(6-bromo-5-fluoro-quinazolin-2-ylamino)-5-(morpholinomethyl)-phenyl)-acetamide		+	25
26		N-(3-(5-fluoro-6-(thiazol-2-yl)quinazolin-2-ylamino)-5-(morpholino-methyl)phenyl)-acetamide	479.2 2.5	+	26
27		4-(6-(thiazol-2-yl)-quinazolin-2-ylamino)-benzenesulfonamide	384 3.2	++++	27
28		5-chloro-N-(4-morpholino-phenyl)-6-(thiazol-2-yl)-quinazolin-2-amine	473	+	28
29		N-(3-(6-bromoquinazolin-2-ylamino)-5-(morpholinomethyl)-phenyl)acetamide	456/458 2.14	++++	29

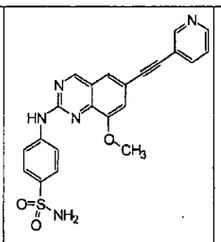
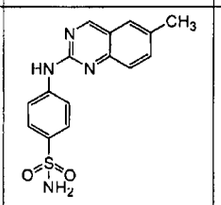
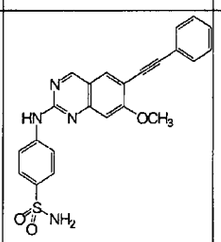
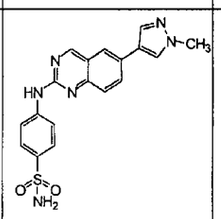
30		N-(3-(6-(1H-pyrazol-4-yl)-quinazolin-2-ylamino)-5-(morpholinomethyl)phenyl)-acetamide	444.3 1.73	++++	30
31		N-(3-(6-bromoquinazolin-2-ylamino)-5-iodophenyl)-acetamide	483.0/485.0 3.19	++++	31
32		N-(3-(6-bromoquinazolin-2-ylamino)-5-(pyridin-3-yl)phenyl)acetamide	434.1/436.1 2.21	++++	32
33		N-(3-(pyridin-3-yl)-5-(6-(pyridin-3-yl)quinazolin-2-ylamino)phenyl)acetamide	433.2 1.66	+	33
34		N-(3-(6-ethynylquinazolin-2-ylamino)-5-(pyridin-3-yl)phenyl)acetamide	433.2 2.08	++++	34

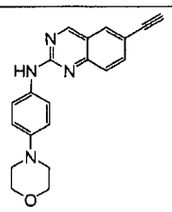
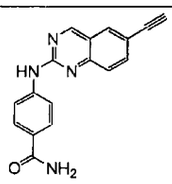
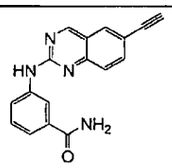
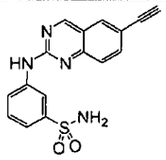
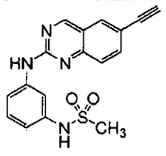
35		4-(6,7-dimethoxy-quinazolin-2-ylamino)-benzenesulfonamide	361.0 2.01	++++	35
36		4-(6-methoxyquinazolin-2-ylamino)benzamide	295.1	++++	21
37		N-methyl-2-(4-sulfamoyl-phenylamino)quinazoline-6-carboxamide	358 2.0	+++	18,19, 20
38		N-(1-methylpiperidin-4-yl)-2-(4-sulfamoylphenyl-amino)quinazoline-6-carboxamide	441 1.71	+	18,19, 20
39		4-(6-(4-isopropyl-piperazine-1-carbonyl)-quinazolin-2-ylamino)-benzenesulfonamide	427.1 1.54	+	18,19, 20

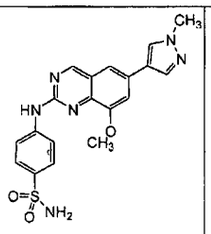
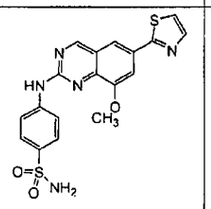
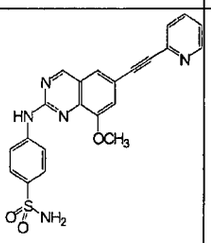
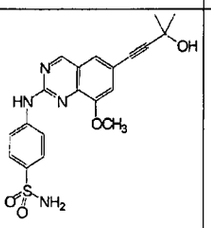
40		N-isopropyl-2-(4-sulfamoylphenylamino)-quinazoline-6-carboxamide	386 2.5	+	18,19, 20
41		4-(6-(pyrrolidine-1-carbonyl)quinazolin-2-ylamino)benzene-sulfonamide	398.1 2.07	+	18, 19, 20
42		2-(4-sulfamoylphenyl-amino)quinazoline-6-carboxamide	344.0 1.68	++++	18, 19, 20
43		N-cyclopropyl-2-(4-sulfamoylphenylamino)-quinazoline-6-carboxamide	384.0 1.97	++++	18, 19, 20
44		4-(6-(2-fluoropyridin-3-yl)quinazolin-2-ylamino)-benzenesulfonamide	396 3.08	++++	21

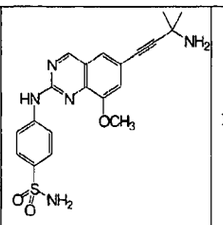
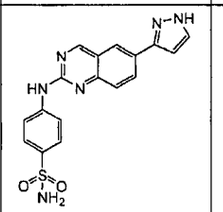
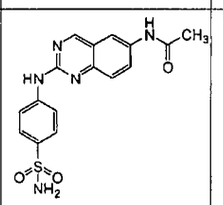
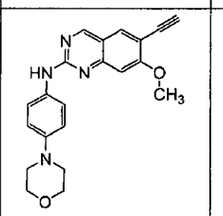
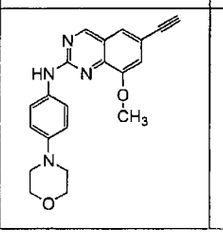
45		4-(6-(2-(4-methyl-piperazin-1-yl)pyridin-4-yl)quinazolin-2-ylamino)-benzenesulfonamide	476.1 1.75	++++	21
46		N-(3-benzamidophenyl)-2-(4-sulfamoylphenylamino)-quinazoline-6-carboxamide	539.1 3.42	+	18,19, 20
47		4-(6-bromo-7-methoxy-quinazolin-2-ylamino)-benzenesulfonamide	409/411 2.62	++++	47
48		6-bromo-7-methoxy-N-(4-(morpholinosulfonyl)phenyl)-quinazolin-2-amine	479/481 3.07	++++	47

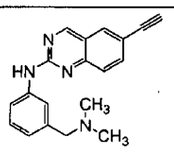
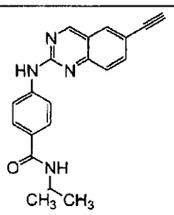
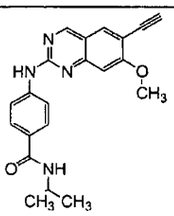
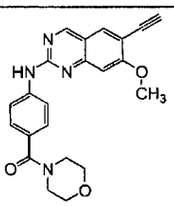
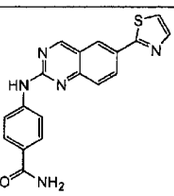
49		4-(6-ethynyl-7-methoxy-quinazolin-2-ylamino)-benzenesulfonamide	355 2.35	++++	47, 2
50		6-ethynyl-7-methoxy-N-(4-(morpholinosulfonyl)-phenyl)-quinazolin-2-amine	425 2.85	++++	47, 2
51		6-ethynyl-N-(3-morpholinophenyl)-quinazolin-2-amine	331.1 2.50	++++	9, 10
52		4-(8-methoxy-6-(phenyl-ethynyl)quinazolin-2-ylamino)benzene-sulfonamide	431.0 3.08	+	9, 10

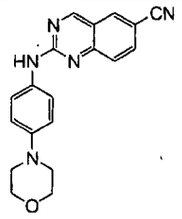
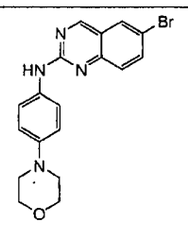
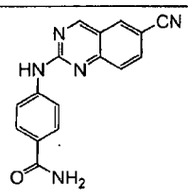
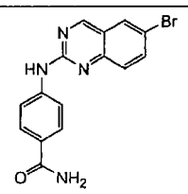
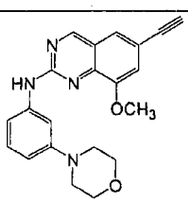
53		4-(8-methoxy-6-(pyridin-3-ylethynyl)quinazolin-2-ylamino)benzene-sulfonamide	432.0 2.10	++	9, 10
54		4-(6-methylquinazolin-2-ylamino)benzene-sulfonamide	315 2.7	++++	21
55		4-(7-methoxy-6-(phenyl-ethynyl)quinazolin-2-ylamino)benzene-sulfonamide	431 3.05	+	47, 2
56		4-(6-(1-methyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)benzene-sulfonamide	381.1 2.54	++++	21

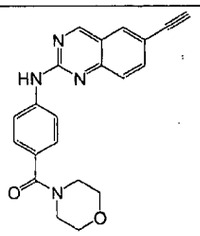
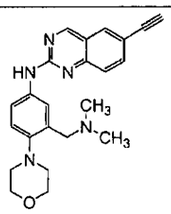
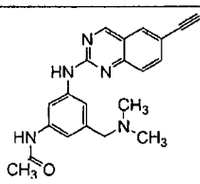
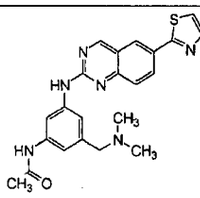
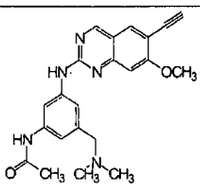
57		6-ethynyl-N-(4-morpholinophenyl)-quinazolin-2-amine	331.1 2.24	++++	9, 10
58		4-(6-ethynylquinazolin-2-ylamino)benzamide	289 2.25	++++	9, 10
59		3-(6-ethynylquinazolin-2-ylamino)benzamide	289 2.22	++++	9, 10
60		3-(6-ethynylquinazolin-2-ylamino)benzene-sulfonamide	325.1 2.42	++++	9, 10
61		N-(3-(6-ethynylquinazolin-2-ylamino)phenyl)-methane-sulfonamide	339.0 2.55	++++	9, 10

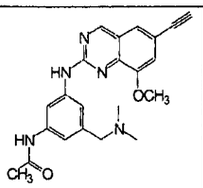
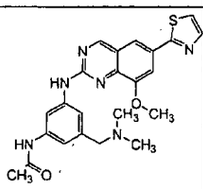
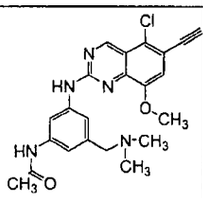
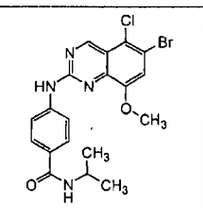
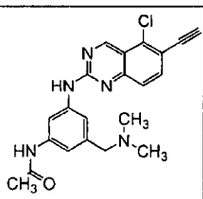
62		4-(8-methoxy-6-(1-methyl-1H-pyrazol-4-yl)-quinazolin-2-ylamino)-benzenesulfonamide	411 2.56	++++	1, 30
63		4-(8-methoxy-6-(thiazol-2-yl)quinazolin-2-ylamino)-benzenesulfonamide	414 3.07	++++	1, 30
64		4-(8-methoxy-6-(pyridin-2-ylethynyl)quinazolin-2-ylamino)benzene-sulfonamide	432 2.22	+	2
65		4-(6-(3-hydroxy-3-methylbut-1-ynyl)-8-methoxyquinazolin-2-ylamino)benzenesulfonamide	413 2.33	++++	2

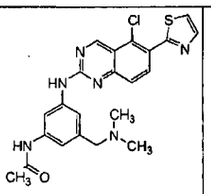
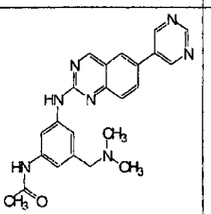
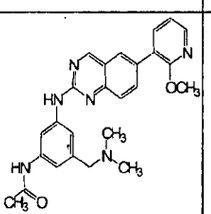
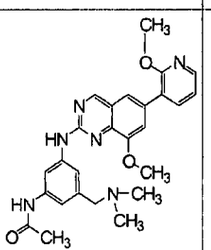
66		4-(6-(3-amino-3-methylbut-1-ynyl)-8-methoxyquinazolin-2-ylamino)benzenesulfonamide	412 1.77	++	2
67		4-(6-(1H-pyrazol-3-yl)-quinazolin-2-ylamino)-benzenesulfonamide	367 2.4	++++	21
68		N-(2-(4-sulfamoylphenyl-amino)quinazolin-6-yl)-acetamide	358 1.9	++++	68
69		6-ethynyl-7-methoxy-N-(4-morpholinophenyl)-quinazolin-2-amine	361 2.56	++++	47, 2
70		6-ethynyl-8-methoxy-N-(4-morpholinophenyl)-quinazolin-2-amine	361.2 2.6	++++	1, 2

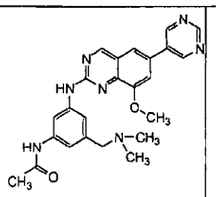
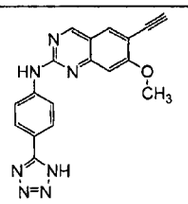
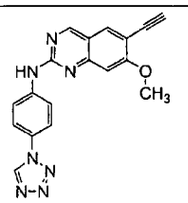
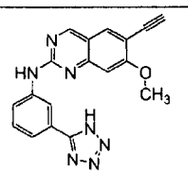
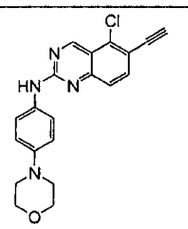
71		N-(3-((dimethylamino)-methyl)phenyl)-6-ethynylquinazolin-2-amine	303.1 2.11	++++	9, 10
72		4-(6-ethynylquinazolin-2-ylamino)-N-isopropyl-benzamide	331.2 2.75	++++	9, 10
73		4-(6-ethynyl-7-methoxy-quinazolin-2-ylamino)-N-isopropylbenzamide	361 3.38	++++	47, 2
74		(4-(6-ethynyl-7-methoxy-quinazolin-2-ylamino)-phenyl)(morpholino)-methanone	389 3.00	++++	47, 2
75		4-(6-(thiazol-2-yl)-quinazolin-2-ylamino)-benzamide	348.1 2.27	++++	12

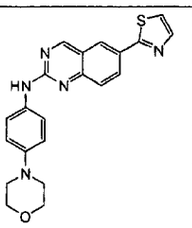
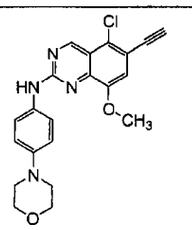
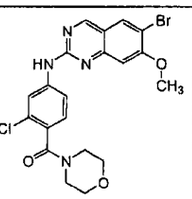
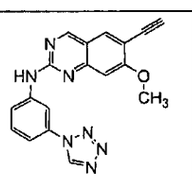
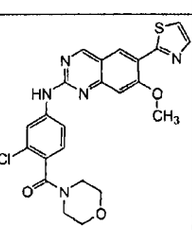
76		2-(4-morpholinophenyl-amino)quinazoline-6-carbonitrile	332.1 2.21	++++	13
77		6-bromo-N-(4-morpholino-phenyl)quinazolin-2-amine	385/387 2.51	++++	9
78		4-(6-cyanoquinazolin-2-ylamino)benzamide	290.1 2.06	++++	13
79		4-(6-bromoquinazolin-2-ylamino)benzamide	343/345 2.46	++++	9
80		6-ethynyl-8-methoxy-N-(3-morpholinophenyl)-quinazolin-2-amine	361.1 2.76	++++	9, 10

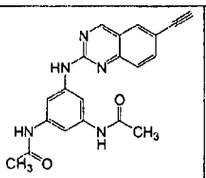
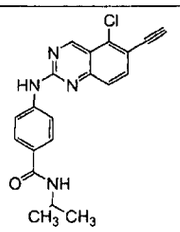
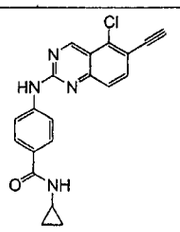
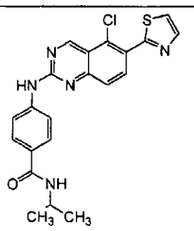
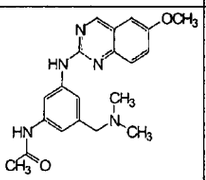
81		(4-(6-ethynylquinazolin-2-ylamino)phenyl)-(morpholino)methanone	359.1 2.52	++++	9, 10
82		N-(3-((dimethylamino)-methyl)-4-morpholino-phenyl)-6-ethynyl-quinazolin-2-amine	388.2 2.25	++++	9, 10
83		N-(3-((dimethylamino)-methyl)-5-(6-ethynyl-quinazolin-2-ylamino)-phenyl)acetamide	360.1 2.00	++++	9, 10
84		N-(3-((dimethylamino)-methyl)-5-(6-(thiazol-2-yl)quinazolin-2-ylamino)-phenyl)acetamide	419.3 2.00	++++	12
85		N-(3-((dimethylamino)methyl)-5-(6-ethynyl-7-methoxy-quinazolin-2-ylamino)-phenyl)acetamide	390 2.21	++++	47, 2

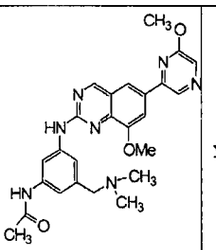
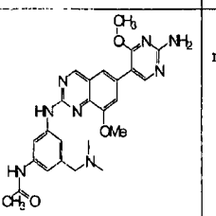
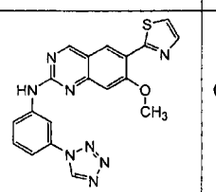
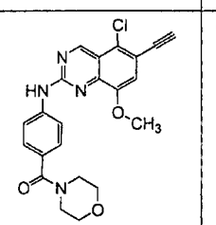
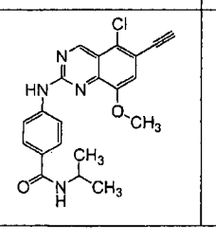
86		N-(3-((dimethylamino)-methyl)-5-(6-ethynyl-8-methoxyquinazolin-2-ylamino)phenyl)acetamide	390.2 2.05	++++	1, 2
87		N-(3-((dimethylamino)-methyl)-5-(8-methoxy-6-(thiazol-2-yl)quinazolin-2-ylamino)phenyl)acetamide	449.1 2.04	++++	12
88		N-(3-(5-chloro-6-ethynyl-8-methoxyquinazolin-2-ylamino)-5-((dimethyl-amino)methyl)phenyl)-acetamide	424.1 2.25	++++	14, 9, 10
89		4-(6-bromo-5-chloro-8-methoxyquinazolin-2-ylamino)-N-isopropyl-benzamide	451.0 3.16	++++	14
90		N-(3-(5-chloro-6-ethynyl-quinazolin-2-ylamino)-5-((dimethylamino)methyl)-phenyl)acetamide	394.1 2.25	++++	22

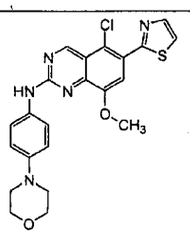
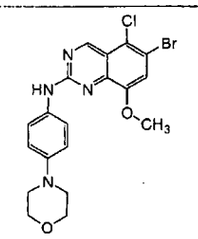
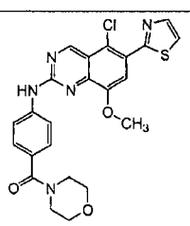
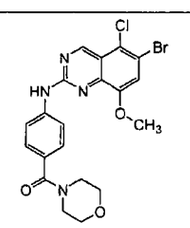
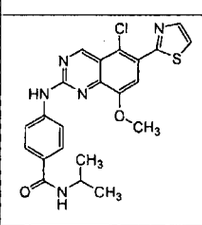
91		N-(3-(5-chloro-6-(thiazol-2-yl)quinazolin-2-ylamino)-5-((dimethyl-amino)methyl)phenyl)-acetamide	453.1 2.27	++++	28
92		N-(3-((dimethylamino)-methyl)-5-(6-(pyrimidin-5-yl)quinazolin-2-ylamino)-phenyl)acetamide	414.2 183	++++	9, 21
93		N-(3-((dimethylamino)-methyl)-5-(6-(2-methoxy-pyridin-3-yl)quinazolin-2-ylamino)phenyl)acetamide	443.2 2.38	+++	9, 21
94		N-(3-((dimethylamino)-methyl)-5-(8-methoxy-6-(2-methoxypyridin-3-yl)-quinazolin-2-ylamino)-phenyl)acetamide	473.2 2.41	+++	21

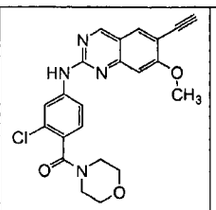
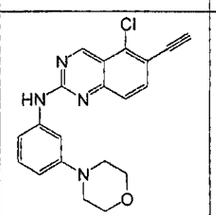
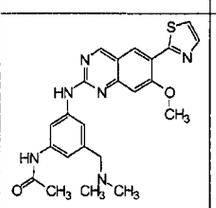
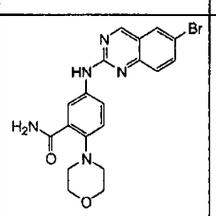
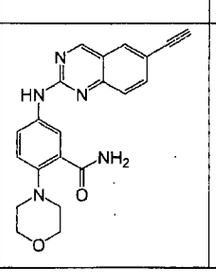
95		N-(3-((dimethylamino)-methyl)-5-(8-methoxy-6-(pyrimidin-5-yl)-quinazolin-2-ylamino)-phenyl)acetamide	444.2 1.9	++++	21
96		N-(4-(1H-tetrazol-5-yl)-phenyl)-6-ethynyl-7-methoxyquinazolin-2-amine	344 3.11	++++	47, 2
97		N-(4-(1H-tetrazol-1-yl)phenyl)-6-ethynyl-7-methoxyquinazolin-2-amine	344 3.39	++++	47, 2
98		N-(3-(1H-tetrazol-5-yl)phenyl)-6-ethynyl-7-methoxyquinazolin-2-amine	344 3.04	++++	47, 2
99		5-chloro-6-ethynyl-N-(4-morpholinophenyl)quinazolin-2-amine	365.1 2.56	++++	22

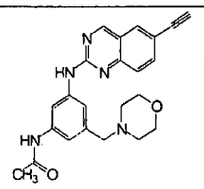
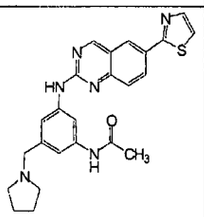
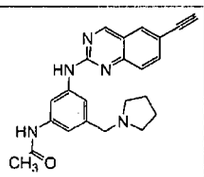
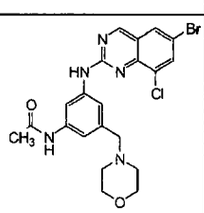
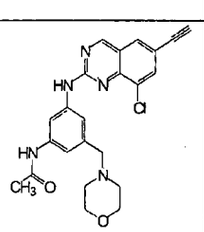
100		N-(4-morpholinophenyl)-6-(thiazol-2-yl)quinazolin-2-amine	390.1 2.32	++++	12
101		5-chloro-6-ethynyl-8-methoxy-N-(4-morpholinophenyl)-quinazolin-2-amine	480.2 2.5	++++	14, 2
102		(4-(6-bromo-7-methoxy-quinazolin-2-ylamino)-2-chlorophenyl)(morpholino)-methanone	477/479 3.83	++++	47
103		N-(3-(1H-tetrazol-1-yl)phenyl)-6-ethynyl-7-methoxyquinazolin-2-amine	344 3.48	++++	47, 2
104		(2-chloro-4-(7-methoxy-6-(thiazol-2-yl)quinazolin-2-ylamino)phenyl)(morpholino)-methanone	482 3.46	++++	47, 12

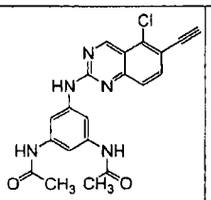
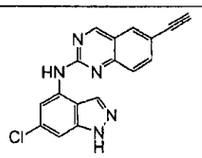
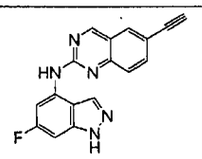
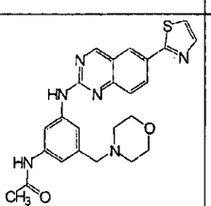
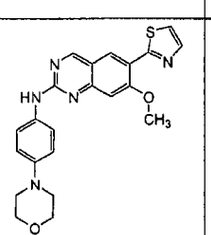
105		N,N'-(5-(6-ethynyl-quinazolin-2-ylamino)-1,3-phenylene)diacetamide	360.1 2.14	++++	9, 10
106		4-(5-chloro-6-ethynyl-quinazolin-2-ylamino)-N-isopropylbenzamide	365.1 3.05	++++	22
107		4-(5-chloro-6-ethynyl-quinazolin-2-ylamino)-N-cyclopropylbenzamide	363.1 2.88	++++	22
108		4-(5-chloro-6-(thiazol-2-yl)quinazolin-2-ylamino)-N-isopropylbenzamide	424.1 3.08	+	28
109		N-(3-((dimethylamino)-methyl)-5-(6-methoxy-quinazolin-2-ylamino)-phenyl)acetamide	367.1	++++	21

110		N-(3-((dimethylamino)-methyl)-5-(8-methoxy-6-(6-methoxypyrazin-2-yl)quinazolin-2-ylamino)phenyl)acetamide	473.1	++++	21
111		N-(3-(6-(2-amino-4-methoxypyrimidin-5-yl)-8-methoxyquinazolin-2-ylamino)-5-((dimethyl-amino)methyl)-phenyl)-acetamide	489.1	+++	21
112		N-(3-(1H-tetrazol-1-yl)phenyl)-7-methoxy-6-(thiazol-2-yl)quinazolin-2-amine	375 3.28	++++	1, 12
113		(4-(5-chloro-6-ethynyl-8-methoxyquinazolin-2-ylamino)phenyl)-(morpholino)methanone	423.2 2.77	++++	14, 2
114		4-(5-chloro-6-ethynyl-8-methoxyquinazolin-2-ylamino)-N-isopropyl-benzamide	395.2 3.01	++++	14, 2

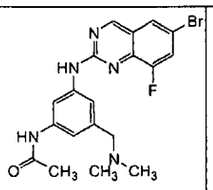
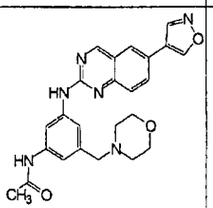
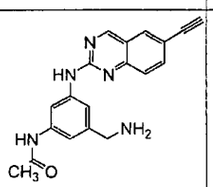
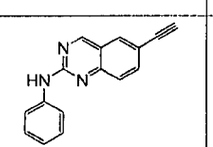
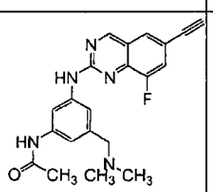
115		5-chloro-8-methoxy-N-(4-morpholinophenyl)-6-(thiazol-2-yl)quinazolin-2-amine	454.1 2.59	++++	14, 12
116		6-bromo-5-chloro-8-methoxy-N-(4-morpholinophenyl)-quinazolin-2-amine	451.0 2.68	++++	14
117		(4-(5-chloro-8-methoxy-6-(thiazol-2-yl)quinazolin-2-ylamino)phenyl)-(morpholino)-methanone	482.1 2.80	++++	14, 12
118		(4-(6-bromo-5-chloro-8-methoxyquinazolin-2-ylamino)phenyl)-(morpholino)-methanone	479.0 2.93	++++	14
119		4-(5-chloro-8-methoxy-6-(thiazol-2-yl)quinazolin-2-ylamino)-N-isopropyl-benzamide	454.1 3.04	++++	14, 12

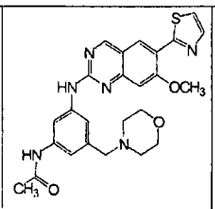
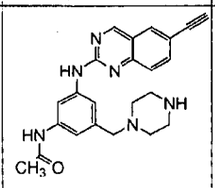
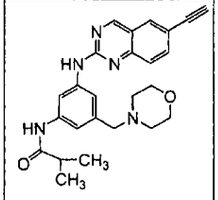
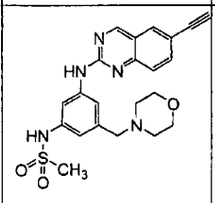
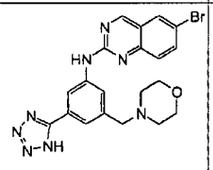
120		(2-chloro-4-(6-ethynyl-7-methoxyquinazolin-2-ylamino)phenyl)-(morpholino)methanone	423 3.40	++++	1, 2
121		5-chloro-6-ethynyl-N-(3-morpholinophenyl)-quinazolin-2-amine	365.1 2.90	++++	22
122		N-(3-((dimethylamino)-methyl)-5-(7-methoxy-6-(thiazol-2-yl)quinazolin-2-ylamino)phenyl)acetamide	449 2.27	++++	1, 12
123		5-(6-bromoquinazolin-2-ylamino)-2-morpholino-benzamide	428/430 2.37	+++	9, 10
124		5-(6-ethynylquinazolin-2-ylamino)-2-morpholino-benzamide	374 2.20	++++	9, 10

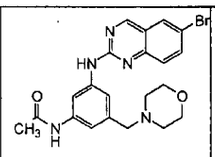
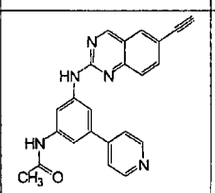
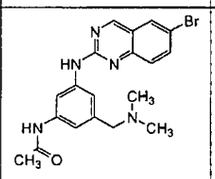
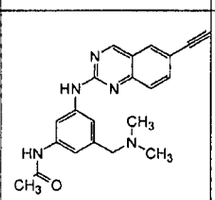
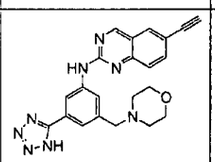
125		N-(3-(6-ethynylquinazolin-2-ylamino)-5-(morpholino-methyl)phenyl)acetamide	402.2 2.07	++++	9, 10
126		N-(3-(pyrrolidin-1-ylmethyl)-5-(6-(thiazol-2-yl)quinazolin-2-ylamino)-phenyl)acetamide	445.2 2.32	++++	21
127		N-(3-(6-ethynylquinazolin-2-ylamino)-5-(pyrrolidin-1-ylmethyl)phenyl)-acetamide	386.2 2.34	++++	9, 10
128		N-(3-(6-bromo-8-chloro-quinazolin-2-ylamino)-5-(morpholinomethyl)-phenyl)-acetamide	490/492 2.34	++++	6
129		N-(3-(8-chloro-6-ethynyl-quinazolin-2-ylamino)-5-(morpholinomethyl)-phenyl)-acetamide	436 2.24	++++	6, 7

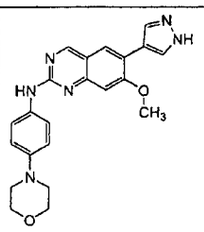
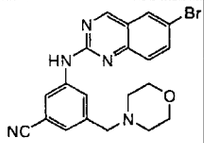
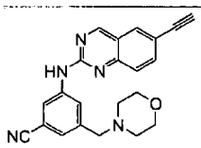
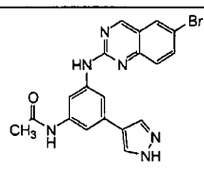
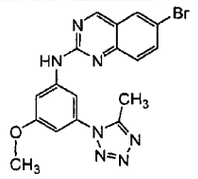
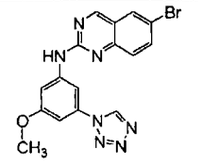
130		N,N'-(5-(5-chloro-6-ethynylquinazolin-2-ylamino)-1,3-phenylene-)diacetamide	394.1 2.47	++++	22
131		N-(6-chloro-1H-indazol-4-yl)-6-ethynylquinazolin-2-amine	320.1 3.06	+	9, 10
132		6-ethynyl-N-(6-fluoro-1H-indazol-4-yl)quinazolin-2-amine	304.1 2.69	+	9, 10
133		N-(3-(morpholinomethyl)-5-(6-(thiazol-2-yl)-quinazolin-2-ylamino)-phenyl)acetamide	461.2 2.05	++++	12
134		7-methoxy-N-(4-morpholinophenyl)-6-(thiazol-2-yl)quinazolin-2-amine	420.2 2.67	+	47, 12

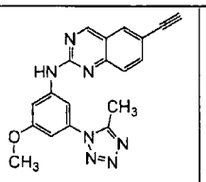
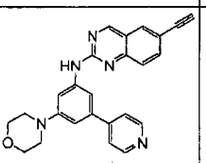
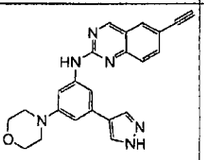
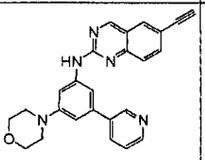
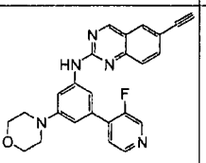
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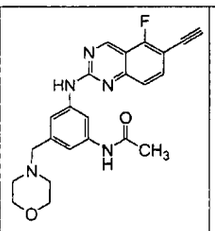
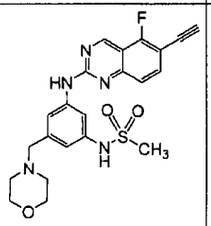
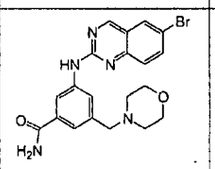
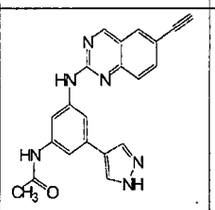
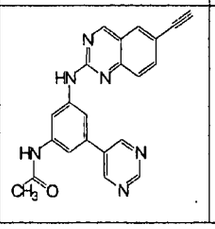
135		N-(3-(6-bromo-8-fluoro-quinazolin-2-ylamino)-5-((dimethylamino)methyl)-phenyl)acetamide	432/434 2.50	++++	135
136		N-(3-(6-(isoxazol-4-yl)quinazolin-2-ylamino)-5-(morpholinomethyl)-phenyl)-acetamide	445.2 1.84	++++	30
137		N-(3-(aminomethyl)-5-(6-ethynylquinazolin-2-ylamino)phenyl)acetamide	332.1 1.96	++++	9, 10
138		6-ethynyl-N-phenyl-quinazolin-2-amine	246.1 2.98	++++	9, 10
139		N-(3-((dimethylamino)-methyl)-5-(6-ethynyl-8-fluoroquinazolin-2-ylamino)phenyl)acetamide	378 2.38	++++	139

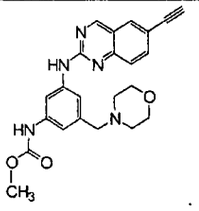
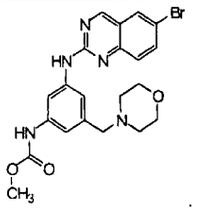
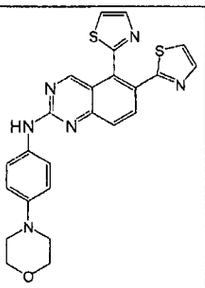
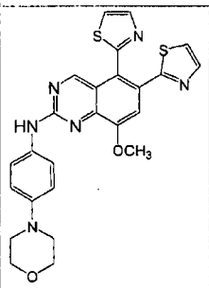
140		N-(3-(7-methoxy-6-(thiazol-2-yl)quinazolin-2-ylamino)-5-(morpholino-methyl)phenyl)-acetamide	491.2 2.23	++++	47, 12
141		N-(3-(6-ethynylquinazolin-2-ylamino)-5-(piperazin-1-ylmethyl)phenyl)acetamide	401.2 1.90	++++	9, 10
142		N-(3-(6-ethynylquinazolin-2-ylamino)-5-(morpholino-methyl)phenyl)-isobutyramide	430.2 2.7	++++	9, 10
143		N-(3-(6-ethynylquinazolin-2-ylamino)-5-(morpholino-methyl)phenyl)methane-sulfonamide	438.1 2.4	++++	9, 10
144		6-bromo-N-(3-(morpholinomethyl)-5-(1H-tetrazol-5-yl)phenyl)-quinazolin-2-amine	467/469 2.18	++++	9

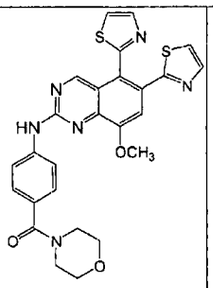
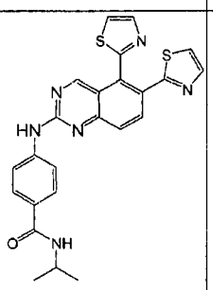
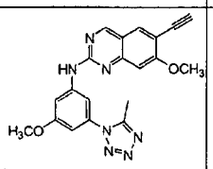
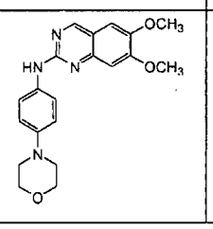
145		N-(3-(6-bromoquinazolin-2-ylamino)-5-(morpholinomethyl)phenyl)acetamide	456/458 2.14	++++	9
146		N-(3-(6-ethynylquinazolin-2-ylamino)-5-(pyridin-4-yl)phenyl)acetamide	380.1 2.10	++++	31, 32, 34
147		N-(3-(6-bromoquinazolin-2-ylamino)-5-((dimethylamino)methyl)phenyl)-acetamide	414/416 2.11	++++	9
148		N-(3-((dimethylamino)methyl)-5-(6-(prop-1-ynyl)quinazolin-2-ylamino)phenyl)acetamide	374.2 2.13	++++	9, 10
149		6-ethynyl-N-(3-(morpholinomethyl)-5-(1H-tetrazol-5-yl)phenyl)-quinazolin-2-amine	413 2.07	++++	9, 10

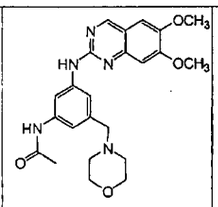
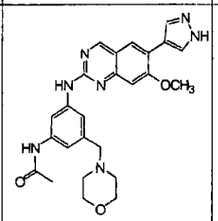
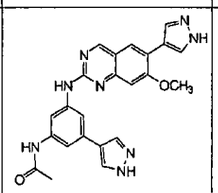
150		7-methoxy-N-(4-morpholinophenyl)-6-(1H-pyrazol-4-yl)quinazolin-2-amine	403.1 2.09	++++	47, 21
151		3-(6-bromoquinazolin-2-ylamino)-5-(morpholino-methyl)benzonitrile	424/426 2.37	++++	9
152		3-(6-ethynylquinazolin-2-ylamino)-5-(morpholino-methyl)benzonitrile	370 2.27	++++	9, 10
153		N-(3-(6-bromoquinazolin-2-ylamino)-5-(1H-pyrazol-4-yl)phenyl)acetamide	423.0/425.0 2.32	++++	31, 32
154		6-bromo-N-(3-methoxy-5-(5-methyl-1H-tetrazol-1-yl)phenyl)quinazolin-2-amine	412.1/414.1 3.08	+	9
155		6-bromo-N-(3-methoxy-5-(1H-tetrazol-1-yl)phenyl)-quinazolin-2-amine	398.0/400.1 3.10	+	9

156		6-ethynyl-N-(3-methoxy-5-(5-methyl-1H-tetrazol-1-yl)phenyl)quinazolin-2-amine	358.1 2.86	++++	9, 10
157		6-ethynyl-N-(3-morpholino-5-(pyridin-4-yl)phenyl)quinazolin-2-amine	408.2 2.77	++++	9, 10
158		6-ethynyl-N-(3-morpholino-5-(1H-pyrazol-4-yl)phenyl)-quinazolin-2-amine	397.2 2.86	++++	9, 10
159		6-ethynyl-N-(3-morpholino-5-(pyridin-3-yl)phenyl)quinazolin-2-amine	408.2 2.72	++++	9, 10
160		6-ethynyl-N-(3-(3-fluoro-pyridin-4-yl)-5-morpholinophenyl)-quinazolin-2-amine	426.2 3.46	++++	9, 10

161		N-(3-(6-ethynyl-5-fluoro-quinazolin-2-ylamino)-5-(morpholinomethyl)-phenyl)-acetamide	420.1 2.39	++++	23, 24
162		N-(3-(6-ethynyl-5-fluoro-quinazolin-2-ylamino)-5-(morpholinomethyl)-phenyl)-methanesulfonamide	456.1 2.4	++++	23, 24
163		3-(6-bromoquinazolin-2-ylamino)-5-(morpholino-methyl)benzamide	442/444	+	9
164		N-(3-(6-ethynylquinazolin-2-ylamino)-5-(1H-pyrazol-4-yl)phenyl)acetamide	369.1 2.19	+	31, 32, 34
165		N-(3-(6-ethynylquinazolin-2-ylamino)-5-(pyrimidin-5-yl)phenyl)acetamide	381.1 2.34	+	31, 32, 34

166		methyl 3-(6-ethynyl-quinazolin-2-ylamino)-5-(morpholinomethyl)-phenylcarbamate	418.2 2.20	+	9,10
167		methyl 3-(6-bromo-quinazolin-2-ylamino)-5-(morpholinomethyl)-phenylcarbamate	472.0/474.0 2.27	+	9
168		N-(4-morpholinophenyl)-5,6-di(thiazol-2-yl)-quinazolin-2-amine	473.0 2.31	+	28
169		8-methoxy-N-(4-morpholinophenyl)-5,6-di(thiazol-2-yl)quinazolin-2-amine	503.0 2.28	++++	14, 12

170		(4-(8-methoxy-5,6-di(thiazol-2-yl)quinazolin-2-ylamino)phenyl)-(morpholino)methanone	531.1 249	+++	14, 12
171		4-(5,6-di(thiazol-2-yl)quinazolin-2-ylamino)-N-isopropylbenzamide	473.1 2.73	+	14, 12
172		6-ethynyl-7-methoxy-N-(3-methoxy-5-(5-methyl-1H-tetrazol-1-yl)phenyl)-quinazolin-2-amine		+++	
173		6,7-dimethoxy-N-(4-morpholinophenyl)-quinazolin-2-amine		+	

174		N-(3-(6,7-dimethoxy-quinazolin-2-ylamino)-5-(morpholinomethyl)-phenyl)acetamide		++++	
175		N-(3-(7-methoxy-6-(1H-pyrazol-4-yl)quinazolin-2-ylamino)-5-(morpholino-methyl)phenyl)acetamide		++++	
176		N-(3-(7-methoxy-6-(1H-pyrazol-4-yl)quinazolin-2-ylamino)-5-(1H-pyrazol-4-yl)phenyl)acetamide		+	

The Compounds in Table 1 were named using the structure naming program in ChemDraw 9.0.1, implementing IUPAC standardized nomenclature.

Additional compounds of the invention are listed in Table 2 (Figure 1), and Table 3 (Figure 2).

It is intended that the compounds of the invention are stable. As used herein "stable" refers to a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and preferably capable of formulation into an efficacious therapeutic agent. It is further intended that the compounds of the invention are those that can be prepared by one skilled in the art according to the methods described herein and any other suitable method, routine or otherwise.

Further provided are compounds of the invention and mixtures thereof where any asymmetric carbon atom(s) present can have either the R or S configuration. Substituents at a double bond or a ring of the compounds of formula I may be present in either the cis (-Z-) or trans (-E-) configurations. The compounds may thus be present as mixtures of isomers, diastereomers, and enantiomers or may be present as pure isomers. In some embodiments, the compounds are enantiomerically pure where only one enantiomer is present. In other embodiments, the compound may be present as a mixture of enantiomers which includes more of one enantiomer than it does of the other, or a racemic mixture. Where absolute stereochemistry is indicated in the specific examples, the compound as isolated is believed to correspond substantially to the indicated absolute stereochemistry but will often contain at least some of the opposite stereochemistry.

It is further intended that the compounds of the invention include various solid forms such as crystalline, microcrystalline, nanocrystalline, and amorphous forms, as well as hydrated, solvated, anhydrous, and non-solvated forms.

Compounds of the invention can also include different atomic isotopes. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl, respectively. Compounds of the present invention, tautomers thereof, prodrugs thereof, and pharmaceutically acceptable salts of the compounds and of the prodrugs that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, *i.e.*, ^{3}H, and carbon-14, *i.e.*, ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, *i.e.*, ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out known or referenced procedures and by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

In some embodiments, the compounds of the invention, and their salts, esters, tautomers, etc., are isolated. By "isolated" or "substantially isolated" is meant that the compound is at least partially or substantially separated from the environment in which is was formed or discovered. Partial separation can include, for example, a composition enriched in the compound of the invention. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, and at least about 99% by weight of the compound of the invention, or salt thereof. Methods for isolating compounds and their salts and other derivatives are routine in the art.

The present invention further provides prodrugs of the compounds described herein. As used herein, "prodrugs" refer to any covalently bonded carriers which release the active parent drug when administered to a mammalian subject. Prodrugs can be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds wherein hydroxyl, amino, sulfhydryl, or carboxyl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, sulfhydryl, or carboxyl group respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the invention. Preparation and use of prodrugs is discussed 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 hereby incorporated by reference in their entirety.

In accordance with further embodiments of the present invention, therapeutic compositions are provided. Such compositions include a therapeutically effective amount of a compound of the invention (*i.e.*, a compound of Formula I) and at least one pharmaceutically acceptable carrier.

Pharmaceutical compositions that include the compounds described herein may include additives such as pharmaceutically acceptable carriers or excipients. Suitable pharmaceutically acceptable carriers include processing agents and drug delivery modifiers and enhancers, such as, for example, calcium phosphate, magnesium stearate, talc, monosaccharides, disaccharides, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, dextrose, hydroxypropyl-β-cyclodextrin, polyvinylpyrrolidinone,

low melting waxes, ion exchange resins, and the like, as well as combinations of any two or more of these. Other suitable pharmaceutically acceptable carriers are described in Remington: The Science And Practice Of Pharmacy, Lippincott Williams & Wilkins; Baltimore, MD, 21st ed. (May 28, 2005), which is hereby incorporated herein by reference in its entirety and for all purposes as if fully set forth herein.

Pharmaceutical compositions that include the compounds of the invention may be in any form suitable for the intended method of administration, including, for example, as a solution, a suspension, or an emulsion. Liquid carriers are typically used in preparing solutions, suspensions, and emulsions. Liquid carriers contemplated for use in the practice of the present invention include, for example, water, saline, pharmaceutically acceptable organic solvent(s), pharmaceutically acceptable oils or fats, and the like, as well as mixtures of two or more of these. The liquid carrier may include other suitable pharmaceutically acceptable additives such as solubilizers, emulsifiers, nutrients, buffers, preservatives, suspending agents, thickening agents, viscosity regulators, stabilizers, and the like. Suitable organic solvents include, for example, monohydric alcohols, such as ethanol, and polyhydric alcohols, such as glycols. Suitable oils include, but are not limited to, soybean oil, coconut oil, olive oil, safflower oil, cottonseed oil, and the like. For parenteral administration, the carrier may be an oily ester such as ethyl oleate, isopropyl myristate, and the like. Compositions of the present invention may also be in the form of microparticles, microcapsules, and the like, as well as combinations of any two or more of these.

The compounds and combinations of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multilamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form may include, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. Preferred lipids include phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic. Methods of forming liposomes are known in the art. See, for example, Prescott, Ed., *Methods in Cell Biology*, Volume XIV, Academic Press, New York, N.W., p. 33 *et seq* (1976).

Controlled release delivery systems may also be used, such as a diffusion controlled matrix system or an erodible system, as described for example in: Lee, "Diffusion-Controlled Matrix Systems", pp. 155-198 and Ron and Langer, "Erodible Systems", pp. 199-224, in "Treatise on Controlled Drug Delivery", A. Kydonieus Ed., Marcel Dekker, Inc., New York

1992. The matrix may be, for example, a biodegradable material that can degrade spontaneously *in situ* and *in vivo* for, example, by hydrolysis or enzymatic cleavage, *e.g.*, by proteases. The delivery system may be, for example, a naturally occurring or synthetic polymer or copolymer, for example in the form of a hydrogel. Exemplary polymers with cleavable linkages include polyesters, polyorthoesters, polyanhydrides, polysaccharides, poly(phosphoesters), polyamides, polyurethanes, poly(imidocarbonates) and poly(phosphazenes).

The compounds of the invention may be administered enterally, orally, parenterally, sublingually, by inhalation spray, rectally, or topically in dosage unit formulations that include conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. For example, suitable modes of administration include oral, subcutaneous, transdermal, transmucosal, iontophoretic, intravenous, intramuscular, intraperitoneal, intranasal, subdermal, rectal, and the like. Topical administration may also include the use of transdermal administration such as transdermal patches or ionophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-propanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols that are solid at ordinary temperatures but liquid at the rectal temperature and will, therefore, melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also include, as is normal practice, additional substances other than inert diluents, *e.g.*, lubricating

agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also include buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, cyclodextrins, and sweetening, flavoring, and perfuming agents.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and severity of the particular disease undergoing therapy. The therapeutically effective amount for a given situation can be readily determined by routine experimentation and is within the skill and judgment of the ordinary clinician.

In some embodiments, the compounds of the invention can be administered to a patient in combination with one or more further pharmaceutical agents. Administration of the different agents can be made separately either sequentially or simultaneously, or the agents can be administered together in a single composition. Example further pharmaceutical agents include anti-cancer drugs including chemotherapeutics and other kinase inhibiting compounds.

"Aryl" or refers to a monovalent aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring or multiple condensed rings. Non-limiting examples of aryl groups include phenyl, naphthyl, anthryl, and the like.

"Substituted aryl" refers to aryl groups which are substituted with 1 to 5, or 1 to 3, or 1 to 2 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy, cycloalkenylthio, guanidino, substituted guanidino, halo,

hydroxy, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, substituted sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, and alkylthio;

wherein the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, heterocyclyl, and heteroaryl moieties contained within any of the preceding "substituted aryl" groups are optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of alkenyl, alkynyl, alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy, cycloalkenylthio, guanidino, guanidino, halo, hydroxy, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, alkylthio, and alkylthio; and wherein said substituents are defined herein.

"Aryloxy" refers to the group –O-aryl, where aryl is as defined herein, that includes, by way of example, phenoxy and naphthoxy.

"Substituted aryloxy" refers to the group –O-(substituted aryl) where substituted aryl is as defined herein.

"Arylthio" refers to the group –S-aryl, where aryl is as defined herein.

"Substituted arylthio" refers to the group –S-(substituted aryl), where substituted aryl is as defined herein.

"Alkyl" refers to monovalent saturated aliphatic hydrocarbyl groups having from 1 to 10 carbon atoms or from 1 to 6 carbon atoms. This term includes, by way of example, linear and branched hydrocarbyl groups such as methyl (CH_3-), ethyl (CH_3CH_2-), *n*-propyl ($CH_3CH_2CH_2$-), isopropyl ($(CH_3)_2CH$-), *n*-butyl ($CH_3CH_2CH_2CH_2$-), isobutyl ($(CH_3)_2CHCH_2$-), *sec*-butyl ($(CH_3)(CH_3CH_2)CH$-), *t*-butyl ($(CH_3)_3C$-), *n*-pentyl ($CH_3CH_2CH_2CH_2CH_2$-), and neopentyl ($(CH_3)_3CCH_2$-).

"Substituted alkyl" refers to an alkyl group having from 1 to 5, or 1 to 3, or 1 to 2 substituents selected from the group consisting of alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy, cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, heteroaryloxy,

heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, substituted sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, and alkylthio;

wherein the alkyl, aryl, cycloalkyl, cycloalkenyl, heterocyclyl, and heteroaryl moieties contained within any of the preceding "substituted alkyl" groups, are optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of alkenyl, alkynyl, alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy, cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, alkylthio, and alkylthio; and wherein said substituents are defined herein.

"Alkoxy" refers to the group –O-alkyl wherein alkyl is defined herein. Alkoxy includes, by way of example, methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *t*-butoxy, *sec*-butoxy, and *n*-pentoxy.

"Substituted alkoxy" refers to the group –O-(substituted alkyl) wherein substituted alkyl is defined herein.

"Acyl" refers to the groups H-C(O)-, alkyl-C(O)-, substituted alkyl-C(O)-, alkenyl-C(O)-, substituted alkenyl-C(O)-, alkynyl-C(O)-, substituted alkynyl-C(O)-, cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, cycloalkenyl-C(O)-, substituted cycloalkenyl-C(O)-, aryl-C(O)-, substituted aryl-C(O)-, heteroaryl-C(O)-, substituted heteroaryl-C(O)-, heterocyclic-C(O)-, and substituted heterocyclic-C(O)-, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein. Acyl includes the "acetyl" group $CH_3C(O)$-.

"Acylamino" refers to the groups –NRC(O)alkyl, -NRC(O)substituted alkyl, -NRC(O)cycloalkyl, -NRC(O)substituted cycloalkyl, -NRC(O)cycloalkenyl, -NRC(O)substituted cycloalkenyl, -NRC(O)alkenyl, -NRC(O)substituted alkenyl, -NRC(O)alkynyl, -NRC(O)substituted alkynyl, -NRC(O)aryl, -NRC(O)substituted aryl, -NRC(O)heteroaryl, -NRC(O)substituted heteroaryl, -NRC(O)heterocyclic, and -NRC(O)substituted heterocyclic wherein R is hydrogen or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl,

substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Acyloxy" refers to the groups alkyl-C(O)O-, substituted alkyl-C(O)O-, alkenyl-C(O)O-, substituted alkenyl-C(O)O-, alkynyl-C(O)O-, substituted alkynyl-C(O)O-, aryl-C(O)O-, substituted aryl-C(O)O-, cycloalkyl-C(O)O-, substituted cycloalkyl-C(O)O-, cycloalkenyl-C(O)O-, substituted cycloalkenyl-C(O)O-, heteroaryl-C(O)O-, substituted heteroaryl-C(O)O-, heterocyclic-C(O)O-, and substituted heterocyclic-C(O)O- wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

"Amino" refers to the group $-NH_2$.

"Substituted amino" refers to the group –NR'R" where R' and R" are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, heteroaryl, heterocyclic, $-SO_2$-alkyl, $-SO_2$-alkenyl, $-SO_2$-cycloalkyl, $-SO_2$-cycloalkenyl, $-SO_2$-aryl, $-SO_2$-heteroaryl, and $-SO_2$-heterocyclic, wherein R′ and R″ are optionally joined, together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, provided that R′ and R″ are both not hydrogen;

wherein the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, heterocyclyl, and heteroaryl moieties contained within any of the preceding "substituted amino" groups are optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of alkenyl, alkynyl, alkoxy, acyl, acylamino, acyloxy, amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy, cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, and alkylthio;

and wherein said substituents are defined herein.

When R′ is hydrogen and R″ is alkyl, the substituted amino group is sometimes referred to herein as alkylamino. When R′ and R″ are alkyl, the substituted amino group is sometimes referred to herein as dialkylamino. When referring to a monosubstituted amino, it

is meant that either R′ or R″ is hydrogen but not both. When referring to a disubstituted amino, it is meant that neither R′ nor R″ are hydrogen.

"Aminocarbonyl" refers to the group -C(O)N $R^{10}R^{11}$ where R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{10} and R^{11} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminothiocarbonyl" refers to the group -C(S)N $R^{10}R^{11}$ where R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{10} and R^{11} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminocarbonylamino" refers to the group -NRC(O)N $R^{10}R^{11}$ where R is hydrogen or alkyl and R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{10} and R^{11} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminothiocarbonylamino" refers to the group -NRC(S)N $R^{10}R^{11}$ where R is hydrogen or alkyl and R^{10} and R^{11} are independently selected from the group consisting of

hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{10} and R^{11} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminocarbonyloxy" refers to the group $-O-C(O)NR^{10}R^{11}$ where R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{10} and R^{11} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminosulfonyl" refers to the group $-SO_2NR^{10}R^{11}$ where R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{10} and R^{11} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminosulfonyloxy" refers to the group $-O-SO_2NR^{10}R^{11}$ where R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{10} and R^{11} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted

heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminosulfonylamino" refers to the group $-NR-SO_2NR^{10}R^{11}$ where R is hydrogen or alkyl and R^{10} and R^{11} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{10} and R^{11} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Amidino" refers to the group $-C(=NR^{12})R^{10}R^{11}$ where R^{10}, R^{11}, and R^{12} are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{10} and R^{11} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Alkenyl" refers to alkenyl groups having from 2 to 6 carbon atoms or from 2 to 4 carbon atoms and having at least 1 and in some embodiments, from 1 to 2 sites of alkenyl unsaturation. Such groups are exemplified, for example, by vinyl, allyl, and but-3-en-1-yl.

"Substituted alkenyl" refers to alkenyl groups having from 1 to 3 substituents, or from 1 to 2 substituents, selected from the group consisting of alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy, cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy,

heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, and alkylthio,

wherein the alkyl, aryl, cycloalkyl, cycloalkenyl, heterocyclyl, and heteroaryl moieties contained within any of the preceding "substituted alkenyl" groups are optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy, cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, and alkylthio; wherein said substituents are defined herein and with the proviso that any hydroxy substitution is not attached to a vinyl (unsaturated) carbon atom.

"Alkynyl" refers to alkynyl groups having from 2 to 6 carbon atoms or from 2 to 3 carbon atoms and having at least 1 and, in some embodiments, 1 to 2 sites of alkynyl unsaturation.

"Substituted alkynyl" refers to alkynyl groups having from 1 to 3 substituents, and, in some embodiments, 1 to 2 substituents, selected from the group consisting of alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy, cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, substituted sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, and alkylthio,

wherein the alkyl, aryl, cycloalkyl, cycloalkenyl, and heteroaryl moieties contained within any of the preceding "substituted alkynyl" are optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl,

cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy, cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, and alkylthio; wherein said substituents are defined herein and with the proviso that any hydroxy substitution is not attached to an acetylenic carbon atom.

"Carbonyl" refers to the divalent group –C(O)– which is equivalent to –C(=O)–.

"Carboxyl" or "carboxy" refers to –COOH or salts thereof.

"Carboxyl ester" or "carboxy ester" refers to the groups -C(O)O-alkyl, -C(O)O-substituted alkyl, -C(O)O-alkenyl, -C(O)O-substituted alkenyl, -C(O)O-alkynyl, -C(O)O-substituted alkynyl, -C(O)O-aryl, -C(O)O-substituted aryl, -C(O)O-cycloalkyl, -C(O)O-substituted cycloalkyl, -C(O)O-cycloalkenyl, -C(O)O-substituted cycloalkenyl, -C(O)O-heteroaryl, -C(O)O-substituted heteroaryl, -C(O)O-heterocyclic, and -C(O)O-substituted heterocyclic wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

"(Carboxyl ester)amino" refers to the group -NR-C(O)O-alkyl, substituted -NR-C(O)O-alkyl, -NR-C(O)O-alkenyl, -NR-C(O)O-substituted alkenyl, -NR-C(O)O-alkynyl, -NR-C(O)O-substituted alkynyl, -NR-C(O)O-aryl, -NR-C(O)O-substituted aryl, -NR-C(O)O-cycloalkyl, -NR-C(O)O-substituted cycloalkyl, -NR-C(O)O-cycloalkenyl, -NR-C(O)O-substituted cycloalkenyl, -NR-C(O)O-heteroaryl, -NR-C(O)O-substituted heteroaryl, -NR-C(O)O-heterocyclic, and -NR-C(O)O-substituted heterocyclic wherein R is alkyl or hydrogen, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

"(Carboxyl ester)oxy" refers to the group -O-C(O)O-alkyl, substituted -O-C(O)O-alkyl, -O-C(O)O-alkenyl, -O-C(O)O-substituted alkenyl, -O-C(O)O-alkynyl, -O-C(O)O-substituted alkynyl, -O-C(O)O-aryl, -O-C(O)O-substituted aryl, -O-C(O)O-cycloalkyl, -O-C(O)O-substituted cycloalkyl, -O-C(O)O-cycloalkenyl, -O-C(O)O-substituted cycloalkenyl, -O-C(O)O-heteroaryl, -O-C(O)O-substituted heteroaryl, -O-C(O)O-heterocyclic, and -O-C(O)O-substituted heterocyclic wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted

cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

"Cyano" refers to the group –CN.

"Cycloalkyl" refers to cyclic alkyl groups of from 3 to 10 carbon atoms having single or multiple cyclic rings including fused, bridged, and spiro ring systems. Cycloalkyl groups can include Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the cycloalkyl ring, for example, benzo derivatives of cyclopentane, cyclopentene, cyclohexane, and the like. A cycloalkyl group having one or more fused aromatic rings can be attached though either the aromatic or non-aromatic portion. One or more ring-forming carbon atoms of a cycloalkyl group can be oxidized, for example, having an oxo or sulfido substituent. Examples of suitable cycloalkyl groups include, for instance, adamantyl, cyclopropyl, cyclobutyl, cyclopentyl, and cyclooctyl.

"Cycloalkenyl" refers to non-aromatic cyclic alkyl groups of from 3 to 10 carbon atoms having single or multiple cyclic rings and having at least one >C=C< ring unsaturation and, in some embodiments, from 1 to 2 sites of >C=C< ring unsaturation.

"Substituted cycloalkyl" and "substituted cycloalkenyl" refers to a cycloalkyl or cycloalkenyl group having from 1 to 5 and, in some embodiments, 1 to 3 substituents selected from the group consisting of oxo, thione, alkyl, alkenyl, alkynyl, alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)-amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy, cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, substituted sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, and alkylthio;

wherein the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, heterocyclyl, and heteroaryl moieties contained within any of the preceding "substituted cycloalkyl" or "substituted cycloalkenyl" groups, are optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of alkenyl, alkynyl, alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyl, cycloalkyloxy, cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy,

cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, alkylthio, and alkylthio; and wherein said substituents are defined herein.

"Cycloalkyloxy" refers to –O-cycloalkyl.

"Substituted cycloalkyloxy refers to –O-(substituted cycloalkyl).

"Cycloalkylthio" refers to –S-cycloalkyl.

"Substituted cycloalkylthio" refers to –S-(substituted cycloalkyl).

"Cycloalkenyloxy" refers to –O-cycloalkenyl.

"Substituted cycloalkenyloxy refers to –O-(substituted cycloalkenyl).

"Cycloalkenylthio" refers to –S-cycloalkenyl.

"Substituted cycloalkenylthio" refers to –S-(substituted cycloalkenyl).

"Guanidino" refers to the group $–NHC(=NH)NH_2$.

"Substituted guanidino" refers to $–NR^{13}C(=NR^{13})N(R^{13})_2$ where each R^{13} is independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, heterocyclic, and two R^{13} groups attached to a common guanidino nitrogen atom are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, provided that at least one R^{13} is not hydrogen;

wherein the alkyl, aryl, heterocyclyl, and heteroaryl moieties contained within any of the preceding "substituted guanidino" groups are optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of alkenyl, alkynyl, alkoxy, acyl, acylamino, acyloxy, amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, amino-sulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)-amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy, cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, and alkylthio.

"Halo" or "halogen" refers to fluoro, chloro, bromo and iodo.

"Hydroxy" or "hydroxyl" refers to the group –OH.

"Heteroaryl" refers to an aromatic group of from 1 to 10 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur within the ring. Such heteroaryl groups can be monocyclic, *i.e.*, have a single ring (*e.g.*, pyridinyl or furyl) or polycyclic, *i.e.*, having multiple condensed rings (*e.g.*, indolizinyl or benzothienyl)

wherein the condensed rings may or may not be aromatic and/or contain a heteroatom provided that the point of attachment is through an atom of the aromatic heteroaryl group. In one embodiment, the nitrogen and/or the sulfur ring atom(s) of the heteroaryl group are optionally oxidized to provide for the N-oxide (N→O), sulfinyl, or sulfonyl moieties. Monocyclic heteroaryls include without limitation, pyrrolyl, furanyl, thiophenyl (thienyl), imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,3-traizolyl, 1,2,4-triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and the like. Polycyclic heteroaryls include without limitation, indolyl, isoindolyl, benzimidazolyl, benzothiophenyl, benzofuranyl, benzoxazolyl, benzothiazolyl, quinolinyl, isoquinolyl, quinazolyl, quinozalyl, cinnolyl, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, phthalazine, naphthylpyridine, phenazine, purine and the like.

"Substituted heteroaryl" refers to heteroaryl groups that are substituted with from 1 to 5, and, in some embodiments, 1 to 3, and, in some embodiments, 1 to 2 substituents selected from the group consisting of the same group of substituents defined for substituted aryl.

"Heteroaryloxy" refers to –O-heteroaryl.

"Substituted heteroaryloxy refers to the group –O-(substituted heteroaryl).

"Heteroarylthio" refers to the group –S-heteroaryl.

"Substituted heteroarylthio" refers to the group –S-(substituted heteroaryl).

"Heterocycle" or "heterocyclic" or "heterocycloalkyl" or "heterocyclyl" refers to a non-aromatic heterocycle where one or more of the ring-forming atoms is a heteroatom such as an O, N, or S atom. Heterocycloalkyl groups can include mono- or polycyclic (*e.g.*, having 2, 3 or 4 fused rings) ring systems as well as spirocycles. Example "heterocycloalkyl" groups include morpholino, thiomorpholino, piperazinyl, tetrahydrofuranyl, tetrahydrothienyl, 2,3-dihydrobenzofuryl, 1,3-benzodioxole, benzo-1,4-dioxane, piperidinyl, pyrrolidinyl, isoxazolidinyl, isothiazolidinyl, pyrazolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, and the like. Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings fused (*i.e.*, having a bond in common with) to the nonaromatic heterocyclic ring, for example phthalimidyl, naphthalimidyl, and benzo derivatives of heterocycles such as indolene and isoindolene groups. A heterocycloalkyl group having one or more fused aromatic rings can be attached though either the aromatic or non-aromatic portion. In some embodiments, the heterocycloalkyl group has from 1 to about 20 carbon atoms, and in further embodiments from about 3 to about 20 carbon atoms. In some embodiments, the heterocycloalkyl group contains 3 to about 20, 3 to about 14, 3 to about 7, or 5 to 6 ring-forming atoms. In some embodiments, the heterocycloalkyl group has 1 to about 4, 1 to

about 3, or 1 to 2 heteroatoms. In some embodiments, the heterocycloalkyl group contains 0 to 3 double bonds. In some embodiments, the heterocycloalkyl group contains 0 to 2 triple bonds. In some embodiments, the nitrogen and/or sulfur atom(s) of the heterocyclic group are optionally oxidized to provide for the N-oxide, sulfoxide, and sulfone moieties.

"Substituted heterocyclic" or "substituted heterocycloalkyl" or "substituted heterocyclyl" refers to heterocyclyl groups that are substituted with from 1 to 5 and, in some embodiments, 1 to 3 of the same substituents as defined for substituted cycloalkyl.

"Heterocyclyloxy" refers to the group –O-heterocyclyl.

"Substituted heterocyclyloxy refers to the group –O-(substituted heterocyclyl).

"Heterocyclylthio" refers to the group –S-heterocyclyl.

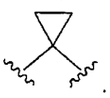
"Substituted heterocyclylthio" refers to the group –S-(substituted heterocyclyl).

Examples of heterocycles include, but are not limited to, azetidine, indolizine, dihydroindole, indazole, quinolizine , isothiazole, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, phthalimide, 1,2,3,4-tetrahydroisoquinoline, 4,5,6,7-tetrahydrobenzo[b]thiophene, thiazolidine, morpholinyl, thiomorpholinyl (also referred to as thiamorpholinyl), 1,1-dioxothiomorpholinyl, piperidinyl, pyrrolidine, tetrahydrofuranyl, and the like.

"Nitro" refers to the group $-NO_2$.

"Oxo" refers to the atom (=O) or (-O-).

"Spirocycloalkyl" refers to divalent cyclic groups from 3 to 10 carbon atoms having a cycloalkyl ring with a spiro union (the union formed by a single atom which is the only common member of the rings) as exemplified by the following structure:



"Sulfonyl" or "sulfone" refers to the divalent group $-S(O)_2-$.

"Substituted sulfonyl" refers to the group $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-alkenyl, $-SO_2$-substituted alkenyl, $-SO_2$-cycloalkyl, $-SO_2$-substituted cycloalkyl, $-SO_2$-cycloalkenyl, $-SO_2$-substituted cycloalkenyl, $-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl, $-SO_2$-substituted heteroaryl, $-SO_2$-heterocyclic, $-SO_2$-substituted heterocyclic, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as

defined herein. Substituted sulfonyl includes groups such as methyl-SO_2-, phenyl-SO_2-, and 4-methylphenyl-SO_2-.

"Sulfonyloxy" refers to the group –OSO_2-alkyl, -OSO_2-substituted alkyl, -OSO_2-alkenyl, -OSO_2-substituted alkenyl, -OSO_2-cycloalkyl, -OSO_2-substituted cycloalkyl, -OSO_2-cycloalkenyl, -OSO_2-substituted cylcoalkenyl,-OSO_2-aryl, -OSO_2-substituted aryl, -OSO_2-heteroaryl, -OSO_2-substituted heteroaryl, -OSO_2-heterocyclic, -OSO_2-substituted heterocyclic, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Thioacyl" refers to the groups H-C(S)-, alkyl-C(S)-, substituted alkyl-C(S)-, alkenyl-C(S)-, substituted alkenyl-C(S)-, alkynyl-C(S)-, substituted alkynyl-C(S)-, cycloalkyl-C(S)-, substituted cycloalkyl-C(S)-, cycloalkenyl-C(S)-, substituted cycloalkenyl-C(S)-, aryl-C(S)-, substituted aryl-C(S)-, heteroaryl-C(S)-, substituted heteroaryl-C(S)-, heterocyclic-C(S)-, and substituted heterocyclic-C(S)-, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Thiol" refers to the group -SH.

"Thiocarbonyl" refers to the divalent group -C(S)- which is equivalent to –C(=S)-.

"Thione" refers to the atom (=S).

"Alkylthio" refers to the group -S-alkyl wherein alkyl is as defined herein.

"Substituted alkylthio" refers to the group -S-(substituted alkyl) wherein substituted alkyl is as defined herein.

The expression "an alkyl interrupted with -O-, -S-, -SO-, -SO_2-, -NH-, carbonyl, carbonylamino, or aminocarbonyl" refers to an alkyl group wherein one divalent carbon unit, *i.e.*, a methylene (-CH_2-) in the alkyl group is replaces by one of the listed divalent moieties.

At various places in the present specification, substituents of compounds of the invention are disclosed in groups or in ranges. It is specifically intended that the invention include each and every individual subcombination of the members of such groups and ranges. For example, the term "C_{1-6} alkyl" is specifically intended to individually disclose methyl, ethyl, C_3 alkyl (propyl and isopropyl), C_4 alkyl, C_5 alkyl, and C_6 alkyl.

Unless indicated otherwise, the nomenclature of substituents that are not explicitly defined herein are arrived at by naming the terminal portion of the functionality followed by

the adjacent functionality toward the point of attachment. For example, the substituent "arylalkyloxycabonyl" refers to the group (aryl)-(alkyl)-O-C(O)-.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present invention include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or ACN are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and *Journal of Pharmaceutical Science*, 66, 2 (1977), each of which is incorporated herein by reference in its entirety.

As used herein, the term "tautomer" or "tautomer thereof" is meant to refer to any tautomeric form of a compound of the invention. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone – enol pairs, amide - imidic acid pairs, lactam – lactim pairs, amide - imidic acid pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H- and 4H-1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

As used herein, the term "ester" or "pharmaceutically acceptable ester" refers to esters which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Representative examples of particular esters include, but are not limited to, formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

As used herein, the term "treating" or "treatment" refers to (1) inhibiting a disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder; (2) preventing the disease; for example, preventing a disease, condition or disorder in an individual who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease; (3) delaying recurrence of the disease, for example, increasing the duration of a period of remission in a proliferative disorder such as a cancer; or (4) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder. Treatment of a patient is typically carried out by administration of a compound of the invention to the patient in a pharmaceutically effective amount.

A "subject," "individual" or "patient" is meant to describe a human or vertebrate animal including, for example, a dog, cat, horse, cow, pig, sheep, goat, monkey, owl, rat, and mouse. In some embodiments, the "subject," "individual" or "patient" is human. In further embodiments, the "subject," "individual" or "patient" is in need of treatment, that is, the patient can be afflicted with, is likely to be afflicted with, or might be afflicted with a disease which is treatable by administration of a compound of the invention, or pharmaceutically acceptable salt, ester, or tautomer thereof, or composition comprising the same.

As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician, such as prevent or inhibit a particular disease or medical disorder.

The compounds of the invention are useful for human or veterinary use where, for example, inhibition of PDK1 or inhibition of PDK1 variants is indicated, such as in the

treatment of various diseases associated with abnormal PDK1 signaling and/or abnormal signaling upstream or downstream of PDK1 (or variants thereof), such as that related to up-regulated activity of one or more receptor tyrosine kinases, Ras, PI3K, PDK1, AKT, RSK, PKC, 70S6K, or SGK. In some embodiments, the compounds of the invention are useful in inhibiting PDK1 variants wherein the wild type PDK1 contains one or more point mutations, insertions, or deletions. Example PDK1 variants include as $PDK1^{T354M}$ and $PDK1^{D527E}$.

The term "PDK1" is meant to refer to wild type PDK1. The term "PDK1 variant" or "variant of PDK1" is meant to refer to PDK1 having at least one point mutation, insertion, or deletion.

The compounds of the invention can be used in the treatment of diseases characterized by "abnormal cellular proliferation." The term "abnormal cellular proliferation" includes, for example, any disease or disorder characterized by excessive or pathologically elevated cell growth such as is characteristic of various cancers and non-cancer proliferative disorders.

Example cancers include, for example, lung cancer, bronchial cancer, prostate cancer, breast cancer, pancreatic cancer, colon cancer, rectal cancer, colorectal cancer, thyroid cancer, liver cancer, intrahepatic bile duct cancer, hepatocellular cancer, gastric cancer, glioma/glioblastoma, endometrial cancer, melanoma, kidney cancer, renal pelvic cancer, urinary bladder cancer; uterine corpus cancer; uterine cervical cancer, ovarian cancer, multiple myeloma, esophageal cancer, acute myelogenous leukemia, chronic myelogenous leukemia, lymphocytic leukemia, myeloid leukemia, brain cancer, oral cavity cancer, and pharyngeal cancer, laryngeal cancer, small intestinal cancer, non-Hodgkin lymphoma, and villous colon adenoma.

Example non-cancer proliferative disorders include neuro-fibromatosis, atherosclerosis, pulmonary fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis, proliferative diabetic retinopathy (PDR), hypertrophic scar formation, inflammatory bowel disease, transplantation rejection, angiogenesis, and endotoxic shock.

In some embodiments, the compounds of the invention are used to treat cancers of the prostate, lung, colon, and breast.

The present invention further provides methods of inhibiting tumor growth in a patient by administration of a compound of the invention, or salt, ester or tautomer thereof. In some embodiments, the tumor is characterized by elevated receptor tyrosine kinase, Ras, PI3K, PDK1, AKT, RSK, PKC, 70S6K, or SGK activity.

The present invention further provides methods of treating cancer in a patient by administering to the patient a therapeutically effective amount of a compound of the invention, or pharmaceutically acceptable salt, ester, or tautomer thereof. In some embodiments, the cancer is characterized by activity of PDK1. In some embodiments, the cancer is characterized by activity of a PDK1 variant such as $PDK1^{T354M}$ or $PDK1^{D527E}$.

In further embodiments, the present invention provides methods for inhibition of Cdk1 and/or Cdk2. Another embodiment provides a methods of treating diseases such as cancer which are responsive to inhibition of Cdk1 and/or Cdk2 by administering a compound of the invention to a patient.

In further embodiments, the invention provides methods of inhibiting phosphorylation of Akt by administering a compound of the invention to a human in need thereof. Another embodiment provides a method of treating diseases such as cancer which are responsive to inhibition of phosphorylation of Akt, by administering a compound of the invention to a patient. Another embodiment provides a method of inhibiting phosphorylation of Akt comprising contacting a cell with a compound of the invention.

The foregoing is further illustrated by reference to the following Examples that are not intended to limit the scope of the inventive concepts. The Example compounds and their analogs can be synthesized by one skilled in the art from procedures described herein, as well as in patents or patent applications listed herein which are all hereby incorporated by reference in their entireties and for all purposes as if fully set forth herein.

EXAMPLES

Referring to the examples that follow, compounds representing specific embodiments were synthesized using the methods described herein, or other methods, which are known in the art.

The compounds and/or intermediates were characterized by high performance liquid chromatography (HPLC) using a Waters Millenium chromatography system with a 2695 Separation Module (Milford, MA). The analytical columns were reversed phase Phenomenex Luna C18 -5 μ, 4.6 x 50 mm, from Alltech (Deerfield, IL). A gradient elution was used (flow 2.5 mL/min), typically starting with 5% acetonitrile/95% water and progressing to 100% acetonitrile over a period of 10 minutes. All solvents contained 0.1% trifluoroacetic acid (TFA). Compounds were detected by ultraviolet light (UV) absorption at

either 220 or 254 nm. HPLC solvents were from Burdick and Jackson (Muskegan, MI), or Fisher Scientific (Pittsburgh, PA).

In some instances, purity was assessed by thin layer chromatography (TLC) using glass or plastic backed silica gel plates, such as, for example, Baker-Flex Silica Gel 1B2-F flexible sheets. TLC results were readily detected visually under ultraviolet light, or by employing well known iodine vapor and other various staining techniques.

Mass spectrometric analysis was performed according to two different liquid chromatography / mass spectroscopy (LCMS) methods. Method A employed a Waters System (Alliance HT HPLC and a Micromass ZQ mass spectrometer for the LCMS instrument, an Eclipse XDB-C18, 2.1 x 50 mm for the chromatography column, and a solvent system that was a 5-95% gradient of acetonitrile in water with 0.05% TFA over a 4 min period (flow rate 0.8 mL/min molecular weight range 200-1500; cone Voltage 20 V; column temperature 40°C). Method B employed a Hewlett Packard System (Series 1100 HPLC and a Micromass ZQ mass spectrometer for the LCMS instrument, an Eclipse XDB-C18, 2.1 x 50 mm for the chromatography column, and a solvent system that was a 5-95% gradient of acetonitrile in water with 0.05% TFA over a 4 min period (flow rate 0.8 mL/min molecular weight range 150-850; cone Voltage 50 V; column temperature 30°C). All masses were reported as those of the protonated parent ions.

Gas chromatography / mass spectroscopy (GCMS) analysis was performed on a Hewlett Packard instrument (HP6890 Series gas chromatograph with a Mass Selective Detector 5973; injector volume: 1 μL; initial column temperature: 50°C; final column temperature: 250°C; ramp time: 20 minutes; gas flow rate: 1 mL/min; column: 5% phenyl methyl siloxane, Model No. HP 190915-443, dimensions: 30.0 m x 25 m x 0.25 m).

Nuclear magnetic resonance (NMR) analysis was performed on some of the compounds with a Varian 300 MHz NMR (Palo Alto, CA). The spectral reference was either tetramethylsilane (TMS) or the known chemical shift of the solvent. Some compound samples were run at elevated temperatures (*e.g.*, 75°C) to promote increased sample solubility.

The purity of some of the compounds was assessed by elemental analysis (Desert Analytics, Tucson, AZ).

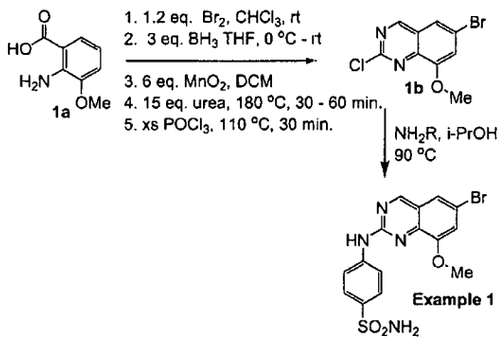
Melting points were determined on a Laboratory Devices Mel-Temp apparatus (Holliston, MA).

Preparative separations were carried out using a Flash 40 chromatography system and KP-Sil, 60A (Biotage, Charlottesville, VA), or by flash column chromatography using silica gel (230-400 mesh) packing material, or by HPLC using a Waters 2767 Sample Manager, C-18 reversed phase column, 30X50 mm, flow 75 mL/min. Typical solvents employed for the Flash 40 Biotage system and flash column chromatography are dichloromethane (DCM), methanol (MeOH), ethyl acetate (EtOAc), hexane (hex), acetone, aqueous ammonia (or ammonium hydroxide), and triethylamine (TEA). Typical solvents employed for the reverse phase HPLC are varying concentrations of acetonitrile (ACN) and water with 0.1% trifluoroacetic acid (TFA).

Example 1: 4-(6-Bromo-8-methoxyquinazolin-2-ylamino)benzenesulfonamide

The subject compound was prepared according to the general Scheme 1, below:

Scheme 1



Step 1: 2-Amino-5-bromo-3-methoxybenzoic acid

To a 0.24 M chloroform solution of 2-amino-3-methoxybenzoic acid (**4**, 11.87 g, 71.7 mmol) at 0 °C was added bromine (1.08 eq. 0.31 M) in chloroform dropwise. The mixture was warmed to room temperature (RT) and stirred under argon for 16 hours. A precipitate formed and was collected by filtration and washed thoroughly with chloroform. The crude material was dried *in vacuo* to give the title as a hydrobromide (HBr) salt in 99% yield. ES/MS *m/z* 248/250 (MH^+).

Step 2: (2-Amino-5-bromo-3-methoxyphenyl)methanol

To a 0.24 M tetrahydrofuran (THF) suspension of 2-amino-5-bromo-3-methoxybenzoic acid, **1a** (71.7 mmol) at 0 °C was added borane THF solution (1 M, 220 mL, 220 mmol). The mixture was stirred under argon at RT for 66 hours. The reaction was quenched by adding ethanol (15 mL) at 0 °C and stirred for 15 minutes. The mixture was poured into water and extracted with DCM. The organic extracts were combined, washed with brine, dried with sodium sulfate and concentrated *in vacuo* to give crude material as a white solid (10.16 g, 62% yield). ES/MS *m/z* 230/232 (MH^+).

Step 3: 2-Amino-5-bromo-3-methoxybenzaldehyde

To a 0.15 M chloroform solution of (2-amino-5-bromo-3-methoxyphenyl)methanol (10.16 g, 43.96 mmol) was added manganese dioxide (19.9 g, 280.5 mmol). The mixture was stirred under argon at RT for 16 hours. The mixture was then filtered through diatomaceous earth and washed with DCM. The filtrate was concentrated to dryness and used in next step. ES/MS *m/z* 228/230 (MH^+).

*Step 4: 6-Bromo-8-methoxyquinazolin-2-ol, **1a***

The mixture of 2-amino-5-bromo-3-methoxybenzaldehyde (43.96 mmol, crude material from Step 3) and urea (35 g, 583 mmol) from the previous step was heated to 180 °C under argon for 1 hour. Water (300 mL) was added after cooling to RT. A solid precipitate formed and was collected by filtration and air dried to give 12.45 g of a powder. ES/MS *m/z* 254/256 (MH^+).

*Step 5: 6-Bromo-2-chloro-8-methoxyquinazoline, **1b***

A suspension of 6-bromo-8-methoxyquinazolin-2-ol, **1a** (43.96 mmol) in $POCl_3$ (120 mL) was heated to 110 °C for 30 minutes The mixture was cooled to RT, evaporated $POCl_3$ and partitioned between water and DCM. The organic portion was concentrated to give a crude material which was purified by column chromatography (silica gel, eluted with 2% MeOH in DCM) to yield a pure material as a yellow solid in 30% yield (3 steps, 3.62 g). ES/MS *m/z* 272/274 (MH^+).

Step 6: 4-(6-Bromo-8-methoxyquinazolin-2-ylamino)benzenesulfonamide

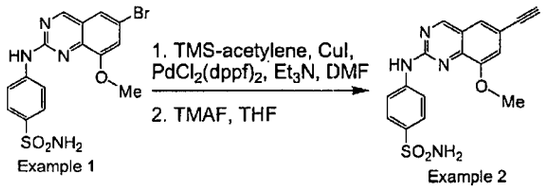
To a solution of 50 mg of **1b** in 2-propanol (1 mL) was added sulfanilamide (1.0 eq). The reaction was stirred at 90 °C for 18 hours. The hydrochloride was collected by vacuum

filtration and air dried to give a crude material (80 mg) which can be used for further chemical modifications. The pure material was obtained by HPLC purification. ES/MS *m/z* 409/411 (MH^+).

Example 2: 4-(6-Ethynyl-8-methoxyquinazolin-2-ylamino)benzenesulfonamide

The subject compound was prepared according to the general Scheme 2, below:

Scheme 2



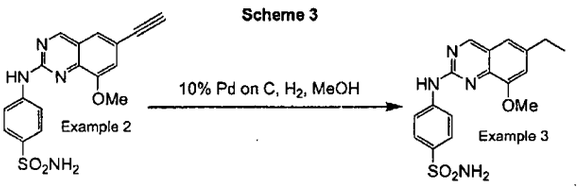
Example 1 Example 2

Step 1 and Step 2 were carried out in one pot. A mixture of the starting material (4-(6-bromo-8-methoxyquinazolin-2-ylamino)benzenesulfonamide; synthesized following Example 1, 67 mg), ethynyltrimethylsilane (0.12 mL), copper(I) iodide (6 mg), 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) (12 mg), TEA (0.8 mL) and DMF (0.8 mL) was microwaved at 120 °C for 6 min. LC/MS showed complete conversion of starting material to 4-(8-methoxy-6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)benzene-sulfonamide. To this intermediate was added THF (0.8 mL) and tetramethylammonium fluoride (60 mg). The resulting mixture was stirred at RT for 16 hrs. The mixture was then diluted with water and extracted with ethyl acetate (3X). The organic extracts were combined, washed with brine, dried with sodium sulfate and concentrated to give a crude material which was purified by HPLC to yield the title compound 4-(6-ethynyl-8-methoxyquinazolin-2-ylamino)benzenesulfonamide. ES/MS *m/z* 355 (MH^+).

Example 3: 4-(6-Ethyl-8-methoxyquinazolin-2-ylamino)benzenesulfonamide

The subject compound was prepared according to the general Scheme 3, below:

Scheme 3

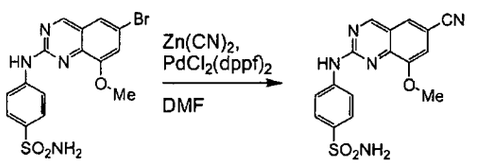


To a 0.015M solution of the product of Example 2 (1.0 eq) in MeOH was added 10% palladium on carbon (20% by mass). The reaction vessel was evacuated and flushed with hydrogen gas. The resulting mixture was stirred 14 h at ambient temperature and then filtered through diatomaceous earth and concentrated. The crude product was purified by reverse-phase HPLC, and lyophilized to give the desired compound as its trifluoroacetic acid salt. ES/MS *m/z* 359 (MH^+).

Example 4: 4-(6-Cyano-8-methoxyquinazolin-2-ylamino)benzenesulfonamide

The subject compound was prepared according to the general Scheme 4, below:

Scheme 4

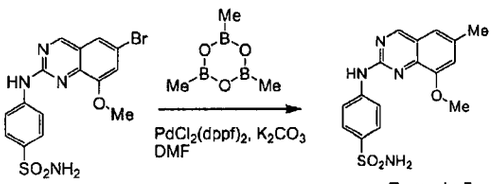


A mixture of 4-(6-bromo-8-methoxyquinazolin-2-ylamino)benzenesulfonamide (synthesized following Example 1, 36 mg), zinc(II) cyanide (36 mg), 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) (12 mg) and DMF (1 mL) was microwaved at 120 °C for 22 min. The resulting mixture was diluted with ethyl acetate, washed with water and brine, dried with sodium sulfate and concentrated. The crude material was purified by HPLC to give the pure title compound 4-(6-cyano-8-methoxyquinazolin-2-ylamino)benzenesulfonamide. ES/MS *m/z* 356 (MH^+).

Example 5: 4-(8-Methoxy-6-methylquinazolin-2-ylamino)benzenesulfonamide

The subject compound was prepared according to the general Scheme 5, below:

Scheme 5

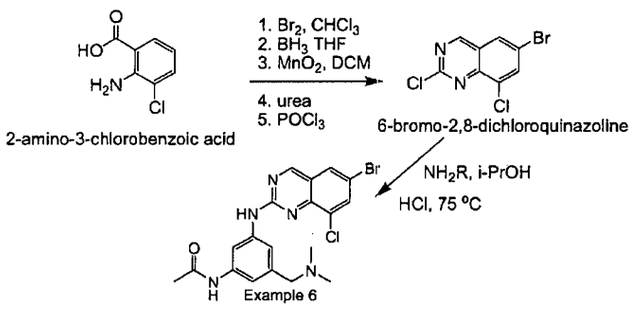


A mixture of 4-(6-bromo-8-methoxyquinazolin-2-ylamino)benzenesulfonamide (synthesized following Example 1, 20 mg), trimethylboroxine (20 μL), 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) (12 mg), potassium carbonate (0.6 mL of 2 M aqueous solution) and DMF (1.2 mL) was microwaved at 130 °C for 10 min. The resulting mixture was diluted with ethyl acetate, washed with water and brine, dried with sodium sulfate and concentrated. The crude material was purified by HPLC to give the pure title compound 4-(8-methoxy-6-methylquinazolin-2-ylamino)benzenesulfonamide. ES/MS *m/z* 345 (MH^+).

Example 6: *N*-(3-(6-Bromo-8-chloroquinazolin-2-ylamino)-5-((dimethylamino)-methyl)phenyl)acetamide

The subject compound was prepared according to the general Scheme 6, below:

Scheme 6



Step 1:

To a suspension of 2-amino-3-chlorobenzoic acid (2 g, 11.6 mmol) in chloroform (120 mL) was added dropwise bromine (1.1 equiv.) in chloroform (12 mL) solution. The mixture was stirred at RT for 16 hrs. The resulting white solid was collected by filtration and washed thoroughly with DCM until the filtrate was colorless. The solid was air-dried to give 3.35 g of white powder as HBr salt of 2-amino-5-bromo-3-chlorobenzoic acid (87% yield). ES/MS *m/z* 250/252 (MH^+).

Step 2:

To the above intermediate (3.35 g, 10.1 mmol) in THF (40 mL) at 0 °C was added borane-THF complex solution (1 M in THF, 40 mL, 4 equiv.). The mixture was stirred at RT for 18 hrs. Additional borane-THF (20 mL) was added and continued reaction for another 24 hrs until the complete conversion of the starting material. The solvent was removed *in vacuo* and the excess reagent was quenched by addition of ethanol (20 mL) slowly. Water was added and the pH (~3) was adjusted by adding sodium bicarbonate (sat. aq.) to pH 7. The resulting mixture was extracted with DCM. The organic extracts were combined, washed with brine, dried with sodium sulfate and concentrated to give a crude material as white solid. ES/MS *m/z* 236/238 (MH^+).

Step 3:

To the above intermediate (10.1 mmol) in DCM (80 mL) was added manganese dioxide (MnO_2, 6 g, 70 mmol). The mixture was stirred at RT under argon for 40 hrs. Additional manganese dioxide (6 g) was added and the reaction was continued for another 20 hrs until the complete conversion of the starting material. The mixture was filtered through diatomaceous earth and washed thoroughly with DCM. The filtrate was concentrated *in vacuo* to give a crude product, (2-amino-5-bromo-3-chlorophenyl)methanol (3.3 g, orange solid) which was used for the next step without further purification. ES/MS *m/z* 234/236 (MH^+).

Step 4:

A mixture of (2-amino-5-bromo-3-chlorophenyl)methanol (3.3 g, obtained from Step 3) and urea (10.5 g, 15 equiv.) was heated to 180 °C with vigorous stirring for 1 hr. The reaction was cooled to RT and water was added. The solid was collected by filtration. The

filtered solid was air-dried to give 2-hydroxyquinazoline as a yellow powder (2.18 g, crude). ES/MS *m/z* 259/261 (MH^+).

Step 5: 6-Bromo-2,8-dichloroquinazoline

To the above crude material was added phosphorus oxychloride ($POCl_3$, 25 mL) and heated to 130 °C for 30 min. The resulting mixture was cooled to RT and concentrated *in vacuo* to nearly dryness. Ice water was added and pH was adjusted to ~8 using sodium bicarbonate. The mixture was extracted with DCM and the extract was dried with sodium sulfate and concentrated *in vacuo* yielded desired product 6-bromo-2,8-dichloroquinazoline as brown foam (1.4 g). This material was used in the following step and in other chemical medications without further purification.

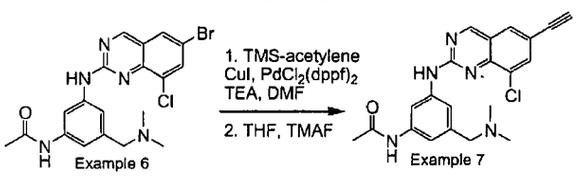
Step 6: N-(3-(6-Bromo-8-chloroquinazolin-2-ylamino)-5-((dimethylamino)methyl)phenyl)-acetamide

A mixture of 6-bromo-2,8-dichloroquinazoline (0.175 g), N-(3-amino-5-((dimethyl-amino)methyl)phenyl)acetamide (1 equiv.) and HCl in dioxane (1 equiv.) in isopropanol (2.5 mL) was heated to 75 °C for 16 hrs. The resulting mixture was diluted with water, washed with ethyl acetate to remove organic impurities, basified the aqueous portion with sodium bicarbonate (aq.) to pH 9, and then brine was added. The basified aqueous solution was extracted with chloroform (3X). The organic extracts were combined, washed with brine, dried with sodium sulfate and concentrated to give a crude material which was used for the next step. Purification by HPLC then yielded pure N-(3-(6-bromo-8-chloroquinazolin-2-ylamino)-5-((dimethylamino)methyl)phenyl)acetamide. ES/MS *m/z* 448/450 (MH^+).

Example 7: *N*-(3-(8-Chloro-6-ethynylquinazolin-2-ylamino)-5((dimethylamino)methyl)-phenyl)acetamide

The subject compound was prepared according to the general Scheme 7, below:

Scheme 7



Step 1:

A mixture of *N*-(3-(6-bromo-8-chloroquinazolin-2-ylamino)-5-((dimethylamino)-methyl)phenyl)acetamide (63 mg, from Example 6), ethynyltrimethylsilane (0.063 mL), copper(I) iodide (6 mg), 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) (12 mg), TEA (0.8 mL) and DMF (0.8 mL) was microwaved at 120 °C for 8 min. The resulting mixture was diluted with ethyl acetate, washed with water and brine, dried with sodium sulfate and concentrated to give a dark brown residue.

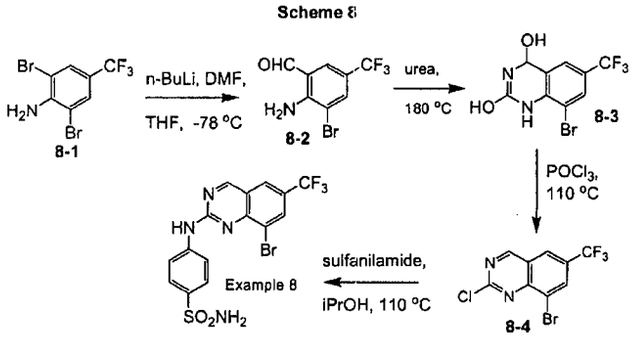
Step 2: N-(3-(8-Chloro-6-ethynylquinazolin-2-ylamino)-5-((dimethylamino)methyl)phenyl)-acetamide

To the intermediate from Step 1 was added THF (3 mL), 2-propanol (0.4 mL) and tetramethylammonium fluoride (18 mg). The mixture was stirred at RT for 20 min. The resulting mixture was diluted with water and extracted with ethyl acetate (3X). The organic extracts were combined, washed with brine, dried with sodium sulfate and concentrated to give a crude material which was purified by HPLC to yield the title compound N-(3-(8-chloro-6-ethynylquinazolin-2-ylamino)-5-((dimethylamino)methyl)phenyl)acetamide. ES/MS *m/z* 394 (MH^+).

Example 8: 4-(8-Bromo-6-(trifluoromethyl)quinazolin-2-ylamino)benzenesulfonamide

The subject compound was prepared according to the general Scheme 8, below:

Scheme 8



Step 1: 2-Amino-3-bromo-5-(trifluoromethyl)benzaldehyde, **8-2**.

2,6-Dibromo-4-(trifluoromethyl)aniline, **8-1** (3.19 g, 10.0 mmol, 1.00 eq) was dissolved in THF (50 mL) and cooled to –78 °C. A 2.5 M solution of n-butyllithium in hexanes (8.40 mL, 21.0 mmol, 2.10 eq) was added dropwise over 15 min. The mixture was stirred at -78 °C for 1 h. A solution of DMF (1.03 mL, 14.0 mmol, 1.40 eq) in THF (5 mL) was added, and the mixture was stirred an additional 1 h at –78 °C. The reaction was allowed to come to –15 °C over 30 min and then quenched with brine. The mixture was diluted with ethyl acetate, washed sequentially with water and brine, dried over sodium sulfate, filtered, and concentrated to give 1.74 g of the desired product as a pale yellow, crystalline solid. ES/MS *m/z* 268,270 (MH^+).

Step 2: 8-Bromo-6-(trifluoromethyl)-1,4-dihydroquinazoline-2,4-diol, **8-3**

2-Amino-3-bromo-5-(trifluoromethyl)benzaldehyde, **8-2** (1.74 g, 6.49 mmol, 1.00 eq) and urea (5.85 g, 97.4 mmol, 15.0 eq) were stirred at 190 °C for 3 h. The resulting solid was returned to ambient temperature, stirred in water (60 mL) for 20 min, and filtered. This was repeated for a total of three washes. The solid was dried in a desiccator to give 3.79 g of the desired product as an off-white solid. ES/MS *m/z* 311,313 (MH^+).

Step 3: 8-Bromo-2-chloro-6-(trifluoromethyl)quinazoline, **8-4**

8-Bromo-6-(trifluoromethyl)-1,4-dihydroquinazoline-2,4-diol, **8-3** (3.79 g, 6.49 mmol, 1.00 eq) and phosphorus oxychloride (20 mL) were stirred together at 110 °C for 1.5 h. Volatiles were removed under reduced pressure. Ice water was added, and the pH was adjusted to 6-7 with aqueous sodium hydroxide and sodium bicarbonate. The precipitate was filtered off, rinsed with water, and dried under high vacuum. The crude material was triturated with THF. The mother liquor was concentrated to yield 332 mg of the desired product as an orange, crystalline solid. ES/MS *m/z* 313 (MH^+).

Step 4: 4-(8-bromo-6-(trifluoromethyl)quinazolin-2-ylamino)benzenesulfonamide

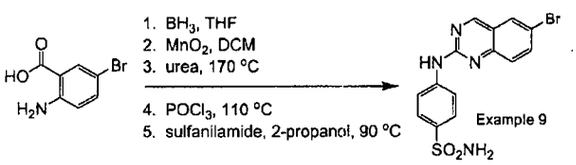
To a 0.30 M solution of 8-bromo-2-chloro-6-(trifluoromethyl)quinazoline, **8-4**, in 2-propanol was added sulfanilamide (1.0 eq). The reaction was stirred at 110 °C for 14 h. The hydrochloride was collected by vacuum filtration and then stirred in aqueous sodium bicarbonate. The solid was collected by vacuum filtration and rinsed with water. The light yellow solid was dried in a desiccator to give 343 mg of the desired product. ES/MS *m/z* 447,449 (MH^+).

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Example 9: 4-(6-Bromoquinazolin-2-ylamino)benzenesulfonamide

The subject compound was prepared according to the general Scheme 9, below:

Scheme 9



Step 1: 2-Amino-5-bromobenzylalcohol

To a 0.50M solution of 2-amino-5-bromobenzoic acid (1.0 eq) in THF was added a 1.0 M solution of borane-THF complex in THF (2.0 eq) dropwise over 15 min at 0 °C. The mixture was stirred for 2 d at ambient temperature. The reaction was quenched by the sequential addition ethanol (6.0 eq) and water. The mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated to give the desired product. ES/MS *m/z* 202,204 (MH^+).

Step 2: 2-Amino-5-bromobenzaldehyde

Manganese (IV) oxide (6.0 eq) was added to a 0.20M solution of 2-amino-5-bromobenzyl alcohol (1.0 eq) in DCM. The mixture was stirred at ambient temperature for 16 h and then filtered through Celite. The filtrate was concentrated to give the desired product as an orange-brown, crystalline solid. ES/MS *m/z* 200,202 (MH^+).

Step 3: 6-Bromo-2-hydroxyquinazoline

2-Amino-5-bromobenzaldehyde (1.0 eq) and urea (8.0 eq) were stirred at 170 °C for 1 h. The resulting solid was returned to ambient temperature, stirred in water for 20 min, and filtered. This was repeated for a total of three washes. The solid was dried in a desiccator to give the desired product as an off-white solid. ES/MS *m/z* 225,227 (MH^+).

Step 4: 6-Bromo-2-chloroquinazoline

A 0.50M solution of 6-bromo-2-hydroquinazoline in phosphorus oxychloride was stirred at 110 °C for 1.5 h. Volatiles were removed under reduced pressure. Ice water was

added, and the pH was adjusted to 6-7 with aqueous sodium hydroxide and sodium bicarbonate. The precipitate was filtered off, rinsed with water, and dried under high vacuum to yield the desired product as a yellow solid. ES/MS *m/z* 245 (MH^+).

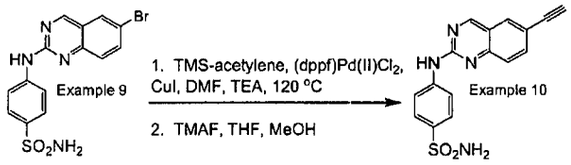
Step 5: 4-(6-Bromoquinazolin-2-ylamino)benzenesulfonamide

To a 0.50 M solution of 6-bromo-2-chloroquinazoline in 2-propanol was added sulfanilamide (1.0 eq). The reaction was stirred at 90 °C for 14 h. The hydrochloride was collected by vacuum filtration and used without further purification. Alternatively, the crude reaction mixture was concentrated, purified by reverse-phase HPLC, and lyophilized to give the desired compound as its trifluoroacetic acid salt. ES/MS *m/z* 379,381 (MH^+).

Example 10: 4-(6-Ethynylquinazolin-2-ylamino)benzenesulfonamide

The subject compound was prepared according to the general Scheme 10, below:

Scheme 10



Step 1:

To a 0.15 M solution of the product of Example 9 in 1:1 DMF:TEA was added trimethylsilylacetylene (TMS-acetylene) (4.0 eq); copper(I) iodide (0.10 eq); and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with DCM (0.050 eq). The reaction was microwaved at 120 °C for 10 min. The mixture was diluted with ethyl acetate and filtered through a pad of silica gel. The filtrate was concentrated and used without further purification. ES/MS *m/z* 397 (MH^+).

Step 2: 4-(6-Ethynylquinazolin-2-ylamino)benzenesulfonamide

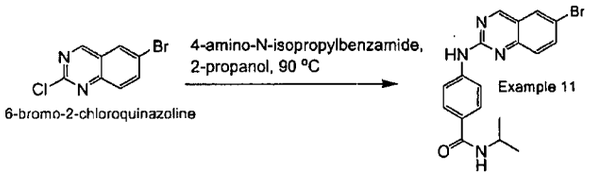
To a 0.10 M solution of the product of Step 1 in 1:1 THF:MeOH was added tetramethylammonium fluoride (1.5 eq). The reaction was stirred for 30 min at ambient temperature. Volatiles were removed under reduced pressure, and the residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic phase was

dried over sodium sulfate, filtered, and concentrated. The crude material was purified by reverse-phase HPLC, and lyophilized to give the desired compound as its trifluoroacetic acid salt. ES/MS *m/z* 325 (MH^+).

Example 11: 4-(6-Bromoquinazolin-2-ylamino)-*N*-isopropylbenzamide

The subject compound was prepared according to the general Scheme 11, below:

Scheme 11

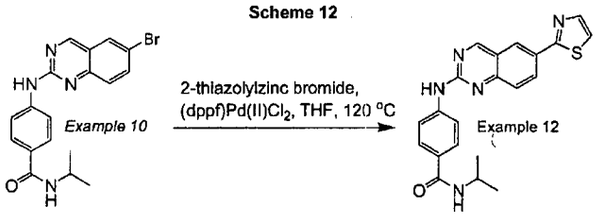


The procedure is analogous to Example 9 Step 5, using 4-amino-*N*-isopropyl-benzamide in place of sulfanilamide. ES/MS *m/z* 385,387 (MH^+).

Example 12: *N*-Isopropyl-4-(6-(thiazol-2-yl)quinazolin-2-ylamino)benzamide

The subject compound was prepared according to the general Scheme 12, below:

Scheme 12

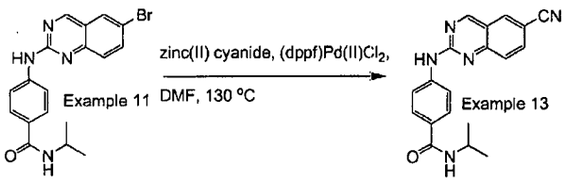


To the product of Example 10 was added [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) complex with DCM (0.10 eq) and a 0.5M solution of 2-thiazolyl zinc bromide in THF (3.0 eq). The reaction was microwaved at 120 °C for 10 min. The mixture was then diluted with ethyl acetate and washed with aqueous EDTA pH~9 buffer. The organic phase was dried over sodium sulfate, concentrated, purified by reverse-phase HPLC, and lyophilized to give the desired compound as its trifluoroacetic acid salt. ES/MS *m/z* 390 (MH^+).

Example 13: 4-(6-Cyanoquinazolin-2-ylamino)-*N*-isopropylbenzamide

The subject compound was prepared according to the general Scheme 13, below:

Scheme 13

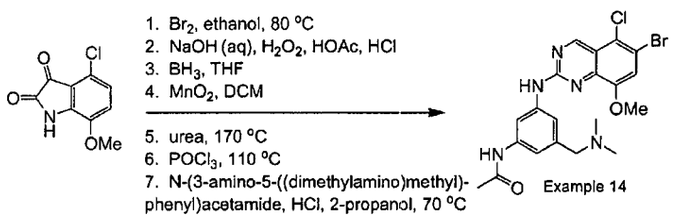


To a 0.10 M solution of the product of Example 11 in DMF was added zinc(II) cyanide (4.0 eq) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with DCM (0.10 eq). The reaction was microwaved at 130 °C for 10 min. The mixture was diluted with ethyl acetate and washed with aqueous EDTA pH~9 buffer. The organic phase was dried over sodium sulfate, concentrated, purified by reverse-phase HPLC, and lyophilized to give the desired compound as its trifluoroacetic acid salt. ES/MS *m/z* 332 (MH^+).

Example 14: *N*-(3-(6-Bromo-5-chloro-8-methoxyquinazolin-2-ylamino)-5-((dimethylamino)methyl)phenyl)acetamide

The subject compound was prepared according to the general Scheme 14, below:

Scheme 14



Step 1: 5-Bromo-4-chloro-7-methoxyisatin

To a 0.50M solution of 4-chloro-7-methoxyisatin (1.0 eq) in ethanol at 80 °C was added a 1.0M ethanolic solution of bromine (2.0 eq) over 45 min. The reaction was stirred at 70 °C for 14 h and then concentrated. The residue was re-dissolved to make a 0.20M solution

in 10:1 acetone:water and stirred for 45 min. The mixture was concentrated to give the desired product as a dark red solid. ES/MS *m/z* 292 (MH^+).

Step 2: 2-Amino-5-bromo-6-chloro-3-methoxybenzoic acid

5-Bromo-4-chloro-7-methoxyisatin (1.0 eq) was suspended in 1.0N aqueous sodium hydroxide (10 eq). A 30% solution of hydrogen peroxide in water (4.0 eq) was added, and the reaction was stirred for 20 min at ambient temperature. The mixture was cooled to 0 °C. Glacial acetic acid (10 eq) and 3.0N aqueous hydrochloric acid (10 eq) were added. The solid was collected by vacuum filtration and dried in a vacuum desiccator to give the desired product. ES/MS *m/z* 282 (MH^+).

Step 3: 2-Amino-5-bromo-6-chloro-3-methoxybenzylalcohol

Analogous to Example 9, step 1 using 2-amino-5-bromo-6-chloro-3-methoxybenzoic acid in place of 2-amino-5-bromobenzoic acid. ES/MS *m/z* 268 (MH^+).

Step 4: 2-Amino-5-bromo-6-chloro-3-methoxybenzaldehyde

Analogous to Example 9 step 2 using 2-amino-5-bromo-6-chloro-3-methoxybenzyl alcohol in place of 2-amino-5-bromobenzyl alcohol. ES/MS *m/z* 266 (MH^+).

Step 5: 6-Bromo-5-chloro-2-hydroxy-8-methoxyquinazoline

Analogous to Example 9, step 3 using 2-amino-5-bromo-6-chloro-3-methoxybenzaldehyde in place of 2-amino-5-bromobenzaldehyde. ES/MS *m/z* 291 (MH^+).

Step 6: 6-Bromo-2,5-dichloro-8-methoxyquinazoline

Analogous to Example 9, step 4 using 6-bromo-5-chloro-2-hydroxy-8-methoxyquinazoline in place of 6-bromo-2-hydroxyquinazoline. ES/MS *m/z* 309 (MH^+).

Step 7: N-(3-(6-Bromo-5-chloro-8-methoxyquinazolin-2-ylamino)-5-((dimethylamino)-methyl)phenyl)acetamide

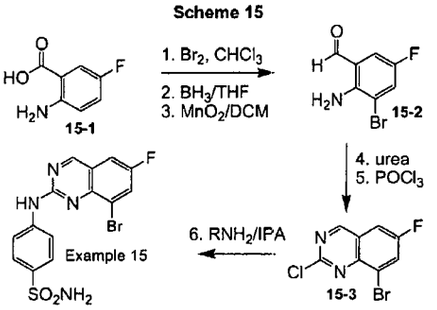
To a 0.25M solution of 6-bromo-2,5-dichloro-8-methoxyquinazoline in 2-propanol was added *N*-(3-amino-5-((dimethylamino)methyl)phenyl)acetamide (1.0 eq) and 4.0M HCl in dioxane (1.2 eq). The reaction was stirred at 70 °C for 14 h. The mixture was then concentrated and the resulting residue was used without further purification. Alternatively

the crude material was purified by reverse-phase HPLC and lyophilized to yield the desired product as its trifluoroacetic acid salt. ES/MS *m/z* 480 (MH^+).

Example 15: 4-(8-Bromo-6-fluoroquinazolin-2-ylamino)benzenesulfonamide

The subject compound was prepared according to the general Scheme 15, below:

Scheme 15



Step 1:

To 2-amino-5-fluorobenzoic acid **15-1**, (5 g, 32.2 mmol) in chloroform (90 mL) was added bromine (1.82 mL, 35.4 mmol) in chloroform (10 mL) solution dropwise via an additional funnel. The mixture was stirred at RT for 16 hrs. and LC/MS showed about 50% conversion of the starting material. Additional bromine (1.8 mL) was added to the reaction and continued stirring for another 24 hrs. The resulting white precipitate was collected by filtration, washed thoroughly with DCM and air-dried to give 2-amino-3-bromo-5-fluorobenzoic acid, as its HBr salt. ES/MS *m/z* 234/236 (MH^+).

Step 2: (2-Amino-3-bromo-5-fluorophenyl)methanol

To a 0.5M suspension of 2-amino-3-bromo-5-fluorobenzoic acid in THF in an ice bath was slowly added borane (1.0M /THF, 3eq). The reaction mixture was stirred at ambient temperature for 24 h. The mixture was recooled to 0°C and quenched with MeOH and concentrated to remove solvent. The residue was taken into ethyl acetate and organic phase was washed with water, saturated sodium bicarbonate, brine, dried over sodium sulfate and concentrated to give yellow solid in 90% yield. ES/MS *m/z* 220/222 (MH^+).

*Step 3: 2-Amino-3-bromo-5-fluorobenzaldehyde, **15-2***

Manganese (IV) oxide (5eq) was added to a 0.2M solution of (2-amino-3-bromo-5-fluorophenyl)methanol in DCM. The resulting suspension was stirred at ambient temperature under Argon for 12 h. The reaction mixture was filtered through diatomaceous earth and the filter cake was washed with DCM. The combined filtrate was concentrated to give brown color solid. ES/MS *m/z* 218/220 (MH^+).

Step 4: 8-Bromo-6-fluoroquinazolin-2-ol

Solid 8-bromo-6-fluoroquinazolin-2-ol (1eq) and urea (14eq) were thoroughly mixed together in a round bottom flask. The mixture was heated to 180 °C in an oil bath for 2.5 h. The reaction mixture was cooled to ambient temperature and water was added to the flask. Filtration gave yellow color solid, which was rinsed with ether and air dried. Yield: 62%. ES/MS *m/z* 243/245 (MH^+).

*Step 5: 8-Bromo-2-chloro-6-fluoroquinazoline, **15-3***

A 0.5M suspension of 8-bromo-6-fluoroquinazolin-2-ol in phosphorus oxychloride was heated to 110 °C in an oil bath. The suspension was turned to a brown color solution in 20min. LCMS data showed that the reaction was complete after 1 h. The phosphorus oxychloride was removed by concentration. The residue was mixed with ice water, and adjusted pH to 7 by adding sodium bicarbonate. Reaction mixture was extracted with ethyl acetate. Combined organic phase was washed with water, brine, dried over sodium sulfate and concentrated to give desired product in 89% yield. ES/MS *m/z* 261/263 (MH^+).

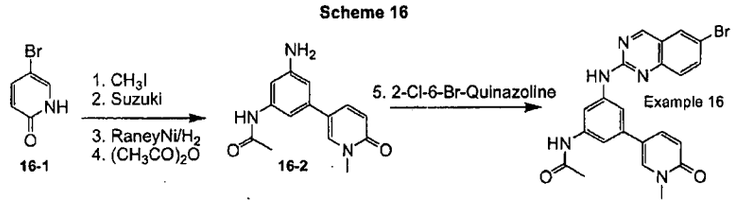
Step 6: 4-(8-Bromo-6-fluoroquinazolin-2-ylamino)benzensulfonamide

To a 0.4M suspension of 8-bromo-2-chloro-6-fluoroquinazoline, **15-3** in isopropanol was added 4-aminobenzensulfonamide (1eq). The reaction mixture was heated to 120 °C in an oil bath for 2days. LCMS showed that reaction was complete under the condition. Ethyl acetate was added to the reaction flask and the suspension was stirred at ambient temperature for 30 min and was filtered. Filter cake was rinsed with hexane and dried in vacuum to give product in 81% yield. ES/MS *m/z* 397/399 (MH^+).

Example 16: *N*-(3-(6-Bromoquinazolin-2-ylamino)-5-(1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl)¬phenyl)acetamide

The subject compound was prepared according to the general Scheme 16, below:

Scheme 16



Step 1: 5-Bromo-1-methylpyridin-2(1H)-one

To a 0.3M suspension of 5-bromo-2(1H)-pyridone in THF in an ice bath was added sodium hydride (2.0eq). After stirring at 0 °C for 5min, iodomethane (4.0eq) was added. The reaction mixture was stirred at ambient temperature for 15 h. Solvent was removed under reduced pressure. The residue was diluted with ethyl acetate and was washed with water, brine, dried over sodium sulfate and concentrated. The crude compound was triturated with hexane and filtered off to collect desired product in 72% yield. ES/MS *m/z* 188/190 (MH^+).

Step 2: 2-(3,5-Dinitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

To a 0.2M solution of 1-iodo-3,5-dinitrobenzene in dioxane were added bis(pinacolate)diboron (1.5eq), $Pd(dppf)_2Cl_2CH_2Cl_2$ (0.2eq) and flame dried potassium carbonate (2.0eq). The mixture was purged with Argon for 10min and was heated to 120 °C for in an oil bath 12 h. The reaction mixture was filtered through diatomaceous earth, and the filter cake was rinsed with dioxane. The combined filtrate was concentrated to provide a residue. The crude residue was purified by Biotage using 20% ethyl acetate in hexane, to give desired product. The structure was confirmed by 1H NMR spectrum.

Step 3: 5-(3,5-Dinitrophenyl)-1-methylpyridin-2(1H)-one

A 0.2 M mixture of 5-bromo-1-methylpyridin-2(1H)-one (1.0eq), 2-(3,5-dinitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.0eq), $Pd(dppf)_2Cl_2CH_2Cl_2$ (0.1eq), 2.0M potassium carbonate (1eq) in DME was microwave at 120 °C for 15min. The reaction mixture was diluted with ethyl acetate, and was washed with water, brine, dried and concentrated. The residue was purified by Biotage using 5% MeOH in dichloromethane (DCM). Product was a brown color solid in 38% yield. ES/MS *m/z* 276 (MH^+).

Step 4: N-(3-Amino-5-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)acetamide

Acetic anhydride (1.0eq) was added to a 0.06M solution of 5-(3,5-diaminophenyl)-1-methylpyridin-2(1H)-one (1.0eq), TEA (1.2eq) in THF in an ice bath. The reaction was monitored by LCMS and was complete in 1h. Solvent was removed under reduced pressure and residue was purified by RP HPLC. Lyophilization gave product as TFA salt. ES/MS *m/z* 258 (MH^+).

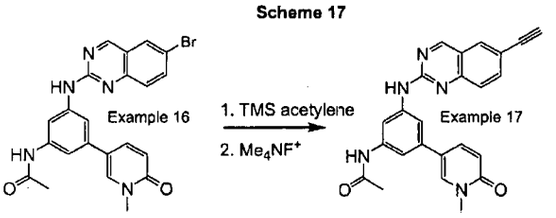
Step 5: N-(3-(6-Bromoquinazolin-2-ylamino)-5-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-phenyl)acetamide

A 0.08 M suspension of 6-bromo-2-chloroquinazoline(1.0eq), *N*-(3-amino-5-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)acetamide (1.0eq) in isopropanol was heated to 120 °C in an oil bath for 15 h. LCMS showed that conversion was complete under the condition. Solvent was removed under reduced pressure and residue was purified by RP HPLC to give desired product as TFA salt. ES/MS *m/z* 464/466 (MH^+).

Example 17: *N*-(3-(6-Ethynylquinazolin-2-ylamino)-5-(1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl)phenyl)acetamide

The subject compound was prepared according to the general Scheme 17, below:

Scheme 17



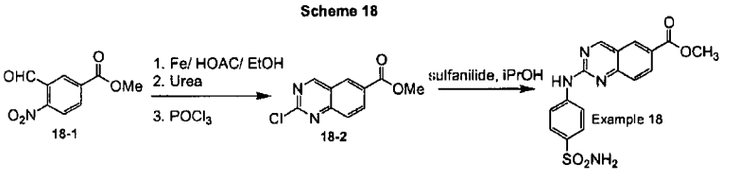
To a 0.04 M mixture of *N*-(3-(6-bromoquinazolin-2-ylamino)-5-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)acetamide (from Example 16)(0.08 mmol), TEA (0.4mL), $Pd(dppf)2Cl_2CH_2Cl_2$ (0.1eq), copper(I) iodide (0.1eq), in DMF was added trimethylsilyl-acetylene (10eq).The suspension was microwaved at 120 °C for 20min. The reaction mixture was diluted with ethyl acetate and was washed with water, brine, dried and concentrated. The oil residue was treated with tetramethylammonium fluoride (1.0eq) in THF/MeOH (1:1, 0.02M) at ambient temperature for 1 h. Solvent was removed under reduced pressure, and the residue was diluted with ethyl acetate. The organic phase was washed with water, brine, dried

and concentrated. The crude product was purified by RP HPLC. Lyophilization gave the desired product. ES/MS *m/z* 410 (MH^+).

Example 18: Methyl 2-(4-sulfamoylphenylamino)quinazolin-6-carboxylate

The subject compound was prepared according to the general Scheme 18, below:

Scheme 18



Step 1: Methyl 3-formyl-4-aminobenzoate, 18-1

To a 1:1 mixture of ethanol and acetic acid was added methyl-3-formyl-4-nitrobenzoate (1eq) and Fe dust (3eq)was added in portions. The reduction was complete in 1h. The reaction mixture was filtered and then concentrated and partitioned between ethyl acetate and water. The organic layer was washed with saturated sodium bicarbonate and dried and concentrated to give methyl 3-formyl-4-aminobenzoate in 85 % yield. ES/MS *m/z* 180(MH^+).

Step 2: Methyl 2-hydroxyquinazoin-6-carboxylate

To methyl 3-formyl-4-aminobenzoate, **18-1** (1eq) was added urea (5eq) and the mixture was heated to145°C for 16h. To the crude was added water and the precipitated solid was filtered to give methyl 2-hydroxyquinazoin-6-carboxylate in quantitative yield. ES/MS *m/z* 205(MH^+).

Step 3: Methyl 2-chloroquinazoin-6-carboxylate, 18-2

To 2-hydroxyquinazoin-7-carboxylate was added $POCL_3$ and the mixture was added heated to 100°C for 20min when the reaction went to completion. To the reaction mixture was added ice and water and the precipitated solid was filtered and dried on the high vacuum overnight to give methyl 2-chloroquinazoin-7-carboxylate in 60% yield. ES/MS *m/z* 223(MH^+).

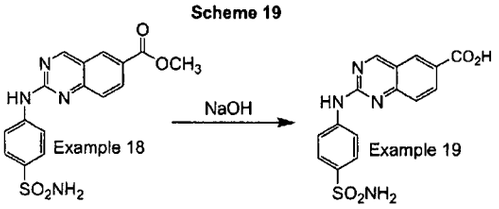
Step 4: Methyl 2-(4-sulfamoylphenylamino)quinazolin-6-carboxylate

To methyl 2-chloroquinazoin-6-carboxylate (1eq) was added sulfanilamide (1eq) and isopropanol and the mixture was heated to 90 °C for 2h. The reaction went to completion. The reaction mixture was cooled to RT and filtered to give methyl 2-(4-sulfamoylphenyl amino)quinazolin-7-carboxylate in quantitative yield. ES/MS *m/z* 359(MH^+).

Example 19: Methyl 2-(4-sulfamoylphenylamino)quinazolin-6-carboxylic acid

The subject compound was prepared according to the general Scheme 19, below:

Scheme 19

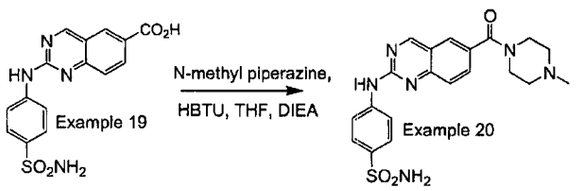


To methyl-2-(4-sulfamoylphenyl amino)quinazolin-7-carboxylate (the compound of Example 18) was added 2N sodium hydroxide (4eq) and MeOH and the resulting mixture was heated to 80 °C for 10min. The saponification went to completion. The reaction mixture was concentrated and 1N HCl was added to precipitate methyl 2-(4-sulfamoylphenylamino)-quinazolin-7-carboxylic acid as the HCl salt in quantitative yield. ES/MS *m/z* 344(MH^+).

Example 20: 4-(6-(4-Methylpiperazine-1-carbonyl)quinazolin-2-ylamino-benzene sulfonamide

The subject compound was prepared according to the general Scheme 20, below:

Scheme 20



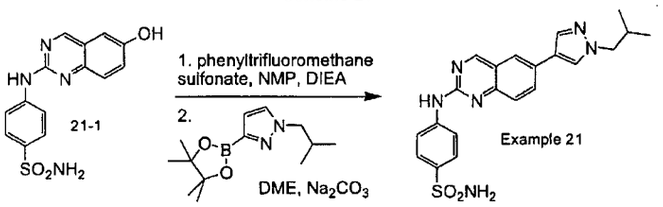
To 2-(4-sulfamoylphenylamino)quinazolin-6-carboxylic acid (from example 19)(1eq) was added *N*-methylpiperazine, THF and diisopropylethylamine (DIEA) (4eq) and HBTU (2eq) and the mixture was stirred at RT overnight. The coupling went to completion and the

mixture was concentrated and partitioned between ethyl acetate and water. The organic layers were concentrated and purified on the prep HPLC to give 4-(6-(4-methylpiperazine-1-carbonyl)quinazolin-2-ylamino-benzene sulfonamide in 50% yield. ES/MS *m/z* 427(MH^+).

Example 21: 4-(6-(1-Isobutyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)benzene-sulfonamide

The subject compound was prepared according to the general Scheme 21, below:

Scheme 21



Step 1: 2-(4-Sulfamoylphenylamino) quinazolin-6-yltrifluoromethane sulfonate

To a solution of 4-(6-hydroxyquinazolin-2-ylamino) benzenesulfonamide, **21-1** (1eq) in NMP was added phenyltrifluoromethanesulfonate (1.2eq) and DIEA (2.5eq) and the reaction mixture was stirred over night at ambient temperature. The reaction mixture was then partitioned between ethyl acetate and water. The organic layers were washed with saturated sodium chloride and dried and concentrated. To the crude was added DCM and few drops of MeOH. The white solid hence formed was filtered to give 2-(4-sulfamoylphenyl-amino)quinazolin-6-yltrifluoromethane sulfonate in 80% yield. ES/MS *m/z* 447(MH^+).

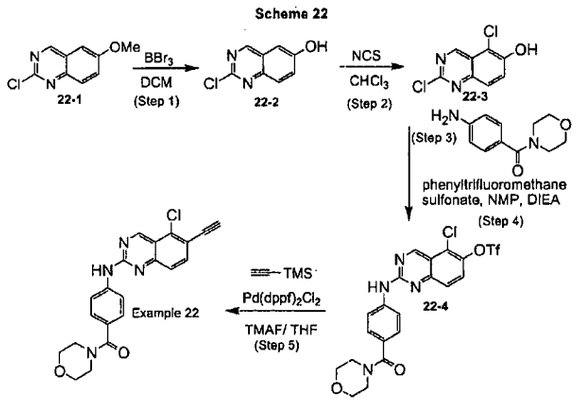
Step 2: 4-(6-(1-Isobutyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)benzenesulfonamide

To a solution of 2-(4-sulfamoylphenylamino)quinazolin-7-yltrifluoromethane sulfonate (1eq) in DME was added 2M sodium carbonate solution and 1-isobutyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (3eq) and $Pd(dppf)_2Cl_2.CH_2Cl_2$ (0.05eq) and the mixture was micro waved for 10 min at 120°C. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was concentrated to yield 4-(6-(1-isobutyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)benzenesulfonamide. ES/MS *m/z* 423(MH^+).

Example 22: (4-(5-Chloro-6-ethynylquinazolin-2-ylamino)phenyl)(morpholino) methanone

The subject compound was prepared according to the general Scheme 22 below:

Scheme 22



*Step 1: 2-Chloroquinazolin-6-ol, **22-2***

To 2-chloro-6-methoxy quinazoline, **22-1** in DCM was added boron tribromide (2eq) and the mixture was heated at 40°C for 16h. The deprotection of the methyl ether goes to completion by LC/MS. The mixture was concentrated and the solid was filtered and washed with ice/water and the solid was dried on high vacuum to give 2-chloroquinazolin-6-ol. ES/MS *m/z* 181(MH^+).

*Step 2: 2,5-Dichloroquinazolin-6-ol, **22-3***

To 2-chloroquinazolin-6-ol, **22-2** (1eq) in chloroform was added N-chlorosuccinimide (1eq) and the mixture was heated to 40°C for 16h. The reaction goes to completion to give 2,5-dichloroquinazolin-6-ol that was observed by LC/MS and the structure was confirmed by ^{1}HNMR. The mixture was concentrated and purified on silica gel to give the product. ES/MS *m/z* 215(MH^+).

Step 3: 2-Chloro5-bromoquinazolin-6-ol

To 2-chloroquinazolin-6-ol, **22-2** (1eq) in chloroform was added *N*-bromosuccinimide (1eq) and the mixture was stirred at ambient temperature for 1h. The reaction goes to completion to give 2-chloro5-bromoquinazolin-6-ol that was observed by LC/MS and the

structure was confirmed by ^{1}HNMR. The mixture was concentrated and passed through a silica gel plug to give the product in quantitative yield. ES/MS *m/z* 260(MH^+).

Step 4: (4-(5-Chloro-6-hydroxyquinazolin-2-ylamino)phenyl)(morpholino)methanone

To 2,5-dichloroquinazolin-6-ol, **22-3** (1eq) in isopropanol was added (4-amino-phenyl)(morpholino)methanone (1eq) and the reaction mixture was heated to 90 °C for 1h. The reaction went to completion by LC/MS. The mixture was then concentrated and used without further purification. ES/MS *m/z* 386(MH^+).

Step 5: 5-Chloro-2-(4-(morpholine-4-carbonyl)phenylamino)quinazolin-6-yl trifluoro-methanesulfonates, 22-4

To a solution of (4-(5-chloro-6-hydroxyquinazolin-2-ylamino)phenyl)(morpholino) methanone (1eq) in NMP was added phenyltrifluoromethanesulfonate (1.2eq) and DIEA (2.5eq) and the reaction mixture was stirred over night at ambient temperature. The reaction mixture was then partitioned between ethyl acetate and water. The organic layers were washed with saturated sodium chloride and dried and concentrated. To the crude was added methylene chloride and few drops of MeOH. The white solid hence formed was filtered to give 5-chloro-2-(4-(morpholine-4-carbonyl)phenylamino) quinazolin-6-yl trifluoromethane-sulfonate in 80% yield. ES/MS *m/z* 517(MH^+).

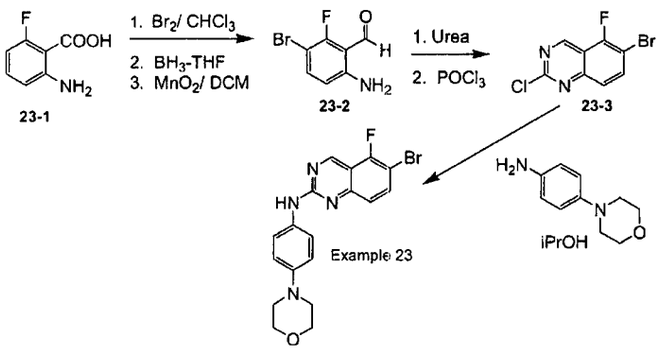
Step 6: (4-(5-Chloro-6-ethynylquinazolin-2-ylamino)phenyl)(morpholino) methanone

To 5-chloro-2-(4-(morpholine-4-carbonyl)phenylamino) quinazolin-6-yl trifluoro-methanesulfonate, **22-4** (1eq) in 4:1 DMF and TEA was added TMS acetylene (4eq) and copper iodide (0.2eq) and $Pd(dppf)_2Cl_2.CH_2Cl_2$ (0.2eq) and the mixture was microwaved for 10 min at 120 °C. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was concentrated to yield (4-(5-chloro-6-((trimethylsilyl)ethynyl)-quinazolin-2-ylamino)phenyl)(morpholino)methanone. ES/MS *m/z* 465(MH^+). To the crude was added THF and tetramethylammonium fluoride (1eq) and the mixture was stirred at ambient temperature for 1h. It was then partitioned between ethyl acetate and water and the organic layer was concentrated and purified on prep HPLC to give (4-(5-chloro-6-ethynyl-quinazolin-2-ylamino)phenyl)(morpholino) methanone. ES/MS *m/z* 393(MH^+).

Example 23: 6-Bromo-5-fluoro-N-(4-morpholinophenyl)quinazolin-2-amine

The subject compound was prepared according to the general Scheme 23 below:

Scheme 23



Step 1: 6-Amino-3-bromo-2-fluorobenzoic acid

To 2-amino-6-fluorobenzoic acid, **23-1** (1eq) in chloroform at 0 °C was added bromine (1.2eq) drop-wise and the mixture was stirred at ambient temperature for 16h. Formation of 6-amino-3-bromo-2-fluorobenzoic acid (47%) was observed by LC/MS along with 2-amino-3-bromo-6-fluorobenzoic acid (22%) and 20% of 2-amino-3,5-dibromo-6-fluorobenzoic acid and 9% starting material remained. The structures of the isomers were confirmed by ^{1}HNMR. The reaction mixture was concentrated and filtered and the solid was washed with chloroform to give an off white solid. The crude mixture was carried on to the next step without purification. ES/MS *m/z* 235(MH^+).

Step 2: (6-Amino-3-bromo-2-fluorophenyl)methanol

To the crude mixture from step 1 in THF at 0°C in a flame dry flask was added borane-THF complex (4eq) dropwise. The mixture was brought to ambient temperature and was stirred for 16h. The formation of (6-amino-3-bromo-2-fluorophenyl)methanol was observed by LC/MS. The reaction mixture was concentrated and to the crude was partitioned between water and ethyl acetate. The organic layer was washed with brine and dried (Na_2SO_4). The crude yellow oil was purified on silica gel and the formation of (6-amino-3-bromo-2-fluorophenyl)methanol was confirmed by ^{1}HNMR. ES/MS *m/z* 218(MH^+).

*Step 3: 6-Amino-3-bromo-2-fluorobenzaldehyde, **23-2***

To (6-amino-3-bromo-2-fluorophenyl)methanol (1eq) in methylene chloride was added manganese dioxide (8eq) and the mixture was stirred at ambient temperature for 16h. Formation of 6-amino-3-bromo-2-fluorobenzaldehyde was confirmed by LC/MS. The mixture was then filtered and the filtrate was concentrated to give 6-amino-3-bromo-2-fluorobenzaldehyde. ES/MS *m/z* 218(MH^+).

Step 4: 6-Bromo-5-fluoroquinazolin-2-ol

To methyl 6-amino-3-bromo-2-fluorobenzaldehyde, **23-2** (1eq) was added urea (8eq) and the mixture was heated to180°C for 1h. To the crude was added water and the precipitated solid was filtered and dried under vacuum to give 6-bromo-5-fluoroquinazolin-2-ol. ES/MS *m/z* 242(MH^+).

*Step 5: 6-Bromo-2-chloro-5-fluoroquinazoline, **23-3***

To 6-bromo-5-fluoroquinazolin-2-ol was added $POCl_3$ and the mixture was added heated to 100 °C for 2h when the reaction went to completion. To the reaction mixture was added ice and water and the precipitated solid was filtered and dried on the high vacuum overnight to give 6-bromo-2-chloro-5-fluoroquinazoline. ES/MS *m/z* 260(MH^+).

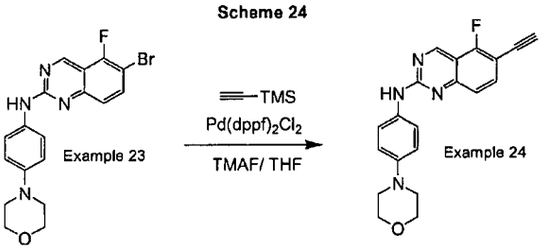
Step 6: 6-Bromo-5-fluoro-N-(4-morpholinophenyl)quinazolin-2-amine

To a solution of 6-bromo-2-chloro-5-fluoroquinazoline, **23-3** (1eq) in isopropanol was added 4-morpholinoaniline (1eq) and the mixture was heated to 90 °C for 1h in a scaled tube. The SNAR went to completion by LC/MS and purification on prep HPLC yielded 6-bromo-5-fluoro-N-(4-morpholinophenyl)quinazolin-2-amine in quantitative yield. ES/MS *m/z* 403(MH^+).

Example 24: 6-Ethynyl-5-fluoro-N-(4-morpholinophenyl)quinazolin-2-amine

The subject compound was prepared according to the general Scheme 24 below:

Scheme 24

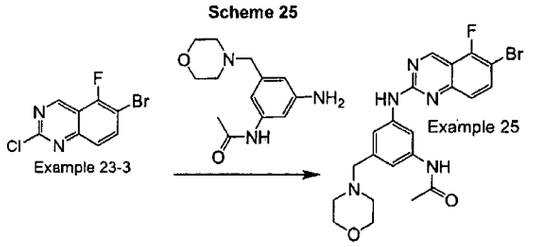


To 6-bromo-5-fluoro-N-(4-morpholinophenyl)quinazolin-2-amine (the compound of Example 20)(1eq) in 4:1 DMF and TEA was added TMS acetylene (4eq) and copper iodide (0.2eq) and $Pd(dppf)_2Cl_2.CH_2Cl_2$ (0.2eq) and the mixture was microwaved for 10 min at 120 °C. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was concentrated to yield 6-ethynyl-5-fluoro-N-(4-morpholinophenyl)-quinazolin-2-amine ES/MS *m/z* 420(MH^+). To the crude was added THF and tetramethyl ammonium fluoride (1eq) and the mixture was stirred at ambient temperature for 1h. It was then partitioned between ethyl acetate and water and the organic layer was concentrated and the resulting residue was purified on prep HPLC to give (4-(5-chloro-6-ethynylquinazolin-2-ylamino)phenyl)(morpholino) methanone. ES/MS *m/z* 349(MH^+).

Example 25: *N*-(3-(6-Bromo-5-fluoroquinazolin-2-ylamino)-5-(morpholinomethyl)-phenyl) acetamide

The subject compound was prepared according to the general Scheme 25 below:

Scheme 25

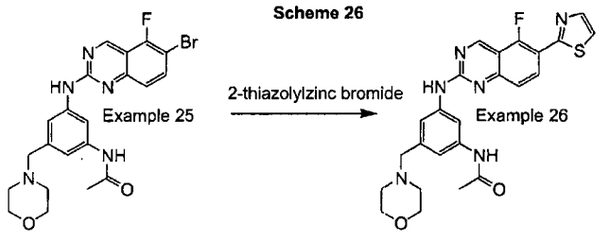


The compound *N*-(3-(6-bromo-5-fluoroquinazolin-2-ylamino)-5-(morpholinomethyl)-phenyl) acetamide, was prepared by a procedure analogous to Example 23.

Example 26: *N*-(3-(5-Fluoro-6-(thiazol-2-yl)quinazolin-2-ylamino)-5-(morpholino-methyl)phenyl)acetamide

The subject compound was prepared according to the general Scheme 26 below:

Scheme 26

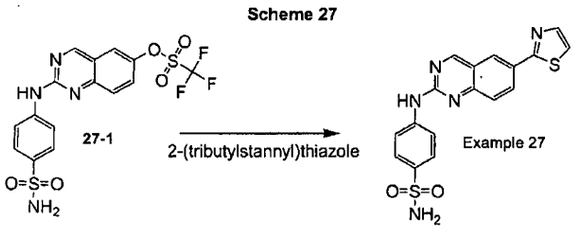


To N-(3-(6-bromo-5-fluoroquinazolin-2-ylamino)-5-(morpholinomethyl)phenyl) acetamide (from Example 25) (1eq) was added 2-thiazolylzinc bromide solution in THF an the mixture a microwaved at 120 °C for 10min. Formation of *N*-(3-(5-fluoro-6-(thiazol-2-yl)quinazolin-2-ylamino)-5-(morpholinomethyl)phenyl)acetamide was confirmed by LC/MS. It was then concentrated and purified on prep HPLC to give the product. ES/MS *m/z* 479(MH^+).

Example 27: 4-(6-(Thiazol-2-yl)quinazolin-2-ylamino)benzenesulfonamide

The subject compound was prepared according to the general Scheme 27 below:

Scheme 27

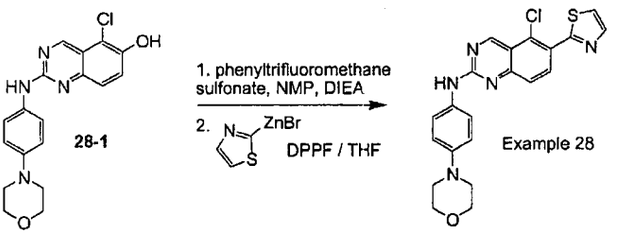


To 2-(4-sulfamoylphenylamino)quinazolin-6-yltrifluoromethane sulfonate (prepared by following Example 18 step 1) (1eq) in DMF was added 2-(tributylstannyl)thiazole (3eq) and TEA (6eq). The mixture was microwaved at 120 °C for 10min. The LC/MS showed formation of the 4-(6-(thiazol-2-yl)quinazolin-2-ylamino)benzenesulfonamide. The crude mixture after work up was then purified on prep HPLC to give 4-(6-(thiazol-2-yl)quinazolin-2-ylamino) benzene sulfonamide. ES/MS *m/z* 384(MH^+).

Example 28: 5-Chloro-*N*-(4-morpholinophenyl)-6-(thiazole-2-yl) quinazolin-2-amine

The subject compound was prepared according to the general Scheme 28 below:

Scheme 28



Step 1: 5-Chloro-2- (4-(morpholinophenylamino) quinazolin-6-yltrifluoromethane sulfonate

See, Example 22 for the synthesis. ES/MS *m/z* 489.1(MH^+).

Step 2: 5-Chloro-N-(4-morpholinophenyl)-6-(thiazole-2-yl) quinazolin-2-amine

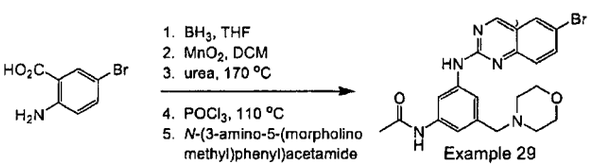
A mixture of 5-chloro-2- (4-(morpholinophenylamino) quinazolin-6-yltrifluoro-methane sulfonate (1eq), 2-thiazolylzincbromide (5eq, 0.5M soln in THF)) and Pd $(dppf)_2Cl_2.CH_2Cl_2$ (0.2eq) in THF was microwaved for 20 min at 120 °C. The LC-MS shows formation of two products in 1:1 ratio. The reaction mixture was concentrated and purified by semi-preparative HPLC to provide 5-chloro-N-(4-morpholinophenyl)-6-(thiazole-2-yl) quinazolin-2-amine in 25%yield. ES/MS *m/z* 424.1(MH^+).

The second product of the reaction was identified as: N-(4-morpholinophenyl)-5,6-di (thiazole-2-yl) quinazolin-2-amine. ES/MS *m/z* 473.0(MH^+).

Example 29: *N-(3-(6-Bromoquinazolin-2-ylamino)-5-(morpholinomethyl) phenyl) acetamide*

The subject compound was prepared according to the general Scheme 29 below:

Scheme 29

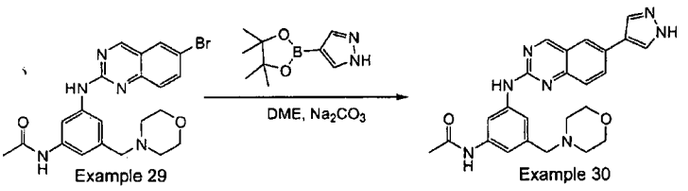


The compound, *N*-(3-(6-bromoquinazolin-2-ylamino)-5-(morpholinomethyl) phenyl) acetamide, was prepared by a synthesis analogous to that used in Example 9. ES/MS *m/z* 456.0 (MH^+).

Example 30: *N*-(3-(6-(1H-Pyrazol-4-yl) quinazolin-2-ylamino)-5-(morpholinomethyl) phenyl) acetamide

The subject compound was prepared according to the general Scheme 30 below:

Scheme 30

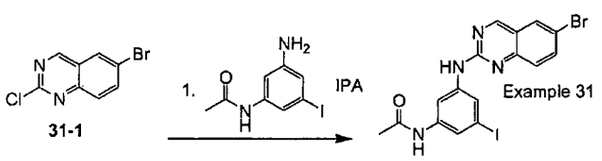


To a solution of *N*-(3-(6-bromoquinazolin-2-ylamino)-5-(morpholinomethyl) phenyl) acetamide (from Example 29) (1eq) in DME was added 2M sodium carbonate solution and 4-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (3eq) and Pd $(dppf)_2Cl_2.CH_2Cl_2$ (0.05eq) and the mixture was microwaved for 10 min at 120 °C. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was washed with brine, dried, concentrated and purified by semi-preparative HPLC to provide *N*-(3-(6-(1H-pyrazol-4-yl) quinazolin-2-ylamino)-5-(morpholinomethyl) phenyl) acetamide; 25%yield. ES/MS *m/z* 444.3 (MH^+). *N*-(3-(morpholinomethyl)-5-(quinazolin-2-ylamino) phenyl) acetamide was isolated as a side product. ES/MS *m/z* 378.2 (MH^+).

Example 31: *N*-(3-(6-Bromoquinazolin-2-ylamino)-5-iodophenyl)acetamide

The subject compound was prepared according to the general Scheme 31 below:

Scheme 31



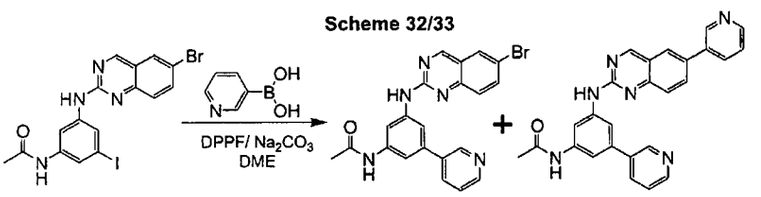
A mixture of 6-bromo-2-chloroquinazoline, **31-1** (1eq) and N- (3-amino-5-iodo-phenyl) acetamide (1eq) in 2-propanol was heated at 110°C overnight. Product was precipitated in the reaction mixture. The precipitate was filtered, washed and dried under vacuum to provide pure product as a yellow solid in 99% yield. ES/MS *m/z* 482.9(MH^+).

Example 32: *N*-(3-(6-Bromoquinazolin-2-ylamino)-5-(pyridine-3-yl) phenyl) acetamide; and

Example 33: *N*-(3-(Pyridin-3-yl)-5-(6-(pyridin-3-yl) quinazolin-2-ylamino) phenyl) acetamide

The subject compounds were prepared according to the general Scheme 32/33, below:

Scheme 32/33



Example 31 Example 32 Example 33

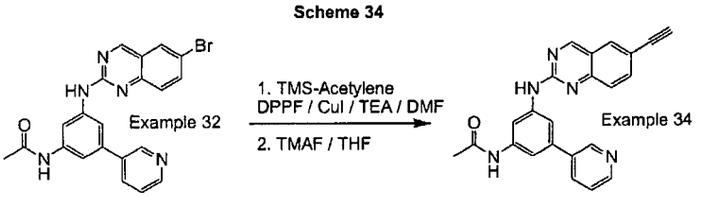
To the compound of Example 26 (1eq) in DME was added 2M sodium carbonate solution, 3-pyridyl boronic acid (2eq) and $Pd(dppf)_2Cl_2.CH_2Cl_2$ (0.05eq) and the mixture was microwaved for 10 min at 120 °C. LC-MS shows formation of two products. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was washed with brine, dried, concentrated and purified by semi-preparative HPLC to provide *N*-(3-(6-bromoquinazolin-2-ylamino)-5-(pyridine-3-yl) phenyl) acetamide in 60%yield. ES/MS *m/z* 434.1 (MH^+).

The second product of this reaction (Example 33), was identified as: *N*-(3-(pyridin-3-yl)-5-(6-(pyridin-3-yl) quinazolin-2-ylamino) phenyl) acetamide. ES/MS *m/z* 433.2 (MH^+).

Example 34: *N*-(3-(6-Ethynylyquinazolin-2-ylamino)-5-(pyridine-3-yl) phenyl) acetamide

The subject compound was prepared according to the general Scheme 34 below:

Scheme 34

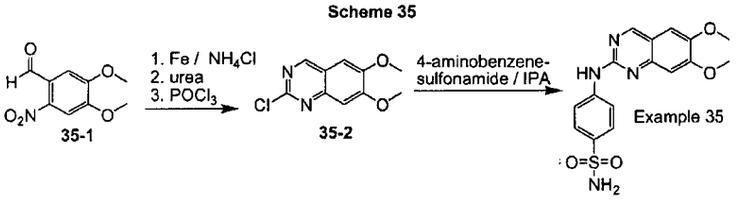


To *N*-(3-(6-bromoquinazolin-2-ylamino)-5-(pyridine-3-yl) phenyl) acetamide (1eq) in 4:1 DMF and TEA was added TMS acetylene (4eq) and copper iodide (0.2eq) and $Pd(dppf)_2Cl_2.CH_2Cl_2$ (0.2eq) and the mixture was micro waved for 10 min at 120 °C. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was concentrated to yield *N*-(3-(pyridine-3-yl)-5-(6-((trimethylsilyl)ethynyl) quinazolin-2-ylamino)phenyl) acetamide. ES/MS *m/z* 452.1(MH^+). To the crude was added THF and tetramethyl ammonium fluoride (1eq) and the mixture was stirred at ambient temperature for 1h. It was then partitioned between ethyl acetate and water and the organic layer was concentrated and purified by semi-prep HPLC to provide *N*-(3-(6-ethynylquinazolin-2-yl-amino)-5-(pyridine-3-yl) phenyl) acetamide. ES/MS *m/z* 380.1(MH^+).

Example 35: 4-(6,7-Dimethoxyquinazolin-2-ylamino) benzenesulfonamide

The subject compound was prepared according to the general Scheme 35 below:

Scheme 35



Step 1: 2-Amino-4,5-dimethoxybenzaldehyde

To a solution of 4, 5-dimethoxy-2-nitrobenzaldehyde (1eq) in ethanol and water (2:1) was added ammonium chloride (10eq). The solution was heated at 90 °C followed by the addition of iron powder (4eq) in portions. The reaction mixture was heated at 90 °C for 30min., cooled, diluted with DCM and filtered through diatomaceous earth. The organic layer was separated from aq layer, washed with brine and dried over sodium sulfate, filtered,

concentrated and dried under vacuum to provide the product in 93% yield. ES/MS *m/z* 182.1 (MH^+).

Step 2: 6,7-Dimethoxyquinazolin-2-ol

A mixture of 2-amino-4, 5-dimethoxybenzaldehyde (1eq) (obtained from step 1) and urea (15 equiv.) was heated to 175 °C with vigorous stirring for 2h. The reaction was cooled to RT and water was added. A solid precipitate formed and was collected by filtration, and air-dried to give 6,7-dimethoxyquinazolin-2-ol as a brown solid in 40%yield. ES/MS *m/z* 207.0 (MH^+).

Step 3: 2-Chloro-6, 7-dimethoxyquinazoline, 35-2

The crude 6,7-dimethoxyquinazolin-2-ol was heated in neat phosphorus oxychloride ($POCl_3$) at 110 °C for 2h. The resulting mixture was cooled to RT and concentrated *in vacuo* to nearly dryness. Ice water was added and the pH was adjusted to ~6 using sodium bicarbonate. Extraction with DCM followed by drying with sodium sulfate and concentration *in vacuo* yielded 2-chloro-6, 7-dimethoxyquinazoline as a brown solid. ES/MS *m/z* 225.0 (MH^+).

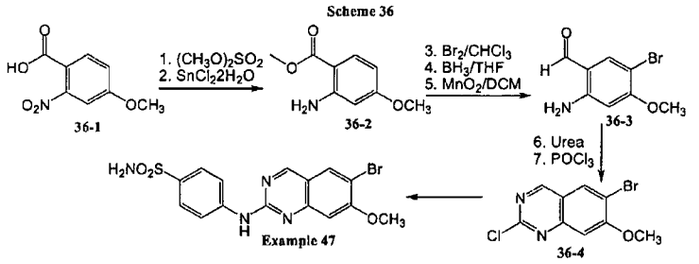
Step 4: 4-(6,7-Dimethoxyquinazolin-2-ylamino) benzenesulfonamide

A mixture of 2-chloro-6,7-dimethoxyquinazoline (1eq) and 4-aminobenzenesulfonamide (1eq) in isopropanol was heated at 90 °C for 16h. The product precipitated in the reaction mixture, and was separated by filtration, washed and dried to provide the pure product as a yellow solid in 87%yield. ES/MS *m/z* 361.0 (MH^+).

Example 47: 4-(6-Bromo-7-methoxyquinazolin-2-ylamino)benzenesulfonamide

The subject compound was prepared according to the general Scheme 36 below:

Scheme 36



Step 1: Methyl 4-methoxy-2-nitrobenzoate

To an ice cooled 0.4M solution of 4-methoxy-2-nitrobenzoic acid **36-1**, in THF was added TEA (6.0eq), followed by the addition of dimethyl sulfate (4.0eq). The resulting mixture was stirred at 0 °C for 1 h, and then at ambient temperature overnight. LCMS showed about 90% conversion to the product. The solvent was removed under reduced pressure. The resulting residue was diluted with ethyl acetate and then washed sequentially with saturated sodium bicarbonate and brine, and then dried over sodium sulfate. Concentration of the dried solution provided the desired product as an off-white solid in 94% yield. The structure of the product was confirmed by proton NMR spectrum.

Step 2: Methyl 2-amino-4-methoxybenzoate, 36-2

To a 0.4M solution of methyl 4-methoxy-2-nitrobenzoate in DMF in an ice bath was added Tin(II) chloride dihydrate (7.0eq). The mixture was stirred at ambient temperature overnight, then diluted with ethyl acetate (40mL ethyl acetate for each mM of the nitro compound). TEA (14eq) was added, and the resulting white suspension was stirred for 1 h, and was then filtered. The filter cake was rinsed with ethyl acetate. The combined organic phase was washed with water and then brine, and was then dried over sodium sulfate. Concentration of the dried organic phase provided the desired product in 95% yield. ES/MS *m/z* 182 (MH^+).

Step 3: Methyl 2-amino-5-bromo-4-methoxybenzoate

To a 0.06M solution of methyl 2-amino-4-methoxybenzoate, **36-2**, in chloroform was added bromine (1.0eq as a 0.05M solution in chloroform) via an additional funnel. The resulting mixture was stirred at RT for 3 h. LCMS data showed that the bromination reaction had proceeded to about 72% conversion. The resulting white precipitate was collected by filtration, washed thoroughly with DCM and then air-dried to provide methyl 2-amino-5-bromo-4-methoxybenzoate as its HBr salt. Yield: 70%. ES/MS *m/z* 260/262 (MH^+).

Step 4: (2-Amino-5-bromo-4-methoxyphenyl)methanol

To a 0.25M suspension of methyl 2-amino-5-bromo-4-methoxybenzoate in THF in an ice bath was slowly added borane (4.5eq as a 1.0M THF solution). The reaction mixture was stirred at ambient temperature for 48 h. The mixture was then recooled to 0°C, quenched with

MeOH and concentrated to remove the solvent. The resulting residue was dissolved in ethyl acetate and the resulting organic phase was washed with water, and then brine, and then dried over sodium sulfate and concentrated to provide (2-amino-5-bromo-4-methoxyphenyl)-methanol, as a brown colored oil. ES/MS *m/z* 214/216 (MH^+).

Step 5: 2-Amino-5-bromo-4-methoxybenzaldehyde, 36-3

Manganese (IV) oxide (8eq) was added to a 0.22M solution of (2-amino-5-bromo-4-methoxyphenyl)methanol in DCM. The resulting suspension was stirred at ambient temperature under Argon for 12 h. The reaction mixture was then filtered through diatomaceous earth and the resulting filter cake was washed with DCM. The combined filtrate was concentrated to provide the product as a brown colored solid in 67% yield. ES/MS *m/z* 230/232 (MH^+).

Step 6: 6-Bromo-7-methoxyquinazolin-2-ol

A mixture of 2-amino-5-bromo-4-methoxybenzaldehyde, **36-3**, (1eq) and urea (14eq) was heated to 180 °C in an oil bath under Argon for 2 h. Water was added after cooling to ambient temperature. The solid was collected by filtration and air dried to give product in 90% yield. ES/MS *m/z* 255/257 (MH^+).

Step 7: 6-Bromo-2-chloro-7-methoxyquinazoline, 36-4

A 0.5M suspension of 6-bromo-7-methoxyquinazolin-2-ol in phosphorus oxychloride was heated to 110 °C in an oil bath for 3 h. The mixture was then cooled to RT. The volatiles were removed under reduced pressure. The resulting residue was triturated with ice water. The resulting solid was collected by filtration and air dried to provide the product in 55% yield. ES/MS *m/z* 273/275 (MH^+).

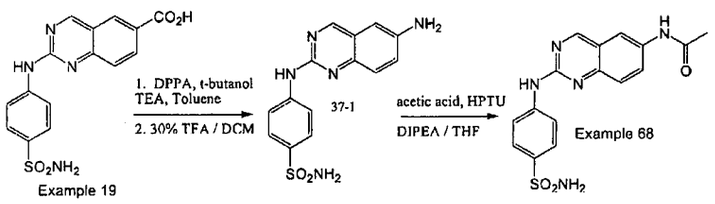
Step 8: 4-(6-Bromo-7-methoxyquinazolin-2-ylamino)benzenesulfonamide

To a solution of 50 mg of **36-4** in 2-propanol (1 mL) was added sulfanilamide (1.0 eq). The reaction was stirred at 90 °C for 18 hours. The hydrochloride was collected by vacuum filtration and air dried to give a crude material which can be used for further chemical modifications. The pure material was obtained by HPLC purification. ES/MS *m/z* 409/411 (MH^+).

Example 68: *N*-(2-(4-Sulfamoylphenylamino)quinazolin-6-yl)acetamide

The subject compound was prepared according to the general Scheme 37 below:

Scheme 37



Step 1: 2-(4-Sulfamoylphenylamino)quinazolin-6-yl tert-butylcarbamate

To 2-(4-sulfamoylphenylamino) quinazoline-6-carboxylic acid (1eq) (prepared as in Example 19) in toluene was added diphenylphosphorylazide (DPPA) (1.2eq), *tert*-butanol (10eq) and TEA (2eq). The resulting mixture was heated to 70 °C for 30min, and was then heated further to 100 °C and maintained at 100 °C overnight. The reaction mixture was then concentrated and the resulting residue was purified by semi-prep HPLC to provide the pure product.

Step 2: 4-(6-Aminoquinazolin-2-ylamino)benzenesulfonamide, 37-1

A solution of 2-(4-sulfamoylphenylamino)quinazolin-6-yl *tert*-butylcarbamate in 30%TFA / DCM was stirred at RT for 30 min. The solvent was then evaporated, and the resulting crude residue was purified by semi-prep HPLC to provide the product.

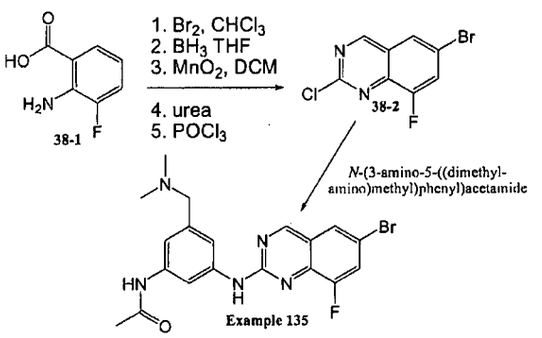
Step 3: N-(2-(4-Sulfamoylphenylamino)quinazolin-6-yl)acetamide

To a solution of 4-(6-aminoquinazolin-2-ylamino)benzenesulfonamide, **37-1**. (1eq) in THF was added acetic acid (5eq), HBTU (4eq) and DIEA (10eq). The resulting mixture was stirred at RT for 48h. The reaction does not go to completion. The reaction mixture was diluted with ethyl acetate and the resulting diluted mixture was washed with water, and then brine and then was dried over sodium sulfate. The dried mixture was filtered, and then concentrated. The concentrate was purified by semi-prep HPLC to provide *N*-(2-(4-sulfamoylphenylamino)quinazolin-6-yl)acetamide.

Example 135: *N*-(3-(6-Bromo-8-fluoroquinazolin-2-ylamino)-5-((dimethylamino)-methyl)phenyl)acetamide

The subject compound was prepared according to the general Scheme 38 below:

Scheme 38



Step 1: 2-Amino-5-bromo-3-fluorobenzoic acid

To a suspension of 2-amino-3-fluorobenzoic acid, **38-1**, (5 g, 32.2 mmol) in chloroform (200 mL) was added dropwise bromine (1.1 equiv.) in chloroform (125 mL) solution. The mixture was stirred at RT for 16 hrs. The resulting white solid was collected by filtration and washed thoroughly with DCM until the filtrate was colorless. The solid was air-dried to give 9.6 g of white powder as the HBr salt of 2-amino-5-bromo-3-fluorobenzoic acid (95% yield). ES/MS *m/z* 234/236 (MH^+).

Step 2:

To the above intermediate (30.6 mmol) in THF (100 mL) at 0 °C was added boron-THF complex solution (1 M in THF, 129 mL, 4 equiv.). The resulting mixture was stirred at RT for 40 hrs. The solvent was removed *in vacuo* and the excess reagent was quenched by the addition of water (30 mL) slowly. The pH (~3) of the quenched mixture was adjusted to pH 7 by adding sodium bicarbonate (sat. aq.). The mixture was then extracted with DCM. The organic extracts were combined, washed with brine, dried with sodium sulfate and concentrated to provide a crude material as a white solid. ES/MS *m/z* 220/222 (MH^+).

Step 3: 2-Amino-5-bromo-3-fluorophenyl)methanol

To the above intermediate (30.6 mmol) in DCM (450 mL) was added manganese dioxide (MnO_2, 22 g, 258 mmol). The resulting mixture was stirred at RT under argon for 18

hrs. The mixture was then filtered through diatomaceous earth and washed thoroughly with DCM. The filtrate was then concentrated *in vacuo* to provide the crude product (2-amino-5-bromo-3-fluorophenyl)methanol (5.6 g) which was used for the next step without further purification. ES/MS *m/z* 218/220 (MH^+).

Step 4: 2-Hydroxyquinazoline

A mixture of (2-amino-5-bromo-3-fluorophenyl)methanol (5.6 g, 23.7 mmol, obtained from step 3) and urea (21 g, 15 equiv.) was heated to 175 °C with vigorous stirring for 15 min. The reaction was then cooled to RT and water was added. A solid precipitate formed and was collected by filtration and air-dried to provide 2-hydroxyquinazoline as a light brown solid.

Step 5: 6-Bromo-2-chloro-8-fluoroquinazoline, 38-2

To the above crude material was added phosphorus oxychloride ($POCl_3$, 20 mL) and this mixture was heated to 110 °C for 30 min. The mixture was then cooled to RT and concentrated *in vacuo* to nearly dryness. Ice water was added to the concentrate and the pH of the resulting mixture was adjusted to ~6 using sodium bicarbonate. The pH adjusted mixture was extracted with DCM. The extract was dried with sodium sulfate and concentrated *in vacuo* to provide the desired product, 6-bromo-2-chloro-8-fluoroquinazoline, as light brown powder (1.63 g).

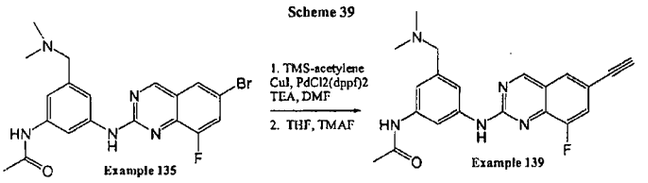
Step 6: N-(3-(6-Bromo-8-fluoroquinazolin-2-ylamino)-5-((dimethylamino)methyl)phenyl)-acetamide

A mixture of 6-bromo-2-chloro-8-fluoroquinazoline, **38-2**, *N*-(3-amino-5-((dimethyl-amino)methyl)phenyl)acetamide (1 equiv.) and HCl in dioxane (1 equiv.) in isopropanol (2.5 mL) was heated to 75 °C for 16 hrs. The resulting mixture was diluted with water, washed with ethyl acetate to remove organic impurities, basified the aqueous portion with sodium bicarbonate (aq.) to pH 9, and then brine was added. The basified aqueous solution was extracted with chloroform (3X). The organic extracts were combined, washed with brine, dried with sodium sulfate and concentrated to give a crude material which was purified by HPLC.

Example 139: *N*-(3-((Dimethylamino)methyl)-5-(6-ethynyl-8-fluoroquinazolin-2-ylamino)-phenyl)acetamide

The subject compound was prepared according to the general Scheme 39 below:

Scheme 39



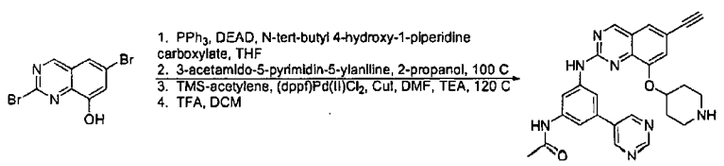
Step 1:

A mixture of *N*-(3-(6-bromo-8-fluoroquinazolin-2-ylamino)-5-((dimethylamino)-methyl)phenyl)acetamide, (from Example 135), ethynyltrimethylsilane, copper(I) iodide, 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II), TEA and DMF, prepared according to the same stoichiometry as employed in the reaction of Example 7, step 1, is microwaved at 120 °C for 8 min. The resulting mixture is diluted with ethyl acetate, washed with water and brine, dried with sodium sulfate and concentrated to provide a crude residue.

Step 2: N-(3-(8-Fluoro-6-ethynylquinazolin-2-ylamino)-5-((dimethylamino)methyl)phenyl)-acetamide (Example 139)

To the intermediate from Step 1 is added THF, 2-propanol and tetramethylammonium fluoride, according to the same stoichiometry as employed in the reaction of Example 7, step 2 . The mixture is stirred at RT for 20 min. The resulting mixture is diluted with water and extracted with ethyl acetate (3X). The organic extracts are combined, washed with brine, dried with sodium sulfate and concentrated to provide a crude material which is purified by HPLC to yield the title compound.

Example 216: N-(3-(6-ethynyl-8-(piperidin-4-yloxy)quinazolin-2-ylamino)-5-(pyrimidin-5-yl)phenyl)acetamide



Step 1. Preparation of 2,6-dibromo -8-(N-Boc-piperidin-4-yloxy)quinazoline

To a 0.30M solution of triphenylphosphine (2.0 eq) in THF was added diethylazodicarboxylate (2.0 eq). The mixture was stirred 15 min at ambient temperature. N-Tert-butyl-4-Hydroxy-1-piperidine carboxylate (4.0 eq) was added. The mixture was stirred 15 min at ambient temperature. 2,6-Dibromo-8-hydroxyquinazoline (1.0 eq) was added. The mixture was stirred an additional 24 h. The crude mixture was concentrated, purified by flash chromatography (2:1 hexanes:EtOAc), and concentrated to give the desired product.

Step 2. Displacement

To a 0.30M solution of 2,6-dibromo-8-(N-Boc-piperidin-4-yloxy)quinazoline in 2-propanol was added 3-acetamido-5-pyrimidin-5-ylaniline (1.0 eq). The reaction was stirred at 100 °C for 14 h. The crude mixture was concentrated and used without further purification.

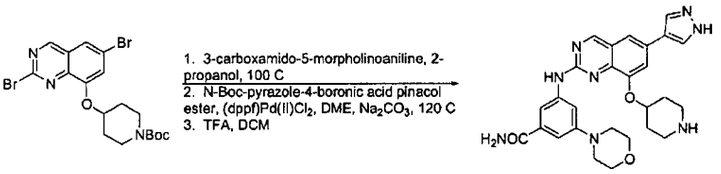
Step 3. Sonogashira & desilylation

The product from Step 2 was treated analogously to Example 281 step 2 and carried on to Step 4 without purification.

Step 4. Deprotection

The product from Step 3 was dissolved in enough 1:1 DCM:TFA to make a 0.20M solution. The mixture was stirred for 30 min at ambient temperature and concentrated. The crude product was purified by reverse-phase HPLC and lyophilized to give the desired product as its trifluoroacetic acid salt. ES/MS *m/z* 480 (MH^+).

Example 220: 3-morpholino-5-(8-(piperidin-4-yloxy)-6-(1H-pyrazol-4-yl)quinazolin-2-ylamino)benzamide



Step 1. Displacement

To a 0.30M solution of the product from Example 283 step 1 in 2-propanol was added 3-carboxamido-5-morpholinoaniline (1.0 eq). The reaction was stirred at 100 °C for 14 h. The crude mixture was concentrated and used without further purification.

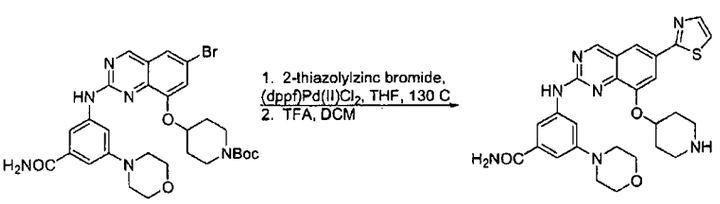
Step 2. Suzuki

To a 0.10M solution of the product from Step 1 (1.0eq) in DME was added N-Boc-pyrazole-4-boronic acid pinacol ester (4.0 eq), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with DCM (0.10 eq), and 2.0M aqueous sodium carbonate (5.0 eq). The reaction was microwaved at 120 C for 10 min. The mixture was diluted with THF, filtered, concentrated, and carried on to Step 4 without purification.

Step 3. Deprotection

The product from Step 2 was dissolved in enough 1:1 DCM:TFA to make a 0.20M solution. The mixture was stirred for 30 min at ambient temperature and concentrated. The crude product was purified by reverse-phase HPLC and lyophilized to give the desired product as its trifluoroacetic acid salt. ES/MS *m/z* 515 (MH^+).

Example 229: 3-morpholino-5-(8-(piperidin-4-yloxy)-6-(thiazol-2-yl)quinazolin-2-ylamino)benzamide



Step 1. Negishi

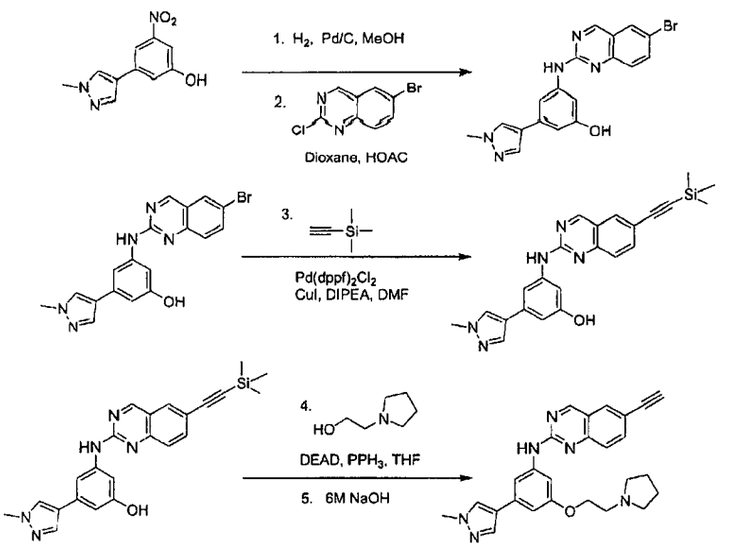
To the product of Example 284 step 1 was added zinc(II) cyanide (4.0 eq) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with DCM (0.10 eq). The reaction was microwaved at 130 °C for 10 min. The mixture was diluted with ethyl acetate and washed with aqueous EDTA pH~9 buffer. The organic phase was dried over sodium sulfate, and concentrated to give the desired product.

Step 2. Deprotection

The product from Step 1 was dissolved in enough 1:1 DCM:TFA to make a 0.20M solution. The mixture was stirred for 30 min at ambient temperature and concentrated. The crude product was purified by reverse-phase HPLC and lyophilized to give the desired product as its trifluoroacetic acid salt. ES/MS *m/z* 532 (MH^+).

Example 459: 6-ethynyl-N-(3-(1-methyl-1H-pyrazol-4-yl)-5-(2-(pyrrolidin-1-yl)ethoxy)phenyl)quinazolin-2-amine

The subject compound was prepared according to the general Scheme, below:



Step 1: 3-amino-5-(1-methyl-1H-pyrazol-4-yl)phenol

To the starting crude material 3-(1-methyl-1H-pyrazol-4-yl)-5-nitrophenol (7.04g, 32 mmol) was added 10% Pd on Carbon (2.1g, 30% by wt.) under argon. Under argon with a syringe carefully add 95 ml methanol. To this reaction mixture was added a hydrogen balloon and was evacuated and refilled 6 times. The reaction was stirred at room temperature

for 22 hours or until done by LC. To the reaction mixture add ethyl acetate and under argon filtered through celite and washed with a 1:1 solution of ethyl acetate and methanol. The filtrate was concentrated under reduced pressure to give 3-amino-5-(1-methyl-1H-pyrazol-4-yl)phenol, as crude material (8.0 grams). ES/MS *m/z* 190(MH^+).

Step 2: 3-(6-bromonaphthalen-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenol

To the reaction mixture of 3-amino-5-(1-methyl-1H-pyrazol-4-yl)phenol (2.6 g, 13.68 mmol) in 20 ml of dioxane was added 6-bromo-2-chloroquinazoline (1.75g, 7.20 mmol) and acetic acid (1.73 ml, 28.8mmol). The reaction solution was stirred at 95-100 °C for 60 hours or until done by LCMS. To the crude reaction mixture add 30ml dioxane, let cool, filter solids off and the concentrate the filtrate (product). The crude residue was purified by silica gel column chromatography and concentrated *in vaccuo* to give 3-(6-bromonaphthalen-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenol, (1.13 grams). ES/MS *m/z* 396/398(MH^+). Additional purification can be done by prep HPLC and lyophilized to make a TFA salt.

Step 3: 3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenol

To the reaction mixture of 3-(6-bromonaphthalen-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenol (1.13 g, 2.85 mmol) in 7 ml of DMF was added $Pd(dppf)_2Cl_2$ (232 mg, 0.28 mmol), CuI (119 mg, 0.622 mmol), ethynyltrimethylsilane (838 mg , 8.55 mmol) and last add N-ethyl-N-isopropylpropan-2-amine (DIPEA) (1.5 ml, 8.55 mmol). This reaction mixture was stirred at 95 °C for 1 hour or until done by LCMS. Concentrate most of the DMF off, add 350ml of ethyl acetate, 75 ml of saturated sodium bicarbonate and briefly stirred. The mixture formed an emulsion that was filtered through celite and flushed with 100 ml ethyl acetate. The organic layer was extracted and washed with water, saturated NaCl, dried with Na_2SO_4, filtered through a 2"x 3" silica gel plug, flushed with ethyl acetate and concentrated *in vaccuo* to give 3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenol, (1.20 grams). ES/MS *m/z* 414(MH^+).

Step 4: N-(3-(1-methyl-1H-pyrazol-4-yl)-5-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-6-((trimethylsilyl)ethynyl)quinazolin-2-amine

To the reaction mixture of triphenyl phosphine (32 mg, 0.12mmol) in 0.5 ml of THF add 2-(pyrrolidin-1-yl)ethanol (17.3 mg, 0.15 mmol), then add DEAD (21 mg, 0.12 mmol) and stir at room temperature for 10 minutes. The above reaction mixture was added to 3-(1-

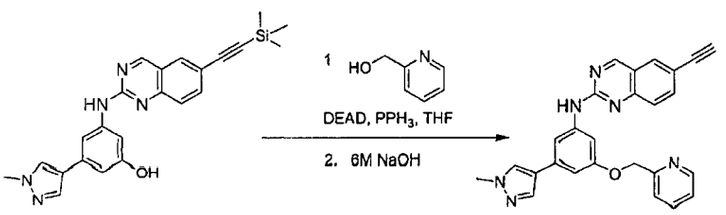
methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenol (24.8 mg, 0.06 mmol) and stirred at room temperature for 20 hours or until done by LCMS. The reaction mixture was concentrated under reduced pressure to give N-(3-(1-methyl-1H-pyrazol-4-yl)-5-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-6-((trimethylsilyl)ethynyl)quinazolin-2-amine as a crude residue used in the next step. ES/MS *m/z* 511(MH^+).

Step 5: 6-ethynyl-N-(3-(1-methyl-1H-pyrazol-4-yl)-5-(2-(pyrrolidin-1-yl)ethoxy)phenyl)quinazolin-2-amine

To the crude reaction mixture of N-(3-(1-methyl-1H-pyrazol-4-yl)-5-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-6-((trimethylsilyl)ethynyl)quinazolin-2-amine (0.06 mmol) in 1ml of DMF was added 6M NaOH (0.06 ml, 0.36mmol) and stirred at room temperature for 10 minutes and checked by LCMS. If the de-protection is incomplete add more 6 M NaOH and recheck in 10 minutes. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give 6-ethynyl-N-(3-(1-methyl-1H-pyrazol-4-yl)-5-(2-(pyrrolidin-1-yl)ethoxy)phenyl)quinazolin-2-amine as TFA salt (4.4 mg) . ES/MS *m/z* 439(MH^+).

Example 536: 6-ethynyl-N-(3-(1-methyl-1H-pyrazol-4-yl)-5-(pyridin-2-ylmethoxy)phenyl)quinazolin-2-amine

The subject compound was prepared according to the general Scheme, below:



Step 1: N-(3-(1-methyl-1H-pyrazol-4-yl)-5-(pyridin-2-ylmethoxy)phenyl)-6-((trimethylsilyl)ethynyl)quinazolin-2-amine

To the reaction mixture of 3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenol (24.8 mg, 0.06 mmol) in 0.4 ml of THF add pyridin-2-ylmethanol (16.5, 0.15 mmol), triphenyl phosphine (32 mg, 0.12mmol) and then DEAD (21 mg, 0.12 mmol) last. The reaction mixture was stirred at room temperature for 20 hours or until done by LCMS. If the reaction is not done add more DEAD (10.5mg,

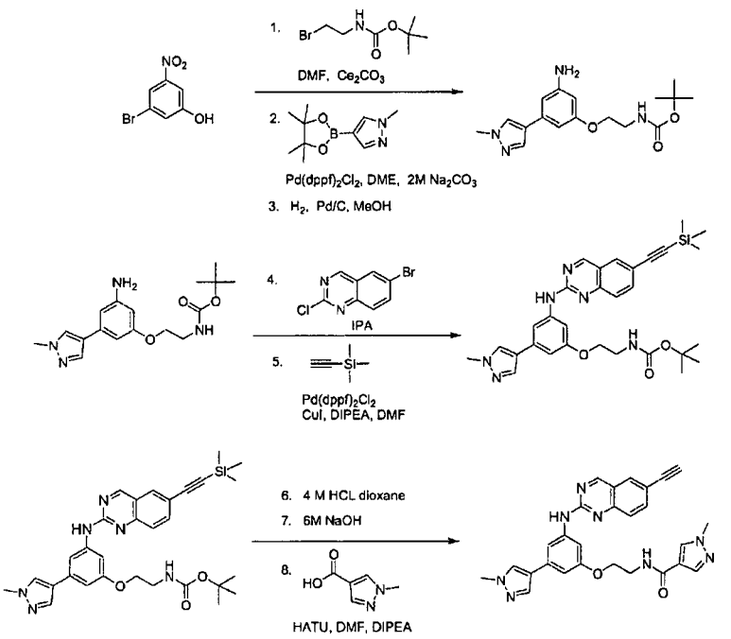
0.06 mol) and stir at room temperature 1 to 2 hours. The reaction mixture was concentrated under reduced pressure to give N-(3-(1-methyl-1H-pyrazol-4-yl)-5-(pyridin-2-ylmethoxy)phenyl)-6-((trimethylsilyl)ethynyl)quinazolin-2-amine as a crude residue used in the next step. ES/MS *m/z* 505(MH^+).

Step 2: 6-ethynyl-N-(3-(1-methyl-1H-pyrazol-4-yl)-5-(pyridin-2-ylmethoxy)phenyl)quinazolin-2-amine

To the crude reaction mixture of N-(3-(1-methyl-1H-pyrazol-4-yl)-5-(pyridin-2-ylmethoxy)phenyl)-6-((trimethylsilyl)ethynyl)quinazolin-2-amine (0.06 mmol) in 1.2 ml of DMF was added 6M NaOH (0.125 ml, 0.75 mmol) and stirred at room temperature for 10 minutes and checked by LCMS. If the de-protection is incomplete add more 6 M NaOH and recheck in 10 minutes. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give 6-ethynyl-N-(3-(1-methyl-1H-pyrazol-4-yl)-5-(pyridin-2-ylmethoxy)phenyl)quinazolin-2-amine as TFA salt (5.6 mg) . ES/MS *m/z* 433(MH^+).

Example 469: N-(2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethyl)-1-methyl-1H-pyrazole-4-carboxamide

The subject compound was prepared according to the general Scheme, below:



Step 1: tert-butyl 2-(3-bromo-5-nitrophenoxy)ethylcarbamate

To the reaction mixture of 3-bromo-5-nitrophenol (4.0g, 18.35 mmol) in 40 ml of DMF add cesium carbonate (12.0 g, 367. mmol) and stir at room temperature for 30 minutes. To the above reaction mixture was added tert-butyl 2-bromoethylcarbamate (6.16 g, 27.5 mmol), cap with argon balloon and stirred at 40°C for 18 hours or until done by LCMS. Concentrate about half of the DMF off, add 500 ml of ethyl acetate, wash organic layer 1M NaOH (3x), water, saturated NaCl, dried with Na_2SO_4, filtered and concentrated *in vaccuo* to give crude, tert-butyl 2-(3-bromo-5-nitrophenoxy)ethylcarbamate (6.6 grams) used in the next reaction.

Step 2: tert-butyl 2-(3-(1-methyl-1H-pyrazol-4-yl)-5-nitrophenoxy)ethylcarbamate

To the reaction mixture of above crude tert-butyl 2-(3-bromo-5-nitrophenoxy)ethylcarbamate (6.6 g, 18.28 mmol) in 125 ml of DME was added $Pd(dppf)_2Cl_2$ (1.2 g, 1.46 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-

1H-pyrazole (5.7 g, 27.4 mmol) and last add 2M Na_2CO_3 (41.3 ml, 82.5 mmol). This reaction mixture was stirred at 100 °C for 2 hours or until done by LCMS. Concentrate most of the DME off, add 600ml of ethyl acetate, 100 ml of water and briefly stirred. The mixture formed an emulsion that was filtered. The organic layer was extracted and washed with 1M NaOH (2x), water, saturated NaCl, dried Na_2SO_4, filtered and concentrated *in vaccuo* to give tert-butyl 2-(3-(1-methyl-1H-pyrazol-4-yl)-5-nitrophenoxy)ethylcarbamate, (6.2 grams). ES/MS *m/z* 363(MH^+).

Step 3: tert-butyl 2-(3-amino-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethylcarbamate

Analogous to Example 459, step1 but using tert-butyl 2-(3-(1-methyl-1H-pyrazol-4-yl)-5-nitrophenoxy)ethylcarbamate as starting material. ES/MS *m/z* 333(MH^+).

Step 4: tert-butyl 2-(3-(6-bromoquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethylcarbamate

To the reaction mixture of tert-butyl 2-(3-amino-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethylcarbamate (5.53 g, 16.66 mmol) in 50 ml of IPA in a glass bomb was added 6-bromo-2-chloroquinazoline (3.9 g, 16.66 mmol) and caped. The reaction solution was stirred at 95-100 °C for 22 hours or until done by LCMS. To the crude reaction mixture add 20 ml of IPA, let cool, collect solids (product) wash 2 x IPA. The crude solid was dried *in vaccuo* to give, tert-butyl 2-(3-(6-bromoquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethylcarbamate, (6.88 grams). ES/MS *m/z* 539/541(MH^+). Additional purification can be done by prep HPLC and lyophilized to make TFA salt.

Step 5: tert-butyl 2-(3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenoxy)ethylcarbamate

To the reaction mixture of tert-butyl 2-(3-(6-bromoquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethylcarbamate (6.0 g, 11.13 mmol) in 38 ml of DMF was added $Pd(dppf)_2Cl_2$ (1.09g, 1.36 mmol), CuI (529 mg, 2.78 mmol), ethynyltrimethylsilane (3.3 g , 33.4 mmol) and last add DIPEA (5.81 ml, 33.4 mmol). This reaction mixture was stirred at 95 °C for 1 hour or until done by LCMS. The BOC group may come partially off , if so add di-tert-butyl dicarbonate (1.5 g, 6.88 mmol) and stir at room temperature 30 minutes, re-check LCMS, add more if needed. Concentrate most of the DMF off, add 750ml of ethyl acetate, 200 ml of saturated sodium bicarbonate and shake. The mixture formed an emulsion that was filtered, as necessary. The organic layer was extracted and washed with

water (2x), saturated NaCl, dried Na_2SO_4, filtered through a 3.5"x 3" silica gel plug, flushed with ethyl acetate and concentrated *in vaccuo* to give, tert-butyl 2-(3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenoxy)ethylcarbamate (5.45 grams). ES/MS *m/z* 557(MH^+).

Step 6: N-(3-(2-aminoethoxy)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-6-((trimethylsilyl)ethynyl)quinazolin-2-amine

To the reaction mixture of tert-butyl 2-(3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenoxy)ethylcarbamate (1.3 g, 2.3 mmol) add excess 4 M HCl in Dioxane (20 ml, 80 mmol). This reaction mixture was stirred at room temperature for 1 hour or until done by LCMS and concentrated *in vaccuo* to give crude, N-(3-(2-aminoethoxy)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-6-((trimethylsilyl)ethynyl)quinazolin-2-amine, (1.49 grams). ES/MS *m/z* 457(MH^+).

Step 7: N-(3-(2-aminoethoxy)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-6-ethynylquinazolin-2-amine

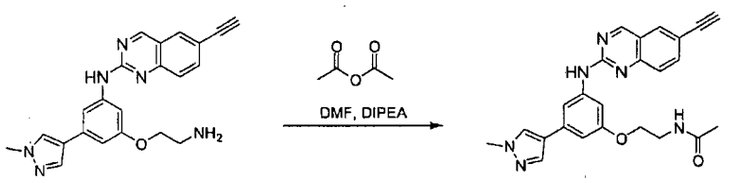
To the above crude reaction mixture of, N-(3-(2-aminoethoxy)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-6-((trimethylsilyl)ethynyl)quinazolin-2-amine (2.33 mmol) in 20 ml of THF and 12 ml of MeOH add 6M NaOH (1.16 ml, 6.99 mmol) stir at room temperature for 15 minutes or until done by LCMS add more 6 M NaOH if necessary. The reaction mixture was concentrated *in vaccuo* until dry to give crude, N-(3-(2-aminoethoxy)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-6-ethynylquinazolin-2-amine, (1.72 grams). ES/MS *m/z* 385(MH^+).

Step 8: N-(2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethyl)-1-methyl-1H-pyrazole-4-carboxamide

To the reaction mixture of 1-methyl-1H-pyrazole-4-carboxylic acid (11 mg, 0.0875 mmol) in 0.65 ml of NMP add HATU (40 mg, 0.105 mmol), DIPEA (0.031 ml, 0.175 mmol) and stir at room temperature for about 3 minutes. To the above reaction mixture add N-(3-(2-aminoethoxy)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-6-ethynylquinazolin-2-amine (22.4 mg, 0.058 mmol) and stir at room temperature for 2 hours or until done by LCMS. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give N-(2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethyl)-1-methyl-1H-pyrazole-4-carboxamide as TFA salt (2.9 mg). ES/MS *m/z* 493(MH^+).

Example 400: N-(2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethyl)acetamide

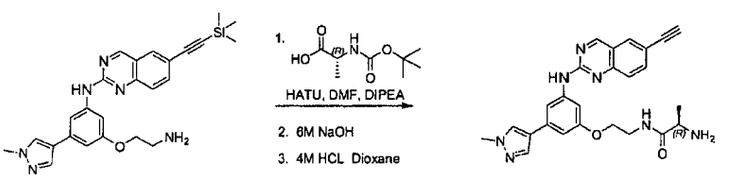
The subject compound was prepared according to the general Scheme below:



To the reaction mixture of N-(3-(2-aminoethoxy)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-6-ethynylquinazolin-2-amine (21 mg, 0.055 mmol) in 0.65 ml of DMF add DIPEA (0.035 ml, 0.195mmol), and acetic anhydride (11.3 mg , 0.111 mmol). The reaction mixtue was stirred at room temperature for about 90 minutes or until done by LCMS. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give, N-(2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethyl)acetamide as TFA salt (4.3 mg). ES/MS *m/z* 427(MH^+).

Example 491: (R)-2-amino-N-(2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethyl)propanamide

The subject compound was prepared according to the general Scheme below:



Step 1: (R)-tert-butyl 1-(2-(3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenoxy)ethylamino)-1-oxopropan-2-ylcarbamate

To the reaction mixture of (R)-2-(tert-butoxycarbonylamino)propanoic acid (25.5 mg, 0.135 mmol) in 0.15 ml of DMF add HATU (55 mg, 0.144 mmol), DIPEA (0.028 ml, 0.16

mmol) and stir at room temperature for about 10 minutes. To the above reaction mixture add a solution of N-(3-(2-aminoethoxy)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-6-((trimethylsilyl)ethynyl)quinazolin-2-amine (41 mg, 0.09 mmol) in 0.5 ml DMF with DIPEA (0.028 ml, 0.16 mmol) and stir at room temperature for 18 hours or until done by LCMS. The crude reaction solution with the product (R)-tert-butyl 1-(2-(3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenoxy)ethylamino)-1-oxopropan-2-ylcarbamate, was used in the next step without purification. ES/MS *m/z* 628(MH^+).

Step 2: (R)-tert-butyl 1-(2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethylamino)-1-oxopropan-2-ylcarbamate

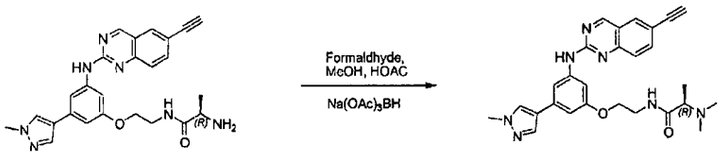
To the above crude material (R)-tert-butyl 1-(2-(3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenoxy)ethylamino)-1-oxopropan-2-ylcarbamate (0.09 mmol) add 6 M NaOH (0.120 ml, 0.72 mmol) and stir at room temperature for 10 minutes or until done by LCMS. If the reaction is not complete add more 6M NaOH as needed. The crude reaction mixture with product, (R)-tert-butyl 1-(2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethylamino)-1-oxopropan-2-ylcarbamate was use in the next step without purification. ES/MS *m/z* 556(MH^+).

Step 3: (R)-2-amino-N-(2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethyl)propanamide

To the above crude material (R)-tert-butyl 1-(2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethylamino)-1-oxopropan-2-ylcarbamate (0.09 mmol) add 4 M HCl in dioxane (3 ml, 12 mmol) and stir at room temperature for 1 hour. The reaction mixture was concentrated, 1 ml DMF added, filtered, purified on prep HPLC and lyophilized to give (R)-2-amino-N-(2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethyl)propanamide, as TFA salt (14.1 mg). ES/MS *m/z* 456(MH^+).

Example 495: (R)-2-(dimethylamino)-N-(2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethyl)propanamide

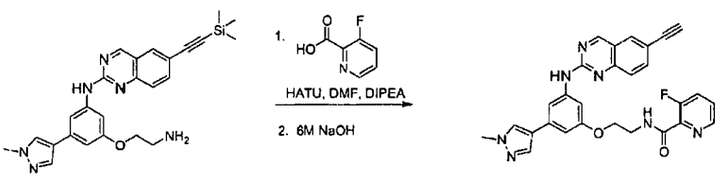
The subject compound was prepared according to the general Scheme, below:



To the reaction mixture of (R)-2-amino-N-(2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethyl)propanamide (12 mg, 0.026 mmol) in 1.2 ml of methanol add acetic acid (0.08 ml , 1.3 mmol) and 37 % formaldehyde solution in water (0.034 ml, 0.39 mmol). The reaction mixture was stirred at room temperature for about 20 minutes. To this reaction solution was added sodium triacetoxy borohydride (44 mg, 0.208 mmol) and stirred at room temperature 1-2 hours or until done by LCMS. The crude reaction mixture was concentrated, 1 ml of DMF added, filtered, purified on prep HPLC and lyophilized to give, (R)-2-(dimethylamino)-N-(2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethyl)propanamide as TFA salt (1.1 mg). ES/MS *m/z* 484(MH^+).

Example 523: N-(2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethyl)-3-fluoropicolinamide

The subject compound was prepared according to the general Scheme below:



Step 1: 3-fluoro-N-(2-(3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenoxy)ethyl)picolinamide

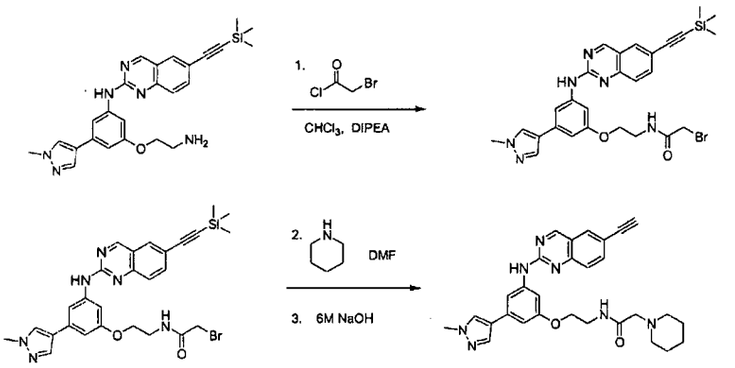
Analogous to Example 114, step1 but using 3-fluoropicolinic acid as starting material. ES/MS *m/z* 457(MH^+).

Step 2: N-(2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethyl)-3-fluoropicolinamide

To the above crude product from step 1 (0.048 mmol) add 6 M NaOH (0.100 ml, 0.60 mmol) and stir at room temperature for 10 minutes or until done by LCMS. If the reaction is not complete add more 6M NaOH as needed. The crude reaction mixture was purified by the addition of DMF about 0.7 ml, filtered, purified on prep HPLC and lyophilized to give, N-(2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethyl)-3-fluoropicolinamide as TFA salt (6.3 mg). ES/MS *m/z* 508(MH^+).

Example 506: N-(2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethyl)-2-(piperidin-1-yl)acetamide

The subject compound was prepared according to the general Scheme below:



Step 1: 2-bromo-N-(2-(3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenoxy)ethyl)acetamide

To the reaction mixture of N-(3-(2-aminoethoxy)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-6-((trimethylsilyl)ethynyl)quinazolin-2-amine (295 mg, 0.646 mmol) in 9ml of chloroform was added DIPEA (0.394 ml, 2.26 mmol) and cooled to (–5 °C) with stirring. To the above reaction mixture at (–5 °C) add dropwise a solution of 2-bromoacetyl chloride (122.5 mg, 0.775 mmol) in 2 ml of chloroform . This reaction mixture was stirred at (–5 °C) for 20 minutes then allowed to warm to room temperature for 70 minutes or until done by LCMS The chloroform was concentrated off, 300 ml of ethyl acetate was added, washed with saturated $NaHCO_3$, water, brine, dried with Na_2SO_4, filtered and concentrated to residue.

The crude residue was purified by silica gel column chromatography and concentrated *in vaccuo* to give 2-bromo-N-(2-(3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenoxy)ethyl)acetamide, (155 mg). ES/MS *m/z* 577/579(MH^+).

Step 2: N-(2-(3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenoxy)ethyl)-2-(piperidin-1-yl)acetamide

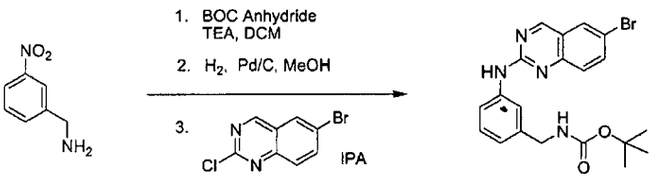
To the reaction mixture of 2-bromo-N-(2-(3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenoxy)ethyl)acetamide (10.3 mg, 0.0178 mmol) in 0.4ml of DMF was added piperidine (6 mg, 0.0712 mmol) and stirred at room temperature for 4.5 hours or until done by LCMS. The crude reaction mixture with product, N-(2-(3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenoxy)ethyl)-2-(piperidin-1-yl)acetamide was use in the next step without purification. ES/MS *m/z* 582(MH^+).

Step 3: N-(2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethyl)-2-(piperidin-1-yl)acetamide

To the above crude material, N-(2-(3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenoxy)ethyl)-2-(piperidin-1-yl)acetamide (0.0178 mmol) add 6 M NaOH (0.03 ml, 0.18 mmol) and stir at room temperature for 10 minutes or until done by LCMS. If the reaction is not complete add more 6M NaOH as needed. The crude reaction mixture was purified by the addition of 0.5ml of DMF, filtered, purified on prep HPLC and lyophilized to give, N-(2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethyl)-2-(piperidin-1-yl)acetamide as TFA salt (6.9 mg). ES/MS *m/z* 510(MH^+).

Example 379: tert-butyl 3-(6-bromoquinazolin-2-ylamino)benzylcarbamate

The subject compound was prepared according to the general Scheme below:



Step 1: tert-butyl 3-nitrobenzylcarbamate

To the reaction mixture of (3-nitrophenyl)methanamine HCl (2.00g, 10.6 mmol) in 15 ml of DCM was added TEA (3.7 ml, 26.5 mmol) and di-tert-butyl dicarbonate (2.78 g, 12.72 mmol) . The reaction was stirred at room temperature for 90 minutes or until done by LC. Concentrate most of the DCM of add 200 ml ethyl acetate and washed with sat. $NaHCO_3$ (2x), water (2x), brine, dried with Na_2SO_4, filtered and concentrated *in vaccuo* to give, tert-butyl 3-nitrobenzylcarbamate as crude material used in next step. (2.96 grams). ES/MS *m/z* 253(MH^+).

Step 2: tert-butyl 3-aminobenzylcarbamate

To the starting crude material tert-butyl 3-nitrobenzylcarbamate (2.96 g crude,10.6 mmol) was added 10% Pd on Carbon (444 mg, 15% by wt.) under argon. Under argon with a syringe carefully add 19 ml methanol. To this reaction mixture was added a hydrogen balloon and was evacuated and refilled 5 times. The reaction was stirred at room temperature for 18 hours or until done by LC. To the reaction mixture add ethyl acetate and under argon filtered through celite and washed with a 1:1 solution of ethyl acetate and methanol. The filtrate was concentrated to residue. To the residue add 150 ml ethyl acetate and wash with sat. $NaHCO_3$ (2x), water (2x), brine, dried with Na_2SO_4, filtered and concentrated *in vaccuo* to give, tert-butyl 3-aminobenzylcarbamate as crude material used in next step. (2.45 grams). ES/MS *m/z* 223(MH^+).

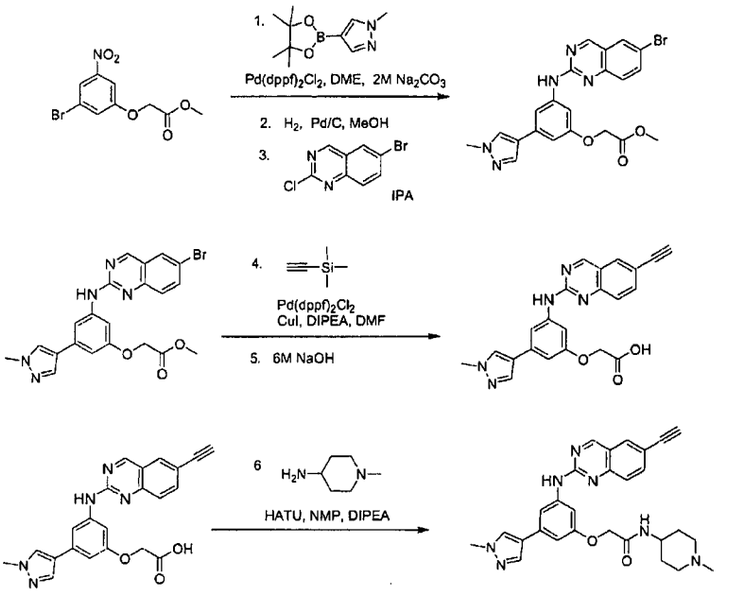
Step 3: tert-butyl 3-(6-bromoquinazolin-2-ylamino)benzylcarbamate

To the reaction mixture of tert-butyl 3-aminobenzylcarbamate (840 mg, 3.76 mmol) in 6 ml of IPA in a glass bomb was added 6-bromo-2-chloroquinazoline (750 mg, 3.08 mmol) and caped. The reaction solution was stirred at 95 °C for 20 hours or until done by LCMS. To the crude reaction mixture add 6 ml of IPA, filter solids off and the concentrate the filtrate (product). The crude material was purified by silica gel column chromatography and concentrated *in vaccuo* to give, tert-butyl 3-(6-bromoquinazolin-2-ylamino)benzylcarbamate

(860 mg). ES/MS *m/z* 429/431(MH^+) Additional purification can be done by prep HPLC, lyophilized and converted to an TFA ammonium salt.

Example 340: 2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)-N-(1-methylpiperidin-4-yl)acetamide

The subject compound was prepared according to the general Scheme below:



Step 1: methyl 2-(3-(1-methyl-1H-pyrazol-4-yl)-5-nitrophenoxy)acetate

To the reaction mixture of methyl 2-(3-bromo-5-nitrophenoxy)acetate (1.65 g, 5.69 mmol) in 35 ml of DME was added $Pd(dppf)_2Cl_2$ (465 mg, 0.569 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.4 g, 11.4 mmol) and last add 2M Na_2CO_3 (11.4 ml, 22.8 mmol). This reaction mixture was stirred at 85°C for 90 minutes or until done by LCMS. Concentrate about half of the DME off, add 350ml of ethyl acetate and 50 ml of water. The organic layer was extracted and washed with saturated Na_2CO_3, water (2x), saturated NaCl, dried Na_2SO_4, filtered and concentrated to residue. The crude material was purified by silica gel column chromatography and concentrated *in vaccuo* to

give, methyl 2-(3-(1-methyl-1H-pyrazol-4-yl)-5-nitrophenoxy)acetate, (480 mg). ES/MS *m/z* 292(MH^+).

Step 2: methyl 2-(3-amino-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)acetate

Analogous to Example 459, step1 but using, methyl 2-(3-(1-methyl-1H-pyrazol-4-yl)-5-nitrophenoxy)acetate as starting material. ES/MS *m/z* 262(MH^+).

Step 3: methyl 2-(3-(6-bromoquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)acetate

Analogous to Example 112, step 4 but using, methyl 2-(3-amino-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)acetate as starting material. ES/MS *m/z* 468/470(MH^+).

Step 4: methyl 2-(3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenoxy)acetate

Analogous to Example 459, step 3 but using, methyl 2-(3-(6-bromoquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)acetate as starting material. ES/MS *m/z* 486(MH^+).

Step 5: 2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)acetic acid

To the reaction mixture of, methyl 2-(3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenoxy)acetate (740 mg, 1.52 mmol) in 6 ml of THF and 3 ml of MeOH add 6M NaOH (0.75 ml, 4.52 mmol) stir at room temperature for 1 hour or until done by LCMS add more 6 M NaOH if necessary. The reaction mixture was concentrated *in vaccuo* until dry to give crude residue. To this residue add 6M HCl aq (0.91 ml, 5.48 mmol) stir briefly and concentrated *in vaccuo* until dry to give, 2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)acetic acid , as crude solid used in next step (840 mg). ES/MS *m/z* 400(MH^+).

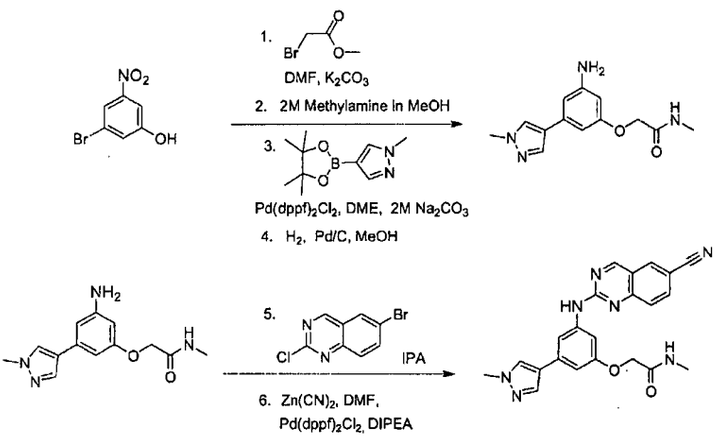
Step 6: 2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)-N-(1-methylpiperidin-4-yl)acetamide

To the reaction mixture of, 2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)acetic acid (24 mg, 0.060 mmol) in 0.5 ml of NMP add HATU (39 mg, 0.102 mmol), DIPEA (0.023 ml, 0.132 mmol) and stir at room temperature for about 3

minutes. To the above reaction mixture add 1-methylpipcridin-4-aminc (27 mg, 0.24 mmol) and stir at room temperature for 4 hours or until done by LCMS. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give, 2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)-N-(1-methylpiperidin-4-yl)acetamide as TFA salt (7.6 mg). ES/MS *m/z* 496(MH^+).

Example 356: 2-(3-(6-cyanoquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)-N-methylacetamide

The subject compound was prepared according to the general Scheme below:



Step 1: methyl 2-(3-bromo-5-nitrophenoxy)acetate

To the reaction mixture of 3-bromo-5-nitrophenol (7.0 g, 32.1 mmol) in 30 ml of DMF add K_2CO_3 (9.8 g, 70.6 mmol) and stir for 3-5 minutes. To the reaction mixture add methyl 2-bromoacetate (5.4 g, 35.3 mmol) and stir at room temperature 18 hours or until done by LC. To the crude reaction add 450 ml of ethyl acetate and wash with saturated Na_2CO_3, water (3x), saturated NaCl, dried Na_2SO_4, filtered and concentrated *in vaccuo* to give crude, methyl 2-(3-bromo-5-nitrophenoxy)acetate, (9.0 g).

Step 2: 2-(3-bromo-5-nitrophenoxy)-N-methylacetamide

To the crude product from step1, methyl 2-(3-bromo-5-nitrophenoxy)acetate (1.75 g, 6.0 mmol) add 2M methylamine in methanol (18 ml, 36 mmol) and stir at room temperature

24 hours or until done by LCMS. The crude reaction mixture was concentrated *in vaccuo* to give crude, 2-(3-bromo-5-nitrophenoxy)-N-methylacetamide, (1.74 g). ES/MS *m/z* *289/291*(MH^+).

Step 3: N-methyl-2-(3-(1-methyl-1H-pyrazol-4-yl)-5-nitrophenoxy)acetamide

To the reaction mixture of 2-(3-bromo-5-nitrophenoxy)-N-methylacetamide (800 mg, 2.77 mmol) in 17 ml of DME was added $Pd(dppf)_2Cl_2$ (226 mg, 0.277 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.04 g, 5.0 mmol) and last add 2M Na_2CO_3 (5.5 ml, 11 mmol). This reaction mixture was stirred at 85-90°C for 18 hours or until done by LCMS. Concentrate most of the DME off, add about 200 ml of ethyl acetate and 50 ml of water and stir. The solids (product) were collected by filtration, washed with water (1x) and dried under vaccum to give crude, N-methyl-2-(3-(1-methyl-1H-pyrazol-4-yl)-5-nitrophenoxy)acetamide, (660 mg). ES/MS *m/z* 291(MH^+).

Step 4: 2-(3-amino-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)-N-methylacetamide

To the starting crude material, N-methyl-2-(3-(1-methyl-1H-pyrazol-4-yl)-5-nitrophenoxy)acetamide (660 mg, 2.27 mmol) was added 10% Pd on Carbon (132 mg, 20% by wt.) under argon. Under argon with a syringe carefully add 5 ml methanol. To this reaction mixture was added a hydrogen balloon and was evacuated and refilled 5 times. The reaction was stirred at room temperature for 22 hours or until done by LC. To the reaction mixture add ethyl acetate and under argon filtered through celite and washed with a 1:1 solution of ethyl acetate and methanol. The filtrate was concentrated *in vaccuo* to give, 2-(3-amino-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)-N-methylacetamide as crude material used in next step. (565mg). ES/MS *m/z* 261(MH^+).

Step5: 2-(3-(6-bromoquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)-N-methylacetamide

Analogous to Example 112, step 4 but using, 2-(3-amino-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)-N-methylacetamide as starting material. ES/MS *m/z* 467/469(MH^+).

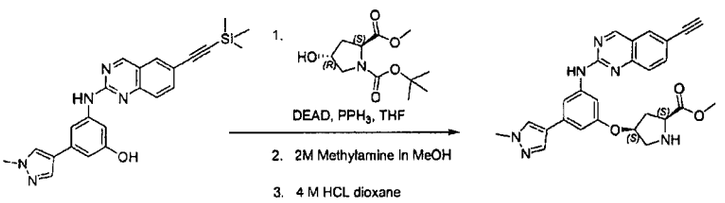
Step 6: 2-(3-(6-cyanoquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)-N-methylacetamide

To the reaction mixture of 2-(3-(6-bromoquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)-N-methylacetamide (30 mg, 0.064 mmol) in 0.6ml of DMF was

added $Pd(dppf)_2Cl_2$ (10.5 mg, 0.0128 mmol), $Zn(CN)_2$ (30 mg, 0.256mmol) and DIPEA (34 ul, 0.192 mmol). This reaction mixture was microwaved at 170°C for 800 seconds then again at 210°C for 800 seconds. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give, 2-(3-(6-cyanoquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)-N-methylacetamide as TFA salt (8.2 mg). ES/MS *m/z* 414(MH^+).

Example 543: ***(2S,4S)-methyl 4-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)pyrrolidine-2-carboxylate***

The subject compound was prepared according to the general Scheme below:



Step 1: (2S,4S)-1-tert-butyl 2-methyl 4-(3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenoxy)pyrrolidine-1,2-dicarboxylate

Analogous to Example 459, step 4 but using, (2S,4R)-1-tert-butyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate as the starting material (alcohol). ES/MS *m/z* 641(MH^+).

Step 2: (2S,4S)-1-tert-butyl 2-methyl 4-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)pyrrolidine-1,2-dicarboxylate

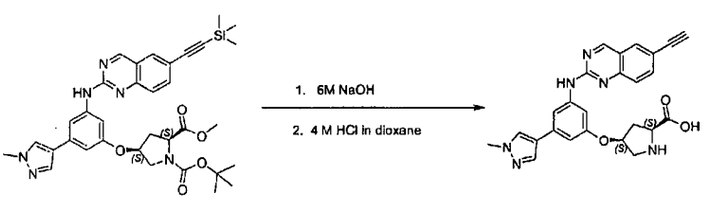
To the reaction mixture of (2S,4S)-1-tert-butyl 2-methyl 4-(3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenoxy)pyrrolidine-1,2-dicarboxylate (38 mg, 0.06 mmol) in 0.375 ml of THF was added 2M methylamine in MeOH (2.0 ml, 4.0 mmol). The reaction mixture was stirred at room temperature for 20 hours or until done by LCMS. The crude reaction mixture was concentrated *in vaccuo* until dry, to give a crude product used in next step, (2S,4S)-1-tert-butyl 2-methyl 4-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)pyrrolidine-1,2-dicarboxylate. ES/MS *m/z* 569(MH^+).

Step 3: (2S,4S)-methyl 4-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)pyrrolidine-2-carboxylate

To the reaction mixture of (2S,4S)-1-tert-butyl 2-methyl 4-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)pyrrolidine-1,2-dicarboxylate (0.06 mmol) was added 4M HCl in Dioxane (3.5 ml, 14.0 mmol). The reaction mixture was stirred at room temperature for 1 hours or until done by LCMS. The crude reaction mixture was concentrate, about 1 ml of DMF was added, filtered, purified on prep HPLC and lyophilized to give, (2S,4S)-methyl 4-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)pyrrolidine-2-carboxylate as TFA salt (3.7 mg). ES/MS *m/z 469*(MH^+).

Example 555: (2S,4S)-4-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)pyrrolidine-2-carboxylic acid

The subject compound was prepared according to the general Scheme below:



Step 1: (2S,4S)-1-(tert-butoxycarbonyl)-4-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)pyrrolidine-2-carboxylic acid

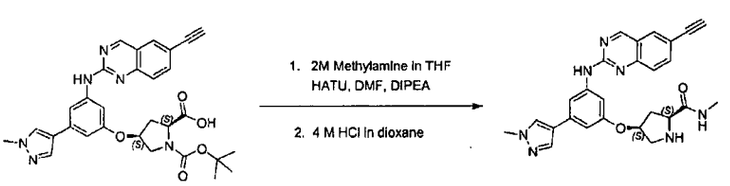
To the reaction mixture of (2S,4S)-1-tert-butyl 2-methyl 4-(3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenoxy)pyrrolidine-1,2-dicarboxylate (115 mg, 0.18 mmol) in 0.75 ml of THF was added 6M NaOH (0.9 ml, 5.4 mmol) and 1 ml of methanol. The reaction mixture was stirred at room temperature for 1 hour or until done by LCMS. The crude reaction mixture was concentrated *in vaccuo* until solid, 2 ml of DMF was added, filtered, purified on prep HPLC and lyophilized to give (2S,4S)-1-(tert-butoxycarbonyl)-4-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)pyrrolidine-2-carboxylic acid as TFA salt (45 mg). ES/MS *m/z* 555(MH^+).

Step 2: (2S,4S)-4-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)pyrrolidine-2-carboxylic acid

To the reaction mixture of (2S,4S)-1-(tert-butoxycarbonyl)-4-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)pyrrolidine-2-carboxylic acid (15 mg, 0.027 mmol) was added 4M HCl in Dioxane (1.5 ml, 6.0 mmol). The reaction mixture was stirred at room temperature for 1 hour or until done by LCMS. The crude reaction mixture was concentrate, about1 ml of DMF was added, filtered, purified on prep HPLC and lyophilized to give (2S,4S)-4-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)pyrrolidine-2-carboxylic acid as TFA salt (3.2 mg). ES/MS *m/z* 455(MH^+).

Example 557: (2S,4S)-4-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)-N-methylpyrrolidine-2-carboxamide

The subject compound was prepared according to the general Scheme below:



Step 1: (2S,4S)-tert-butyl 4-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)-2-(methylcarbamoyl)pyrrolidine-1-carboxylate

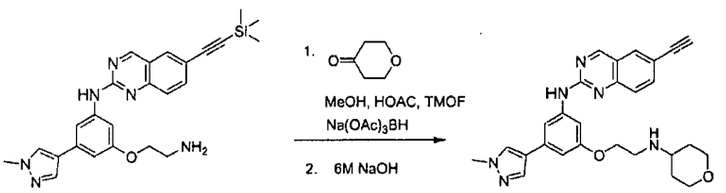
To the reaction mixture of (2S,4S)-1-(tert-butoxycarbonyl)-4-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)pyrrolidine-2-carboxylic acid (15 mg, 0.027 mmol) in 0.5 ml of DMF add HATU (31 mg, 0.081 mmol), DIPEA (0.014 ml, 0.081 mmol) and stir at room temperature for about 3-5 minutes. To the above reaction mixture add 2M methylamine in THF (0.081 ml, 0.162 mmol) and was stirred at room temperature for 20 hours or until done by LCMS. The crude reaction mixture with product, (2S,4S)-tert-butyl 4-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)-2-(methylcarbamoyl)pyrrolidine-1-carboxylate was use in the next step without purification. ES/MS *m/z* 568(MH^+).

Step 2: (2S,4S)-4-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)-N-methylpyrrolidine-2-carboxamide

To the reaction mixture of (2S,4S)-tert-butyl 4-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)-2-(methylcarbamoyl)pyrrolidine-1-carboxylate (0.027 mmol) was added 4M HCl in Dioxane (2.0 ml, 8.0 mmol). The reaction mixture was stirred at room temperature for 1 hours or until done by LCMS. The crude reaction mixture was concentrate, about 1 ml of DMF was added, filtered, purified on prep HPLC and lyophilized to give (2S,4S)-4-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)-N-methylpyrrolidine-2-carboxamide as TFA salt (5.0 mg). ES/MS *m/z* 468(MH^+).

Example 552: 6-ethynyl-N-(3-(1-methyl-1H-pyrazol-4-yl)-5-(2-(tetrahydro-2H-pyran-4-ylamino)ethoxy)phenyl)quinazolin-2-amine

The subject compound was prepared according to the general Scheme below:



Step 1: N-(3-(1-methyl-1H-pyrazol-4-yl)-5-(2-(tetrahydro-2H-pyran-4-ylamino)ethoxy)phenyl)-6-((trimethylsilyl)ethynyl)quinazolin-2-amine

To the reaction mixture of N-(3-(2-aminoethoxy)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-6-((trimethylsilyl)ethynyl)quinazolin-2-amine (41 mg, 0.09 mmol) in 0.75 ml of methanol add acetic acid (0.162 ml, 2.7 mmol), dihydro-2H-pyran-4(3H)-one (90 mg, 0.9 mmol) and trimethylorthoformate (TMOF) (57 mg, 0.54 mmol). The reaction mixture was stirred at room temperature for about 4 hours. To this reaction solution was added sodium triacetoxy borohydride (76 mg, 0.36 mmol) and stirred at room temperature 20 hours. To the crude reaction mixture was added more sodium triacetoxy borohydride (38 mg, 0.18 mmol) and stirred at room temperature for another 26 hours. The crude reaction mixture with product, N-(3-(1-methyl-1H-pyrazol-4-yl)-5-(2-(tetrahydro-2H-pyran-4-

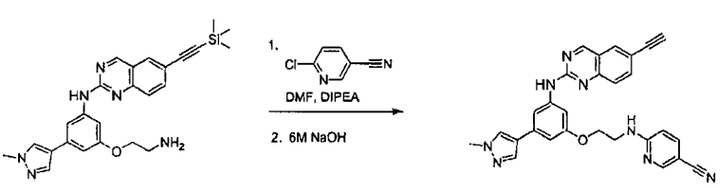
ylamino)ethoxy)phenyl)-6-((trimethylsilyl)ethynyl)quinazolin-2-amine was concentrated to solid and used in the next step without purification. ES/MS *m/z* 541(MH^+).

Step 2: 6-ethynyl-N-(3-(1-methyl-1H-pyrazol-4-yl)-5-(2-(tetrahydro-2H-pyran-4-ylamino)ethoxy)phenyl)quinazolin-2-amine

To the crude reaction mixture of N-(3-(1-methyl-1H-pyrazol-4-yl)-5-(2-(tetrahydro-2H-pyran-4-ylamino)ethoxy)phenyl)-6-((trimethylsilyl)ethynyl)quinazolin-2-amine (0.09 mmol) in 2 ml of methanol was added 6M NaOH (2.0 ml, 12.0 mmol) and stirred at room temperature for 10 minutes and checked by LCMS. If the de-protection is incomplete add more 6 M NaOH and recheck in 10 minutes. To the crude reaction add 100 ml of ethyl acetate and wash with water (2x), saturated NaCl, dried Na_2SO_4, filtered and concentrated to residue. To the crude residue add DMF, filter, purified on prep HPLC and lyophilized to give 6-ethynyl-N-(3-(1-methyl-1H-pyrazol-4-yl)-5-(2-(tetrahydro-2H-pyran-4-ylamino)ethoxy)phenyl)quinazolin-2-amine as TFA salt (2.0 mg). ES/MS *m/z* 469(MH^+).

Example 530: 6-(2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethylamino)nicotinonitrile

The subject compound was prepared according to the general Scheme below:



Step 1: 6-(2-(3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenoxy)ethylamino)nicotinonitrile

To the reaction mixture of N-(3-(2-aminoethoxy)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-6-((trimethylsilyl)ethynyl)quinazolin-2-amine (26.7 mg, 0.0479 mmol) in DMF add 6-chloronicotinonitrile (13.2 mg, 0.096) and DIPEA (0.025 ml, 0.144 mmol). This reaction mixture was stirred at 105°C for 20 hours. The crude reaction mixture with product, 6-(2-(3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenoxy)ethylamino)nicotinonitrile was used in the next step without purification. ES/MS *m/z* 559(MH^+).

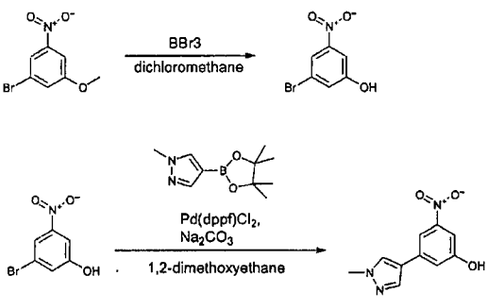
Step 2: 6-(2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethylamino)nicotinonitrile

To the crude reaction mixture of, 6-(2-(3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenoxy)ethylamino)nicotinonitrile (0.0479 mmol) was added 6M NaOH (0.08 ml, 0.48 mmol) and stirred at room temperature for 10 minutes and checked by LCMS. If the de-protection is incomplete add more 6 M NaOH and recheck in 10 minutes. To the crude reaction mixture add DMF, filter, purified on prep HPLC and lyophilized to give, 6-(2-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)ethylamino)nicotinonitrile as TFA salt (1.7 mg). ES/MS *m/z* 487(MH^+).

Example 606: (R)-2-(dimethylamino)-N-(1-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)propan-2-yl)acetamide

3-(1-methyl-1H-pyrazol-4-yl)-5-nitrophenol

The subject compound was prepared according to the general Scheme below:



Step1: Preparation of 3-bromo-5-nitrophenol

To the solution of 1-bromo-3-methoxy-5-nitrobenzene (13.5 g, 58.2 mmole) in 50 ml of dichloromethane was added the solution of 1 M of boron tribromide (163 ml, 163 mmole) in dichloromethane slowly over 10 minutes at 0°c. The reaction mixture was stirred at 0°c for 20 minutes and then at room temperature for 48 hour. The deprotection of the methyl ether went to completion and was monitored by LC/MS. Removal of all solvent in vaccuo, followed by quenching with water and diluted $NaHCO_3$ solution at 0°c, and extraction of

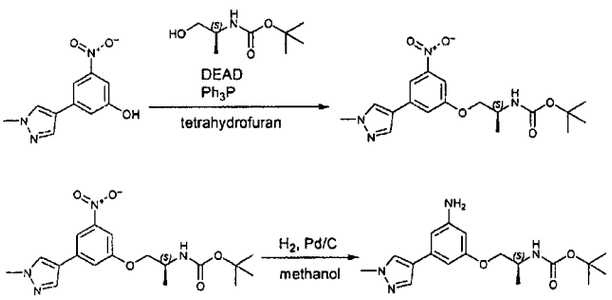
aqueous phase with ethyl acetate and drying of combined organic extracts over Na_2SO_4 and subsequent removal of ethyl acetate *in vaccuo* yielded the desired product that was dried under vacuum to give 12.3 g of 3-bromo-5-nitrophenol as purple solid.

Step 2: Preparation of 3-(1-methyl-1H-pyrazol-4-yl)-5-nitrophenol

To the reaction mixture of 3-bromo-5-nitrophenol (2.2 g, 10 mmole) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.7 g, 13 mmole) in 37.5 ml of 1,2-dimethoxyethane, $Pd(dppf)Cl_2$ (660 mg, 0.8 mmole) and aq. 2M Na_2CO_3 (12.5 ml, 25 mmole) were added. The reaction mixture was stirred at 85°c for 24 hours or until done by LC. The reaction mixture was diluted with 250 ml of acetone and filtered through celite and washed with a 1:1 solution of ethyl acetate and methanol . The combined organic filtrate was evaporated *in vaccuo* to give a brown solid (4g) that was purified by silica gel column plug eluting with ethyl acetate to give 3-(1-methyl-1H-pyrazol-4-yl)-5-nitrophenol as yellow brown powder (1.87 g). ES/MS *m/z* 220.0(MH^+).

(S)-tert-butyl 1-(3-amino-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)propan-2-ylcarbamate

The subject compound was prepared according to the general Scheme below:



Step 1: Preparation of (S)-tert-butyl 1-(3-(1-methyl-1H-pyrazol-4-yl)-5-nitrophenoxy)propan-2-ylcarbamate

To the reaction solution of 3-(1-methyl-1H-pyrazol-4-yl)-5-nitrophenol (700 mg, 3.2 mmole) and triphenyl phosphine (1.26 g, 4.84 mmole) in 26 ml of tetrahydrofuran, (S)-tert-

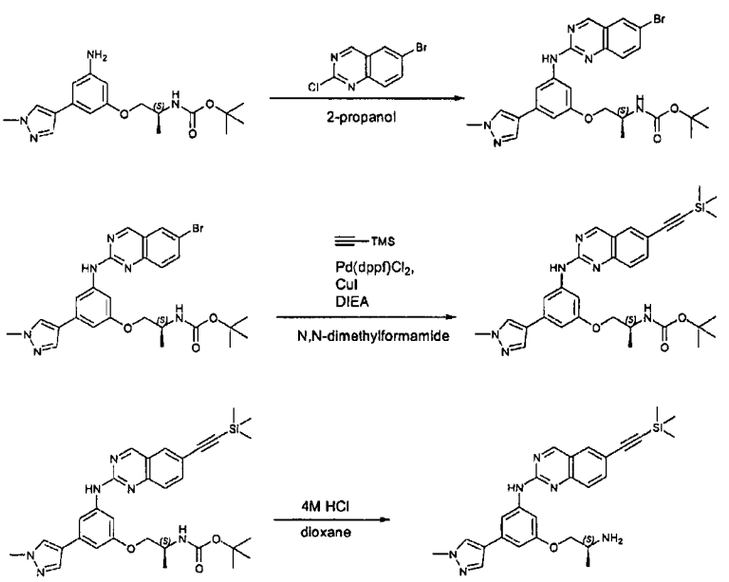
butyl 1-hydroxypropan-2-ylcarbamate (848 mg, 4.84 mmole) and diethyl azodicarboxylate (860 ul, 5.46 mmole) were added. The resulting solution was stirred at 65°c for 20 hours or until done by LCMS. The reaction solution was concentrated under reduced pressure to give dark brown glue (4 g) as a crude product that was purified by column chromatography over silica gel with ethyl acetate: hexane (60: 40) to give 1.08 g of (S)-tert-butyl 1-(3-(1-methyl-1H-pyrazol-4-yl)-5-nitrophenoxy)propan-2-ylcarbamate as yellow solid. ES/MS *m/z* 377.2 (MH^+).

Step 2: Preparation of (S)-tert-butyl 1-(3-amino-5-(1-methyl-1H-pyrazol-4-yl)phenoxy) propan-2-ylcarbamate

To the starting crude material (S)-tert-butyl 1-(3-(1-methyl-1H-pyrazol-4-yl)-5-nitrophenoxy)propan-2-ylcarbamate (1.09 g, 2.89 mmole) was added 10% Pd on Carbon (1.02 g, 0.96 mmole, 30% by wt.) under argon. Under argon add 11 ml of methanol with a syringe carefully. To this reaction mixture was added a balloon of hydrogen and was evacuated and refilled 6 times. The reaction mixture was stirred at room temperature for 22 hours or until done by LC. To the reaction mixture add ethyl acetate and under argon filtered through celite and washed with a 1:1 solution of ethyl acetate and methanol. The filtrate was concentrated under reduced pressure to give (S)-tert-butyl 1-(3-amino-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)propan-2-ylcarbamate as powder (945 mg). ES/MS *m/z* 347.1 (MH^+).

(S)-N-(3-(2-aminopropoxy)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-6-((trimethylsilyl)ethynyl)quinazolin-2-amine

The subject compound was prepared according to the general Scheme below



Step 1: Preparation of (S)-tert-butyl 1-(3-(6-bromoquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)propan-2-ylcarbamate

To the reaction mixture give (S)-tert-butyl 1-(3-amino-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)propan-2-ylcarbamate (945 mg, 2.73 mmole) in 25 ml of isopropyl alcohol in a glass bomb was added 6-bromo-2-chloroquinazoline (665 mg, 2.73 mmole) and sealed. The reaction solution was stirred at 95°c for 22 hours or until done by LCMS. The reaction solution was concentrated under reduced pressure to give a reddish brown oil that was then diluted with 160 ml of ethyl acetate. The organic phase was washed with saturated $NaHCO_3$ solution (2x60 ml), water (30 ml) and brine (50 ml), then dried over $MgSO_4$ and evaporated in vacuo to give a reddish brown solid. The crude solid was purified by column chromatography over silica gel with ethyl acetate: hexane (70: 30) to give (S)-tert-butyl 1-(3-(6-bromoquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)propan-2-ylcarbamate (131 mg) as yellow solid. ES/MS *m/z* 553.1/555.1 (MH^+).

Step 2: Preparation of (S)-tert-butyl 1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenoxy)propan-2-ylcarbamate

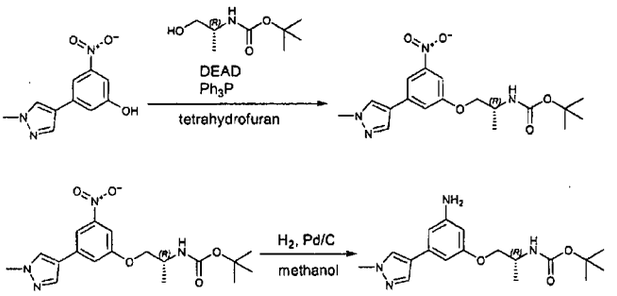
To the reaction mixture of (S)-tert-butyl 1-(3-(6-bromoquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)propan-2-ylcarbamate (131 mg, 237 umole), $Pd(dppf)Cl_2$ (20 mg, 24 umole), CuI (10mg, 47.4 umole) and DIPEA (200 ul, 1.15 mmole) in 2 ml of N,N-dimethylformamide, trimethylsilylacetylene (99 ul, 710 umole) was added. The reaction mixture was stirred at 60°c for 2 hour. The crude reaction mixture was partitioned between 80 ml of ethyl acetate and 20 ml of saturated $NaHCO_3$ solution. The organic layer was washed with water (30 ml) and brine (50 ml), then dried over Na_2SO_4 and evaporated in vacuo to give a brown solid that was purified by column chromatography over silica gel with ethyl acetate : hexane (50 : 50) to give (S)-tert-butyl 1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenoxy)propan-2-ylcarbamate (73 mg) as yellow solid . ES/MS *m/z* 571.3 (MH^+).

Step 3: Preparation of (S)-N-(3-(2-aminopropoxy)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-6-((trimethylsilyl)ethynyl)quinazolin-2-amine

To the reaction mixture (S)-tert-butyl 1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenoxy)propan-2-ylcarbamate (73 mg, 0.13 mmole) add excess 4 M HCl in dioxane (4 ml, 16 mmole). This reaction mixture was stirred at room temperature for 1 hour or until done by LCMS and concentrated *in vaccuo* to give a yellow solid that was dissolved with 60 ml of ethyl acetate. The organic phase was washed with 1N NaOH solution (10 ml), water (10 ml) and brine solution (20 ml), then dried over Na_2SO_4 and evaporated in vacuo to give (S)-N-(3-(2-aminopropoxy)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-6-((trimethylsilyl)ethynyl)quinazolin-2-amine as a yellow brown powder (60 mg). ES/MS *m/z* 471.2 (MH^+).

(R)-tert-butyl 1-(3-amino-5-(1-methyl-1H-pyrazol-4-yl)phenoxy) propan-2-ylcarbamate

The subject compound was prepared according to the general Scheme below:



Step 1: Preparation of (R)-tert-butyl 1-(3-(1-methyl-1H-pyrazol-4-yl)-5-nitrophenoxy)propan-2-ylcarbamate

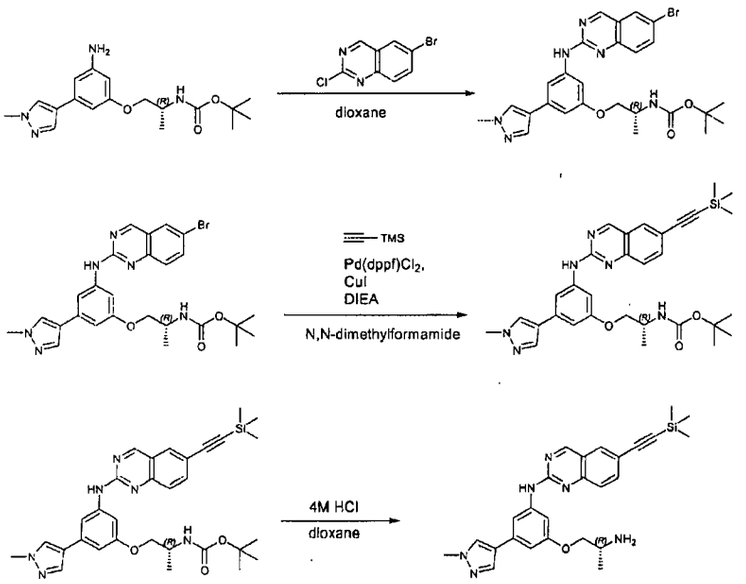
To the reaction solution of 3-(1-methyl-1H-pyrazol-4-yl)-5-nitrophenol (700 mg, 3.2 mmole) and triphenyl phosphine (1.26 g, 4.84 mmole) in 26 ml of tetrahydrofuran, (R)-tert-butyl 1-hydroxypropan-2-ylcarbamate (848 mg, 4.84 mmole) and diethyl azodicarboxylate (790 ul, 5 mmole) were added. The resulting solution was stirred at 65°c for 20 hours or until done by LCMS. The reaction solution was concentrated under reduced pressure to give brown glue (4 g) as a crude product that was purified by column chromatography over silica gel with ethyl acetate: hexane (60: 40) to give 1.03 g of (R)-tert-butyl 1-(3-(1-methyl-1H-pyrazol-4-yl)-5-nitrophenoxy)propan-2-ylcarbamate as yellow glue. ES/MS *m/z* 377.1 (MH^+).

Step 2: Preparation of (R)-tert-butyl 1-(3-amino-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)propan-2-ylcarbamate

To the starting crude material (R)-tert-butyl 1-(3-(1-methyl-1H-pyrazol-4-yl)-5-nitrophenoxy)propan-2-ylcarbamate (1.03 g, 2.73 mmole) was added 10% Pd on Carbon (968 mg, 0.91 mmole, 30% by wt.) under argon. Under argon add 11 ml of methanol with a syringe carefully. To this reaction mixture was added a balloon of hydrogen and was evacuated and refilled 6 times. The reaction mixture was stirred at room temperature for 22 hours or until done by LC. To the reaction mixture add ethyl acetate and under argon filtered through celite and washed with a 1:1 solution of ethyl acetate and methanol. The filtrate was concentrated under reduced pressure to give (R)-tert-butyl 1-(3-amino-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)propan-2-ylcarbamate as powder (905 mg). ES/MS *m/z* 347.2 (MH^+).

(R)-N-(3-(2-aminopropoxy)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-6-((trimethylsilyl)ethynyl)quinazolin-2-amine

The subject compound was prepared according to the general Scheme below



Step 1: Preparation of (R)-tert-butyl 1-(3-(6-bromoquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)propan-2-ylcarbamate

To the reaction mixture of (R)-tert-butyl 1-(3-amino-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)propan-2-ylcarbamate (905 mg, 2.35 mmole) and 6-bromo-2-chloroquinazoline (572 mg, 2.35 mmole) in 11 ml of dioxane in a glass bomb, acetic acid (350 ul) was added and then sealed. The reaction solution was stirred at 92°c for 22 hours or until done by LCMS. The reaction solution was concentrated under reduced pressure to give a brown solid that was then diluted with 180 ml of ethyl acetate. The organic phase was washed with saturated $NaHCO_3$ solution (2x60 ml), water (30 ml) and brine (50 ml), then dried over Na_2SO_4 and evaporated in vacuo to give a brown solid. The crude solid was purified by column chromatography over silica gel with ethyl acetate: hexane (70: 30) to give (R)-tert-

butyl 1-(3-(6-bromoquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)propan-2-ylcarbamate (405 mg) as yellow solid. ES/MS *m/z* 553.1/555.1 (MH^+).

Step 2: Preparation of (R)-tert-butyl 1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenoxy)propan-2-ylcarbamate

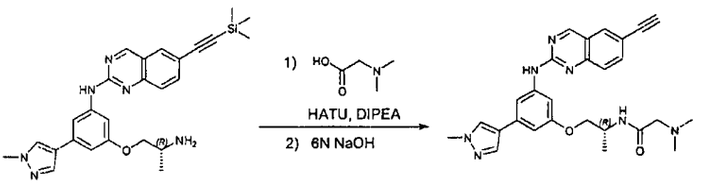
To the reaction mixture of (R)-tert-butyl 1-(3-(6-bromoquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)propan-2-ylcarbamate (408 mg, 737 umole), $Pd(dppf)Cl_2$ (90 mg, 111 umole), CuI (43 mg, 222 umole) and DIPEA (500 ul, 2.87 mmole) in 5 ml of N,N-dimethylformamide, trimethylsilylacctylene (307 ul, 2.21 mmole) was added. The reaction mixture was stirred at 80°c for 1.5 hour. The crude reaction mixture was partitioned between 100 ml of ethyl acetate and 40 ml of saturated $NaHCO_3$ solution. The organic layer was washed with water (30 ml) and brine (50 ml), then dried over Na_2SO_4 and evaporated in vacuo to give a brown solid that was purified by column chromatography over silica gel with ethyl acetate : hexane (60 : 40) to give (R)-tert-butyl 1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino) phenoxy)propan-2-ylcarbamate (370 mg) as yellow solid . ES/MS *m/z* 571.3 (MH^+).

Step 3: Preparation of (R)-N-(3-(2-aminopropoxy)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-6-((trimethylsilyl)ethynyl)quinazolin-2-amine

To the reaction mixture (R)-tert-butyl 1-(3-(1-methyl-1H-pyrazol-4-yl)-5-(6-((trimethylsilyl)ethynyl)quinazolin-2-ylamino)phenoxy)propan-2-ylcarbamate (370 mg, 0.65 mmole) add excess 4 M HCl in dioxane (16 ml, 64 mmole). This reaction mixture was stirred at room temperature for 1 hour or until done by LCMS and concentrated *in vaccuo* to give a yellow solid that was dissolved with 100 ml of ethyl acetate. The organic phase was washed with 1N NaOH solution (20 ml), water (30 ml) and brine solution (40 ml), then dried over Na_2SO_4 and evaporated in vacuo to give (R)-N-(3-(2-aminopropoxy)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-6-((trimethylsilyl)ethynyl) quinazolin-2-amine as a yellow brown powder (304 mg). ES/MS *m/z* 471.2 (MH^+).

(R)-2-(dimethylamino)-N-(1-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)propan-2-yl)acetamide

The subject compound was prepared according to the general Scheme below

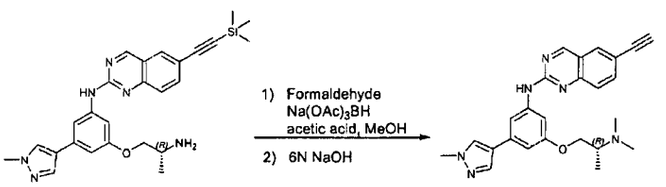


Step 1: Preparation of (R)-2-(dimethylamino)-N-(1-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)propan-2-yl)acetamide

To the reaction mixture of 2-(dimethylamino)acetic acid (11 mg, 100 umole) in 0.7 ml of N,N-dimethylformamide add HATU (38 mg, 100 umole), DIPEA (45 ul, 250 umole) and stir at room temperature for about 3 minutes. To the above reaction mixture add (R)-N-(3-(2-aminopropoxy)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-6-((trimethylsilyl)ethynyl) quinazolin-2-amine (19 mg, 32 umole) and stir at room temperature for 1 hours or until done by LCMS. The crude product was deprotected with 60 ul of 6N NaOH solution for 5 minutes and then neutralized with 60 ul of acetic acid. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give (R)-2-(dimethylamino)-N-(1-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)propan-2-yl)acetamide as TFA salt (10.3 mg). ES/MS *m/z* 483.2(MH^+).

Example 607: (R)-N-(3-(2-(dimethylamino)propoxy)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-6-ethynylquinazolin-2-amine

The subject compound was prepared according to the general Scheme below



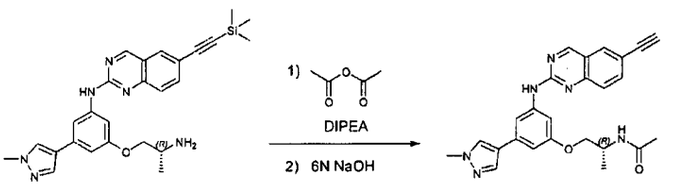
Step 1: Preparation of (R)-N-(3-(2-(dimethylamino)propoxy)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-6-ethynylquinazolin-2-amine

To the reaction mixture of (R)-N-(3-(2-aminopropoxy)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-6-((trimethylsilyl)ethynyl)quinazolin-2-amine (18.5 mg, 32 umole) in 0.6 ml of

methanol, add acetic acid (36 ul, 600 umole) and 37 % formaldehyde solution in water (26 ul, 300 umole). The reaction mixture was stirred at room temperature for about 30 minutes. To this reaction solution was added sodium triacctoxy borohydride (51 mg, 240 umole) and stirred at room temperature 1-2 hours or until done by LCMS. The crude product was deprotected with 60 ul of 6N NaOH solution for 5 minutes and then neutralized with 60 ul of acetic acid. The crude reaction mixture was concentrated, 1 ml of DMF added, filtered, purified on prep HPLC and lyophilized to give (R)-N-(3-(2-(dimethylamino)propoxy)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-6-ethynylquinazolin-2-amine as TFA salt (8 mg). ES/MS *m/z* 426.2(MH^+).

Example 618: (R)-N-(1-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)propan-2-yl)acetamide

The subject compound was prepared according to the general Scheme below

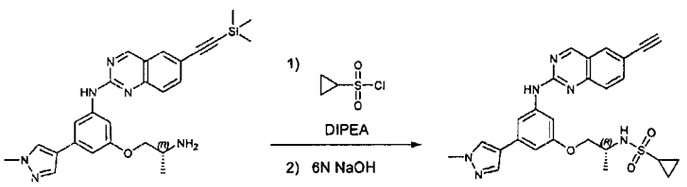


Step 1: Preparation of (R)-N-(1-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)propan-2-yl)acetamide

To the reaction mixture of (R)-N-(3-(2-aminopropoxy)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-6-((trimethylsilyl)ethynyl)quinazolin-2-amine (15 mg, 30 umole) in 0.5 ml of N,N-dimethylformamide, acetic anhydride (9 ul , 90 umole) and DIPEA (17 ul, 100 umole) were added. The reaction solution was stirred at room temperature for about 90 minutes or until done by LCMS. The crude product was deprotected with 60 ul of 6N NaOH solution for 5 minutes and then neutralized with 60 ul of acetic acid. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give (R)-N-(1-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)propan-2-yl)acetamide as TFA salt (4.2 mg). ES/MS *m/z* 441.2(MH^+).

Example 619: (R)-N-(1-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)propan-2-yl)cyclopropanesulfonamide

The subject compound was prepared according to the general Scheme below

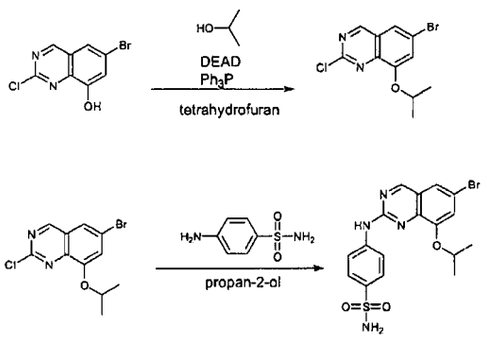


Step 1: Preparation of (R)-N-(1-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)propan-2-yl)cyclopropanesulfonamide

To the reaction mixture of (R)-N-(3-(2-aminopropoxy)-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-6-((trimethylsilyl)ethynyl)quinazolin-2-amine (15 mg, 30 umole) in 0.5 ml of N,N-dimethylformamide, cyclopropanesulfonyl chloride (10 ul , 98 umole) and DIPEA (35 ul, 200 umole) were added. The reaction solution was stirred at room temperature for 16 hours minutes or until done by LCMS. The crude product was deprotected with 60 ul of 6N NaOH solution for 5 minutes and then neutralized with 60 ul of acetic acid. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give (R)-N-(1-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-1H-pyrazol-4-yl)phenoxy)propan-2-yl)cyclopropanesulfonamideas TFA salt (4.3 mg). ES/MS *m/z* 503.2(MH^+).

Example 593: 4-(6-bromo-8-isopropoxyquinazolin-2-ylamino)benzenesulfonamide and 4-(6-ethynyl-8-isopropoxyquinazolin-2-ylamino) benzenesulfonamide

The subject compound was prepared according to the general Scheme below



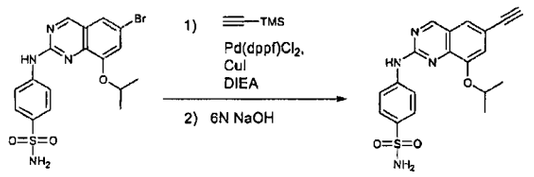
Step 1: Preparation of 6-bromo-2-chloro-8-isopropoxyquinazoline

To the reaction solution of triphenyl phosphine (1.91 g, 7.3 mmole), isopropyl alcohol (782 ul, 10.22 mmole) and diethyl azodicarboxylate (1.15 ml, 7.3 mmole) in 18 ml of tetrahydrofuran, 6-bromo-2-chloroquinazolin-8-ol (928 mg, 3.64 mmole) in 20 ml of tetrahydrofuran was added. The resulting solution was stirred at 65°c for 24 hours or until done by LCMS. The reaction solution was concentrated under reduced pressure to give brown glue as a crude product that was purified by column chromatography over silica gel with ethyl acetate: hexane (15: 85) to give 587 mg of 6-bromo-2-chloro-8-isopropoxyquinazoline as yellow solid. ES/MS *m/z* 300.9/302.9 (MH^+).

Step2: Preparation of 4-(6-bromo-8-isopropoxyquinazolin-2-ylamino) benzenesulfonamide

To the reaction mixture of 6-bromo-2-chloro-8-isopropoxyquinazoline (45 mg, 150 umole) in 0.8 ml of isopropyl alcohol, 4-aminobenzenesulfonamide (51 mg, 300 umole) was added and stirred at 82°c for 20 hours or until done by LCMS. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give 4-(6-bromo-8-isopropoxyquinazolin-2-ylamino)benzenesulfonamide as TFA salt (57 mg). ES/MS *m/z* 437.0/439.0(MH^+).

The ethynyl compound was prepared according to the general Scheme below

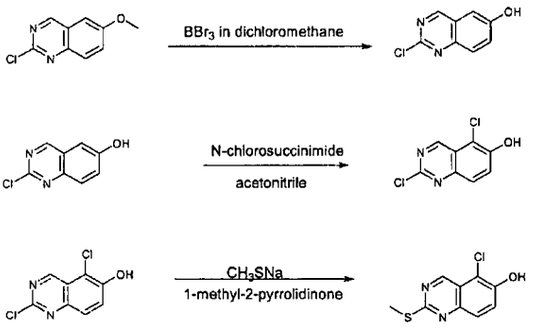


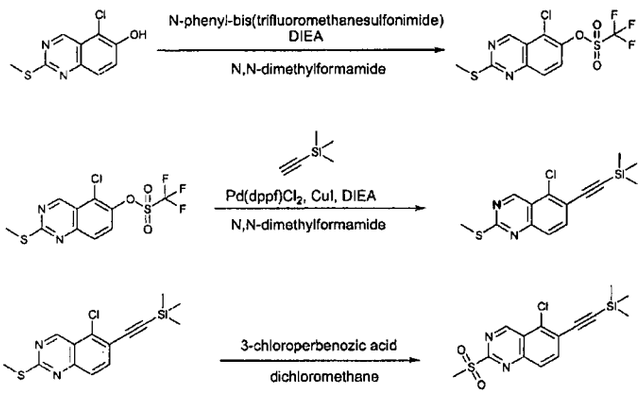
Step 1: Preparation of 4-(6-ethynyl-8-isopropoxyquinazolin-2-ylamino) benzenesulfonamide

To the reaction mixture of 4-(6-bromo-8-isopropoxyquinazolin-2-ylamino) benzenesulfonamide (57 mg, 130 umole), $Pd(dppf)Cl_2$ (11 mg, 13 umole), CuI (5 mg, 26 umole) and DIPEA (80 ul, 460 umole) in 0.8 ml of N,N-dimethylformamide, trimethylsilylacetylene (55 ul, 390 umole) was added. The reaction mixture was stirred at 55°c for 2 hour or until done by LCMS. The crude product was deprotected with 50 ul of 6N NaOH solution for 5 minutes and then neutralized with 60 ul of acetic acid. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give 4-(6-ethynyl-8-isopropoxyquinazolin-2-ylamino)benzenesulfonamide as TFA salt (22 mg). ES/MS *m/z* 383.1(MH^+).

INTERMEDIATE for 5-Chloro Compounds: 5-chloro-2-(methylsulfonyl)-6-((trimethylsilyl)ethynyl)quinazoline

The subject compound was prepared according to the general Scheme below





Step 1: Preparation of 2-chloroquinazolin-6-ol

To the solution of 2-chloro-6-methoxy quinazoline (1eq) in dichloromethane was added the solution of 1 M of boron tribromide (2eq) in dichloromethane slowly over 3 minutes at 0°c. The reaction mixture was stirred at 0°c for 20 minutes and heated at 40°c for 16 hours. The deprotection of the methyl ether went to completion and was monitored by LC/MS. Removal of all solvent in vaccuo, followed by quenching with water and diluted $NaHCO_3$ solution at 0°c, and extraction of aqueous phase with ethyl acetate and drying of combined organic extracts over Na_2SO_4 and subsequent removal of ethyl acetate *in vaccuo* yielded the desired product that was dried under vacuum to give 2-chloroquinazolin- 6-ol as brown solid. ES/MS *m/z* 181.0(MH^+).

Step 2: Preparation of 2,5-dichloroquinazolin-6-ol

To the solution of 2-chloroquinazolin - 6-ol (3.61 g, 20 mmole) in acetonitrile was added N-chlorosuccinimide (2.67g, 20 mmole) and the mixture was stirred at room temperature and became a deep brown reaction solution. The reaction went to completion in 30 minutes to give 2,5-dichloroquinazolin-6-ol (85% of the desired isomer) that was observed by LC/MS and the structure was confirmed by ^{1}HNMR. The reaction solution was concentrated and then dissolved into 300 ml of ethyl acetate. The organic phase was washed with diluted hydrochloric acid (2x70 ml), water (2x50 ml) and brine (50 ml), then dried over Na_2SO_4 and evaporated in vacuo to give a brown solid (3.1 g) that was purified by column

chromatography over silica gel with ethyl acetate: hexane (30: 70) to give yellow powder as 2,5-dichloroquinazolin-6-ol (1.92 g). ES/MS *m/z* 215.0(MH^+).

Step 3: Preparation of 5-chloro-2- (methylthio) quinazolin-6-ol

To the solution of 2,5-dichloroquinazolin-6-ol (1.75 g, 7.41 mmole) in 23 ml of N-methyl-2-pyrrolidone, sodium thiomethoxide (1.5 g, 22.23 mmole) was added. The reaction mixture was stirred at 60°c for overnight. The reaction mixture was poured into 100 ml of saturated $NaHCO_3$ solution and extracted with ethyl acetate (2x150 ml). The combined organic layers were washed with diluted $NaHCO_3$ solution (80 ml), water (2x30 ml) and brine (40 ml), then dried over Na_2SO_4 and evaporated in vacuo to give a brown glue that was recrystallized in hexane/dichloromethane to give 5-chloro-2- (methylthio) quinazolin-6-ol as brown solid. ES/MS *m/z* 227.0(MH^+).

Step 4: Preparation of 5-chloro-2- (methylthio) quinazolin-6-yl trifluoromethanesulfonate

To the solution of 5-chloro-2- (methylthio) quinazolin-6-ol (1.98 g, 7.93 mmole) in 30 ml of N, N-dimethylformamide at 0°c was added N-phenyl-bis (trifluoromethanesulfonimide) (2.55g, 7.13 mmole) and DIPEA (2.76 ml, 15.86 mmole). The resulting solution was stirred at room temperature for 2.5 hour and became a deep brown reaction solution. The reaction solution was partitioned between 250 ml of ethyl acetate and 80 ml of diluted hydrochloric acid. The organic layer was washed with diluted hydrochloric acid (60 ml), water (50 ml) and brine (50 ml), then dried over Na_2SO_4 and evaporated in vacuo to give a brown solid (4.72 g) that was purified by column chromatography over silica gel with ethyl acetate: hexane (10: 90) to give beige color solid as 5-chloro-2- (methylthio) quinazolin-6-yl trifluoromethanesulfonate (2.8 g). ES/MS *m/z* 358.8(MH^+).

Step 5: Preparation of 5-chloro-2- (methylthio)-6-((trimethylsilyl) ethynyl) quinazoline

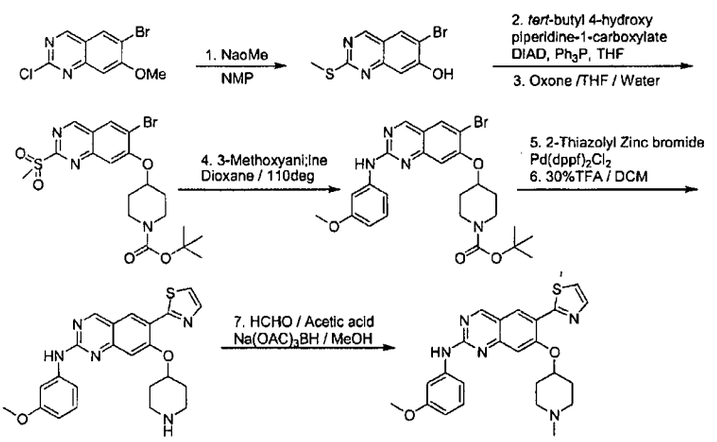
To the reaction mixture of 5-chloro-2- (methylthio) quinazolin-6-yl trifluoromethanesulfonate (2.05 g, 5.39 mmole), $Pd(dppf)Cl_2$ (440 mg, 0.539 mmole), CuI (220 mg, 1.15 mmole) and DIPEA (3.6 ml, 20.7 mmole) in 36 ml of N,N-dimethylformamide was added trimethylsilylacetylene (2.2 ml, 16.2 mmole). The reaction mixture was stirred at 100°c for 1.5 hour. The crude reaction mixture was partitioned between 300 ml of ethyl acetate and 80 ml of diluted hydrochloric acid. The organic layer was washed with diluted hydrochloric acid (60 ml), water (50 ml) and brine (50 ml), then dried over Na_2SO_4 and

evaporated in vacuo to give a brown glue (~2.5 g) that was purified by column chromatography over silica gel with ethyl acetate : hexane (10 : 90) to give 5-chloro-2-(methylthio)-6-((trimethylsilyl)ethynyl)quinazoline (723mg) as yellow solid . ES/MS *m/z* 351.0 (MH^+).

Step 6: Preparation of 5-chloro-2-(methylsulfonyl)-6-((trimethylsilyl)ethynyl)quinazoline

To the solution of 5-chloro-2-(methylthio)-6-((trimethylsilyl)ethynyl)quinazoline (723 mg, 2.2 mmole) in 20 ml of dichloromethane at 0°c was added the solution of 3-chloroperbenozic acid (~77% pure, 926 mg, 4.13 mmole) in 10 ml of dichloromethane. The reaction solution was stirred at room temperature for overnight and was monitored by LC/MS. After completion, the reaction solution was diluted with 200 ml of dichloromethane. The organic phase was washed with saturated $NaHCO_3$ solution (2x60 ml), water (30 ml) and brine (50 ml), then dried over Na_2SO_4 and evaporated in vacuo to give 5-chloro-2-(methylsulfonyl)-6-((trimethylsilyl)ethynyl)quinazoline as yellowish brown powder (732 mg) that was used in next step without further purification. ES/MS *m/z* 339.0(MH^+).

Example 1020: N- (3-methoxyphenyl)-7-(1-methylpiperidin-4-yloxy)-6-(thiazol-2-yl) quinazolin-2-amine



Step 1. Preparation of 6-Bromo-2- (methylthio) quinazolin-7-ol

To a solution of 6-bromo-2-chloro-7-methoxyquinazoline (1eq) (See example 11) in NMP (5ml) was added NaOMe (2eq). The reaction mixture was heated at 80°C for 2h. The reaction mixture was diluted with water and pH was adjusted to 5.5 with 1NHCl. The precipitate was filtered, washed and dried under vacuum to provide title product as a yellow solid (yield, 60%). ES/MS *m/z* 271.0 / 273.0 (MH^+).

2,6-bis (methylthio) quinazolin-7-ol was formed as a side product (40%)

Step 2. Preparation of tert-butyl-4- (6-bromo-2- (methylthio) quinazolin-7-yloxy) piperidine-1-carboxylate

To a solution of triphenylphosphine (2eq) in THF was added di-ethylazodicarboxylate (2eq). The mixture was stirred 15 minutes at ambient temperature under nitrogen atmosphere. To that was added tert-butyl-4-hydroxypiperidine-1-carboxylate (3eq). The mixture was stirred 15 minutes at ambient temperature followed by addition of 6-bromo-2- (methylthio) quinazolin-7-ol (1eq). The mixture was stirred overnight at ambient temperature. The reaction mixture was concentrated and purified by flash column chromatography (10%EtOAc / Hexane) to provide product as a white solid in 70% yield. ES/MS *m/z* 454.0 / 456.0 (MH^+).

Step 3. Preparation of tert-butyl 4-(6-bromo-2- (methyl sulfonyl) quinazolin-7-yloxy) piperidine-1-carboxylate

To a solution of tert-butyl-4- (6-bromo-2- (methylthio) quinazolin-7-yloxy) piperidine-1-carboxylate (1eq) in THF (10ml) was added a solution of oxone in water (10ml) at 0°C. The reaction mixture was stirred for 30min at 0°C then warmed to room temperature and stirred overnight. The reaction was cooled to 0°C and quenched with satd. sodium thiosulfate solution. The product was extracted in ethylacetate. The ethylacetate extracts were combined together, washed with brine and dried over sodium sulfate. Filtered, evaporated and dried under vacuum to provide product in 90%yield. ES/MS *m/z* 486.0 / 488.0(MH^+). Used for next step without further purification.

Step 4. Preparation of tert-butyl 4-(6-bromo-2- (3-methoxyphenylamino) quinazolin-7-yloxy) piperidine-1- carboxylate

A solution of tert-butyl 4-(6-bromo-2- (methyl sulfonyl) quinazolin-7-yloxy) piperidine-1-carboxylate (1eq) and 3-methoxyaniline (2eq) in dioxane was heated in sealed

tube at 110°C for 24h. The product was purified by semi-prep HPLC and lyophilyzed to provide pure product as a yellow solid in 50% yield. ES/MS *m/z* 529.0 / 531.0 (MH^+).

Step 5. Preparation of tert-butyl 4-(2-(3-methoxyphenylamino)-6-(thiazol-2-yl) quinazolin-7-yloxy) piperidine-1- carboxylate

A mixture of tert-butyl 4-(6-bromo-2- (3-methoxyphenylamino) quinazolin-7-yloxy) piperidine-1- carboxylate (1eq), 2-thiazolylzincbromide (5eq, 0.5M solution in THF) and $Pd(dppf)_2Cl_2$ (0.1eq) was heated in microwave at 120°C for 10min. The reaction mixture was diluted with ethylacetate and washed with water and brine. Dried over sodium sulfate, filtered, evaporated to provide crude product in quantitative yield.

ES/MS *m/z* 534.2 (MH^+).

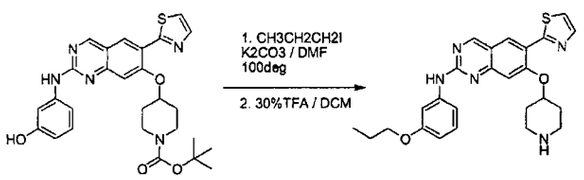
Step 6. Preparation of N- (3-methoxyphenyl)-7-(piperidin-4-yloxy)-6-(thiazol-2-yl) quinazolin-2-amine

A solution of crude tert-butyl 4-(2-(3-methoxyphenylamino)-6-(thiazol-2-yl) quinazolin-7-yloxy) piperidine-1- carboxylate in 30%TFA / DCM was stirred at room temperature for 30min. The solvent was evaporated and crude was purified by semi-prep HPLC to provide pure product in 40% yield. ES/MS *m/z* 434.2 (MH^+).

Step 7. Preparation of N- (3-methoxyphenyl)-7-(1-methylpiperidin-4-yloxy)-6-(thiazol-2-yl) quinazolin-2-amine

To a solution of N- (3-methoxyphenyl)-7-(piperidin-4-yloxy)-6-(thiazol-2-yl) quinazolin-2-amine (1eq) in methanol was added HCHO (10eq) and a drop of acetic acid. Stirred 10min at room temperature, followed by the addition of $Na(OAc)_3BH$ (4eq). The reaction mixture was stirred 1h / rt. Purified by semi-prep HPLC to provide product as a yellow solid in 70% yield. ES/MS *m/z* 448.2 (MH^+).

Example 1075: Synthesis of 7-(piperidin-4-yloxy)-N- (3-propoxyphenyl)-6-(thiazol-2-yl) quinazolin-2-amine



Step1. Preparation of tert-butyl-4- (2- (3-propoxyphenylamino)-6-(thiazol-2-yl) quinazolin-7-yloxy) piperidine-1-carboxylate

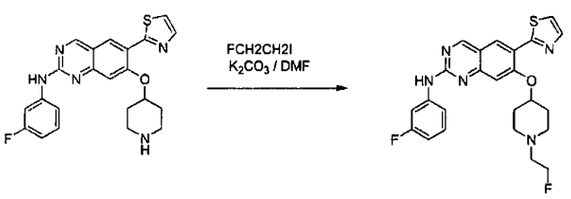
To tert-butyl-4- (2- (3-hydroxyphenylamino)-6-(thiazol-2-yl) quinazolin-7-yloxy) piperidine-1-carboxylate (1eq) (For synthesis, see example 21) in DMF (2ml) was added K_2CO_3 (5eq) and iodopropane (3eq). The reaction mixture was heated at 100°C for 48h.

The reaction mixture was partitioned between ethylacetate and water. Ethylacetate layer was separated and washed with water, brine and dried over sodium sulfate. Filtered and evaporated to provide crude product. ES/MS *m/z* 562.2 (MH^+).

Step2. Preparation 7-(piperidin-4-yloxy)-N- (3-propoxyphenyl)-6-(thiazol-2-yl) quinazolin-2-amine

For synthesis, see example 1020, step 6. ES/MS *m/z* 462.2 (MH^+).

Example 1082: 7-(1-(2-fluoromethylpiperidin-4-yloxy)-N-(3-fluorophenyl)-6-(thiazol-2-yl) quinazolin-2-amine

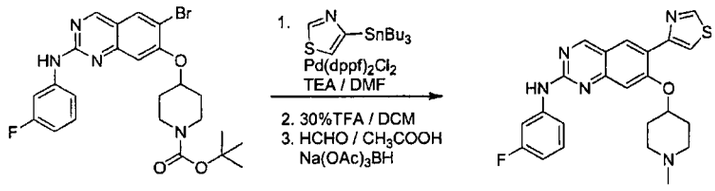


To N- (3-fluorophenyl)-7-(piperidin-4-yloxy)-6-(thiazol-2-yl) quinazolin-2-amine (1eq) (For synthesis, see example 11) in DMF was added K_2CO_3 (5eq) and 1-fluoro-3-

iodoethane (1.2eq). The reaction mixture was stirred overnight at rt. Product was purified by semi-prep HPLC. ES/MS *m/z* 468.2 (MH^+).

Example 1084

Synthesis of N- (3-fluorophenyl)-7-(1-methylpiperidin-4-yloxy)--6-(thiazol-4-yl) quinazolin-2-amine



Step 1. Preparation of tert-butyl 4-(2-(3-fluorophenylamino)-6-(thiazol-4-yl) quinazolin-7-yloxy) piperidin-1-carboxylate

A mixture of tert-butyl-4- (6-bromo-2- (3-fluorophenylamino) quinazolin-7-yloxy) piperidine-1-carboxylate (1eq, see example11 for synthesis), 4-tributyltin thiazole (3eq), TEA (3.5eq) and Pd $(dppf)_2Cl_2$ (0.1eq) in DMF (1.5ml) was heated in microwave at 120°C for 10min. The reaction mixture was partitioned between ethylacetate and water. Ethylacetate layer was separated and washed with water, brine and dried over sodium sulfate. Filtered, evaporated and purified by semi-prep HPLC to provide pure product in 50%yield ES/MS *m/z* 522.1 (MH^+).

Step 2. Preparation of N- (3-fluorophenyl)-7-(piperidin-4-yloxy)--6-(thiazol-4-yl) quinazolin-2-amine

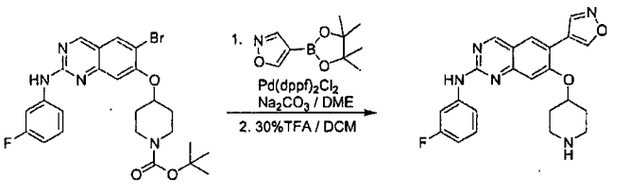
For synthesis see example 21, step 6. ES/MS *m/z* 422.1 (MH^+).

Step 3. Preparation of N- (3-fluorophenyl)-7-(1-methylpiperidin-4-yloxy)--6-(thiazol-4-yl) quinazolin-2-amine

For synthesis see example 1020, step 7. ES/MS *m/z* 436.1 (MH^+).

Example 1066

Synthesis of N- (3-fluorophenyl)- 6-(isoxazol-4-yl) -7-(piperidin-4-yloxy) quinazolin-2-amine



Step1. Preparation of tert-butyl 4-(2-(3-fluorophenylamino)-6-(isoxazol-4-yl) quinazolin-7-yloxy) piperidin-1-carboxylate

A mixture of tert-butyl-4- (6-bromo-2- (3-fluorophenylamino) quinazolin-7-yloxy) piperidine-1-carboxylate (1eq, see example11 for synthesis), 4-isoxazole boronic ester (3eq), 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) (0.1eq), sodium carbonate (0.5ml of 2M aqueous solution) in DME (2ml) was heated in microwave at 120°C for 10min. The reaction mixture was partitioned between ethylacetate and water. Ethylacetate layer was separated and washed with water, brine and dried over sodium sulfate. Filtered, evaporated and purified by semi-prep HPLC to provide pure product in 50%yield ES/MS *m/z* 506.1 (MH^+).

Note: Some debrominated product was also observed in above reaction

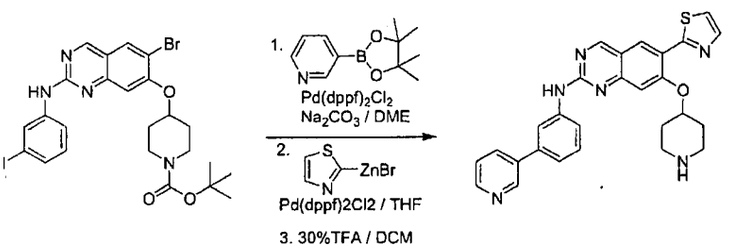
Step 2. Preparation of N- (3-fluorophenyl)- 6-(isoxazol-4-yl) -7-(piperidin-4-yloxy) quinazolin-2-amine

For synthesis see example 1020, step 6. ES/MS *m/z* 406.1 (MH^+).

Example 1135

Synthesis of 7-(piperidin-4-yloxy)-N- (3-(pyridine-3-yl) phenyl)-6-(thiazol-2-yl) quinazolin-2-amine

The subject compound was prepared according to the general Scheme below:



Step 1. Preparation of tert-butyl 4-(6-bromo-2- (3-(pyridine-3-yl) phenylamino) quinazolin-7-yloxy) piperidin-1-carboxylate

A mixture of tert-butyl-4- (6-bromo-2- (3-iodophenylamino) quinazolin-7-yloxy) piperidine-1-carboxylate (1eq, see example11 for synthesis), 3-pyridine boronic ester (1.2eq), 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) (0.1eq), sodium carbonate (0.5ml of 2M aqueous solution) in DME (2ml) was heated in microwave at 120°C for 10min. The reaction mixture was partitioned between ethylacetate and water. Ethylacetate layer was separated and washed with water, brine and dried over sodium sulfate. Filtered, evaporated and purified by semi-prep HPLC to provide pure product in.50%yield ES/MS *m/z* 576.2 / 578.2.1 (MH^+).

Note: Some bis-substituted product was also isolated in above reaction

Step 2. Preparation of tert-butyl 4-(2- (3-(pyridine-3-yl) phenylamino)-6-(thiazol-2-yl) quinazolin-7-yloxy) piperidin-1-carboxylate

For Synthesis, see example 1020, step5. ES/MS m/z 581.2 (MH^+).

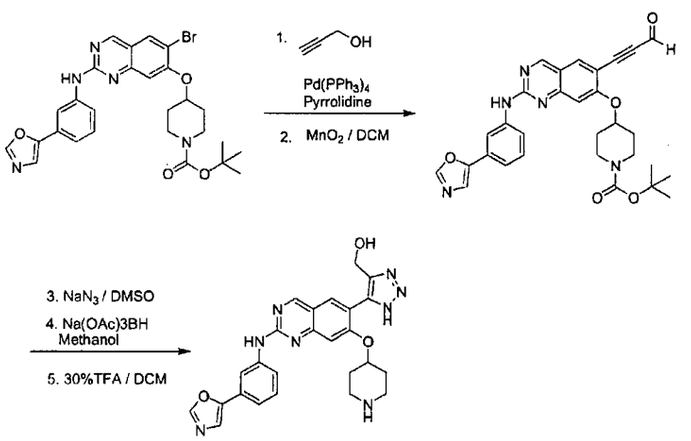
Step 3. Preparation of 7-(piperidin-4-yloxy)-N- (3-(pyridine-3-yl) phenyl)-6-(thiazol-2-yl) quinazolin-2-amine

For Synthesis, see example 1020, step 6. ES/MS *m/z* 481.2 (MH^+).

Example 1117

Synthesis of (5-(2-(3-(oxazol-5-yl) phenylamino (7-(piperidin-4-yloxy) quinazolin-6-yl)-1H-1, 2, 3-triazol-4-yl) methanol

The subject compound was prepared according to the general Scheme below:



Step 1. Preparation of tert-butyl 4-(6- (3-hydroxyprop-1-ynyl)-2-(3-(oxazol-5-yl) phenylamino)quinazolin-7-yloxy) piperidin-1-carboxylate

To tert-butyl 4-(6-bromo-2- (3-(oxazol-5-yl) phenylamino)quinazolin-7-yloxy) piperidin-1-carboxylate (1eq) and tetrakis (PPH_3)Pd(0) (0.02eq) in pyrrolidine(1.5ml) at room temperature was added propargyl alcohol (2eq, in 1ml of pyrrolidine). The reaction mixture was heated in sealed tube at 80°C for 1h. The reaction was quenched with satd. NH_4Cl and product was extracted with diethyl ether. Ether extracts were washed with brine, dried over sodium sulfate, filtered and evaporated. Purified by semi-prep HPLC to provide pure product as a yellow solid in 40% yield. ES/MS *m/z* 542.2 (MH^+).

Step 2. Preparation of tert-butyl 4-(2-(3-(oxazol-5-yl) phenylamino)-6-(3-oxoprop-1-ynyl) quinazolin-7-yloxy) piperidin-1-carboxylate

A mixture of tert-butyl 4-(6- (3-hydroxyprop-1-ynyl)-2-(3-(oxazol-5-yl) phenylamino) quinazolin-7-yloxy) piperidin-1-carboxylate (1eq) and MnO_2 (5eq) in DCM (5ml) was stirred overnight at rt. The product was filtered through celite and solvent was evaporated to provide pure prduct in 90% yield. ES/MS *m/z* 540.3 (MH^+).

Step 3. Preparation of tert-butyl 4-(6-(4-formyl-1H-1,2,3-triazol-5yl)-2-(3-(oxazol-5-yl) phenylamino) quinazolin-7-yloxy) piperidin-1-carboxylate

To a stirred solution of sodium azide (1.2eq) in DMSO (2ml) in ice-water bath was added tert-butyl 4-(2-(3-(oxazol-5-yl) phenylamino)-6-(3-oxoprop-1-ynyl) quinazolin-7-yloxy) piperidin-1-carboxylate in DMSO (1ml). The reaction mixture was stirred 30min at room temperature then poured to vigorously stirred biphasic solution of 5%KH_2PO_4 and diethyl ether. Ether layer was separated, washed with brine and dried over sodium sulfate. Filtered, evaporated and dried under vacuum to provide product as a white solid in 70% yield. ES/MS *m/z* 583.31 (MH^+).

Step 4. Preparation of tert-butyl 4-(6-(4-(hydroxymethyl)-1H-1,2,3-triazol-5yl)-2-(3-(oxazol-5-yl) phenylamino) quinazolin-7-yloxy) piperidin-1-carboxylate

To tert-butyl 4-(6-(4-formyl-1H-1,2,3-triazol-5yl)-2-(3-(oxazol-5-yl) phenylamino) quinazolin-7-yloxy) piperidin-1-carboxylate(1eq) in methanol was added $Na(OAc)_3BH$ (5eq). The reaction mixture was stirred 1h at room temperature. Purified by semi-prep HPLC to provide pure product as a yellow solid in 40% yield. ES/MS *m/z* 584.2 (MH^+).

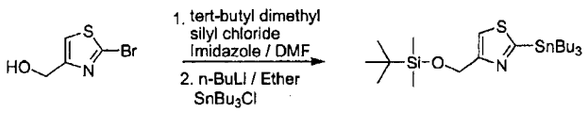
Step 5. Preparation of (5-(2-(3-(oxazol-5-yl) phenylamino (7-(piperidin-4-yloxy) quinazolin-6-yl)-1H-1, 2, 3-triazol-4-yl) methanol

For Synthesis, see example 1020, step 6. ES/MS *m/z* 484.2 (MH^+).

EXAMPLE 1140: (2R,4S)-4-(2-(3-fluorophenylamino)- 6-(thiazol-2-yl)quinazolin -7-yloxy)piperidine-2-carboxamide

Synthesis of 4-((tert-butyldimethylsilyloxy) methyl)-2-(tributylstannyl)thiazole

The subject compound was prepared according to the general Scheme below:



Step 1. Preparation of 2-bromo-4- (tert-butylsilyloxy)methyl)thiazole

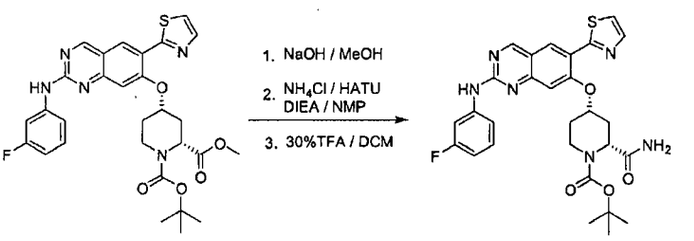
A mixture of 2-bromothiazol-4-yl) methanol (1eq), imidazole (4eq) and tert-butyl-dimethylsilylchloride (2eq) in DMF(10ml) was stirred 2h at room temperature. The reaction mixture was partitioned between ethylacetate and water. Ethylacetate layer was separated and washed with water, brine and dried over sodium sulfate. Filtered, evaporated and purified by flash chromatography (10%EtOAc / Hexane) to provide pure product as a colorless liquid in 95%yield ES/MS *m/z* 307.9 / 309.9 (MH^+).

Step 2. Preparation of 4-((tert-butyldimethylsilyloxy)methyl)-2-(tributylstannyl)thiazole

To flame dried flask under nitrogen at-78°C was added anhydrous ether (10ml) and n-butyl lithium (1.5eq, 2.5M solution in hexane) followed by addition of 2-bromo-4- (tert-butylsilyloxy) methyl) thiazole solution in ether (1eq, 3ml). Stirred at -78°C for 1h. Then a solution of tributyltinchloride in ether (1.5eq, 1ml) was added dropwise. Stirred at this temperature additional 1h. The reaction mixture was quenched with satd. sodium bicarbonate and compound was extracted in ether. Ether extracts were combined, washed with brine and dried over sodium sulfate. Filtered, evaporated and dried under vacuum to provide product as a light yellow liquid. Used without further purification.

Synthesis of (2R,4S)-4-(2-(3-fluorophenylamino)- 6-(thiazol-2-yl)quinazolin -7-yloxy)piperidine-2-carboxamide

The subject compound was prepared according to the general Scheme below:



Step1. Preparation of (2R,4S)-1-(tert-butoxycarbonyl)-4-(2-(3-fluorophenylamino)- 6-(thiazol-2-yl)quinazolin -7-yloxy)piperidine-2-carboxylic acid

To (2R,4S)-1-tert-butyl-2-methyl-4-(2-(3-fluorophenylamino)- 6-(thiazol-2-yl)quinazolin -7-yloxy)piperidine-1,2-dicarboxylate (1eq) in methanol (3ml) was added aqueous solution of sodium hydroxide (5eq). The reaction mixture was stirred overnight at rt. The solvent was evaporated; residue was taken in water and made acidic with 1NHCl. Product was extracted in ethylacetate. The extracts were combined, washed with brine and dried over sodium sulfate. Filtered, evaporated and dried under vacuum to provide product as a light brown solid in 70% yield. ES/MS *m/z* 566.1 (MH^+).

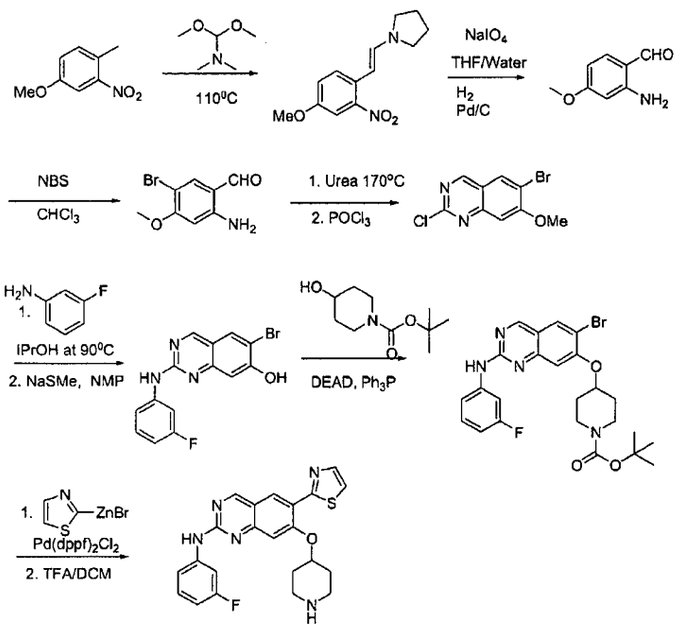
Step2. Preparation of (2R,4S)-tert-butyl-2-carbamoyl-4-(2-(3-fluorophenylamino)- 6-(thiazol-2-yl)quinazolin -7-yloxy)piperidine-1-carboxylate

A mixture of (2R,4S)-1-(tert-butoxycarbonyl)-4-(2-(3-fluorophenylamino)- 6-(thiazol-2-yl)quinazolin -7-yloxy)piperidine-2-carboxylic acid (1eq), NH_4Cl (10eq), HATU(1.75eq) and DIEA (5eq) in NMP (2ml) was stirred overnight at rt. The product was purified by semi-prep HPLC. ES/MS *m/z* 565.1 (MH^+).

Step3. Preparation of (2R,4S)-4-(2-(3-fluorophenylamino)- 6-(thiazol-2-yl)quinazolin -7-yloxy)piperidine-2-carboxamide

For Synthesis, see example 21, step6. ES/MS *m/z* 465.1 (MH^+).

Example 997: Preparation of N-(3-fluorophenyl)-7-(piperidin-4-yloxy)-6-(thiazol-2-yl)quinazolin-2-amine



A. Preparation of 4-methoxy-2-aminobenzaldehyde

To a mixture of 4-methyl-3-nitroanisole in pyrrolidine (1.9eq) was added N,Ndimethylformamidedimethylacetal and the mixture was heated to 120°C or 16h. The formation of the enaminone was confirmed by TLC. The mixture was cooled to RT and poured in to ice and was then extracted with ethyl acetate, dried (Na_2SO_4) and concentrated. To the crude enaminone in THF was added $NaIO_4$ (2.5eq) dissolved in water while maintaining the reaction temperature at 40°C with an ice/water bath. After the addition the pale yellow suspension was stirred at 35°C for 16h. The reaction mixture was then concentrated and the aqueous phase was then extracted with ethyl acetate , dried (Na_2SO_4) and the crude 4-methoxy-2-nitrobenzaldehyde was obtained as a brown solid. The crude brown solid was purified on silica gel to get the product. The hence obtained 4-methoxy-2-nitrobenzaldehyde was hydrogenated in methanol with catalytic amounts of 10% Pd/C to give the 4-methoxy-2-aminobenzaldehyde in quantitative yield. ES/MS *m/z* 152(MH^+).

B. Preparation of 5-bromo-4-methoxy-2-nitrobenzaldehyde

To 4-methoxy-2-aminobenzaldehyde in chloroform was added NBS(1eq) and the reaction goes to completion by LC/MS and 1H NMR. To the reaction mixture was added dichloromethane and water and the separated organic layer was dried (Na_2SO_4) and concentrated to give the 5-bromo-4-methoxy-2-nitrobenzaldehyde. ES/MS *m/z* 229/231(MH^+).

C. Preparation of 2-chloro-6-bromo-7-methoxyquinazoline

5-bromo-4-methoxy-2- aminobenzaldehyde (1.0 eq) and urea (8.0 eq) were stirred at 170 °C for 1 h. The resulting solid was returned to ambient temperature, stirred in water for 20 min, and filtered. This was repeated for a total of three washes. The solid was dried in a desiccator to give the 6-bromo-7-methoxyquinazolin-2-ol as the desired product. A 0.50M solution of 6-bromo-7-methoxyquinazolin-2-ol in phosphorus oxychloride was stirred at 110 °C for 1.5 h. Volatiles were removed under reduced pressure. Ice water was added and the precipitate was filtered off, rinsed with water, and dried under high vacuum to yield the 2-chloro-6-bromo-7-methoxyquinazoline as a yellow solid. ES/MS *m/z* 272/274(MH^+).

D. Preparation of 6-bromo-2-(3-fluorophenylamino)quinazolin-7-ol

To a solution of 2-chloro-6-bromo-7-methoxyquinazoline in isopropanol was added 3-fluoroaniline(1.0 eq). The reaction was stirred at 90 °C for 18 hours. The hydrochloride was collected by vacuum filtration and air dried to give a crude material which can be used for further chemical modifications. The pure material was obtained by HPLC purification. To the crude product was added NMP and NaSMe(4eq) and the mixture was heated to 80°C for 2h. The conversion in to the phenol was observed by LC/MS. The reaction mixture was cooled and to it was added ethyl acetate and 1N HCl to bring it to neutral pH. The 6-bromo-2-(3-fluorophenylamino)quinazolin-7-ol crashed out as a solid which was filtered and dried on high vacuum to give the product in quantitative yield. ES/MS *m/z* 333/335(MH^+).

E. Preparation of tert-butyl 4-(6-bromo-2-(3-fluorophenylamino)quinazolin-7-yloxy)piperidine-1-carboxylate

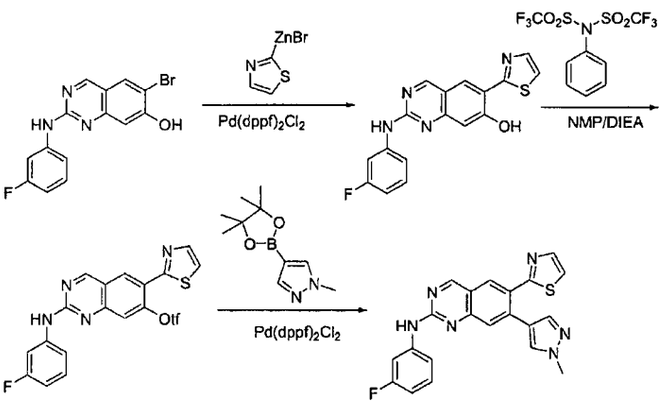
To a mixture of DEAD (2eq) and triphenylphosphine (2eq) was added tert-butyl 4-hydroxypiperidine-1-carboxylate (4eq) and to the resulting mixture was added 6-bromo-2-(3-fluorophenylamino)quinazolin-7-ol and was stirred for 16h at RT. The formation of the

product was observed on LC/MS. The mixture was then concentrated and purified on silica gel to obtain tert-butyl 4-(6-bromo-2-(3-fluorophenylamino)quinazolin-7-yloxy)piperidine-1-carboxylate as the product. ES/MS *m/z* 517/519(MH^+).

F. Preparation of N-(3-fluorophenyl)-7-(piperidin-4-yloxy)-6-(thiazol-2-yl)quinazolin-2-amine

To tert-butyl 4-(6-bromo-2-(3-fluorophenylamino)quinazolin-7-yloxy)piperidine-1-carboxylate (50mgs) was added 0.5M 2-thiazolylzincbromide and the mixture was micro waved at 120°C for 10mins. Complete conversion to the product was seen by LC/MS. The mixture was concentrated and partitioned between ethyl acetate and water. The organic layer was dried (Na_2SO_4) and the product was isolated. To the crude product was added 30% TFA/DCM and stirred for 2h for the deprotection of the tert-butyl group. The formation of N-(3-fluorophenyl)-7-(piperidin-4-yloxy)-6-(thiazol-2-yl)quinazolin-2-amine was observed by LC/MS. It was then purified by preparative chromatography to give the product. ES/MS *m/z* 421(MH^+).

Example 889: Preparation of N-(3-fluorophenyl)-7-(1-methyl-1H-pyrazol-4-yl)-6-(thiazol-2-yl)quinazolin-2-amine



A. Preparation of 2-(3-fluorophenylamino)-6-(thiazol-2-yl)quinazolin-7-ol

To 6-bromo-2-(3-fluorophenylamino)quinazolin-7-ol was added 0.5M 2-thiazolylzincbromide and the mixture was micro waved at 120°C for 10mins. Complete conversion to the product was seen by LC/MS. The mixture was concentrated and partitioned between ethyl acetate and water. The organic layer was dried (Na_2SO_4) and the product was isolated.ES/MS *m/z* 330(MH^+).

B. Preparation of 2-(3-fluorophenylamino)-6-(thiazol-2-yl)quinazolin-7-yl trifluoromethanesulfonate

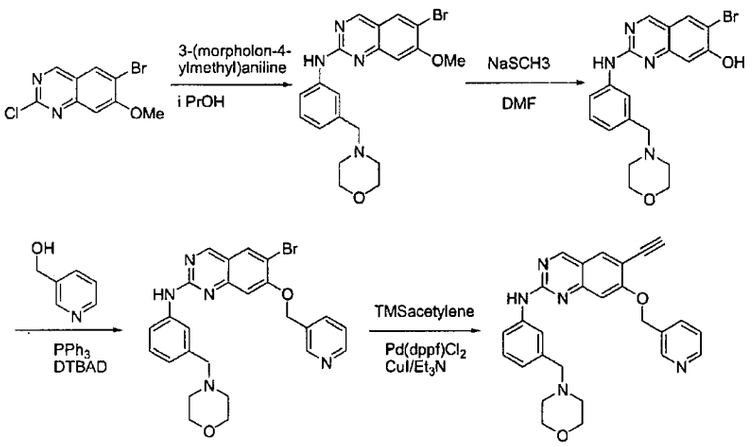
To a solution of 2-(3-fluorophenylamino)-6-(thiazol-2-yl)quinazolin-7-ol (1eq) in NMP was added phenyltrifluoromethanesulfonate (1.2eq) and DIEA (2.5eq) and the reaction mixture was stirred over night at ambient temperature. The reaction mixture was then partitioned between ethyl acetate and water. The organic layers were washed with saturated sodium chloride and dried and concentrated. To the crude was added methylene chloride and few drops of methanol. The white solid hence formed was filtered to give 2-(3-fluorophenylamino)-6-(thiazol-2-yl)quinazolin-7-yl trifluoromethanesulfonate in 80% yield. ES/MS *m/z* 471(MH^+).

C. Preparation of N-(3-fluorophenyl)-7-(1-methyl-1H-pyrazol-4-yl)-6-(thiazol-2-yl)quinazolin-2-amine

To a solution of 2-(3-fluorophenylamino)-6-(thiazol-2-yl)quinazolin-7-yl trifluoromethanesulfonate (1eq) in DME was added 2M sodium carbonate solution and 4-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)-1methyl-pyrazole (3eq) and Pd $(dppf)_2Cl_2.CH_2Cl_2$ (0.05eq) and the mixture was micro waved for 10 min at 120 °C. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was washed with brine, dried, concentrated and purified by semi-preparative HPLC to provide N-(3-fluorophenyl)-7-(1-methyl-1H-pyrazol-4-yl)-6-(thiazol-2-yl)quinazolin-2-amine ES/MS *m/z* 402 (MH^+).

Example 804: Preparation of 6-ethynyl-N-(3-(morpholinomethyl)phenyl)-7-(pyridin-3-ylmethoxy)quinazolin-2-amine

The subject compound was prepared according to the general Scheme below:



A. Preparation of 6-bromo-7-methoxy-N-(3-(morpholinomethyl)phenyl)quinazolin-2-amine

To a 0.25M suspension of 6-bromo-2-chloro-7-methoxyquinazoline in isopropanol was added 3-(morpholin-4-ylmethyl)aniline (1.1eq), and 4.0M hydrogen chloride in 1,4-dioxane (0.5eq). The reaction mixture was heated to 95 °C in an oil bath for 15 h. Reaction mixture was diluted with ethyl acetate and filtered to collect desired product. ES/MS *m/z* 429/431 (MH^+).

B. Preparation of 6-bromo-2-(3-(morpholinomethyl)phenylamino)quinazolin-7-ol

A 0.2M suspension of 6-bromo-7-methoxy-N-(3-(morpholinomethyl)phenyl)quinazolin-2-amine (1.0eq) and sodium thiomethoxide (4.0eq) in DMF was heated to 90 °C in an oil bath for 10 h. The mixture was partitioned between ethyl acetate and water. The pH of aqueous phase was adjusted to 4 by adding saturated ammonium hydrochloride. Aqueous phase was extracted with ethyl acetate, and combined organic phase was washed with brine, dried over sodium sulfate, concentrated to give desired product. ES/MS *m/z* 415/417 (MH^+).

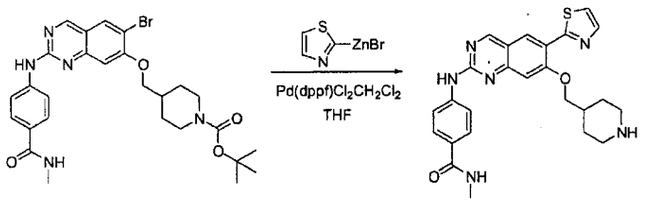
C. Preparation of 6-bromo-N-(3-(morpholinomethyl)phenyl)-7-(pyridin-3-ylmethoxy)quinazolin-2-amine

To a 0.55M solution of triphenylphosphine (3.0eq) in THF was added di-tert-butylazodicarboxylate (3.0eq). The mixture was stirred for 20 min at ambient temperature. 3-pyridylcarbinol (3.0eq) was added, and reaction mixture was stirred at ambient temperature for another 30 min. Then, 6-bromo-2-(3-(morpholinomethyl) phenylamino) quinazolin-7-ol (1.0eq) was added to reaction flask. The mixture was stirred at ambient temperature for additional 14 h. Solvent was removed under reduced pressure and the residue was triturated with ethyl acetate and filtered. Filter cake was rinsed with cold ethyl acetate and was air dried to give 6-bromo-N-(3-(morpholinomethyl)phenyl)-7-(pyridin-3-ylmethoxy)quinazolin-2-amine. ES/MS *m/z* 506/508 (MH^+).

D. Preparation of 6-ethynyl-N-(3-(morpholinomethyl)phenyl)-7-(pyridin-3-ylmethoxy)quinazolin-2-amine

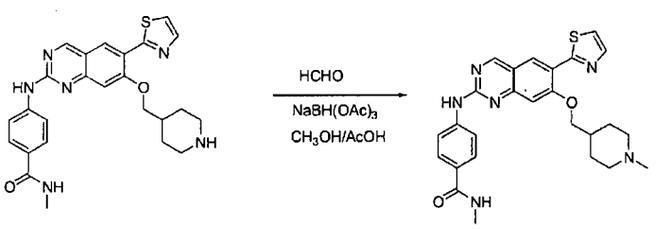
To a 0.05M mixture of 6-bromo-N-(3-(morpholinomethyl)phenyl)-7-(pyridin-3-ylmethoxy)quinazolin-2-amine (0.1 mmol), triethylamine (0.4ml), Pd(dppf)Cl2CH2Cl2 (0.1eq), Copper(I) iodide (0.1eq) in DMF was added trimethylsilylacetylene (10eq). The mixture was microwaved at 120 °C for 15 min. Reaction mixture was diluted with ethyl acetate and was washed with water, brine, dried and concentrated. Without further purification, the crude compound was treated with tetramethylammonium fluoride (2.0eq) in THF/isopropanol (10:1, 0.02M) at ambient temperature for 15 min. Solvent was removed under reduced pressure. The residue was taken into ethyl acetate and was washed with water, brine, dried and concentrated. The crude product was purified by RP HPLC. Lyophilization gave desired product 6-ethynyl-N-(3-(morpholinomethyl)phenyl)-7-(pyridin-3-ylmethoxy)quinazolin-2-amine. ES/MS *m/z* 452 (MH^+).

Example 724: Preparation of N-methyl-4-(7-(piperidin-4-ylmethoxy)-6-(thiazol-2-yl)quinazolin-2-ylamino)benzamide



To a 0.05M solution of tert-butyl 4-((6-bromo-2-(4-(methylcarbamoyl)phenylamino) quinazolin-7-yloxy)methyl)piperidine-1-carboxylate (0.12 mmol) in THF was added 0.5M 2-thiazolylzincbromide (3.0eq), Pd(dppf)Cl2CH2Cl2 (0.2eq). The mixture was microwaved at 120°C for 15mins. Complete conversion to the product was seen by LC/MS. The mixture was concentrated and partitioned between ethyl acetate and water. The organic layer was dried (Na_2SO_4) and was concentrated. The residue was treated with 50% TFA/DCM and stirred for 10 min to remove tert-butylcarboxylate group. The crude compound was then purified by RP HPLC to give desired product N-methyl-4-(7-(piperidin-4-ylmethoxy)-6-(thiazol-2-yl)quinazolin-2-ylamino)benzamide. ES/MS *m/z* 475 (MH^+).

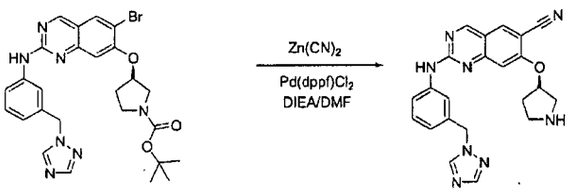
Example 729: Preparation of N-methyl-4-(7-(piperidin-4-ylmethoxy)-6-(thiazol-2-yl)quinazolin-2-ylamino)benzamide



A solution of N-methyl-4-(7-(piperidin-4-ylmethoxy)-6-(thiazol-2-yl)quinazolin-2-ylamino)benzamide (0.05 mmol), formaldehyde (10eq), catalytic amount acetic acid in

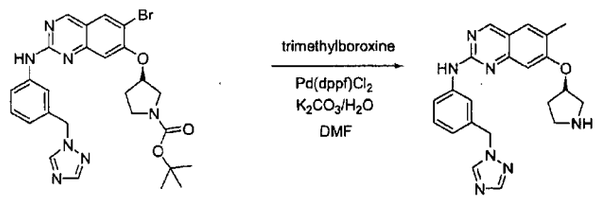
methanol (2.0 ml) was stirred at ambient temperature for 1 h. Then sodium triacetoxyborohydride (2.0eq) was added and reaction mixture was stirred at ambient temperature for 2 h. LCMS data showed reaction was complete. Solvent was removed under reduced pressure. The residue was taken into ethyl acetate and was washed with water, brine, dried and concentrated. Purification by RP HPLC gave desired product N-methyl-4-(7-(piperidin-4-ylmethoxy)-6-(thiazol-2-yl)quinazolin-2-ylamino)benzamide. ES/MS *m/z* 489 (MH^+).

Example 767: Preparation of (S)-2-(3-((1H-1,2,4-triazol-1-yl)methyl)phenylamino)-7-(pyrrolidin-3-yloxy)quinazoline-6-carbonitrile



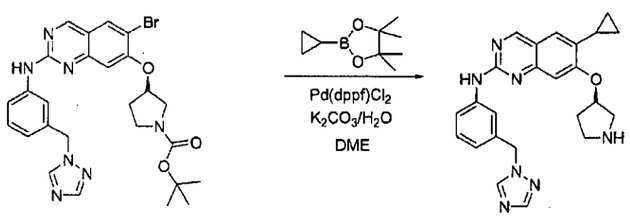
To a 0.1M solution of (S)-tert-butyl 3-(2-(3-((1H-1,2,4-triazol-1-yl)methyl) phenylamino)-6-bromoquinazolin-7-yloxy)pyrrolidine-1-carboxylate (0.18 mmol) in DMF was added zinc cyanide (5.0eq), Pd(dppf)Cl2CH2Cl2 (0.2eq), and diisopropylethyl amine (1.5eq). The mixture was microwaved at 150°C for 20mins. Complete conversion to the product was seen by LC/MS. The mixture was partitioned between ethyl acetate and water. The organic layer was dried (Na_2SO_4) and was concentrated. The residue was treated with 50% TFA/DCM and stirred for 10 min to remove tert-butylcarboxylate group. The crude compound was then purified by RP HPLC to give desired product (S)-2-(3-((1H-1,2,4-triazol-1-yl)methyl)phenylamino)-7-(pyrrolidin-3-yloxy)quinazoline-6-carbonitrile. ES/MS *m/z* 413 (MH^+).

Example 765: Preparation of (S)-N-(3-((1H-1,2,4-triazol-1-yl)methyl)phenyl)-6-methyl-7-(pyrrolidin-3-yloxy)quinazolin-2-amine



To a 0.06 M solution of (S)-tert-butyl 3-(2-(3-((1H-1,2,4-triazol-1-yl)methyl) phenylamino)-6-bromoquinazolin-7-yloxy)pyrrolidine-1-carboxylate (0.11 mmol) in DMF was added trimethylboroxine (4.0eq), Pd(dppf)Cl2CH2Cl2 (0.1eq), and 2.0M potassium carbonate aqueous solution (4.0eq). The mixture was microwaved at 120 °C for 20mins. Complete conversion to the product was seen by LC/MS. The mixture was partitioned between ethyl acetate and water. The organic layer was dried (Na_2SO_4) and was concentrated. The residue was treated with 50% TFA/DCM and stirred for 10 min to remove tert-butylcarboxylate group. The crude compound was then purified by RP HPLC to give desired product (S)-N-(3-((1H-1,2,4-triazol-1-yl)methyl)phenyl)-6-methyl-7-(pyrrolidin-3-yloxy)quinazolin-2-amine. ES/MS *m/z* 402 (MH^+).

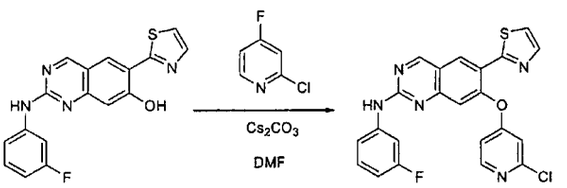
Example 764: Preparation of (S)-N-(3-((1H-1,2,4-triazol-1-yl)methyl)phenyl)-6-cyclopropyl-7-(pyrrolidin-3-yloxy)quinazolin-2-amine



To a 0.06 M solution of (S)-tert-butyl 3-(2-(3-((1H-1,2,4-triazol-1-yl)methyl) phenylamino)-6-bromoquinazolin-7-yloxy)pyrrolidine-1-carboxylate (0.13 mmol) in DME

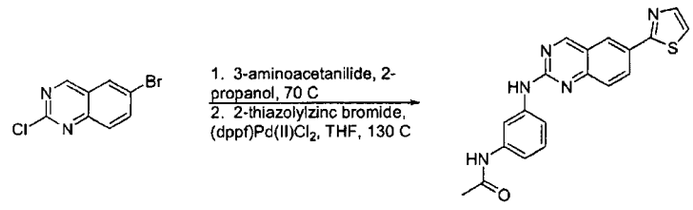
was added 2-cyclopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10eq), Pd(dppf)Cl2CH2Cl2 (0.2eq), and 2.0M potassium carbonate aqueous solution (4.0eq). The mixture was microwaved at 120°C for 20mins. Complete conversion to the product was confirmed by LC/MS. The mixture was partitioned between ethyl acetate and water. The organic layer was dried (Na_2SO_4) and was concentrated. The residue was treated with 50% TFA/DCM and stirred for 10 min to remove tert-butylcarboxylate group. The crude compound was then purified by RP HPLC to give desired product (S)-N-(3-((1H-1,2,4-triazol-1-yl)methyl)phenyl)-6-cyclopropyl-7-(pyrrolidin-3-yloxy)quinazolin-2-amine. ES/MS *m/z* 428 (MH^+).

Example 797: Preparation of 7-(2-chloropyridin-4-yloxy)-N-(3-fluorophenyl)-6-(thiazol-2-yl)quinazolin-2-amine



A 0.1 M suspension of 2-(3-fluorophenylamino)-6-(thiazol-2-yl)quinazolin-7-ol (0.15 mmol), 2-chloro-4-fluoropyridine (1.5eq), Cesium carbonate (3.0eq) in DMF was heated to 95 °C in an oil bath for 18 h. LCMS data indicated desired product formation. The mixture was partitioned between ethyl acetate and water. The organic layer was dried (Na_2SO_4) and was concentrated. The crude compound was then purified by RP HPLC to give desired product 7-(2-chloropyridin-4-yloxy)-N-(3-fluorophenyl)-6-(thiazol-2-yl)quinazolin-2-amine. ES/MS *m/z* 450 (MH^+).

Example 902: N-(3-(6-(thiazol-2-yl)quinazolin-2-ylamino)phenyl)acetamide



Step 1. Displacement

A mixture of 6-bromo-2-chloroquinazoline (1 eq) and 3-aminoacetanilide (0.9 eq) in 2-propanol was heated to 70 °C for 16 hr and concentrated to give the crude product which was used without further purification.

Step 2. Negishi

To the product of step 1 was added a 0.5 M THF solution of 2-thiazolylzinc bromide (4.0 eq) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with DCM (0.10 eq). The reaction was microwaved at 130 °C for 10 min. The mixture was diluted with ethyl acetate and washed with aqueous EDTA pH~9 buffer. The organic phase was dried over sodium sulfate, and concentrated. Purification by reverse-phase HPLC and lyophilization gave the desired product as its TFA salt. ES/MS *m/z* 392 (MH^+).

6-Bromo-2,7-dichloroquinazoline



Step 1: Bromination

To a suspension of 2-amino-4-chlorobenzoic acid (2 g, 11.6 mmol) in chloroform (120 mL) was added dropwise bromine (1.1 equiv.) in chloroform (12 mL) solution. The mixture was stirred at RT for 16 hrs. The resulting white solid was collected by filtration and washed thoroughly with DCM until the filtrate was colorless. The solid was air-dried to give 3.35 g of white powder as HBr salt of 2-amino-5-bromo-4-chlorobenzoic acid (87% yield). ES/MS *m/z* 250/252 (MH^+).

Step 2: Reduction

To the above intermediate (3.35 g, 10.1 mmol) in THF (40 mL) at 0 °C was added borane-THF complex solution (1 M in THF, 40 mL, 4 equiv.). The mixture was stirred at RT for 18 hrs. Excess reagent was quenched by addition of ethanol (20 mL) slowly. Water was added and the pH (~3) was adjusted by adding sodium bicarbonate (sat. aq.) to pH 7. Volatiles were removed under reduced pressure. The resulting mixture was extracted with DCM. The organic extracts were combined, washed with brine, dried with sodium sulfate and concentrated to give the crude product as a white solid. ES/MS *m/z* 236/238 (MH^+)

Step 3: Oxidation

To the above intermediate (10.1 mmol) in DCM (80 mL) was added manganese (IV) oxide (MnO_2, 6 g, 70 mmol). The mixture was stirred at RT under argon for 40 hrs. The mixture was filtered through diatomaceous earth and washed thoroughly with DCM. The filtrate was concentrated *in vacuo* to give crude 2-amino-5-bromo-4-chlorobenzyl alcohol (3.3 g, orange solid) which was used for the next step without further purification. ES/MS *m/z* 234/236 (MH^+).

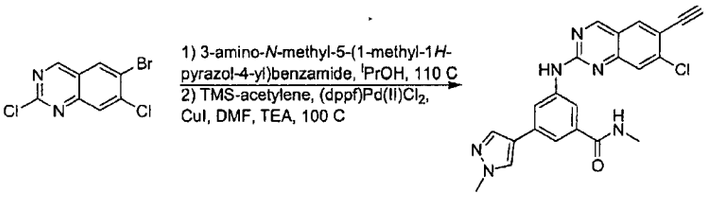
Step 4: Cyclization

A mixture of crude 2-amino-5-bromo-4-chlorobenzyl alcohol (3.3 g, obtained from Step 3) and urea (10.5 g, 15 equiv.) was heated to 170 °C with vigorous stirring for 1 hr. The reaction was cooled to RT and water was added. The solid was collected by filtration. The filtered solid was air-dried to give the crude product as a yellow powder (2.18 g, crude). ES/MS *m/z* 259/261 (MH^+).

Step 5: Chlorination

To the above crude material was added phosphorus oxychloride ($POCl_3$, 25 mL) and heated to 110 °C for 30 min. The resulting mixture was cooled to RT and concentrated *in vacuo* to nearly dryness. Ice water was added and pH was adjusted to ~8 using sodium bicarbonate. The mixture was extracted with DCM and the extract was dried with sodium sulfate and concentrated *in vacuo*. Crude 6-bromo-2,7-dichloroquinazoline was purified by flash chromatography over silica gel eluting with 2:1 hexanes:ethyl acetate. ES/MS *m/z* 279 (MH^+).

Example 904: 3-(7-chloro-6-ethynylquinazolin-2-ylamino)-N-methyl-5-(1-methyl-1H-pyrazol-4-yl)benzamide



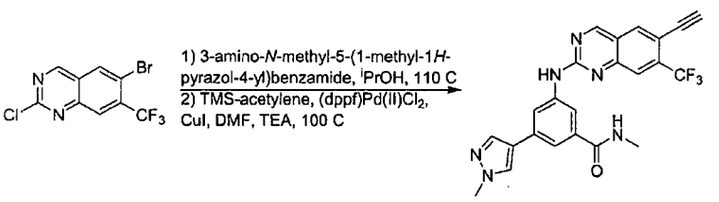
Step 1. Displacement

A mixture of 6-bromo-2,7-dichloroquinazoline (1 eq) and 3-amino-N-methyl-5-(1-methyl-1H-pyrazol-4-yl)benzamide (1 eq) in 2-propanol was heated to 110 °C for 16 hr and concentrated to give the crude product which was used without further purification.

Step 2. Sonogashira and desilylation

To a 0.15 M solution of the product of step 1 in de-gassed 1:1 DMF:TEA was added TMS-acetylene (4.0 eq); copper(I) iodide (0.10 eq); and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with DCM (0.050 eq). The reaction was stirred at 100 °C for 40 min. The mixture was concentrated and re-dissolved in 3:2 tetrahydrofuran:methanol to make a 0.15 M solution. A 6M aqueous solution of sodium hydroxide (2.5 eq) was added, and the mixture was stirred for 20 min. Volatiles were removed under reduced pressure. The residue was purified by reverse-phase HPLC and lyophilized to give the desired product as its TFA salt. ES/MS m/z 417.1 (MH^+).

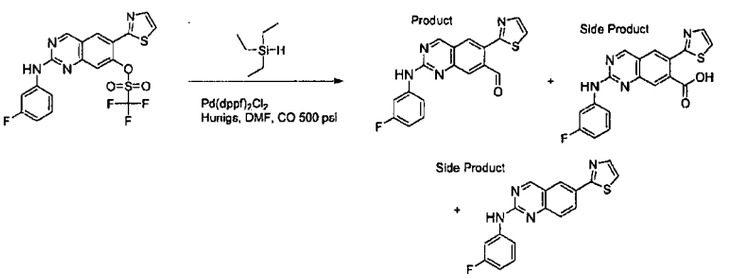
Example 905: 3-(6-ethynyl-7-(trifluoromethyl)quinazolin-2-ylamino)-N-methyl-5-(1-methyl-1H-pyrazol-4-yl)benzamide



3-(6-Ethynyl-7-(trifluoromethyl)quinazolin-2-ylamino)-N-methyl-5-(1-methyl-1H-pyrazol-4-yl)benzamide was prepared following Examples 62 and 63. ES/MS *m/z* 451.0 (MH^+).

Example 907: 2-(3-fluorophenylamino)-6-(thiazol-2-yl)quinazoline-7-carbaldehyde

The subject compound was prepared according to the general Scheme below:



2-(3-fluorophenylamino)-6-(thiazol-2-yl)quinazoline-7-carbaldehyde

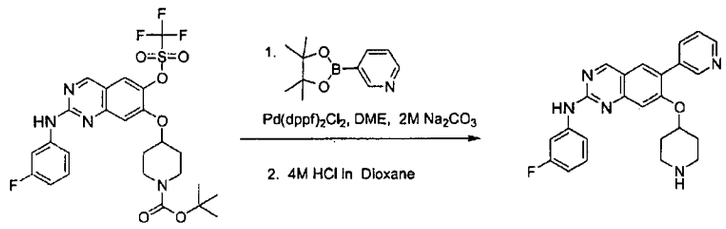
To the reaction mixture of 2-(3-fluorophenylamino)-6-(thiazol-2-yl)quinazolin-7-yl trifluoromethanesulfonate (50 mg, 0.106mmol) in 1.4 ml of DMF in a steel bomb was added $Pd(dppf)_2Cl_2$ (8.7 mg, 0.0106 mmol), triethylsilane (37 mg , 0.318 mmol) and TEA (0.037 ml, 0.265 mmol). The steel bomb was sealed and carefully CO was added to 500 psi. and slowly released (3x in a Hood) then recharged to 500 psi. and stirred at 50-55°C for 18 hours. This reaction mixture was cooled and vented in a hood. The crude reaction mixture was filtered, purified on prep HPLC and lyophilized to give, 2-(3-fluorophenylamino)-6-(thiazol-2-yl)quinazoline-7-carbaldehyde as TFA salt (6.0 mg) . ES/MS *m/z* 351(MH^+).

Side Products

In addition two side products were also collect on prep HPLC and lyophilized to give, 2-(3-fluorophenylamino)-6-(thiazol-2-yl)quinazoline-7-carboxylic acid as TFA salt (8.0 mg) ES/MS *m/z* 367(MH^+) and N-(3-fluorophenyl)-6-(thiazol-2-yl)quinazolin-2-amine as TFA salt (3.3 mg) ES/MS *m/z* 323(MH^+).

Example 916: N-(3-fluorophenyl)-7-(piperidin-4-yloxy)-6-(pyridin-3-yl)quinazolin-2-amine

The subject compound was prepared according to the general Scheme below:



Step 1: tert-butyl 4-(2-(3-fluorophenylamino)-6-(pyridin-3-yl)quinazolin-7-yloxy)piperidine-1-carboxylate

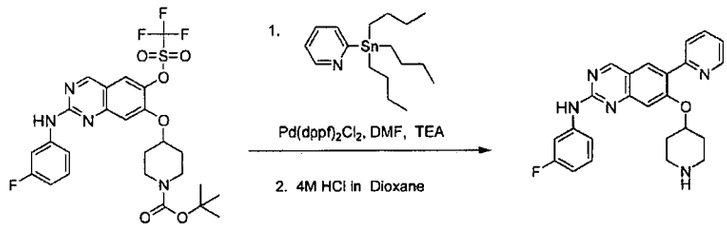
To the reaction mixture of, tert-butyl 4-(2-(3-fluorophenylamino)-6-(trifluoromethylsulfonyloxy)quinazolin-7-yloxy)piperidine-1-carboxylate (30 mg, 0.058 mmol) in 0.7 ml of DME was added $Pd(dppf)_2Cl_2$ (9.5 mg, 0.0116 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (36 mg, 0.174 mmol) and last add 2M Na_2CO_3 (0.2 ml, 0.4 mmol). This reaction mixture was stirred at 100 °C for 3 hours or until done by LCMS. To the crude reaction mixture add 1.5 ml of methanol, transfer the reaction and concentrate to solid to give a crude product, tert-butyl 4-(2-(3-fluorophenylamino)-6-(pyridin-3-yl)quinazolin-7-yloxy)piperidine-1-carboxylate used in next step without purification. ES/MS *m/z* 516(MH^+).

Step 2: N-(3-fluorophenyl)-7-(piperidin-4-yloxy)-6-(pyridin-3-yl)quinazolin-2-amine

To the crude reaction mixture of tert-butyl 4-(2-(3-fluorophenylamino)-6-(pyridin-3-yl)quinazolin-7-yloxy)piperidine-1-carboxylate (0.058 mmol) was added 4M HCl in Dioxane (4.0 ml, 16.0 mmol). The reaction mixture was stirred at room temperature for 1 hours or until done by LCMS. The crude reaction mixture was concentrate, about 1 ml of DMF was added, filtered, purified on prep HPLC and lyophilized to give N-(3-fluorophenyl)-7-(piperidin-4-yloxy)-6-(pyridin-3-yl)quinazolin-2-amine as TFA salt (8.3 mg). ES/MS *m/z* 416(MH^+).

Example 913: N-(3-fluorophenyl)-7-(piperidin-4-yloxy)-6-(pyridin-2-yl)quinazolin-2-amine

The subject compound was prepared according to the general Scheme below:



Step 1: tert-butyl 4-(2-(3-fluorophenylamino)-6-(pyridin-2-yl)quinazolin-7-yloxy)piperidine-1-carboxylate

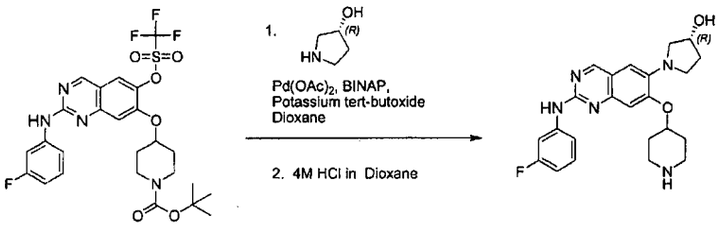
To the reaction mixture of tert-butyl 4-(2-(3-fluorophenylamino)-6-(trifluoromethylsulfonyloxy)quinazolin-7-yloxy)piperidine-1-carboxylate (30 mg, 0.058 mmol) in 0.5 ml of DMF was added $Pd(dppf)_2Cl_2$ (9.5 mg, 0.0116 mmol), 2-(tributylstannyl)pyridine (66 mg, 0.174 mmol) and last add TEA (0.021 ml, 0.145 mmol). This reaction mixture was stirred at 105°C for 1 hours or microwaved at 120°C for 800 seconds until done by LCMS. The crude reaction mixture with product, tert-butyl 4-(2-(3-fluorophenylamino)-6-(pyridin-2-yl)quinazolin-7-yloxy)piperidine-1-carboxylate was use in the next step without purification. ES/MS *m/z* 516(MH^+).

Step 2: N-(3-fluorophenyl)-7-(piperidin-4-yloxy)-6-(pyridin-2-yl)quinazolin-2-amine

To the crude reaction mixture of, tert-butyl 4-(2-(3-fluorophenylamino)-6-(pyridin-3-yl)quinazolin-7-yloxy)piperidine-1-carboxylate (0.058 mmol) was added 4M HCl in Dioxane (3.0 ml, 12.0 mmol). The reaction mixture was stirred at room temperature for 1 hours or until done by LCMS. The crude reaction mixture was concentrate, about 1 ml of DMF was added, filtered, purified on prep HPLC and lyophilized to give, N-(3-fluorophenyl)-7-(piperidin-4-yloxy)-6-(pyridin-2-yl)quinazolin-2-amine as TFA salt (4.6 mg). ES/MS *m/z* 416(MH^+).

Example 920: (R)-1-(2-(3-fluorophenylamino)-7-(piperidin-4-yloxy)quinazolin-6-yl)pyrrolidin-3-ol

The subject compound was prepared according to the general Scheme below:



Step 1: (R)-tert-butyl 4-(2-(3-fluorophenylamino)-6-(3-hydroxypyrrolidin-1-yl)quinazolin-7-yloxy)piperidine-1-carboxylate

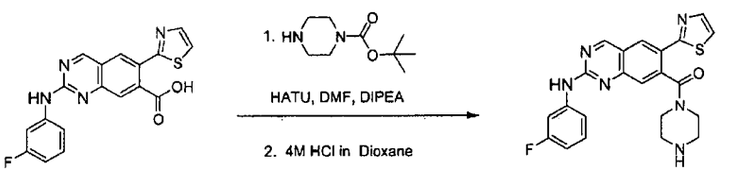
To the reaction mixture of $Pd(OAc)_2$ (9.5 mg, 0.0116 mmol) and BINAP (10.8 mg, 0.0174 mmol) add 0.5 ml of dioxane and stir for 3-5 minutes at room temperature. To this reaction mixture add, tert-butyl 4-(2-(3-fluorophenylamino)-6-(trifluoromethylsulfonyloxy)quinazolin-7-yloxy)piperidine-1-carboxylate (30 mg, 0.058 mmol), (R)-pyrrolidin-3-ol (20 mg, 0.232 mmol) and then last add potassium tertbutoxide (19.5 mg, 0.174 mmol). This reaction mixture was stirred at 90°C for 5 hours or until done by LCMS. The crude reaction mixture with product, (R)-tert-butyl 4-(2-(3-fluorophenylamino)-6-(3-hydroxypyrrolidin-1-yl)quinazolin-7-yloxy)piperidine-1-carboxylate was use in the next step without purification. ES/MS *m/z* 524(MH^+).

Step 2: (R)-1-(2-(3-fluorophenylamino)-7-(piperidin-4-yloxy)quinazolin-6-yl)pyrrolidin-3-ol

To the crude reaction mixture of (R)-tert-butyl 4-(2-(3-fluorophenylamino)-6-(3-hydroxypyrrolidin-1-yl)quinazolin-7-yloxy)piperidine-1-carboxylate (0.058 mmol) was added 4M HCl in Dioxane (3.0 ml, 12.0 mmol). The reaction mixture was stirred at room temperature for 1 hours or until done by LCMS. The crude reaction mixture was concentrate, about 1 ml of DMF was added (if needed add about 0.2 ml of water), filter, purified on prep HPLC and lyophilized to give, (R)-1-(2-(3-fluorophenylamino)-7-(piperidin-4-yloxy)quinazolin-6-yl)pyrrolidin-3-ol as TFA salt (1.1 mg). ES/MS *m/z* 424(MH^+).

Example 909: (2-(3-fluorophenylamino)-6-(thiazol-2-yl)quinazolin-7-yl)(piperazin-1-yl)methanone

The subject compound was prepared according to the general Scheme below:



Step 1: tert-butyl 4-(2-(3-fluorophenylamino)-6-(thiazol-2-yl)quinazoline-7-carbonyl)piperazine-1-carboxylate

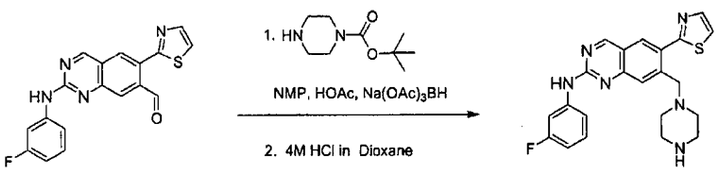
To the reaction mixture of 2-(3-fluorophenylamino)-6-(thiazol-2-yl)quinazoline-7-carboxylic acid (7 mg, 0.019 mmol) in 0.4 ml of DMF add HATU (18.2 mg, 0.048 mmol), DIPEA (0.014 ml, 0.076 mmol) and stir at room temperature for about 3-5 minutes. To the above reaction mixture add tert-butyl piperazine-1-carboxylate (14 mg, 0.076 mmol) and stir at room temperature for 2 hours or until done by LCMS. The crude reaction mixture with product, tert-butyl 4-(2-(3-fluorophenylamino)-6-(thiazol-2-yl)quinazoline-7-carbonyl)piperazine-1-carboxylate was use in the next step without purification. ES/MS *m/z* 535(MH^+).

Step 2: (2-(3-fluorophenylamino)-6-(thiazol-2-yl)quinazolin-7-yl)(piperazin-1-yl)methanone

To the crude reaction mixture of tert-butyl 4-(2-(3-fluorophenylamino)-6-(thiazol-2-yl)quinazoline-7-carbonyl)piperazine-1-carboxylate (0.019 mmol) was added 4M HCl in Dioxane (2.0 ml, 8.0 mmol). The reaction mixture was stirred at room temperature for 1 hours or until done by LCMS. The crude reaction mixture was concentrate, about 1 ml of DMF was added, filtered, purified on prep HPLC and lyophilized to give, (2-(3-fluorophenylamino)-6-(thiazol-2-yl)quinazolin-7-yl)(piperazin-1-yl)methanone as TFA salt (2.1 mg). ES/MS *m/z* 435(MH^+).

Example 908: N-(3-fluorophenyl)-7-(piperazin-1-ylmethyl)-6-(thiazol-2-yl)quinazolin-2-amine

The subject compound was prepared according to the general Scheme below:



Step 1: tert-butyl 4-((2-(3-fluorophenylamino)-6-(thiazol-2-yl)quinazolin-7-yl)methyl)piperazine-1-carboxylate

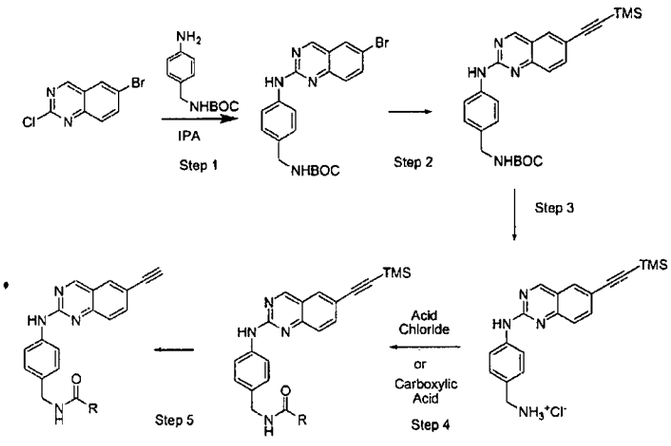
To the reaction mixture of 2-(3-fluorophenylamino)-6-(thiazol-2-yl)quinazoline-7-carbaldehyde (12 mg, 0.034 mmol) in 0.75 ml of NMP add acetic acid (0.070 ml , 1.02 mmol) and tert-butyl piperazine-1-carboxylate (65 mg, 0.35 mmol). This reaction mixture was stirred at room temperature for about 16 hours. To this reaction solution was added sodium triacetoxy borohydride (18 mg, 0.085 mmol) and stirred at room temperature 2 hours or until done by LCMS. The crude reaction mixture with product, tert-butyl 4-((2-(3-fluorophenylamino)-6-(thiazol-2-yl)quinazolin-7-yl)methyl)piperazine-1-carboxylate was use in the next step without purification. ES/MS *m/z* 521(MH^+).

Step 2: N-(3-fluorophenyl)-7-(piperazin-1-ylmethyl)-6-(thiazol-2-yl)quinazolin-2-amine

To the crude reaction mixture of tert-butyl 4-((2-(3-fluorophenylamino)-6-(thiazol-2-yl)quinazolin-7-yl)methyl)piperazine-1-carboxylate (0.034 mmol) was added 4M HCl in Dioxane (4.0 ml, 16.0 mmol). The reaction mixture was stirred at room temperature for 1 hours or until done by LCMS. The crude reaction mixture was concentrate, about 1 ml of DMF was added, filtered, purified on prep HPLC and lyophilized to give, N-(3-fluorophenyl)-7-(piperazin-1-ylmethyl)-6-(thiazol-2-yl)quinazolin-2-amine as TFA salt (1.7 mg). ES/MS *m/z* 421(MH^+).

Examples 1161, 1165-1171, and 1174

The subject compounds were prepared according to the general Scheme below:



Step 1:

This reaction was conducted in a similar manner to that described in Example 9, step 5.

Step 2:

This reaction was conducted in a similar manner to that described in Example 10, step 1.

Step 3:

Boc Amine was dissolved in Dioxane and treated with 4 M HCl/Dioxane (20 eq). Reaction stirred at room temperature for 2 hours. Reaction was concentrated to a white solid identified as desired product.

Step 4:

Method A

Amine was dissolved in DMF and Et_3N (3 eq) at room temperature and treated with appropriate acid chloride (1.5 eq). Reaction stirred at room temperature for 10 hours and was directly purified by RPHPLC to yield desired compounds.

Method B

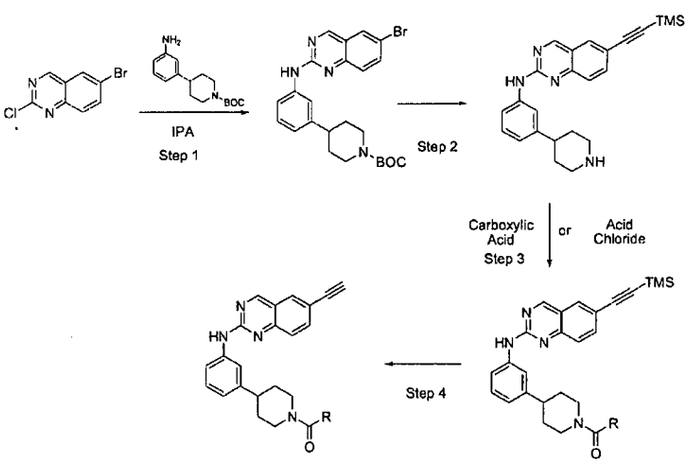
Amine, HOAT (1.5 eq), HATU (1.5 eq) and Et_3N (3.0 eq) were combined in DMF. Corresponding carboxylic acid (1.2 eq) was added and reactions stirred at room temperature for 10 hours and was directly purified by RPHPLC to yield desired compounds

Step 5:

This reaction was conducted in a similar manner to that described in Example 10, step 2.

Examples 1153-1155, 1157, 1158, 1160, 1162-1164, 1172, and 1173

The subject compounds were prepared according to the general Scheme below:



Step 1:

This reaction was conducted in a similar manner to that described in Example 9, step 5.

Step 2:

This reaction was conducted in a similar manner to that described in Example 10, step 1.

Step 3:

Method A

Amine was dissolved in DMF and Et_3N (3 eq) at room temperature and treated with appropriate acid chloride (1.5 eq). Reactions stirred at room temperature for 10 hours and was directly purified by RPHPLC to yield desired compounds

Method B .

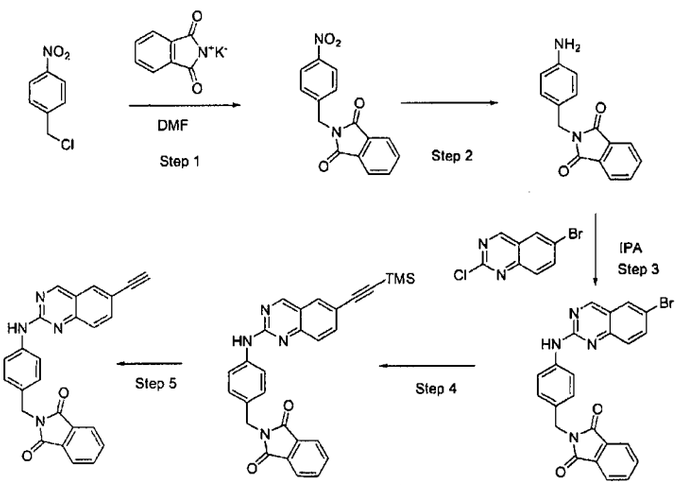
Amine, HOAT (1.5 eq), HATU (1.5 eq) and Et_3N (3.0 eq) were combined in DMF. Corresponding carboxylic acid (1.2 eq) was added and reactions stirred at room temp for 10 hours and was directly purified by RPHPLC to yield desired compounds.

Step 4:

This reaction was conducted in a similar manner to that described in Example 10, step 2.

Examples 1156 and 1159

The subject compounds were prepared according to the general Scheme below:



Step 1:

Chloride and potassium phthalamide (1.5 eq) were combined in DMF and heated at 120 °C for 10 minutes in the microwave. Reaction was concentrated and purified on silica with a 0 to 100% EtOAc/Hexane gradient to provide desired compound as a white solid.

Step 2:

This reaction was conducted in a similar manner to that described in Example 459, step 1.

Step 3:

This reaction was conducted in a similar manner to that described in Example 9, step 5.

Step 4:

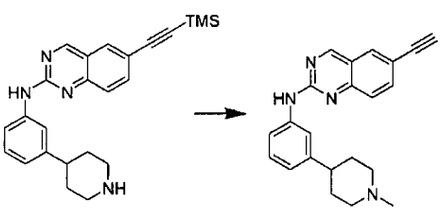
This reaction was conducted in a similar manner to that described in Example 10, step 1.

Step 5:

This reaction was conducted in a similar manner to that described in Example 10, step 2.

Example 1175

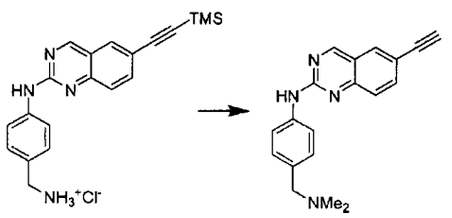
The subject compound was prepared according to the general Scheme below:



Amine (from Example 1153 or 1154) and formaldehyde (5.0 eq of 37% aq. Solution) were suspended in CH_2Cl_2 at room temperature. Sodium triacctoxyborohydride was added at once and reaction stirred for 10 hours. After this time, reaction was quenched by addition of water followed by concentration and purification by RPHPLC. Purified fractions were combined and treated as per Example 10, step 2 to yield desired compound.

Example 1176

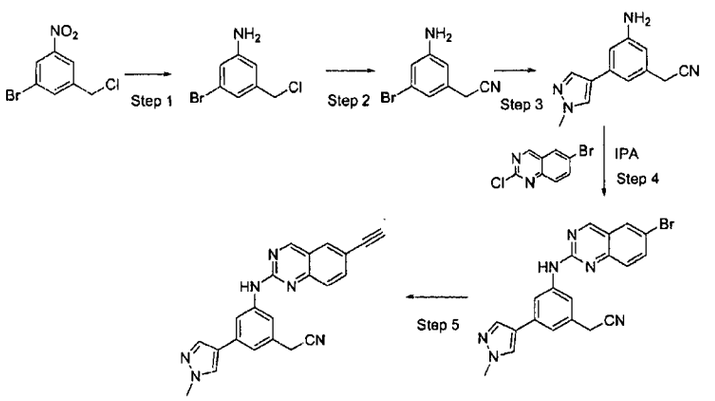
The subject compound was prepared according to the general Scheme below:



Amine (from Example 1161 or 1165) and formaldehyde (5.0 eq of 37% aq. Solution) were suspended in CH_2Cl_2 at room temperature. Sodium triacetoxyborohydride was added at once and reaction stirred for 10 hours. After this time, reaction was quenched by addition of water followed by concentration and purification by RPHPLC. Purified fractions were combined and treated as per Example 10, step 2 to yield desired compound.

Example 1151

The subject compound was prepared according to the general Scheme below:



Step 1:

Nitro and $SnCl_2$-$(H_2O)_2$ (10 eq) were combined in a solution of isopropanol and 12 N HCl. Reaction was heated at 110 °C for 2 hours and was concentrated to 25% original volume. Resulting suspension was dissolved in a 3:1 mix of EtOAc:CH_2Cl_2 and slowly neutralized with $NaHCO_3$ (sat. aq.) to pH 7. Resulting mixture was filtered through a Celite plug and the organic layers were separated. The aqueous layer was extracted 3x with CH_2Cl_2 and the combined organics were dried and concentrated to provide 5.7 g of yellow solid which was used without further purification.

Step 2:

To a solution of amine in DMSO was added NaCN (2.0 eq) at room temperature. Reaciton stirred for 1 hour and was quenched with water and extracted 2x with EtOAc. Combined organics were dried over $MgSO_4$ and concentrated to a yellow oil. Silica gel purification with a 0 to 80% gradient provided the desired product as a white solid.

Step 3:

This reaction was conducted in a similar manner to that described in Example 469, step 2.

Step 4:

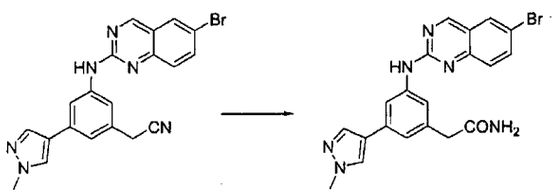
This reaction was conducted in a similar manner to that described in Example 9, step 5.

Step 5:

This conversion was achieved in a similar manner to that described in Example 10, step 1 and step 2.

Example 1177

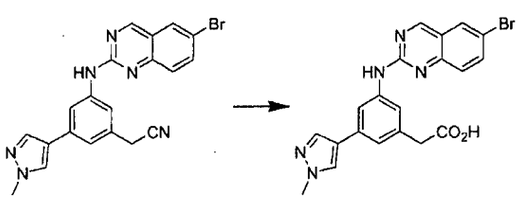
The subject compound was prepared according to the general Scheme below:



Nitrile (from Example 1151) was treated with 1N NaOH (10 eq) in microwave at 120 °C for 10 minutes. Reaction was purified directly by RPHPLC to provide desired product.

Example 1178

The subject compound was prepared according to the general Scheme below:

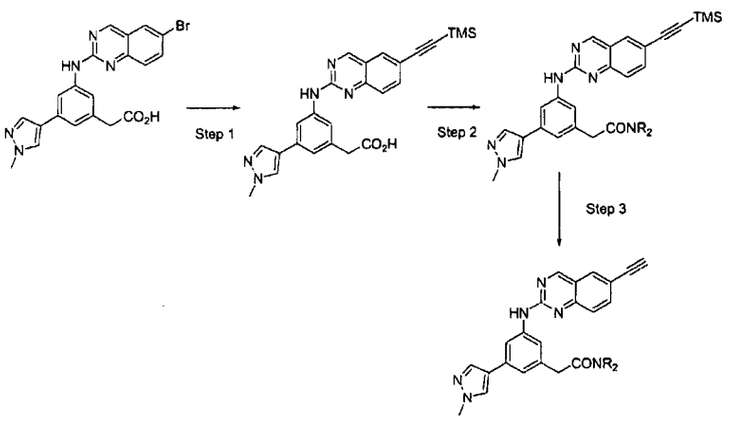


Nitrile (from Example 1151) was treated with 1N NaOH (10 eq) in sealed glass bomb at 110 °C for 12 hours. Reaction was cooled to room temperature and concentrated to 20%

original volume. 1N HCl was added to pH 7 and resulting yellow solid was collected and dried to provide desired product.

Examples 1179-1184

The subject compound was prepared according to the general Scheme below:



Step 1:

This reaction was conducted in a similar manner to that described in Example 10, step 1 using acid from Example 1178..

Step 2:

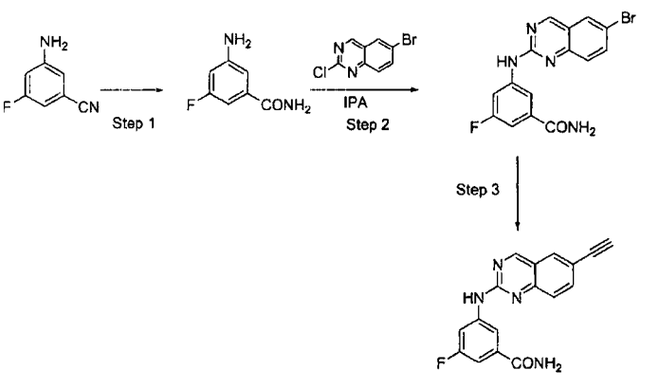
Acid, HOAT (1.5 eq), HATU (1.5 eq) and Et_3N (3.0 eq) were combined in DMF. Corresponding amine was added and reactions stirred at room temp for 10 hours and was directly purified by RPHPLC to yield desired compounds.

Step 3:

This reaction was conducted in a similar manner to that described in Example 10, step 2.

Example 1150

The subject compound was prepared according to the general Scheme below:



Step 1:

Amine was suspended in NH_4OH and heated at 130 °C for 15 minutes in microwave. Reaction was concentrated to a yellow solid which was used without further purification.

Step 2:

This reaction was conducted in a similar manner to that described in Example 9, step 5.

Step 3:

This conversion was achieved in a similar manner to that described in Example 10, step 1 and step 2.

Examples 1144-1149 and 1152

The subject compounds were prepared using commercially available amines according to the general procedures described in Example 9, step 5 and Example 10, step 1 and step 2.

Biological Examples

1. PDK1 Kinase Alpha Screen Assay

Reagents/Concentrations: The PDK1-4 peptide substrate, biotin-GGGGRTWTLCG-NH_2, (SEQ ID NO: 1), was purchased from the Tufts University Core Facility. The final concentration of PDK1-4 peptide substrate was 50 nM. The ATP substrate (adenosine-5'-triphosphate) was purchased from Roche Diagnostics. The final concentration of ATP substrate was 10μM. Phospho-(Ser/Thr) PKA substrate antibody was purchased from Cell Signaling Technology. The final concentration of antibody was 0.3 mg/mL. The Alpha Screen Protein A detection kit containing donor and acceptor beads was purchased from PerkinElmer Life Sciences. The final concentration of both donor and acceptor beads was 25 μg/mL. Alpha Screen was used for detection. The biotinylated-PDK1-4 peptide was phosphorylated by PDK1 kinase using the ATP substrate. The biotinylated-PDK1-4 peptide substrate was bound to the streptavidin coated donor bead. The antibody was bound to the protein A coated acceptor bead. The antibody bound to the phosphorylated form of the biotinylated PDK-1 peptide substrate, bringing the donor and acceptor beads into close proximity. Laser irradiation of the donor bead at 680nm generated a flow of short-lived singlet oxygen molecules. When the donor and acceptor beads were in close proximity, the reactive oxygen generated by the irradiation of the donor beads initiated a luminescence/fluorescence cascade in the acceptor beads. This process led to a highly amplified signal with output in the 530-620 nm range. Assays were carried out in 50 mM Tris, pH=7.5, 10 mM $MgCl_2$, 0.1% BSA, 0.01% Tween-20, 2 mM dithiolthreitol, 2.5% dimethyl sulfoxide. Reactions were stopped by adding 50 mM Tris, pH=7.5, 90 mM EDTA, 0.1% BSA, 0.01% Tween-20.

Procedure: To 10 μL of PDK1-4 peptide, 0.5 μl of test compound in dimethyl sulfoxide was added. PDK1 kinase and ATP were mixed, and 10 μL of the PDK1 kinase/ATP mix was added to start the reaction. The reaction was allowed to proceed for 3-18 hours. The reactions were then stopped by adding 10 μL of the EDTA-containing stop buffer. Beads were mixed with antibody, and 25 μL of the bead/antibody mix was then added to the stopped reactions. Plates were incubated at room temperature overnight to allow for detection development before being read. The assay was run in a 384-well format plate.

Results: As shown in Table 1 herein, of the Example compounds in the table, 140 compounds demonstrated IC_{50}'s of less than 25 μm in the above screen, and of those, 131 compounds demonstrated IC_{50}'s of less than 5 μm.

II. CDK1 (CDC2) Kinase Inhibition In Vitro Screen Assay

Reagents/Concentrations: Human full length Cdk1 is purchased from Upstate (# 14-450) as a co-purification with Cyclin B. The final enzyme concentration in the assay is 0.8 nM. Histone H1 peptide substrate is purchased from Research Genetics. The peptide, with the sequence lcBiotin-GGCGPKTPKKAKKL[$CONH_2$], (SEQ ID NO: 2), is used in the assay at a final concentration 0.5 μM. The ATP substrate (Adenosine-5'-triphosphate) was purchased from Roche Diagnostics. The final concentration of ATP substrate is 1 μM. P^{33} γ-ATP is purchased from NEN. The biotinylated peptide substrate is phosphorylated by Cdk1/Cyclin B enzyme, in the presence of varying concentrations of compounds, using the ATP substrate. A fraction of ATP in the reaction is radiolabeled to provide a detectable phosphorylation signal. The phosphorylation reaction is stopped with the addition of 25 mM EDTA. The solutions are then transferred to White BioBind Streptavidin Coated Assay plates, purchased from Thermo Electron Corporation. After washing, Microscint 20 scintillation fluid, purchased from Perkin Elmer, is added to each well and counts per minute (cpm) is measured using a Packard TopCount Microscintillation Counter. The highest cpms measured indicates the maximum phosphorylation of the substrate possible under the assay conditions. Reactions run without enzyme present give cpms indicative of complete inhibition of the enzyme. Each concentration of compound produced a measurable percent inhibition from the maximum signal based on these values. Assays were carried out in 50 mM Tris-HCl pH7.5, 10 mM $MgCl_2$, 1 mM DTT, 1 mM EGTA, 25 mM β-glycerol phosphate, 1 mM NaF, 0.01% BSA/PBS, 0.5 μM peptide substrate, and 0.8 nM Cdk1.

Procedure: Reaction Buffer (100 μL) containing 50 mM Tris-HCl pH7.5, 10 mM $MgCl_2$, 0.01% BSA/PBS, 1.5 mM DTT, 1.5 mM EGTA, 37.5 mM β-glycerol phosphate, 1.5 mM NaF, 0.75 μM peptide substrate, and 1.2 nM Cdk1 was distributed to each well. 100% inhibition control wells contain no Cdk1. The compounds to be tested were added to wells in desired 10X concentrations with 10% DMSO, 50 mM Tris-HCl pH7.5, 10 mM $MgCl_2$, and 0.01% BSA/PBS. The reactions were initiated by adding 15 μL of ATP concentrated at 10 μM, with P^{33} γ-ATP at < 10 nM as label. The reactions were allowed to continue for four

hours at room temperature with shaking. Streptavidin coated plates were blocked for one hour with 1% BSA in PBS. EDTA (100 µL, 50 mM) was added to each streptavidin well. An aliquot (100 µL) of each assay solution was transferred to the corresponding streptavidin well containing EDTA. The capture of radiolabeled substrate was then carried out by shaking the plate at room temperature for one hour. After binding the wells were washed 4 times with PBS, 200 µL Microscint 20 was added to each well, and cpms were measured. The assay was run in a 96-well format.

Results: Many of the compounds listed in Table 1 were screened according the method above, and exhibited an IC_{50} value of less than or equal to 25 µM, with respect to inhibition of Cdk1. Additionally, many of the compounds exhibited an IC_{50} of less than 10 µM, or less than 1 µM, or less than 0.1 µM.

III. CDK2 Kinase Inhibition *In Vitro* Screen Assay

Reagents/Concentrations: Human full length Cdk2 was purchased from Upstate (# 14-407) as a co-purification with Cyclin A. The final enzyme concentration in the assay was 5 nM. Histone H1 peptide substrate was purchased from Research Genetics. The peptide, with the sequence lcBiotin-GGCGPKTPKKAKKL[$CONH_2$], (SEQ ID NO: 2), was used in the assay at a final concentration 0.5 µM. The ATP substrate (adenosine-5'-triphosphate) was purchased from Roche Diagnostics. The final concentration of ATP substrate was 1 µM. P^{33} γ-ATP was purchased from NEN. The biotinylated peptide substrate was phosphorylated by Cdk2/Cyclin A enzyme, in the presence of varying concentrations of compounds, using the ATP substrate. A fraction of ATP in the reaction was radiolabeled to provide a detectable phosphorylation signal. The phosphorylation reaction was stopped by the addition of 25 mM EDTA. The solutions were then transferred to White BioBind Streptavidin Coated Assay plates, purchased from Thermo Electron Corporation. After washing, Microscint 20 scintillation fluid, purchased from Perkin Elmer, was added to each well and counts per minute (cpm) were measured using a Packard TopCount Microscintillation Counter. The highest cpms measured indicate the maximum phosphorylation of the substrate possible under the assay conditions. Reactions run without enzyme present gave cpms indicative of complete inhibition of the enzyme. Each concentration of compound produced a measurable percent inhibition from the maximum signal based on these values. Assays were carried out in 50 mM Tris-HCl pH7.5, 10 mM $MgCl_2$, 1 mM DTT, 1 mM EGTA, 25 mM β-glycerol phosphate, 1 mM NaF, 0.01% BSA/PBS, 0.5 µM peptide substrate, and 5 nM Cdk1.

Procedure: Reaction Buffer (100 μL) containing 50 mM Tris-HCl pH7.5, 10 mM $MgCl_2$, 0.01% BSA/PBS, 1.5 mM DTT, 1.5 mM EGTA, 37.5 mM β-glycerol phosphate, 1.5 mM NaF, 0.75 μM peptide substrate, and 7.5 nM Cdk2 was distributed to each well. 100% inhibition control wells contain no Cdk2. The compounds to be tested were added to wells in desired 10X concentrations with 10% DMSO, 50 mM Tris-HCl pH7.5, 10 mM $MgCl_2$, and 0.01% BSA/PBS. The reactions were initiated by adding 15 μL of ATP concentrated at 10 μM, with P^{33} γ-ATP at < 10 nM as label. The reactions were allowed to proceed for four hours at room temperature with shaking. Streptavidin coated plates were blocked for one hour with 1% BSA in PBS. EDTA (100 μL, 50 mM) was added to each streptavidin well. An aliquot (100 μL) of each assay solution was transferred to corresponding streptavidin wells containing EDTA. The radiolabeled substrate was captured by shaking at the plate at room temperature for one hour. After binding, the wells were washed 4 times with PBS, 200 μL Microscint 20 was added to each well, and cpms were measured. The assay was run in a 96-well format plate.

Results: Many of the compounds listed in Table 1 were screened according the method above, and exhibited an IC_{50} value of less than or equal to 25 μM, with respect to inhibition of Cdk2. Additionally, many of the compounds exhibited an IC_{50} of less than 10 μM, or less than 1 μM, or less than 0.1 μM. IC_{50} values for additional compounds are provided in Tables 2 and 3.

IV. Cell Proliferation Assay Protocol: A2780 of PC-3 Cell Line

A2780 or PC-3 cells were seeded at 1000 cells/well in 100 μL/well (10.000 cells/mL) growth media in 96-well plates. Cells were allowed to adhere to the bottom of plates for 3-5 hours in a 37 °C 5% CO_2 incubator. Compounds were dissolved in DMSO and then transferred to the cell plates. The cells were incubated with the compounds for 3 days in a 37 °C 5% CO_2 incubator. The growth medium containing the compounds was then removed from the cells and fresh medium was added, followed by 100 μL of Cell Titer Glo assay reagent (Promega). This mixture was shaken for 1 minute and then incubated without shaking for 10 minutes. Activity determinations for the compounds were made by detection on a Trilux Instrument. Of the Example compounds in Table 1, 101 compounds demonstrated IC_{50}'s of less than 10 μm and of those, 87 compounds demonstrated IC_{50}'s of less than 5 μm.

V. Cell Proliferation Assay Protocol: PC-3 Cell Line

PC-3 cells were seeded at 1000 cells/well in 100 μL/well (10.000 cells/mL) along with growth media into black-walled, clear bottom 96-well plates. The cells were allowed to adhere to the bottom of the plate for 3-5 hours in a 37 °C 5% CO_2 incubator.

Test compounds were diluted to 500x in DMSO. The DMSO solutions of six of the compounds were transferred to the cells in the 96 well round bottom plate, column 2, row B-F.

A 1:3 serial dilution of each compound was carried out. The serial dilution comprised adding 20 μL of DMSO to the wells containing the compounds and doing a 1:3 dilution across the plate from columns 2-10. Column 11 contained only DMSO. The serial dilution was carried out using a BioMek 2000 protocol "CP Serial Dilution using 250 μL tips" or "Proliferation Compound" (if using 20 μL tips).

To a 96 deep well block, columns 2-11 rows B-F, was transferred 500 μL of growth medium. Using the FX protocol "HH_CellAssay_2μL to 500 μL", 2 μL of compound from each cell of the compound plate was transferred to the corresponding cell in the 96 deep well block containing 500 μL of growth medium. The instrument was programmed to dilute the compound in growth medium and then transfer 100 μL of that mixture to cell plates containing cells.

The cell plates, to which test compounds had been added, were incubated for 3 days at 37 °C. Following the incubation, the medium was removed and replaced with fresh medium. Cell Titer Glo (100 μL) was added to each well and the plate was shaken for 1 minute and then incubated without shaking for 10 minutes. The plates were then read using a Trilux instrument.

VI. The $pAkt^{T308}$ ECL Assay Protocol

On Day 1, PC-3 cells were seeded at 15,000 cells/well in 100 μL/well (10.000 cells/mL) growth media into black-walled, clear bottom, poly-L-lysine coated plates. The cells were incubated overnight in a 37 °C, 5% CO_2 incubator.

On Day 2, a MSD ECL plate was blocked for two hours with 150 μL per well of 3% MSD blocker A.

Test compounds were diluted to 500x in DMSO and then were subjected to further serial dilution using a BioMek 2000 instrument. DMSO diluted compounds were then diluted into growth media and then added to the cell plates.

The cell plates incubated with compounds for six hours in a 37 °C, 5% CO_2 incubator after which the growth medium was removed and 55 µl of MSD lysis buffer was added to cell plates on ice. The plates were lysed on ice for five minutes followed by 15 minutes of vigorous shaking on a plate shaker at 4 °C. The blocked MSD assay plates were washed twice with 1x MSD wash buffer followed by the addition of cell lysate as follows: 30 µl of cell lysate was added to the pAkt308 plates and 13µl of lysate + 12µl lysis buffer was added to the tAkt plates. The plates were then sealed and shaken at 4 °C overnight.

On Day 3, the MSD plates were washed four times with 1x MSD wash buffer then, 25 µl/well of MSD SULFO-TAG antibodies diluted to 10nM final concentration in 1% blocker. A buffer was added to the antibody diluent which was added to assay plates. The plates were then sealed and incubated at RT for 1.5 hour. The plates were then washed twice with 1x MSD wash buffer followed by the addition of 150µl/well of 1.5x MSD read buffer. The plates were read immediately after the addition of read buffer using a Trilux instrument.

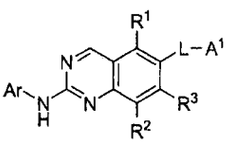
Of the Example compounds in Table 1, 62 compounds demonstrated IC_{50}'s of less than 10 µm and of those, 57 compounds demonstrated IC_{50}'s of less than 5 µm. Specific IC_{50} values for representative compounds are also provided in Tables 2 and 3 (see Figures 1 and 2).

The contents of each of the patents, patent applications and journal articles cited above are hereby incorporated by reference herein and for all purposes as if fully set forth in their entireties.

A number of embodiments of the invention have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the invention. Accordingly, other embodiments are within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A compound of Formula I:



I

or a pharmaceutically acceptable salt, ester, or tautomer thereof, wherein:

Ar is aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R^1 is H, C_{1-3} alkyl, halo, cyano, nitro, CF_3, imidazolyl, thiazolyl, oxazolyl, or amino;

R^2 is selected from the group consisting of H, alkoxy, substituted alkoxy, alkyl, substituted alkyl, CN, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, and halo;

R^3 is selected from the group consisting of H, halo, CN, carboxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryloxy, substituted aryloxy, cycloalkyloxy, substituted cycloalkyloxy, heterocyclylalkyloxy, substituted heterocyclylalkyloxy, heteroaryloxy, substituted heteroaryloxy, heteroarylalkyloxy, substituted heteroarylalkyloxy, arylalkyloxy, substituted arylalkyloxy, heteroaryl, substituted heteroaryl, heterocyclyl, substituted heterocyclyl, heteroarylalkyl, substituted heteroarylalkyl, heterocyclylalkyl, and substituted heterocyclylalkyl;

L is a covalent bond, carbonyl, carbonylamino, aminocarbonyl, -O-, -S-, -SO-, $-SO_2-$, -NH-, C_{1-3} alkyl, substituted C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl or an alkyl interrupted with -O-, -S-, -SO-, or $-SO_2-$;

A^1 is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, halo, hydroxy, nitro, SO_3H, sulfonyl, substituted sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, alkylthio, substituted alkylthio, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl, or substituted heterocyclyl;

with the provisos:

a) when R^1, R^2, and R^3 are each H and L is a covalent bond, then A^1 is other than aryl or substituted aryl;

b) when R^1, R^2, and R^3 are each H, L is a covalent bond, and A^1 is Br, substituted phenyl, or substituted pyridinyl, then Ar is other than phenyl, phenyl substituted with piperazinyl or heterocyclylalkyloxy, or pyridinyl;

c) when R^1, R^2, and R^3 are each H, L is a covalent bond, and A^1 is hydroxy or alkoxy, then Ar is other than phenyl substituted with one or more alkyl or halo; and

d) when R^1, R^2, and R^3 are each H and L is O, then A^1 is other than pyridinyl or substituted pyridinyl.

2. The compound according to claim 1, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein L is a covalent bond.

3. The compound according to claim 1, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein L is carbonyl.

4. The compound according to claim 1, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein L is -NH-.

5. The compound according to claim 1, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein L is aminocarbonyl or carbonylamino.

6. The compound according to claim 1, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein L is -O-.

7. The compound according to any of claims 1-6, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein A^1 is alkyl.

8. The compound according to any of claims 1-6, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein A^1 is alkynyl.

9. The compound according to claim 8, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein A^1 is ethynyl, propynyl, phenylethynyl or pyridylethynyl.

10. The compound according to any of claims 1-6, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein A^1 is aryl or substituted aryl.

11. The compound according to any of claims 1-6, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein A^1 is substituted phenyl.

12. The compound according to any of claims 1-6, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein A^1 is heteroaryl or substituted heteroaryl.

13. The compound according to claim 12, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein said heteroaryl or substituted heteroaryl is selected from the group consisting of pyridyl, pyrazolyl, thiazolyl, pyrimidyl, pyridazinyl, oxazolyl, isoxazolyl, substituted pyridyl, substituted pyrazolyl, substituted thiazolyl, substituted pyrimidyl, substituted pyridazinyl, substituted oxazolyl and substituted isoxazolyl.

14. The compound according to any of claims 1-6, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein A^1 is heterocyclyl or substituted heterocyclyl.

15. The compound according to claim 14, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein said heterocyclyl or substituted heterocyclyl is selected from the group consisting of piperidinyl, piperazinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, morpholinyl, thiomorpholino, substituted piperidinyl, substituted piperazinyl, substituted pyrrolidinyl, substituted tetrahydrofuranyl, substituted tetrahydrothiophenyl, substituted morpholinyl and substituted thiomorpholino.

16. The compound according to claim 2, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein A^1 is halo.

17. The compound according to claim 2, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein A^1 is cyano.

18. The compound according to any of claims 1-17, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein R^1 is H or halo.

19. The compound according to claim 18, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein R^2 and R^3 are independently selected from the group consisting of H, halo and alkoxy.

20. The compound according to claim 19, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein R^2 and R^3 are independently selected from the group consisting of H and methoxy.

21. The compound according to claim 20, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein at least one of R^2 and R^3 is H.

22. The compound according to claim 19, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein R^2 and R^3 are both H.

23. The compound of any of claims 1-17, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein one of R^2 and R^3 is H and the other of R^2 and R^3 is alkoxy, substituted alkoxy, aryloxy, substituted aryloxy, cycloalkyloxy, substituted cycloalkyloxy, heterocyclylalkyloxy, substituted heterocyclylalkyloxy, heteroaryloxy, substituted heteroaryloxy, heteroarylalkyloxy, substituted heteroarylalkyloxy, arylalkyloxy, or substituted arylalkyloxy,.

24. The compound according to any of claims 1-23, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein Ar is substituted aryl or substituted heteroaryl.

25. The compound according to claim 24, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein Ar is aryl, substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy, cycloalkenylthio, guanidino, substituted

guanidino, halo, hydroxy, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, substituted sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, and alkylthio;

wherein the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, heterocyclyl, and heteroaryl moieties contained within any of the listed substituted aryl groups are optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of alkenyl, alkynyl, alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy, cycloalkenylthio, guanidino, guanidino, halo, hydroxy, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, alkylthio, and alkylthio.

26. The compound according to claim 25, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein Ar is aryl substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of aminosulfonyl, aminocarbonyl, aryl, heteroaryl, heterocyclyl, amino, substituted amino, alkyl, halo, and cyano;

wherein the alkyl, aryl, and heteroaryl moieties contained within any of the listed substituted aryl groups are optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of alkenyl, alkynyl, alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy, cycloalkenylthio, guanidino, guanidino, halo, hydroxy, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, alkylthio, and alkylthio.

27. The compound according to claim 25, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein Ar is substituted phenyl.

28. The compound according to claim 24, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein Ar is heteroaryl, substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy, cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, substituted sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, and alkylthio;

wherein the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, heterocyclyl, and heteroaryl moieties contained within any of the listed substituted aryl groups are optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of alkenyl, alkynyl, alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio, cycloalkenyl, cycloalkenyloxy, cycloalkenylthio, guanidino, guanidino, halo, hydroxy, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, alkylthio, and alkylthio.

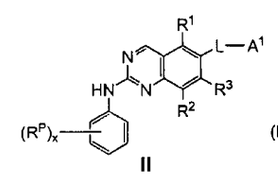
29. The compound according to claim 28, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein Ar is heteroaryl substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of aminosulfonyl, aminocarbonyl, aryl, heteroaryl, heterocyclyl, amino, substituted amino, alkyl, halo, and cyano;

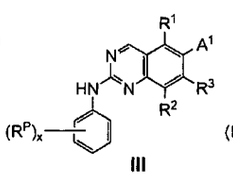
wherein the alkyl, aryl, and heteroaryl moieties contained within any of the listed substituted aryl groups are optionally substituted by 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of alkenyl, alkynyl, alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, cycloalkyloxy, cycloalkylthio,

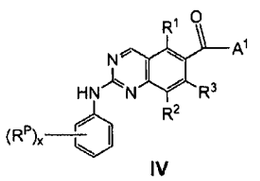
cycloalkenyl, cycloalkenyloxy, cycloalkenylthio, guanidino, guanidino, halo, hydroxy, heteroaryl, heteroaryloxy, heteroarylthio, heterocyclic, heterocyclyloxy, heterocyclylthio, nitro, SO_3H, sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, alkylthio, and alkylthio.

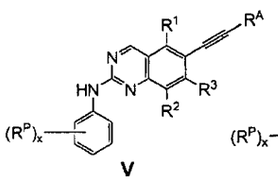
30. The compound according to claim 29, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein Ar is selected from the group consisting of substituted pyridyl, substituted pyrazolyl, substituted thiazolyl, substituted pyrimidyl, substituted pyridazinyl, substituted oxazolyl and substituted isoxazolyl.

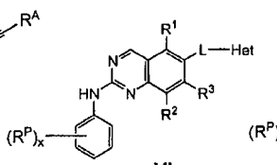
31. A compound according claim 1, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein the Formula I compound is a compound according to one of Formulae II-VII:

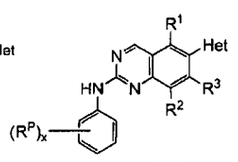

II


III


IV


V


VI


VII

wherein R^P is independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, aryloxy, substituted aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, cycloalkenyl, substituted cycloalkenyl, cycloalkenyloxy, substituted cycloalkenyloxy, cycloalkenylthio, substituted cycloalkenylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl,

heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO_3H, substituted sulfonyl, sulfonyloxy, sulfonylamino, thioacyl, thiol, alkylthio, and substituted alkylthio;

R^A is selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclyl and substituted heterocyclyl;

Het is selected from the group consisting of heteroaryl, substituted heteroaryl, heterocyclyl and substituted heterocyclyl; and

x is 1, 2, 3, 4 or 5.

32. The compound of claim 27, or pharmaceutically acceptable salt, ester, or tautomer thereof, wherein said substituted phenyl is substituted by 1, 2 or 3 groups that are not attached to said phenyl ortho to the NH of formula I.

33. A compound according to claim 1 selected from the group consisting of:

4-(6-bromo-8-methoxyquinazolin-2-ylamino)benzenesulfonamide;

4-(6-ethynyl-8-methoxyquinazolin-2-ylamino)benzenesulfonamide;

4-(6-ethyl-8-methoxyquinazolin-2-ylamino)benzenesulfonamide;

4-(6-cyano-8-methoxyquinazolin-2-ylamino)benzenesulfonamide;

4-(8-methoxy-6-methylquinazolin-2-ylamino)benzenesulfonamide;

N-(3-(6-bromo-8-chloroquinazolin-2-ylamino)-5-((dimethylamino)methyl)phenyl)-acetamide;

N-(3-(8-chloro-6-ethynylquinazolin-2-ylamino)-5-((dimethylamino)methyl)phenyl)-acetamide;

4-(8-bromo-6-(trifluoromethyl)quinazolin-2-ylamino)benzenesulfonamide;

4-(6-bromoquinazolin-2-ylamino)benzenesulfonamide;

4-(6-ethynylquinazolin-2-ylamino)benzenesulfonamide;

4-(6-bromoquinazolin-2-ylamino)-*N*-isopropylbenzamide;

N-isopropyl-4-(6-(thiazol-2-yl)quinazolin-2-ylamino)benzamide;

4-(6-cyanoquinazolin-2-ylamino)-*N*-isopropylbenzamide;

N-(3-(6-bromo-5-chloro-8-methoxyquinazolin-2-ylamino)-5-((dimethylamino)-methyl)phenyl)acetamide;

4-(8-bromo-6-fluoroquinazolin-2-ylamino)benzenesulfonamide;

N-(3-(6-bromoquinazolin-2-ylamino)-5-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)acetamide;

N-(3-(6-ethynylquinazolin-2-ylamino)-5-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)acetamide;

methyl 2-(4-sulfamoylphenylamino)quinazoline-6-carboxylate;

2-(4-sulfamoylphenylamino)quinazoline-6-carboxylic acid;

4-(6-(4-methylpiperazine-1-carbonyl)quinazolin-2-ylamino)benzenesulfonamide;

4-(6-(1-isobutyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)benzenesulfonamide;

(4-(5-chloro-6-ethynylquinazolin-2-ylamino)phenyl)(morpholino)methanone;

6-bromo-5-fluoro-*N*-(4-morpholinophenyl)-quinazolin-2-amine;

6-ethynyl-5-fluoro-*N*-(4-morpholinophenyl)-quinazolin-2-amine;

N-(3-(6-bromo-5-fluoroquinazolin-2-ylamino)-5-(morpholinomethyl)-phenyl)-acetamide;

N-(3-(5-fluoro-6-(thiazol-2-yl)quinazolin-2-ylamino)-5-(morpholinomethyl)phenyl)-acetamide;

4-(6-(thiazol-2-yl)quinazolin-2-ylamino)benzenesulfonamide;

5-chloro-*N*-(4-morpholinophenyl)-6-(thiazol-2-yl)quinazolin-2-amine;

N-(3-(6-bromoquinazolin-2-ylamino)-5-(morpholinomethyl)phenyl)acetamide;

N-

(3-(6-(1H-pyrazol-4-yl)quinazolin-2-ylamino)-5-(morpholinomethyl)phenyl)-acetamide;

N-(3-(6-bromoquinazolin-2-ylamino)-5-iodophenyl)acetamide;

N-(3-(6-bromoquinazolin-2-ylamino)-5-(pyridin-3-yl)phenyl)acetamide;

N-(3-(pyridin-3-yl)-5-(6-(pyridin-3-yl)quinazolin-2-ylamino)phenyl)acetamide;

N-(3-(6-ethynylquinazolin-2-ylamino)-5-(pyridin-3-yl)phenyl)acetamide;

4-(6,7-dimethoxyquinazolin-2-ylamino)benzenesulfonamide;

4-(6-methoxyquinazolin-2-ylamino)benzamide;

N-methyl-2-(4-sulfamoylphenylamino)quinazoline-6-carboxamide;

N-(1-methylpiperidin-4-yl)-2-(4-sulfamoylphenylamino)quinazoline-6-carboxamide;

4-(6-(4-isopropylpiperazine-1-carbonyl)quinazolin-2-ylamino)benzenesulfonamide;

N-isopropyl-2-(4-sulfamoylphenylamino)quinazoline-6-carboxamide;

4-(6-(pyrrolidine-1-carbonyl)quinazolin-2-ylamino)benzenesulfonamide;

2-(4-sulfamoylphenylamino)quinazoline-6-carboxamide;

N-cyclopropyl-2-(4-sulfamoylphenylamino)quinazoline-6-carboxamide;

4-(6-(2-fluoropyridin-3-yl)quinazolin-2-ylamino)benzenesulfonamide;

4-(6-(2-(4-methylpiperazin-1-yl)pyridin-4-yl)quinazolin-2-ylamino)benzene-sulfonamide;

N-(3-benzamidophenyl)-2-(4-sulfamoylphenylamino)-quinazoline-6-carboxamide;

4-(6-bromo-7-methoxyquinazolin-2-ylamino)benzenesulfonamide;

6-bromo-7-methoxy-*N*-(4-(morpholinosulfonyl)phenyl)-quinazolin-2-amine;

4-(6-ethynyl-7-methoxyquinazolin-2-ylamino)benzenesulfonamide;

6-ethynyl-7-methoxy-*N*-(4-(morpholinosulfonyl)phenyl)-quinazolin-2-amine;

6-ethynyl-*N*-(3-morpholinophenyl)quinazolin-2-amine;

4-(8-methoxy-6-(phenylethynyl)quinazolin-2-ylamino)benzenesulfonamide;

4-(8-methoxy-6-(pyridin-3-ylethynyl)quinazolin-2-ylamino)benzenesulfonamide;

4-(6-methylquinazolin-2-ylamino)benzenesulfonamide;

4-(7-methoxy-6-(phenylethynyl)quinazolin-2-ylamino)benzenesulfonamide;

4-(6-(1-methyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)benzenesulfonamide;

6-ethynyl-*N*-(4-morpholinophenyl)quinazolin-2-amine;

4-(6-ethynylquinazolin-2-ylamino)benzamide;

3-(6-ethynylquinazolin-2-ylamino)benzamide;

3-(6-ethynylquinazolin-2-ylamino)benzenesulfonamide;

N-(3-(6-ethynylquinazolin-2-ylamino)phenyl)methanesulfonamide;

4-(8-methoxy-6-(1-methyl-1H-pyrazol-4-yl)quinazolin-2-ylamino)benzene-sulfonamide;

4-(8-methoxy-6-(thiazol-2-yl)quinazolin-2-ylamino)benzenesulfonamide;

4-(8-methoxy-6-(pyridin-2-ylethynyl)quinazolin-2-ylamino)benzenesulfonamide;

4-(6-(3-hydroxy-3-methylbut-1-ynyl)-8-methoxyquinazolin-2-ylamino)benzene-sulfonamide;

4-(6-(3-amino-3-methylbut-1-ynyl)-8-methoxyquinazolin-2-ylamino)benzene-sulfonamide;

4-(6-(1H-pyrazol-3-yl)quinazolin-2-ylamino)benzenesulfonamide;

N-(2-(4-sulfamoylphenylamino)quinazolin-6-yl)acetamide;

6-ethynyl-7-methoxy-*N*-(4-morpholinophenyl)quinazolin-2-amine;

6-ethynyl-8-methoxy-*N*-(4-morpholinophenyl)quinazolin-2-amine;

N-(3-((dimethylamino)methyl)phenyl)-6-ethynylquinazolin-2-amine;

4-(6-ethynylquinazolin-2-ylamino)-*N*-isopropylbenzamide;

4-(6-ethynyl-7-methoxyquinazolin-2-ylamino)-*N*-isopropylbenzamide;

(4-(6-ethynyl-7-methoxyquinazolin-2-ylamino)phenyl)(morpholino)methanone;

4-(6-(thiazol-2-yl)quinazolin-2-ylamino)benzamide;

2-(4-morpholinophenylamino)quinazoline-6-carbonitrile;

6-bromo-*N*-(4-morpholinophenyl)quinazolin-2-amine;

4-(6-cyanoquinazolin-2-ylamino)benzamide;

4-(6-bromoquinazolin-2-ylamino)benzamide;

6-ethynyl-8-methoxy-*N*-(3-morpholinophenyl)quinazolin-2-amine;

(4-(6-ethynylquinazolin-2-ylamino)phenyl)(morpholino)methanone;

N-(3-((dimethylamino)methyl)-4-morpholinophenyl)-6-ethynylquinazolin-2-amine;

N-(3-((dimethylamino)methyl)-5-(6-ethynylquinazolin-2-ylamino)phenyl)acetamide;

N-(3-((dimethylamino)methyl)-5-(6-(thiazol-2-yl)quinazolin-2-ylamino)phenyl)-acetamide;

N-(3-((dimethylamino)methyl)-5-(6-ethynyl-7-methoxyquinazolin-2-ylamino)-phenyl)acetamide;

N-(3-((dimethylamino)methyl)-5-(6-ethynyl-8-methoxyquinazolin-2-ylamino)-phenyl)acetamide;

N-(3-((dimethylamino)methyl)-5-(8-methoxy-6-(thiazol-2-yl)quinazolin-2-ylamino)-phenyl)acetamide;

N-(3-(5-chloro-6-ethynyl-8-methoxyquinazolin-2-ylamino)-5-((dimethylamino)-methyl)phenyl)acetamide;

4-(6-bromo-5-chloro-8-methoxyquinazolin-2-ylamino)-*N*-isopropylbenzamide;

N-(3-(5-chloro-6-ethynylquinazolin-2-ylamino)-5-((dimethylamino)methyl)-phenyl)-acetamide;

N-(3-(5-chloro-6-(thiazol-2-yl)quinazolin-2-ylamino)-5-((dimethylamino)methyl)-phenyl)acetamide;

N-(3-((dimethylamino)methyl)-5-(6-(pyrimidin-5-yl)quinazolin-2-ylamino)phenyl)-acetamide;

N-(3-((dimethylamino)methyl)-5-(6-(2-methoxypyridin-3-yl)quinazolin-2-ylamino)-phenyl)acetamide;

N-(3-((dimethylamino)methyl)-5-(8-methoxy-6-(2-methoxypyridin-3-yl)quinazolin-2-ylamino)phenyl)acetamide;

N-(3-((dimethylamino)methyl)-5-(8-methoxy-6-(pyrimidin-5-yl)quinazolin-2-ylamino)phenyl)acetamide;

N-(4-(1H-tetrazol-5-yl)phenyl)-6-ethynyl-7-methoxyquinazolin-2-amine;

N-(4-(1H-tetrazol-1-yl)phenyl)-6-ethynyl-7-methoxyquinazolin-2-amine;

N-(3-(1H-tetrazol-5-yl)phenyl)-6-ethynyl-7-methoxyquinazolin-2-amine;

5-chloro-6-ethynyl-*N*-(4-morpholinophenyl)quinazolin-2-amine;

N-(4-morpholinophenyl)-6-(thiazol-2-yl)quinazolin-2-amine;

5-chloro-6-ethynyl-8-methoxy-*N*-(4-morpholinophenyl)quinazolin-2-amine;

(4-(6-bromo-7-methoxyquinazolin-2-ylamino)-2-chlorophenyl)(morpholino)-methanone;

N-(3-(1H-tetrazol-1-yl)phenyl)-6-ethynyl-7-methoxyquinazolin-2-amine;

(2-chloro-4-(7-methoxy-6-(thiazol-2-yl)quinazolin-2-ylamino)phenyl)(morpholino)-methanone;

N,N'-(5-(6-ethynylquinazolin-2-ylamino)-1,3-phenylene)diacetamide;

4-(5-chloro-6-ethynylquinazolin-2-ylamino)-*N*-isopropylbenzamide;

4-(5-chloro-6-ethynylquinazolin-2-ylamino)-*N*-cyclopropylbenzamide;

4-(5-chloro-6-(thiazol-2-yl)quinazolin-2-ylamino)-*N*-isopropylbenzamide;

N-(3-((dimethylamino)methyl)-5-(6-methoxyquinazolin-2-ylamino)phenyl)acetamide;

N-(3-((dimethylamino)methyl)-5-(8-methoxy-6-(6-methoxypyrazin-2-yl)quinazolin-2-ylamino)phenyl)acetamide;

N-(3-(6-(2-amino-4-methoxypyrimidin-5-yl)-8-methoxyquinazolin-2-ylamino)-5-((dimethylamino)methyl)-phenyl)acetamide;

N-(3-(1H-tetrazol-1-yl)phenyl)-7-methoxy-6-(thiazol-2-yl)quinazolin-2-amine;

(4-(5-chloro-6-ethynyl-8-methoxyquinazolin-2-ylamino)phenyl)(morpholino)-methanone;

4-(5-chloro-6-ethynyl-8-methoxyquinazolin-2-ylamino)-N-isopropylbenzamide;

5-chloro-8-methoxy-N-(4-morpholinophenyl)-6-(thiazol-2-yl)quinazolin-2-amine;

6-bromo-5-chloro-8-methoxy-N-(4-morpholinophenyl)quinazolin-2-amine;

(4-(5-chloro-8-methoxy-6-(thiazol-2-yl)quinazolin-2-ylamino)phenyl)-(morpholino)-methanone;

(4-(6-bromo-5-chloro-8-methoxyquinazolin-2-ylamino)phenyl)-(morpholino)-methanone;

4-(5-chloro-8-methoxy-6-(thiazol-2-yl)quinazolin-2-ylamino)-N-isopropylbenzamide;

(2-chloro-4-(6-ethynyl-7-methoxyquinazolin-2-ylamino)phenyl)(morpholino)-methanone;

5-chloro-6-ethynyl-N-(3-morpholinophenyl)quinazolin-2-amine;

N-(3-((dimethylamino)methyl)-5-(7-methoxy-6-(thiazol-2-yl)quinazolin-2-ylamino)-phenyl)acetamide;

5-(6-bromoquinazolin-2-ylamino)-2-morpholinobenzamide;

5-(6-ethynylquinazolin-2-ylamino)-2-morpholinobenzamide;

N-(3-(6-ethynylquinazolin-2-ylamino)-5-(morpholinomethyl)phenyl)acetamide;

N-(3-(pyrrolidin-1-ylmethyl)-5-(6-(thiazol-2-yl)quinazolin-2-ylamino)phenyl)-acetamide;

N-(3-(6-ethynylquinazolin-2-ylamino)-5-(pyrrolidin-1-ylmethyl)phenyl)acetamide;

N-(3-(6-bromo-8-chloroquinazolin-2-ylamino)-5-(morpholinomethyl)-phenyl)-acetamide;

N-(3-(8-chloro-6-ethynylquinazolin-2-ylamino)-5-(morpholinomethyl)-phenyl)-acetamide;

N,N'-(5-(5-chloro-6-ethynylquinazolin-2-ylamino)-1,3-phenylene)diacetamide;

N-(6-chloro-1H-indazol-4-yl)-6-ethynylquinazolin-2-amine;

6-ethynyl-N-(6-fluoro-1H-indazol-4-yl)quinazolin-2-amine;

N-(3-(morpholinomethyl)-5-(6-(thiazol-2-yl)quinazolin-2-ylamino)phenyl)acetamide;

7-methoxy-N-(4-morpholinophenyl)-6-(thiazol-2-yl)quinazolin-2-amine;

N-(3-(6-bromo-8-fluoroquinazolin-2-ylamino)-5-((dimethylamino)methyl)-phenyl)-acetamide;

N-(3-(6-(isoxazol-4-yl)quinazolin-2-ylamino)-5-(morpholinomethyl)phenyl)-acetamide;

N-(3-(aminomethyl)-5-(6-ethynylquinazolin-2-ylamino)phenyl)acetamide;

6-ethynyl-N-phenylquinazolin-2-amine;

N-(3-((dimethylamino)methyl)-5-(6-ethynyl-8-fluoroquinazolin-2-ylamino)phenyl)-acetamide;

N-(3-(7-methoxy-6-(thiazol-2-yl)quinazolin-2-ylamino)-5-(morpholinomethyl)-phenyl)-acetamide;

N-(3-(6-ethynylquinazolin-2-ylamino)-5-(piperazin-1-ylmethyl)phenyl)acetamide;

N-(3-(6-ethynylquinazolin-2-ylamino)-5-(morpholinomethyl)phenyl)-isobutyramide;

N-(3-(6-ethynylquinazolin-2-ylamino)-5-(morpholinomethyl)phenyl)methane-sulfonamide;

6-bromo-N-(3-(morpholinomethyl)-5-(1H-tetrazol-5-yl)phenyl)quinazolin-2-amine;

N-(3-(6-bromoquinazolin-2-ylamino)-5-(morpholinomethyl)phenyl)acetamide;

N-(3-(6-ethynylquinazolin-2-ylamino)-5-(pyridin-4-yl)phenyl)acetamide;

N-(3-(6-bromoquinazolin-2-ylamino)-5-((dimethylamino)methyl)phenyl)acetamide;

N-(3-((dimethylamino)methyl)-5-(6-(prop-1-ynyl)quinazolin-2-ylamino)phenyl)-acetamide;

6-ethynyl-N-(3-(morpholinomethyl)-5-(1H-tetrazol-5-yl)phenyl)quinazolin-2-amine;

7-methoxy-N-(4-morpholinophenyl)-6-(1H-pyrazol-4-yl)quinazolin-2-amine;

3-(6-bromoquinazolin-2-ylamino)-5-(morpholinomethyl)benzonitrile;

3-(6-ethynylquinazolin-2-ylamino)-5-(morpholinomethyl)benzonitrile;

N-(3-(6-bromoquinazolin-2-ylamino)-5-(1H-pyrazol-4-yl)phenyl)acetamide;

6-bromo-N-(3-methoxy-5-(5-methyl-1H-tetrazol-1-yl)phenyl)quinazolin-2-amine;

6-bromo-N-(3-methoxy-5-(1H-tetrazol-1-yl)phenyl)quinazolin-2-amine;

6-ethynyl-N-(3-methoxy-5-(5-methyl-1H-tetrazol-1-yl)phenyl)quinazolin-2-amine;

6-ethynyl-N-(3-morpholino-5-(pyridin-4-yl)phenyl)quinazolin-2-amine;

6-ethynyl-N-(3-morpholino-5-(1H-pyrazol-4-yl)phenyl)quinazolin-2-amine;

6-ethynyl-N-(3-morpholino-5-(pyridin-3-yl)phenyl)quinazolin-2-amine;

6-ethynyl-N-(3-(3-fluoropyridin-4-yl)-5-morpholinophenyl)quinazolin-2-amine;

N-(3-(6-ethynyl-5-fluoroquinazolin-2-ylamino)-5-(morpholinomethyl)-phenyl)-acetamide;

N-(3-(6-ethynyl-5-fluoroquinazolin-2-ylamino)-5-(morpholinomethyl)-phenyl)-methanesulfonamide;

3-(6-bromoquinazolin-2-ylamino)-5-(morpholinomethyl)benzamide;

N-(3-(6-ethynylquinazolin-2-ylamino)-5-(1H-pyrazol-4-yl)phenyl)acetamide;

N-(3-(6-ethynylquinazolin-2-ylamino)-5-(pyrimidin-5-yl)phenyl)acetamide;

methyl 3-(6-ethynylquinazolin-2-ylamino)-5-(morpholinomethyl)phenylcarbamate;

methyl 3-(6-bromoquinazolin-2-ylamino)-5-(morpholinomethyl)phenylcarbamate;

N-(4-morpholinophenyl)-5,6-di(thiazol-2-yl)quinazolin-2-amine;

8-methoxy-N-(4-morpholinophenyl)-5,6-di(thiazol-2-yl)quinazolin-2-amine;

(4-(8-methoxy-5,6-di(thiazol-2-yl)quinazolin-2-ylamino)phenyl)(morpholino)-methanone;

4-(5,6-di(thiazol-2-yl)quinazolin-2-ylamino)-N-isopropylbenzamide;

6-ethynyl-7-methoxy-N-(3-methoxy-5-(5-methyl-1H-tetrazol-1-yl)phenyl)quinazolin-2-amine;

6,7-dimethoxy-N-(4-morpholinophenyl)-quinazolin-2-amine;

N-(3-(6,7-dimethoxyquinazolin-2-ylamino)-5-(morpholinomethyl)-phenyl)acetamide;

N-(3-(7-methoxy-6-(1H-pyrazol-4-yl)quinazolin-2-ylamino)-5-(morpholinomethyl)-phenyl)acetamide; and

N-(3-(7-methoxy-6-(1H-pyrazol-4-yl)quinazolin-2-ylamino)-5-(1H-pyrazol-4-yl)phenyl)acetamide;

or a pharmaceutically acceptable salt, ester, or tautomer of one of these compounds.

34. The compound of claim 1, or pharmaceutically acceptable salt, ester, or tautomer thereof, which is selected from the compounds in Table 2 (Figure 1).

35. The compound of claim 1, or pharmaceutically acceptable salt, ester, or tautomer thereof, which is selected from the compounds in Table 3 (Figure 2).

36. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and at least one compound according to any one of the previous claims, or pharmaceutically acceptable salt, ester, or tautomer thereof.

37. A method of inhibiting PDK1 or a PDK1 variant in a patient comprising administering to said patient, a therapeutically effective amount of a compound of any one of claim 1 to 31, or pharmaceutically acceptable salt, ester, or tautomer thereof.

38. The method of claim 37, which comprises a method of inhibiting PDK1.

39. The method of claim 37, which comprises a method of inhibiting a PDK1 variant.

40. The method of claim 37 wherein said PDK1 variant is $PDK1^{T354M}$ or $PDK1^{D527E}$.

41. A method of treating a disease characterized by abnormal cellular proliferation in a patient comprising administering to said patient a therapeutically effective amount of a compound of any one of claims 1 to 35, or pharmaceutically acceptable salt, ester, or tautomer thereof.

42. The method of claim 41, wherein the abnormal cellular proliferation is mediated by PDK1.

43. The method of claim 41, wherein the disease is a cancer.

44. The method of claim 43, wherein the cancer is selected from the group consisting of: lung cancer, bronchial cancer, prostate cancer, breast cancer, pancreatic cancer, colon cancer, rectal cancer, colorectal cancer, thyroid cancer, liver cancer, intrahepatic bile duct cancer, hepatocellular cancer, gastric cancer, glioma/glioblastoma, endometrial cancer, melanoma, kidney cancer, renal pelvic cancer, urinary bladder cancer; uterine corpus cancer; uterine cervical cancer, ovarian cancer, multiple myeloma, esophageal cancer, acute myelogenous leukemia, chronic myelogenous leukemia, lymphocytic leukemia, myeloid leukemia, brain cancer, oral cavity cancer, and pharyngeal cancer, laryngeal cancer, small intestinal cancer, non-Hodgkin lymphoma, and villous colon adenoma.

45. The method of claim 44, wherein the cancer is selected from the group consisting of cancers of the prostate, lung, colon, and breast.

46. The method of claim 41, wherein the disease is a non-cancer proliferative disorder.

47. The method of claim 46, wherein the disease is selected from the group consisting of neuro-fibromatosis, atherosclerosis, pulmonary fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis, proliferative diabetic retinopathy, hypertrophic scar formation, inflammatory bowel disease, transplantation rejection, angiogenesis and endotoxic shock.

48. A method of inhibiting the tumor growth in a patient, the method comprising administering to said patient a therapeutically effective amount of a compound of any one of claims 1 to 31, or pharmaceutically acceptable salt, ester, or tautomer thereof.

49. The method of claim 48, wherein said tumor is characterized by elevated receptor tyrosine kinases, Ras, PI3K, PDK1, AKT, RSK, PKC, 70S6K, or SGK activity.

50. A method of treating cancer in a patient, the method comprising administering to said patient a therapeutically effective amount of a compound of any one of claims 1 to 31, or pharmaceutically acceptable salt, ester, or tautomer thereof.

51. The method of claim 50 wherein said cancer is characterized by increased activity of PDK1.

52. The method of claim 49 wherein said cancer is characterized by activity of a PDK1 variant.

53. The method of claim 52 wherein said PDK1 variant is $PDK1^{T354M}$ or $PDK1^{D527E}$.

Table 2

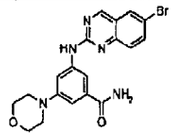
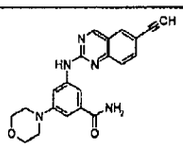
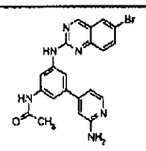
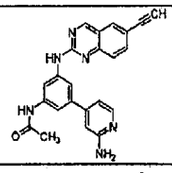
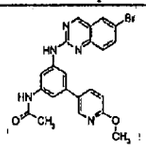
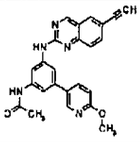
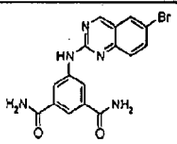
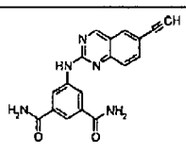
Example	Structure	Activity	Molecular Weight	LC/MS (4.5min run) MS (M+1) m/z Rt (min)	LC/MS (1.5min run) MS (M+1) m/z Rt (min)
177		*	428.2882	428/430 3.84	
178		***	373.4141	374.1 3.51	
179		**	449.3103	249/251 3.66	
180		***	394.4362	395.1 3.39	
181		*	464.3212	464/466 4.92	
182		***	409.4471	410.1 4.57	
183		*	386.2078	386/388 3.16	
184		**	331.3337	332.1 2.88	

FIG. 1 (PART 1 of 59)

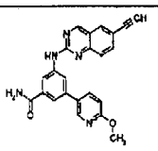
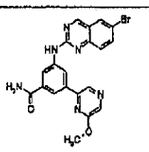
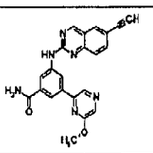
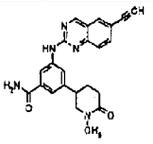
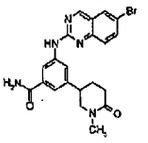
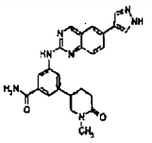
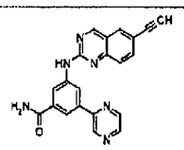
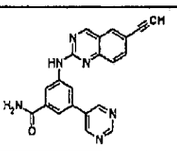
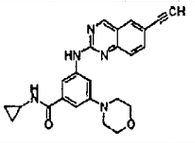
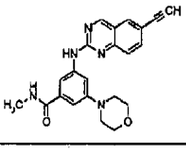
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189		**	454.326	454/456 3.64	
190		****	441.4927	442.1 2.51	
191		*	366.3826	367.1 3.77	
192		*	366.3826	367.1 3.56	
193		**	413.4787	414.1 4.14	
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FIG. 1 (PART 2 of 59)

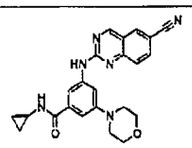
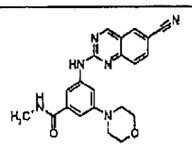
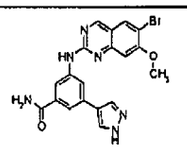
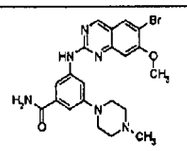
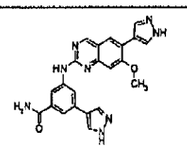
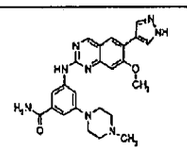
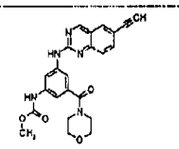
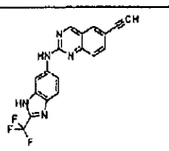
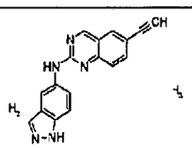
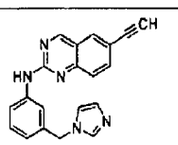
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198		*	471.3567	471/473 1.9	
199		***	426.4382	427.1 1.7	
200		**	458.5234	459.1 1.6	
201		**	431.4499	432.1 2.4	
202		**	353.306	354.1 2.6	
203		**	285.3089	286.2 2.18	
204		*	325.3735	326.1 1.89	

FIG. 1 (PART 3 of 59)

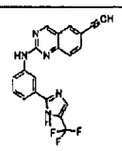
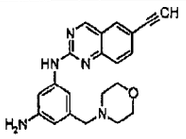
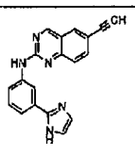
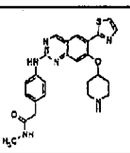
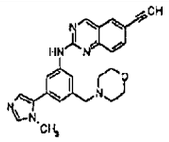
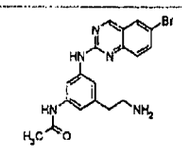
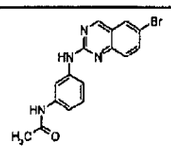
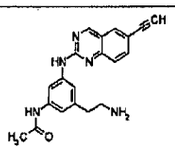
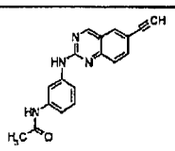
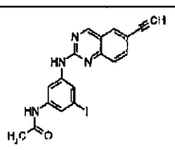
205		*	379.3438	380.1 2.9	
206		****	359.4309	360.1 1.87	
207		*	311.3467	312 2.1	
208		****	474.5864	475.2 1.8	
209		*	424.5056	425.2 1.89	
210		***	400.2782	400/402 2.03	
211		***	357.2097	357/359 2.53	
212		****	345.4041	346 1.94	
213		****	302.3356	303 2.38	
214		***	428.2277	428.8 2.94	

FIG. 1 (PART 4 of 59)

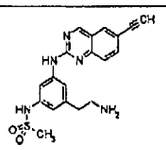
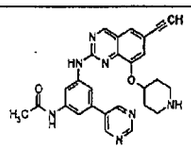
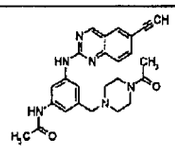
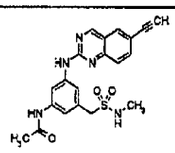
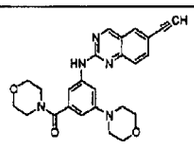
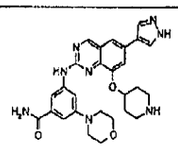
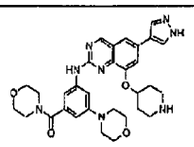
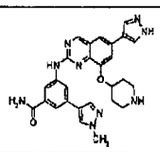
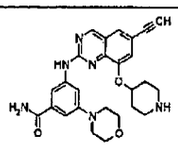
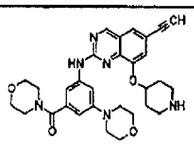
215		****	381.4581	381.9 2.03	
216		****	479.5415	480.0 2.05	
217		***	442.5204	443 1.98	
218		*	409.4681	410 2.26	
219		*	443.5045	444 2.42	
220		**	514.587	515 1.79	
221		**	584.6774	585 1.90	
222		**	509.5713	510 1.83	
223		***	472.5462	473 1.98	
224		*	542.6366	543 2.11	

FIG. 1 (PART 5 of 59)

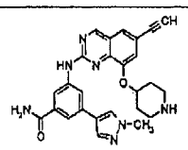
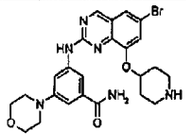
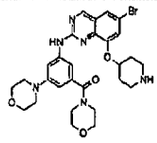
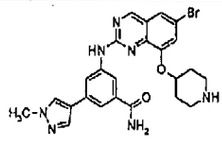
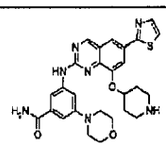
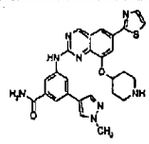
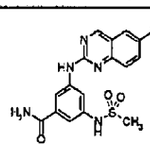
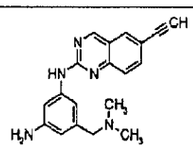
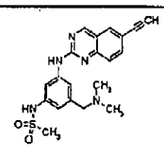
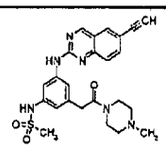
225		****	467.5305	468 2.01	
226		*	527.4203	527/529 2.03	
227		*	597.5107	597/599 2.16	
228		**	522.4046	522/524 2.07	
229		*	531.6381	532 2.09	
230		*	526.6224	527 2.13	
231		**	381.4145	381.9 2.18	
232		****	317.3941	318.1 1.74	
233		***	395.4849	396 2.03	
234		***	478.5744	479 2.01	

FIG. 1 (PART 6 of 59)

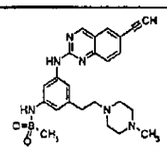
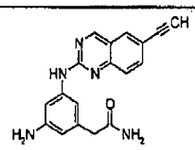
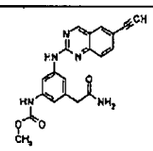
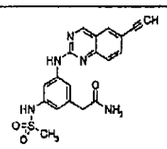
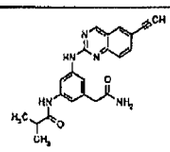
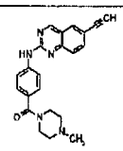
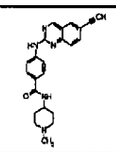
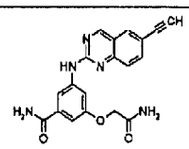
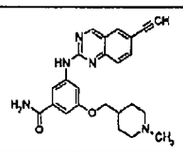
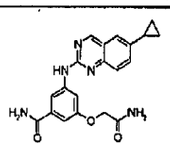
235		***	464.5912	465.0 1.96	
236		****	317.3505	318 0.61	
237		****	375.3863	376 0.61	
238		****	395.4413	396 0.60	
239		****	387.4409	388 0.60	
240		*	371.4419	372 2.03	
241		**	385.4687	386.1 2.11	
242		****	361.3595	362.1 2.14	
243		**	415.4945	416.0 2.16	
244		**	377.4021	378.1 2.07	

FIG. 1 (PART 7 of 59)

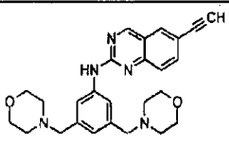
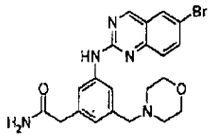
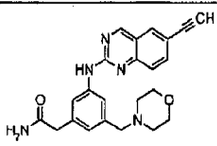
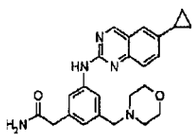
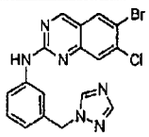
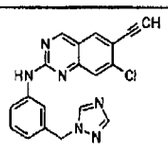
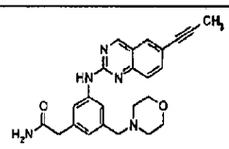
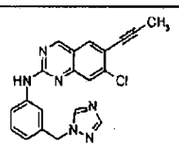
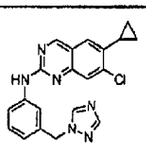
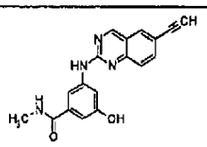
245		**	443.5481	444.0 0.51	
246		**	456.3418	456/458 0.78	
247		****	401.4677	402.1 0.57	
248		*	417.5103	418.2 0.59	
249		*	415.6808	416.9 0.92	
250		***	360.8067	361.0 0.84	
251		****	415.4945	416.1 0.70	
252		**	374.8335	375.0 1.02	
253		*	376.8493	377.1 1.03	
254		***	318.3346	319.2 2.16	

FIG. 1 (PART 8 of 59)

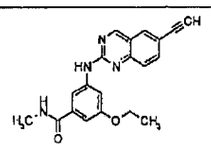
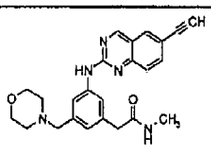
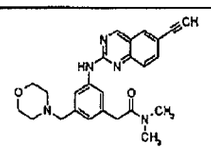
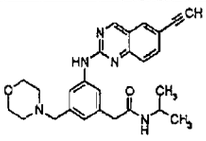
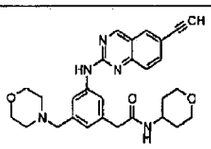
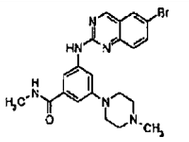
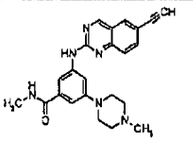
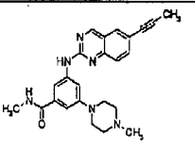
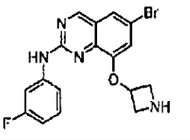
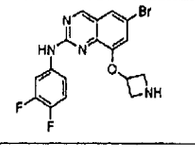
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256		***	415.4945	416.2 2.01	
257		***	429.5213	430.2 2.17	
258		***	443.5481	444.1 2.27	
259		***	485.5849	486.2 2.14	
260		**	455.3577	455/457 0.61	
261		****	400.4838	401.2 0.56	
262		***	414.5104	415.2 0.61	
263		*	389.2266	389/391 0.71	
264		*	407.2167	407/409 0.73	

FIG. 1 (PART 9 of 59)

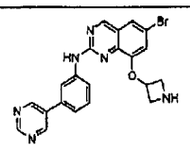
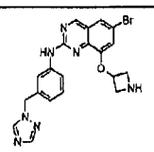
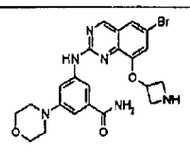
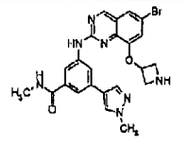
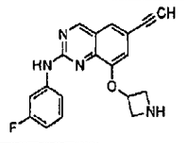
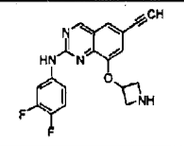
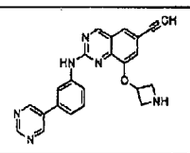
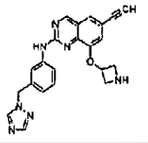
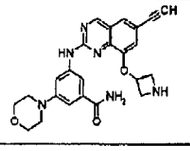
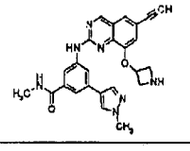
265		*	449.3103	449/451 0.63	
266		**	452.3142	452/454 0.58	
267		*	499.3667	499/501 0.56	
268		*	508.3778	508/510 0.60	
269		***	334.3525	335.1 0.67	
270		**	352.3426	353.1 0.69	
271		**	394.4362	395.1 0.60	
272		***	397.4401	398.2 0.54	
273		**	444.4926	445.2 0.52	
274		**	453.5037	454.2 0.57	

FIG. 1 (PART 10 of 59)

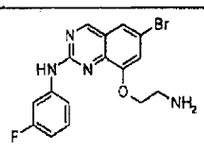
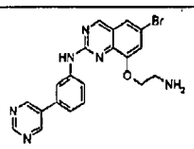
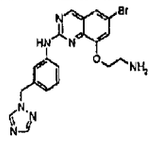
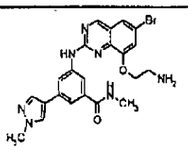
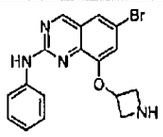
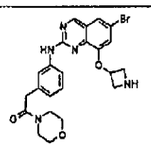
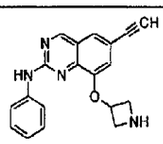
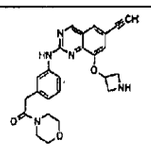
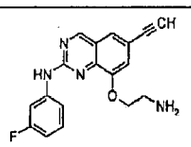
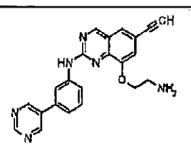
275		*	377.2156	377/379 0.73	
276		*	437.2993	437/439 0.66	
277		**	440.3032	440/442 0.60	
278		*	496.3668	496/498 0.62	
279		*	371.2365	371/373 0.70	
280		**	498.3786	498/500 0.62	
281		**	316.3624	317.1 0.67	
282		***	443.5045	444.1 0.61	
283		**	322.3415	323.1 0.70	
284		**	382.4252	383.1 0.63	

FIG. 1 (PART 11 of 59)

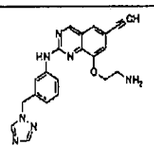
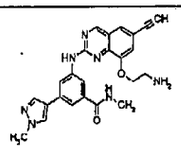
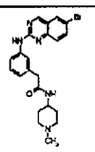
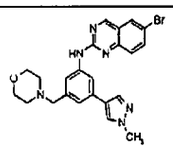
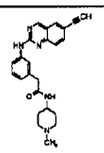
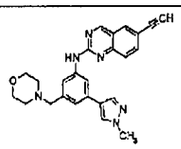
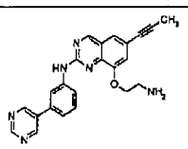
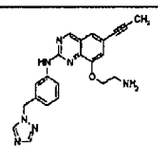
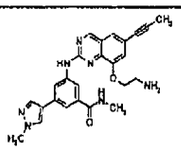
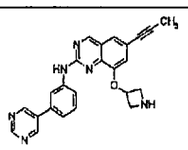
285		***	385.4291	386.1 0.58	
286		**	441.4927	442.1 0.60	
287		*	454.3696	454/456 0.71	
288		**	479.3797	479/481 0.75	
289		*	399.4955	400.1 0.65	
290		***	424.5056	425.1 0.69	
291		*	396.452	397.1 0.71	
292		**	399.4559	400.1 0.65	
293		*	455.5195	456.1 0.67	
294		**	408.463	409.1 0.68	

FIG. 1 (PART 12 of 59)

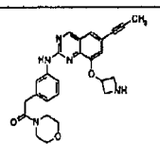
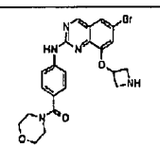
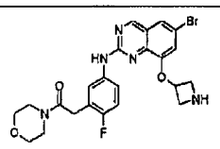
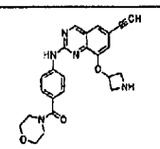
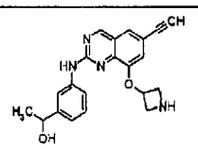
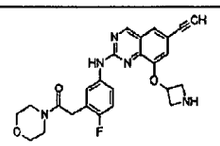
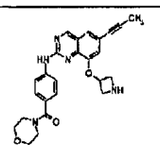
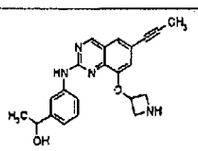
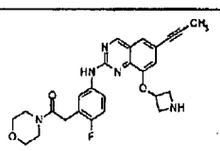
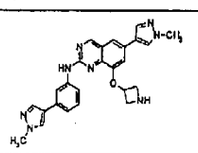
295		**	457.5313	458.1 0.65	
296		**	484.3518	484/486 0.66	
297		**	516.3687	516/518 0.68	
298		***	429.4777	430.1 0.60	
299		**	360.415	361.1 0.61	
300		***	461.4946	462.1 0.63	
301		**	443.5045	444.1 0.63	
302		N/A	374.4418	375.2 0.66	
303		**	475.5214	476.1 0.67	
304		*	452.5196	453.1 0.66	

FIG. 1 (PART 13 of 59)

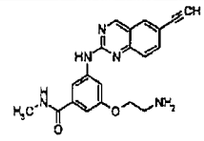
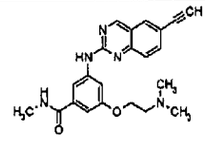
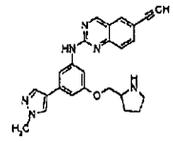
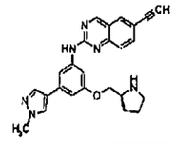
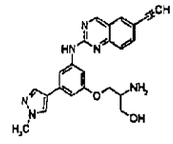
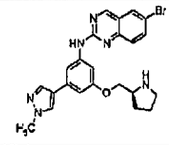
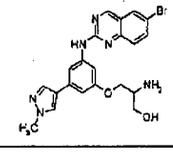
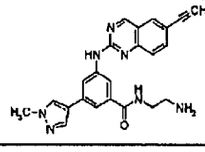
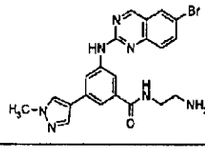
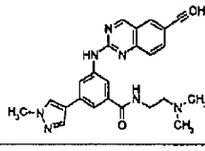
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306		**	389.4567	390.1 0.60	
307		N/A	424.5056		
308		****	424.5056	425.1 0.68	
309		****	414.4668	415.1 0.62	
310		***	479.3797	479/481 0.73	
311		****	469.3409	469/471 0.68	
312		***	411.4669	412.1 0.62	
313		*	466.341	466/468 0.68	
314		****	439.5205	440.1 0.64	

FIG. 1 (PART 14 of 59)

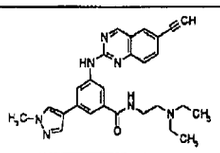
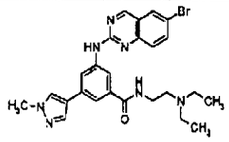
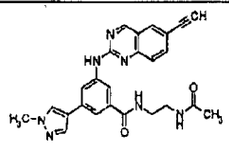
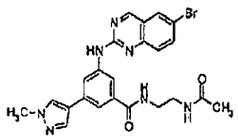
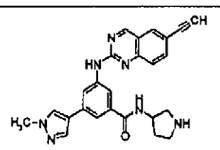
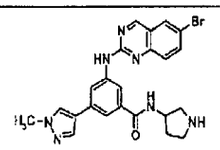
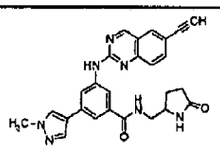
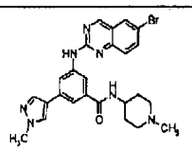
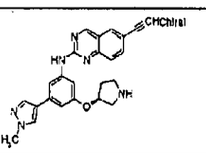
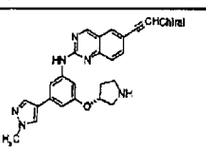
315		***	467.5741	468.2 0.68	
316		*	522.4482	522/524 0.73	
317		**	453.5037	454.1 0.68	
318		*	508.3778	508/510 0.74	
319		**	437.5047	438.1 0.64	
320		*	492.3788	492/494 0.69	
321		**	465.5147	466.2 0.68	
322		*	520.4324	520/522 0.70	
323		****	410.4788	411.1 0.67	
324		****	410.4788	411.1 0.67	

FIG. 1 (PART 15 of 59)

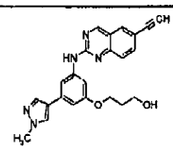
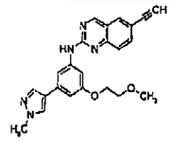
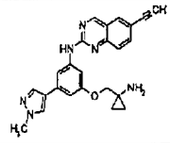
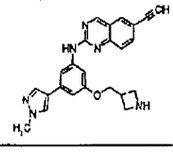
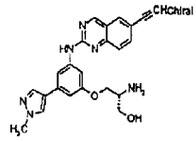
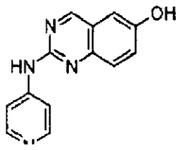
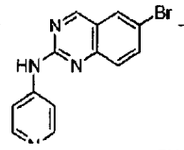
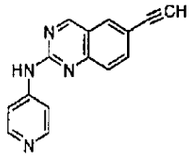
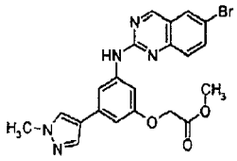
325		**	399.4519	400.1 0.78	
326		**	399.4519	400.0 0.88	
327		****	410.4788	411.1 0.67	
328		****	410.4788	411.1 0.67	
329		****	414.4668	415.1 0.62	
330		*	238.249	239.0 1.69	
331		*	301.1461	300.9/302.9 2.11	
332		*	246.272	247.1 2.03	
333		*	468.3092	468.0/470.0 3.00	

FIG. 1 (PART 16 of 59)

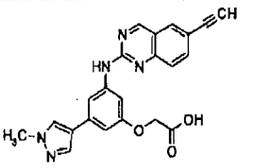
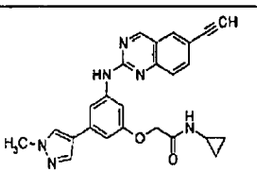
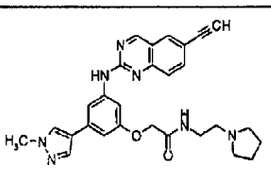
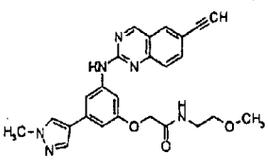
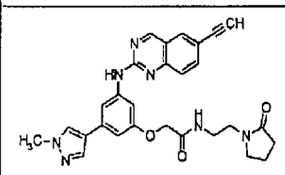
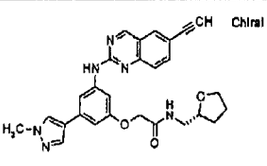
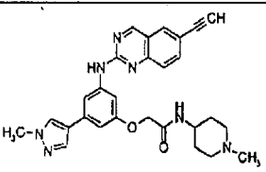
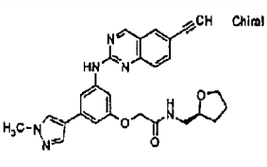
334		**	399.4083	400.1 2.48	
335		***	438.4888	439.2 2.62	
336		****	495.5841	496.2 2.28	
337		***	456.5036	457.2 2.54	
338		***	509.5673	510.2 2.39	
339	 Chiral	***	482.5414	483.2 2.63	
340		***	495.5841	496.2 2.22	
341	 Chiral	**	482.5414	483.2 2.62	

FIG. 1 (PART 17 of 59)

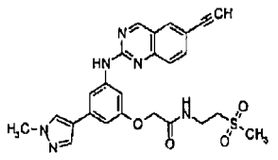
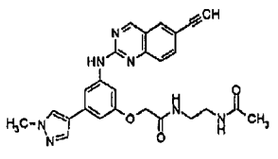
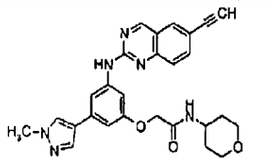
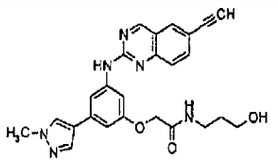
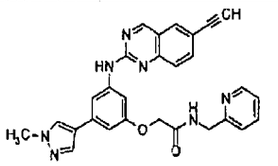
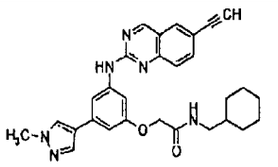
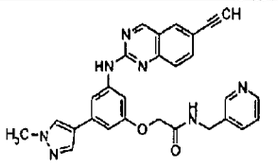
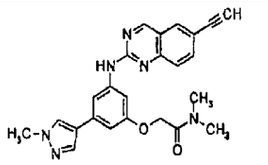
342		***	504.5686	505.2 2.41	
343		****	483.5295	484.2 2.30	
344		**	482.5414	483.2 2.53	
345		**	456.5036	457.2 2.36	
346		****	489.5367	490.2 2.26	
347		*	494.596	495.2 3.14	
348		****	489.5367	490.2 2.25	
349		**	426.4778	427.2 2.47	

FIG. 1 (PART 18 of 59)

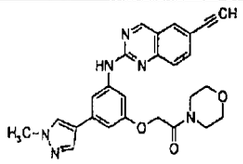
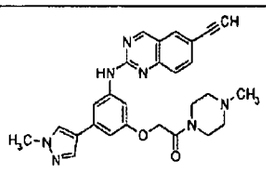
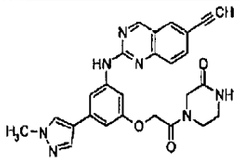
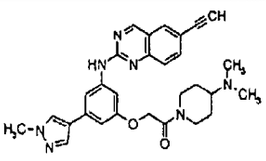
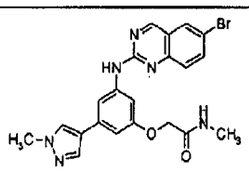
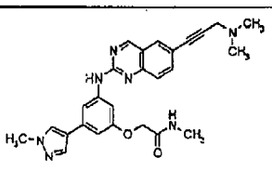
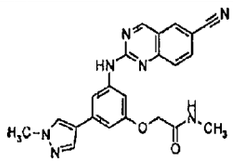
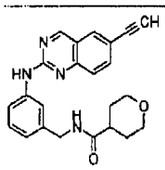
350		**	468.5146	469.2 2.47	
351		*	481.5573	482.2 2.18	
352		***	481.5137	482.2 2.23	
353		*	509.6109	510.3 2.21	
354		***	467.3251	467.1/469.1 2.61	
355		*	469.5463	470.2 1.96	
356		**	413.4391	414.2 2.33	
357		***	386.4528	387.2 2.41	

FIG. 1 (PART 19 of 59)

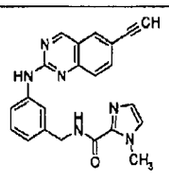
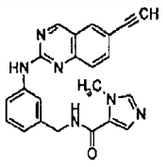
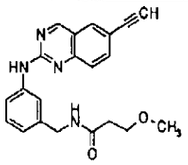
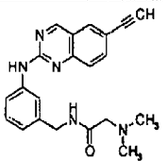
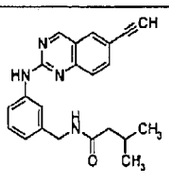
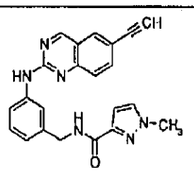
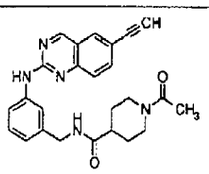
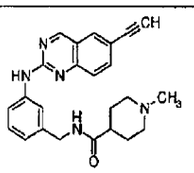
358		**	382.4252	383.2 2.34	
359		****	382.4252	383.2 2.21	
360		***	360.415	361.2 2.38	
361		****	359.4309	360.2 2.13	
362		**	358.4428	359.3 2.75	
363		**	382.4252	383.2 2.52	
364		***	427.5055	428.3 2.29	
365		**	399.4955	400.3 2.15	

FIG. 1 (PART 20 of 59)

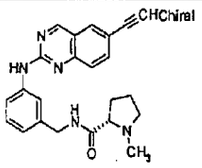
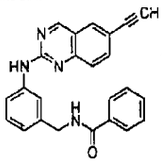
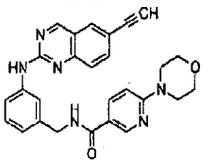
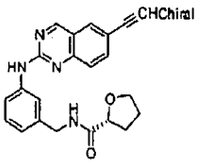
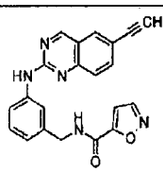
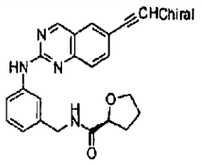
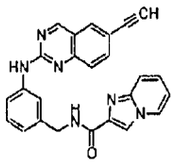
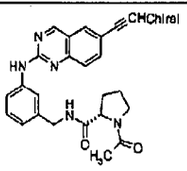
366		***	385.4687	386.3 2.19	
367		**	378.4332	379.2 2.83	
368		****	464.5266	465.2 2.30	
369		***	372.426	373.2 2.56	
370		***	369.3825	370.2 2.60	
371		**	372.426	373.2 2.55	
372		****	418.4582	419.2 2.31	
373		**	413.4787	414.2 2.30	

FIG. 1 (PART 21 of 59)

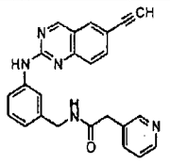
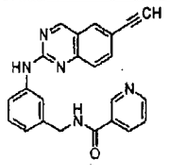
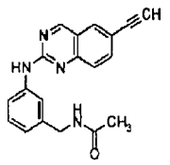
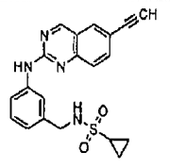
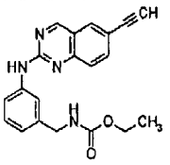
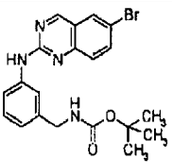
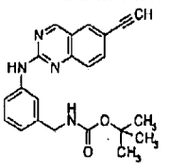
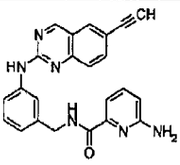
374		**	393.4481	394.2 2.17	
375		***	379.4213	380.2 2.26	
376		***	316.3624	317.2 2.29	
377		***	378.4542	379.2 2.71	
378		***	346.3882	347.1 2.78	
379		*	429.3159	429.1/431.2 3.41	
380		**	374.4418	375.2 3.20	
381		*	394.4362	395.2 2.36	

FIG. 1 (PART 22 of 59)

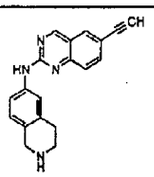
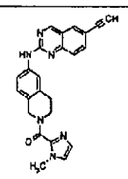
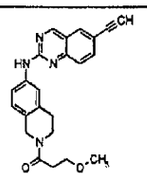
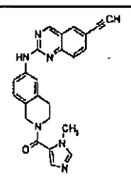
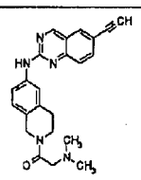
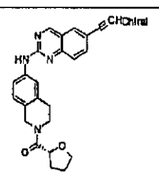
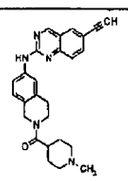
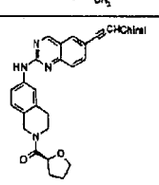
382		**	300.3634	301.2 2.05	
383		***	408.463	409.2 2.26	
384		***	386.4528	387.3 2.56	
385		**	408.463	409.2 2.24	
386		**	385.4687	386.3 2.17	
387		****	398.4638	399.2 2.61	
388		**	425.5333	426.3 2.20	
389		**	398.4638	399.2 2.61	

FIG. 1 (PART 23 of 59)

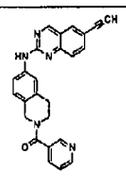
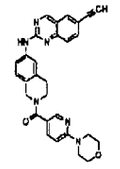
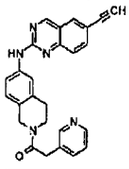
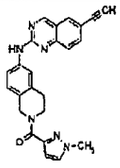
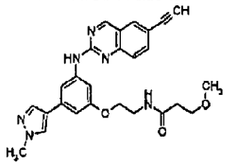
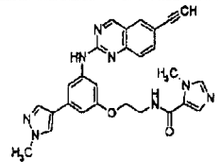
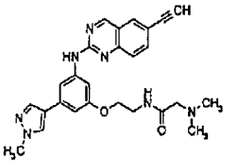
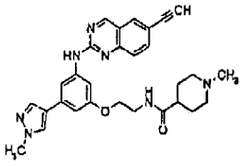
390		***	405.4591	406.2 2.27	
391		**	490.5644	491.2 2.37	
392		***	419.4859	420.2 2.21	
393		***	408.463	409.2 2.60	
394		***	470.5304	471.3 2.48	
395		***	492.5406	493.2 2.29	
396		***	469.5463	470.3 2.24	
397		****	509.6109	510.3 2.24	

FIG. 1 (PART 24 of 59)

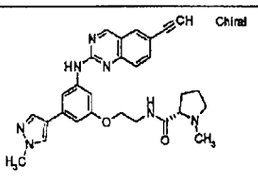
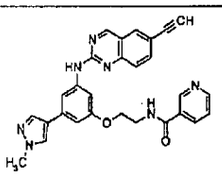
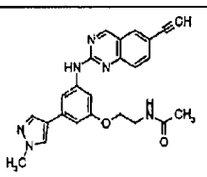
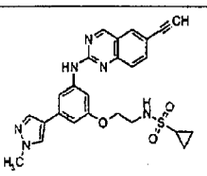
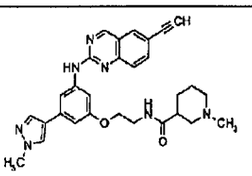
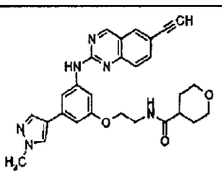
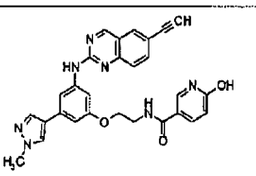
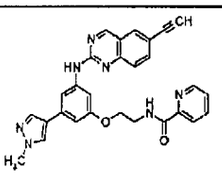
398		***	495.5841	496.3 2.28	
399		***	489.5367	490.2 2.32	
400		****	426.4778	427.3 2.42	
401		***	488.5696	489.2 2.72	
402		***	509.6109		510.3 0.66
403		***	496.5682		497.2 0.73
404		****	505.5357		506.1 0.67
405		***	489.5367		490.2 0.83

FIG. 1 (PART 25 of 59)

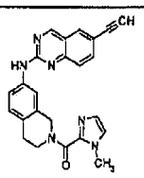
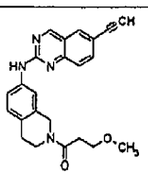
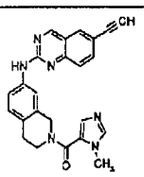
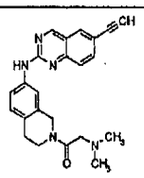
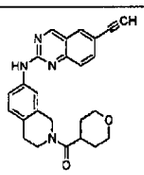
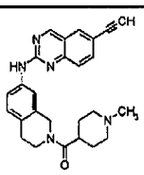
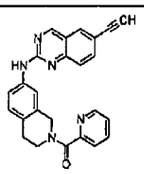
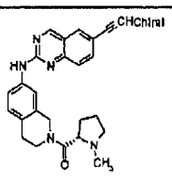
406		**	408.463		409.1 0.69
407		**	386.4528		387.2 0.81
408		**	408.463		409.2 0.68
409		**	385.4687		386.2 0.66
410		**	412.4906		413.2 0.82
411		**	425.5333		426.2 0.68
412		**	405.4591		406.1 0.80
413		**	411.5065		412.1 0.69

FIG. 1 (PART 26 of 59)

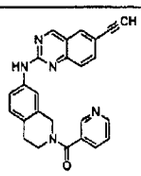
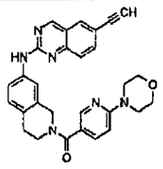
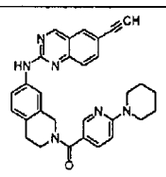
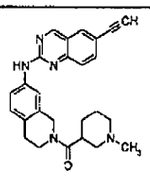
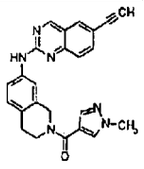
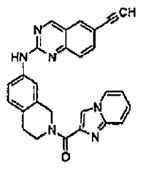
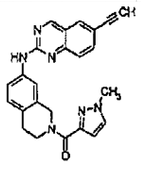
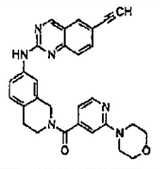
414		**	405.4591		406.1 0.69
415		*	490.5644		491.1 0.73
416		*	488.5922		489.1 0.77
417		**	425.5333		426.2 0.70
418		***	408.463		409.1 0.77
419		**	444.496		445.1 0.70
420		**	408.463		409.1 0.82
421		*	490.5644		491.1 0.72

FIG. 1 (PART 27 of 59)

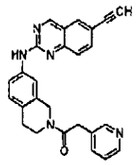
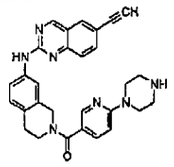
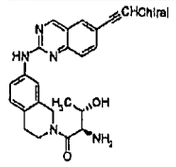
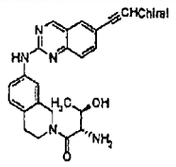
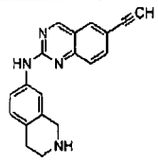
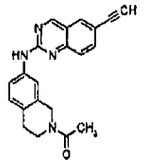
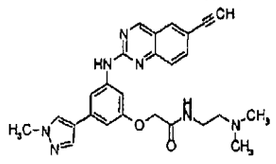
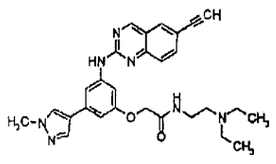
422		***	419.4859		420.1 0.68
423		**	489.5803		490.2 0.68
424		**	401.4677		402.2 0.64
425		**	401.4677		402.2 0.64
426		**	300.3634		301.1 0.59
427		**	342.4002		343.1 0.75
428		***	469.5463		470.2 0.68
429		***	497.5999		498.3 0.71

FIG. 1 (PART 28 of 59)

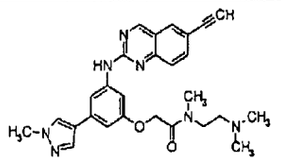
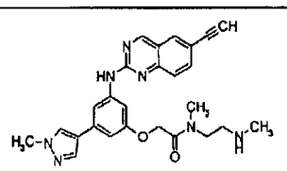
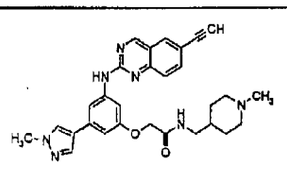
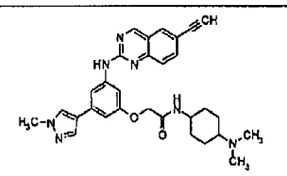
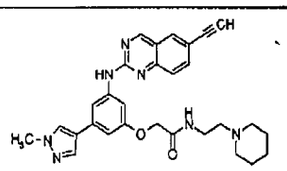
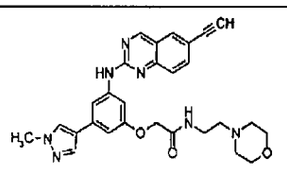
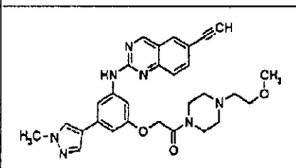
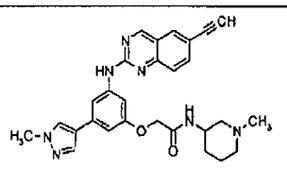
430		**	483.5731		484.3 0.68
431		**	469.5463		470.2 0.67
432		***	509.6109		510.3 0.69
433		**	523.6377		524.3 0.70
434		***	509.6109		510.3 0.72
435		***	511.5831		512.3 0.69
436		*	525.6099		526.3 0.69
437		**	495.5841		496.2 0.69

FIG. 1 (PART 29 of 59)

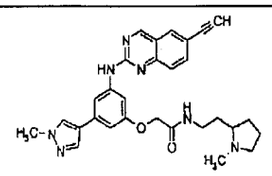
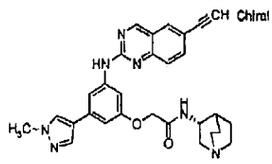
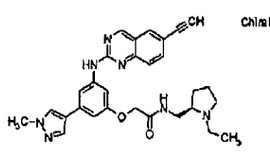
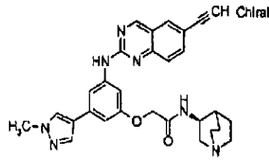
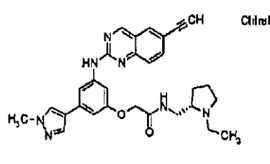
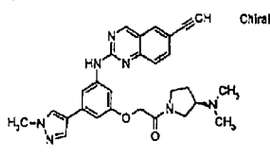
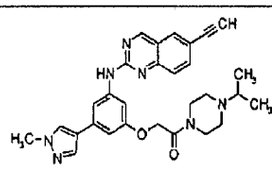
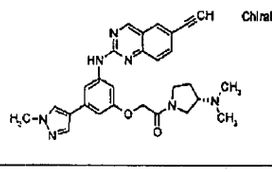
438		**	509.6109		510.3 0.70
439		**	507.5951		508.3 0.69
440		***	509.6109		510.3 0.72
441		**	507.5951		508.3 0.69
442		***	509.6109		510.3 0.72
443		*	495.5841		496.2 0.66
444		*	509.6109		510.3 0.70
445		*	495.5841		496.3 0.66

FIG. 1 (PART 30 of 59)

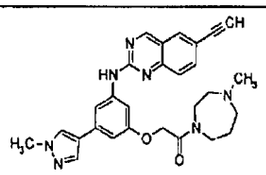
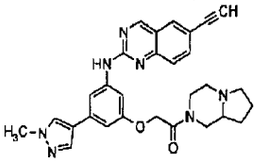
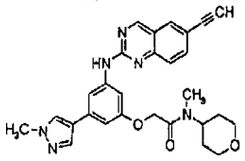
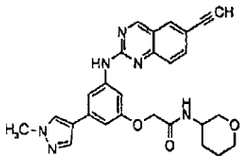
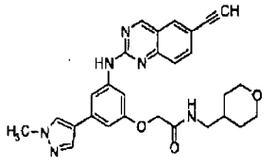
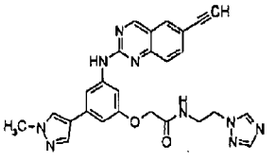
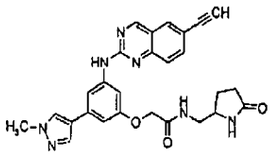
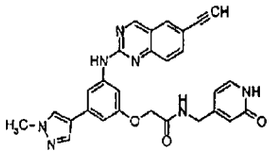
446		*	495.5841		496.2 0.67
447		*	507.5951		508.3 0.69
448		*	496.5682		497.2 0.81
449		**	482.5414		483.2 0.83
450		***	496.5682		497.2 0.81
451		***	493.5287		494.2 0.71
452		****	495.5405		496.2 0.71
453		****	505.5357		506.2 0.70

FIG. 1 (PART 31 of 59)

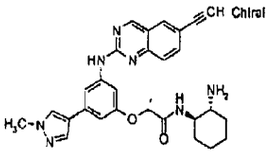
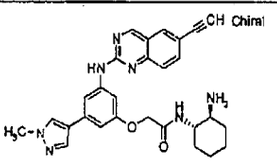
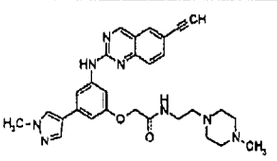
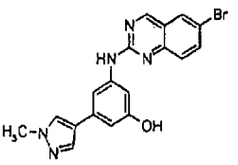
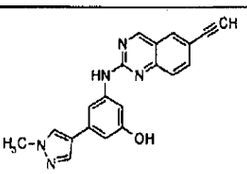
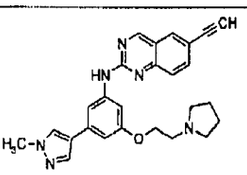
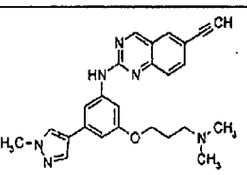
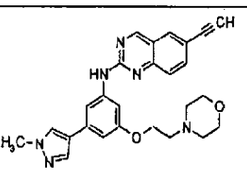
454		****	495.5841		496.2 0.73
455		**	495.5841		496.2 0.73
456		***	524.6258		525.3 0.66
457		**	396.2466		396.0/398.0 1.01
458		***	341.3725		342.1 0.72
459		****	438.5324		439.2 0.69
460		***	426.5214		427.2 0.68
461		**	454.5314		455.2 0.67

FIG. 1 (PART 32 of 59)

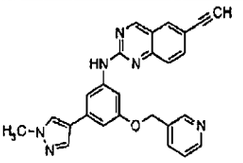
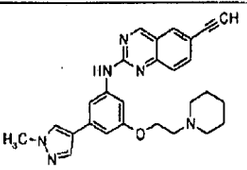
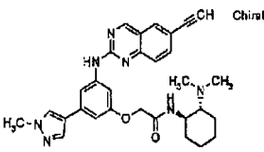
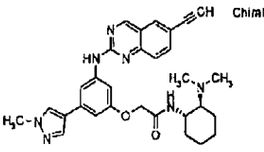
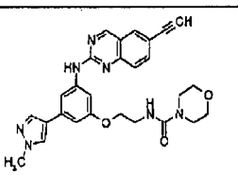
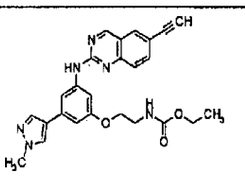
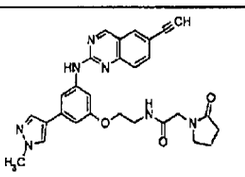
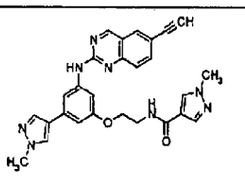
462		**	432.485		433.2 0.70
463		***	452.5592		453.2 0.71
464		****	523.6377		524.3 0.73
465		**	523.6377		524.3 0.73
466		**	497.5563		498.3 0.75
467		**	456.5036		457.2 0.87
468		***	509.5673		510.3 0.72
469		***	492.5406		493.2 0.74

FIG. 1 (PART 33 of 59)

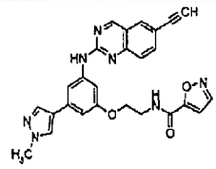
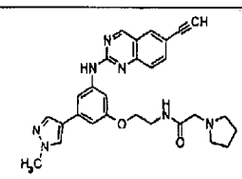
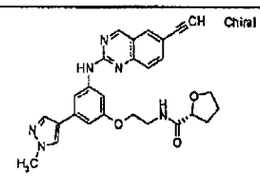
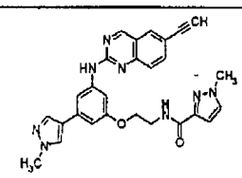
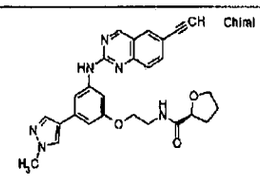
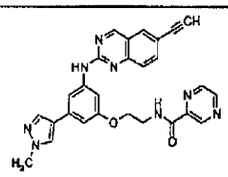
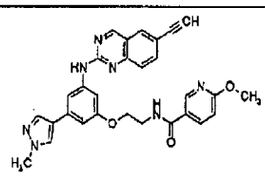
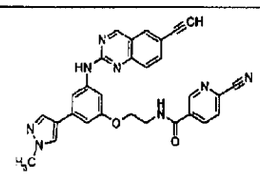
470		***	479.4979		480.2 0.80
471		***	495.5841		496.3 0.68
472		**	482.5414		483.1 0.81
473		**	492.5406		493.1 0.80
474		**	482.5414		483.1 0.81
475		**	490.5248		491.1 0.81
476		*	519.5625		520.2 0.84
477		***	514.5468		515.2 0.84

FIG. 1 (PART 34 of 59)

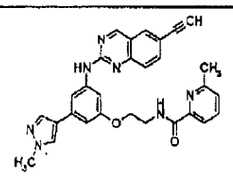
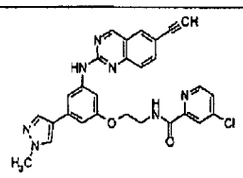
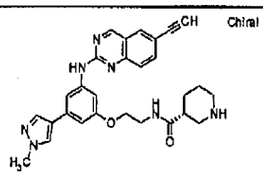
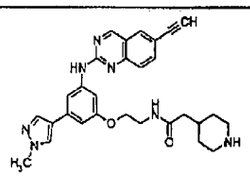
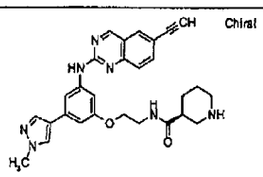
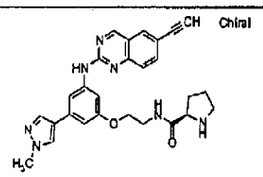
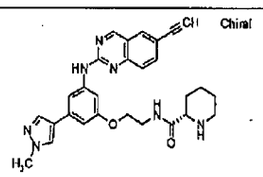
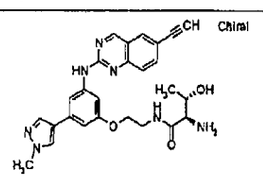
478		*	503.5635		504.2 0.88
479		*	523.9818		524.2 0.96
480		***	495.5841		496.2 0.69
481		***	509.6109		510.3 0.68
482		***	495.5841		496.2 0.69
483		***	481.5573		482.2 0.69
484		***	495.5841		496.2 0.70
485		***	485.5453		486.3 0.66

FIG. 1 (PART 35 of 59)

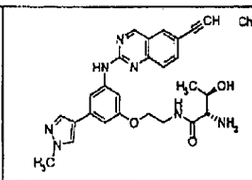
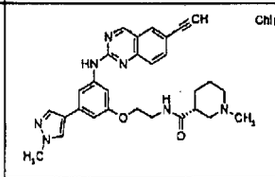
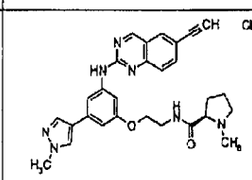
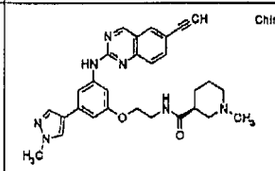
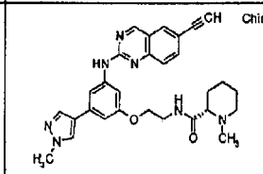
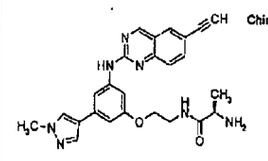
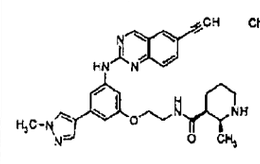
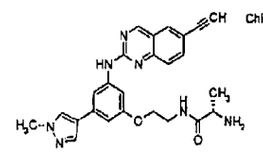
486		**	485.5453		486.3 0.66
487		***	509.6109		510.3 0.69
488		***	495.5841		496.2 0.69
489		***	509.6109		510.3 0.69
490		***	509.6109		510.3 0.70
491		***	455.5195		456.1 0.65
492		****	509.6109		510.2 0.68
493		***	455.5195		456.0 0.65

FIG. 1 (PART 36 of 59)

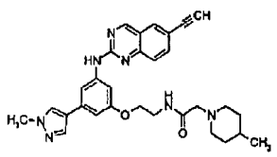
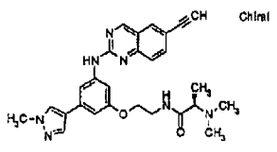
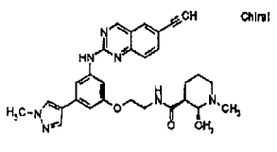
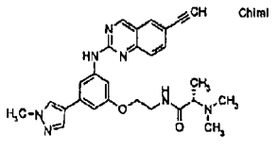
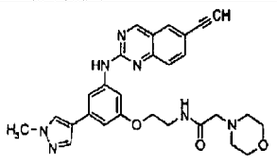
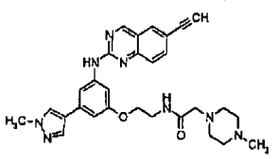
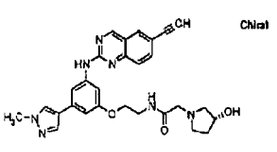
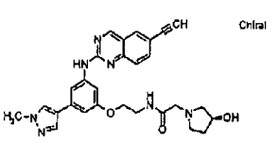
494		***	523.6377		524.2 0.72
495		**	483.5731		484.2 0.66
496		***	523.6377		524.3 0.67
497		***	483.5731		484.2 0.66
498		***	511.5831		512.3 0.65
499		**	524.6258		525.3 0.64
500		***	511.5831		512.2 0.64
501		***	511.5831		512.2 0.64

FIG. 1 (PART 37 of 59)

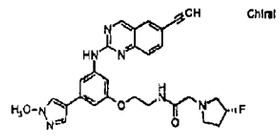
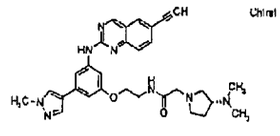
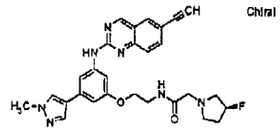
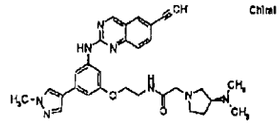
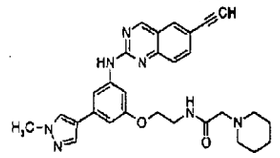
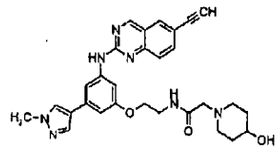
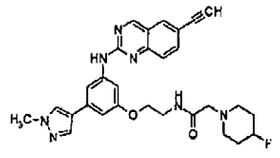
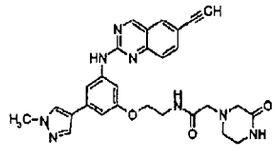
502		***	513.5742		514.2 0.66
503		**	538.6526		539.3 0.61
504		***	513.5742		514.3 0.66
505		***	538.6526		539.3 0.61
506		***	509.6109		510.3 0.68
507		***	525.6099		526.3 0.63
508		***	527.601		528.3 0.68
509		***	524.5822		525.3 0.62

FIG. 1 (PART 38 of 59)

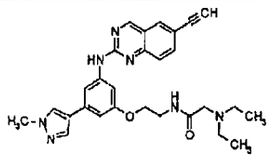
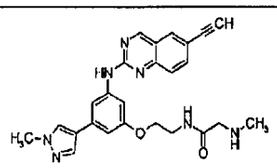
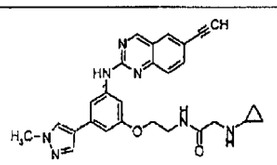
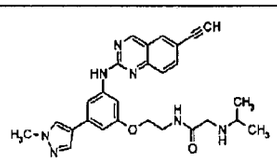
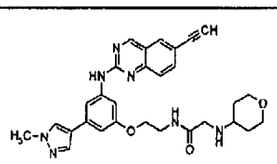
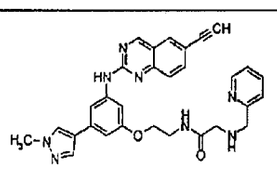
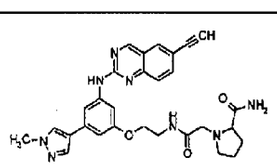
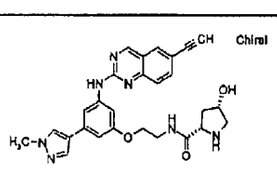
510		***	497.5999		498.3 0.67
511		***	455.5195		456.2 0.63
512		***	481.5573		482.2 0.66
513		***	483.5731		484.2 0.66
514		***	525.6099		526.3 0.65
515		***	532.6052		533.3 0.67
516		***	538.609		539.3 0.64
517	 Chiral	***	497.5563		498.2 0.63

FIG. 1 (PART 39 of 59)

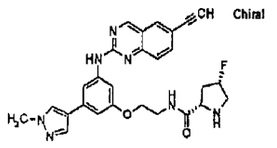
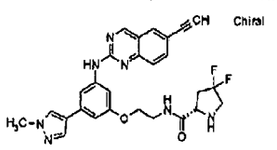
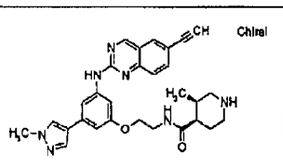
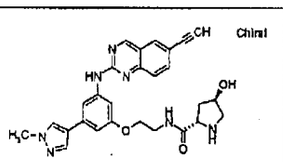
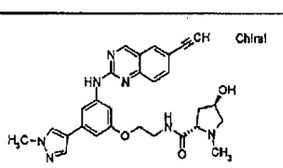
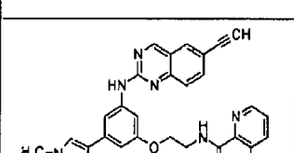
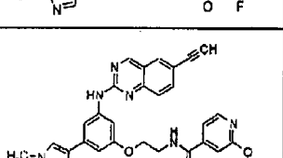
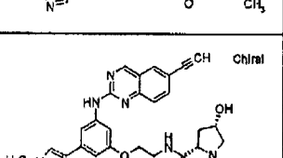
518		***	499.5474		500.2 0.66
519		***	517.5375		518.2 0.68
520		***	509.6109		510.3 0.66
521		****	497.5563		498.3 0.63
522		****	511.5831		512.3 0.64
523		***	507.5268		508.2 0.81
524		**	519.5625		520.2 0.81
525		***	511.5831		512.3 0.63

FIG. 1 (PART 40 of 59)

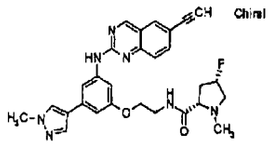
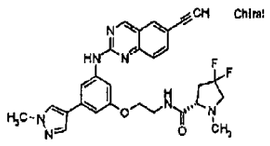
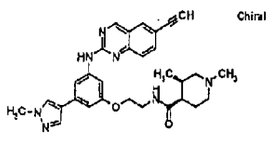
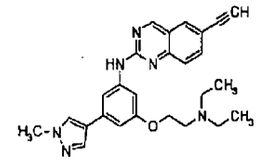
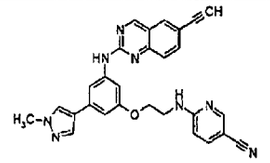
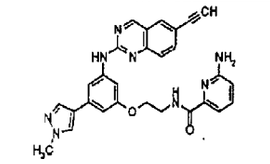
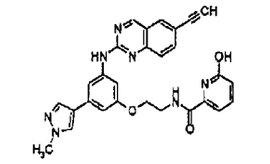
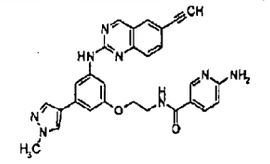
526		**	513.5742		514.3 0.66
527		**	531.5643		532.3 0.71
528		**	523.6377		524.4 0.68
529		***	440.5482		441.3 0.69
530		**	486.5368		487.2 0.82
531		**	504.5516		505.2 0.68
532		**	505.5357		506.2 0.71
533		***	504.5516		505.2 0.66

FIG. 1 (PART 41 of 59)

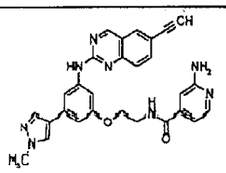
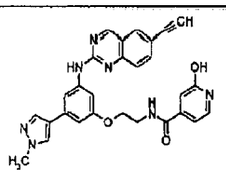
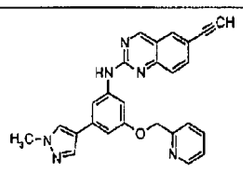
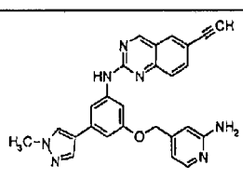
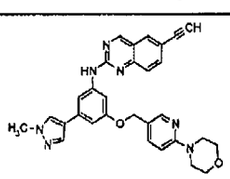
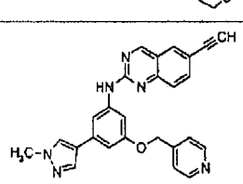
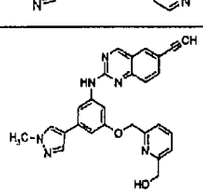
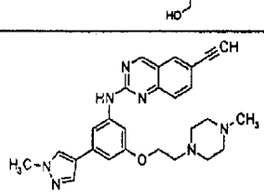
534		****	504.5516		505.2 0.67
535		***	505.5357		506.2 0.68
536		**	432.485		433.2 0.70
537		**	447.4999		448.2 0.70
538		*	517.5903		518.2 0.75
539		**	432.485		433.1 0.70
540		**	462.5108		463.1 0.71
541		***	467.5741		468.2 0.62

FIG. 1 (PART 42 of 59)

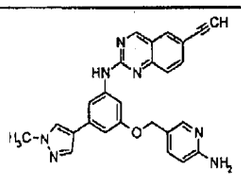
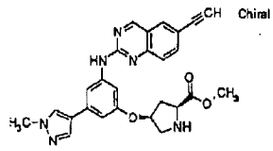
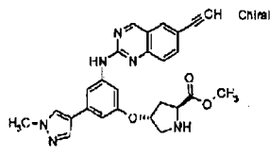
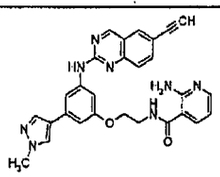
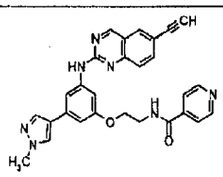
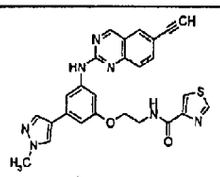
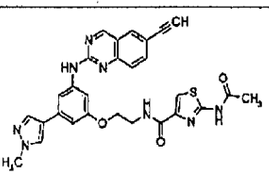
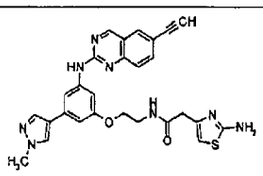
542		**	447.4999		448.2 0.69
543		**	468.5146		469.2 0.68
544		***	468.5146		496.2 0.68
545		***	504.5516		505.1 0.71
546		****	489.5367		490.1 0.70
547		***	495.5649		496.1 0.83
548		***	552.6166		553.2 0.76
549		***	524.6066		525.1 0.69

FIG. 1 (PART 43 of 59)

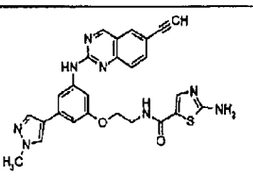
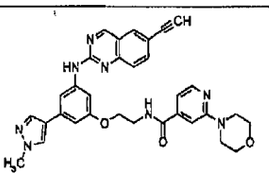
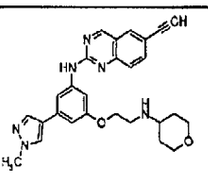
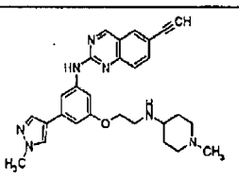
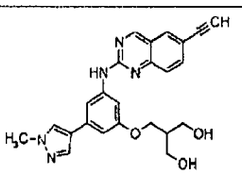
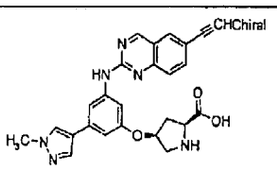
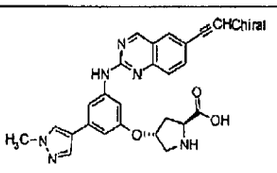
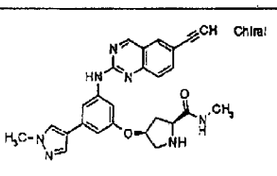
550		****	510.5798		511.1 0.71
551		*	574.642		575.2 0.73
552		****	468.5582		469.1 0.67
553		****	481.6009		482.1 0.61
554		***	429.4777		430.0 0.69
555		N/A	454.4878		455.2 0.62
556		N/A	454.4878		455.2 0.63
557		N/A	467.5305		468.2 0.64

FIG. 1 (PART 44 of 59)

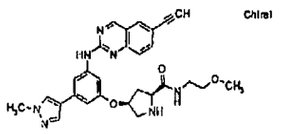
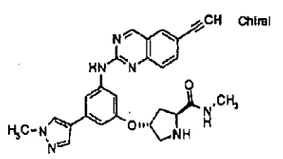
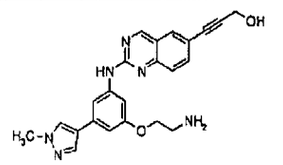
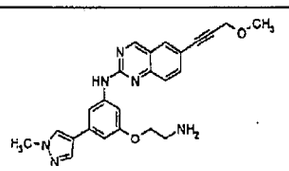
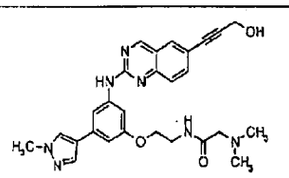
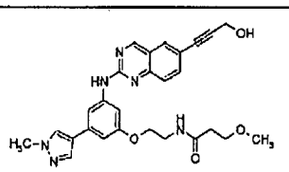
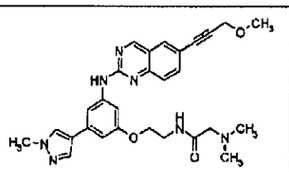
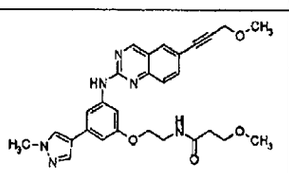
558		N/A	511.5831		512.2 0.66
559		N/A	467.5305		468.2 0.64
560		N/A	414.4668		415.2 0.52
561		N/A	428.4936		429.2 0.65
562		N/A	499.5721		500.3 0.55
563		N/A	500.5562		501.3 0.61
564		N/A	513.5989		514.3 0.67
565		N/A	514.583		515.3 0.75

FIG. 1 (PART 45 of 59)

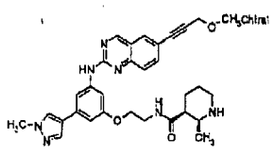
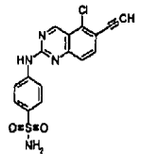
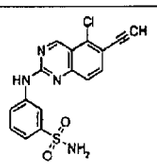
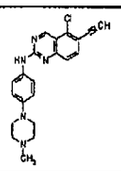
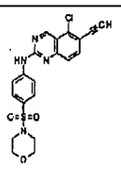
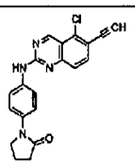
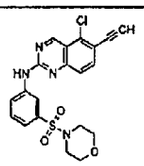
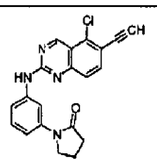
566		N/A	553.6635		554.3 0.69
567		**	358.8079	359.0 2.58	
568		****	358.8079	359.0 2.59	
569		***	377.877	378.1 2.22	
570		*	428.8983	429.1 3.04	
571		***	362.8185	363.1 2.81	
572		*	428.8983	429.1 3.05	
573		****	362.8185	363.1 2.88	

FIG. 1 (PART 46 of 59)

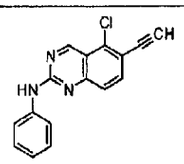
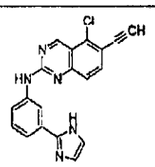
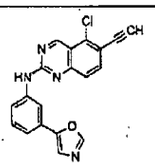
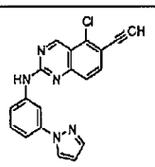
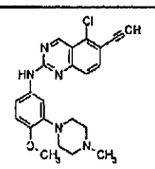
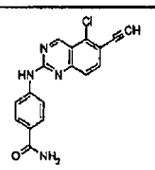
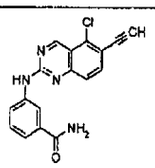
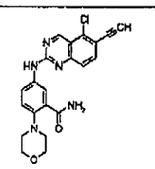
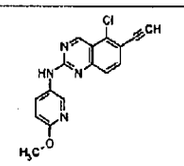
574		*	279.729	280.0 3.28	
575		*	345.7918		
576		*	346.7759	347.1 3.12	
577		*	345.7918	346.1 3.21	346.0 0.71
578		****	407.9028	408.1 2.26	
579		***	322.7539	323.1 2.45	
580		**	322.7539	323.1 2.45	
581		*	407.8592	408.1 2.33	
582		*	310.7429	311.01 2.73	

FIG. 1 (PART 47 of 59)

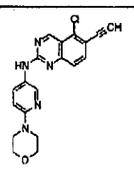
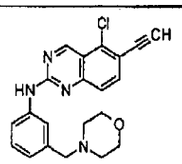
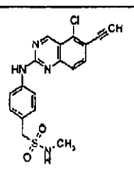
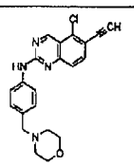
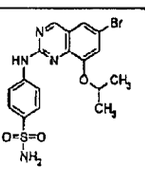
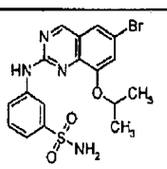
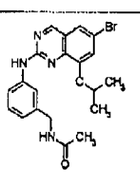
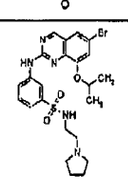
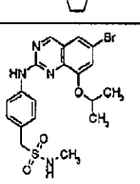
583		***	365.8224	366.0 2.19	
584		***	378.8611	379.1 2.25	
585		****	386.8615	387.1 2.79	
586		**	378.8611	379.1 2.41	
587		**	437.3163	437.0/439.0 2.89	
588		*	437.3163	437.0/439.0 2.88	
589		**	429.3159	429.1/431.1 2.90	
590		*	534.4762	534.1/536.1 2.75	
591		**	465.3699	465.0/467.0 3.13	

FIG. 1 (PART 48 of 59)

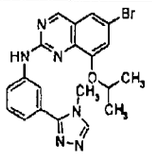
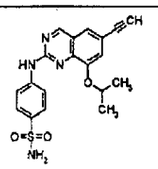
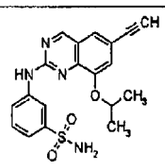
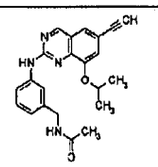
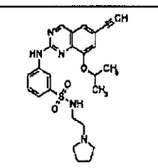
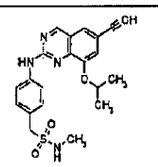
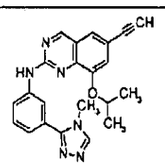
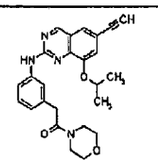
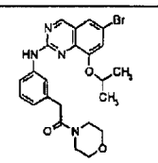
592		*	439.3151	439.1/441.1 2.68	
593		****	382.4422	383.1 2.57	
594		***	382.4422	383.1 2.57	
595		***	374.4418		375.2 0.79
596		*	479.6021		480.2 0.77
597		***	410.4958		411.2 0.86
598		*	384.441		385.2 0.74
599		**	430.5054		431.2 0.85
600		*	485.3795		485.1/487.2 0.92

FIG. 1 (PART 49 of 59)

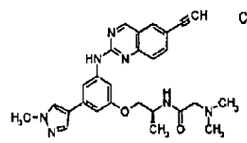
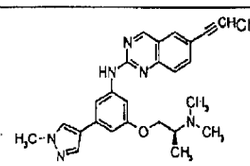
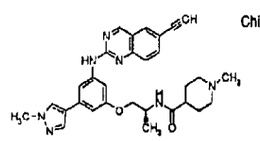
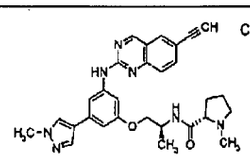
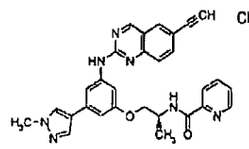
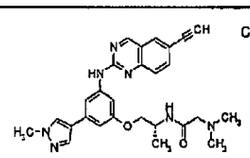
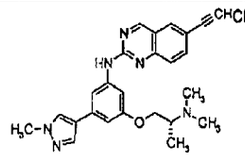
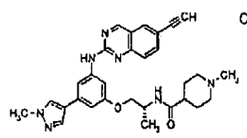
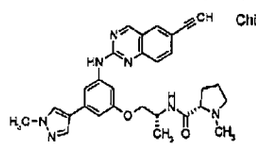
601		**	483.5731	484.2 2.1	
602		****	426.5214	427.2 2.07	
603		**	523.6377	524.3 2.15	
604		**	509.6109	510.2 2.17	
605		*	503.5635	504.2 2.75	
606		***	483.5731		484.3 0.67
607		****	426.5214		427.2 0.66
608		***	523.6377		524.2 0.69
609		***	509.6109		510.2 0.71

FIG. 1 (PART 50 of 59)

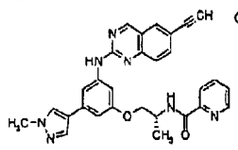
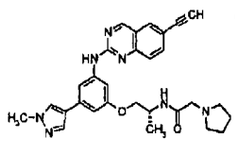
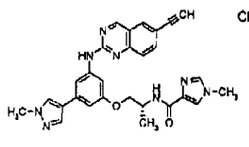
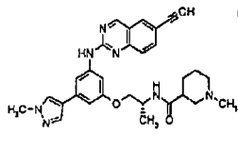
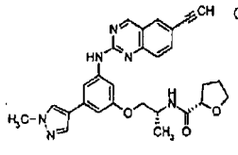
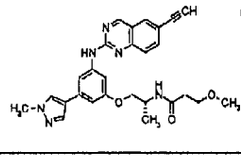
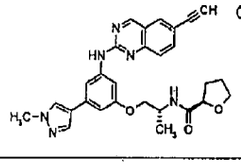
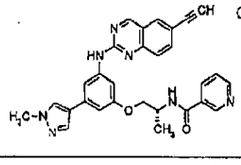
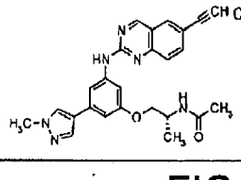
610	 Chiral	***	503.5635		504.2 0.90
611	 Chiral	***	509.6109		510.2 0.70
612	 Chiral	***	506.5674		507.2 0.70
613	 Chiral	***	523.6377		524.2 0.70
614	 Chiral	***	496.5682	497.2 2.48	
615	 Chiral	***	484.5572	485.2 2.36	
616	 Chiral	****	496.5682		497.2 0.82
617	 Chiral	****	503.5635		504.2 0.71
618	 Chiral	****	440.5046		441.2 0.75

FIG. 1 (PART 51 of 59)

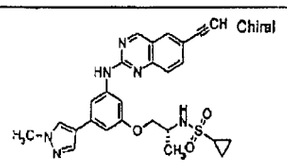
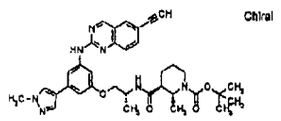
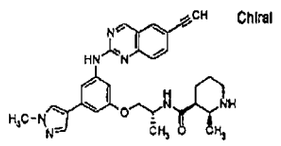
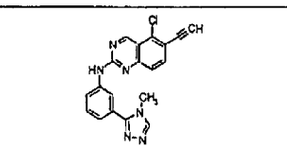
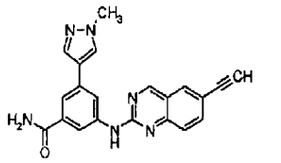
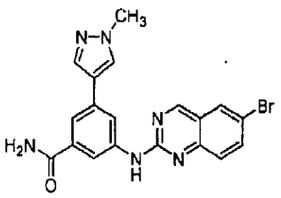
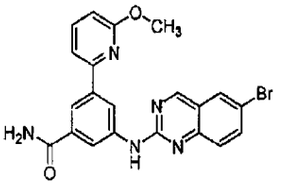
619		***	502.5964		503.2 0.86
620		**	623.7539	624.3 2.98	
621		****	523.6377		524.3 0.69
622		****	360.8067	361.1 2.290	
623		***	368.3984	369	
624		*	423.2725	424	
625		*	450.2944	451	

FIG. 1 (PART 52 of 59)

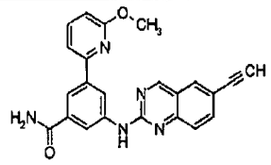
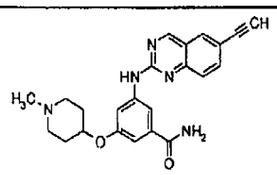
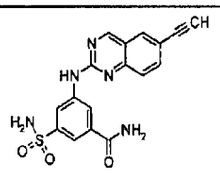
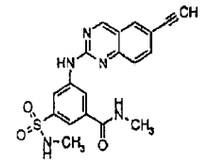
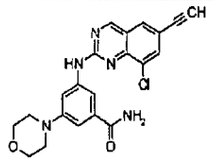
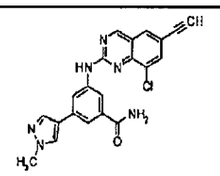
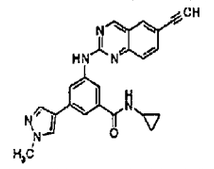
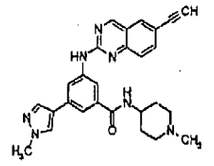
626		*	395.4203	396	
627		**	401.4677	402	
628		**	367.3877	368	
629		*	395.4413	396	
630		***	407.8592	409	
631		***	402.8435	404	
632		**	408.463	409	
633		*	465.5583	466	

FIG. 1 (PART 53 of 59)

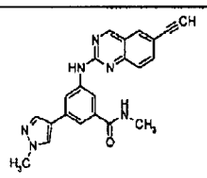
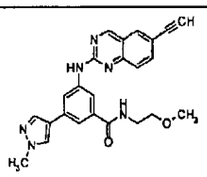
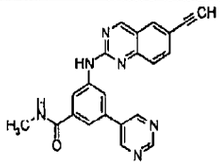
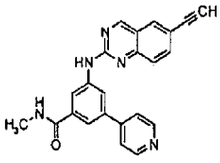
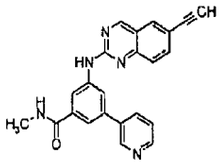
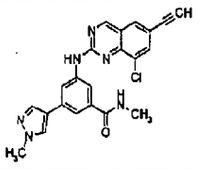
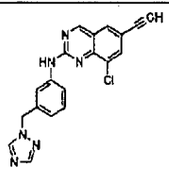
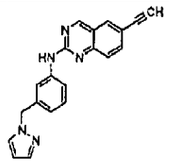
634		***	382.4252	383	
635		**	426.4778	427	
636		*	380.4094	381	
637		*	379.4213	380	
638		*	379.4213	380	
639		***	416.8703	418	
640		****	360.8067	362	
641		***	325.3735	326	

FIG. 1 (PART 54 of 59)

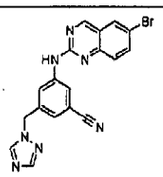
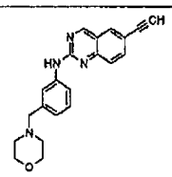
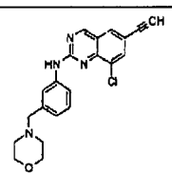
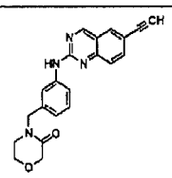
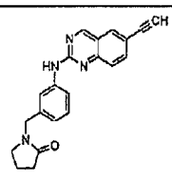
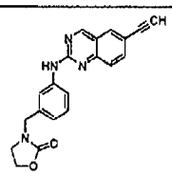
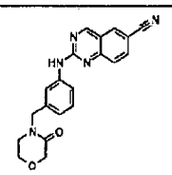
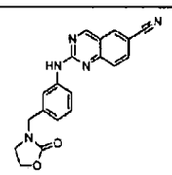
642		*	406.2458	407	
643		**	344.416	345	
644		****	378.8611	380	
645		****	358.3992	359	
646		****	342.4002	343	
647		***	344.3724	345	
648		*	359.3873	360	
649		*	345.3605	346	

FIG. 1 (PART 55 of 59)

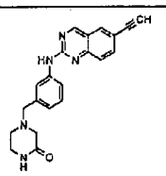
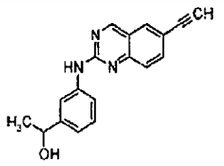
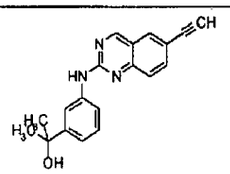
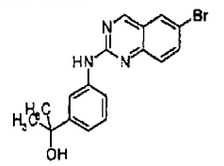
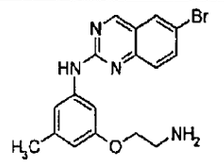
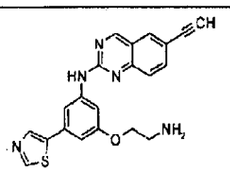
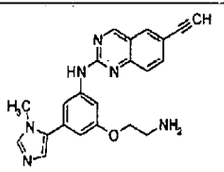
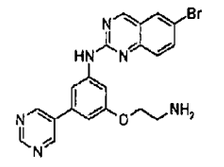
650		**	357.4151	358	
651		**	289.3365	290	
652		*	303.3633	304	
653		*	358.2374	359	
654		*	373.2523	374	
655		****	387.4653	388	
656		***	384.441	385	
657		**	437.2993	438	

FIG. 1 (PART 56 of 59)

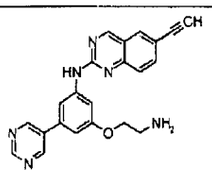
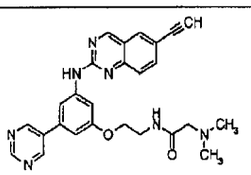
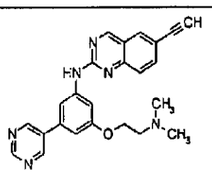
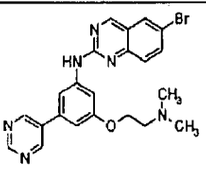
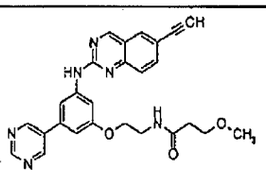
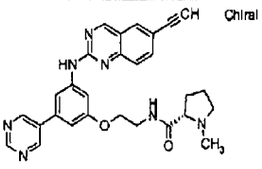
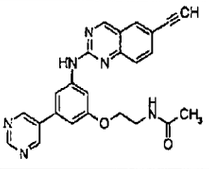
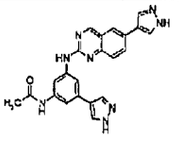
658		***	382.4252	383	
659		***	467.5305	468	
660		**	410.4788	411	
661		**	465.3529	465/467	
662		**	468.5146	469	
663		**	493.5683	494	
664		***	424.462	425	
665		****	410.4392	411.1 1.77	

FIG. 1 (PART 57 of 59)

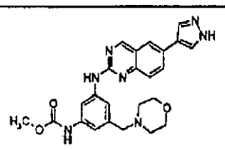
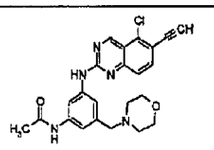
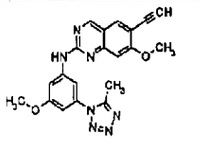
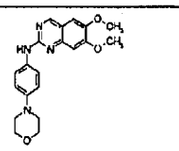
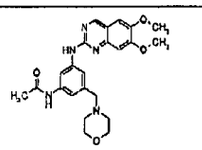
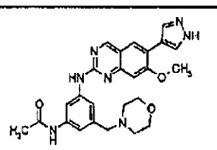
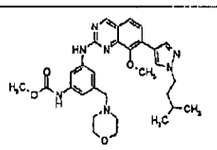
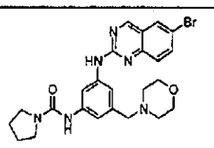
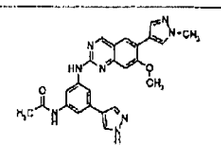
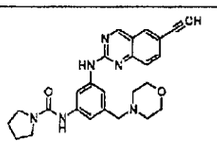
666		***	459.5075	460.2 1.83	
667		****	435.9128	436.1 2.23	
668		*	387.4013	388.1 2.75	
669		*	366.4188	367.1 1.92	
670		*	437.4973	438.1 1.73	
671		****	473.5343	474.2 1.72	
672		****	559.6673	560.2 2.51	
673		**	511.4213	511.1 / 513.1 2.29	
674		**	454.4918	455.1 1.94	
675		***	456.5472	457.1 2.18	

FIG. 1 (PART 58 of 59)

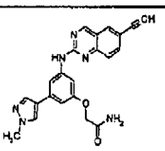
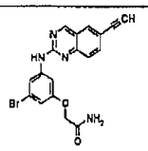
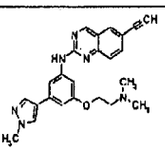
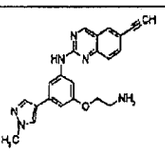
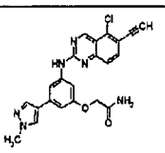
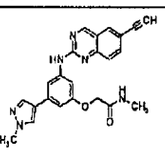
676		****	398.4242	399.0 2.34	
677		**	397.2307	396.9 / 398.9 2.77	
678		****	412.4946	413.1 2.21	
679		***	384.441	385.1 2.16	
680		***	432.8693	433.0 2.62	
681		****	412.451	413.1 2.47	

FIG. 1 (PART 59 of 59)

Table 3

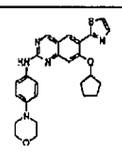
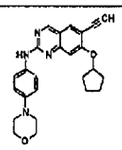
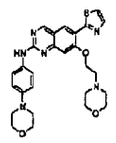
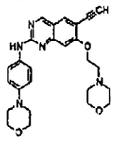
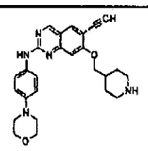
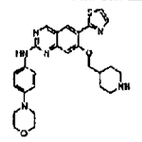
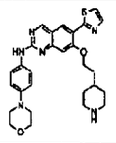
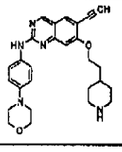
Example	Structure	Activity	LC/MS (4.5min run) MS (M+1) m/z Rt (min)	LC/MS (1.5min run) MS (M+1) m/z Rt (min)
682		*	474.1 4.82	
683		***	415.0 4.71	
684		*	519.0 2.78	
685		***	460.1 2.68	
686		****	444.0 2.90	
687		***	503.1 2.96	
688		***	517.1 3.16	
689		***	458.1 3.06	

FIG. 2 (PART 1 of 55)

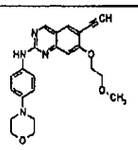
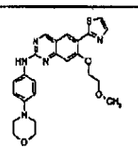
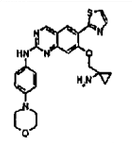
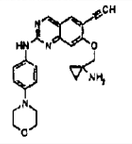
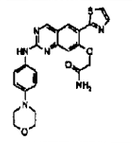
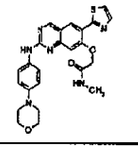
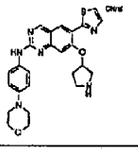
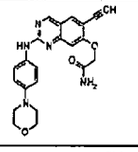
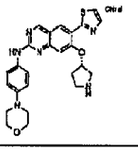
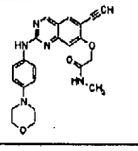
690		****	405.1 3.57	
691		*	464.0 3.69	
692		**	475.0 2.91	
693		***	416.1 2.73	
694		*	463.1 2.93	
695		*	477.0 0.60	
696		****	475.1 2.80	
697		**	404.1 2.86	
698		***	475.0 2.78	
699		**	418.1 3.05	

FIG. 2 (PART 2 of 55)

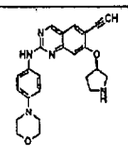
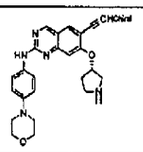
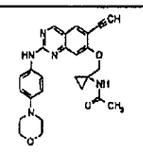
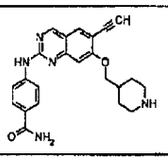
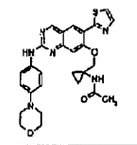
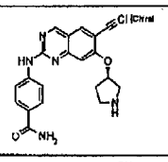
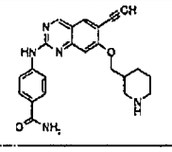
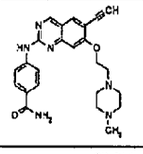
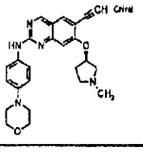
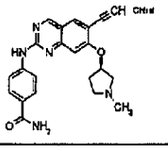
700		****	416.2 2.63	
701		****	416.1 1.83	
702		***	458.1 3.20	
703		****	402.0 2.85	
704		**	517.0 3.31	
705		****	374.0 2.59	
706		****	402.1 2.88	
707		**	431.0 2.44	
708		***	430.1 2.68	
709		****	388. 2.66	

FIG. 2 (PART 3 of 55)

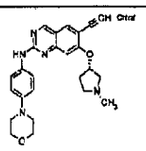
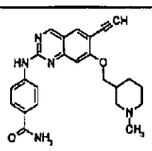
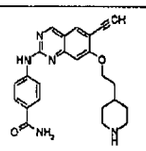
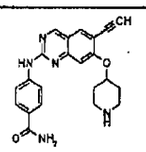
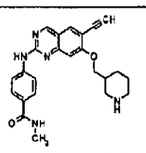
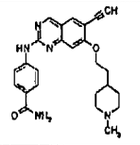
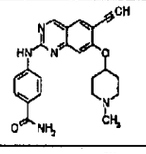
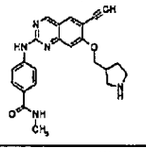
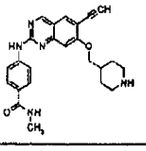
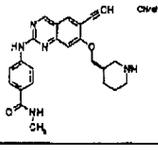
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711		****	416.0 2.90	
712		****	416.0 3.01	
713		****	388.0 2.76	
714		****	416.0 3.07	
715		***	430.1 3.12	
716		****	402.1 2.83	
717		****	402.2 2.94	
718		****	416.0 3.12	
719		****	416.0 2.96	

FIG. 2 (PART 4 of 55)

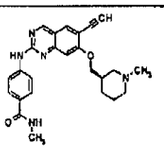
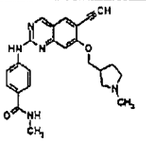
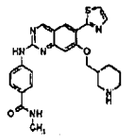
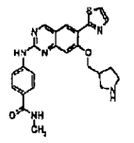
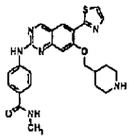
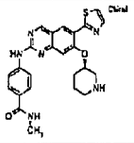
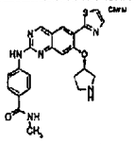
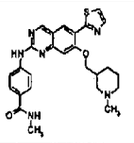
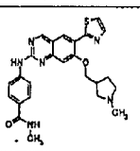
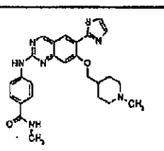
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721		***	416.0 2.86	
722		****	475.1 3.05	
723		****	461.0 2.92	
724		****	475.0 3.01	
725		**	461.0 3.10	
726		****	447.2 2.85	
727		**	489.2 3.09	
728		**	475.2 2.98	
729		**	489.2 3.03	

FIG. 2 (PART 5 of 55)

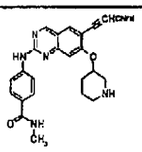
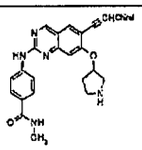
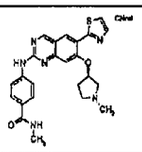
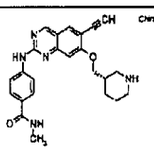
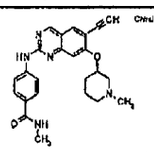
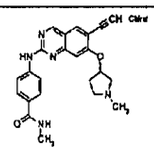
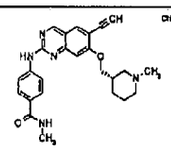
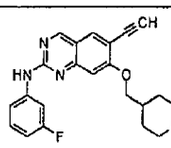
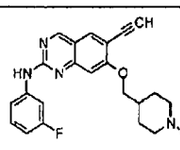
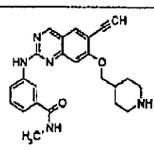
730		**	402.2 2.90	
731		****	388.0 2.72	
732		***	461.2 2.88	
733		****	416.2 0.54	
734		**	416.2 0.52	
735		****	402.2 0.50	
736		***	430.2 0.55	
737		***	377.1 0.74	
738		**	391.2 0.73	
739		***	416.2 0.54	

FIG. 2 (PART 6 of 55)

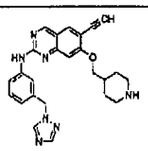
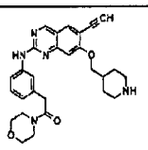
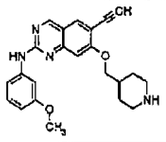
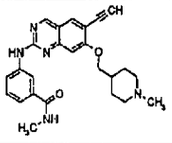
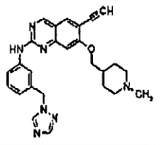
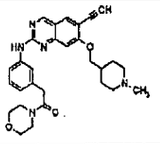
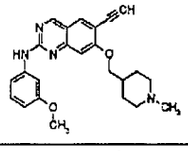
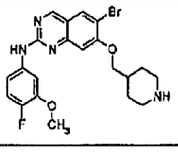
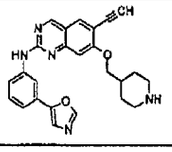
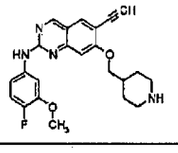
740		****	440.2 0.57	
741		****	486.3 0.58	
742		****	389.0 0.69	
743		**	430.2 0.57	
744		***	454.2 0.59	
745		***	500.3 0.59	
746		**	403.2 0.70	
747		***	461/463 0.76	
748		**	426.2 0.69	
749		****	407.2 0.71	

FIG. 2 (PART 7 of 55)

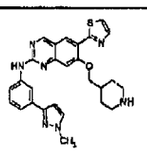
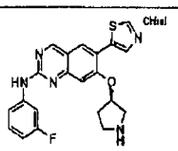
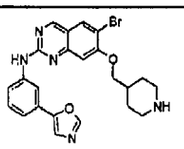
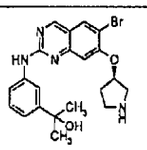
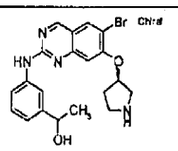
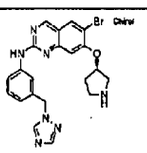
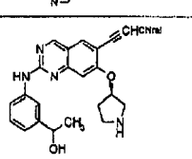
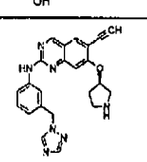
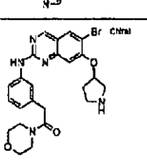
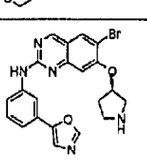
750		**	498.3 0.69	
751		*	408.1 0.68	
752		**	480/482 0.75	
753		**	443/445 0.75	
754		**	429/431 0.71	
755		***	466/468 0.69	
756		****	375.2 0.54	
757		****	412.2 0.53	
758		***	512/514 0.56	
759		**	452/454 0.67	

FIG. 2 (PART 8 of 55)

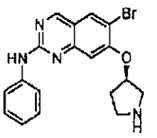
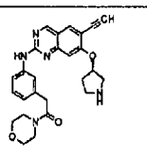
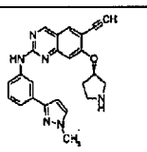
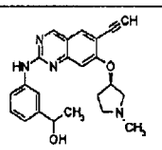
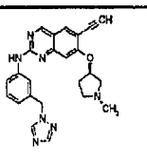
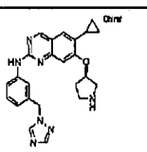
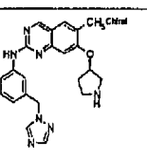
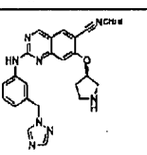
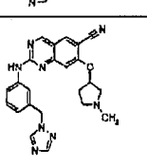
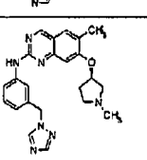
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761		****	458.2 0.56	
762		****	411.2 0.65	
763		***	389.2 0.57	
764		****	426.1 0.56	
765		*	428.2 0.54	
766		**	402.2 0.47	
767		****	413.1 0.51	
768		***	427.1 0.52	
769		**	416.1 0.48	

FIG. 2 (PART 9 of 55)

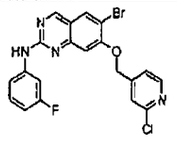
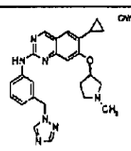
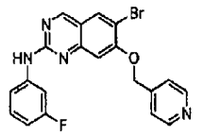
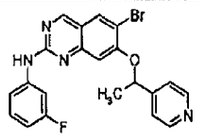
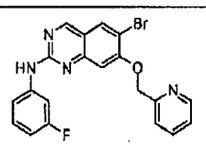
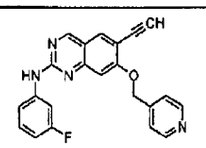
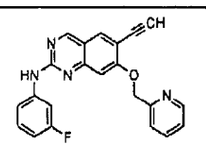
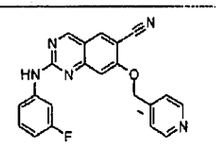
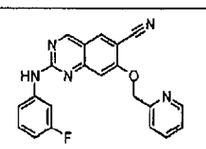
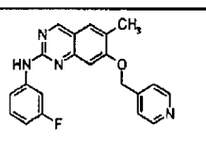
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771		*	442.2 0.54	
772		*	425/427 0.76	
773		*	439/441 0.79	
774		*	425/427 0.87	
775		**	371.0 0.74	
776		**	371.0 0.80	
777		**	372.0 0.69	
778		*	372.0 0.77	
779		*	361.1 0.68	

FIG. 2 (PART 10 of 55)

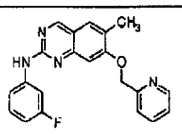
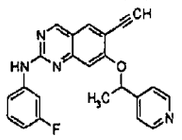
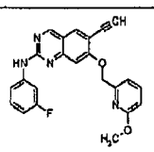
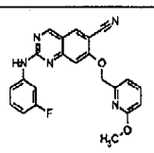
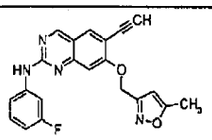
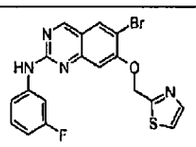
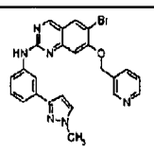
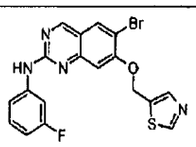
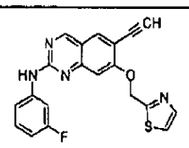
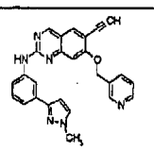
780		*	361.1 0.75	
781		**	385.2 0.74	
782		*	401.1 1.14	
783		*	402.1 1.12	
784		*	375.1 1.02	
785		*	431/433 1.06	
786		**	487/489 0.69	
787		*	431/433 0.97	
788		**	377.0 0.98	
789		****	433.1 0.68	

FIG. 2 (PART 11 of 55)

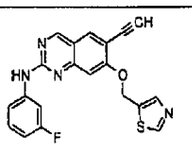
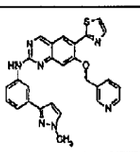
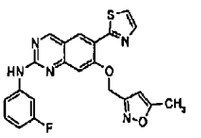
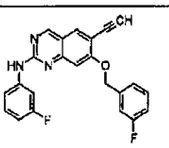
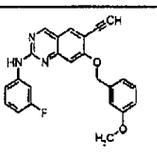
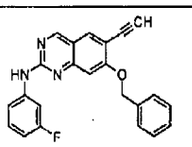
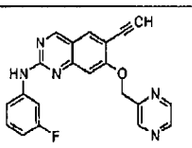
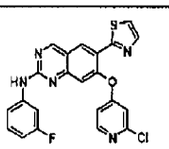
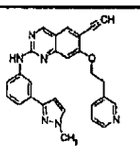
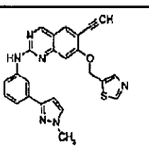
790		***	377.0 0.93	
791		*	492.1 0.67	
792		*	434.1 1.03	
793		*	388.0 1.18	
794		*	400.1 1.15	
795		*	370.1 1.16	
796		****	372.0 0.93	
797		*	450.0 1.14	
798		**	447.1 0.70	
799		***	439.1 0.81	

FIG. 2 (PART 12 of 55)

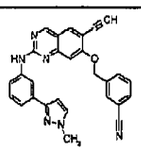
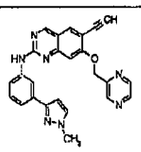
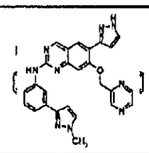
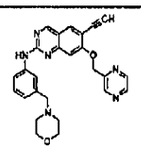
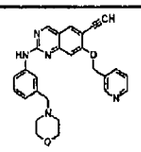
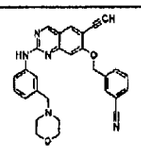
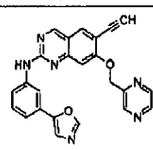
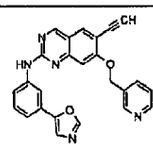
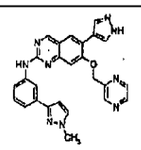
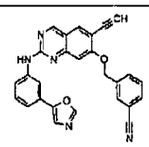
800		***	457.1 0.97	
801		*	434.1 0.81	
802		***	476.2 0.68	
803		***	453.1 0.62	
804		****	452.1 0.49	
805		****	476.1 0.78	
806		***	421.0 0.84	
807		****	420.0 0.68	
808		****	476.0 0.64	
809		***	444.0 1.01	

FIG. 2 (PART 13 of 55)

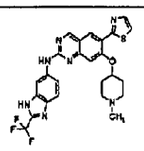
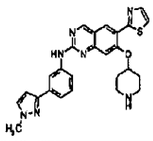
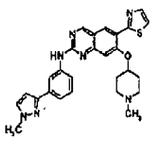
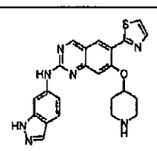
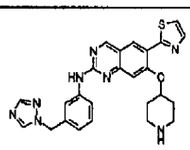
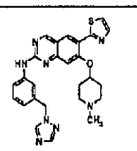
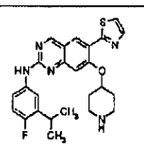
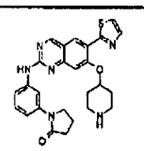
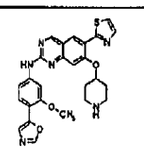
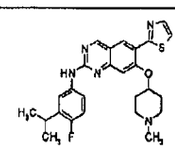
810		**	526.1 2.16	
811		****	484.1 2.2	
812		***	498.1 2.2	
813		****	444.1 1.92	
814		****	485.2 1.9	
815		****	499.2 1.9	
816		****		464.1 0.78
817		****		487.2 0.5
818		****		501.2 0.6
819		***		478.2 0.81

FIG. 2 (PART 14 of 55)

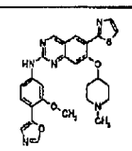
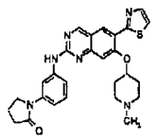
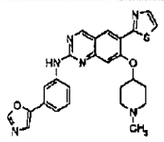
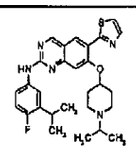
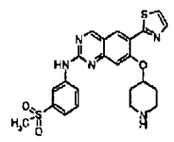
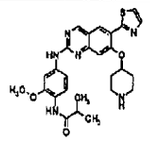
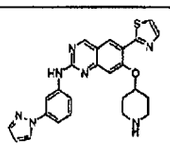
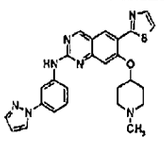
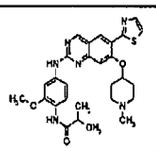
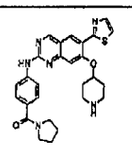
820		****		515.2 0.69
821		****		501.2 0.61
822		***	485.1 2.2	
823		*	506.2 3.3	
824		**		482.2 0.6
825		****		519.2 0.58
826		****		470.2 0.6
827		****		484.2 0.6
828		****	533.2 2.2	
829		****		501.1 0.56

FIG. 2 (PART 15 of 55)

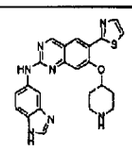
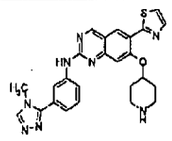
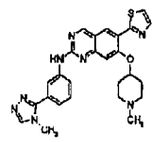
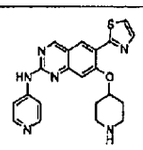
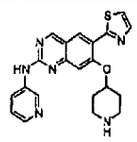
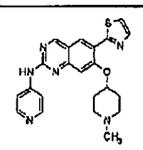
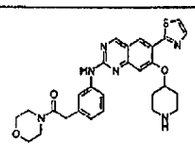
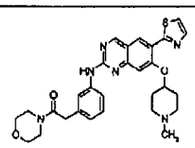
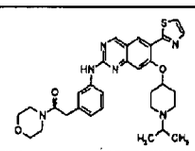
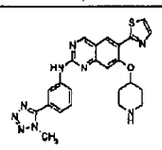
830		****	444.1 1.7	
831		****	485.1 1.9	
832		***	499.2 1.9	
833		*	405.2 1.7	
834		*	405.2 1.7	
835		*	419.2 1.79	
836		****	531.2 1.97	
837		****	545.2 1.9	
838		***	573.2 2.1	
839		****	486.2 2.1	

FIG. 2 (PART 16 of 55)

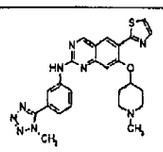
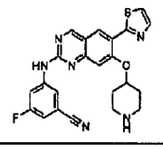
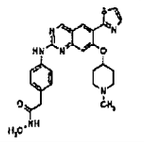
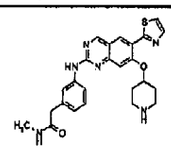
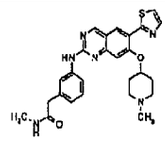
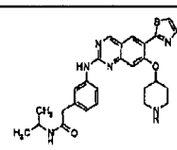
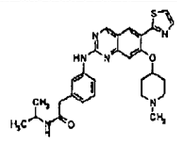
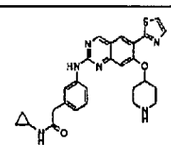
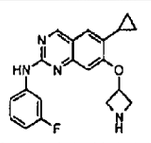
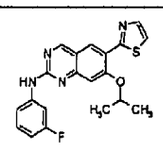
840		***	500.2 2.1	
841		***	447.2 2.35	
842		***	489.2 2.01	
843		****	475.1 1.86	
844		****	489.2 1.9	
845		****	503.3 2.01	
846		****	517.3 2.07	
847		****	501.3 1.95	
848		*		351.1 0.66
849		*	381.1 1.07	

FIG. 2 (PART 17 of 55)

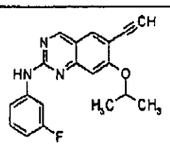
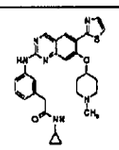
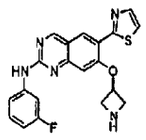
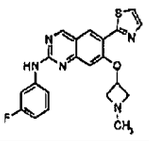
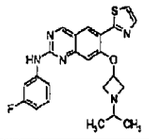
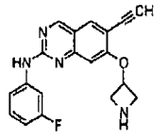
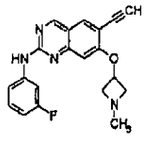
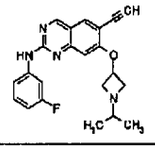
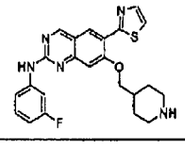
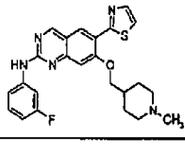
850		*	322.1 1.04	
851		****	515.2 1.99	
852		*		394 0.64
853		*		408.1 0.65
854		*		436.1 0.7
855		****		335.2 0.64
856		***	349.2 2.7	
857		*		377.2 0.73
858		**		436.1 0.73
859		*		450.2 0.72

FIG. 2 (PART 18 of 55)

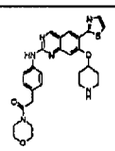
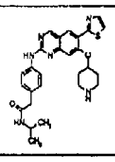
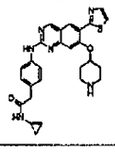
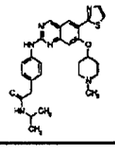
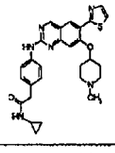
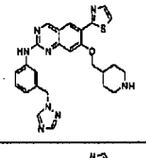
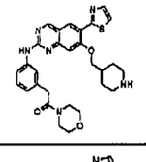
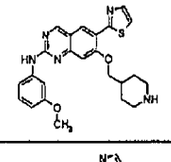
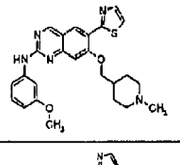
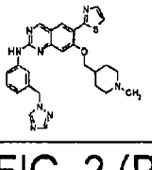
860		****		531.3 0.54
861		****		503.2 0.57
862		****		501.2 0.55
863		***		517.2 0.58
864		**		515.2 0.55
865		***		499.2 0.57
866		***		545.3 0.57
867		**		448.2 0.68
868		**		462.2 0.69
869		**		513.3 0.59

FIG. 2 (PART 19 of 55)

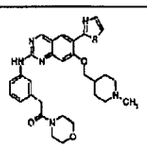
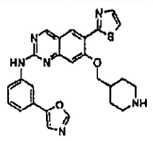
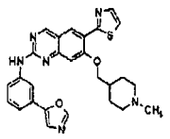
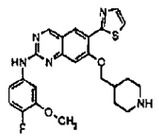
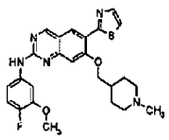
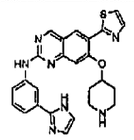
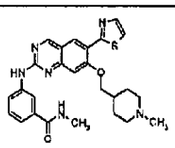
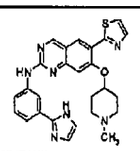
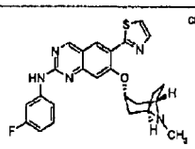
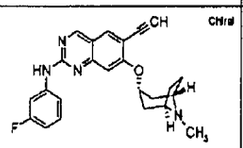
870		**		559.3 0.59
871		*	485.2 2.5	
872		*	499.2 2.69	
873		**		466.2 0.7
874		**		480.2 0.73
875		****		470.2 0.53
876		*	489.2 2.1	
877		***		484.2 0.56
878		****		462.3 0.74
879		****		403.2 0.73

FIG. 2 (PART 20 of 55)

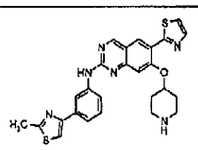
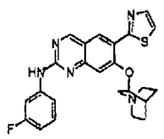
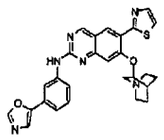
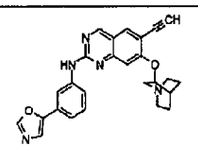
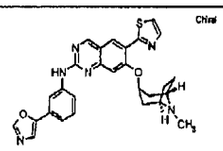
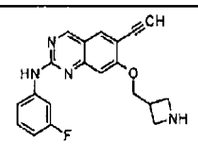
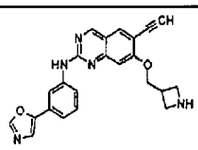
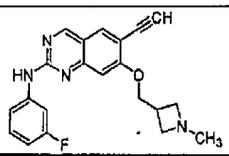
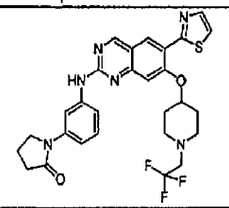
880		***		501.2 0.74
881		*		448.2 0.74
882		*		497.2 0.69
883		*		438.2 0.71
884		*		511.2 0.83
885		**		349.1 0.70
886		**		398.2 0.64
887		*		363.1 0.73
888		*		569.2 0.79

FIG. 2 (PART 21 of 55)

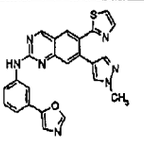
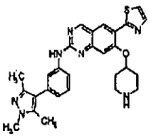
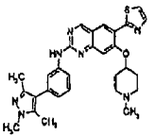
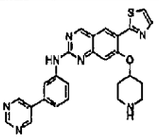
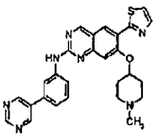
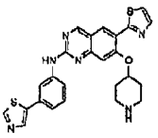
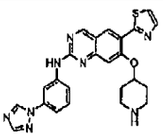
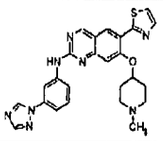
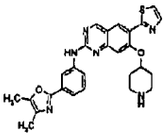
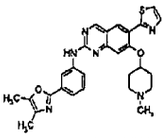
889		*		452.1 0.76
890		***		512.2 0.61
891		***		526.2 0.6
892		****		482.2 0.58
893		****		496.2 0.6
894		**		487.2 0.66
895		****		471.2 0.57
896		***		485.2 0.59
897		**		499.2 0.72
898		*		513.3 0.72

FIG. 2 (PART 22 of 55)

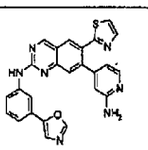
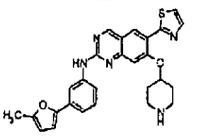
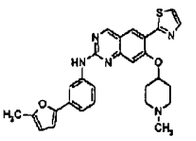
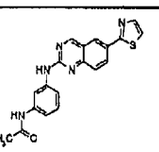
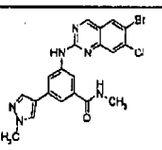
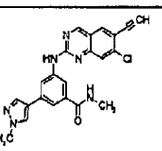
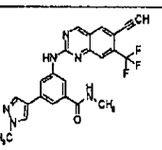
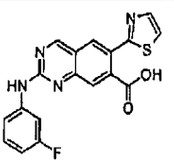
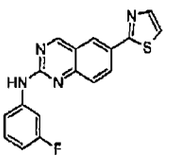
899		*		464.2 0.64
900		**		484.2 0.85
901		*		496.2 0.82
902		**	392 2.31	
903		*	472.8 0.89	
904		**	417.1 0.80	
905		*	451.0 0.86	
906		N/A		367.1 0.78
907		N/A		323.1 1.01

FIG. 2 (PART 23 of 55)

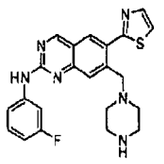
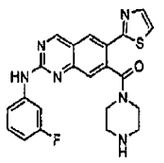
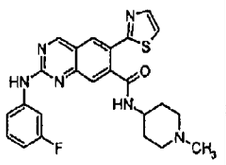
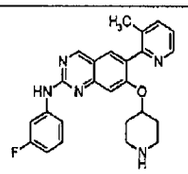
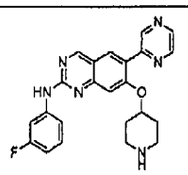
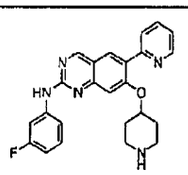
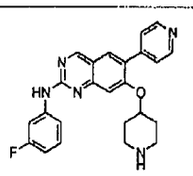
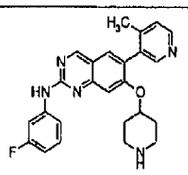
908		N/A		421.1 0.61
909		N/A		435.0 0.65
910		N/A		463.1 0.64
911		N/A		430.1 0.57
912		N/A		417.1 0.65
913		N/A		416.1 0.55
914		N/A		416.1 0.56
915		N/A		430.2 0.57

FIG. 2 (PART 24 of 55)

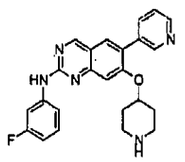
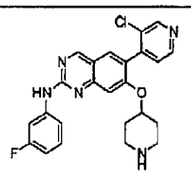
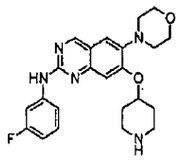
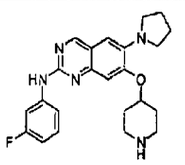
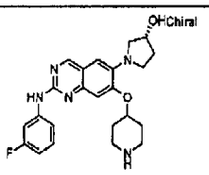
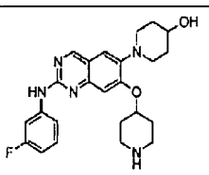
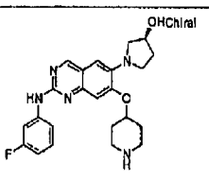
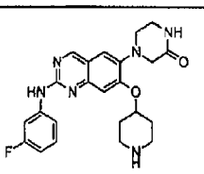
916		N/A		416.2 0.55
917		N/A		450.1 0.71
918		N/A		424.1 0.61
919		N/A		408.1 0.57
920		N/A		424.1 0.56
921		N/A		438.1 0.53
922		N/A		424.1 0.55
923		N/A		437.1 0.55

FIG. 2 (PART 25 of 55)

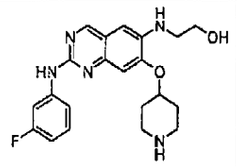
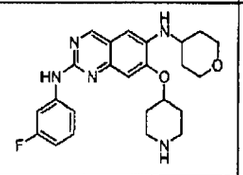
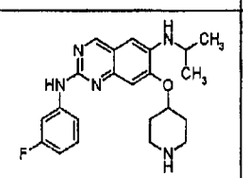
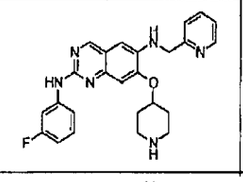
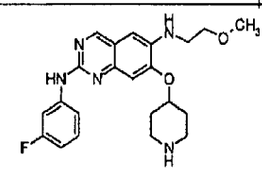
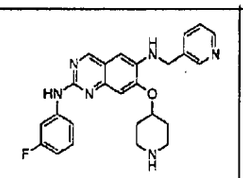
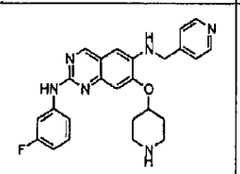
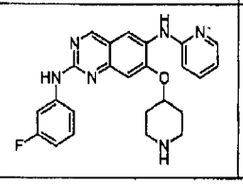
924		N/A		398.1 0.55
925		N/A		438.1 0.63
926		N/A		396.1 0.64
927		N/A		445.1 0.52
928		N/A		412.1 0.62
929		N/A		445.2 0.51
930		N/A		445.1 0.51
931		N/A		431.1 0.54

FIG. 2 (PART 26 of 55)

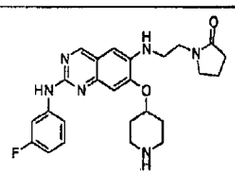
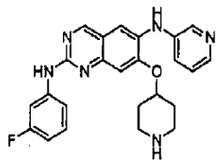
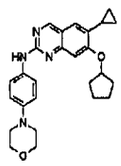
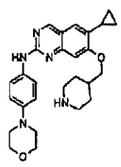
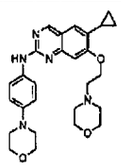
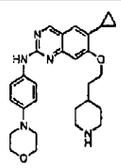
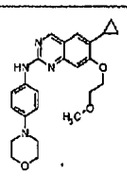
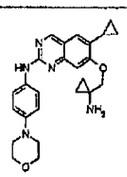
932		N/A		465.1 0.60
933		N/A		431.1 0.53
934		*	431	
935		**	460	
936		*	476	
937		*	474	
938		*	421	
939		*	432	

FIG. 2 (PART 27 of 55)

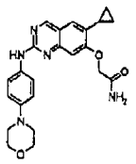
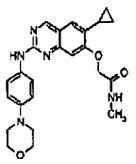
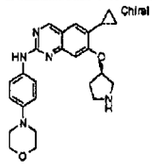
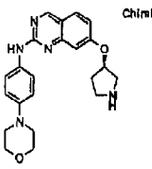
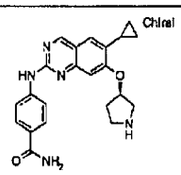
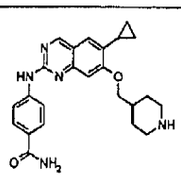
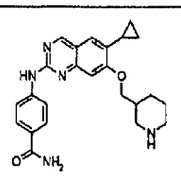
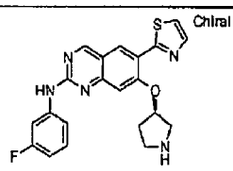
940		*	420	
941		*	434	
942		*	432	
943		**	392	
944		**	390	
945		**	418	
946		**	418	
947		***	408	

FIG. 2 (PART 28 of 55)

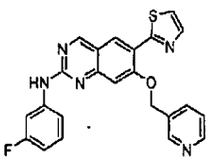
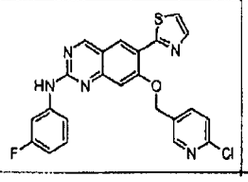
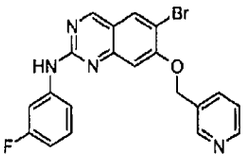
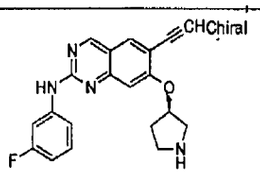
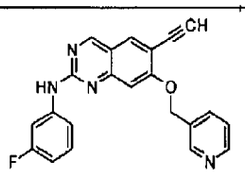
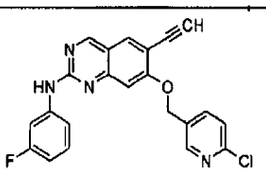
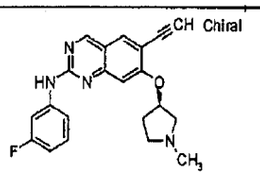
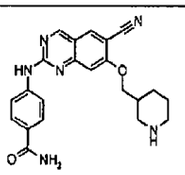
948		*	430	
949		*	465	
950		**	426	
951		***	349	
952		***	371	
953		***	405	
954		**	363	
955		****	403	

FIG. 2 (PART 29 of 55)

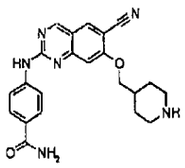
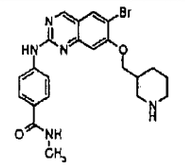
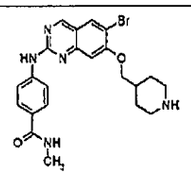
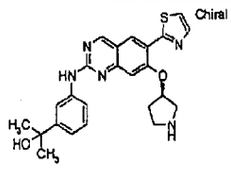
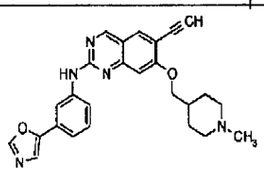
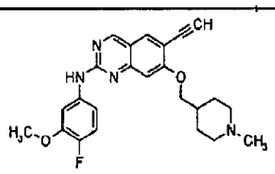
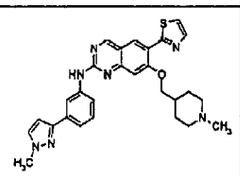
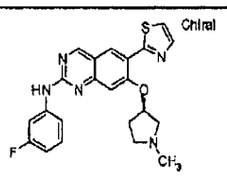
956		****	403	
957		****	470/472	
958		****	470/472	
959		**	448	
960		**	440	
961		***	421	
962		*	512	
963		**	422	

FIG. 2 (PART 30 of 55)

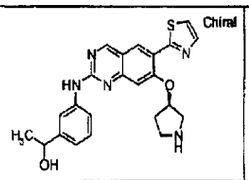
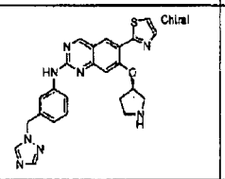
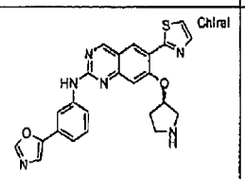
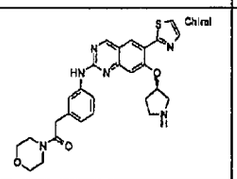
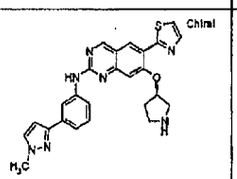
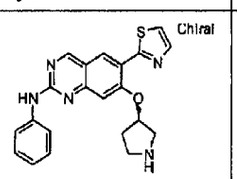
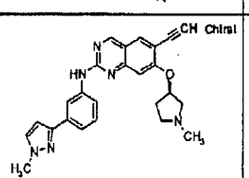
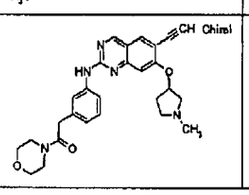
964		***	434	
965		****	471	
966		***	457	
967		****	518	
968		****	470	
969		****	390	
970		***	425	
971		****	472	

FIG. 2 (PART 31 of 55)

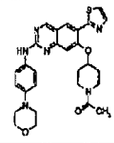
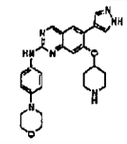
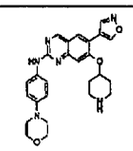
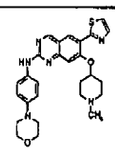
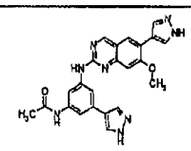
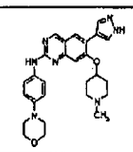
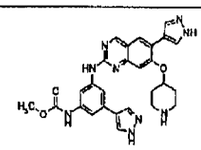
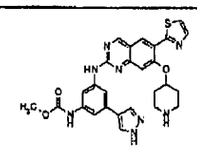
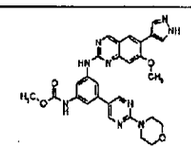
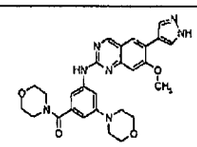
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973		****	472.1 1.55	
974		****	473.1 1.68	
975		****	503.1 1.97	
976		****	441.1 1.79	
977		****	486.1 1.73	
978		****	526.1 1.79	
979		****	543.2 2.03	
980		*	554.1 2.27	
981		**	516.1 1.94	

FIG. 2 (PART 32 of 55)

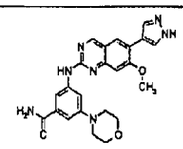
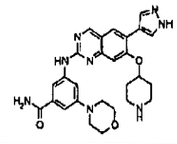
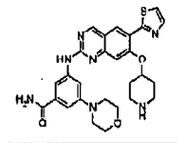
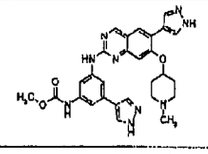
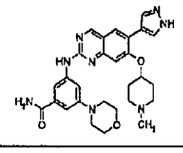
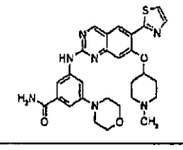
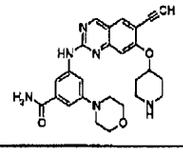
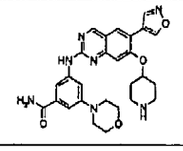
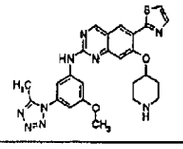
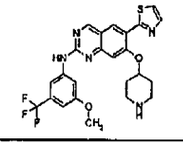
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983		****	515.2 1.77	
984		****	532.2 1.94	
985		****	540.1 1.83	
986		***	529.2 1.71	
987		***	546.1 1.90	
988		****	473.0 1.86	
989		***	516.1 1.84	
990		****	516.1 2.21	
991		**	502.0 2.58	

FIG. 2 (PART 33 of 55)

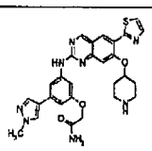
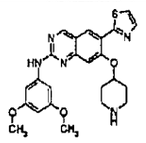
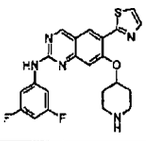
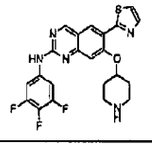
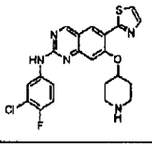
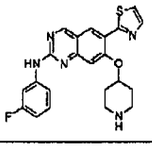
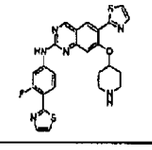
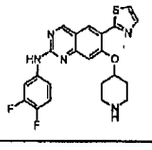
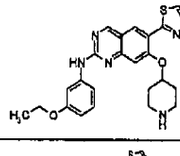
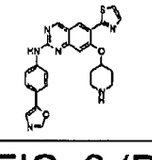
992		****	557.0 1.99	
993		*	464.3 2.11	
994		***	440.0 2.42	
995		***	458.0 2.47	
996		****	456.1 2.47	
997		****	422.1 2.34	
998		****	505.2 2.36	
999		****	440.1 2.40	
1000		****	448.1 2.38	
1001		****	471.1 2.19	

FIG. 2 (PART 34 of 55)

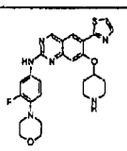
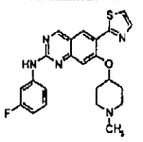
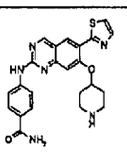
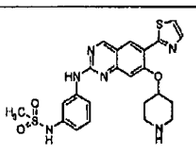
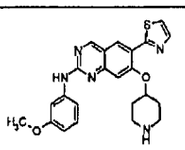
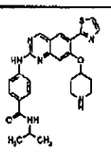
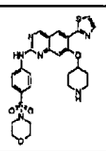
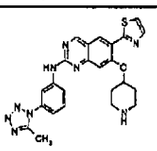
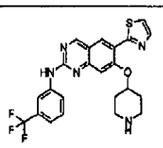
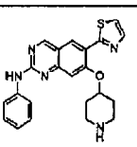
1002		****	507.2 2.18	
1003		****	436.1 2.32	
1004		****	447.1 1.90	
1005		****	497.1 2.05	
1006		****	434.2 2.21	
1007		****	489.3 2.14	
1008		****	553.2 2.23	
1009		****	486.1 2.14	
1010		***	472.1 2.56	
1011		****	404.1 2.16	

FIG. 2 (PART 35 of 55)

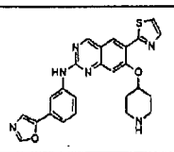
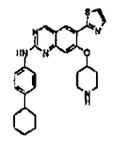
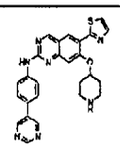
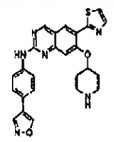
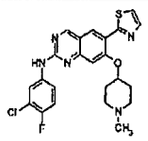
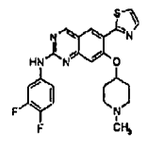
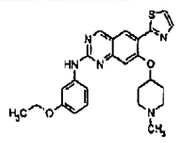
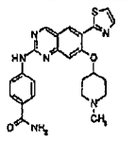
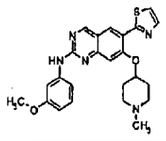
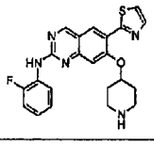
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1013		*	486.1 2.80	
1014		****	482.1 2.08	
1015		****	471.1 2.25	
1016		***	470.0 2.47	
1017		***	454.1 2.38	
1018		**	462.2 2.34	
1019		****	461.1 1.92	
1020		****	448.1 2.23	
1021		*	422.1 2.23	

FIG. 2 (PART 36 of 55)

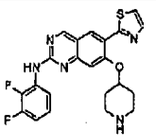
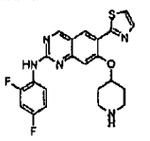
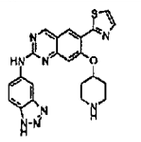
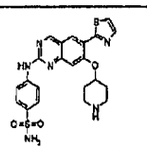
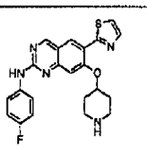
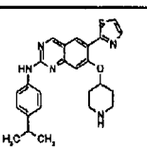
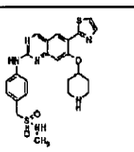
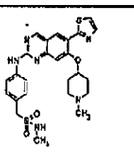
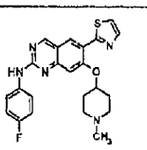
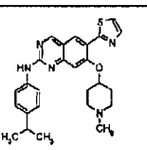
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1023		*	440.0 2.25	
1024		****	445.1 1.94	
1025		****	483.1 1.95	
1026		****	422.1 2.18	
1027		****	446.1 2.49	
1028		****	511.1 2.01	
1029		****	525.1 2.03	
1030		****	436.2 2.21	
1031		****	460.2 2.53	

FIG. 2 (PART 37 of 55)

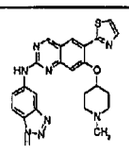
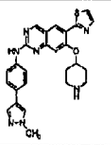
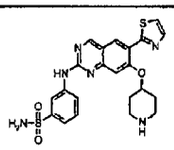
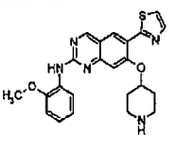
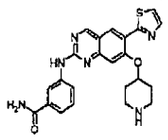
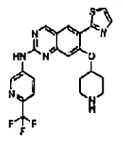
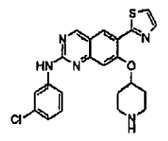
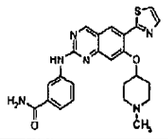
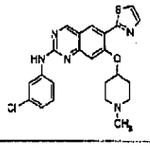
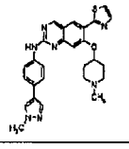
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1033		****	484.1 2.12	
1034		****	483.1 1.97	
1035		*	434.2 2.19	
1036		****	447.2 1.88	
1037		****	473.0 2.32	
1038		****	438.2 2.40	
1039		****	461.2 1.90	
1040		**	452.1 2.47	
1041		****	498.2 2.16	

FIG. 2 (PART 38 of 55)

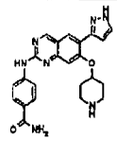
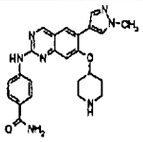
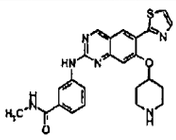
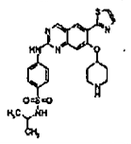
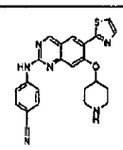
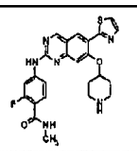
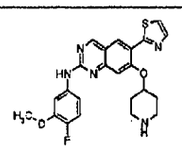
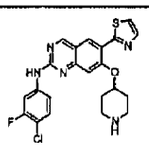
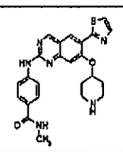
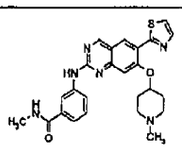
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1043		***	444.2 1.77	
1044		****	461.1 1.94	
1045		****	525.1 2.27	
1046		****	429.1 2.25	
1047		****	479.2 2.07	
1048		****	452.1 2.21	
1049		****	456.1 2.51	
1050		****	461.2 2.01	
1051		***	475.2 2.03	

FIG. 2 (PART 39 of 55)

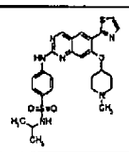
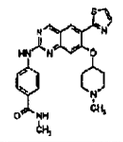
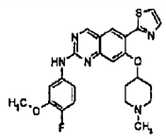
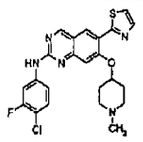
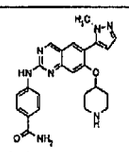
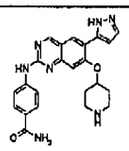
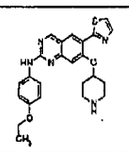
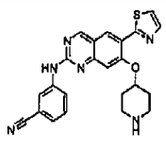
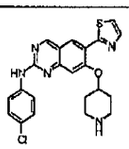
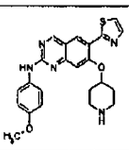
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1053		****	475.2 2.05	
1054		****	466.2 2.34	
1055		**	470.1 2.64	
1056		*	444.2 1.81	
1057		****	430.2 1.73	
1058		****	448.2 2.19	
1059		****	429.2 2.23	
1060		****	438.2 2.38	
1061		****	434.2 2.07	

FIG. 2 (PART 40 of 55)

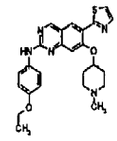
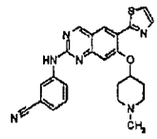
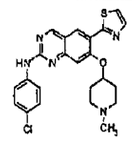
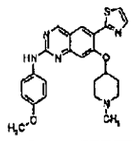
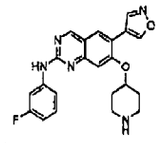
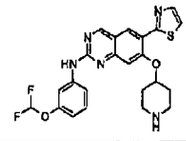
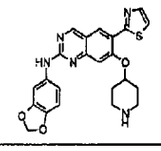
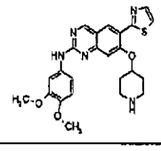
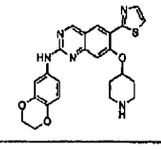
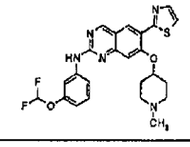
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1063		**	443.2 2.32	
1064		***	452.2 2.47	
1065		***	448.2 2.14	
1066		***	406.2 2.25	
1067		****	470.1 2.38	
1068		****	448.2 2.07	
1069		****	464.2 2.015	
1070		****	462.2 2.08	
1071		***	484.2 0.711	

FIG. 2 (PART 41 of 55)

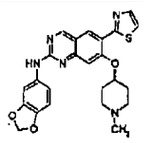
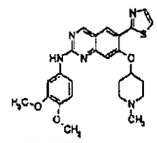
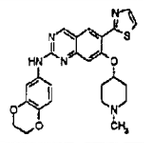
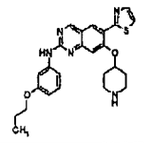
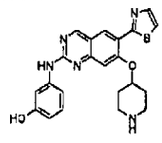
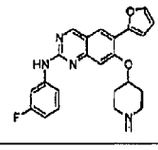
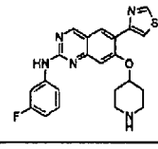
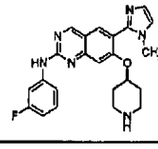
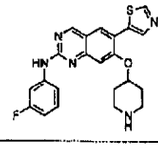
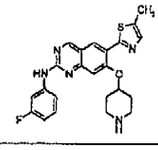
1072		***	462.1 0.58	
1073		****	478.2 0.55	
1074		**	476.2 0.59	
1075		****	462.2 0.75	
1076		****	420.2 0.55	
1077		****	405.2 0.76	
1078		****	422.1 0.68	
1079		*	419.2 0.55	
1080		***	422.1 0.67	
1081		*	436.1 0.73	

FIG. 2 (PART 42 of 55)

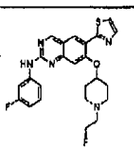
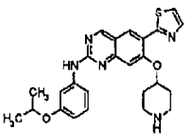
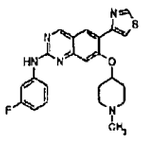
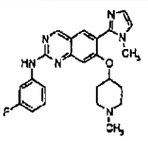
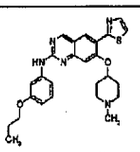
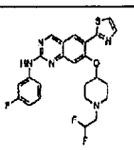
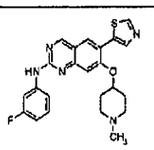
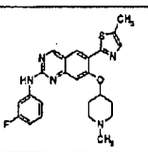
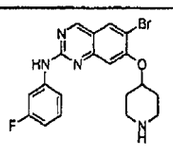
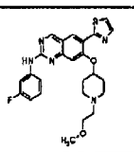
1082		**	468.2 0.73	
1083		***	462.2 0.75	
1084		**	436.2 0.69	
1085		*	433.2 0.55	
1086		***	476.2 0.76	
1087		*	486.1 0.74	
1088		*	436.1 0.66	
1089		*	450.1 0.73	
1090		***	417.1 / 419.1 0.72	
1091		*	480.2, 0.79	

FIG. 2 (PART 43 of 55)

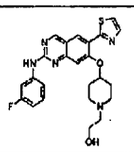
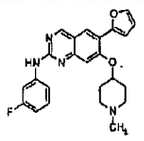
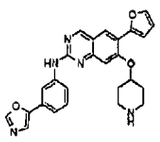
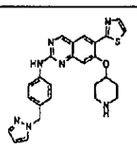
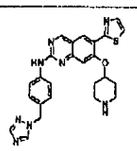
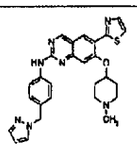
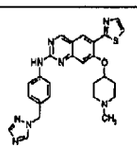
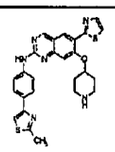
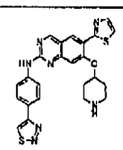
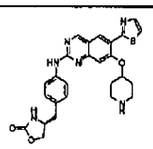
1092		***	466.2 0.73	
1093		****	419.2 0.82	
1094		****	454.2 0.76	
1095		****	484.1 0.64	
1096		****	485.0 0.56	
1097		****	498.2 0.63	
1098		***	499.1 0.54	
1099		****	501.0 0.68	
1100		****	488.0 0.68	
1101		****	503.0 0.55	

FIG. 2 (PART 44 of 55)

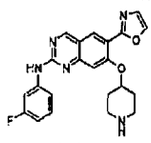
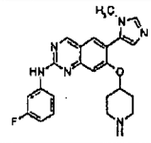
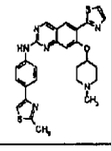
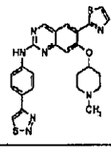
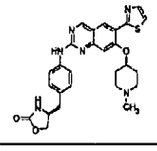
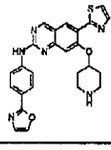
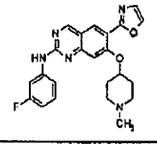
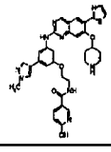
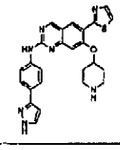
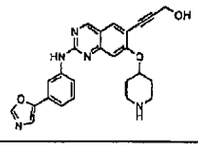
1102		***	406.1 0.68	
1103		*	419.1 0.55	
1104		**	515.1 0.70	
1105		****	502.1 0.71	
1106		****	517.1 0.56	
1107		****	471.1 0.67	
1108		**	420.0 0.69	
1109		****	664.2 0.55	
1110		****	470.1 0.59	
1111		****	442.1 0.60	

FIG. 2 (PART 45 of 55)

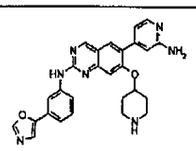
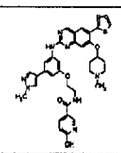
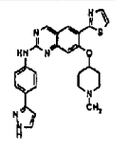
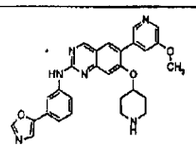
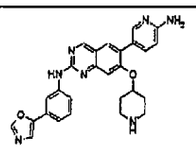
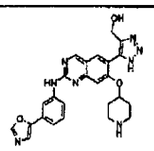
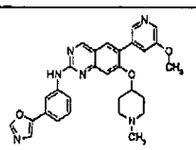
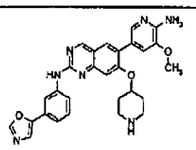
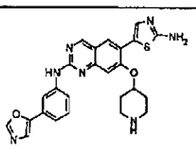
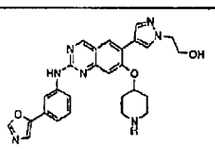
1112		*	480.0 0.54	
1113		***	678.3 0.56	
1114		****	484.1 0.59	
1115		*	495.0 0.55	
1116		*	480.0 0.53	
1117		*	485.2 0.52	
1118		*	509.2 0.58	
1119		*	510.2 0.55	
1120		***	486.1 0.55	
1121		**	498.2 0.57	

FIG. 2 (PART 46 of 55)

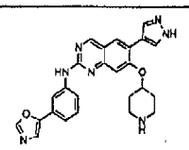
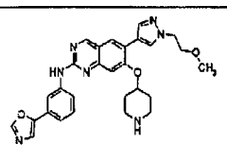
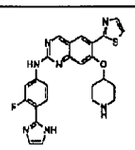
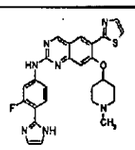
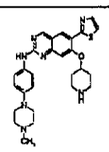
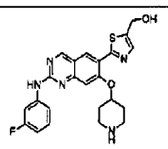
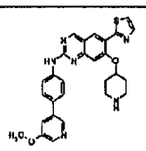
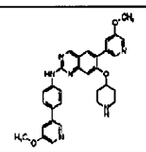
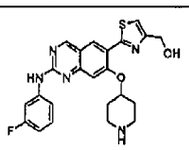
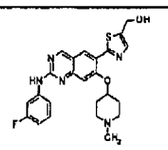
1122		****	454.1 0.57	
1123		*	512.2 0.62	
1124		****	488.1 0.50	
1125		***	502.1 0.52	
1126		****	502.1 0.48	
1127		**	452.1 0.65	
1128		****	511.0 0.57	
1129		**	535.1 0.48	
1130		***	452.1 0.64	
1131		**	466.1 0.66	

FIG. 2 (PART 47 of 55)

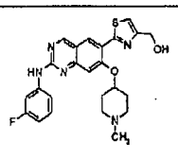
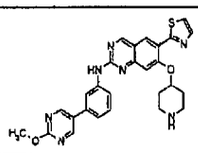
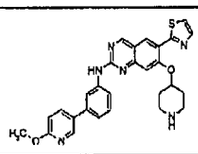
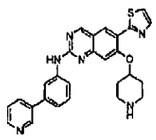
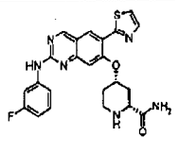
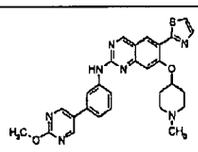
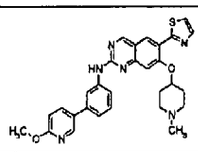
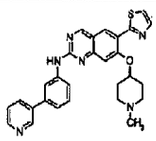
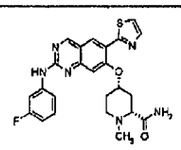
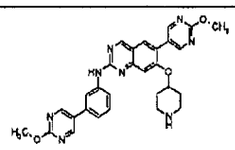
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1133		****	512.1 0.68	
1134		***	511.1 0.73	
1135		****	481.1 0.53	
1136		*	465.1 0.66	
1137		***	526.1 0.69	
1138		**	525.1 0.75	
1139		****	495.1 0.54	
1140		*	479.0 0.68	
1141		*	537.0 0.66	

FIG. 2 (PART 48 of 55)

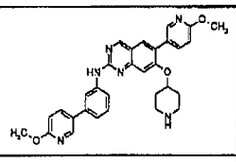
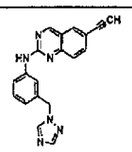
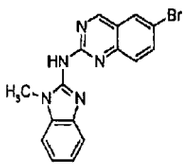
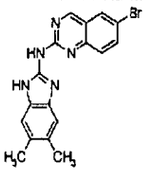
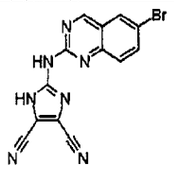
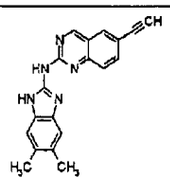
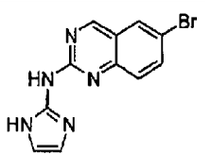
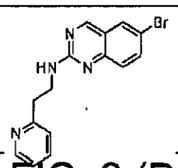
1142		*	535.1 0.74	
1143		****	327.1	
1144		*	354.9 2.57	
1145		*	368.9 2.86	
1146		*	339.9 2.94	
1147		*	314.0 2.63	
1148		*	289.9 2.20	
1149		*	328.9 1.78	

FIG. 2 (PART 49 of 55)

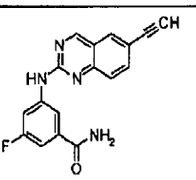
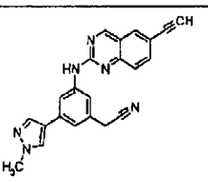
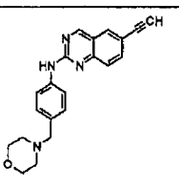
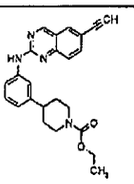
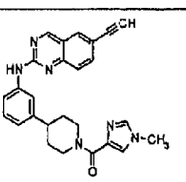
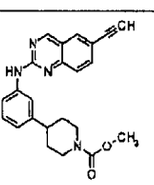
1150		**	307.0 2.58	
1151		***	365.3 0.84	
1152		*	345.2 2.15	
1153		*	387.1 0.98	
1154		**	437.2 0.72	
1155		*	387.2 0.99	

FIG. 2 (PART 50 of 55)

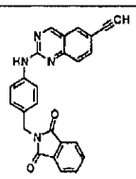
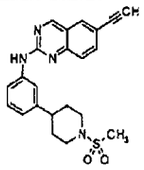
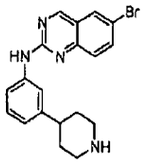
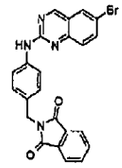
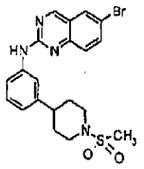
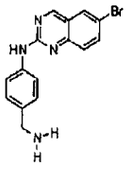
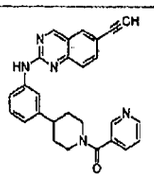
1156		**	405.1 0.98	
1157		**	407.1 0.91	
1158		**	383.1 0.73	
1159		*	459.1 1.08	
1160		*	461.0 1.00	
1161		*	329.1 0.63	
1162		**	434.2 0.73	

FIG. 2 (PART 51 of 55)

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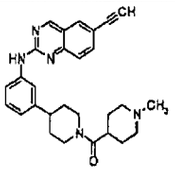
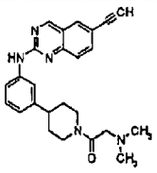
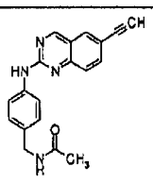
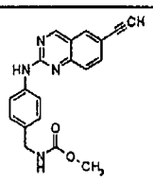
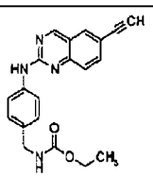
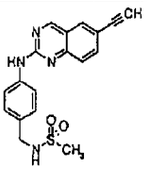
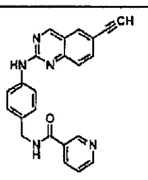
1163		*	454.1 0.72	
1164		*	414.2 0.71	
1165		**	317.1 0.69	
1166		*	333.2 0.69	
1167		*	347.2 0.86	
1168		**	353.1 0.76	
1169		*	380.1 0.65	

FIG. 2 (PART 52 of 55)

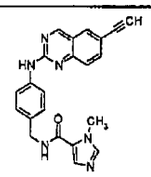
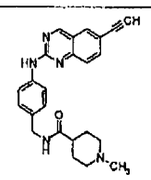
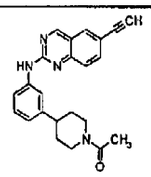
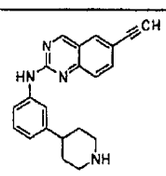
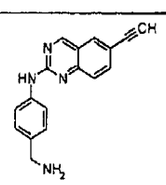
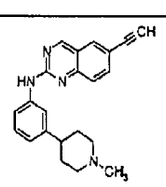
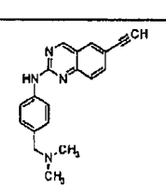
1170		*	383.1 0.66	
1171		*	400.1 0.62	
1172		*	371.1 0.86	
1173		**	329.2 0.71	
1174		*	275.2 0.62	
1175		**	343.2 0.82	
1176		*	303.2 0.76	

FIG. 2 (PART 53 of 55)

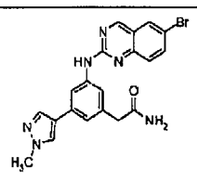
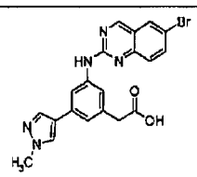
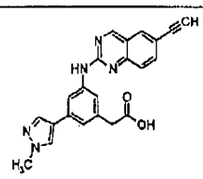
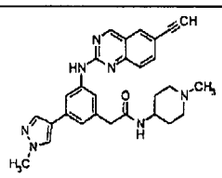
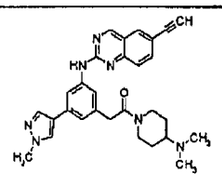
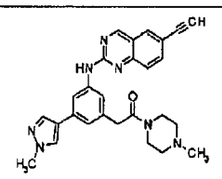
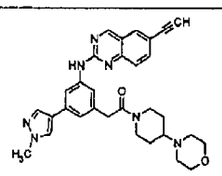
1177		**	436.9 0.68	
1178		*	437.9 0.78	
1179		*	384.2 0.70	
1180		**	480.2 0.63	
1181		**	494.3 0.63	
1182		****	466.3 0.62	
1183		**	536.4 0.63	

FIG. 2 (PART 54 of 55)

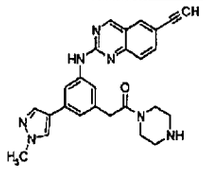
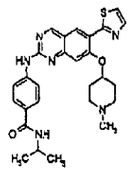
1184		***	452.1 0.63	
1185		****	503.2 0.57	

FIG. 2 (PART 55 of 55)

(12) **SOLICITUD INTERNACIONAL PUBLICADA DE ACUERDO CON EL TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES (TCP)**
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(19) **Organización Mundial de la Propiedad Intelectual**
Oficina Internacional

TCP

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Tabla 2

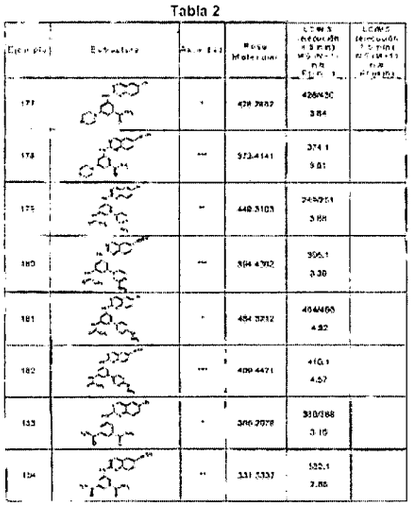


FIG. 1 (Parte 1 de 59)

(54) Título: QUINAZOLINAS PARA LA INHIBICIÓN DE PDK1

(57) **Resumen:** La invención proporciona compuestos novedosos que son inhibidores de PDK1. También se proporcionan composiciones farmacéuticas que incluyen a los compuestos, y métodos para el tratamiento de enfermedades proliferativas, tales como cánceres, con los compuestos o composiciones.

QUINAZOLINAS PARA LA INHIBICIÓN DE PDK1

CAMPO DE LA INVENCIÓN

La presente invención se refiere en términos generales a inhibidores de molécula pequeña de la cinasa dependiente de 3-fosfoinositida (PDK1/PDPK1). En algunas modalidades, los compuestos se pueden utilizar como productos terapéuticos en el tratamiento de enfermedades proliferativas celulares.

ANTECEDENTES

La PDK1 (cinasa dependiente de 3-fosfoinositida 1) es una cinasa de serina/treonina que pertenece a la súper-familia de cinasas AGC. PDK1 fue primeramente identificada como la cinasa corriente arriba responsable de la activación de la cinasa de proteína B/AKT en la presencia de lípidos de fosfoinositida (PIP_3). PDK1 activa la AKT mediante la fosforilación de un residuo específico (treonina 308) localizado en el ciclo de activación de esta cinasa. La subsiguiente investigación ha demostrado que la PDK1 es responsable de la fosforilación del ciclo de activación de muchas cinasas AGC, incluyendo la cinasa S6 ribosomal p90 (RSK), los miembros de la familia de la cinasa C de proteína (PKC), la cinasa S6 ribosomal p70 (70S6K), y la cinasa de proteína de suero e inducida por glucocorticoide (SGK). Por consiguiente, PDK1 es un activador central de múltiples sendas de señalización que están involucradas en la proliferación, sobrevivencia, y control de apoptosis celular. Es importante que las alteraciones en estas

sendas de señalización se observan con frecuencia en una variedad de cánceres humanos. Por ejemplo, AKT es altamente activada en un gran porcentaje de tipos de tumores, incluyendo melanoma, cáncer de mama, de pulmón, de próstata y de ovarios. Los niveles de RSK se elevan en los cánceres de próstata, y Recientemente se ha demostrado que un inhibidor específico de RSK (SL0101) inhibe la proliferación de múltiples líneas celulares de cáncer de próstata. De una manera similar, se ha demostrado que la PKCε tiene un papel importante en la regulación de la apoptosis y en la promoción de la sobrevivencia de las células de glioma.

El gen PDK1 humano codifica una proteína de 556 aminoácidos con un dominio catalítico amino-terminal y un carboxilo terminal no catalítico que contiene un dominio de homología de pleckstrina (PH). Los estudios recientes sugieren que PDK1 es una cinasa constitutivamente activa, y que la regulación de PDK1 se presenta a través de la localización o del estado de conformación de las proteínas objetivo de PDK1. Por ejemplo, se requiere el dominio PH de PDK1 para el enlace de los lípidos PIP_3 producidos por la cinasa PI3 (PI3K). El enlace de PDK1 con los lípidos PIP_3 da como resultado la co-localización en membrana con AKT, otra proteína que contiene el dominio PH. Una vez co-localizadas, la PDK1 activa la AKT mediante la fosforilación de la treonina 308. De una manera alternativa, PDK1 puede activar otras cinasas AGC independientemente de los lípidos PIP_3 mediante su enlace directamente a un motivo conservado que se encuentra en estos

objetivos. Debido a que PDK1 regula dos clases distintas de sustratos de señalización corriente abajo (los objetivos dependientes de PI3K e independientes), los inhibidores de esta enzima podrían tener un valor terapéutico importante en una variedad de cánceres humanos. Por ejemplo, los inhibidores de PDK1 podrían ser eficaces en los tumores en los que se sobre-regule la senda de señalización de PI3K debido a mutaciones activadoras, amplificación de la PI3K misma o de sus cinasas de tirosina receptoras corriente arriba, o supresión de PTEN, la fosfatasa que contrarresta la actividad de PI3K. El hallazgo de que los ratones que expresan la mitad de la cantidad normal de PTEN se protegen del desarrollo de un amplio número de tumores mediante la reducción de los niveles de expresión de PDK1 apoya esta idea. De una manera alternativa, los inhibidores de PDK1 podrían ser útiles en el tratamiento de cánceres impulsados por las sendas de señalización de PDK1 independientes de PIP_3 (por ejemplo, los cánceres impulsados por K-ras o H-ras).

Finalmente, la reciente identificación de las mutaciones de PDK1 ($PDK1^{T354M}$, $PDK1^{D527E}$) en los cánceres colo-rectales humanos sugiere que los inhibidores de esta cinasa pueden tener un valor terapéutico mediante la inhibición directamente de cualquiera de las formas de tipo silvestre o mutantes de esta proteína. Véase Parsons y colaboradores, *Nature* 436, 792 (11 de Agosto de 2005) "Colo-rectal cancer: Mutations in a signaling pathway."

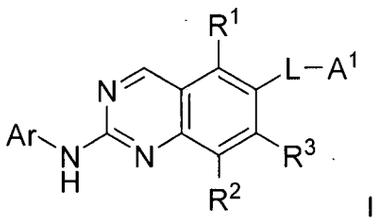
En resumen, PDK1 es un activador central de varias sendas de señalización que se alteran con frecuencia en los cánceres humanos,

haciéndola un objetivo atractivo para la intervención terapéutica.

BREVE DESCRIPCIÓN DE LA INVENCIÓN

En un aspecto, la presente invención proporciona inhibidores de PDK1 que son útiles como agentes terapéuticos, para el tratamiento de enfermedades y trastornos caracterizados por una proliferación celular anormal, por ejemplo cánceres de próstata, pulmón, colon, mama, entre otras.

La presente invención proporciona, entre otras cosas, los compuestos de la fórmula I:



I

o las sales farmacéuticamente aceptables, ésteres, o tautómeros de los mismos, en donde los miembros constituyentes se proporcionan en la presente.

La presente invención proporciona además composiciones que comprenden un compuesto de la fórmula I y cuando menos un vehículo farmacéuticamente aceptable.

La presente invención proporciona además métodos para inhibir PDK1 o una variante de PDK1 en un paciente, los cuales comprenden administrar a este paciente, una cantidad terapéuticamente efectiva de un compuesto de la invención, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo.

La presente invención proporciona además métodos para el

tratamiento de una enfermedad caracterizada por una proliferación celular anormal en un paciente, los cuales comprenden administrar a este paciente, una cantidad terapéuticamente efectiva de un compuesto de la invención, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo.

La presente invención proporciona además métodos para inhibir el crecimiento tumoral en un paciente, comprendiendo el método administrar a este paciente, una cantidad terapéuticamente efectiva de un compuesto de la invención, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo.

La presente invención proporciona además métodos para el tratamiento de cáncer en un paciente, comprendiendo el método administrar a este paciente, una cantidad terapéuticamente efectiva de un compuesto de la invención, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo.

La presente invención proporciona además un compuesto de la invención, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, para utilizarse en terapia.

La presente invención proporciona además un compuesto de la invención, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, para utilizarse en la preparación de un medicamento para utilizarse en terapia.

Otras características, objetos, y ventajas de la invención serán evidentes a partir de la descripción, y a partir de las reivindicaciones.

BREVE DESCRIPCIÓN DE LOS DIBUJOS

La Figura 1 proporciona las estructuras químicas y los datos de actividad para los Ejemplos 177 a 681.

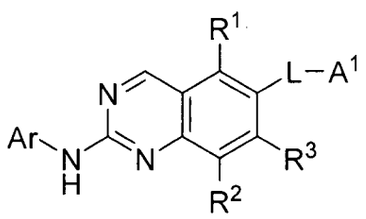
La Figura 2 proporciona las estructuras químicas y los datos de actividad para los Ejemplos 682 a 1185.

En estas dos Figuras, la columna marcada con "Actividad" indica la actividad del compuesto en el Ensayo de Rastreo de Cinasa Alfa PDK1; el símbolo "*" indica que el valor IC_{50} es mayor de 0.30μM; el símbolo "**" indica que el valor IC_{50} es menor o igual a 0.30 μM pero mayor de 0.10 μM; el símbolo "***" indica que el valor IC_{50} es menor o igual a 0.10 μM pero mayor de 0.05 μM; y el símbolo "****" indica que el valor IC_{50} es menor o igual a 0.05 μM.

DESCRIPCIÓN DETALLADA

De acuerdo con la presente invención, los Solicitantes han descubierto novedosos inhibidores de quinazolina PDK1 que pueden proporcionar tratamientos efectivos para trastornos tales como los descritos en la presente, y aquéllos evidentes para un experto en este campo.

En algunas modalidades, la invención proporciona los compuestos que tienen la fórmula I:



I

o una sal farmacéuticamente aceptable de los mismos, en

donde:

Ar es arilo, arilo sustituido, heteroarilo, o heteroarilo sustituido, incluyendo los sistemas bicíclicos fusionados;

R^1 es H, alquilo de 1 a 3 átomos de carbono, halógeno, ciano, nitro, CF_3, imidazolilo, tiazolilo, oxazolilo, o amino;

R^2 y R^3 se seleccionan independientemente a partir del grupo que consiste en H, alcoxilo, alcoxilo sustituido, y halógeno;

L es un enlace covalente, carbonilo, carbonil-amino, amino-carbonilo, -O-, -S-, -SO-, $-SO_2-$, -NH-, alquilo de 1 a 3 átomos de carbono, alquilo de 1 a 3 átomos de carbono sustituido, o un alquilo interrumpido con -O-, -S-, -SO-, $-SO_2-$, -NH-, carbonilo, carbonil-amino, o amino-carbonilo; y

A^1 es alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, alcoxilo, alcoxilo sustituido, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, halógeno, hidroxilo, nitro, SO_3H, sulfonilo, sulfonilo sustituido, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, tioalquilo, tioalquilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, heterociclilo, o heterociclilo sustituido.

De acuerdo con algunas modalidades, cuando R^1, R^2, y R^3 son cada uno H, y L es un enlace covalente, entonces A^1 es diferente de

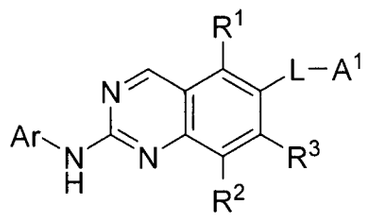
arilo o arilo sustituido.

De acuerdo con algunas modalidades, cuando R^1, R^2, y R^3 son cada uno H, L es un enlace covalente, y A^1 es Br, fenilo sustituido, o piridinilo sustituido, entonces Ar es diferente de fenilo, fenilo sustituido con piperazinilo, o heterociclil-alquiloxilo, o piridinilo.

De acuerdo con algunas modalidades, cuando R^1, R^2, y R^3 son cada uno H, L es un enlace covalente, y A^1 es hidroxilo o alcoxilo, entonces Ar es diferente de fenilo sustituido con uno o más de alquilo o halógeno.

De acuerdo con algunas modalidades, cuando R^1, R^2, y R^3 son cada uno H, y L es O, entonces A^1 es diferente de piridinilo o piridinilo sustituido.

En algunas modalidades, la invención proporciona los compuestos que tienen la fórmula I:



I

o una sal farmacéuticamente aceptable de los mismos, en donde:

Ar es arilo, arilo sustituido, heteroarilo, o heteroarilo sustituido, incluyendo los sistemas bicíclicos fusionados;

R^1 es H, alquilo de 1 a 3 átomos de carbono, halógeno, ciano, nitro, CF_3, imidazolilo, tiazolilo, oxazolilo, o amino;

R^2 se selecciona a partir del grupo que consiste en H, alcoxilo,

alcoxilo sustituido, alquilo, alquilo sustituido, CN, heteroariloxilo, heteroariloxilo sustituido, hetero-cicliloxilo, heterocicliloxilo sustituido, y halógeno;

R^3 se selecciona a partir del grupo que consiste en H, halógeno, CN, carboxilo, alquilo, alquilo sustituido, alcoxilo, alcoxilo sustituido, ariloxilo, ariloxilo sustituido, cicloalquiloxilo, cicloalquiloxilo sustituido, heterociclil-alquiloxilo, heterociclil-alquiloxilo sustituido, heteroariloxilo, heteroariloxilo sustituido, heteroaril-alquiloxilo, heteroaril-alquiloxilo sustituido, aril-alquiloxilo, aril-alquiloxilo sustituido, heteroarilo, heteroarilo sustituido, heterociclilo, heterociclilo sustituido, heteroaril-alquilo, heteroaril-alquilo sustituido, heterociclil-alquilo, heterociclil-alquilo sustituido;

L es un enlace covalente, carbonilo, carbonil-amino, amino-carbonilo, -O-, -S-, -SO-, $-SO_2-$, -NH-, alquilo de 1 a 3 átomos de carbono, alquilo de 1 a 3 átomos de carbono sustituido, alquenilo de 2 a 3 átomos de carbono, alquinilo de 2 a 3 átomos de carbono, o un alquilo interrumpido con -O-, -S-, -SO-, $-SO_2-$, -NH-, carbonilo, carbonil-amino, o amino-carbonilo; y

A^1 es alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, alcoxilo, alcoxilo sustituido, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, halógeno, hidroxilo, nitro, SO_3H,

sulfonilo, sulfonilo sustituido, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, tioalquilo, tioalquilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, heterociclilo, o heterociclilo sustituido.

De acuerdo con algunas modalidades, cuando R^1, R^2, y R^3 son cada uno H, y L es un enlace covalente, entonces A^1 es diferente de arilo o arilo sustituido.

De acuerdo con algunas modalidades, cuando R^1, R^2, y R^3 son cada uno H, L es un enlace covalente, y A^1 es Br, fenilo sustituido, o piridinilo sustituido, entonces Ar es diferente de fenilo, fenilo sustituido con piperazinilo, o heterociclil-alquiloxilo, o piridinilo.

De acuerdo con algunas modalidades, cuando R^1, R^2, y R^3 son cada uno H, L es un enlace covalente, y A^1 es hidroxilo o alcoxilo, entonces Ar es diferente de fenilo sustituido con uno o más de alquilo o halógeno.

De acuerdo con algunas modalidades, cuando R^1, R^2, y R^3 son cada uno H, y L es O, entonces A^1 es diferente de piridinilo o piridinilo sustituido.

De acuerdo con algunas modalidades, L es un enlace covalente. En algunas de estas modalidades, A^1 es un alquino opcionalmente sustituido, o un heterociclilo o heteroarilo opcionalmente sustituido. Los alquinos preferidos incluyen etino, 1-propino, 3-hidroxi-propino, y 3-metoxi-propino, así como otros 3-alcoxi-propinos. Los heteroarilos preferidos para estas modalidades incluyen tiazol, piridina, imidazol, furano, 1,2,3-triazol, 1,2,4-triazol,

pirazol, isotiazol, oxazol, e isoxazol, cada uno de los cuales puede estar sustituido. Los heteroarilos específicos para estas modalidades incluyen 2-tiazolilo; 5-hidroxi-metil-2-tiazolilo; 3-piridilo, 5-metoxi-3-piridilo; 6-amino-3-piridilo; 4-tiazolilo; 3-pirazolilo; y 4-pirazolilo. Los grupos heterociclilo preferidos incluyen pirrolidina, morfolina, piperidina, y piperazina, cada una de las cuales puede estar sustituida.

Algunas modalidades específicas incluyen los compuestos en donde A^1 se selecciona a partir de los siguientes grupos:

OH, Br, metilo, etilo, etino (-C≡CH), CN, CF_3, fenilo, COOH, COOMe, $CONH_2$,

1-hidroxi-1-metil-etilo,

1-amino-1-metil-etilo,

2-tiazolilo,

5-tiazolilo,

4-tiazolilo,

isoxazol-4-ilo,

3-pirazolilo,

4-pirazolilo,

1-metil-4-pirazolilo,

1-metil-pirazol-5-ilo,

2-furanilo, ciclopropilo,

4-hidroxi-metil-1,2-3-triazol-5-ilo,

5-metoxi-piridin-3-ilo,

2-amino-3-metoxi-piridin-5-ilo,

3-metil-piridin-2-ilo,

2-piridilo,

3-piridilo,

4-piridilo,

4-metil-piridin-3-ilo,

3-cloro-piridin-4-ilo,

1-morfolinilo,

1-pirrolidinilo,

3-hidroxi-pirrolidin-1-ilo,

R-3-hidroxi-pirrolidin-1-ilo,

S-4-hidroxi-piperidin-1-ilo,

3-ceto-piperazin-1-ilo,

1-metil-imidazol-2-ilo,

5-metil-tiazol-2-ilo,

1-metil-imidazol-5-ilo,

3-hidroxi-1-propinilo,

3-metoxi-1-propinilo,

2-amino-piridin-4-ilo,

3-metoxi-piridin-5-ilo,

2-amino-piridin-5-ilo,

4-hidroxi-metil-1,2,3-triazol-5-ilo,

2-amino-3-metoxi-piridin-5-ilo,

2-aminotiazol-5-ilo,

1-(2-hidroxi-etil)-pirazol-4-ilo,

1-(2-metoxi-etil)-pirazol-4-ilo,

4-hidroxi-metil-tiazol-2-ilo,

5-hidroxi-metil-tiazol-2-ilo,

2-metoxi-pirimidin-5-ilo,

2-metoxi-piridin-5-ilo,

2-hidroxi-etil-amino,

tetrahidro-piran-4-iloxilo,

isopropil-amino,

2-piridinil-metil-amino,

2-metoxi-etil-amino,

3-piridil-metil-amino,

4-piridil-metil-amino,

2-piridil-amino, 3-piridil-amino,

2-(2-ceto-pirrolidin-1-il)-etil-amino,

4-metil-piperazin-1-ilo,

1-isopropil-metil-pirazol-4-ilo,

metil-amino,

1-metil-piperidin-4-il-amino,

4-isopropil-piperazin-1-ilo,

isopropil-amino,

pirrolidin-1-ilo,

ciclopropil-amino,

2-fluoro-piridin-3-ilo,

2-(4-metil-piperazin-1-il)-piridin-4-ilo,

3-(benzoil-amino)-fenilo, y

2-amino-4-metoxi-pirimidin-5-ilo.

De acuerdo con algunas modalidades, L es -O-.

De acuerdo con algunas modalidades, L es -S-.

De acuerdo con algunas modalidades, L es $-SO_2-$.

De acuerdo con algunas modalidades, L es NH.

De acuerdo con algunas modalidades, L es carbonilo.

De acuerdo con algunas modalidades, L es amino-carbonilo o carbonil-amino.

De acuerdo con algunas modalidades, L es carbonil-amino.

De acuerdo con algunas modalidades, L es amino-carbonilo.

De acuerdo con algunas modalidades, L es un alquilo interrumpido con -O-, -S-, -SO-, $-SO_2-$, -NH-, carbonilo, carbonil-amino, o amino-carbonilo.

De acuerdo con algunas modalidades, L es -CH=CH- o -C≡C-.

De acuerdo con algunas modalidades, A^1 es alquilo.

De acuerdo con algunas modalidades, A^1 es alquilo sustituido.

De acuerdo con algunas modalidades, A^1 es alquenilo.

De acuerdo con algunas modalidades, A^1 es alquenilo sustituido.

De acuerdo con algunas modalidades, A^1 es alquinilo.

De acuerdo con algunas modalidades, A^1 es etinilo, propinilo, fenil-etinilo o piridil-etinilo.

De acuerdo con algunas modalidades, A^1 es alquinilo sustituido.

De acuerdo con algunas modalidades, A^1 es alcoxilo.

De acuerdo con algunas modalidades, A^1 es alcoxilo sustituido.

De acuerdo con algunas modalidades, A^1 es acilo.

De acuerdo con algunas modalidades, A^1 es ciano.

De acuerdo con algunas modalidades, A^1 es arilo.

De acuerdo con algunas modalidades, A^1 es arilo sustituido.

De acuerdo con algunas modalidades, A^1 es fenilo sustituido.

De acuerdo con algunas modalidades, A^1 es heteroarilo.

De acuerdo con algunas modalidades, A^1 es heteroarilo sustituido.

De acuerdo con algunas modalidades, el heteroarilo o heteroarilo sustituido se selecciona a partir del grupo que consiste en piridilo, pirazolilo, tiazolilo, pirimidilo, piridazinilo, oxazolilo, isoxazolilo, piridilo sustituido, pirazolilo sustituido, tiazolilo sustituido, pirimidilo sustituido, piridazinilo sustituido, oxazolilo sustituido, e isoxazolilo sustituido.

De acuerdo con algunas modalidades, A^1 es cicloalquilo.

De acuerdo con algunas modalidades, A^1 es cicloalquilo sustituido.

De acuerdo con algunas modalidades, A^1 es heterociclilo.

De acuerdo con algunas modalidades, A^1 es heterociclilo sustituido.

De acuerdo con algunas modalidades, el heterociclilo o heterociclilo sustituido se selecciona a partir del grupo que consiste en piperidinilo, piperazinilo, pirrolidinilo, tetrahidro-furanilo, tetrahidro-tiofenilo, morfolinilo, tiomorfolino, piperidinilo sustituido, piperazinilo sustituido, pirrolidinilo sustituido, tetrahidro-furanilo

sustituido, tetrahidro-tiofenilo sustituido, morfolinilo sustituido, y tiomorfolino sustituido.

De acuerdo con algunas modalidades, A^1 es hidroxilo.

De acuerdo con algunas modalidades, A^1 es halógeno.

De acuerdo con algunas modalidades, A^1 es ciano.

En algunas modalidades, -L-A^1 es -Br, -C≡CH, -C≡N, 2-tiazolilo, o 1-metil-imidazol-2-ilo.

De acuerdo con algunas modalidades, R^1 es H, alquilo de 1 a 3 átomos de carbono, halógeno, ciano, nitro, CF_3 o amino.

De acuerdo con algunas modalidades, R^1 es H, alquilo de 1 a 3 átomos de carbono, halógeno, ciano, nitro o amino.

De acuerdo con algunas modalidades, R^1 es H, alquilo de 1 a 3 átomos de carbono, halógeno, ciano, imidazolilo, tiazolilo, oxazolilo o amino.

De acuerdo con algunas modalidades, R^1 es H, alquilo de 1 a 3 átomos de carbono, halógeno, o ciano.

De acuerdo con algunas modalidades, R^1 es H, alquilo de 1 a 3 átomos de carbono, o halógeno.

De acuerdo con algunas modalidades, R^1 es H o halógeno.

De acuerdo con algunas modalidades, R^1 es H.

De acuerdo con algunas modalidades, R^1 es halógeno.

De acuerdo con algunas modalidades, R^2 y R^3 se seleccionan independientemente a partir del grupo que consiste en H, alcoxilo, alcoxilo sustituido, y halógeno;

De acuerdo con algunas modalidades, R^2 y R^3 se seleccionan

independientemente a partir del grupo que consiste en H, halógeno, y alcoxilo.

De acuerdo con algunas modalidades, R^2 y R^3 se seleccionan independientemente a partir del grupo que consiste en H y halógeno.

De acuerdo con algunas modalidades, R^2 y R^3 se seleccionan independientemente a partir del grupo que consiste en H y alcoxilo.

De acuerdo con algunas modalidades, R^2 y R^3 se seleccionan independientemente a partir del grupo que consiste en H y alcoxilo de 1 a 6 átomos de carbono.

De acuerdo con algunas modalidades, R^2 y R^3 se seleccionan independientemente a partir del grupo que consiste en H y metoxilo.

De acuerdo con algunas modalidades, cuando menos uno de R^2 y R^3 es H.

De acuerdo con algunas modalidades, ambos R^2 y R^3 son H.

De acuerdo con algunas modalidades, R^2 es H.

De acuerdo con algunas modalidades, R^3 es H.

En algunas modalidades, uno de R^2 y R^3 es H, y el otro de R^2 y R^3 es alcoxilo, alcoxilo sustituido, ariloxilo, ariloxilo sustituido, cicloalquiloxilo, cicloalquiloxilo sustituido, heterociclil-alquiloxilo, heterociclil-alquiloxilo sustituido, heteroariloxilo, heteroariloxilo sustituido, heteroaril-alquiloxilo, heteroaril-alquiloxilo sustituido, aril-alquiloxilo, o aril-alquiloxilo sustituido.

En algunas modalidades, uno de R^2 y R^3 es H, y el otro es aril-alcoxilo, alcoxilo, o alcoxilo sustituido, o un heteroariloxilo sustituido o insustituido, heteroaril-alquiloxilo, hetero-cicliloxilo, o heterociclil-

alquiloxilo. En estas modalidades, R^2 es con frecuencia H, y R^3 es un grupo alcoxilo o hetero-cicliloxilo sustituido o insustituido.

En ciertas modalidades, R^2 se selecciona a partir de H, F, Cl, Br, CN, CF_3, metoxilo, etoxilo, isopropoxilo, 4-piperidiniloxilo, 3-azetidiniloxilo, y 2-amino-etoxilo.

En algunas modalidades, R^3 se selecciona a partir de:

H, Cl, CF_3, CN, COOH,

isopropoxilo, metoxilo, ciclopentiloxilo,

2-amino-etoxilo,

4-piperidiniloxilo,

1-isopropil-piperidin-4-ilo,

4-piperidinil-metoxilo,

1-metil-piperidin-3-il-metoxilo,

2-(4-piperidinil)-etoxilo,

2-(1-metil-4-piperidinil)-etoxilo,

(1-metil-4-piperidinil)-metoxilo,

2-tiazolil-metoxilo,

3-piridil-metoxilo,

4-piridil-metoxilo,

1-(4-piridil)-1-etoxilo,

2-piridil-metoxilo,

5-tiazolil-metoxilo,

2-(4-piperidinil)-etoxilo,

1-metil-4-piperidiniloxilo,

ciclopentiloxilo,

2-(4-morfolinil)-etoxilo,

2-metoxi-etoxilo,

1-amino-ciclopropil-metoxilo,

1-N-acetil-amino-cicloprop-1-il-metoxilo,

amino-carbonil-metoxilo,

N-metil-amino-carbonil-metoxilo,

3-pirrolidiniloxilo,

R-3-pirrolidiniloxilo,

S-3-pirrolidiniloxilo,

R-(1-metil-pirrolidin-3-il)-oxilo,

S-(1-metil-pirrolidin-3-il)-oxilo,

pirrolidin-3-il-metoxilo,

piperidin-3-il-metoxilo,

R-piperidin-3-il-metoxilo,

S-piperidin-3-il-metoxilo,

2-(4-metil-1-piperazinil)-etilo,

1-metil-pirrolidin-3-il-metoxilo,

R-(1-metil-piperidin-3-il-metoxilo,

S-(1-metil-piperidin-3-il-metoxilo,

(3-cloro-4-piridil)-metoxilo,

2-metoxi-piridin-6-il-metoxilo,

(5-metil-isoxal-3-il)-metoxilo,

5-tiazolil-metoxilo,

(3-fluoro-fenil)-metoxilo,

(3-metoxi-fenil)-metoxilo,

fenil-metoxilo,

(3-ciano-fenil)-metoxilo,

3-fluoro-fenil-metoxilo,

3-metoxi-fenil-metoxilo,

2-pirazinil-metoxilo,

3-cloro-4-piridiniloxilo,

2-(3-piridinil)-etoxilo,

1-isopropil-piperidin-4-iloxilo,

3-azetidiniloxilo,

1-metil-3-azetidiniloxilo,

1-isopropil-3-azetidiniloxilo,

1-(2,2,2-trifluoro-etil)-piperidin-4-iloxilo,

1-metil-4-pirazolilo,

3-amino-piridin-4-ilo,

1-piperazinil-metilo,

1-piperazinil-carbonilo,

1-metil-piperidin-4-il-amino-carbonilo,

2-(N-morfolinil)etoxilo,

2-metoxi-etoxilo,

2-cloro-piridin-5-il-metoxilo,

2-cloro-piridin-4-il-metoxilo,

1-acetil-piperidin-4-iloxilo,

1-(2-fluoro-etil)-piperidin-4-iloxilo,

1-(2,2-difluoro-etil)-piperidin-4-iloxilo,

1-(2-metoxi-etil)-piperidin-4-iloxilo,

1-(2-hidroxi-etil)-piperidin-4-iloxilo,

metil-amino-carbonil-metoxilo,

amino-carbonil-metoxilo,

3-azetidinil-metoxilo,

3-(1-metil-azetidinil)-metoxilo,

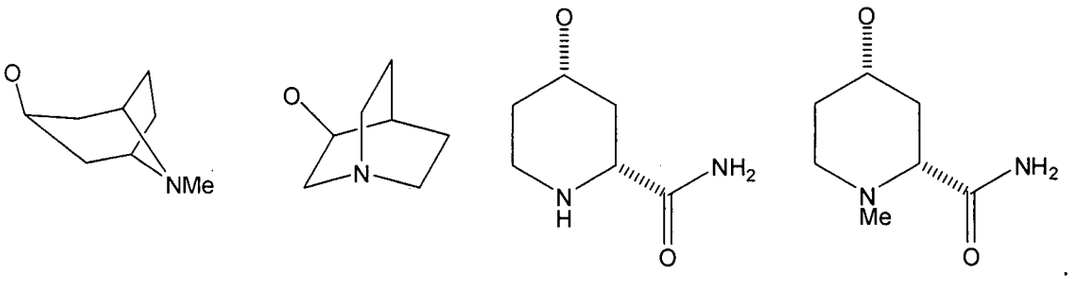
2-amino-piridin-4-ilo,

6-metoxi-piridin-2-il-metoxilo,

5-metil-isoxazol-3-ilo, y

2-(piridin-3-il)-etoxilo;

o R^3 puede ser uno de los siguientes grupos hetero-cicliloxilo:



De acuerdo con algunas modalidades, Ar es arilo sustituido o heteroarilo sustituido.

De acuerdo con algunas modalidades, Ar es arilo sustituido.

De acuerdo con algunas modalidades, Ar es arilo sustituido por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en alquilo, alquenilo, alquinilo, alcoxilo, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-

éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino sustituido, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, hetero-cicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo sustituido, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, y tioalquilo;

en donde las fracciones de alquilo, alquenilo, alquinilo, arilo, cicloalquilo, cicloalquenilo, heterociclilo, y heteroarilo contenidas dentro de cualquiera de los grupos arilo sustituido enlistados, están opcionalmente sustituidas por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en alquenilo, alquinilo, alcoxilo, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, hetero-cicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, tioalquilo, y tioalquilo.

De acuerdo con algunas modalidades, Ar es arilo sustituido por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en amino-sulfonilo, amino-carbonilo,

arilo, heteroarilo, heterociclilo, amino, amino sustituido, alquilo, halógeno, y ciano;

en donde las fracciones de alquilo, arilo, y heteroarilo contenidas dentro de cualquiera de los grupos arilo sustituido enlistados, están opcionalmente sustituidas por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en alquenilo, alquinilo, alcoxilo, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, hetero-cicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, tioalquilo, y tioalquilo.

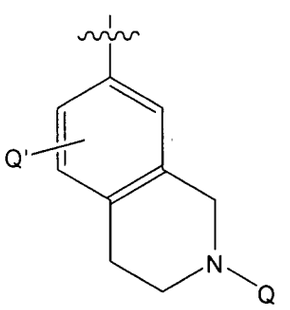
De acuerdo con algunas modalidades, Ar es arilo seleccionado a partir del grupo que consiste en fenilo y naftilo. En donde Ar es fenilo, éste está con frecuencia insustituido en una o ambas de las posiciones adyacentes al NH ilustrado en la fórmula 1 (las posiciones *orto*).

De acuerdo con algunas modalidades, Ar es fenilo sustituido. En algunas modalidades, el fenilo está sustituido con dos o más sustituyentes. En algunas de estas modalidades, dos sustituyentes

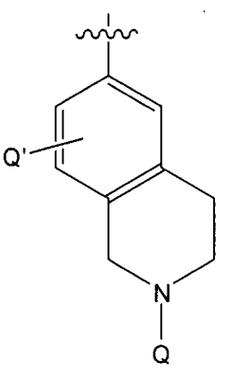
adyacentes se enlazan entre sí para formar un anillo que se fusiona con el anillo de fenilo. El anillo fusionado puede ser saturado, insaturado o aromático, y él mismo puede estar sustituido. Las modalidades preferidas de estos sistemas de anillos fusionados incluyen fenilo fusionado con un 1,3-dioxolano; fenilo fusionado con un 1,4-dioxano; fenilo fusionado con un pirazol; fenilo fusionado con imidazol; fenilo fusionado con triazol; fenilo fusionado con pirazol; y fenilo fusionado con un anillo de pirrolidinilo o piperidinilo.

En algunas modalidades, fenilo está sustituido por 1, 2 ó 3 grupos que no se unen al fenilo *orto* para el NH de la fórmula I.

En ciertas modalidades, Ar es de la fórmula:



ó



en donde Q es un grupo acilo opcionalmente sustituido;

y Q' es alquilo, alcoxilo, halógeno, arilo, heteroarilo, ariloxilo, heteroariloxilo, hetero-cicliloxilo, aril-alquilo, heteroarilo, o hetero-cicliloxilo, cada uno de los cuales puede estar sustituido; o Q' puede ser H, halógeno, CN, COOR', $CONR'_2$, NR'_2, $S(O)_qR'$, o $S(O)_qNR'_2$, en donde cada R' es H o alquilo de 1 a 4 átomos de carbono.

En muchas de estas modalidades, Q' es H o halógeno o

alcoxilo.

Q en estos sistemas fusionados puede ser, por ejemplo:

1-metil-imidazol-2-il-carbonilo,

3-metoxi-propionilo,

1-metil-imidazol-5-il-carbonilo,

N,N-dimetil-amino-acetilo,

tetrahidro-piran-4-il-carbonilo,

1-metil-piperidin-4-il-carbonilo,

1-metil-piperidin-3-il-carbonilo,

2-piridinoílo,

3-piridinoílo,

4-piridinoílo,

1-metil-pirrolidin-2-il-carbonilo,

1-metil-pirrolidin-2S-il-carbonilo,

(2-N-morfolino)-piridin-5-il-carbonilo,

(2-N-morfolino)-piridin-4-il-carbonilo,

(2-N-piperidinil)-piridin-5-il-carbonilo,

1-metil-pirazol-4-il-carbonilo,

1-metil-piperidin-3-il-carbonilo,

piridin-3-il-acetilo,

imidazo-[1,2-a]-piridin-4-il-carbonilo,

2-(piperazin-1-il)-piridin-5-il-carbonilo,

2-amino-3-hidroxi-butanoílo, o

2*S*-amino-3*R*-hidroxi-butanoílo.

En muchas modalidades, Ar es fenilo que tiene cualquiera de 1

ó 2 sustituyentes, o es un fenilo con un anillo adicional fusionado con él. Con frecuencia, Ar es fenilo con un sustituyente que no es hidrógeno en una o ambas de las posiciones '*meta*' del anillo de fenilo, es decir, es un fenilo 3-sustituido o un fenilo 3,5-disustituido. En otras modalidades, Ar es fenilo con un sustituyente que no es hidrógeno en una o ambas de las posiciones 3 y 4, por ejemplo, es un fenilo 4-sustituido o un fenilo 3,4-disustituido.

De acuerdo con algunas modalidades, Ar es heteroarilo.

De acuerdo con algunas modalidades, Ar es heteroarilo seleccionado a partir del grupo que consiste en pirrolilo, furanilo, tiofenilo (tienilo), imidazolilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, 1,2,3-triazolilo, 1,2,4-triazolilo, oxadiazolilo, tiadiazolilo, tetrazolilo, piridinilo, pirazinilo, pirimidinilo, piridazinilo, triazinilo, indolilo, isoindol, bencimidazolilo, benzo-tiofenilo, benzo-furanilo, benzoxazolilo, benzo-tiazolilo, quinolinilo, isoquinolilo, quinazolilo, quinozalilo, cinolilo, pteridina, carbazol, carbolina, fenantridina, acridina, fenantrolina, ftalazina, naftil-piridina, fenazina, y purina.

De acuerdo con algunas modalidades, Ar es un grupo heteroarilo seleccionado a partir del grupo que consiste en 2-piridinilo, 3-piridinilo, 4-piridinilo, 2-pirimidinilo, 4-pirimidinilo, 5-pirimidinilo, 1-pirazolilo, 3-pirazolilo, 4-pirazolilo, 5-pirazolilo, 2-oxazolilo, 4-oxazolilo, 5-oxazolilo, y 2-tiazolilo, 4-tiazolilo, y 5-tiazolilo.

De acuerdo con algunas modalidades, Ar es arilo o heteroarilo

sustituido por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, alcoxilo, alcoxilo sustituido, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, ariloxilo sustituido, tioarilo, tioarilo sustituido, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquilo sustituido, cicloalquiloxilo, cicloalquiloxilo sustituido, tiocicloalquilo, tiocicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, cicloalqueniloxilo, cicloalqueniloxilo sustituido, tiocicloalquenilo, tiocicloalquenilo sustituido, guanidino, guanidino sustituido, halógeno, hidroxilo, heteroarilo, heteroarilo sustituido, heteroariloxilo, heteroariloxilo sustituido, tioheteroarilo, tioheteroarilo sustituido, heterocíclico, heterocíclico sustituido, hetero-cicliloxilo, heterocicliloxilo sustituido, tioheterociclilo, tioheterociclilo sustituido, nitro, SO_3H, sulfonilo sustituido, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, tioalquilo, y tioalquilo sustituido. Típicamente en estas modalidades, Ar tiene uno o dos sustituyentes que no son hidrógeno.

De acuerdo con algunas modalidades, Ar es arilo o heteroarilo sustituido por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en alquilo, alquenilo, alquinilo, alcoxilo, acilo, acil-amino, aciloxilo, amino,

amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino sustituido, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, hetero-cicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo sustituido, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, y tioalquilo;

en donde las fracciones de alquilo, alquenilo, alquinilo, arilo, cicloalquilo, cicloalquenilo, heterociclilo, y heteroarilo contenidas dentro de cualquiera de los grupos "arilo sustituido" precedentes están opcionalmente sustituidas por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en alquenilo, alquinilo, alcoxilo, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, hetero-cicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, tioalquilo,

y tioalquilo.

De acuerdo con algunas modalidades, Ar es heteroarilo sustituido por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en alquilo, alquenilo, alquinilo, alcoxilo, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino sustituido, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, hetero-cicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo sustituido, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, y tioalquilo;

en donde las fracciones de alquilo, alquenilo, alquinilo, arilo, cicloalquilo, cicloalquenilo, heterociclilo, y heteroarilo contenidas dentro de cualquiera de los grupos arilo sustituido enlistados, están opcionalmente sustituidas por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en alquenilo, alquinilo, alcoxilo, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino,

(carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, hetero-cicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, tioalquilo, y tioalquilo.

De acuerdo con algunas modalidades, Ar es arilo o heteroarilo sustituido por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en amino-sulfonilo, amino-carbonilo, arilo, heteroarilo, heteroarilo, heterociclilo, amino, amino sustituido, alquilo, alquilo, halógeno, y ciano;

en donde las fracciones de alquilo, arilo, heterociclilo, y heteroarilo contenidas dentro de cualquiera de los grupos "arilo sustituido" precedentes están opcionalmente sustituidas por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en alquenilo, alquinilo, alcoxilo, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, hetero-

cicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, tioalquilo, y tioalquilo.

De acuerdo con algunas modalidades, Ar es heteroarilo sustituido por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en amino-sulfonilo, amino-carbonilo, arilo, heteroarilo, heterociclilo, amino, amino sustituido, alquilo, halógeno, y ciano;

en donde las fracciones de alquilo, arilo, y heteroarilo contenidas dentro de cualquiera de los grupos arilo sustituido enlistados, están opcionalmente sustituidas por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en alquenilo, alquinilo, alcoxilo, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, hetero-cicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, tioalquilo, y tioalquilo.

De acuerdo con algunas modalidades, Ar es un grupo heteroarilo de 5 ó 6 miembros que tiene 1 ó 2 heteroátomos como miembros del anillo independientemente seleccionados a partir del

grupo que consiste en O, S y N, que está opcionalmente sustituido con 1, 2 ó 3 sustituyentes seleccionados a partir del grupo que consiste en amino-sulfonilo, amino-carbonilo, arilo, heteroarilo, heterociclilo, amino, amino sustituido, alquilo, halógeno, y ciano.

De acuerdo con algunas modalidades, Ar se selecciona a partir del grupo que consiste en piridilo sustituido, pirazolilo sustituido, tiazolilo sustituido, pirimidilo sustituido, piridazinilo sustituido, oxazolilo sustituido, e isoxazolilo sustituido.

Los ejemplos específicos de los grupos Ar preferidos incluyen los siguientes:

fenilo,

3-amino-carbonil-5-N-(morfolino)-fenilo,

4-amino-carbonil-fenilo,

3-metan-sulfonamido-fenilo,

3-acetil-amino-5-N-morfolino-metil-fenilo,

3-metoxi-5-(5-metil-1-tetrazolil)-fenilo,

4-(N-morfolino)-fenilo,

4-(N-morfolino-carbonil)-fenilo,

3-(5-oxazolil)-fenilo,

3-(1-hidroxi-1-metil)-1-etil-fenilo,

3-(1-hidroxi-etil)-fenilo,

3-fluoro-fenilo,

2-fluoro-fenilo,

3,4,5-trifluoro-fenilo,

3-trifluoro-metil-fenilo,

2-trifluoro-metil-piridin-5-ilo,

3-(1-metil-pirazol-3-il)-fenilo,

3-(2-amino-4-piridil)-5-acetil-amino-fenilo,

3-pirrolidinil-carbonil-amino-5-(N-morfolino)-metil-fenilo,

3-acetil-amino-5-(2-metoxi-5-piridinil)-fenilo,

3-acetil-amino-5-(4-pirazolil)-fenilo,

3-metoxi-carbonil-amino-5-(pirazol-4-il)-fenilo,

3-amino-carbonil-5-(4-pirazolil)-fenilo,

3-amino-carbonil-5-(1-metil-4-pirazolil)-fenilo,

3,5-bis-(amino-carbonil)-fenilo,

3,5-bis-(acetil-amino)-fenilo,

3-amino-carbonil-5-(4-metil-1-piperazinil)-fenilo,

4-(3-pirazolil)-fenilo,

3-amino-carbonil-5-(2-metoxi-5-piridinil)-fenilo,

3-amino-carbonil-5-(6-metoxi-2-pirazinil)-fenilo,

3-amino-carbonil-5-(N-metil-piperidin-2-on-5-il)-fenilo,

3-(5-metil-1-tetrazolil)-fenilo,

3-amino-carbonil-5-(2-pirazinil)-fenilo,

3-(metoxi-carbonil-amino)-5-(2-(N-morfolino)-pirimidin-5il)-fenilo,

3-(N-morfolino-carbonil)-5-(N-morfolino)-fenilo,

3-amino-carbonil-5-(1-metil-4-pirazolil)-fenilo,

3-amino-carbonil-5-(5-pirimidinil)-fenilo,

3-(N-metil-amino-carbonil)-fenilo,

4-(amino-carbonil)-fenilo,

4-(N-metil-amino-carbonil)-fenilo,

3-(1,2,4-triazolil-1-metil)-fenilo,

3-(1,2,4-triazolil-4-metil)-fenilo,

3-(N-morfolino-carbonil-metil)-fenilo,

3-metoxi-fenilo,

3-metoxi-4-fluoro-fenilo,

3-(1-metil-3-pirazolil)-fenilo,

(3-N-morfolino-metil)-fenilo,

(2-trifluoro-metil)-bencimidazol-6-ilo,

benzo-pirazol-6-ilo,

3-fluoro-4-isopropil-fenilo,

3-(2-oxo-pirrolidin-1-il)-fenilo,

3-metoxi-4-(5-oxazolil)-fenilo,

3-metan-sulfonil-fenilo,

3-metoxi-4-(isobutiril-amino)-fenilo,

3-(1-pirazolil)-fenilo,

4-(N-pirrolidinil-carbonil)-fenilo,

bencimidazol-5-ilo,

3-(4-metil-1,2,4-triazol-3-il)-fenilo,

4-piridilo,

3-piridilo,

3-(N-morfolinil-carbonil-metil)-fenilo,

3-ciano-5-fluoro-fenilo,

4-(metil-amino-carbonil-metil)-fenilo,

3-(metil-amino-carbonil-metil)-fenilo,

3-(isopropil-amino-carbonil-metil)-fenilo,

3-(ciclopropil-amino-carbonil-metil)-fenilo,

4-(isopropil-amino-carbonil-metil)-fenilo,

4-(ciclopropil-amino-carbonil-metil)-fenilo,

3-(imidazol-2-il)-fenilo,

3-(2-metil-tiazol-4-il)-fenilo,

3-(5-pirimidinil)-fenilo,

3-(2-metoxi-pirimidin-5-il)-fenilo,

3-(1,3,5-trimetil-pirazol-4-il)-fenilo,

3-(4,5-dimetil-oxazol-2-il)-fenilo,

3-(5-metil-furan-2-il)-fenilo,

3-(metil-amino-carbonil-5-(1-metil-pirazol-4-il)-fenilo,

3-(metoxi-carbonil-amino)-5-(2-N-morfolino-pirimidin-5-il)-fenilo,

3-(4-morfolino)-5-(4-morfolino-carbonil)-fenilo,

3-(metoxi-carbonil-amino)-5-(pirazol-4-il)-fenilo,

3-(metoxi-carbonil-amino)-5-(morfolin-4-il-metil)-fenilo,

3-(amino-carbonil)-5-(4-morfolinil)-fenilo,

3-metoxi-5-trifluoro-metil-fenilo,

3-(amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3,5-dimetoxi-fenilo,

3,5-difluoro-fenilo,

3,4-difluoro-fenilo,

3,4,5-trifluoro-fenilo,

3-cloro-4-fluoro-fenilo,

3-fluoro-4-(tiazol-2-il)-fenilo,

3-etoxi-fenilo,

4-(oxazol-5-il)-fenilo,

3-fluoro-4-(morfolin-4-il)-fenilo,

4-(isopropil-amino-carbonil)-fenilo,

4-(morfolin-4-il-sulfonil)-fenilo,

4-ciclohexil-fenilo,

4-(pirimidin-5-il)-fenilo,

4-(isoxazol-4-il)-fenilo,

2-fluoro-fenilo,

2,3-difluoro-fenilo,

2,4-difluoro-fenilo,

benzotriazol-5-ilo,

4-amino-sulfonil-fenilo,

4-isopropil-fenilo,

3-fluoro-4-isopropil-fenilo,

3-metoxi-4-(oxazol-5-il)-fenilo,

4-(metil-amino-sulfonil-metil)-fenilo,

3-(amino-sulfonil)-fenilo,

4-(1-metil-4-pirazolil)-fenilo,

2-metoxi-fenilo,

2-trifluoro-piridin-5-ilo,

4-(isopropil-amino-sulfonil)-fenilo,

4-ciano-fenilo,

4-etoxi-fenilo,

3-difluoro-metoxi-fenilo,

3,4-dioxolanil-fenilo,

3,4-dimetoxi-fenilo,

3,4-dioxanil-fenilo,

3-propoxi-fenilo,

3-hidroxi-fenilo,

4-(1-pirazolil-metil)-fenilo,

4-(1,2,4-triazol-1-il-metil)-fenilo,

4-(1-pirazol-1-il-metil)-fenilo,

4-(2-metil-tiazol-4-il)-fenilo,

4-(1,2,3-tiadiazol-4-il)-fenilo,

4-(oxazolin-2-on-4-il)-fenilo,

4-(2-oxazolil)-fenilo,

3-[2-(2-hidroxi-piridin-5-il-carbonil-amino)-etoxi]-5-(1-metil-pirazol-4-il)-fenilo,

3-fluoro-4-(imidazol-2-il)-fenilo,

4-(3-metoxi-piridin-5-il)-fenilo,

3-(2-metoxi-piridin-5-il)-fenilo,

3-(3-piridinil)-fenilo,

3-(dimetil-amino-metil)-5-(metan-sulfonamido)-fenilo,

3-(4-metil-piperazin-il-etil)- 5-(metan-sulfonamido)-fenilo,

1-metil-bencimidazol-2-ilo,

5,6-dimetil-bencimidazol-2-ilo,

4,5-diciano-imidazol-2-ilo,

3-amino-5-amino-carbonil-metil-fenilo,

imidazol-1-ilo,

2-(piridin-2-il)-etilo,

imidazol-1-il-metil-fenilo,

3-(acetil-amino)-5-(N-metil-2-piridon-5-il)-fenilo,

3-(acetil-amino)-5-yodo-fenilo,

3-(acetil-amino)-5-(piridin-3-il)-fenilo,

4-(N-morfolinil-sulfonil)-fenilo,

3-(acetil-amino)-5-(dimetil-amino-metil)-fenilo,

4-(tetrazol-5-il)-fenilo,

3-(tetrazol-5-il)-fenilo,

3-cloro-4-(N-morfolino-carbonil)-fenilo,

3-(tetrazol-1-il)-fenilo,

3-amino-carbonil-4-(N-morfolino)-fenilo,

3-acetil-amino-5-(pirrolidin-1-il-metil)-fenilo,

6-cloro-benzo-pirazol-4-ilo,

6-fluoro-benzo-pirazol-4-ilo,

3-acetil-amino-5-amino-metil-fenilo,

3-(acetil-amino)-5-(piperazin-1-il-metil)-fenilo,

3-(isobutiril-amino)-5-(N-morfolino-metil)-fenilo,

3-(metil-sulfonamido)-5-(N-morfolino-metil)-fenilo,

3-(N-morfolino-metil)-5-(5-tetrazolil)-fenilo,

3-acetil-amino-5-(piridin-4-il)-fenilo,

3-ciano-5-(N-morfolino-metil)-fenilo,

3-metoxi-5-(5-metil-tetrazol-1-il)-fenilo,

3-metoxi-5-(tetrazol-1-il)-fenilo,

3-(4-morfolino)-5-(pirazol-4-il)-fenilo,

3-(4-morfolino)-5-(piridin-4-il)-fenilo,

3-(4-morfolino)-5-(3-fluoro-piridin-4-il)-fenilo,

3-(4-morfolino)-5-(piridin-3-il)-fenilo,

3-amino-carbonil-5-(N-morfolino-metil)-fenilo,

3-(metoxi-carbonil-amino)-5-(morfolin-4-il-metil)-fenilo,

3-(4-trifluoro-metil-pirazol-2-il)-fenilo,

3-(ciclopropil-amino-carbonil)-5-(1-metil-pirazol-4-il)-fenilo,

3-(1-metil-pirazol-4-il)-5-((1-metil-piperidin-4-il)-amino-carbonil)-fenilo,

3-(metil-amino-carbonil)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-metoxi-etil-amino-carbonil)-5-(1-metil-pirazol-4-il)-fenilo,

3-(amino-carbonil)-5-fluoro-fenilo,

3-metil-amino-carbonil-5-(pirimidin-5-il)-fenilo,

3-metil-amino-carbonil-5-(piridin-4-il)-fenilo,

3-metil-amino-carbonil-5-(piridin-3-il)-fenilo,

3-amino-5-(N-morfolino-metil)-fenilo,

3-(ciano-metil)-5-(1-metil-pirazol-4-il)-fenilo,

3-(amino-carbonil)-5-(amino-carbonil-metoxi)-fenilo,

4-(isobutiril-amino)-3-metoxi-fenilo,

3-(isobutiril-amino)-5-metoxi-fenilo,

3-(amino-carbonil-metil)-5-(N-morfolino-metil)-fenilo,

3-ciano-4-(1,2,4-triazol-1-il-metil)-fenilo,

3-(metoxi-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(hidroxi-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(ciclopropil-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(pirrolidin-1-il)-etil-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(metoxi-etoxi)-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(2-oxo-pirrolidin-1-il)-etil-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-((2-tetrahidrofuranoil)-metil-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-((2-tetrahidrofuranoil)-metil-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-((2-*S*-tetrahidrofuranoil)-metil-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-((2-*R*-tetrahidrofuranoil)-metil-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-((1-metil-piperidin-4-il)-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-((2-metil-sulfonil-etil)-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-((2-acetil-amino-etil)-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(tetrahidro-piran-4-il-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-((2-hidroxi-propil)-amino-carbonil-metoxi)-5-(1-metil-pirazol-

4-il)-fenilo,

3-(piridin-2-il-metil-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(ciclohexil-metil-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(piridin-3-il-metil-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(N,N-dimetil-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(N-morfolino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(4-metil-piperazin-1-il-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(3-oxo-piperazin-1-il-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(4-dimetil-amino-piperidin-1-il-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

4-(metil-amino-sulfonil-metil)-fenilo,

3-(ciclopropil-amino-carbonil)-5-(N-morfolinil)-fenilo,

3-(metil-amino-carbonil)-5-(N-morfolinil)-fenilo,

3-(3-oxomorfolin-4-il-metil)-fenilo,

3-(2-oxo-pirrolidin-1-il-metil)-fenilo,

3-(2-oxo-oxazol-1-il-metil)-fenilo,

3-(metil-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

4-(N-morfolino-metil)-fenilo,

3-(3-metoxi-propanoil-amino-metil)-fenilo,

3-(isoxazol-5-il-carbonil-amino-metil)-fenilo,

3-(tetrahidrofurano-2*R*-il-carbonil-amino-metil)-fenilo,

3-(tetrahidrofurano-2*S*-il-carbonil-amino-metil)-fenilo,

3-(1-acetil-pirrolidin-2*R*-il-carbonil-amino-metil)-fenilo,

3-(1-acetil-pirrolidin-2*S*-il-carbonil-amino-metil)-fenilo,

3-(piridin-3-il-metil-acetil-amino-metil)-fenilo,

3-(piridin-3-oil-amino-metil)-fenilo,

3-(ciclopropil-sulfonil-amino-metil)-fenilo,

3-(etoxi-carbonil-amino-metil)-fenilo,

3-hidroxi-5-(metil-amino-carbonil)-fenilo,

3-etoxi-5-(metil-amino-carbonil)-fenilo,

3-(metil-amino-carbonil-metil)-5-(N-morfolino-metil)-fenilo,

3-(N,N-dimetil-amino-carbonil-metil)-5-(N-morfolino-metil)-fenilo,

3-(isopropil-amino-carbonil-metil)-5-(N-morfolino-metil)-fenilo,

3-(tetrahidro-piran-4-il-amino-carbonil-metil)-5-(N-morfolino-metil)-fenilo,

3-(t-butoxi-carbonil-amino-metil)-fenilo,

3-(metil-amino-carbonil)-5-(5-(4-metil-piperazin-1-il))-fenilo,

2-metoxi-fenilo,

2-trifluoro-piridin-5-ilo,

3-(2-(pirrolidin-1-il)-etil-amino-sulfonil)-fenilo,

3-(ciclopropil-amino-carbonil-metil)-fenilo,

3-(2*R*-(1-metil-pirrolidin-2-il-carbonil-amino)-propoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2*S*-(1-metil-pirrolidin-2-il-carbonil-amino)-propoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(1-metoxi-carbonil-piperidin-4-il)-fenilo,

3-(metoxi-carbonil-amino)-5-(2-(morfolin-4-il)-pirimidin-5-il)-fenilo,

3-(2-(1-pirrolidinil)-etil-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-n-propoxi-fenilo,

3-(N-(1-metil-piperidin-4-il-carbonil)-piperidin-4-il)-fenilo,

3-(N-(N,N-dimetil-amino-acetil)-piperidin-4-il)-fenilo,

4-(etoxi-carbonil-amino-metil)-fenilo,

4-(metil-sulfonil-metil)-fenilo,

4-(1-metil-imidazol-5-il-carbonil-amino-metil)-fenilo,

4-(1-metil-piperidin-4-il-carbonil-amino-metil)-fenilo,

3,5-dimetoxi-fenilo,

3-(1-metil-piperidin-4-il-carbonil-amino-metil)-fenilo,

4-fluoro-3-(N-morfolino-carbonil-metil)-fenilo,

3-(2-(N-morfolino)-etiloxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(*trans*-(2-dimetil-amino)-ciclohexil-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(3-(dimetil-amino)-propoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(pirrolidin-1-il)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(N-morfolino)etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(N-piperidinil)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(etoxi-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(pirrolidin-2-on-1-il-acetil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(isoxazol-2-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(N-pirrolidinil-acetil-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(tetrahidrofurano-2*R*-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(tetrahidrofurano-2*S*-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(1-metil-pirazol-3-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(4-cloro-piridin-2-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(piperidin-3*R*-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(piperidin-3*S*-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(piperidin-4-il-metil-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(pirrolidin-2*R*-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(pirrolidin-2*S*-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(2R-amino-3S-hidroxi-butanoil-amino)-etoxi)-5-(1-metil-

pirazol-4-il)-fenilo,

3-(2-(2S-amino-3R-hidroxi-butanoil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(1-metil-piperidin-3*R*-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(1-metil-piperidin-3*S*-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(1-metil-piperidin-4-il-metil-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(1-metil-pirrolidin-2*R*-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(piperidin-4-il-metil-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(4-dimetil-amino-piperidin-1-il-carbonil-metil)-5-(1-metil-pirazol-4-il)-fenilo,

3-(pirrolidin-2*R*-il-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(pirrolidin-2-il-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(pirrolidin-2*S*-il-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(3-hidroxi-2-amino-propoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2*R*-(N,N-dimetil-amino-acetil-amino)-propoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2*S*-(N,N-dimetil-amino-acetil-amino)-propoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2*R*-(N,N-dimetil-amino-propoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2*S*-(N,N-dimetil-amino-propoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(4-metil-piperidin-1-il-acetil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-amino-etil-amino-carbonil)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(N,N-dimetil-amino)-etil-amino-carbonil)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(N,N-dietil-amino)-etil-amino-carbonil)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(acetil-amino)-etil-amino-carbonil)-5-(1-metil-pirazol-4-il)-fenilo,

3-((pirrolidin-5-on-2-il)-metil-amino-carbonil))-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(3*R*-hidroxi-pirrolidin-1-il-acetil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(3*S*-hidroxi-pirrolidin-1-il-acetil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(1,2*S*-dimetil-piperidin-3*S*-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(2*S*-N,N-dimetil-amino-propionil)-amino-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2*R*-(2-piridinoil-amino)-propoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2*S*-(pirrolidin-1-il-acetil-amino)-propoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2*R*-(pirrolidin-1-il-acetil-amino)-propoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2*R*-(1-metil-imidazol-4-carbonil-amino)-propoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2*R*-(1-metil-piperidinil-3-carbonil-amino)-propoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2*R*-(tetrahidrofurano-2*R*-il-carbonil-amino)-propoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2*R*-(tetrahidrofurano-2*S*-il-carbonil-amino)-propoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2*R*-(3-metoxi-propionil-amino)-propil)-5-(1-metil-pirazol-4-il)-fenilo,

3-(3-hidroxi-propil)-5-(1-metil-pirazol-4-il)-fenil

3-(2-(1-t-butoxi-carbonil-2*S*-metil-piperidin-3*S*-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(1-metil-3*S*-metil-piperidin-4*R*-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(3*R*-fluoro-pirrolidin-1-il-acetil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(3*R*-dimetil-amino-pirrolidin-1-il-acetil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(3*S*-fluoro-pirrolidin-1-il-acetil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-metil-tiazol-4-il)-fenilo,

3-(2-(piridin-2-il-metil-amino-acetil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(2-amino-carbonil)-pirrolidin-1-il-acetil-amino)-etoxi)-5-(1-

metil-pirazol-4-il)-fenilo,

3-(2-(4*S*-fluoro-pirrolidin-2*S*-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(4*S*-hidroxi-pirrolidin-2*S*-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(1-metil-4*S*-fluoro-pirrolidin-2*S*-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(1-metil-4*S*-hidroxi-pirrolidin-2*S*-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(4,4-difluoro-pirrolidin-2*S*-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(4,4-difluoro-pirrolidin-2*R*-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(1-metil-4,4-difluoro-pirrolidin-2*S*-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(1-metil-4,4-difluoro-pirrolidin-2*R*-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(4*S*-hidroxi-pirrolidin-2*S*-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(4-fluoro-pirrolidin-2-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(4-hidroxi-pirrolidin-2-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2*R*-(2*S*-metil-piperidin-3*S*-il-carbonil-amino)-propoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-amino-etoxi)-5-(tiazol-5-il)-fenilo,

3-(2-amino-etoxi)-5-(1-metil-imidazol-5-il)-fenilo,

3-(2-metoxi-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(2-amino-piridin-4-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(2-hidroxi-piridin-4-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-piridil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-amino-piridin-4-il-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-((2-(4-metil-piperazin-1-il)-etil-amino-carbonil)-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(dimetil-amino)-etoxi)-5-(pirimidin-5-il)-fenilo,

3-(2-(3-metoxi-propionil-amino)-etoxi)-5-(pirimidin-5-il)-fenilo,

3-(2-(1-metil-pirrolidin-2S-il-carbonil-amino)-etoxi)-5-(pirimidin-5-il)-fenilo,

3-(1-metil-imidazol-5-il)-5-(N-morfolino-metil)-fenilo,

3-(1-amino-ciclooprop-1-il-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(3-azetidinil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2*S*-amino-3-hidroxi-propil)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2*R*-(metil-amino-carbonil)-pirrolidin-4*R*-iloxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-((imidazo-[1,2-a]-piridin-4-il-carbonil)-amino-metil)-fenilo,

3-(N-acetil-pirrolidin-2-il-carbonil-amino-metil)-fenilo,

3-(2-morfolino-piridin-5-il)-carbonil-amino-metil-fenilo,

3-(2-(ciclopropil-sulfonil-amino)-etoxi)-fenilo,

3-(2-(N,N-dietil-amino-etil)-N-metil-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-((4-N,N-dimetil-amino-ciclohexil-amino)-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(4-(2-metoxi-etoxi)-piperazin-1-il-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(1-metil-pirrolidin-2-il)-etil-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(3*S*-quinuclidil-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(3*R*-quinuclidil-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(N-etil-pirrolidin-2S-il-metil-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(N-etil-pirrolidin-2R-il-metil-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(4-metil-1,4-diazepin-1-il-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(pirrolidino[carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(N-tetrahidro-piran-4-il-N-metil-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(N-tetrahidro-piran-3-il-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(N-tetrahidro-piran-4-il)-metil-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(1,2,4,-triazol-1-il)-etil-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-((pirrolidin-2-on-5-il-metil)-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-((piridin-2-on-4-il-metil)-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-((2R-amino-ciclohex-1R-il)-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(4-metil-piperazin-1-il)-etil-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-((2R-N,N-dimetil-amino-ciclohex-1R-il)-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-((2S-N,N-dimetil-amino-ciclohex-1S-il)-amino-carbonil-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(pirrolidin-2-on-1-il-metil)-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(etoxi-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(N-morfolino-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(1-metil-pirazol-4-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(isoxazol-5-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(pirrolidin-2R-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(pirrolidin-2S-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(piperidin-2R-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(piperidin-2S-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(piperidin-3R-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(piperidin-3S-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(1-metil-pirrolidin-2R-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(1-metil-pirrolidin-2S-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(1-metil-piperidin-2R-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(1-metil-piperidin-2S-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(1-metil-piperidin-3R-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(1-metil-piperidin-3S-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(2R-amino-propionil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(2S-amino-propionil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-

fenilo,

3-(2-(2R-metil-piperidin-3S-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(2S-metil-piperidin-3R-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(4-metil-piperidin-1-il-amino-metil-carbonil)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(2R-N,N-dimetil-amino-propionil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(2S-N,N-dimetil-amino-propionil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(3R-hidroxi-pirrolidin-1-il-metil-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(3S-hidroxi-pirrolidin-1-il-metil-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(3R-fluoro-pirrolidin-1-il-metil-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(3S-fluoro-pirrolidin-1-il-metil-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(3R-N,N-dimetil-amino-pirrolidin-1-il-metil-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(3S-N,N-dimetil-amino-pirrolidin-1-il-metil-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(4-hidroxi-piperidin-1-il-amino-metil-carbonil)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(4-fluoro-piperidin-1-il-amino-metil-carbonil)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(N-morfolino)-piridin-5-il-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(6-hidroxi-metil-piridin-2-il-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(2S-metoxi-carbonil-pirrolidin-4R-iloxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(2S-metoxi-carbonil-pirrolidin-4S-iloxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(2S-carboxi-pirrolidin-4R-iloxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(2S-carboxi-pirrolidin-4S-iloxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(2S-N-metil-amino-carbonil-pirrolidin-4R-iloxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(2S-N-metil-amino-carbonil-pirrolidin-4S-iloxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(2S-N-(2-metoxi-etil)-amino-carbonil-pirrolidin-4R-iloxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(2S-N-(2-metoxi-etil)-amino-carbonil-pirrolidin-4S-iloxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(2-aminotiazol-4-il-metil-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(tiazol-4-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-

fenilo,

3-(2-(2-aminotiazol-5-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(2-aminotiazol-4-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(2-N-acetil-aminotiazol-4-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(tetrahidro-piran-4-il-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-(1-metil-piperidin-4-il-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2-hidroxi-metil-3-hidroxi-propoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(2R-(ciclopropil-sulfonil-amino)-propoxi)-5-(1-metil-pirazol-4-il)-fenilo,

3-(octahidro-pirrolo-[1,2-a]-pirazin-2-il-carbonil-amino-metoxi)-5-(1-metil-pirazol-4-il)-fenilo,

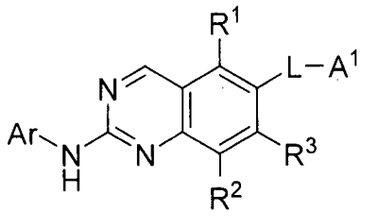
3-(amino-sulfonil)-5-(amino-carbonil)-fenilo,

3-(N-metil-amino-sulfonil)-5-(N-metil-amino-carbonil)-fenilo,

y

3-(2-(2-hidroxi-piridin-5-il-carbonil-amino)-etoxi)-5-(1-metil-pirazol-4-il)-fenilo.

En algunas modalidades, la invención proporciona los compuestos que tienen la fórmula I:



I

o una sal farmacéuticamente aceptable de los mismos, en donde:

Ar es arilo, arilo sustituido, heteroarilo, o heteroarilo sustituido, incluyendo los sistemas bicíclicos fusionados;

R^1 es H, alquilo de 1 a 3 átomos de carbono, halógeno, ciano, nitro, CF_3, imidazolilo, tiazolilo, oxazolilo, o amino;

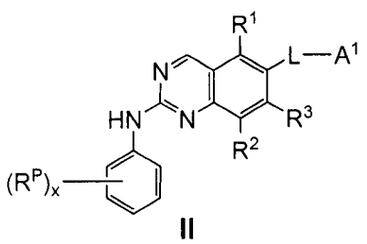
R^2 y R^3 se seleccionan independientemente a partir del grupo que consiste en H, alcoxilo, alcoxilo sustituido, y halógeno;

L es un enlace covalente, carbonilo, carbonil-amino, amino-carbonilo, -O-, -S-, -SO-, $-SO_2-$, -NH-, alquilo de 1 a 3 átomos de carbono, alquilo de 1 a 3 átomos de carbono sustituido, o un alquilo interrumpido con -O-, -S-, -SO-, $-SO_2-$, -NH-, carbonilo, carbonil-amino, o amino-carbonilo; y

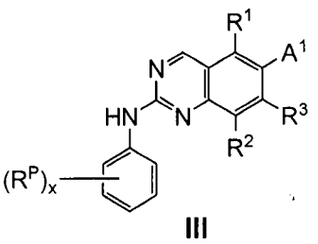
A^1 es alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, alcoxilo, alcoxilo sustituido, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, halógeno, hidroxilo, nitro, SO_3H, sulfonilo, sulfonilo sustituido, sulfoniloxilo, sulfonil-amino, tioacilo,

tiol, tioalquilo, tioalquilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, heterociclilo, o heterociclilo sustituido.

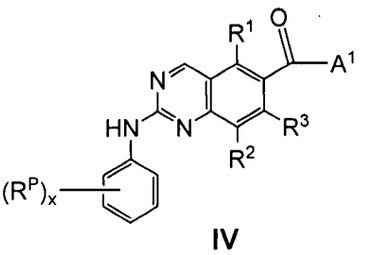
De acuerdo con algunas modalidades, los compuestos de la invención tienen las fórmulas II a VII:



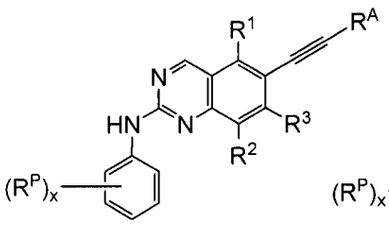
II



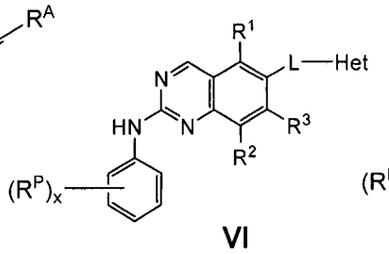
III



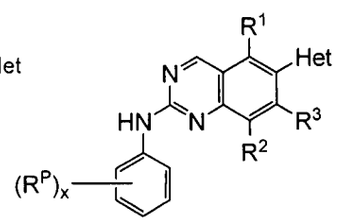
IV



V



VI



VII

en donde R^P se selecciona independientemente a partir del grupo que consiste en alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, alcoxilo, alcoxilo sustituido, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, ariloxilo sustituido, tioarilo, tioarilo sustituido, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquilo sustituido, cicloalquiloxilo, cicloalquiloxilo sustituido, tiocicloalquilo, tiocicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido,

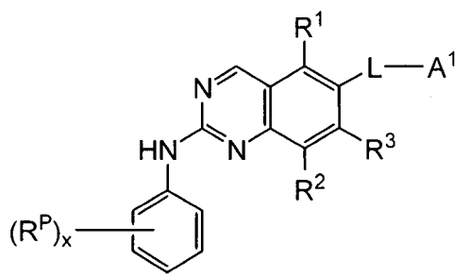
cicloalqueniloxilo, cicloalqueniloxilo sustituido, tiocicloalquenilo, tiocicloalquenilo sustituido, guanidino, guanidino sustituido, halógeno, hidroxilo, heteroarilo, heteroarilo sustituido, heteroariloxilo, heteroariloxilo sustituido, tioheteroarilo, tioheteroarilo sustituido, heterocíclico, heterocíclico sustituido, hetero-cicliloxilo, heterocicliloxilo sustituido, tioheterociclilo, tioheterociclilo sustituido, nitro, SO_3H, sulfonilo sustituido, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, tioalquilo, y tioalquilo sustituido;

R^A se selecciona a partir del grupo que consiste en H, alquilo, alquilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, heterociclilo, y heterociclilo sustituido;

Het se selecciona a partir del grupo que consiste en heteroarilo, heteroarilo sustituido, heterociclilo, y heterociclilo sustituido; y

x es 1, 2, 3, 4 ó 5.

De acuerdo con algunas modalidades, los compuestos de la invención tienen la fórmula II:



II

en donde R^P se selecciona independientemente a partir del grupo que consiste en alquilo, alquenilo, alquinilo, alcoxilo, acilo,

acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino sustituido, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, hetero-cicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo sustituido, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, y tioalquilo;

en donde las fracciones de alquilo, alquenilo, alquinilo, arilo, cicloalquilo, cicloalquenilo, heterociclilo, y heteroarilo contenidas dentro de cualquiera de los grupos "arilo sustituido" precedentes están opcionalmente sustituidas por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en alquenilo, alquinilo, alcoxilo, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, hetero-cicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, tioalquilo,

y tioalquilo;

x es 1, 2, 3, 4 ó 5; y

R^1, R^2, R^3, L y A^1 son como se definen anteriormente.

En algunas modalidades de la fórmula II, x es 1, 2 ó 3; y el anillo de fenilo aislado en la fórmula II no tiene sustituyentes *orto* para el NH con el que está unido. Los patrones de sustitución preferidos para este anillo de fenilo incluyen la mono-sustitución en la posición 3 ('*meta*' para el NH); la mono-sustitución en la posición 4 ('*para*' en relación con el NH); y la disustitución en las posiciones 3 y 4 o en las posiciones 3 y 5.

En ciertas modalidades de los compuestos de la fórmula II, R^1 es H.

En ciertas modalidades de los compuestos de la fórmula II, R^2 es alcoxilo sustituido.

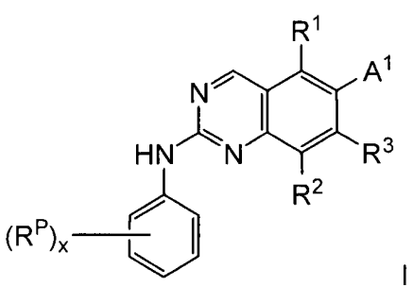
En ciertas modalidades de los compuestos de la fórmula II, R^2 es alcoxilo sustituido, hetero-cicliloxilo, o heterociclil-alcoxilo. En otras modalidades, R^2 es H.

En algunas modalidades de la fórmula II, R^3 es alcoxilo sustituido tal como heteroaril-metoxilo. Los grupos heteroarilo adecuados en estos compuestos incluyen pirazol, imidazol, tiazol, piridina, pirazol y pirimidina. En otras de estas modalidades, R^3 es hetero-cicliloxilo o heterociclil-alcoxilo sustituido tal como heterociclil-metoxilo. En otras de estas modalidades, R^3 es heterociclil-alcoxilo sustituido tal como heterociclil-metoxilo. Los grupos heterociclilo adecuados para estas modalidades incluyen

piperidinilo, pirrolidinilo, tetrahidro-furanilo, y similares.

En algunas modalidades, cuando menos un R^P presente comprende un grupo heteroarilo o heterocíclico. En algunas modalidades, es un grupo heteroarilo, el cual puede estar sustituido. Los heteroarilos adecuados incluyen piridinilo, imidazolilo, pirazolilo, pirimidinilo, tiazolilo, triazolilo, tetrazolilo, oxazolilo, tiazolilo, y tiadiazolilo. En otras, R^P es un grupo de la fórmula $-O-CH_2-C(O)-NR'R"$, en donde R' y R" son independientemente H, alquilo, o alquilo sustituido, y R' y R" se pueden unir entre sí para formar un anillo heterocíclico. En otras modalidades, R^P es un grupo heterociclilo tal como piperazinilo, piperidinilo, morfolinilo, o R^P es un heterociclil-alquilo sustituido tal como piperazinil-metilo, morfolinil-metilo, oxazolinil-metilo, y similares. En algunas modalidades, R^P es un grupo heterociclilo o heteroarilo enlazado al anillo de fenilo de la fórmula II a través de $-O-$ u $-OCH_2-$ u $-OCH_2-CH_2-$.

De acuerdo con algunas modalidades, los compuestos de la invención tienen la fórmula III:

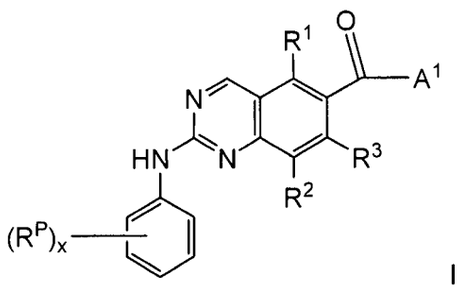


III

en donde R^1, R^2, R^3, A^1, R^P y x son como se definen anteriormente. Éstos corresponden a los compuestos en donde L es un enlace. Típicamente en estas modalidades, cuando menos uno de

R^1, R^2 y R^3 es un grupo diferente de H. Con frecuencia, R^1 es H o halógeno, y cualquiera de R^2 o R^3 es H mientras que el otro de R^2 y R^3 es un grupo seleccionado a partir de alcoxilo, alcoxilo sustituido, heteroariloxilo, heteroariloxilo sustituido, hetero-cicliloxilo, y heterocicliloxilo sustituido.

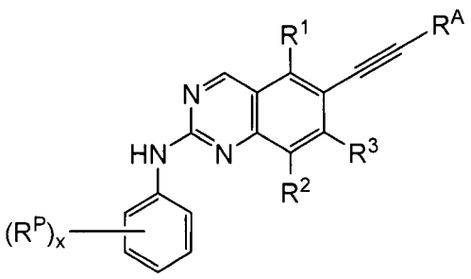
De acuerdo con algunas modalidades, los compuestos de la invención tienen la fórmula IV:



IV

en donde R^1, R^2, R^3, A^1, R^P y x son como se definen anteriormente.

De acuerdo con algunas modalidades, los compuestos de la invención tienen la fórmula V:

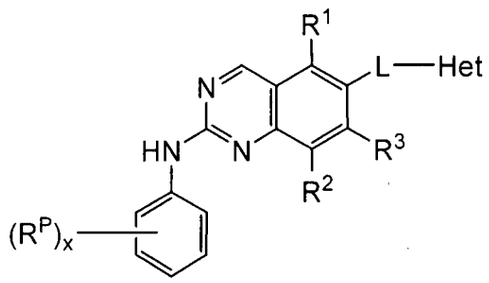


V

en donde R^1, R^2, R^3, R^P y x son como se definen anteriormente; y

R^A se selecciona a partir del grupo que consiste en H, alquilo, alquilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, heterociclilo, y heterociclilo sustituido. Con frecuencia, R^A se selecciona a partir de H, metilo, hidroxi-metilo, metoxi-metilo, y otros grupos alcoxi-metilo. Con frecuencia en estos compuestos, R^1, R^2, R^3, R^P y x son como se describen para los compuestos de la fórmula II anterior.

De acuerdo con algunas modalidades, los compuestos de la invención tienen la fórmula VI:

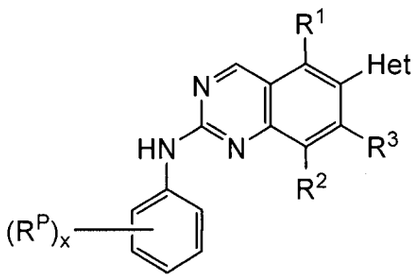


VI

en donde R^1, R^2, R^3, L, R^P y x son como se definen anteriormente; y

Het se selecciona a partir del grupo que consiste en heteroarilo, heteroarilo sustituido, heterociclilo, y heterociclilo sustituido. Con frecuencia en estos compuestos, R^1, R^2, R^3, R^P y x son como se describen para los compuestos de la fórmula II anterior. En algunas de estas modalidades, L es un enlace, -O-, $-OCH_2-$, amino, amino-carbonilo, o carbonil-amino.

De acuerdo con algunas modalidades, los compuestos de la invención tienen la fórmula VII:



VII

en donde R^1, R^2, R^3, R^P, x y Het son como se definen anteriormente. Con frecuencia en estos compuestos, R^1, R^2, R^3, R^P y x son como se describen para los compuestos de la fórmula II anterior. Het en estos compuestos puede ser cualquier grupo heterocíclico o heteroarilo, y algunas veces se selecciona a partir de tiazol, oxazol, isotiazol, isoxazol, pirazol, piridina, triazol, y furano.

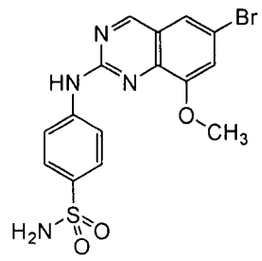
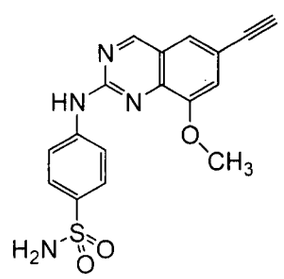
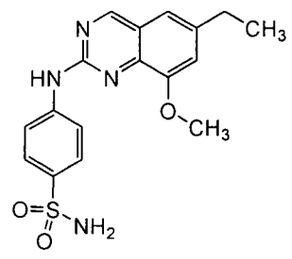
Se aprecia además que ciertas características de la invención, las cuales, para mayor claridad, se describen en el contexto de modalidades separadas, también se pueden proporcionar en combinación en una sola modalidad. Inversamente, diferentes características de la invención que, para mayor brevedad, se describan en el contexto de una sola modalidad, también se pueden proporcionar por separado o en cualquier sub-combinación adecuada.

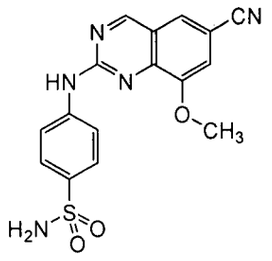
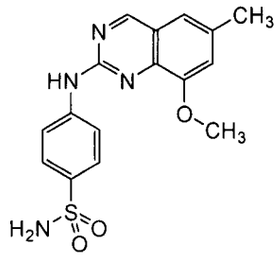
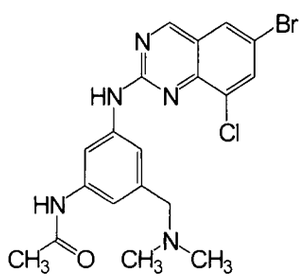
Algunos compuestos de la invención incluyen aquéllos de la Tabla 1 que se encuentra más adelante. Los compuestos de la Tabla 1 se prepararon como se indica en la columna etiquetada con "Ej. de Prep. #" y en la presente se proporcionan los detalles de ciertos procedimientos sintéticos de ejemplo. Los Datos Físicos se proporcionan en la columna marcada con "MS (M+1)..." para cada

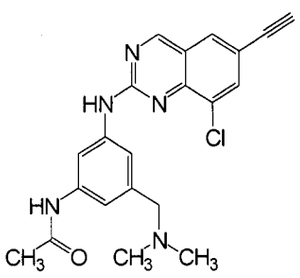
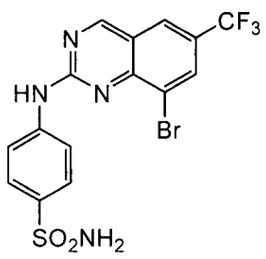
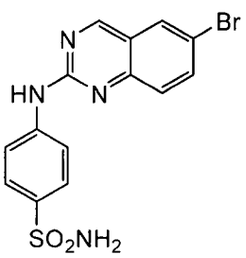
uno de los compuestos, así como los datos del tiempo de retención. Estos Datos Físicos se adquirieron utilizando uno de dos métodos, el Método A y el Método B, los cuales se proporcionan en la presente, en los Ejemplos. El Método B se utilizó para los datos recopilados para los Ejemplos 36, 19, 110, y 111, y el Método A se utilizó para recopilar todos los Datos Físicos restantes de la Tabla 1. Se incluyen compuestos adicionales de la invención en la Tabla 2 (Figura 1), y en la Tabla 3 (Figura 3). En la presente se proporcionan los métodos para la preparación de los compuestos representativos a partir de las Tablas 2 y 3, los Ejemplos para los cuales están numerados para corresponder con la numeración de los compuestos en las Tablas.

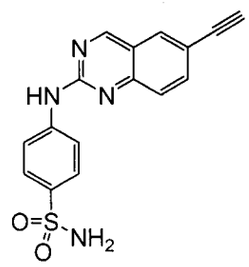
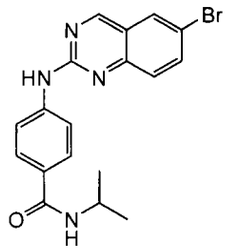
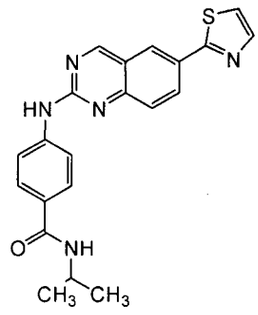
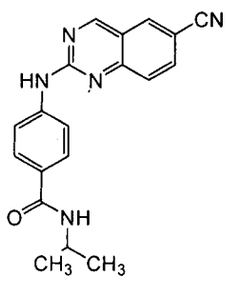
La columna marcada con "Actividad" indica la actividad del compuesto en el Ensayo de Rastreo de Cinasa-Alfa PDK1 descrito más adelante. El símbolo "+" indica los valores IC_{50} de 25 µM o mayores (o los compuestos no evaluados), el símbolo "++" indica los valores IC_{50} entre menos de 25 µM y mayores de 10 µM, el símbolo "+++" indica los valores IC_{50} de 10 µM o menos y mayores de 5 µM, y el símbolo "++++" indica los valores IC_{50} menores de 5 µM. De conformidad con lo anterior, como se muestra en la Tabla 1, se ha mostrado que 131 de los compuestos de ejemplo, o aproximadamente el 75 por ciento de los compuestos de ejemplo demuestran valores IC_{50} de menos de 5 µM.

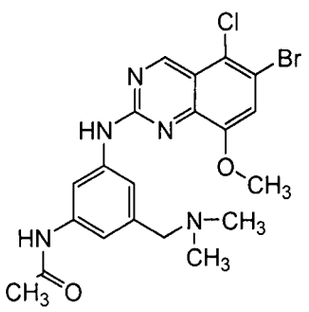
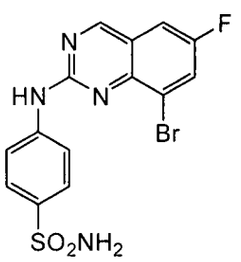
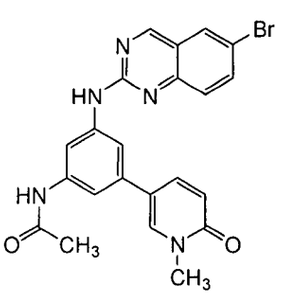
Tabla 1

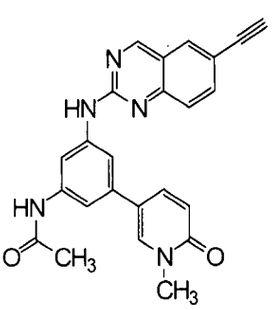
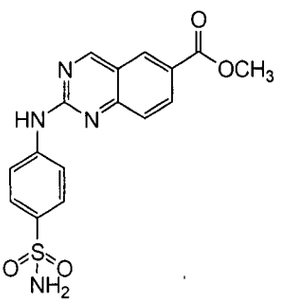
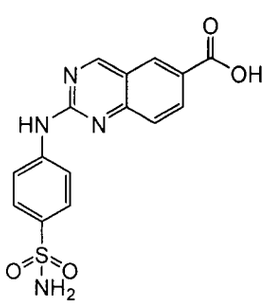
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
1		4-(6-bromo-8-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida	409/411 2.60	++++	1
2		4-(6-etinil-8-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida	355 2.45	++++	2
3		4-(6-etil-8-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida	359 2.50	++++	3

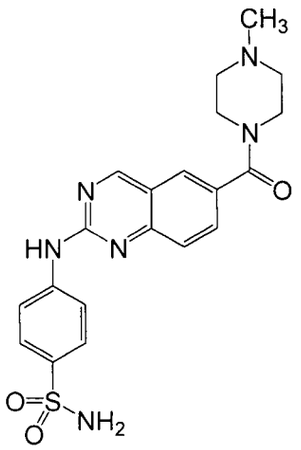
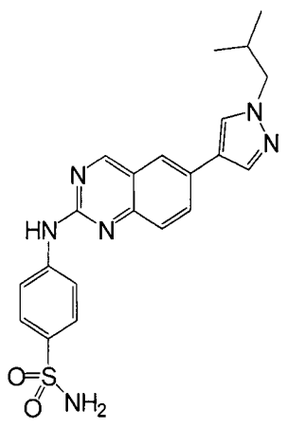
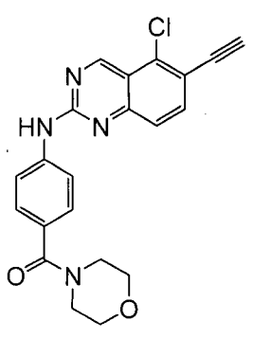
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
4		4-(6-ciano-8-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida	356 2.20	++++	4
5		4-(8-metoxi-6-metil-quinazolin-2-il-amino)-bencen-sulfonamida	345 2.35	++++	5
6		N-(3-(6-bromo-8-cloro-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-acetamida	448/450 2.30	++++	6

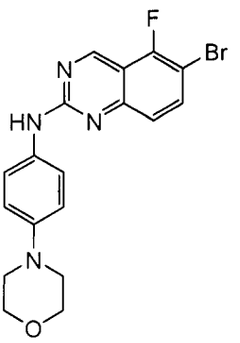
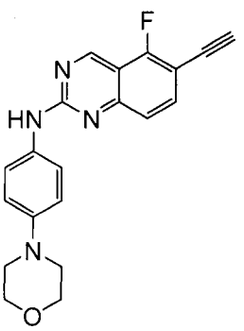
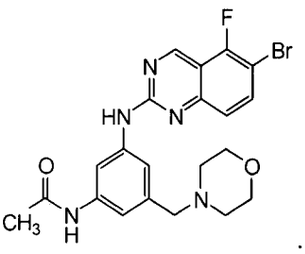
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
7		N-(3-(8-cloro-6-etinil-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-acetamida	394 2.13	++++	7
8		4-(8-bromo-6-(trifluoro-metil)-quinazolin-2-il-amino)-bencen-sulfonamida	447/449	+	8
9		4-(6-bromo-quinazolin-2-il-amino)-bencen-sulfonamida	379/381	+	9

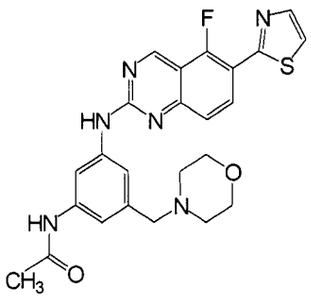
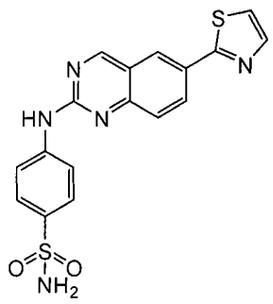
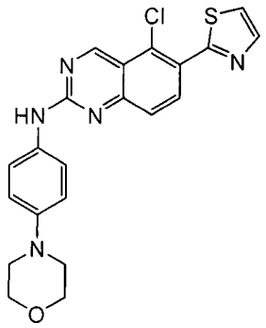
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
10		4-(6-etinil-quinazolin-2-il-amino)-bencen-sulfonamida	325.1 2.44	++++	10
11		4-(6-bromo-quinazolin-2-il-amino)-N-isopropil-benzamida	385/387	+	11
12		N-isopropil-4-(6-(tiazol-2-il)-quinazolin-2-il-amino)-benzamida	390.1 2.71	++++	12
13		4-(6-ciano-quinazolin-2-il-amino)-N-isopropil-benzamida	332.1 2.51	++++	13

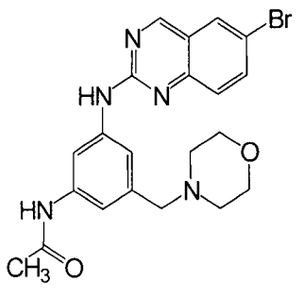
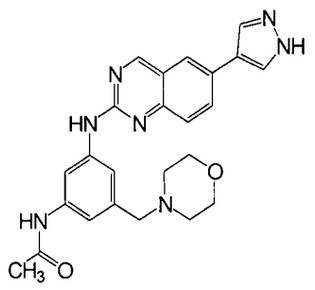
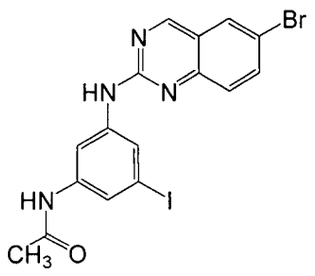
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
14		N-(3-(6-bromo-5-cloro-8-metoxi-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-acetamida	480.0 2.36	++++	14
15		4-(8-bromo-6-fluoro-quinazolin-2-il-amino)-bencen-sulfonamida	397/399	+	15
16		N-(3-(6-bromo-quinazolin-2-il-amino)-5-(1-metil-6-oxo-1,6-dihidro-piridin-3-il)-fenil)-acetamida	464/466 3.10	+	16

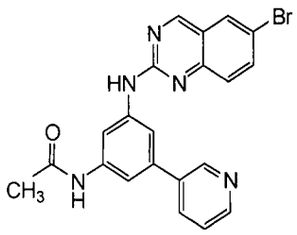
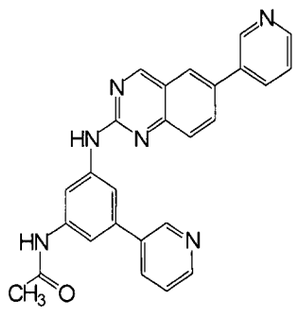
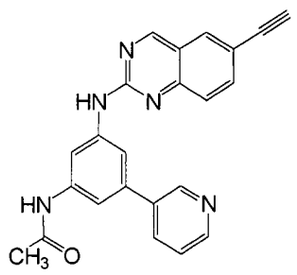
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
17		N-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-6-oxo-1,6-dihidro-piridin-3-il)-fenil)-acetamida	410 2.76	+	17
18		2-(4-sulfamoil-fenil-amino)-quinazolin-6-carboxilato de metilo	359	+	18
19		ácido 2-(4-sulfamoil-fenil-amino)-quinazolin-6-carboxílico	345 2.2	++++	19

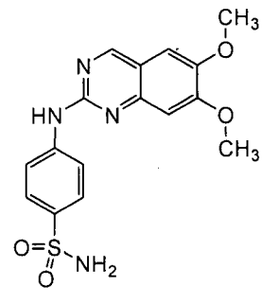
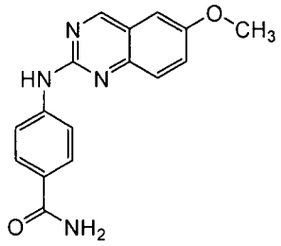
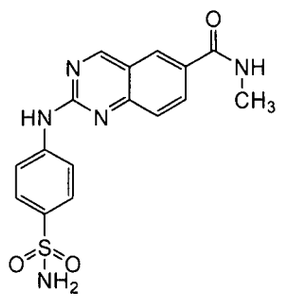
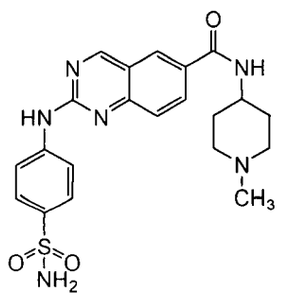
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
20		4-(6-(4-metil-piperazin-1-carbonil)-quinazolin-2-il-amino)-bencen-sulfonamida	427.1 1.54	+	20
21		4-(6-(1-isobutil-1H-pirazol-4-il)-quinazolin-2-il-amino)-bencen-sulfonamida	423.1 3.37	+	21
22		(4-(5-cloro-6-etinil-quinazolin-2-il-amino)-fenil)-(morfolino)-metanona	393.1 3.7	++++	22

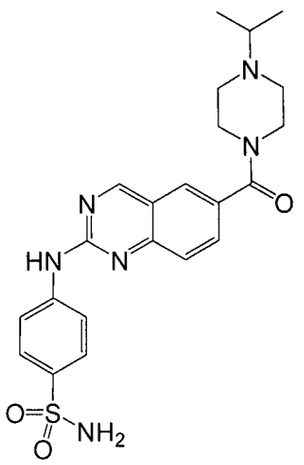
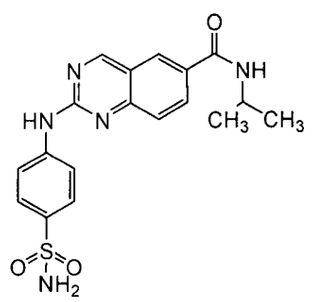
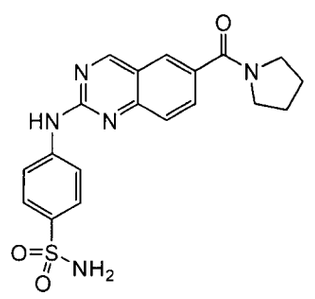
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
23		6-bromo-5-fluoro-N-(4-morfolino-fenil)-quinazolin-2-amina	403.1 3.39	++++	23
24		6-etinil-5-fluoro-N-(4-morfolino-fenil)-quinazolin-2-amina	349.1 2.93	++++	24
25		N-(3-(6-bromo-5-fluoro-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida		+	25

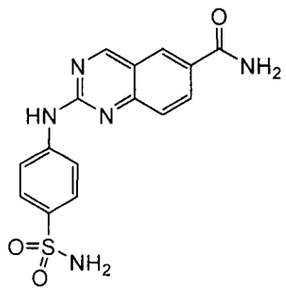
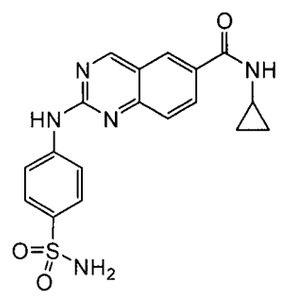
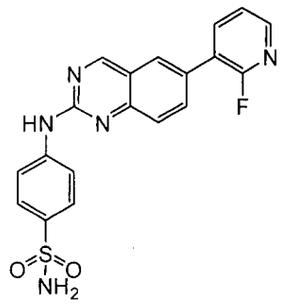
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
26		N-(3-(5-fluoro-6-(tiazol-2-il)-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida	479.2 2.5	+	26
27		4-(6-(tiazol-2-il)-quinazolin-2-il-amino)-bencen-sulfonamida	384 3.2	++++	27
28		5-cloro-N-(4-morfolino-fenil)-6-(tiazol-2-il)-quinazolin-2-amina	473	+	28

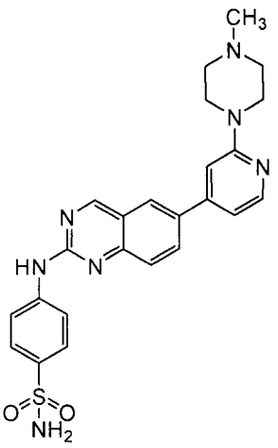
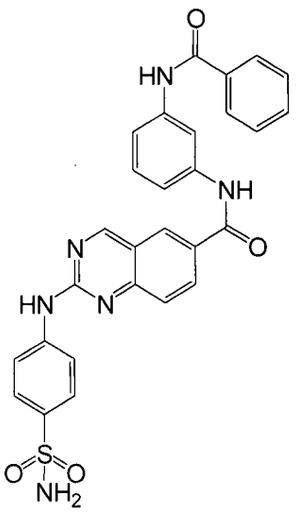
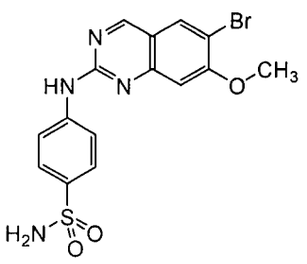
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
29		N-(3-(6-bromo-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida	456/458 2.14	++++	29
30		N-(3-(6-(1H-pirazol-4-il)-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida	444.3 1.73	++++	30
31		N-(3-(6-bromo-quinazolin-2-il-amino)-5-yodo-fenil)-acetamida	483.0/485.0 3.19	++++	31

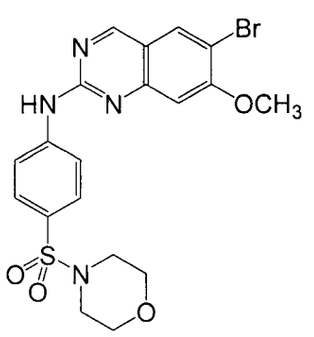
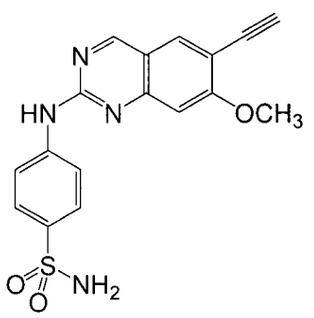
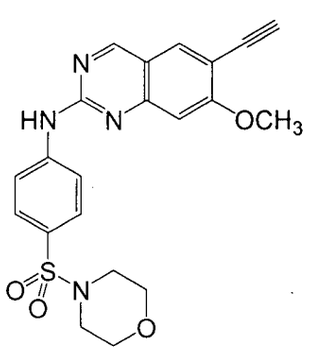
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
32		N-(3-(6-bromo-quinazolin-2-il-amino)-5-(piridin-3-il)-fenil)-acetamida	434.1/436.1 2.21	++++	32
33		N-(3-(piridin-3-il)-5-(6-(piridin-3-il)-quinazolin-2-il-amino)-fenil)-acetamida	433.2 1.66	+	33
34		N-(3-(6-etinil-quinazolin-2-il-amino)-5-(piridin-3-il)-fenil)-acetamida	433.2 2.08	++++	34

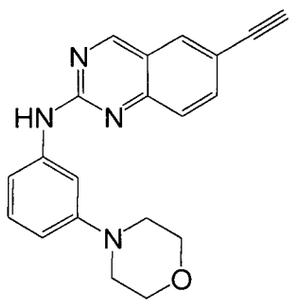
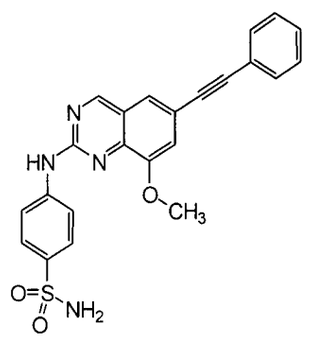
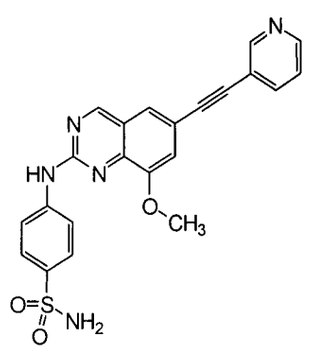
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
35		4-(6,7-dimetoxi-quinazolin-2-il-amino)-bencen-sulfonamida	361.0 2.01	++++	35
36		4-(6-metoxi-quinazolin-2-il-amino)-benzamida	295.1	++++	21
37		N-metil-2-(4-sulfamoil-fenil-amino)-quinazolin-6-carboxamida	358 2.0	+++	18, 19, 20
38		N-(1-metil-piperidin-4-il)-2-(4-sulfamoil-fenil-amino)-quinazolin-6-carboxamida	441 1.71	+	18, 19, 20

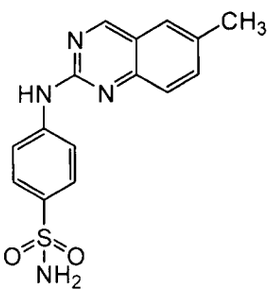
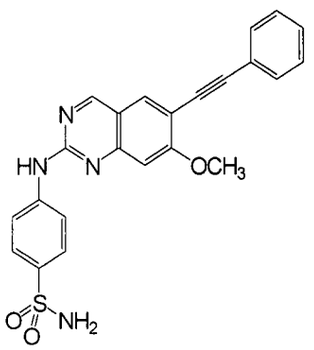
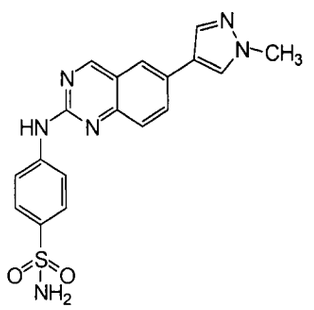
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
39		4-(6-(4-isopropil-piperazin-1-carbonil)-quinazolin-2-il-amino)-bencen-sulfonamida	427.1 1.54	+	18, 19, 20
40		N-isopropil-2-(4-sulfamoil-fenil-amino)-quinazolin-6-carboxamida	386 2.5	+	18, 19, 20
41		4-(6-(pirrolidin-1-carbonil)-quinazolin-2-il-amino)-bencen-sulfonamida	398.1 2.07	+	18, 19, 20

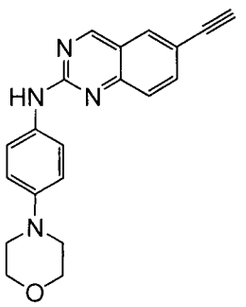
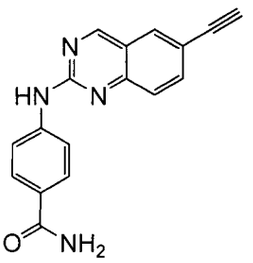
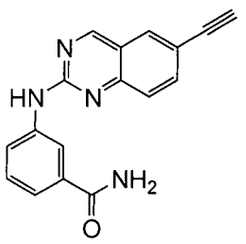
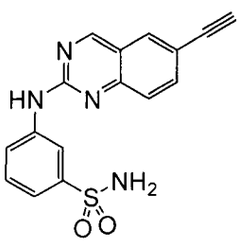
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
42		2-(4-sulfamoil-fenil-amino)-quinazolin-6-carboxamida	344.0 1.68	++++	18, 19, 20
43		N-ciclopropil-2-(4-sulfamoil-fenil-amino)-quinazolin-6-carboxamida	384.0 1.97	++++	18, 19, 20
44		4-(6-(2-fluoro-piridin-3-il)-quinazolin-2-il-amino)-bencen-sulfonamida	396 3.08	++++	21

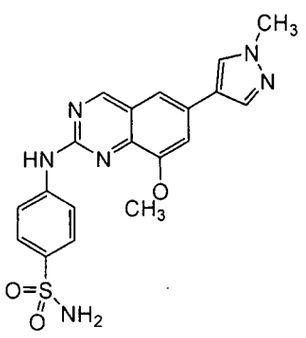
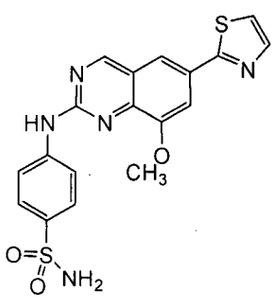
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
45		4-(6-(2-(4-metil-piperazin-1-il)-piridin-4-il)-quinazolin-2-il-amino)-bencen-sulfonamida	476.1 1.75	++++	21
46		N-(3-benzamido-fenil)-2-(4-sulfamoil-fenil-amino)-quinazolin-6-carboxamida	539.1 3.42	+	18, 19, 20
47		4-(6-bromo-7-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida	409/411 2.62	++++	47

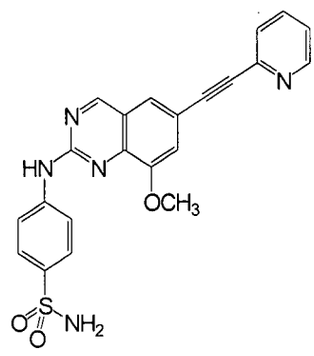
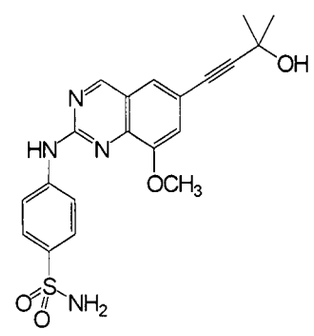
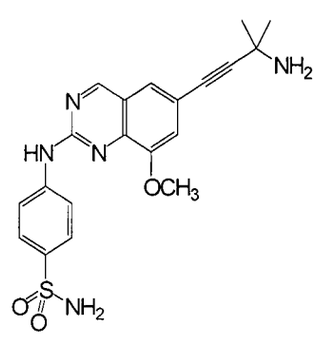
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
48		6-bromo-7-metoxi-N-(4-(morfolino-sulfonil)-fenil)-quinazolin-2-amina	479/481 3.07	++++	47
49		4-(6-etinil-7-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida	355 2.35	++++	47, 2
50		6-etinil-7-metoxi-N-(4-(morfolino-sulfonil)-fenil)-quinazolin-2-amina	425 2.85	++++	47, 2

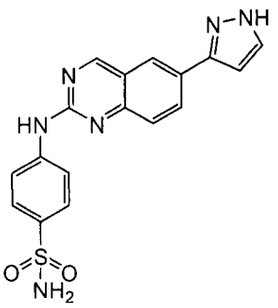
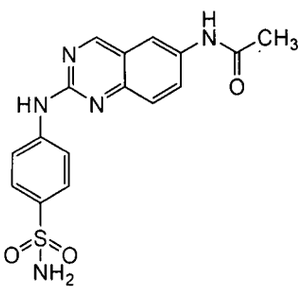
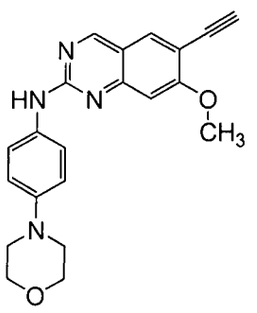
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
51		6-etinil-N-(3-morfolino-fenil)-quinazolin-2-amina	331.1 2.50	++++	9, 10
52		4-(8-metoxi-6-(fenil-etinil)-quinazolin-2-il-amino)-bencen-sulfonamida	431.0 3.08	+	9, 10
53		4-(8-metoxi-6-(piridin-3-il-etinil)-quinazolin-2-il-amino)-bencen-sulfonamida	432.0 2.10	++	9, 10

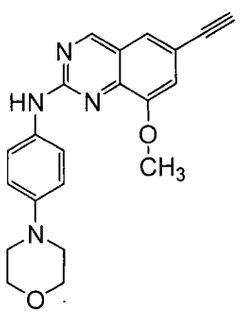
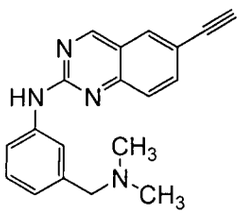
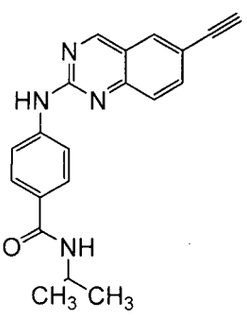
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
54		4-(6-metil-quinazolin-2-il-amino)-bencen-sulfonamida	315 2.7	++++	21
55		4-(7-metoxi-6-(fenil-etinil)-quinazolin-2-il-amino)-bencen-sulfonamida	431 3.05	+	47, 2
56		4-(6-(1-metil-1H-pirazol-4-il)-quinazolin-2-il-amino)-bencen-sulfonamida	381.1 2.54	++++	21

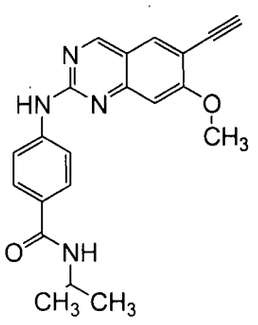
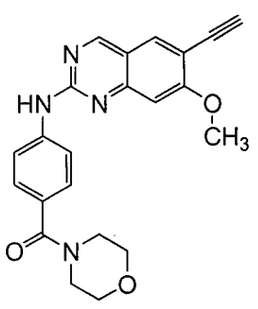
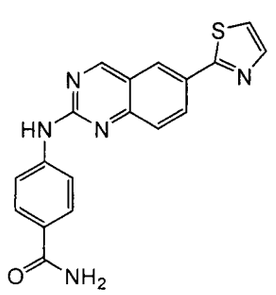
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
57		6-etinil-N-(4-morfolino-fenil)-quinazolin-2-amina	331.1 2.24	++++	9, 10
58		4-(6-etinil-quinazolin-2-il-amino)-benzamida	289 2.25	++++	9, 10
59		3-(6-etinil-quinazolin-2-il-amino)-benzamida	289 2.22	++++	9, 10
60		3-(6-etinil-quinazolin-2-il-amino)-bencen-sulfonamida	325.1 2.42	++++	9, 10

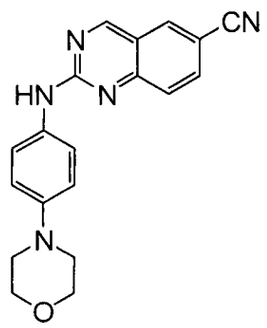
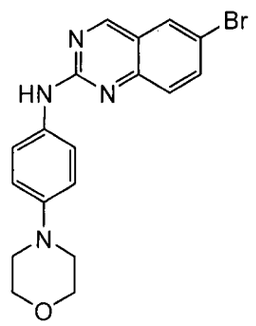
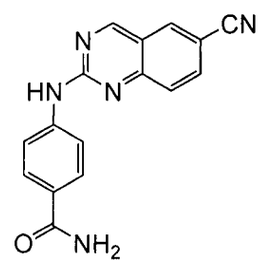
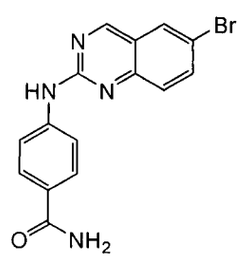
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
61		N-(3-(6-etinil-quinazolin-2-il-amino)-fenil)-metan-sulfonamida	339.0 2.55	++++	9, 10
62		4-(8-metoxi-6-(1-metil-1H-pirazol-4-il)-quinazolin-2-il-amino)-bencen-sulfonamida	411 2.56	++++	1, 30
63		4-(8-metoxi-6-(tiazol-2-il)-quinazolin-2-il-amino)-bencen-sulfonamida	414 3.07	++++	1, 30

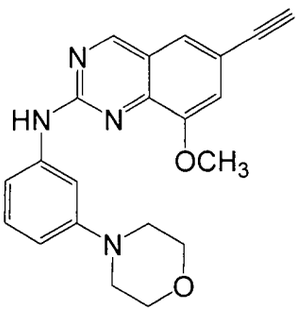
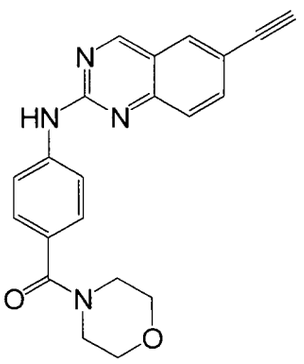
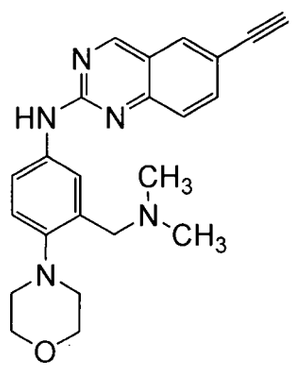
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
64		4-(8-metoxi-6-(piridin-2-il-etinil)-quinazolin-2-il-amino)-bencen-sulfonamida	432 2.22	+	2
65		4-(6-(3-hidroxi-3-metil-but-1-inil)-8-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida	413 2.33	++++	2
66		4-(6-(3-amino-3-metil-but-1-inil)-8-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida	412 1.77	++	2

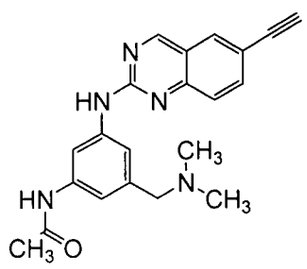
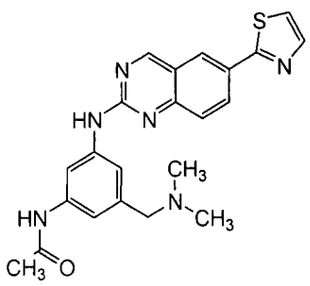
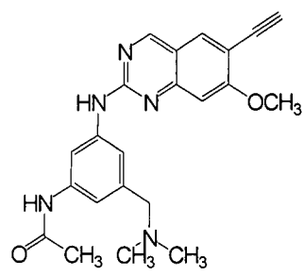
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
67		4-(6-(1H-pirazol-3-il)-quinazolin-2-il-amino)-bencen-sulfonamida	367 2.4	++++	21
68		N-(2-(4-sulfamoil-fenil-amino)-quinazolin-6-il)-acetamida	358 1.9	++++	68
69		6-etinil-7-metoxi-N-(4-morfolino-fenil)-quinazolin-2-amina	361 2.56	++++	47, 2

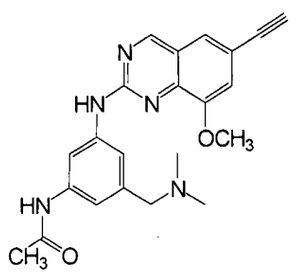
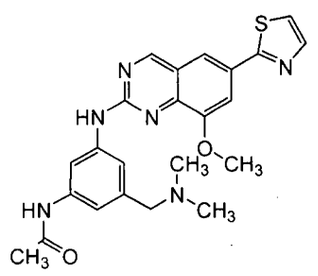
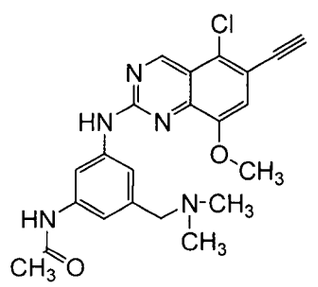
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
70		6-etinil-8-metoxi-N-(4-morfolino-fenil)-quinazolin-2-amina	361.2 2.6	++++	1, 2
71		N-(3-((dimetil-amino)-metil)-fenil)-6-etinil-quinazolin-2-amina	303.1 2.11	++++	9, 10
72		4-(6-etinil-quinazolin-2-il-amino)-N-isopropil-benzamida	331.2 2.75	++++	9, 10

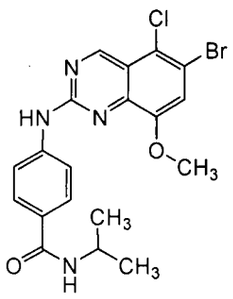
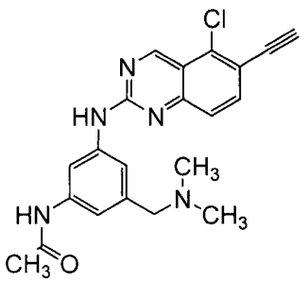
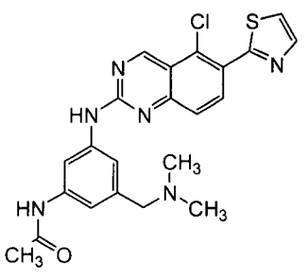
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
73		4-(6-etinil-7-metoxi-quinazolin-2-il-amino)-N-isopropil-benzamida	361 3.38	++++	47, 2
74		(4-(6-etinil-7-metoxi-quinazolin-2-il-amino)-fenil)-(morfolino)-metanona	389 3.00	++++	47, 2
75		4-(6-(tiazol-2-il)-quinazolin-2-il-amino)-benzamida	348.1 2.27	++++	12

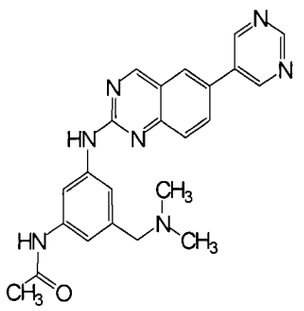
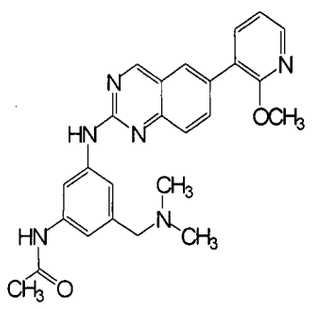
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
76		2-(4-morfolino-fenil-amino)-quinazolin-6-carbonitrilo	332.1 2.21	++++	13
77		6-bromo-N-(4-morfolino-fenil)-quinazolin-2-amina	385/387 2.51	++++	9
78		4-(6-ciano-quinazolin-2-il-amino)-benzamida	290.1 2.06	++++	13
79		4-(6-bromo-quinazolin-2-il-amino)-benzamida	343/345 2.46	++++	9

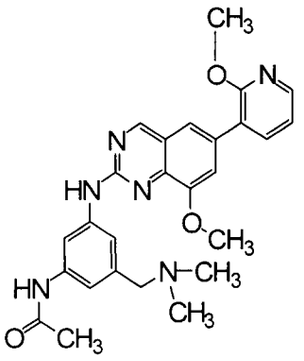
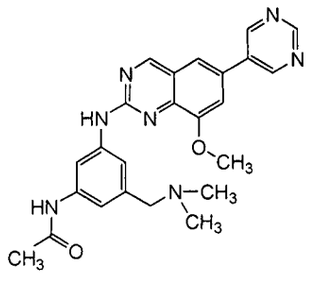
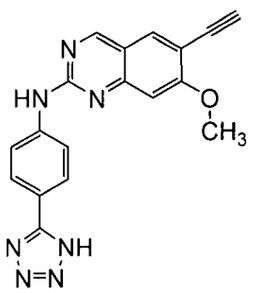
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
80		6-etinil-8-metoxi-N-(3-morfolino-fenil)-quinazolin-2-amina	361.1 2.76	++++	9, 10
81		(4-(6-etinil-quinazolin-2-il-amino)-fenil)-(morfolino)-metanona	359.1 2.52	++++	9, 10
82		N-(3-((dimetil-amino)-metil)-4-morfolino-fenil)-6-etinil-quinazolin-2-amina	388.2 2.25	++++	9, 10

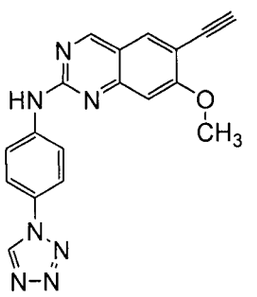
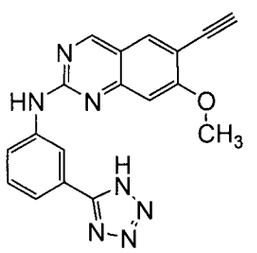
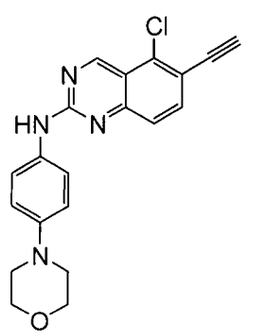
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
83		N-(3-((dimetil-amino)-metil)-5-(6-etinil-quinazolin-2-il-amino)-fenil)-acetamida	360.1 2.00	++++	9, 10
84		N-(3-((dimetil-amino)-metil)-5-(6-(tiazol-2-il)-quinazolin-2-il-amino)-fenil)-acetamida	419.3 2.00	++++	12
85		N-(3-((dimetil-amino)-metil)-5-(6-etinil-7-metoxi-quinazolin-2-il-amino)-fenil)-acetamida	390 2.21	++++	47, 2

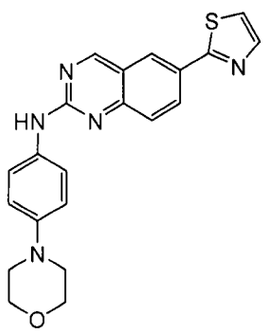
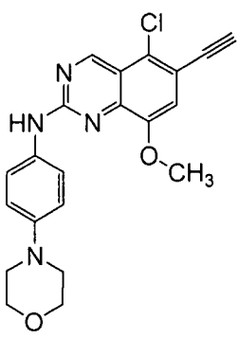
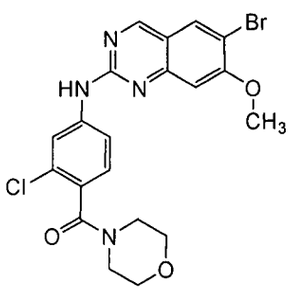
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
86		N-(3-((dimetil-amino)-metil)-5-(6-etinil-8-metoxi-quinazolin-2-il-amino)-fenil)-acetamida	390.2 2.05	++++	1, 2
87		N-(3-((dimetil-amino)-metil)-5-(8-metoxi-6-(tiazol-2-il)-quinazolin-2-il-amino)-fenil)-acetamida	449.1 2.04	++++	12
88		N-(3-(5-cloro-6-etinil-8-metoxi-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-	424.1 2.25	++++	14, 9, 10

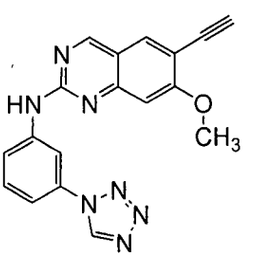
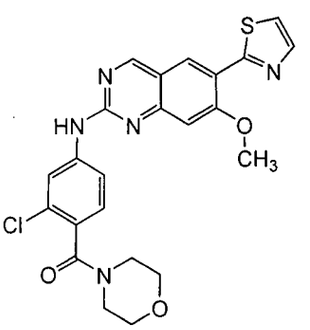
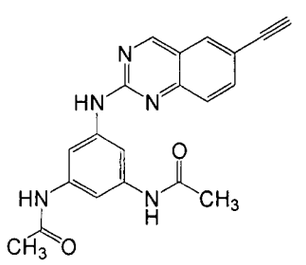
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		acetamida			
89		4-(6-bromo-5-cloro-8-metoxi-quinazolin-2-il-amino)-N-isopropil-benzamida	451.0 3.16	++++	14
90		N-(3-(5-cloro-6-etinil-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-acetamida	394.1 2.25	++++	22
91		N-(3-(5-cloro-6-(tiazol-2-il)-quinazolin-2-il-amino)-5-((dimetil-	453.1 2.27	++++	28

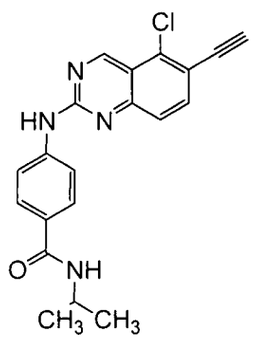
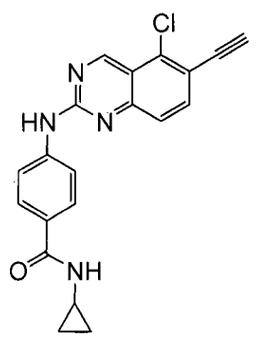
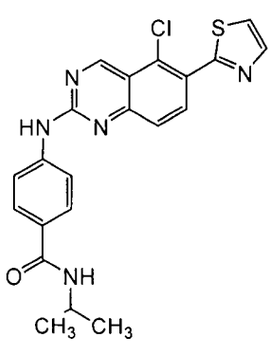
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
		amino)-metil)-fenil)-acetamida			
92		N-(3-((dimetil-amino)-metil)-5-(6-(pirimidin-5-il)-quinazolin-2-il-amino)-fenil)-acetamida	414.2 183	++++	9, 21
93		N-(3-((dimetil-amino)-metil)-5-(6-(2-metoxi-piridin-3-il)-quinazolin-2-il-amino)-fenil)-acetamida	443.2 2.38	+++	9, 21

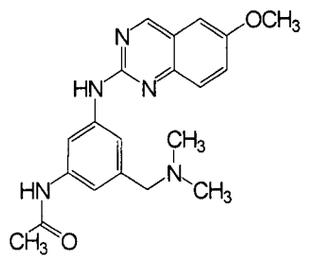
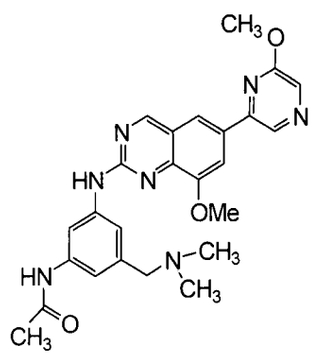
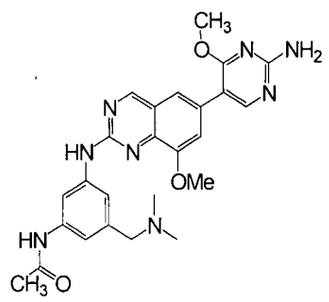
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
94		N-(3-((dimetil-amino)-metil)-5-(8-metoxi-6-(2-metoxi-piridin-3-il)-quinazolin-2-il-amino)-fenil)-acetamida	473.2 2.41	+++	21
95		N-(3-((dimetil-amino)-metil)-5-(8-metoxi-6-(pirimidin-5-il)-quinazolin-2-il-amino)-fenil)-acetamida	444.2 1.9	++++	21
96		N-(4-(1H-tetrazol-5-il)-fenil)-6-etinil-7-metoxi-quinazolin-2-amina	344 3.11	++++	47, 2

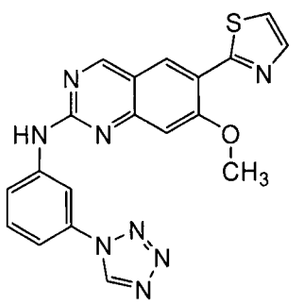
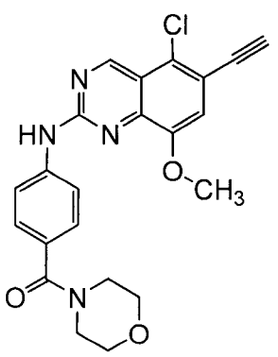
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
97		N-(4-(1H-tetrazol-1-il)-fenil)-6-etinil-7-metoxi-quinazolin-2-amina	344 3.39	++++	47, 2
98		N-(3-(1H-tetrazol-5-il)-fenil)-6-etinil-7-metoxi-quinazolin-2-amina	344 3.04	++++	47, 2
99		5-cloro-6-etinil-N-(4-morfolino-fenil)-quinazolin-2-amina	365.1 2.56	++++	22

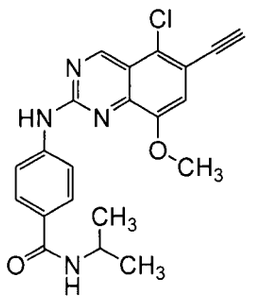
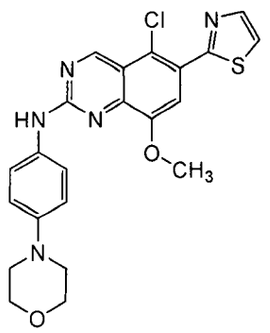
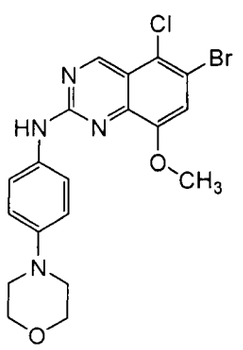
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
100		N-(4-morfolino-fenil)-6-(tiazol-2-il)-quinazolin-2-amina	390.1 2.32	++++	12
101		5-cloro-6-etinil-8-metoxi-N-(4-morfolino-fenil)-quinazolin-2-amina	480.2 2.5	++++	14, 2
102		(4-(6-bromo-7-metoxi-quinazolin-2-il-amino)-2-cloro-fenil)-(morfolino)-metanona	477/479 3.83	++++	47

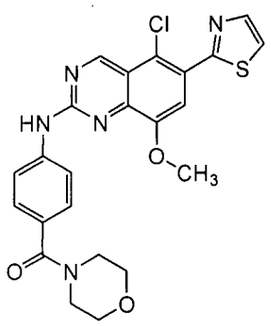
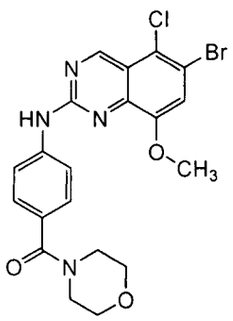
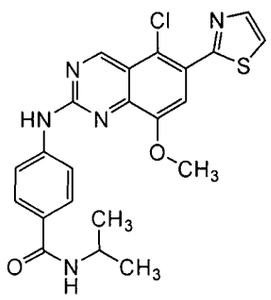
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
103		N-(3-(1H-tetrazol-1-il)-fenil)-6-etinil-7-metoxi-quinazolin-2-amina	344 3.48	++++	47, 2
104		(2-cloro-4-(7-metoxi-6-(tiazol-2-il)-quinazolin-2-il-amino)-fenil)-(morfolino)-metanona	482 3.46	++++	47, 12
105		N,N'-(5-(6-etinil-quinazolin-2-il-amino)-1,3-fenileno)-diacetamida	360.1 2.14	++++	9, 10

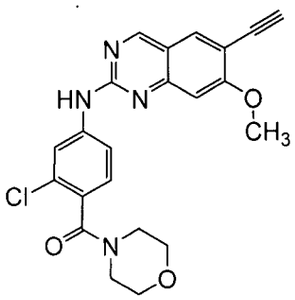
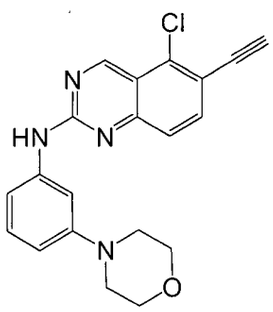
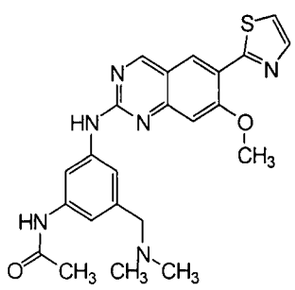
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
106		4-(5-cloro-6-etinil-quinazolin-2-il-amino)-N-isopropil-benzamida	365.1 3.05	++++	22
107		4-(5-cloro-6-etinil-quinazolin-2-il-amino)-N-ciclopropil-benzamida	363.1 2.88	++++	22
108		4-(5-cloro-6-(tiazol-2-il)-quinazolin-2-il-amino)-N-isopropil-benzamida	424.1 3.08	+	28

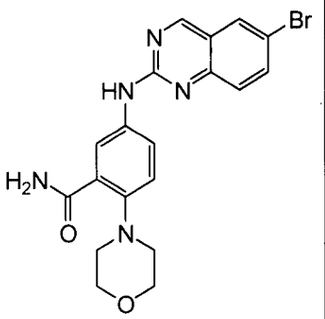
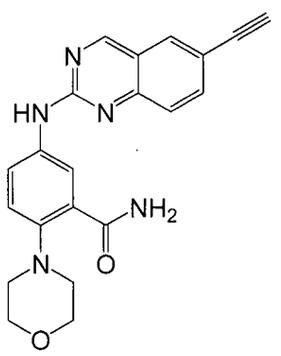
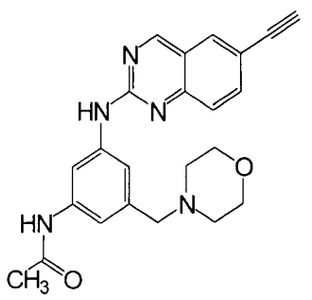
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
109		N-(3-((dimetil-amino)-metil)-5-(6-metoxi-quinazolin-2-il-amino)-fenil)-acetamida	367.1	++++	21
110		N-(3-((dimetil-amino)-metil)-5-(8-metoxi-6-(6-metoxi-pirazin-2-il)-quinazolin-2-il-amino)-fenil)-acetamida	473.1	++++	21
111		N-(3-(6-(2-amino-4-metoxi-pirimidin-5-il)-8-metoxi-quinazolin-2-il-amino)-5-	489.1	+++	21

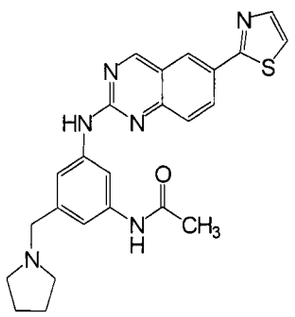
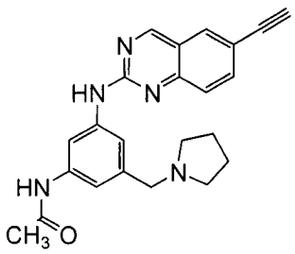
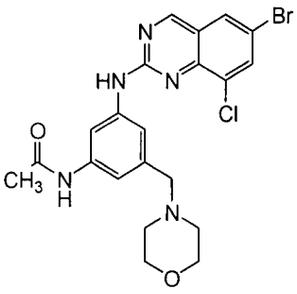
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
		((dimetil-amino)-metil)-fenil)-acetamida			
112		N-(3-(1H-tetrazol-1-il)-fenil)-7-metoxi-6-(tiazol-2-il)-quinazolin-2-amina	375 3.28	++++	1, 12
113		(4-(5-cloro-6-etinil-8-metoxi-quinazolin-2-il-amino)-fenil)-(morfolino)-metanona	423.2 2.77	++++	14, 2

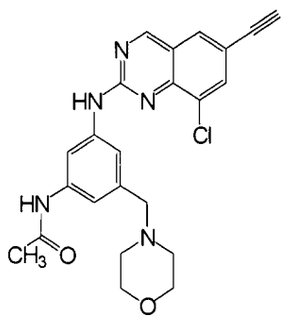
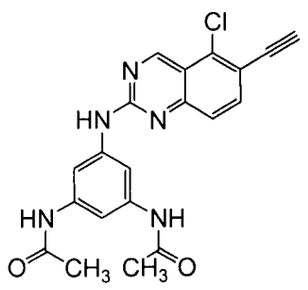
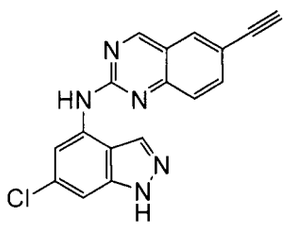
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
114		4-(5-cloro-6-etinil-8-metoxi-quinazolin-2-il-amino)-N-isopropil-benzamida	395.2 3.01	++++	14, 2
115		5-cloro-8-metoxi-N-(4-morfolino-fenil)-6-(tiazol-2-il)-quinazolin-2-amina	454.1 2.59	++++	14, 12
116		6-bromo-5-cloro-8-metoxi-N-(4-morfolino-fenil)-quinazolin-2-amina	451.0 2.68	++++	14

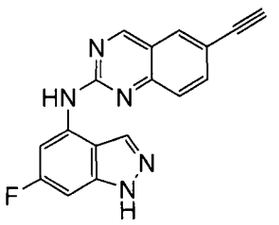
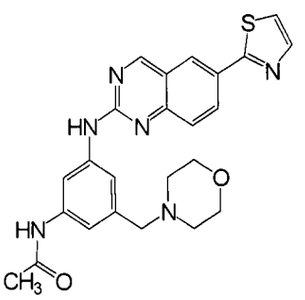
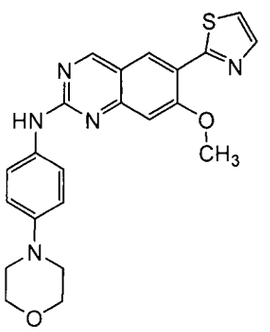
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
117		(4-(5-cloro-8-metoxi-6-(tiazol-2-il)-quinazolin-2-il-amino)-fenil)-(morfolino)-metanona	482.1 2.80	++++	14, 12
118		(4-(6-bromo-5-cloro-8-metoxi-quinazolin-2-il-amino)-fenil)-(morfolino)-metanona	479.0 2.93	++++	14
119		4-(5-cloro-8-metoxi-6-(tiazol-2-il)-quinazolin-2-il-amino)-N-isopropil-benzamida	454.1 3.04	++++	14, 12

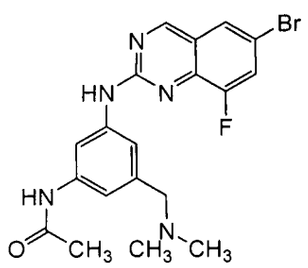
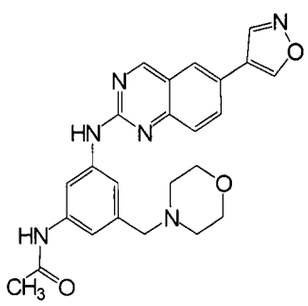
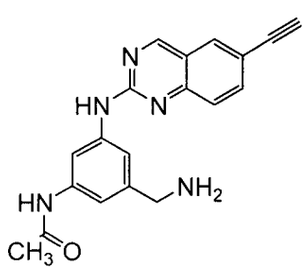
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
120		(2-cloro-4-(6-etinil-7-metoxi-quinazolin-2-il-amino)-fenil)-(morfolino)-metanona	423 3.40	++++	1, 2
121		5-cloro-6-etinil-N-(3-morfolino-fenil)-quinazolin-2-amina	365.1 2.90	++++	22
122		N-(3-((dimetil-amino)-metil)-5-(7-metoxi-6-(tiazol-2-il)-quinazolin-2-il-amino)-fenil)-acetamida	449 2.27	++++	1, 12

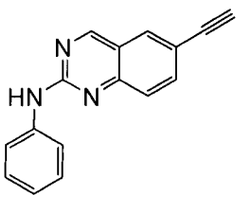
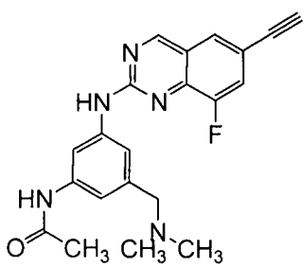
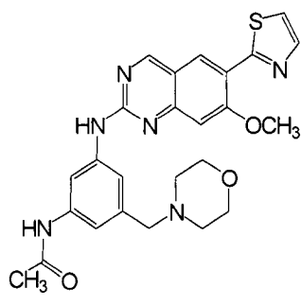
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
123		5-(6-bromo-quinazolin-2-il-amino)-2-morfolino-benzamida	428/430 2.37	+++	9, 10
124		5-(6-etinil-quinazolin-2-il-amino)-2-morfolino-benzamida	374 2.20	++++	9, 10
125		N-(3-(6-etinil-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida	402.2 2.07	++++	9, 10

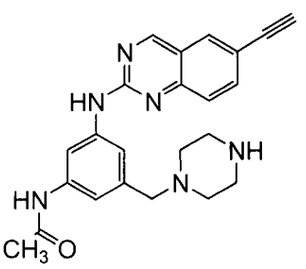
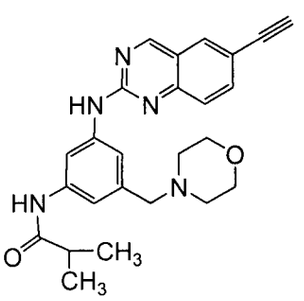
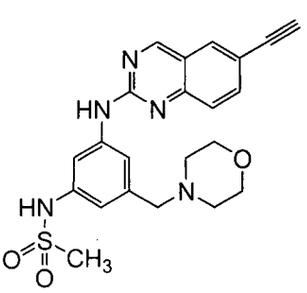
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
126		N-(3-(pirrolidin-1-il-metil)-5-(6-(tiazol-2-il)-quinazolin-2-il-amino)-fenil)-acetamida	445.2 2.32	++++	21
127		N-(3-(6-etinil-quinazolin-2-il-amino)-5-(pirrolidin-1-il-metil)-fenil)-acetamida	386.2 2.34	++++	9, 10
128		N-(3-(6-bromo-8-cloro-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida	490/492 2.34	++++	6

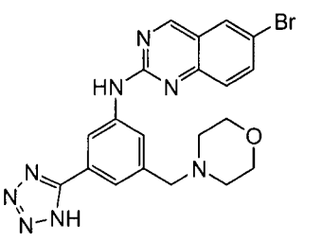
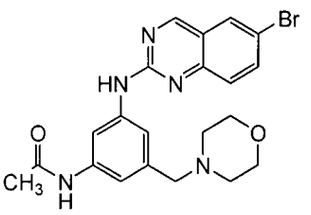
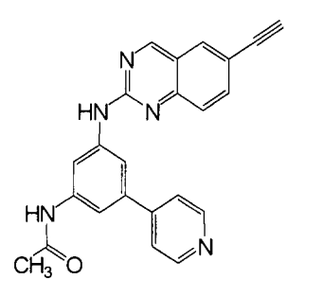
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
129		N-(3-(8-cloro-6-etinil-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida	436 2.24	++++	6, 7
130		N,N'-(5-(5-cloro-6-etinil-quinazolin-2-il-amino)-1,3-fenileno)-diacetamida	394.1 2.47	++++	22
131		N-(6-cloro-1H-indazol-4-il)-6-etinil-quinazolin-2-amina	320.1 3.06	+	9, 10

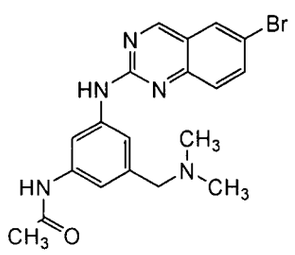
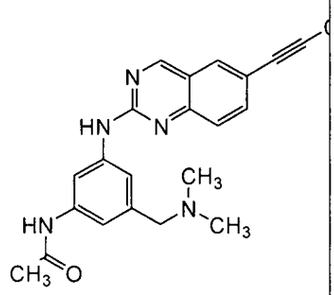
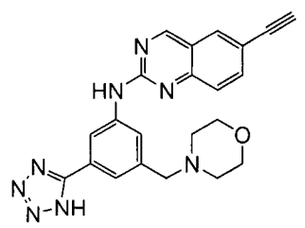
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
132		6-etinil-N-(6-fluoro-1H-indazol-4-il)-quinazolin-2-amina	304.1 2.69	+	9, 10
133		N-(3-(morfolino-metil)-5-(6-(tiazol-2-il)-quinazolin-2-il-amino)-fenil)-acetamida	461.2 2.05	++++	12
134		7-metoxi-N-(4-morfolino-fenil)-6-(tiazol-2-il)-quinazolin-2-amina	420.2 2.67	+	47, 12

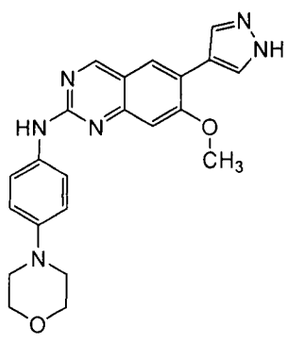
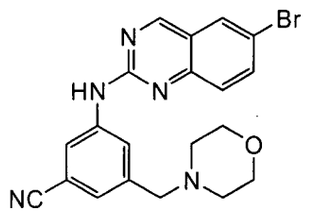
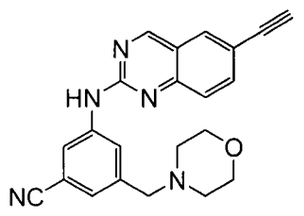
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
135		N-(3-(6-bromo-8-fluoro-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-acetamida	432/434 2.50	++++	135
136		N-(3-(6-(isoxazol-4-il)-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida	445.2 1.84	++++	30
137		N-(3-(amino-metil)-5-(6-etinil-quinazolin-2-il-amino)-fenil)-	332.1 1.96	++++	9, 10

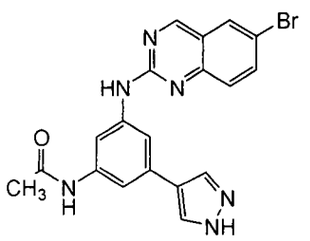
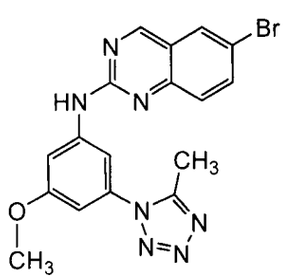
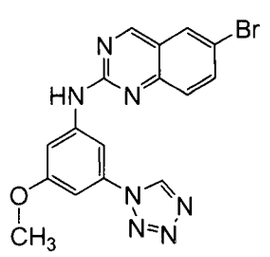
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
		acetamida			
138		6-etinil-N-fenil-quinazolin-2-amina	246.1 2.98	++++	9, 10
139		N-(3-((dimetil-amino)-metil)-5-(6-etinil-8-fluoro-quinazolin-2-il-amino)-fenil)-acetamida	378 2.38	++++	139
140		N-(3-(7-metoxi-6-(tiazol-2-il)-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida	491.2 2.23	++++	47, 12

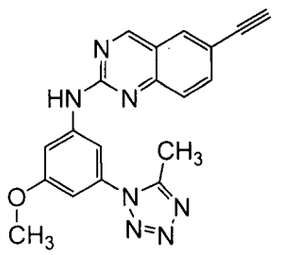
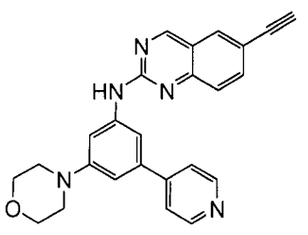
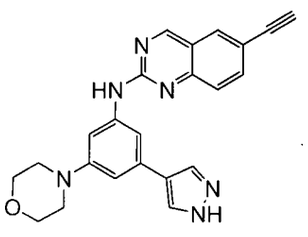
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
141		N-(3-(6-etinil-quinazolin-2-il-amino)-5-(piperazin-1-il-metil)-fenil)-acetamida	401.2 1.90	++++	9, 10
142		N-(3-(6-etinil-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-isobutiramida	430.2 2.7	++++	9, 10
143		N-(3-(6-etinil-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-metan-sulfonamida	438.1 2.4	++++	9, 10

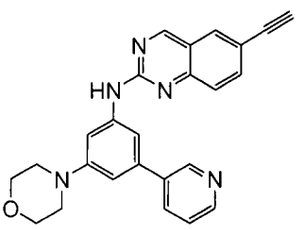
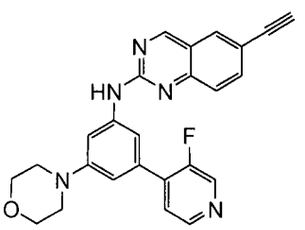
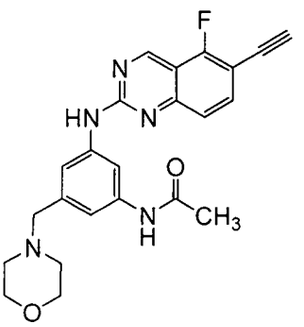
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
144		6-bromo-N-(3-(morfolino-metil)-5-(1H-tetrazol-5-il)-fenil)-quinazolin-2-amina	467/469 2.18	++++	9
145		N-(3-(6-bromo-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida	456/458 2.14	++++	9
146		N-(3-(6-etinil-quinazolin-2-il-amino)-5-(piridin-4-il)-fenil)-acetamida	380.1 2.10	++++	31, 32, 34

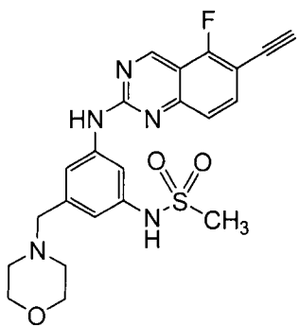
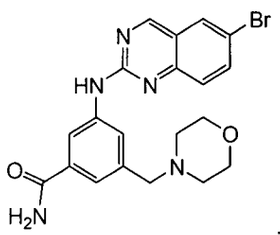
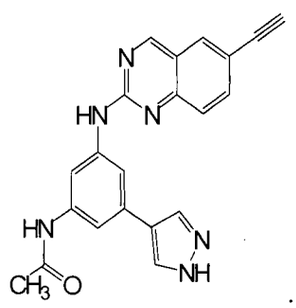
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
147		N-(3-(6-bromo-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-acetamida	414/416 2.11	++++	9
148		N-(3-((dimetil-amino)-metil)-5-(6-(prop-1-inil)-quinazolin-2-il-amino)-fenil)-acetamida	374.2 2.13	++++	9, 10
149		6-etinil-N-(3-(morfolino-metil)-5-(1H-tetrazol-5-il)-fenil)-quinazolin-2-amina	413 2.07	++++	9, 10

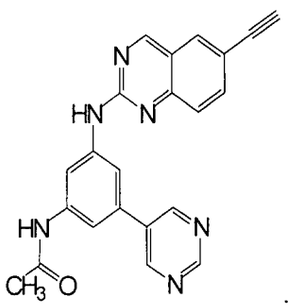
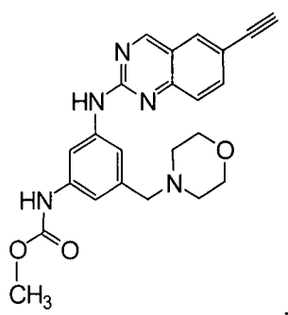
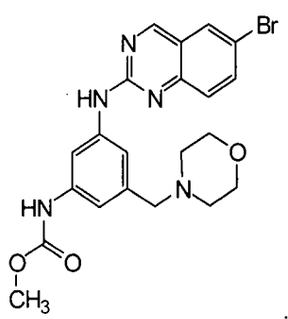
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
150		7-metoxi-N-(4-morfolino-fenil)-6-(1H-pirazol-4-il)-quinazolin-2-amina	403.1 2.09	++++	47, 21
151		3-(6-bromo-quinazolin-2-il-amino)-5-(morfolino-metil)-benzonitrilo	424/426 2.37	++++	9
152		3-(6-etinil-quinazolin-2-il-amino)-5-(morfolino-metil)-benzonitrilo	370 2.27	++++	9, 10

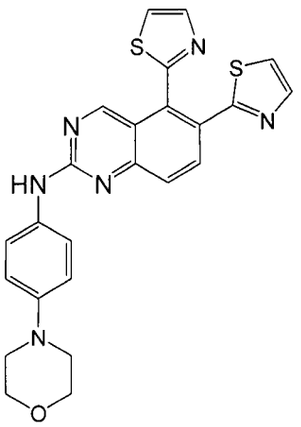
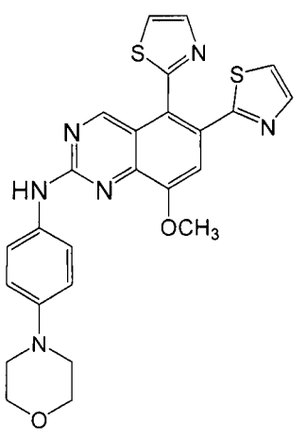
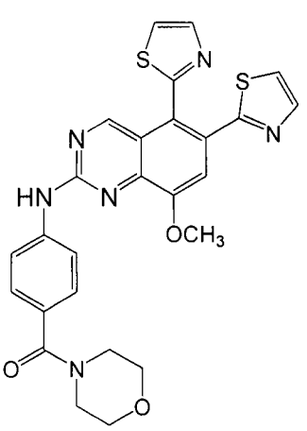
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
153		N-(3-(6-bromo-quinazolin-2-il-amino)-5-(1H-pirazol-4-il)-fenil)-acetamida	423.0/4 25.0 2.32	++++	31, 32
154		6-bromo-N-(3-metoxi-5-(5-metil-1H-tetrazol-1-il)-fenil)-quinazolin-2-amina	412.1/4 14.1 3.08	+	9
155		6-bromo-N-(3-metoxi-5-(1H-tetrazol-1-il)-fenil)-quinazolin-2-amina	398.0/4 00.1 3.10	+	9

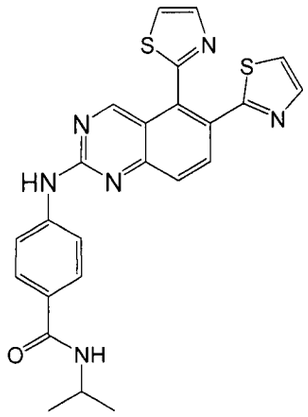
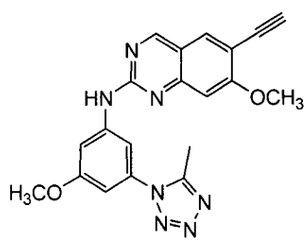
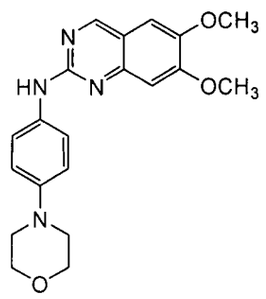
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
156		6-etinil-N-(3-metoxi-5-(5-metil-1H-tetrazol-1-il)-fenil)-quinazolin-2-amina	358.1 2.86	++++	9, 10
157		6-etinil-N-(3-morfolino-5-(piridin-4-il)-fenil)-quinazolin-2-amina	408.2 2.77	++++	9, 10
158		6-etinil-N-(3-morfolino-5-(1H-pirazol-4-il)-fenil)-quinazolin-2-amina	397.2 2.86	++++	9, 10

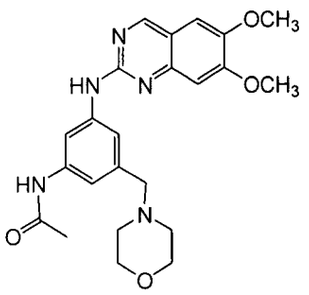
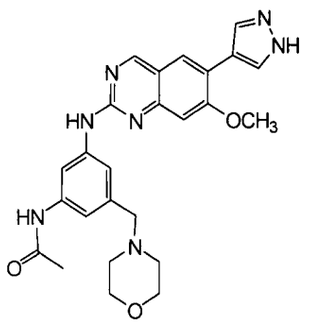
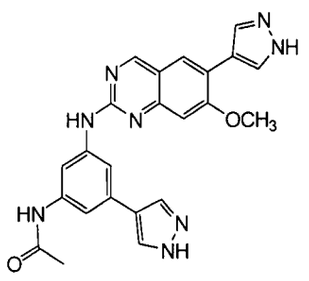
Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
159		6-etinil-N-(3-morfolino-5-(piridin-3-il)-fenil)-quinazolin-2-amina	408.2 2.72	++++	9, 10
160		6-etinil-N-(3-(3-fluoro-piridin-4-il)-5-morfolino-fenil)-quinazolin-2-amina	426.2 3.46	++++	9, 10
161		N-(3-(6-etinil-5-fluoro-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida	420.1 2.39	++++	23, 24

Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
162		N-(3-(6-etinil-5-fluoro-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-metan-sulfonamida	456.1 2.4	++++	23, 24
163		3-(6-bromo-quinazolin-2-il-amino)-5-(morfolino-metil)-benzamida	442/444	+	9
164		N-(3-(6-etinil-quinazolin-2-il-amino)-5-(1H-pirazol-4-il)-fenil)-acetamida	369.1 2.19	+	31, 32, 34

Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
165		N-(3-(6-etinil-quinazolin-2-il-amino)-5-(pirimidin-5-il)-fenil)-acetamida	381.1 2.34	+	31, 32, 34
166		3-(6-etinil-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil-carbamato de metilo	418.2 2.20	+	9, 10
167		3-(6-bromo-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil-carbamato de metilo	472.0/474.0 2.27	+	9

Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
168		N-(4-morfolino-fenil)-5,6-di-(tiazol-2-il)-quinazolin-2-amina	473.0 2.31	+	28
169		8-metoxi-N-(4-morfolino-fenil)-5,6-di-(tiazol-2-il)-quinazolin-2-amina	503.0 2.28	++++	14, 12
170		(4-(8-metoxi-5,6-di-(tiazol-2-il)-quinazolin-2-il-amino)-fenil)-(morfolino)-metanona	531.1 249	+++	14, 12

Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
171		4-(5,6-di-(tiazol-2-il)-quinazolin-2-il-amino)-N-isopropil-benzamida	473.1 2.73	+	14, 12
172		6-etinil-7-metoxi-N-(3-metoxi-5-(5-metil-1H-tetrazol-1-il)-fenil)-quinazolin-2-amina		+++	
173		6,7-dimetoxi-N-(4-morfolino-fenil)-quinazolin-2-amina		+	

Ej. #	Estructura	Nombre	MS (M+1) m/z Rt (min)	Acti-vidad	Ej.de Prep. #
174		N-(3-(6,7-dimetoxi-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida		++++	
175		N-(3-(7-metoxi-6-(1H-pirazol-4-il)-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida		++++	
176		N-(3-(7-metoxi-6-(1H-pirazol-4-il)-quinazolin-2-il-amino)-5-(1H-pirazol-4-il)-fenil)-acetamida		+	

Los compuestos en la Tabla 1 se nombraron utilizando el programa de nombramiento de estructuras en ChemDraw 9.0.1, que implementa la nomenclatura estandarizada de IUPAC.

En la Tabla 2 (Figura 1) y en la Tabla 3 (Figura 2) se enlistan compuestos adicionales de la invención.

Se pretende que los compuestos de la invención sean estables. Como se utiliza en la presente, "estable" se refiere a un compuesto es suficientemente robusto para sobrevivir al aislamiento hasta un grado de pureza útil a partir de una mezcla de reacción, y de preferencia capaz de formularse en un agente terapéutico eficaz. Además se pretende que los compuestos de la invención sean aquéllos que puedan ser preparados por un experto en la técnica de acuerdo con los métodos descritos en la presente, y cualquier otro método adecuado, rutina, o de otra manera.

Además se proporcionan compuestos de la invención y mezclas de los mismos en donde cualesquiera átomos de carbono asimétricos presentes pueden tener cualquiera de la configuración R o S. Los sustituyentes en un doble enlace o en un anillo de los compuestos de la fórmula I puede estar presente en cualquiera de las configuraciones *cis* (-Z-) o *trans* (-E-). Los compuestos, por lo tanto, pueden estar presentes como mezclas de isómeros, diaestereómeros, y enantiómeros, o pueden estar presentes como los isómeros puros. En algunas modalidades, los compuestos son enantioméricamente puros, en donde solamente está presente un

enantiómero. En otras modalidades, el compuesto puede estar presente como una mezcla de enantiómeros que incluya más de un enantiómero que como lo hace en la otra, o una mezcla racémica. En donde se indica la estereoquímica absoluta en los ejemplos específicos, se cree que el compuesto aislado corresponde sustancialmente a la estereoquímica absoluta indicada, pero con frecuencia contendrá cuando menos algo de la estereoquímica opuesta.

Además se pretende que los compuestos de la invención incluyan diferentes formas sólidas, tales como las formas cristalinas, microcristalinas, nanocristalinas, y amorfas, así como las formas hidratadas, solvatadas, anhidras, y no solvatadas.

Los compuestos de la invención también pueden incluir diferentes isótopos atómicos. Los isótopos incluyen los átomos que tienen el mismo número atómico pero diferentes números de masa. Por ejemplo, los isótopos de hidrógeno incluyen tritio y deuterio. Los ejemplos de los isótopos que se pueden incorporar en los compuestos de la invención incluyen los isótopos de hidrógeno, carbono, nitrógeno, oxígeno, fósforo, azufre, flúor y cloro, tales como ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F y ^{36}Cl, respectivamente. Los compuestos de la presente invención, los tautómeros de los mismos, los pro-fármacos de los mismos, y las sales farmacéuticamente aceptables de los compuestos y de los pro-fármacos que contengan los isótopos anteriormente mencionados y/u otros isótopos de otros átomos, están dentro del alcance de esta

invención. Ciertos compuestos isotópicamente marcados de la presente invención, por ejemplo aquéllos en donde se incorporan los isótopos radioactivos, tales como ^{3}H y ^{14}C, son útiles en los ensayos de distribución de fármaco y/o tejido de sustrato. Los isótopos tritiados, es decir, ^{3}H, y de carbono-14, es decir, ^{14}C, se prefieren en particular por su facilidad de preparación y detectabilidad. Además, la sustitución con isótopos más pesados, tales como deuterio, es decir, ^{2}H, puede proporcionar ciertas ventajas terapéuticas resultantes de la mayor estabilidad metabólica, por ejemplo un aumento de la vida media *in vivo* o requerimientos de dosificación reducida y, por consiguiente, se pueden preferir en algunas circunstancias. Los compuestos isotópicamente marcados de esta invención y los pro-fármacos de los mismos se pueden preparar en términos generales llevando a cabo los procedimientos conocidos o referenciados, y mediante la utilización de un reactivo isotópicamente marcado fácilmente disponible para sustituir a un reactivo no isotópicamente marcado.

En algunas modalidades, los compuestos de la invención, y sus sales, ésteres, tautómeros, etc., se aíslan. "Aislado" o "sustancialmente aislado" significa que el compuesto se separa cuando menos parcialmente o sustancialmente del medio ambiente en donde se formó o se descubrió. La separación parcial puede incluir, por ejemplo, una composición enriquecida en el compuesto de la invención. La separación sustancial puede incluir las composiciones que contienen cuando menos aproximadamente el 50

por ciento, cuando menos aproximadamente el 60 por ciento, cuando menos aproximadamente el 70 por ciento, cuando menos aproximadamente el 80 por ciento, cuando menos aproximadamente el 90 por ciento, cuando menos aproximadamente el 95 por ciento, y cuando menos aproximadamente el 99 por ciento en peso del compuesto de la invención, o de una sal del mismo. Métodos para aislar los compuestos y sus sales y otros derivados, son rutinarios en este campo.

La presente invención proporciona además pro-fármacos de los compuestos descritos en la presente. Como se utilizan en la presente, los "pro-fármacos" se refieren a cualesquiera vehículos covalentemente enlazados que liberan el fármaco progenitor activo cuando se administran a un sujeto mamífero. Los pro-fármacos se pueden preparar mediante la modificación de los grupos funcionales presentes en los compuestos, de tal manera que las modificaciones se disocian, ya sea en la manipulación de rutina, o bien *in vivo*, hasta los compuestos progenitores. Los pro-fármacos incluyen los compuestos en donde los grupos hidroxilo, amino, sulfhidrilo, o carboxilo se enlazan a cualquier grupo que, cuando se administra a un sujeto mamífero, se disocia para formar un grupo hidroxilo, amino, sulfhidrilo, o carboxilo libre, respectivamente. Los ejemplos de los pro-fármacos incluyen, pero no se limitan a, derivados de acetato, formato y benzoato de los grupos funcionales de alcohol y amina en los compuestos de la invención. La preparación y el uso de los pro-fármacos se discute en T. Higuchi y V. Stella, "Pro-drugs as

Novel Delivery Systems," Volumen 14 de la A.C.S. Symposium Series, y en *Bioreversible Vehicles in Drug Design*, Editor Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, ambos de los cuales se incorporan a la presente como referencia en su totalidad.

De acuerdo con las modalidades adicionales de la presente invención, se proporcionan composiciones terapéuticas. Estas composiciones incluyen una cantidad terapéuticamente efectiva de un compuesto de la invención (es decir, un compuesto de la fórmula I), y cuando menos un vehículo farmacéuticamente aceptable.

Las composiciones farmacéuticas que incluyen los compuestos descritos en la presente pueden incluir aditivos tales como vehículos o excipientes farmacéuticamente aceptables. Los vehículos farmacéuticamente aceptables adecuados incluyen agentes de procesamiento y modificadores y potenciadores del suministro de fármacos, tales como, por ejemplo, fosfato de calcio, estearato de magnesio, talco, monosacáridos, disacáridos, almidón, gelatina, celulosa, metil-celulosa, carboxi-metil-celulosa de sodio, dextrosa, hidroxi-propil-ß-ciclodextrina, polivinil-pirrolidinona, ceras de bajo punto de fusión, resinas de intercambio de iones, y similares, así como combinaciones de cualesquiera dos o más de los mismos. Otros vehículos farmacéuticamente aceptables adecuados se describen en Remington: The Science And Practice Of Pharmacy, Lippincott Williams & Wilkins; Baltimore, MD, 21ª Edición (28 de Mayo, 2005), el cual se incorpora a la presente como referencia en

su totalidad y para todos los propósitos como si se estipulara completamente en la presente.

Las composiciones farmacéuticas que incluyen los compuestos de la invención pueden estar en cualquier forma adecuada para el método de administración pretendido, incluyendo, por ejemplo, como una solución, una suspensión, o una emulsión. Típicamente se utilizan vehículos líquidos en la preparación de soluciones, suspensiones, y emulsiones. Los vehículos líquidos contemplados para utilizarse en la práctica de la presente invención incluyen, por ejemplo, agua, suero, solventes orgánicos farmacéuticamente aceptables, aceites o grasas farmacéuticamente aceptables, y similares, así como las mezclas de dos o más de los mismos. Los vehículos líquidos pueden incluir otros aditivos farmacéuticamente aceptables adecuados, tales como solubilizantes, emulsionantes, nutrientes, reguladores del pH, conservadores, agentes de suspensión, agentes espesantes, reguladores de viscosidad, estabilizantes, y similares. Los solventes orgánicos adecuados incluyen, por ejemplo, alcoholes monohídricos, tales como etanol, y alcoholes polihídricos, tales como glicoles. Los aceites adecuados incluyen, pero no se limitan a, aceite de semilla de soya, aceite de coco, aceite de oliva, aceite de azafrán, aceite de semilla de algodón, y similares. Para su administración parenteral, el vehículo puede ser un éster oleoso, tal como oleato de etilo, miristato de isopropilo, y similares. Las composiciones de la presente invención también pueden estar en la forma de micropartículas, microcápsulas,

y similares, así como combinaciones de cualesquiera dos o más de los mismos.

Los compuestos y combinaciones de la presente invención también se pueden administrar en la forma de liposomas. Como se conoce en la técnica, los liposomas se derivan generalmente a partir de fosfolípidos u otras sustancias de lípido. Los liposomas se forman mediante cristales líquidos hidratados mono- o multi-lamelares que se dispersan en un medio acuoso. Se puede utilizar cualquier lípido no tóxico, fisiológicamente aceptable y metabolizable capaz de formar liposomas. Las presentes composiciones en forma de liposomas pueden incluir, en adición a un compuesto de la presente invención, estabilizantes, conservadores, excipientes, y similares. Los lípidos preferidos incluyen fosfolípidos y fosfatidil-colinas (lecitinas), tanto naturales como sintéticos. Los métodos para la formación de liposomas son conocidos en la materia. Véase, por ejemplo, Prescott, Editor, *Methods in Cell Biology*, Volumen XIV, Academic Press, Nueva York, N.Y., páginas 33 y siguientes (1976).

También se pueden utilizar sistemas de suministro de liberación controlada, tales como un sistema de matriz controlada por difusión, o un sistema erosionable, como se describe, por ejemplo, en: Lee, "Diffusion-Controlled Matrix Systems", páginas 155-198, y Ron y Langer, "Erodible Systems", páginas 199-224, en "Treatise on Controlled Drug Delivery", A. Kydonieus Editor, Marcel Dekker, Inc., Nueva York 1992. La matriz puede ser, por ejemplo, un material biodegradable que pueda degradarse de una manera

espontánea *in situ* e *in vivo*, por ejemplo, mediante hidrólisis o disociación enzimática, por ejemplo, mediante las proteasas. El sistema de suministro puede ser, por ejemplo, un polímero o copolímero que se presente naturalmente o sintético, por ejemplo en la forma de un hidrogel. Los polímeros de ejemplo con enlaces disociables incluyen poliésteres, poli-orto-ésteres, polianhídridos, polisacáridos, poli-(fosfoésteres), poliamidas, poliuretanos, poli-(imido-carbonatos), y poli-(fosfazenos).

Los compuestos de la invención se pueden administrar enteralmente, oralmente, parenteralmente, sublingualmente, mediante aspersión para inhalación, rectalmente, o tópicamente, en formulaciones unitarias de dosificación que incluyan vehículos no tóxicos farmacéuticamente aceptables convencionales, adyuvantes, y vehículos, según se desee. Por ejemplo, los modos de administración adecuados incluyen administración oral, subcutánea, transdérmica, transmucosal, iontoforética, intravenosa, intramuscular, intraperitoneal, intranasal, subdérmica, rectal, y similares. La administración tópica también puede incluir el uso de administración transdérmica, tal como parches transdérmicos o dispositivos de ionoforesis. El término "parenteral", como se utiliza en la presente, incluye inyección subcutánea, intravenosa, intramuscular, inyección intraesternal, o técnicas de infusión.

Las preparaciones inyectables, por ejemplo, las suspensiones acuosas u oleaginosas inyectables estériles, se pueden formular de acuerdo con la técnica conocida, utilizando agentes dispersantes o

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humectantes adecuados, y agentes de suspensión. La preparación inyectable estéril también puede ser una solución o suspensión inyectable estéril en un diluyente o solvente no tóxico parenteralmente aceptable, por ejemplo, como una solución en 1,3-propanodiol. Entre los vehículos y solventes aceptables que se pueden emplear están agua, solución de Ringer, y solución isotónica de cloruro de sodio. En adición, convencionalmente se emplean aceites fijos estériles como un solvente o como un medio de suspensión. Para este propósito, se puede emplear cualquier aceite fijo blando, incluyendo los mono- o di-glicéridos sintéticos. En adición, los ácidos grasos, tales como el ácido oleico, encuentran uso en la preparación de los inyectables.

Los supositorios para la administración rectal del fármaco se pueden preparar mediante la mezcla del fármaco con un excipiente no irritante adecuado, tal como manteca de cacao y polietilenglicoles, que son sólidos a las temperaturas ordinarias, pero líquidos a la temperatura rectal, y que, por consiguiente, se funden en el recto y liberan el fármaco.

Las formas de dosificación sólidas para su administración oral pueden incluir cápsulas, tabletas, píldoras, polvos, y gránulos. En estas formas de dosificación sólidas, el compuesto activo se puede mezclar con cuando menos un diluyente inerte, tal como sacarosa, lactosa, o almidón. Estas formas de dosificación también pueden incluir, como es la práctica normal, sustancias adicionales diferentes de los diluyentes inertes, por ejemplo, agentes lubricantes, tales

como estearato de magnesio. En el caso de las cápsulas, tabletas, y píldoras, las formas de dosificación también pueden incluir agentes reguladores. Las tabletas y píldoras se pueden preparar adicionalmente con recubrimientos entéricos.

Las formas de dosificación líquidas para su administración oral pueden incluir emulsiones, soluciones, suspensiones, jarabes, y elíxires farmacéuticamente aceptables, conteniendo diluyentes inertes comúnmente utilizados en la materia, tales como agua. Estas composiciones también pueden comprender adyuvantes, tales como agentes humectantes, agentes emulsionantes y de suspensión, ciclodextrinas, y agentes edulcorantes, saborizantes, y perfumantes.

La cantidad de ingrediente activo que se puede combinar con los materiales portadores para producir una sola forma de dosificación variará dependiendo del huésped tratado y del modo particular de administración. Se entenderá, sin embargo, que el nivel de dosis específico para cualquier paciente particular dependerá de una variedad de factores, incluyendo la actividad del compuesto específico empleado, la edad, el peso corporal, la salud general, el sexo, la dieta, el tiempo de administración, la vía de administración, la velocidad de excreción, la combinación de fármacos, y la gravedad de la enfermedad particular que se esté sometiendo a terapia. La cantidad terapéuticamente efectiva para una situación dada se puede determinar fácilmente mediante experimentación de rutina, y está dentro de la experiencia y juicio del clínico ordinario.

En algunas modalidades, los compuestos de la invención se

pueden administrar a un paciente en combinación con uno o más agentes farmacéuticos adicionales. La administración de los diferentes agentes se puede hacer por separado, ya sea en secuencia o de una manera simultánea, o los agentes se pueden administrar juntos en una sola composición. Los agentes farmacéuticos adicionales de ejemplo incluyen fármacos contra el cáncer, incluyendo productos quimioterapéuticos y otros compuestos inhibidores de cinasa.

"Arilo" se refiere a un grupo carbocíclico aromático monovalente de 6 a 14 átomos de carbono, que tiene un solo anillo o múltiples anillos condensados. Los ejemplos no limitantes de los grupos arilo incluyen fenilo, naftilo, antrilo, y similares.

"Arilo sustituido" se refiere a los grupos arilo que están sustituidos con 1 a 5, o con 1 a 3, o con 1 a 2 sustituyentes seleccionados a partir del grupo que consiste en alquilo, alquenilo, alquinilo, alcoxilo, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino sustituido, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, hetero-cicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo sustituido, sulfoniloxilo, sulfonil-amino, tioacilo, tiol,

y tioalquilo;

en donde las fracciones de alquilo, alquenilo, alquinilo, arilo, cicloalquilo, cicloalquenilo, heterociclilo, y heteroarilo contenidas dentro de cualquiera de los grupos "arilo sustituido" precedentes están opcionalmente sustituidas por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en alquenilo, alquinilo, alcoxilo, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino sustituido, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, hetero-cicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, tioalquilo, y tioalquilo; y en donde estos sustituyentes se definen en la presente.

"Ariloxilo" se refiere al grupo –O-arilo, en donde arilo es como se define en la presente, que incluye, a manera de ejemplo, fenoxilo y naftoxilo.

"Ariloxilo sustituido" se refiere al grupo –O-(arilo sustituido), en donde arilo sustituido es como se define en la presente.

"Tioarilo" se refiere al grupo –S-arilo, en donde arilo es como se define en la presente.

"Tioarilo sustituido" se refiere al grupo –S-(arilo sustituido), en donde arilo sustituido es como se define en la presente.

"Alquilo" se refiere a los grupos hidrocarbilo alifáticos saturados monovalentes que tienen de 1 a 10 átomos de carbono, o de 1 a 6 átomos de carbono. Este término incluye, a manera de ejemplo, los grupos hidrocarbilo lineales y Ramificados, tales como metilo (CH_3-), etilo (CH_3CH_2-), propilo normal ($CH_3CH_2CH_2$-), isopropilo ($(CH_3)_2CH$-), butilo normal ($CH_3CH_2CH_2CH_2$-), isobutilo ($(CH_3)_2CHCH_2$-), butilo secundario ((CH_3)-$(CH_3CH_2)CH$-), butilo terciario ($(CH_3)_3C$-), pentilo normal ($CH_3CH_2CH_2CH_2CH_2$-), y neopentilo ($(CH_3)_3CCH_2$-).

"Alquilo sustituido" se refiere a un grupo alquilo que tiene de 1 a 5, o de 1 a 3, o de 1 a 2 sustituyentes seleccionados a partir del grupo que consiste en alcoxilo, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino sustituido, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, hetero-cicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo sustituido, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, y tioalquilo;

en donde las fracciones de alquilo, arilo, cicloalquilo,

cicloalquenilo, heterociclilo, y heteroarilo contenidas dentro de cualquiera de los grupos "alquilo sustituido" precedentes, están opcionalmente sustituidas por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en alquenilo, alquinilo, alcoxilo, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino sustituido, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, hetero-cicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, tioalquilo, y tioalquilo; y en donde estos sustituyentes se definen en la presente.

"Alcoxilo" se refiere al grupo –O-alquilo, en donde alquilo se define en la presente. Alcoxilo incluye, a manera de ejemplo, metoxilo, etoxilo, n-propoxilo, isopropoxilo, n-butoxilo, terbutoxilo, *sec*-butoxilo, y *n*-pentoxilo.

"Alcoxilo sustituido" se refiere al grupo –O-(alquilo sustituido), en donde alquilo sustituido se define en la presente.

"Acilo" se refiere a los grupos H-C(O)-, alquilo-C(O)-, alquilo sustituido-C(O)-, alquenilo-C(O)-, alquenilo sustituido-C(O)-, alquinilo-C(O)-, alquinilo sustituido-C(O)-, cicloalquilo-C(O)-,

cicloalquilo sustituido-C(O)-, cicloalquenilo-C(O)-, cicloalquenilo sustituido-C(O)-, arilo-C(O)-, arilo sustituido-C(O)-, heteroarilo-C(O)-, heteroarilo sustituido-C(O)-, heterocíclico-C(O)-, y heterocíclico sustituido-C(O)-, en donde alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocíclico y heterocíclico sustituido son como se definen en la presente. Acilo incluye el grupo "acetilo" $CH_3C(O)$-.

"Acil-amino" se refiere a los grupos –NRC(O)-alquilo, -NRC(O)-alquilo sustituido, -NRC(O)-cicloalquilo, -NRC(O)-cicloalquilo sustituido, -NRC(O)-cicloalquenilo, -NRC(O)-cicloalquenilo sustituido, -NRC(O)-alquenilo, -NRC(O)-alquenilo sustituido, -NRC(O)-alquinilo, -NRC(O)-alquinilo sustituido, -NRC(O)-arilo, -NRC(O)-arilo sustituido, -NRC(O)-heteroarilo, -NRC(O)-heteroarilo sustituido, -NRC(O)-heterocíclico, y -NRC(O)-heterocíclico sustituido, en donde R es hidrógeno o alquilo, y en donde alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocíclico y heterocíclico sustituido son como se definen en la presente.

"Aciloxilo" se refiere a los grupos alquilo-C(O)O-, alquilo sustituido-C(O)O-, alquenilo-C(O)O-, alquenilo sustituido-C(O)O-, alquinilo-C(O)O-, alquinilo sustituido-C(O)O-, arilo-C(O)O-, arilo sustituido-C(O)O-, cicloalquilo-C(O)O-, cicloalquilo sustituido-

C(O)O-, cicloalquenilo-C(O)O-, cicloalquenilo sustituido-C(O)O-, heteroarilo-C(O)O-, heteroarilo sustituido-C(O)O-, heterocíclico-C(O)O-, y heterocíclico sustituido-C(O)O-, en donde alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocíclico, y heterocíclico sustituido son como se definen en la presente.

"Amino" se refiere al grupo $-NH_2$.

"Amino sustituido" se refiere al grupo –NR'R", en donde R' y R" se seleccionan independientemente a partir del grupo que consiste en hidrógeno, alquilo, alquenilo, alquinilo, arilo, cicloalquilo, cicloalquenilo, heteroarilo, heterocíclico, $-SO_2$-alquilo, $-SO_2$-alquenilo, $-SO_2$-cicloalquilo, $-SO_2$-cicloalquenilo, $-SO_2$-arilo, $-SO_2$-heteroarilo, y $-SO_2$-heterocíclico, en donde R′ y R″ se unen opcionalmente, junto con el nitrógeno enlazado a los mismos, para formar un grupo heterocíclico o heterocíclico sustituido, en el entendido de que R′ y R″ no son ambos hidrógeno;

en donde las fracciones de alquilo, alquenilo, alquinilo, arilo, cicloalquilo, cicloalquenilo, heterociclilo, y heteroarilo contenidas dentro de cualquiera de los grupos "amino sustituido" precedentes están opcionalmente sustituidos por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en alquenilo, alquinilo, alcoxilo, acilo, acil-amino, aciloxilo, amino, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-

tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino sustituido, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, hetero-cicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, y tioalquilo;

y en donde estos sustituyentes se definen en la presente.

Cuando R′ es hidrógeno y R″ es alquilo, el grupo amino sustituido es algunas veces referido en la presente como alquil-amino. Cuando R′ y R″ son alquilo, el grupo amino sustituido es algunas veces referido en la presente como dialquil-amino. Cuando se hace referencia a un mono-amino sustituido, esto significa que cualquiera de R′ o R″ es hidrógeno pero no ambos. Cuando se hace referencia a un diamino sustituido, esto significa que cualquiera de R′ no R″ son hidrógeno.

"Amino-carbonilo" se refiere al grupo $-C(O)N\ R^{10}R^{11}$ en donde R^{10} y R^{11} se seleccionan independientemente a partir del grupo que consiste en hidrógeno, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, arilo, arilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, heteroarilo, heteroarilo sustituido, heterocíclico, y heterocíclico sustituido, y en donde R^{10} y R^{11} se unen opcionalmente, junto con el nitrógeno enlazado a los mismos, para formar un grupo

heterocíclico o heterocíclico sustituido, y en donde alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocíclico y heterocíclico sustituido son como se definen en la presente.

"Amino-tiocarbonilo" se refiere al grupo $-C(S)NR^{10}R^{11}$ en donde R^{10} y R^{11} se seleccionan independientemente a partir del grupo que consiste en hidrógeno, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, arilo, arilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, heteroarilo, heteroarilo sustituido, heterocíclico, y heterocíclico sustituido, y en donde R^{10} y R^{11} se unen opcionalmente, junto con el nitrógeno enlazado a los mismos, para formar un grupo heterocíclico o heterocíclico sustituido, y en donde alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocíclico y heterocíclico sustituido son como se definen en la presente.

"Amino-carbonil-amino" se refiere al grupo $-NRC(O)NR^{10}R^{11}$ en donde R es hidrógeno o alquilo, y R^{10} y R^{11} se seleccionan independientemente a partir del grupo que consiste en hidrógeno, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, arilo, arilo sustituido, cicloalquilo, cicloalquilo

sustituido, cicloalquenilo, cicloalquenilo sustituido, heteroarilo, heteroarilo sustituido, heterocíclico, y heterocíclico sustituido, y en donde R^{10} y R^{11} se unen opcionalmente, junto con el nitrógeno enlazado a los mismos, para formar un grupo heterocíclico o heterocíclico sustituido, y en donde alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocíclico y heterocíclico sustituido son como se definen en la presente.

"Amino-tiocarbonil-amino" se refiere al grupo $-NRC(S)NR^{10}R^{11}$ en donde R es hidrógeno o alquilo, y R^{10} y R^{11} se seleccionan independientemente a partir del grupo que consiste en hidrógeno, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, arilo, arilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, heteroarilo, heteroarilo sustituido, heterocíclico, y heterocíclico sustituido, y en donde R^{10} y R^{11} se unen opcionalmente, junto con el nitrógeno enlazado a los mismos, para formar un grupo heterocíclico o heterocíclico sustituido, y en donde alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocíclico y heterocíclico sustituido son como se definen en la presente.

"Amino-carboniloxilo" se refiere al grupo $-O-C(O)NR^{10}R^{11}$ en donde R^{10} y R^{11} se seleccionan independientemente a partir del grupo que consiste en hidrógeno, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, arilo, arilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, heteroarilo, heteroarilo sustituido, heterocíclico, y heterocíclico sustituido, y en donde R^{10} y R^{11} se unen opcionalmente, junto con el nitrógeno enlazado a los mismos, para formar un grupo heterocíclico o heterocíclico sustituido, y en donde alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocíclico y heterocíclico sustituido son como se definen en la presente.

"Amino-sulfonilo" se refiere al grupo $-SO_2NR^{10}R^{11}$ en donde R^{10} y R^{11} se seleccionan independientemente a partir del grupo que consiste en hidrógeno, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, arilo, arilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, heteroarilo, heteroarilo sustituido, heterocíclico, y heterocíclico sustituido, y en donde R^{10} y R^{11} se unen opcionalmente, junto con el nitrógeno enlazado a los mismos, para formar un grupo heterocíclico o heterocíclico sustituido, y en donde alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo,

cicloalquenilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocíclico y heterocíclico sustituido son como se definen en la presente.

"Amino-sulfoniloxilo" se refiere al grupo $-O-SO_2NR^{10}R^{11}$ en donde R^{10} y R^{11} se seleccionan independientemente a partir del grupo que consiste en hidrógeno, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, arilo, arilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, heteroarilo, heteroarilo sustituido, heterocíclico, y heterocíclico sustituido, y en donde R^{10} y R^{11} se unen opcionalmente, junto con el nitrógeno enlazado a los mismos, para formar un grupo heterocíclico o heterocíclico sustituido, y en donde alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocíclico y heterocíclico sustituido son como se definen en la presente.

"Amino-sulfonil-amino" se refiere al grupo $-NR-SO_2NR^{10}R^{11}$ en donde R es hidrógeno o alquilo, y R^{10} y R^{11} se seleccionan independientemente a partir del grupo que consiste en hidrógeno, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, arilo, arilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, heteroarilo, heteroarilo sustituido, heterocíclico, y heterocíclico sustituido, y en donde R^{10} y R^{11} se unen opcionalmente, junto con el nitrógeno

enlazado a los mismos, para formar un grupo heterocíclico o heterocíclico sustituido, y en donde alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocíclico y heterocíclico sustituido son como se definen en la presente.

"Amidino" se refiere al grupo $-C(=NR^{12})R^{10}R^{11}$ en donde R^{10}, R^{11}, y R^{12} se seleccionan independientemente a partir del grupo que consiste en hidrógeno, alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, arilo, arilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, heteroarilo, heteroarilo sustituido, heterocíclico, y heterocíclico sustituido, y en donde R^{10} y R^{11} se unen opcionalmente, junto con el nitrógeno enlazado a los mismos, para formar un grupo heterocíclico o heterocíclico sustituido, y en donde alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocíclico y heterocíclico sustituido son como se definen en la presente.

"Alquenilo" se refiere a los grupos alquenilo que tienen de 2 a 6 átomos de carbono, o de 2 a 4 átomos de carbono, y que tienen cuando menos 1 y, en algunas modalidades, de 1 a 2 sitios de insaturación de alquenilo. Estos grupos son ejemplificados, por

ejemplo, por vinilo, alilo, y but-3-en-1-ilo.

"Alquenilo sustituido" se refiere a los grupos alquenilo que tienen de 1 a 3 sustituyentes, o de 1 a 2 sustituyentes seleccionados a partir del grupo que consiste en alcoxilo, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino sustituido, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, hetero-cicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo sustituido, sulfoniloxilo, tioacilo, tiol, y tioalquilo,

en donde las fracciones de alquilo, arilo, cicloalquilo, cicloalquenilo, heterociclilo, y heteroarilo contenidas dentro de cualquiera de los grupos "alquenilo sustituido" precedentes están opcionalmente sustituidas por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en alquilo, alquenilo, alquinilo, alcoxilo, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo,

tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino sustituido, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, hetero-cicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, y tioalquilo; en donde estos sustituyentes se definen en la presente, y con la condición de que cualquier sustitución de hidroxilo no está unida a un átomo de carbono de vinilo (insaturado).

"Alquinilo" se refiere a los grupos alquinilo que tienen de 2 a 6 átomos de carbono, o de 2 a 3 átomos de carbono, y que tienen cuando menos 1 y, en algunas modalidades, de 1 a 2 sitios de insaturación de alquinilo.

"Alquinilo sustituido" se refiere a los grupos alquinilo que tienen de 1 a 3 sustituyentes, y, en algunas modalidades, de 1 a 2 sustituyentes seleccionados a partir del grupo que consiste en alcoxilo, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino sustituido, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, hetero-cicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo sustituido, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, y tioalquilo,

en donde las fracciones de alquilo, arilo, cicloalquilo,

cicloalquenilo, y heteroarilo contenidas dentro de cualquiera de los grupos "alquinilo sustituido" precedentes, están opcionalmente sustituidas por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en alquilo, alquenilo, alquinilo, alcoxilo, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino sustituido, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, hetero-cicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, y tioalquilo; en donde estos sustituyentes se definen en la presente, y con la condición de que cualquier sustitución de hidroxilo no está unida a un átomo de carbono acetilénico.

"Carbonilo" se refiere al grupo divalente –C(O)–, el cual es equivalente a –C(=O)–.

"Carboxi" o "carboxilo" se refiere a –COOH o sales de los mismos.

"Carboxi-éster" o "carboxil-éster" se refiere a los grupos -C(O)O-alquilo, -C(O)O-alquilo sustituido, -C(O)O-alquenilo, -C(O)O-alquenilo sustituido, -C(O)O-alquinilo, -C(O)O-alquinilo sustituido, -C(O)O-arilo, -C(O)O-arilo sustituido, -C(O)O-cicloalquilo,

-C(O)O-cicloalquilo sustituido, -C(O)O-cicloalquenilo, -C(O)O-cicloalquenilo sustituido, -C(O)O-heteroarilo, -C(O)O-heteroarilo sustituido, -C(O)O-heterocíclico, y -C(O)O-heterocíclico sustituido, en donde alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocíclico, y heterocíclico sustituido son como se definen en la presente.

"(Carboxil-éster)amino" se refiere al grupo -NR-C(O)O-alquilo, -NR-C(O)O-alquilo sustituido, -NR-C(O)O-alquenilo, -NR-C(O)O-alquenilo sustituido, -NR-C(O)O-alquinilo, -NR-C(O)O-alquinilo sustituido, -NR-C(O)O-arilo, -NR-C(O)O-arilo sustituido, -NR-C(O)O-cicloalquilo, -NR-C(O)O-cicloalquilo sustituido, -NR-C(O)O-cicloalquenilo, -NR-C(O)O-cicloalquenilo sustituido, -NR-C(O)O-heteroarilo, -NR-C(O)O-heteroarilo sustituido, -NR-C(O)O-heterocíclico, y -NR-C(O)O-heterocíclico sustituido, en donde R es alquilo o hidrógeno, y en donde alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocíclico, y heterocíclico sustituido, son como se definen en la presente.

"(Carboxil-éster)oxilo" se refiere al grupo -O-C(O)O-alquilo, -O-C(O)O-alquilo sustituido, -O-C(O)O-alquenilo, -O-C(O)O-alquenilo sustituido, -O-C(O)O-alquinilo, -O-C(O)O-alquinilo sustituido, -O-C(O)O-arilo, -O-C(O)O-arilo sustituido, -O-C(O)O-cicloalquilo,

-O-C(O)O-cicloalquilo sustituido, -O-C(O)O-cicloalquenilo, -O-C(O)O-cicloalquenilo sustituido, -O-C(O)O-heteroarilo, -O-C(O)O-heteroarilo sustituido, -O-C(O)O-heterocíclico, y -O-C(O)O-heterocíclico sustituido, en donde alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocíclico, y heterocíclico sustituido, son como se definen en la presente.

"Ciano" se refiere al grupo –CN.

"Cicloalquilo" se refiere a los grupos alquilo cíclicos de 3 a 10 átomos de carbono, que tienen un solo anillo o múltiples anillos cíclicos, incluyendo los sistemas de anillos fusionados, puenteados, y espiro. Los grupos cicloalquilo pueden incluir también en la definición de cicloalquilo, las fracciones que tienen uno o más anillos aromáticos fusionados (es decir, que tienen un enlace en común con) al anillo de cicloalquilo, por ejemplo, derivados benzo de ciclopentano, ciclopenteno, ciclohexano, y similares. Un grupo cicloalquilo que tiene uno o más anillos aromáticos fusionados, se puede unir a través de cualquiera de las porciones aromáticas o no aromáticas. Uno o más átomos de carbono formadores del anillo de un grupo cicloalquilo pueden ser oxidados, por ejemplo, pueden tener un sustituyente de oxo o sulfuro. Los ejemplos de los grupos cicloalquilo adecuados incluyen, por ejemplo, adamantilo, ciclopropilo, ciclobutilo, ciclopentilo, y ciclo-octilo.

"Cicloalquenilo" se refiere a los grupos alquilo de 3 a 10

átomos de carbono, que tienen anillos cíclicos individuales o múltiples, y que tienen cuando menos una insaturación del anillo >C=C< y, en algunas modalidades, de 1 a 2 sitios de insaturación del anillo >C=C<.

"Cicloalquilo sustituido" y "cicloalquenilo sustituido" se refieren a un grupo cicloalquilo o cicloalquenilo que tiene de 1 a 5 y, en algunas modalidades, de 1 a 3 sustituyentes seleccionados a partir del grupo que consiste en oxo, tiona, alquilo, alquenilo, alquinilo, alcoxilo, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino sustituido, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, hetero-cicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo sustituido, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, y tioalquilo;

en donde las fracciones de alquilo, alquenilo, alquinilo, arilo, cicloalquilo, cicloalquenilo, heterociclilo, y heteroarilo contenidas dentro de cualquiera de los grupos "cicloalquilo sustituido" o "cicloalquenilo sustituido" precedentes, están opcionalmente sustituidas por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en alquenilo, alquinilo, alcoxilo, acilo, acil-amino, aciloxilo, amino, amino

sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquilo, cicloalquiloxilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino sustituido, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, hetero-cicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, tioalquilo, y tioalquilo; y en donde estos sustituyentes se definen en la presente.

"Cicloalquiloxilo" se refiere a –O-cicloalquilo.

"Cicloalquiloxilo sustituido se refiere a –O-(cicloalquilo sustituido).

"Ciclotioalquilo" se refiere a –S-cicloalquilo.

"Sustituido ciclotioalquilo" se refiere a –S-(cicloalquilo sustituido).

"Cicloalqueniloxilo" se refiere a –O-cicloalquenilo.

"Cicloalqueniloxilo sustituido se refiere a –O-(cicloalquenilo sustituido).

"Tiocicloalquenilo" se refiere a –S-cicloalquenilo.

"Tiocicloalquenilo sustituido" se refiere a –S-(cicloalquenilo sustituido).

"Guanidino" se refiere al grupo $–NHC(=NH)NH_2$.

"Guanidino sustituido" se refiere a $–NR^{13}C(=NR^{13})N(R^{13})_2$ en

donde cada R^{13} se selecciona independientemente a partir del grupo que consiste en hidrógeno, alquilo, arilo, heteroarilo, heterocíclico, y dos grupos R^{13} unidos a un átomo de nitrógeno de guanidino común se unen opcionalmente, junto con el nitrógeno enlazado a los mismos, para formar un grupo heterocíclico o heterocíclico sustituido, en el entendido de que cuando menos un R^{13} no es hidrógeno;

en donde las fracciones de alquilo, arilo, heterociclilo, y heteroarilo contenidas dentro de cualquiera de los grupos "guanidino sustituido" precedentes, están opcionalmente sustituidas por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en alquenilo, alquinilo, alcoxilo, acilo, acil-amino, aciloxilo, amino, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino sustituido, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, hetero-cicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, y tioalquilo.

"Halo" o "halógeno" se refiere a flúor, cloro, bromo y yodo.

"Hidroxilo" o "hidroxi" se refiere al grupo –OH.

"Heteroarilo" se refiere a un grupo aromático de 1 a 10 átomos

de carbono, y de 1 a 4 heteroátomos seleccionados a partir del grupo que consiste en oxígeno, nitrógeno y azufre dentro del anillo. Estos grupos heteroarilo pueden ser monocíclicos, es decir, pueden tener un solo anillo (por ejemplo, piridinilo o furilo), o policíclicos, es decir, pueden tener múltiples anillos condensados (por ejemplo, indolizinilo o benzotienilo), en donde los anillos condensados pueden o no ser aromáticos y/o contener un heteroátomo, en el entendido de que el punto de unión es a través de un átomo del grupo heteroarilo aromático. En una modalidad, los átomos de nitrógeno y/o de azufre del anillo del grupo heteroarilo están opcionalmente oxidados para proporcionar las fracciones de N-óxido (N→O), sulfinilo, o sulfonilo. Los heteroarilos monocíclicos incluyen, sin limitación, pirrolilo, furanilo, tiofenilo (tienilo), imidazolilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, 1,2,3-triazolilo, 1,2,4-triazolilo, oxadiazolilo, tiadiazolilo, tetrazolilo, piridinilo, pirazinilo, pirimidinilo, piridazinilo, triazinilo, y similares. Los heteroarilos policíclicos incluyen, sin limitación, indolilo, isoindolilo, bencimidazolilo, benzo-tiofenilo, benzo-furanilo, benzoxazolilo, benzo-tiazolilo, quinolinilo, isoquinolilo, quinazolilo, quinozalilo, cinolilo, pteridina, carbazol, carbolina, fenantridina, acridina, fenantrolina, ftalazina, naftil-piridina, fenazina, purina y similares.

"Heteroarilo sustituido" se refiere a los grupos heteroarilo que están sustituidos con de 1 a 5, y, en algunas modalidades, de 1 a 3, y, en algunas modalidades, de 1 a 2 sustituyentes seleccionados a partir del grupo que consiste en el mismo grupo de sustituyentes

definidos para arilo sustituido.

"Heteroariloxilo" se refiere a –O-heteroarilo.

"Heteroariloxilo sustituido se refiere al grupo –O-(heteroarilo sustituido).

"Tioheteroarilo" se refiere al grupo –S-heteroarilo.

"Tioheteroarilo sustituido" se refiere al grupo –S-(heteroarilo sustituido).

"Heterociclo" o "heterocíclico" o "hetero-cicloalquilo" o "heterociclilo" se refieren a un heterociclo no aromático en donde uno o más de los átomos que forman el anillo es un heteroátomo tal como un átomo de O, N, o S. Los grupos hetero-cicloalquilo pueden incluir sistemas de anillos mono- o policíclicos (por ejemplo, que tienen 2, 3 ó 4 anillos fusionados), así como espiro-ciclos. Los grupos "hetero-cicloalquilo" de ejemplo incluyen morfolino, tiomorfolino, piperazinilo, tetrahidro-furanilo, tetrahidro-tienilo, 2,3-dihidro-benzo-furilo, 1,3-benzodioxol, benzo-1,4-dioxano, piperidinilo, pirrolidinilo, isoxazolidinilo, isotiazolidinilo, pirazolidinilo, oxazolidinilo, tiazolidinilo, imidazolidinilo, y similares. También se incluyen en la definición de hetero-cicloalquilo las fracciones que tienen uno o más anillos aromáticos fusionados (es decir, que tienen un enlace en común con) al anillo heterocíclico no aromático, por ejemplo ftalimidilo, naftalimidilo, y derivados benzo de heterociclos, tales como los grupos indolina e isoindolina. Un grupo hetero-cicloalquilo que tiene uno o más anillos aromáticos fusionados se puede unir a través de cualquiera de la porción aromática o no

aromática. En algunas modalidades, el grupo hetero-cicloalquilo tiene de 1 a aproximadamente 20 átomos de carbono, y en las modalidades adicionales de aproximadamente 3 a aproximadamente 20 átomos de carbono. En algunas modalidades, el grupo hetero-cicloalquilo contiene de 3 a aproximadamente 20, de 3 a aproximadamente 14, de 3 a aproximadamente 7, o de 5 a 6 átomos formadores del anillo. En algunas modalidades, el grupo hetero-cicloalquilo tiene de 1 a aproximadamente 4, de 1 a aproximadamente 3, o de 1 a 2 heteroátomos. En algunas modalidades, el grupo hetero-cicloalquilo contiene de 0 a 3 dobles enlaces. En algunas modalidades, el grupo hetero-cicloalquilo contiene de 0 a 2 triples enlaces. En algunas modalidades, los átomos de nitrógeno y/o azufre del grupo heterocíclico están opcionalmente oxidados para proporcionar las fracciones de N-óxido, sulfóxido, y sulfona.

"Heterocíclico sustituido" o "hetero-cicloalquilo sustituido" o "heterociclilo sustituido" se refiere a grupos heterociclilo que están sustituidos con de 1 a 5 y, en algunas modalidades, de 1 a 3 de los mismos sustituyentes como se definen para cicloalquilo sustituido.

"Hetero-cicliloxilo" se refiere al grupo –O-heterociclilo.

"Heterocicliloxilo sustituido se refiere al grupo –O-(heterociclilo sustituido).

"Tioheterociclilo" se refiere al grupo –S-heterociclilo.

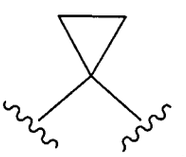
"Tioheterociclilo sustituido" se refiere al grupo –S-(heterociclilo sustituido).

Los ejemplos de heterociclos incluyen, pero no se limitan a, azetidina, indolizina, dihidro-indol, indazol, quinolizina, isotiazol, isoxazol, fenoxazina, fenotiazina, imidazolidina, imidazolina, piperidina, piperazina, indolina, ftalimida, 1,2,3,4-tetrahidro-isoquinolina, 4,5,6,7-tetrahidro-benzo-[b]-tiofeno, tiazolidina, morfolinilo, tiomorfolinilo (también referido como tiamorfolinilo), 1,1-dioxo-tiomorfolinilo, piperidinilo, pirrolidina, tetrahidro-furanilo, y similares.

"Nitro" se refiere al grupo $-NO_2$.

"Oxo" se refiere al átomo de (=O) u (-O-).

"Espiro-cicloalquilo" se refiere a los grupos cíclicos divalentes de 3 a 10 átomos de carbono que tienen un anillo de cicloalquilo con una unión de espiro (la unión formada por un sólo átomo, el cual es el único miembro común de los anillos) como se ejemplifica mediante la siguiente estructura:



"Sulfonilo" o "sulfona" se refiere al grupo divalente $-S(O)_2-$.

"Sulfonilo sustituido" se refiere al grupo $-SO_2$-alquilo, $-SO_2$-alquilo sustituido, $-SO_2$-alquenilo, $-SO_2$-alquenilo sustituido, $-SO_2$-cicloalquilo, $-SO_2$-cicloalquilo sustituido, $-SO_2$-cicloalquenilo, $-SO_2$-

cicloalquenilo sustituido, -SO_2-arilo, -SO_2-arilo sustituido, -SO_2-heteroarilo, -SO_2-heteroarilo sustituido, -SO_2-heterocíclico, -SO_2-heterocíclico sustituido, en donde alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocíclico, y heterocíclico sustituido son como se definen en la presente. Sulfonilo sustituido incluye grupos tales como metil-SO_2-, fenil-SO_2-, y 4-metil-fenil-SO_2-.

"Sulfoniloxilo" se refiere al grupo –OSO_2-alquilo, -OSO_2-alquilo sustituido, -OSO_2-alquenilo, -OSO_2-alquenilo sustituido, -OSO_2-cicloalquilo, -OSO_2-cicloalquilo sustituido, -OSO_2-cicloalquenilo, -OSO_2-cicloalquenilo sustituido, -OSO_2-arilo, -OSO_2-arilo sustituido, -OSO_2-heteroarilo, -OSO_2-heteroarilo sustituido, -OSO_2-heterocíclico, -OSO_2-heterocíclico sustituido, en donde alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocíclico, y heterocíclico sustituido son como se definen en la presente.

"Tioacilo" se refiere a los grupos H-C(S)-, alquilo-C(S)-, alquilo sustituido-C(S)-, alquenilo-C(S)-, alquenilo sustituido-C(S)-, alquinilo-C(S)-, alquinilo sustituido-C(S)-, cicloalquilo-C(S)-, cicloalquilo sustituido-C(S)-, cicloalquenilo-C(S)-, cicloalquenilo sustituido-C(S)-, arilo-C(S)-, arilo sustituido-C(S)-, heteroarilo-C(S)-,

heteroarilo sustituido-C(S)-, heterocíclico-C(S)-, y heterocíclico sustituido-C(S)-, en donde alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, cicloalquilo, cicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, heterocíclico, y heterocíclico sustituido son como se definen en la presente.

"Tiol" se refiere al grupo -SH.

"Tiocarbonilo" se refiere al grupo divalente -C(S)- el cual es equivalente a –C(=S)-.

"Tiona" se refiere al átomo (=S).

"Tioalquilo" se refiere al grupo -S-alquilo, en donde alquilo es como se define en la presente.

"Tioalquilo sustituido" se refiere al grupo -S-(alquilo sustituido), en donde alquilo sustituido es como se define en la presente.

La expresión "un alquilo interrumpido con -O-, -S-, -SO-, -SO_2-, -NH-, carbonilo, carbonil-amino, o amino-carbonilo" se refiere a un grupo alquilo en donde una unidad de carbono divalente, es decir, un metileno (-CH_2-) en el grupo alquilo, es reemplazada por una de las fracciones divalentes enlistadas.

En diferentes lugares de la presente memoria descriptiva, los sustituyentes de los compuestos de la invención se dan a conocer en grupos o en intervalos. Se pretende específicamente que la invención incluya cada y toda sub-combinación individual de los miembros de estos grupos e intervalos. Por ejemplo, el término "alquilo de 1 a 6 átomos de carbono" se pretende específicamente

para dar a conocer individualmente a metilo, etilo, alquilo de 3 átomos de carbono (propilo e isopropilo), alquilo de 4 átomos de carbono, alquilo de 5 átomos de carbono, y alquilo de 6 átomos de carbono.

A menos que se indique de otra manera, se llega a la nomenclatura de los sustituyentes que no se definan de una manera explícita en la presente, nombrando la porción terminal de la funcionalidad, seguida por la funcionalidad adyacente al punto de unión. Por ejemplo, el sustituyente de "aril-alquiloxi-cabonilo" se refiere al grupo (aril)-(alquil)-O-C(O)-.

La frase "farmacéuticamente aceptable" se emplea en la presente para referirse a los compuestos, materiales, composiciones, y/o formas de dosificación que, dentro del alcance de un buen juicio médico, sean adecuados para utilizarse en contacto con los tejidos de los seres humanos y animales sin una toxicidad excesiva, irritación, respuesta alérgica, u otro problema o complicación, de una manera conmensurada con una proporción razonable de beneficio/riesgo.

Como se utiliza en la presente, las "sales farmacéuticamente aceptables" se refieren a los derivados de los compuestos que se dan a conocer, en donde el compuesto progenitor se modifica convirtiendo una fracción de ácido o base existente hasta su forma de sal. Los ejemplos de las sales farmacéuticamente aceptables incluyen, pero no se limitan a, sales de ácidos minerales u orgánicos de los residuos básicos, tales como aminas; sales alcalinas u

orgánicas de los residuos ácidos, tales como ácidos carboxílicos; y similares. Las sales farmacéuticamente aceptables de la presente invención incluyen las sales no tóxicas convencionales del compuesto progenitor formado, por ejemplo, a partir de ácidos inorgánicos u orgánicos no tóxicos. Las sales farmacéuticamente aceptables de la presente invención se pueden sintetizar a partir del compuesto progenitor que contenga una fracción básica o ácida, mediante los métodos químicos convencionales. En términos generales, estas sales se pueden preparar mediante la reacción de las formas de ácido o base libres de estos compuestos con una cantidad estequiométrica de la base o el ácido apropiado en agua o en un solvente orgánico, o en una mezcla de los dos; en términos generales, se prefieren los medios no acuosos como éter, acetato de etilo, etanol, isopropanol, o ACN. Las listas de las sales adecuadas se encuentran en *Remington's Pharmaceutical Sciences*, 17ª Edición, Mack Publishing Company, Easton, Pa., 1985, página 1418, y *Journal of Pharmaceutical Science*, 66, 2 (1977), cada uno de los cuales se incorpora a la presente como referencia en su totalidad.

Como se utiliza en la presente, el término "tautómero" o "tautómero del mismo" significa que se refiere a cualquier forma tautomérica de un compuesto de la invención. Las formas tautoméricas resultan a partir del canje de un solo enlace con un doble enlace adyacente, junto con la migración concomitante de un protón. Las formas tautoméricas incluyen a los tautómeros prototrópicos, los cuales son estados de protonación isomérica que

tienen la misma fórmula empírica y carga total. Los tautómeros prototrópicos de ejemplo incluyen los pares de cetona - enol, los pares de amida - ácido imídico, los pares de lactama - lactima, los pares de amida - ácido imídico, los pares de enamina - imina, y las formas anulares en donde un protón puede ocupar dos o más posiciones de un sistema heterocíclico, por ejemplo, 1H- y 3H-imidazol, 1H-, 2H- y 4H-1,2,4-triazol, 1H- y 2H-isoindol, y 1H- y 2H-pirazol. Las formas tautoméricas pueden estar en equilibrio o se pueden asegurar estéricamente en una forma mediante la sustitución apropiada.

Como se utiliza en la presente, el término "éster" o "éster farmacéuticamente aceptable" se refiere a los ésteres que se hidrolizan *in vivo* e incluyen aquéllos que se descomponen fácilmente en el cuerpo humano para dejar el compuesto progenitor o una sal del mismo. Los grupos éster adecuados incluyen, por ejemplo, aquéllos derivados a partir de los ácidos carboxílicos alifáticos farmacéuticamente aceptables, en particular de los ácidos alcanoicos, alquenoicos, cicloalcanoicos, y alcanodioicos, en donde cada fracción de alquilo o alquenilo convenientemente no tiene más de 6 átomos de carbono. Los ejemplos representativos de los ésteres particulares incluyen, pero no se limitan a, formatos, acetatos, propionatos, butiratos, acrilatos, y etil-succinatos.

Como se utiliza en la presente, el término "tratar" o "tratamiento" se refiere a: (1) inhibir una enfermedad; por ejemplo, inhibir una enfermedad, condición o trastorno en un individuo que

esté experimentando o exhibiendo la patología o sintomatología de la enfermedad, condición o trastorno; (2) prevenir la enfermedad; por ejemplo, prevenir una enfermedad, condición o trastorno en un individuo que pueda estar predispuesto a la enfermedad, condición o trastorno, pero que todavía no experimenta o exhibe la patología o sintomatología de la enfermedad; (3) retardar la recurrencia de la enfermedad, por ejemplo, aumentar la duración de un período de remisión en un trastorno proliferativo, tal como un cáncer; o (4) aminorar la enfermedad0; por ejemplo, aminorar una enfermedad, condición o trastorno en un individuo que esté experimentando o exhibiendo la patología o la sintomatología de la enfermedad, condición o trastorno. El tratamiento de un paciente típicamente se lleva a cabo mediante la administración de un compuesto de la invención al paciente en una cantidad farmacéuticamente efectiva.

Un "sujeto", "individuo" o "paciente" describe un ser humano o un animal vertebrado, incluyendo, por ejemplo, un perro, gato, caballo, vaca, cerdo, oveja, cabra, mono, búho, rata, y ratón. En algunas modalidades, el "sujeto", "individuo" o "paciente" es un ser humano. En las modalidades adicionales, el "sujeto", "individuo" o "paciente" necesita tratamiento, es decir, el paciente puede estar afligido con, tiene probabilidades de estar afligido con, o podría estar afligido con una enfermedad que sea tratable mediante la administración de un compuesto de la invención, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, o una composición que comprenda el mismo.

Como se utiliza en la presente, la frase "cantidad terapéuticamente efectiva" se refiere a la cantidad del compuesto activo o del agente farmacéutico que provoca la respuesta biológica o medicinal que un investigador, veterinario, doctor médico, u otro clínico está buscando en un tejido, sistema, animal, individuo, o ser humano, tal como prevenir o inhibir una enfermedad o trastorno médico particular.

Los compuestos de la invención son útiles para uso humano o veterinario en donde, por ejemplo, se indique la inhibición de PDK1 o la inhibición de variantes de PDK1, tal como en el tratamiento de diferentes enfermedades asociadas con una señalización anormal de PDK1 y/o una señalización anormal corriente arriba o corriente abajo de PDK1 (o variantes de la misma), tal como aquélla relacionada con una actividad sobre-regulada de una o más cinasas de tirosina receptoras, Ras, PI3K, PDK1, AKT, RSK, PKC, 70S6K, o SGK. En algunas modalidades, los compuestos de la invención son útiles en la inhibición de las variantes de PDK1, en donde la PDK1 de tipo silvestre contiene una o más mutaciones puntuales, inserciones, o supresiones. Las variantes de PDK1 de ejemplo incluyen $PDK1^{T354M}$ y $PDK1^{D527E}$.

El término "PDK1" se refiere a PDK1 de tipo silvestre. El término "PDK1 variante" o "variante de PDK1" se refiere a PDK1 que tiene cuando menos una mutación puntual, inserción, o supresión.

Los compuestos de la invención se pueden utilizar en el

tratamiento de enfermedades caracterizadas por una "proliferación celular anormal". El término "proliferación celular anormal" incluye, por ejemplo, cualquier enfermedad o trastorno caracterizado por un crecimiento celular excesivo o patológicamente elevado, tal como es característico en diferentes cáncer y trastornos proliferativos que no son de cáncer.

Los cánceres de ejemplo incluyen, por ejemplo, cáncer de pulmón, cáncer bronquial, cáncer de próstata, cáncer de mama, cáncer pancreático, cáncer de colon, cáncer rectal, cáncer colo-rectal, cáncer de tiroides, cáncer de hígado, cáncer intrahepático del conducto biliar, cáncer hepatocelular, cáncer gástrico, glioma/glioblastoma, cáncer endometrial, melanoma, cáncer de riñón, cáncer pélvico renal, cáncer de vejiga urinaria; cáncer de cuerpo uterino; cáncer cervical uterino, cáncer de ovario, mieloma múltiple, cáncer esofágico, leucemia mielógena aguda, leucemia mielógena crónica, leucemia linfocítica, leucemia mieloide, cáncer de cerebro, cáncer de la cavidad oral, y cáncer faríngeo, cáncer laríngeo, cáncer del intestino delgado, linfoma no de Hodgkin, y adenoma de colon velloso.

Los trastornos proliferativos que no son cáncer de ejemplo incluyen neuro-fibromatosis, ateroesclerosis, fibrosis pulmonar, artritis, soriasis, glomerulonefritis, restenosis, retinopatía diabética proliferativa (PDR), formación de cicatriz hipertrófica, enfermedad inflamatoria del intestino, rechazo de trasplante, angiogénesis, y choque endotóxico.

En algunas modalidades, los compuestos de la invención se utilizan para tratar cánceres de la próstata, pulmón, colon, y mama.

La presente invención proporciona además métodos para inhibir el crecimiento tumoral en un paciente mediante la administración de un compuesto de la invención, o sal, éster o tautómero del mismo. En algunas modalidades, el tumor se caracteriza por una actividad elevada de la cinasa de tirosina receptora, Ras, PI3K, PDK1, AKT, RSK, PKC, 70S6K, o SGK.

La presente invención proporciona además métodos para el tratamiento de cáncer en un paciente mediante la administración al paciente, de una cantidad terapéuticamente efectiva de un compuesto de la invención, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo. En algunas modalidades, el cáncer se caracteriza por actividad de PDK1. En algunas modalidades, el cáncer se caracteriza por actividad de una variante de PDK1, tal como $PDK1^{T354M}$ o $PDK1^{D527E}$.

En las modalidades adicionales, la presente invención proporciona métodos para la inhibición de Cdk1 y/o Cdk2. Otra modalidad proporciona métodos para el tratamiento de enfermedades tales como cáncer, que respondan a la inhibición de Cdk1 y/o Cdk2, mediante la administración de un compuesto de la invención a un paciente.

En las modalidades adicionales, la invención proporciona métodos para inhibir la fosforilación de Akt, mediante la administración de un compuesto de la invención a un ser humano

que lo necesite. Otra modalidad proporciona un método para el tratamiento de enfermedades, tales como cáncer, que respondan a la inhibición de la fosforilación de Akt, mediante la administración de un compuesto de la invención a un paciente. Otra modalidad proporciona un método para inhibir la fosforilación de Akt, el cual comprende poner en contacto una célula con un compuesto de la invención.

Lo anterior se ilustra además haciendo referencia a los siguientes ejemplos, los cuales no pretenden limitar el alcance de los conceptos inventivos. Los compuestos de ejemplo y sus análogos pueden ser sintetizados por un experto en este campo a partir de los procedimientos descritos en la presente, así como en las patentes o solicitudes de patente enlistadas en la presente, que se incorporan todas a la presente como referencia en su totalidad y para todos los propósitos como si se estipularan completamente en la presente.

EJEMPLOS

Haciendo referencia a los siguientes Ejemplos, se sintetizaron los compuestos que representan las modalidades específicas, empleando los métodos descritos en la presente, u otros métodos, que son conocidos en la materia.

Los compuestos y/o intermediarios se caracterizaron mediante cromatografía de líquidos de alto rendimiento (HPLC) utilizando un sistema de cromatografía Waters Millenium con un Módulo de Separación 2695 (Milford, MA). Las columnas analíticas fueron

Phenomenex La C18 de fase inversa, de 5 micras, de 4.6 x 50 milímetros, de Alltech (Deerfield, IL). Se utilizó una elución en gradiente (flujo de 2.5 mililitros/minuto), típicamente empezando con el 5 por ciento de acetonitrilo/95 por ciento de agua, y progresando hasta el 100 por ciento de acetonitrilo durante un período de 10 minutos. Todos los solventes contuvieron ácido trifluoro-acético al 0.1 por ciento (TFA). Los compuestos se detectaron mediante absorción de luz ultravioleta (UV) en cualquiera de 220 ó 254 nanómetros. Los solventes de HPLC fueron de Burdick and Jackson (Muskegan, MI), o de Fisher Scientific (Pittsburgh, PA).

En algunas instancias, la pureza se evaluó mediante cromatografía de capa delgada (TLC) utilizando placas de gel de sílice respaldadas por vidrio o plástico, tales como, por ejemplo, hojas flexibles de gel de sílice Baker-Flex 1B2-F. Los resultados de la TLC se detectaron fácilmente de manera visual bajo luz ultravioleta, o empleando vapor de yodo bien conocido y otras diferentes técnicas de teñido.

El análisis espectrométrico de masas se llevó a cabo de acuerdo con dos diferentes métodos de cromatografía de líquidos / espectroscopía de masas (LCMS). El Método A empleó un Sistema Waters (Alliance HT HPLC) y un espectrómetro de masas Micromass ZQ para el instrumento de LCMS, un Eclipse XDB-C18, de 2.1 x 50 milímetros para la columna de cromatografía, y un sistema de solventes que fue un gradiente del 5 al 95 por ciento de acetonitrilo en agua con ácido trifluoro-acético al 0.05 por ciento durante un

período de 4 minutos (velocidad de flujo de 0.8 mililitros/minuto; intervalo de peso molecular de 200 a 1500; Voltaje del cono de 20 V; temperatura de la columna de 40°C). El Método B empleó un Sistema Hewlett Packard (Serie 1100 HPLC) y un espectrómetro de masas Micromass ZQ para el instrumento de LCMS, un Eclipse XDB-C18, de 2.1 x 50 milímetros para la columna de cromatografía, y un sistema de solventes que fue un gradiente del 5 al 95 por ciento de acetonitrilo en agua con ácido trifluoro-acético al 0.05 por ciento durante un período de 4 minutos (velocidad de flujo de 0.8 mililitros/minuto; intervalo de peso molecular de 150 a 850; Voltaje del cono de 50 V; temperatura de la columna de 30°C). Todas las masas se reportaron como aquéllas de los iones progenitores protonados.

El análisis de cromatografía de gases / espectroscopía de masas (GCMS) se llevó a cabo en un instrumento Hewlett Packard (cromatógrafo de gas Serie HP6890 con un Detector Selectivo de Masas 5973; volumen del inyector: 1 microlitro; temperatura inicial de la columna: 50°C; temperatura final de la columna: 250°C; tiempo de rampa: 20 minutos; velocidad de flujo del gas: 1 mililitro/minuto; columna: 5 por ciento de fenil-metil-siloxano, Modelo No. HP 190915-443, dimensiones: 30.0 metros x 25 metros x 0.25 metros).

El análisis de resonancia magnética nuclear (RMN) se llevó a cabo sobre algunos de los compuestos con un Varian 300 MHz NMR (Palo Alto, CA). La referencia espectral fue cualquiera de tetrametil-silano (TMS) o el cambio químico conocido del solvente. Algunas

muestras de compuestos se ejecutaron a una temperatura elevada (por ejemplo, 75°C) para promover una mayor solubilidad de la muestra.

La pureza de algunos de los compuestos se evaluó mediante análisis elemental (Desert Analytics, Tucson, AZ).

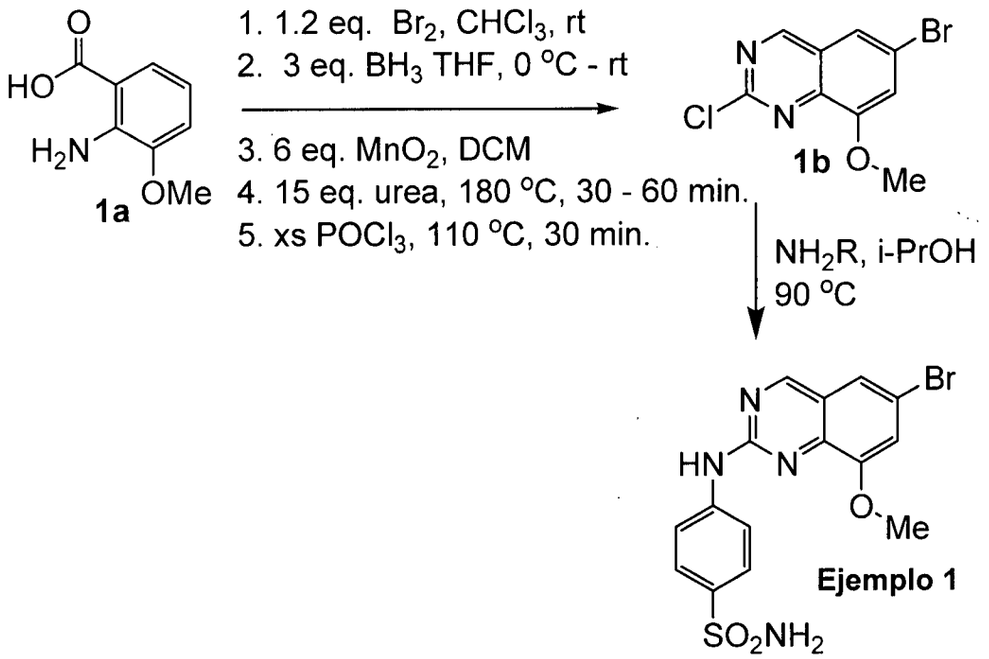
Los puntos de fusión se determinaron en un aparato Laboratory Devices Mel-Temp (Holliston, MA).

Las separaciones de preparación se llevaron a cabo utilizando un sistema de cromatografía Flash 40 y KP-Sil, 60A (Biotage, Charlottesville, VA), o mediante cromatografía en columna por evaporación instantánea utilizando un material de empaque de gel de sílice (malla 230-400), o mediante HPLC utilizando un Manejador de Muestras Waters 2767, columna C-18 de fase inversa, 30 X 50 milímetros, flujo: 75 mililitros/minuto. Los solventes típicos empleados para el sistema Flash 40 Biotage y la cromatografía por evaporación instantánea en columna son dicloro-metano (DCM), metanol (MeOH), acetato de etilo (EtOAc), hexano (hex), acetona, amoníaco acuoso (o hidróxido de amonio), y trietil-amina (TEA). Los solventes típicos empleados para la HPLC en fase inversa son concentraciones variables de acetonitrilo (ACN), y agua con ácido trifluoro-acético al 0.1 por ciento (TFA).

Ejemplo 1: 4-(6-bromo-8-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 1:

Esquema 1



Paso 1: Ácido 2-amino-5-bromo-3-metoxi-benzoico

A una solución en cloroformo 0.24 M del ácido 2-amino-3-metoxi-benzoico (**4**, 11.87 gramos, 71.7 milimoles) a 0°C se le agregó bromo (1.08 equivalentes de 0.31 M) en cloroformo por goteo. La mezcla se calentó a temperatura ambiente (RT), y se agitó bajo argón durante 16 horas. Se formó un precipitado y se recolectó mediante filtración, y se lavó completamente con cloroformo. El material crudo se secó al vacío, para dar el compuesto del título como una sal de bromhidrato (HBr) en un 99 por ciento de rendimiento. ES/MS *m/z* 248/250 (MH^+).

Paso 2: (2-amino-5-bromo-3-metoxi-fenil)-metanol

A una suspensión en tetrahidrofurano 0.24 M (THF) del ácido

2-amino-5-bromo-3-metoxi-benzoico, **1a** (71.7 milimoles) a 0°C, se le agregó una solución de borano-tetrahidrofurano (1 M, 220 mililitros, 220 milimoles). La mezcla se agitó bajo argón a temperatura ambiente durante 66 horas. La reacción se apagó mediante la adición de etanol (15 mililitros) a 0°C, y se agitó durante 15 minutos. La mezcla se vertió en agua, y se extrajo con dicloro-metano. Los extractos orgánicos se combinaron, se lavaron con salmuera, se secaron con sulfato de sodio, y se concentraron al vacío, para dar el material crudo como un sólido blanco (10.16 gramos, 62 por ciento de rendimiento). ES/MS *m/z* 230/232 (MH^+).

Paso 3: *2-amino-5-bromo-3-metoxi-benzaldehído*

A una solución en cloroformo 0.15 M del (2-amino-5-bromo-3-metoxi-fenil)-metanol (10.16 gramos, 43.96 milimoles), se le agregó dióxido de manganeso (19.9 gramos, 280.5 milimoles). La mezcla se agitó bajo argón a temperatura ambiente durante 16 horas. La mezcla entonces se filtró a través de tierra diatomácea, y se lavó con dicloro-metano. El filtrado se concentró a sequedad y se utilizó en el siguiente paso. ES/MS *m/z* 228/230 (MH^+).

Paso 4: *6-bromo-8-metoxi-quinazolin-2-ol,* ***1a***

La mezcla del 2-amino-5-bromo-3-metoxi-benzaldehído (43.96 milimoles, el material crudo a partir del Paso 3), y urea (35 gramos, 583 milimoles) a partir del Paso anterior, se calentó a 180°C bajo argón durante 1 hora. Después de enfriar a temperatura ambiente, se agregó agua (300 mililitros). Se formó un precipitado sólido y se recolectó mediante filtración, y se secó al aire, para dar 12.45

gramos de un polvo. ES/MS *m/z* 254/256 (MH^+).

Paso 5: 6-bromo-2-cloro-8-metoxi-quinazolina, ***1b***

Una suspensión del 6-bromo-8-metoxi-quinazolin-2-ol, **1a** (43.96 milimoles) en $POCl_3$ (120 mililitros) se calentó a 110°C durante 30 minutos. La mezcla se enfrió a temperatura ambiente, el $POCl_3$ se evaporó, y se dividió entre agua y dicloro-metano. La porción orgánica se concentró, para dar un material crudo, el cual se purificó mediante cromatografía en columna (gel de sílice, eluida con metanol al 2 por ciento en dicloro-metano), para proporcionar un material puro como un sólido amarillo en un 30 por ciento de rendimiento (3 pasos, 3.62 gramos). ES/MS *m/z* 272/274 (MH^+).

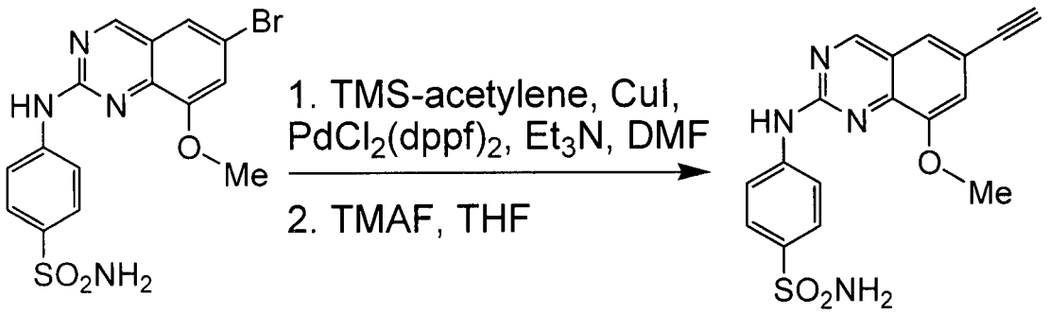
Paso 6: 4-(6-bromo-8-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida

A una solución de 50 miligramos del **1b** en 2-propanol (1 mililitro), se le agregó sulfanil-amida (1.0 equivalentes). La reacción se agitó a 90°C durante 18 horas. El clorhidrato se recolectó mediante filtración al vacío y se secó al aire, para dar un material crudo (80 miligramos), el cual se puede utilizar para otras modificaciones químicas. El material puro se obtuvo mediante purificación con HPLC. ES/MS *m/z* 409/411 (MH^+).

Ejemplo 2: 4-(6-etinil-8-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 2:

Esquema 2



Ejemplo 1 **Ejemplo 2**

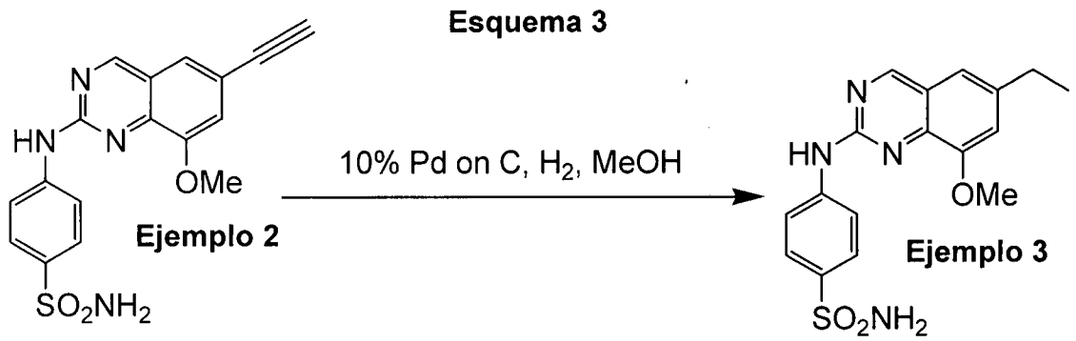
El Paso 1 y el Paso 2 se llevaron a cabo en un recipiente. Una mezcla del material de partida de (4-(6-bromo-8-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida; sintetizada siguiendo el Ejemplo 1, 67 miligramos), etinil-trimetil-silano (0.12 mililitros), yoduro de cobre(I) (6 miligramos), 1,1'-bis-(difenil-fosfino)-ferroceno-dicloro-paladio(II) (12 miligramos), trietil-amina (0.8 mililitros), y dimetil-formamida (0.8 mililitros) se pasó por microondas a 120°C durante 6 minutos. La LC/MS mostró una conversión completa del material de partida hasta la 4-(8-metoxi-6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-bencen-sulfonamida. A este intermediario se le agregaron tetrahidrofurano (0.8 mililitros), y fluoruro de tetrametil-amonio (60 miligramos). La mezcla resultante se agitó a temperatura ambiente durante 16 horas. La mezcla entonces se diluyó con agua, y se extrajo con acetato de etilo (3 veces). Los extractos orgánicos se combinaron, se lavaron con salmuera, se secaron con sulfato de sodio, y se concentraron, para dar un material crudo, el cual se purificó mediante HPLC, para

proporcionar el compuesto del título de la 4-(6-etinil-8-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida. ES/MS *m/z* 355 (MH^+).

Ejemplo 3: 4-(6-etil-8-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 3:

Esquema 3



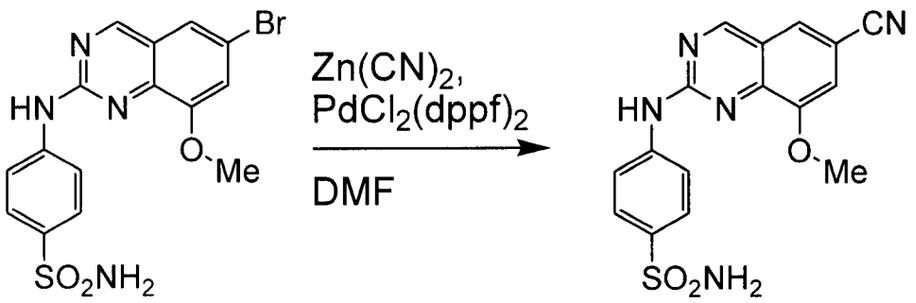
Ejemplo 2 **Ejemplo 3**

A una solución 0.015M del producto del Ejemplo 2 (1.0 equivalentes) en metanol, se le agregó paladio al 10 por ciento sobre carbón (20 por ciento por masa). El recipiente de reacción se evacuó y se inundó con gas de hidrógeno. La mezcla resultante se agitó durante 14 horas a temperatura ambiente, y entonces se filtró a través de tierra diatomácea y se concentró. El producto crudo se purificó mediante HPLC en fase inversa, y se liofilizó, para dar el compuesto deseado como su sal de ácido trifluoro-acético. ES/MS *m/z* 359 (MH^+).

Ejemplo 4: 4-(6-ciano-8-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 4:

Esquema 4



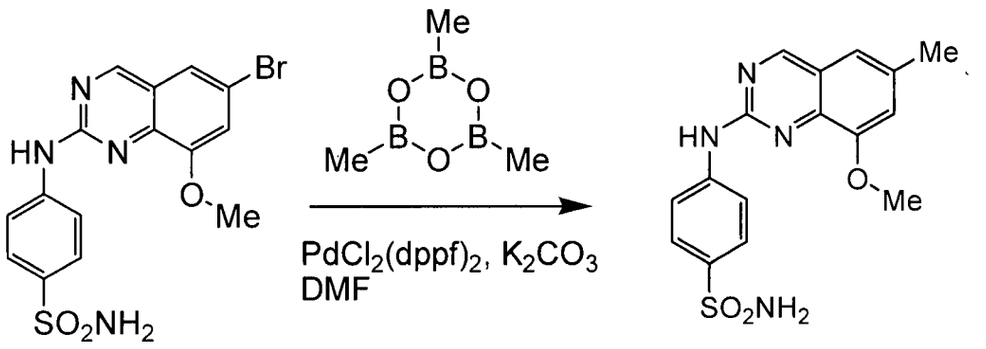
Ejemplo 1 **Ejemplo 4**

Una mezcla de la 4-(6-bromo-8-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida (sintetizada siguiendo el Ejemplo 1, 36 miligramos), cianuro de zinc(II) (36 miligramos), 1,1'-bis-(difenil-fosfino)-ferroceno-dicloro-paladio(II) (12 miligramos), y dimetil-formamida (1 mililitro), se pasó por microondas a 120°C durante 22 minutos. La mezcla resultante se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó con sulfato de sodio, y se concentró. El material crudo se purificó mediante HPLC para dar el compuesto del título puro de la 4-(6-ciano-8-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida. ES/MS *m/z* 356 (MH^+).

Ejemplo 5: 4-(8-metoxi-6-metil-quinazolin-2-il-amino)-bencen-sulfonamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 5:

Esquema 5



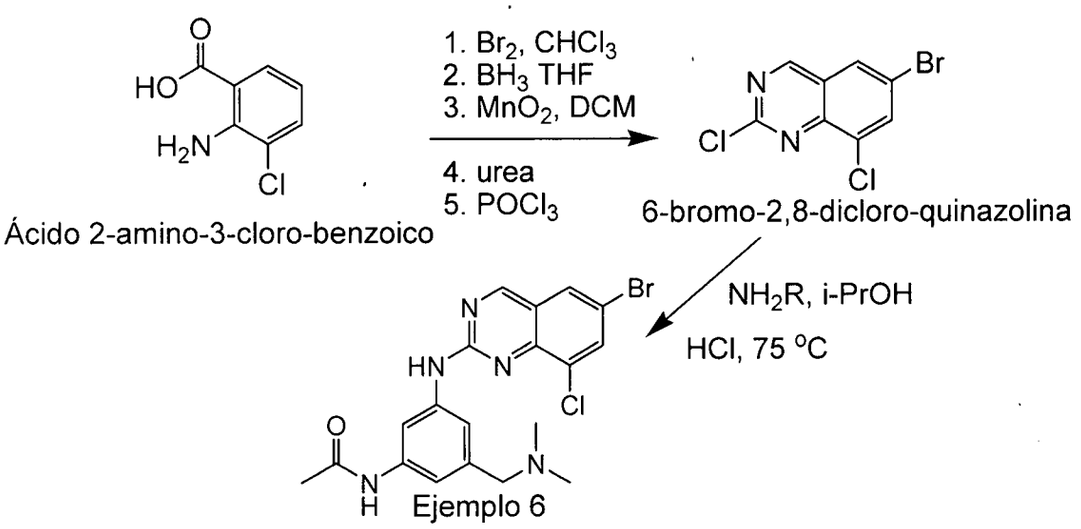
Ejemplo 1 **Ejemplo 5**

Una mezcla de la 4-(6-bromo-8-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida (sintetizada siguiendo el Ejemplo 1, 20 miligramos), trimetil-boroxina (20 microlitros), 1,1'-bis-(difenil-fosfino)-ferroceno-dicloro-paladio(II) (12 miligramos), carbonato de potasio (0.6 mililitros de una solución acuosa 2 M), y dimetil-formamida (1.2 mililitros), se pasó por microondas a 130°C durante 10 minutos. La mezcla resultante se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó con sulfato de sodio, y se concentró. El material crudo se purificó mediante HPLC para dar el compuesto del título puro de la 4-(8-metoxi-6-metil-quinazolin-2-il-amino)-bencen-sulfonamida. ES/MS *m/z* 345 (MH^+).

Ejemplo 6: *N*-(3-(6-bromo-8-cloro-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-acetamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 6:

Esquema 6



Paso 1:

A una suspensión del ácido 2-amino-3-cloro-benzoico (2 gramos, 11.6 milimoles) en cloroformo (120 mililitros), se le agregó por goteo una solución de bromo (1.1 equivalentes) en cloroformo (12 mililitros). La mezcla se agitó a temperatura ambiente durante 16 horas. El sólido blanco resultante se recolectó mediante filtración y se lavó completamente con dicloro-metano hasta que el filtrado fue incoloro. El sólido se secó al aire, para dar 3.35 gramos de un polvo blanco como la sal de HBr del ácido 2-amino-5-bromo-3-cloro-benzoico (87 por ciento de rendimiento). ES/MS *m/z* 250/252 (MH^+).

Paso 2:

Al intermediario anterior (3.35 gramos, 10.1 milimoles) en tetrahidrofurano (40 mililitros) a 0°C, se le agregó una solución de complejo de borano-tetrahidrofurano (1 M en tetrahidrofurano, 40

mililitros, 4 equivalentes). La mezcla se agitó a temperatura ambiente durante 18 horas. Se agregó borano-tetrahidrofurano adicional (20 mililitros), y se continuó la reacción durante otras 24 horas hasta la conversión completa del material de partida. El solvente se removió al vacío y el exceso de reactivo se apagó mediante la adición de etanol (20 mililitros) lentamente. Se agregó agua y el pH (de aproximadamente 3) se ajustó mediante la adición de bicarbonato de sodio (acuoso saturado) a un pH de 7. La mezcla resultante se extrajo con dicloro-metano. Los extractos orgánicos se combinaron, se lavaron con salmuera, se secaron con sulfato de sodio, y se concentraron, para dar un material crudo como un sólido blanco. ES/MS *m/z* 236/238 (MH^+).

Paso 3:

Al intermediario anterior (10.1 milimoles) en dicloro-metano (80 mililitros), se le agregó dióxido de manganeso (MnO_2, 6 gramos, 70 milimoles). La mezcla se agitó a temperatura ambiente bajo argón durante 40 horas. Se agregó dióxido de manganeso adicional (6 gramos), y la reacción se continuó durante otras 20 horas, hasta la conversión completa del material de partida. La mezcla se filtró a través de tierra diatomácea y se lavó completamente con dicloro-metano. El filtrado se concentró al vacío, para dar un producto crudo, (2-amino-5-bromo-3-cloro-fenil)-metanol (3.3 gramos, sólido color naranja), el cual se utilizó para el siguiente paso sin mayor purificación. ES/MS *m/z* 234/236 (MH^+).

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Paso 4:

Una mezcla del (2-amino-5-bromo-3-cloro-fenil)-metanol (3.3 gramos, obtenido a partir del Paso 3), y urea (10.5 gramos, 15 equivalentes), se calentó a 180°C con agitación vigorosa durante 1 hora. La reacción se enfrió a temperatura ambiente, y se agregó agua. El sólido se recolectó mediante filtración. El sólido filtrado se secó al aire, para dar la 2-hidroxi-quinazolina como un polvo amarillo (2.18 gramos, cruda). ES/MS *m/z* 259/261 (MH^+).

Paso 5: 6-bromo-2,8-dicloro-quinazolina

Al material crudo anterior se le agregó oxicloruro de fósforo ($POCl_3$, 25 mililitros), y se calentó a 130°C durante 30 minutos. La mezcla resultante se enfrió a temperatura ambiente, y se concentró al vacío hasta casi la sequedad. Se agregó agua helada, y el pH se ajustó a aproximadamente 8, utilizando bicarbonato de sodio. La mezcla se extrajo con dicloro-metano y el extracto se secó con sulfato de sodio, y se concentró al vacío proporcionando el producto deseado de la 6-bromo-2,8-dicloro-quinazolina como una espuma color café (1.4 gramos). Este material se utilizó en el siguiente paso y en otros medicamentos químicos sin mayor purificación.

Paso 6: N-(3-(6-bromo-8-cloro-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-acetamida

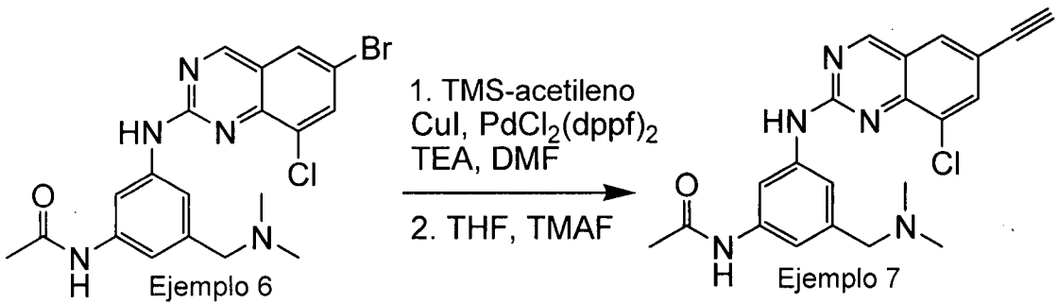
Una mezcla de la 6-bromo-2,8-dicloro-quinazolina (0.175 gramos), N-(3-amino-5-((dimetil-amino)-metil)-fenil)-acetamida (1 equivalente), y HCl en dioxano (1 equivalente) y en isopropanol (2.5

mililitros), se calentó a 75°C durante 16 horas. La mezcla resultante se diluyó con agua, se lavó con acetato de etilo para remover las impurezas orgánicas, se basificó la porción acuosa con bicarbonato de sodio (acuoso) a un pH de 9, y entonces se agregó salmuera. La solución acuosa basificada se extrajo con cloroformo (3 veces). Los extractos orgánicos se combinaron, se lavaron con salmuera, se secaron con sulfato de sodio, y se concentraron, para dar un material crudo, el cual se utilizó para el siguiente paso. La purificación mediante HPLC entonces proporcionó la N-(3-(6-bromo-8-cloro-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-acetamida pura. ES/MS *m/z* 448/450 (MH^+).

Ejemplo 7: *N*-(3-(8-cloro-6-etinil-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-acetamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 7:

Esquema 7



Paso 1:

Una mezcla de la *N*-(3-(6-bromo-8-cloro-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-acetamida (63 miligramos, a partir del Ejemplo 6), etinil-trimetil-silano (0.063 mililitros), yoduro de cobre(I) (6 miligramos), 1,1'-bis-(difenil-fosfino)-ferroceno-dicloro-paladio(II) (12 miligramos), trietil-amina (0.8 mililitros), y dimetil-formamida (0.8 mililitros) se pasó por microondas a 120°C durante 8 minutos. La mezcla resultante se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó con sulfato de sodio, y se concentró, para dar un residuo color café oscuro.

Paso 2: N-(3-(8-cloro-6-etinil-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-acetamida

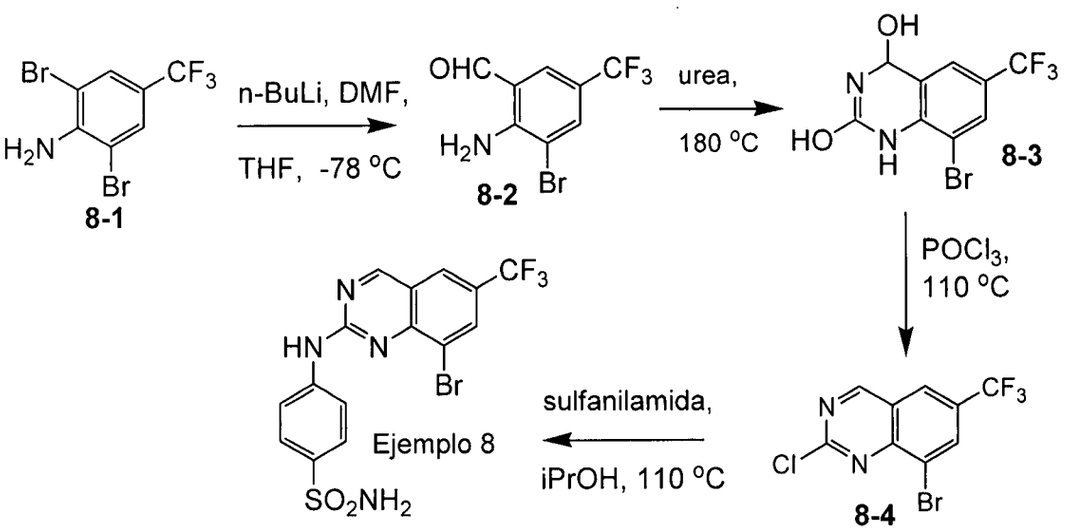
Al intermediario a partir del Paso 1 se le agregaron tetrahidrofurano (3 mililitros), 2-propanol (0.4 mililitros), y fluoruro de tetrametil-amonio (18 miligramos). La mezcla se agitó a temperatura ambiente durante 20 minutos. La mezcla resultante se diluyó con agua, y se extrajo con acetato de etilo (3 veces). Los extractos orgánicos se combinaron, se lavaron con salmuera, se secaron con sulfato de sodio, y se concentraron, para dar un material crudo, el cual se purificó mediante HPLC, para proporcionar el compuesto del título de la N-(3-(8-cloro-6-etinil-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-acetamida. ES/MS *m/z* 394 (MH^+).

Ejemplo 8: 4-(8-bromo-6-(trifluoro-metil)-quinazolin-2-il-amino)-bencen-sulfonamida

El compuesto objeto se preparó de acuerdo con el siguiente

Esquema General 8:

Esquema 8



Paso 1: *2-amino-3-bromo-5-(trifluoro-metil)-benzaldehído*, **8-2**.

La 2,6-dibromo-4-(trifluoro-metil)-anilina, **8-1** (3.19 gramos, 10.0 milimoles, 1.00 equivalentes) se disolvió en tetrahidrofurano (50 mililitros), y se enfrió a –78°C. Se agregó por goteo una solución 2.5 M de n-butil-litio en hexanos (8.40 mililitros, 21.0 milimoles, 2.10 equivalentes) durante 15 minutos. La mezcla se agitó a -78°C durante 1 hora. Se le agregó una solución de dimetil-formamida (1.03 mililitros, 14.0 milimoles, 1.40 equivalentes) en tetrahidrofurano (5 mililitros), y la mezcla se agitó durante 1 hora adicional a –78°C. La reacción se dejó llegar hasta –15°C durante 30 minutos, y entonces se apagó con salmuera. La mezcla se diluyó con acetato de etilo, se lavó en secuencia con agua y salmuera, se secó sobre sulfato de sodio, se filtró, y se concentró, para dar 1.74 gramos del producto

deseado como un sólido cristalino amarillo pálido. ES/MS *m/z* 268,270 (MH^+).

Paso 2: 8-bromo-6-(trifluoro-metil)-1,4-dihidro-quinazolin-2,4-diol, **8-3**

El 2-amino-3-bromo-5-(trifluoro-metil)-benzaldehído, **8-2** (1.74 gramos, 6.49 milimoles, 1.00 equivalentes), y urea (5.85 gramos, 97.4 milimoles, 15.0 equivalentes) se agitaron a 190°C durante 3 horas. El sólido resultante se regresó a la temperatura ambiente, se agitó en agua (60 mililitros) durante 20 minutos, y se filtró. Esto se repitió por un total de tres lavados. El sólido se secó en un desecador, para dar 3.79 gramos del producto deseado como un sólido grisáceo. ES/MS *m/z* 311,313 (MH^+).

Paso 3: 8-bromo-2-cloro-6-(trifluoro-metil)-quinazolina, **8-4**

El 8-bromo-6-(trifluoro-metil)-1,4-dihidro-quinazolin-2,4-diol, **8-3** (3.79 gramos, 6.49 milimoles, 1.00 equivalentes), y oxicloruro de fósforo (20 mililitros), se agitaron juntos a 110°C durante 1.5 horas. Los volátiles se removieron bajo presión reducida. Se agregó agua helada, y el pH se ajustó a 6-7 con hidróxido de sodio acuoso y bicarbonato de sodio. El precipitado se filtró, se enjuagó con agua, y se secó bajo un alto vacío. El material crudo se trituró con tetrahidrofurano. El licor madre se concentró para proporcionar 332 miligramos del producto deseado como un sólido cristalino color naranja. ES/MS *m/z* 313 (MH^+).

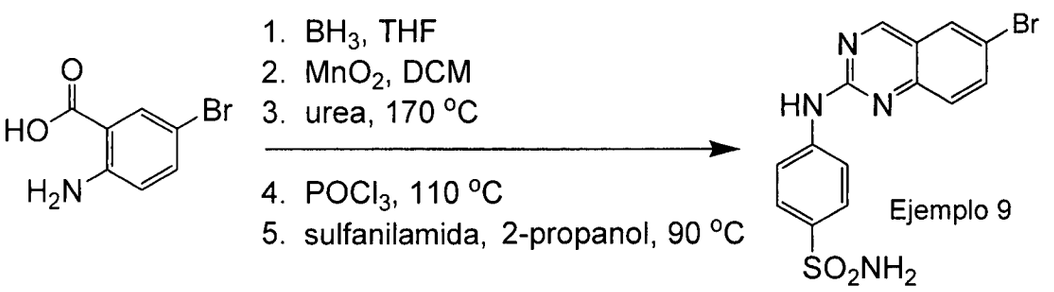
Paso 4: 4-(8-bromo-6-(trifluoro-metil)-quinazolin-2-il-amino)-bencen-sulfonamida

A una solución 0.30 M de 8-bromo-2-cloro-6-(trifluoro-metil)-quinazolina, **8-4**, en 2-propanol se le agregó sulfanil-amida (1.0 equivalentes). La reacción se agitó a 110°C durante 14 horas. El clorhidrato se recolectó mediante filtración al vacío, y entonces se agitó en bicarbonato de sodio acuoso. El sólido se recolectó mediante filtración al vacío y se enjuagó con agua. El sólido amarillo claro se secó en un desecador, para dar 343 miligramos del producto deseado. ES/MS *m/z* 447,449 (MH^+).

Ejemplo 9: 4-(6-bromo-quinazolin-2-il-amino)-bencen-sulfonamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 9:

Esquema 9



Paso 1: Alcohol 2-amino-5-bromo-bencílico

A una solución 0.50 M de ácido 2-amino-5-bromo-benzoico (1.0 equivalentes) en tetrahidrofurano, se le agregó por goteo una solución 1.0 M de complejo de borano-tetrahidrofurano en tetrahidro-furano (2.0 equivalentes) durante 15 minutos a 0°C. La mezcla se agitó durante 2 días a temperatura ambiente. La reacción se apagó

mediante la adición en secuencia de etanol (6.0 equivalentes) y agua. La mezcla se extrajo con acetato de etilo. Los extractos combinados se lavaron con salmuera, se secaron sobre sulfato de sodio, se filtraron, y se concentraron, para dar el producto deseado. ES/MS *m/z* 202,204 (MH^+).

Paso 2: 2-amino-5-bromo-benzaldehído

Se agregó óxido de manganeso (IV) (6.0 equivalentes) a una solución 0.20 M de alcohol 2-amino-5-bromo-bencílico (1.0 equivalentes) en dicloro-metano. La mezcla se agitó a temperatura ambiente durante 16 horas, y entonces se filtró a través de Celite. El filtrado se concentró, para dar el producto deseado como un sólido cristalino color café-naranja. ES/MS *m/z* 200,202 (MH^+).

Paso 3: 6-bromo-2-hidroxi-quinazolina

El 2-amino-5-bromo-benzaldehído (1.0 equivalentes), y urea (8.0 equivalentes), se agitaron a 170°C durante 1 hora. El sólido resultante se regresó hasta la temperatura ambiente, se agitó en agua durante 20 minutos, y se filtró. Esto se repitió por un total de tres lavados. El sólido se secó en un desecador, para dar el producto deseado como un sólido grisáceo. ES/MS *m/z* 225,227 (MH^+).

Paso 4: 6-bromo-2-cloro-quinazolina

Una solución 0.50 M de 6-bromo-2-hidro-quinazolina en oxicloruro de fósforo se agitó a 110°C durante 1.5 horas. Los vclátiles se removieron bajo presión reducida. Se agregó agua helada, y el pH se ajustó a 6-7 con hidróxido de sodio acuoso y bicarbonato de sodio. El precipitado se filtró, se enjuagó con agua, y

se secó bajo un alto vacío, para proporcionar el producto deseado como un sólido amarillo. ES/MS *m/z* 245 (MH^+).

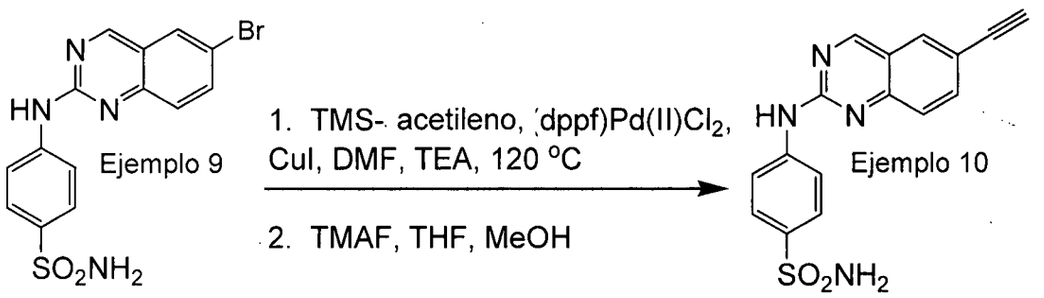
Paso 5: 4-(6-bromo-quinazolin-2-il-amino)-bencen-sulfonamida

A una solución 0.50 M de 6-bromo-2-cloro-quinazolina en 2-propanol se le agregó sulfanil-amida (1.0 equivalentes). La reacción se agitó a 90°C durante 14 horas. El clorhidrato se recolectó mediante filtración al vacío, y se utilizó sin mayor purificación. De una manera alternativa, la mezcla de reacción cruda se concentró, se purificó mediante HPLC en fase inversa, y se liofilizó, para dar el compuesto deseado como su sal de ácido trifluoro-acético. ES/MS *m/z* 379,381 (MH^+).

Ejemplo 10: 4-(6-etinil-quinazolin-2-il-amino)-bencen-sulfonamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 10:

Esquema 10



Paso 1:

A una solución 0.15 M del producto del Ejemplo 9 en 1:1 de DMF:TEA, se le agregó trimetil-silil-acetileno (TMS-acetileno) (4.0 equivalentes); yoduro de cobre(I) (0.10 equivalentes); y complejo de

[1,1'-bis-(difenil-fosfino)-ferroceno]-dicloro-paladio(II) con dicloro-metano (0.050 equivalentes). La reacción se pasó por microondas a 120°C durante 10 minutos. La mezcla se diluyó con acetato de etilo, y se filtró a través de un cojín de gel de sílice. El filtrado se concentró y se utilizó sin mayor purificación. ES/MS *m/z* 397 (MH^+).

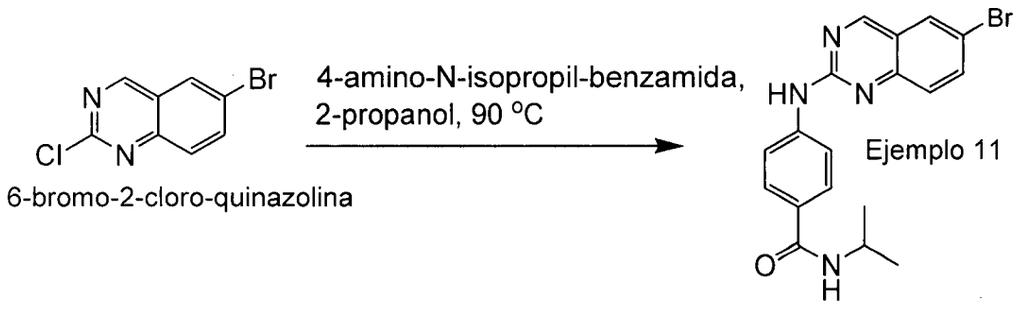
Paso 2: 4-(6-etinil-quinazolin-2-il-amino)-bencen-sulfonamida

A una solución 0.10 M del producto del Paso 1 en 1:1 de THF:MeOH se le agregó fluoruro de tetrametil-amonio (1.5 equivalentes). La reacción se agitó durante 30 minutos a temperatura ambiente. Los volátiles se removieron bajo presión reducida, y el residuo se dividió entre acetato de etilo y bicarbonato de sodio acuoso saturado. La fase orgánica se secó sobre sulfato de sodio, se filtró, y se concentró. El material crudo se purificó mediante HPLC en fase inversa, y se liofilizó, para dar el compuesto deseado como su sal de ácido trifluoro-acético. ES/MS *m/z* 325 (MH^+).

Ejemplo 11: 4-(6-bromo-quinazolin-2-il-amino)-*N*-isopropil-benzamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 11:

Esquema 11

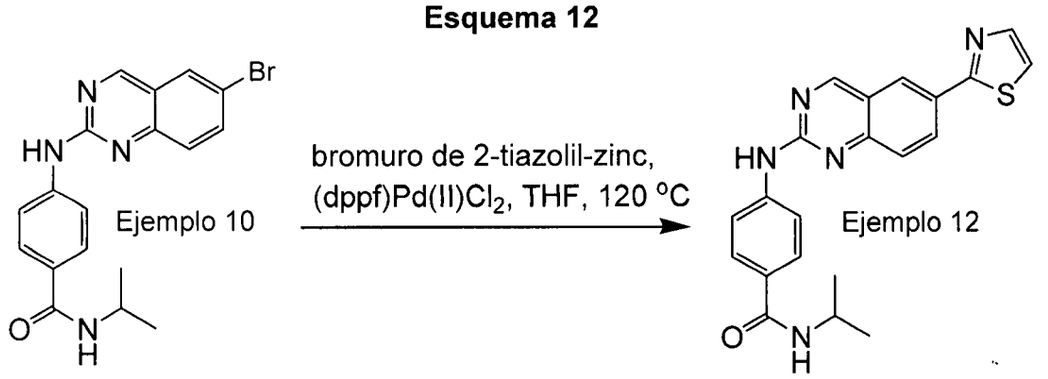


El procedimiento es análogo al Ejemplo 9, Paso 5, utilizando 4-amino-*N*-isopropil-benzamida en lugar de sulfanil-amida. ES/MS *m/z* 385,387 (MH^+).

Ejemplo 12: *N*-isopropil-4-(6-(tiazol-2-il)-quinazolin-2-il-amino)-benzamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 12:

Esquema 12

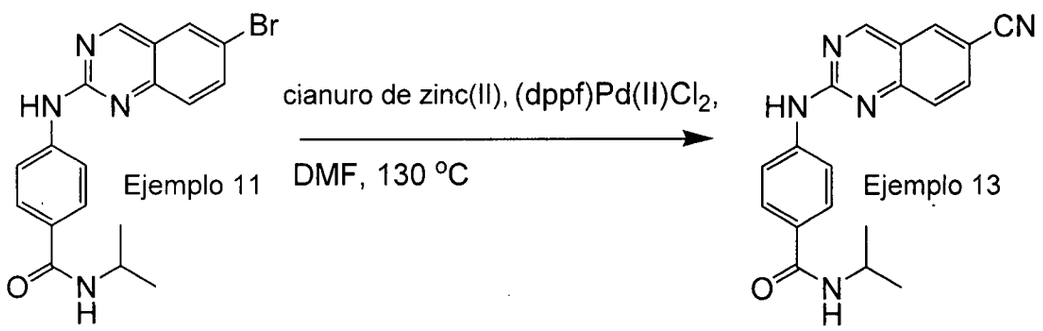


Al producto del Ejemplo 10 se le agregó complejo de [1,1'-bis-(difenil-fosfino)-ferroceno]-dicloro-paladio(II) con dicloro-metano (0.10 equivalentes), y una solución 0.5 M de bromuro de 2-tiazolil-zinc en tetrahidrofurano (3.0 equivalentes). La reacción se pasó por microondas a 120°C durante 10 minutos. La mezcla entonces se diluyó con acetato de etilo, y se lavó con regulador de EDTA acuoso, pH de aproximadamente 9. La fase orgánica se secó sobre sulfato de sodio, se concentró, se purificó mediante HPLC en fase inversa, y se liofilizó, para dar el compuesto deseado como su sal de ácido trifluoro-acético. ES/MS *m/z* 390 (MH^+).

Ejemplo 13: 4-(6-ciano-quinazolin-2-il-amino)-*N*-isopropil-benzamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 13:

Esquema 13

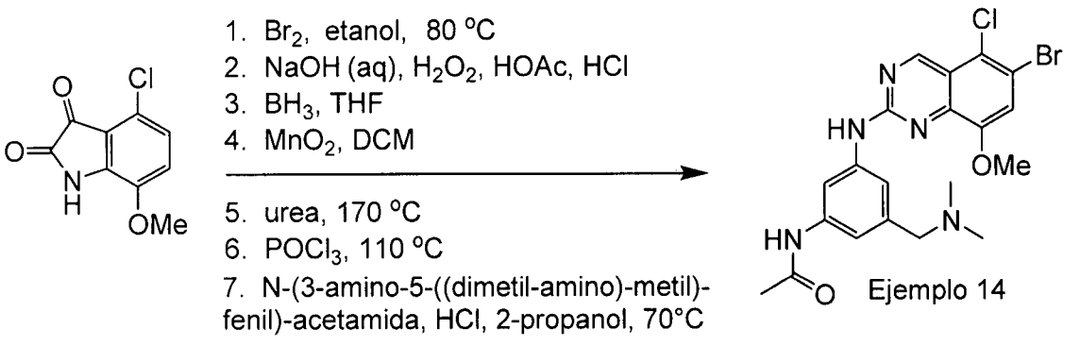


A una solución 0.10 M del producto del Ejemplo 11 en N,N-dimetil-formamida, se le agregó cianuro de zinc(II) (4.0 equivalentes), y complejo de [1,1'-bis-(difenil-fosfino)-ferroceno]-dicloro-paladio(II) con dicloro-metano (0.10 equivalentes). La reacción se pasó por microondas a 130°C durante 10 minutos. La mezcla se diluyó con acetato de etilo, y se lavó con regulador de EDTA acuoso a un pH de aproximadamente 9. La fase orgánica se secó sobre sulfato de sodio, se concentró, se purificó mediante HPLC en fase inversa, y se liofilizó, para dar el compuesto deseado como su sal de ácido trifluoro-acético. ES/MS *m/z* 332 (MH^+).

Ejemplo 14: *N*-(3-(6-bromo-5-cloro-8-metoxi-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-acetamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 14:

Esquema 14



Paso 1: 5-bromo-4-cloro-7-metoxi-isatina

A una solución 0.50 M de 4-cloro-7-metoxi-isatina (1.0 equivalentes) en etanol a 80°C, se le agregó una solución etanólica de bromo 1.0 M (2.0 equivalentes) durante 45 minutos. La reacción se agitó a 70°C durante 14 horas, y entonces se concentró. El residuo se volvió a disolver para hacer una solución 0.20 M en 10:1 de acetona:agua, y se agitó durante 45 minutos. La mezcla se concentró, para dar el producto deseado como un sólido color rojo oscuro. ES/MS *m/z* 292 (MH^+).

Paso 2: Ácido 2-amino-5-bromo-6-cloro-3-metoxi-benzoico

La 5-bromo-4-cloro-7-metoxi-isatina (1.0 equivalentes) se suspendió en hidróxido de sodio acuoso 1.0 N (10 equivalentes). Se agregó una solución al 30 por ciento de peróxido de hidrógeno en agua (4.0 equivalentes), y la reacción se agitó durante 20 minutos a temperatura ambiente. La mezcla se enfrió a 0°C. Se agregaron ácido acético glacial (10 equivalentes), y ácido clorhídrico acuoso 3.0 N (10 equivalentes). El sólido se recolectó mediante filtración al

vacío, y se secó en un desecador al vacío, para dar el producto deseado. ES/MS *m/z* 282 (MH^+).

Paso 3: Alcohol 2-amino-5-bromo-6-cloro-3-metoxi-bencílico

De una manera análoga al Ejemplo 9, Paso 1, utilizando ácido 2-amino-5-bromo-6-cloro-3-metoxi-benzoico en lugar de ácido 2-amino-5-bromo-benzoico. ES/MS *m/z* 268 (MH^+).

Paso 4: 2-amino-5-bromo-6-cloro-3-metoxi-benzaldehído

De una manera análoga al Ejemplo 9, Paso 2, utilizando alcohol 2-amino-5-bromo-6-cloro-3-metoxi-bencílico en lugar de alcohol 2-amino-5-bromo-bencílico. ES/MS *m/z* 266 (MH^+).

Paso 5: 6-bromo-5-cloro-2-hidroxi-8-metoxi-quinazolina

De una manera análoga al Ejemplo 9, Paso 3, utilizando 2-amino-5-bromo-6-cloro-3-metoxi-benzaldehído en lugar de 2-amino-5-bromo-benzaldehído. ES/MS *m/z* 291 (MH^+).

Paso 6: 6-bromo-2,5-dicloro-8-metoxi-quinazolina

De una manera análoga al Ejemplo 9, Paso 4, utilizando 6-bromo-5-cloro-2-hidroxi-8-metoxi-quinazolina en lugar de 6-bromo-2-hidroxi-quinazolina. ES/MS *m/z* 309 (MH^+).

Paso 7: N-(3-(6-bromo-5-cloro-8-metoxi-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-acetamida

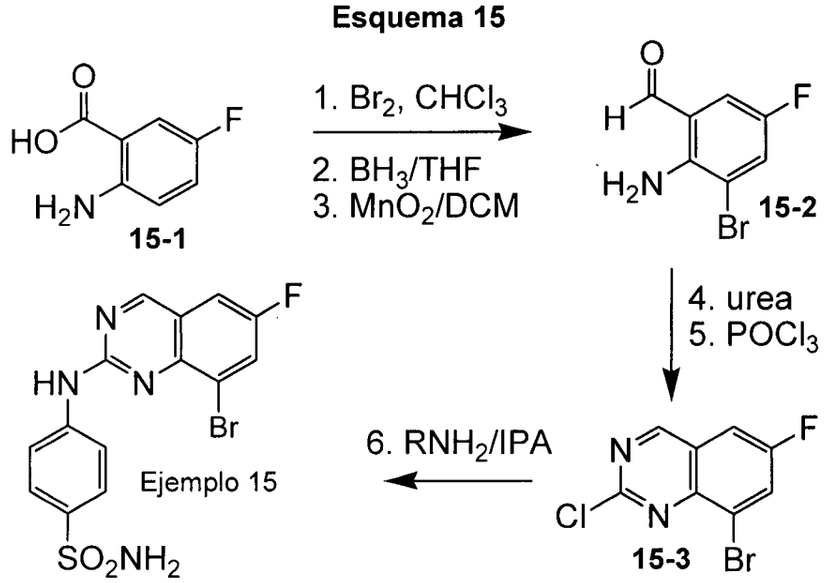
A una solución 0.25 M de 6-bromo-2,5-dicloro-8-metoxi-quinazolina en 2-propanol se le agregó *N*-(3-amino-5-((dimetil-amino)-metil)-fenil)-acetamida (1.0 equivalentes), y HCl 4.0 M en dioxano (1.2 equivalentes). La reacción se agitó a 70°C durante 14 horas. La mezcla se concentró entonces y el residuo resultante se

utilizó sin mayor purificación. De una manera alternativa, el material crudo se purificó mediante HPLC de fase inversa y se liofilizó, para proporcionar el producto deseado como su sal de ácido trifluoro-acético. ES/MS *m/z* 480 (MH^+).

Ejemplo 15: 4-(8-bromo-6-fluoro-quinazolin-2-il-amino)-bencen-sulfonamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 15:

Esquema 15



Paso 1:

Al ácido 2-amino-5-fluoro-benzoico **15-1**, (5 gramos, 32.2 milimoles) en cloroformo (90 mililitros), se le agregó por goteo una solución de bromo (1.82 mililitros, 35.4 milimoles) en cloroformo (10 mililitros) por medio de un embudo adicional. La mezcla se agitó a temperatura ambiente durante 16 horas, y la LC/MS mostró una conversión del material de partida de aproximadamente el 50 por

ciento. Se agregó bromo adicional (1.8 mililitros) a la reacción, y se continuó agitando durante otras 24 horas. El precipitado blanco resultante se recolectó mediante filtración, se lavó completamente con dicloro-metano y se secó al aire, para dar el ácido 2-amino-3-bromo-5-fluoro-benzoico, como su sal de HBr. ES/MS *m/z* 234/236 (MH^+).

Paso 2: *(2-amino-3-bromo-5-fluoro-fenil)-metanol*

A una suspensión 0.5 M del ácido 2-amino-3-bromo-5-fluoro-benzoico en tetrahidrofurano en un baño de hielo, se le agregó lentamente borano (1.0M / tetrahidrofurano, 3 equivalentes). La mezcla de reacción se agitó a temperatura ambiente durante 24 horas. La mezcla se volvió a enfriar hasta 0°C, se apagó con metanol, y se concentró para remover el solvente. El residuo se absorbió en acetato de etilo, y la fase orgánica se lavó con agua, bicarbonato de sodio saturado, salmuera, se secó sobre sulfato de sodio, y se concentró, para dar un sólido amarillo en un 90 por ciento de rendimiento. ES/MS *m/z* 220/222 (MH^+).

Paso 3: *2-amino-3-bromo-5-fluoro-benzaldehído,* ***15-2***

Se agregó óxido de manganeso (IV) (5 equivalentes), a una solución 0.2 M de (2-amino-3-bromo-5-fluoro-fenil)-metanol en dicloro-metano. La suspensión resultante se agitó a temperatura ambiente bajo Argón durante 12 horas. La mezcla de reacción se filtró a través de tierra diatomácea, y la torta del filtro se lavó con dicloro-metano. El filtrado combinado se concentró, para dar un sólido color café. ES/MS *m/z* 218/220 (MH^+).

Paso 4: 8-bromo-6-fluoro-quinazolin-2-ol

El 8-bromo-6-fluoro-quinazolin-2-ol sólido (1 equivalente), y urea (14 equivalentes) se mezclaron completamente juntos en un matraz de fondo redondo. La mezcla se calentó a 180°C en un baño de aceite durante 2.5 horas. La mezcla de reacción se enfrió a temperatura ambiente, y se agregó agua al matraz. La filtración dio un sólido color amarillo, el cual se enjuagó con éter y se secó al aire. Rendimiento: 62 por ciento. ES/MS *m/z* 243/245 (MH^+).

Paso 5: 8-bromo-2-cloro-6-fluoro-quinazolina, ***15-3***

Una suspensión 0.5 M de 8-bromo-6-fluoro-quinazolin-2-ol en oxicloruro de fósforo se calentó a 110°C en un baño de aceite. La suspensión se convirtió hasta una solución color café en 20 minùtos. Los datos de LCMS mostraron que la reacción se completó después de 1 hora. El oxicloruro de fósforo se removió mediante concentración. El residuo se mezcló con agua helada, y el pH se ajustó a 7 mediante la adición de bicarbonato de sodio. La mezcla de reacción se extrajo con acetato de etilo. La fase orgánica combinada se lavó con agua, salmuera, se secó sobre sulfato de sodio, y se concentró, para dar el producto deseado en un rendimiento del 89 por ciento. ES/MS *m/z* 261/263 (MH^+).

Paso 6: 4-(8-bromo-6-fluoro-quinazolin-2-il-amino)-bencen-sulfonamida

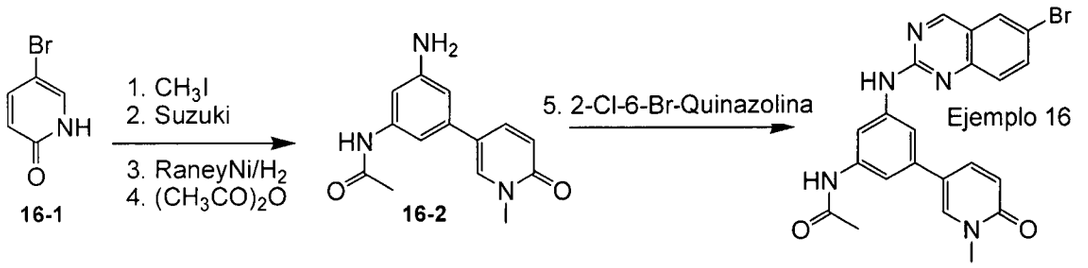
A una suspensión 0.4 M de 8-bromo-2-cloro-6-fluoro-quinazolina, **15-3** en isopropanol, se le agregó 4-amino-bencen-sulfonamida (1 equivalente). La mezcla de reacción se calentó a

120°C en un baño de aceite durante 2 días. La LCMS mostró que la reacción se completó bajo la condición. Se agregó acetato de etilo al matraz de la reacción, y la suspensión se agitó a temperatura ambiente durante 30 minutos y se filtró. La torta del filtro se enjuagó con hexano, y se secó al vacío, para dar el producto en un 81 por ciento de rendimiento. ES/MS *m/z* 397/399 (MH^+).

Ejemplo 16: *N*-(3-(6-bromo-quinazolin-2-il-amino)-5-(1-metil-6-oxo-1,6-dihidro-piridin-3-il)-fenil)-acetamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 16:

Esquema 16



Paso 1: 5-bromo-1-metil-piridin-2(1H)-ona

A una suspensión 0.3 M de 5-bromo-2(1H)-piridona en tetrahidrofurano en un baño de hielo, se le agregó hidruro de sodio (2.0 equivalentes). Después de agitar a 0°C durante 5 minutos, se agregó yodo-metano (4.0 equivalentes). La mezcla de reacción se agitó a temperatura ambiente durante 15 horas. El solvente se removió bajo presión reducida. El residuo se diluyó con acetato de etilo y se lavó con agua, salmuera, se secó sobre sulfato de sodio, y se concentró. El compuesto crudo se trituró con hexano, y se filtró,

para recolectar el producto deseado en un 72 por ciento de rendimiento. ES/MS *m/z* 188/190 (MH^+).

Paso 2: 2-(3,5-dinitro-fenil)-4,4,5,5-tetrametil-1,3,2-dioxa-borolano

A una solución 0.2 M de 1-yodo-3,5-dinitro-benceno en dioxano, se le agregaron bis-(pinacolato)-diboro (1.5 equivalentes), $Pd(dppf)_2Cl_2$ CH_2Cl_2 (0.2 equivalentes), y carbonato de potasio secado en flama (2.0 equivalentes). La mezcla se purgó con Argón durante 10 minutos y se calentó a 120°C en un baño de aceite durante 12 horas. La mezcla de reacción se filtró a través de tierra diatomácea, y la torta del filtro se enjuagó con dioxano. El filtrado combinado se concentró para proporcionar un residuo. El residuo crudo se purificó mediante Biotage utilizando acetato de etilo al 20 por ciento en hexano, para dar el producto deseado. La estructura se confirmó mediante el espectro de ^1H RMN.

Paso 3: 5-(3,5-dinitro-fenil)-1-metil-piridin-2(1H)-ona

Una mezcla 0.2 M de 5-bromo-1-metil-piridin-2(1H)-ona (1.0 equivalentes), 2-(3,5-dinitro-fenil)-4,4,5,5-tetrametil-1,3,2-dioxa-borolano (3.0 equivalentes), $Pd(dppf)_2Cl_2CH_2Cl_2$ (0.1 equivalentes), y carbonato de potasio 2.0 M (1 equivalente) en DME se pasó por microondas a 120°C durante 15 minutos. La mezcla de reacción se diluyó con acetato de etilo, y se lavó con agua, salmuera, se secó y se concentró. El residuo se purificó mediante Biotage utilizando metanol al 5 por ciento en dicloro-metano (DCM). El producto fue un sólido color café en un 38 por ciento de rendimiento. ES/MS *m/z* 276

(MH^+).

Paso 4: N-(3-amino-5-(1-metil-6-oxo-1,6-dihidro-piridin-3-il)-fenil)-acetamida

Se agregó anhídrido acético (1.0 equivalentes) a una solución 0.06 M de 5-(3,5-diamino-fenil)-1-metil-piridin-2(1H)-ona (1.0 equivalentes), y trietil-amina (1.2 equivalentes) en tetrahidrofurano en un baño de hielo. La reacción se monitoreó mediante LCMS y se completó en 1 hora. El solvente se removió bajo presión reducida, y el residuo se purificó mediante HPLC en fase inversa. La liofilización dio el producto como la sal de ácido trifluoro-acético. ES/MS *m/z* 258 (MH^+).

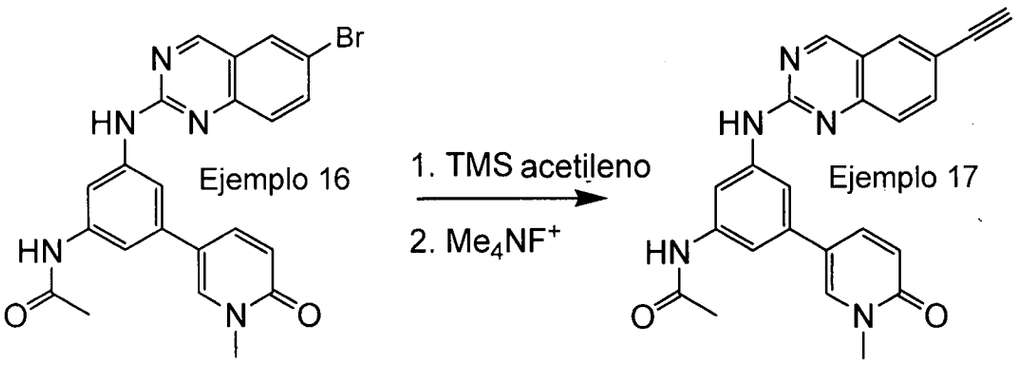
Paso 5: N-(3-(6-bromo-quinazolin-2-il-amino)-5-(1-metil-6-oxo-1,6-dihidro-piridin-3-il)-fenil)-acetamida

Una suspensión 0.08 M de 6-bromo-2-cloro-quinazolina (1.0 equivalentes), y *N*-(3-amino-5-(1-metil-6-oxo-1,6-dihidro-piridin-3-il)-fenil)-acetamida (1.0 equivalentes) en isopropanol, se calentó a 120°C en un baño de aceite durante 15 horas. La LCMS mostró que la conversión se completó bajo la condición. El solvente se removió bajo presión reducida, y el residuo se purificó mediante HPLC en fase inversa, para dar el producto deseado como la sal de ácido trifluoro-acético. ES/MS *m/z* 464/466 (MH^+).

Ejemplo 17: *N*-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-6-oxo-1,6-dihidro-piridin-3-il)-fenil)-acetamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 17:

Esquema 17



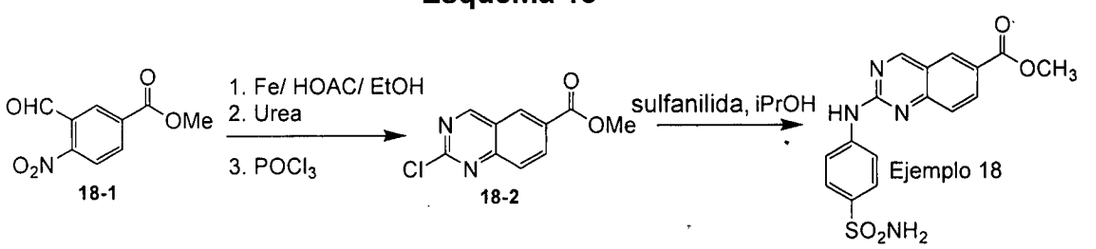
A una mezcla 0.04 M de *N*-(3-(6-bromo-quinazolin-2-il-amino)-5-(1-metil-6-oxo-1,6-dihidro-piridin-3-il)-fenil)-acetamida (a partir del Ejemplo 16) (0.08 milimoles), trietil-amina (0.4 mililitros), $Pd(dppf)2Cl_2CH_2Cl_2$ (0.1 equivalentes), y yoduro de cobre(I) (0.1 equivalentes), en N,N-dimetil-formamida, se le agregó trimetil-silil-acetileno (10 equivalentes). La suspensión se pasó por microondas a 120°C durante 20 minutos. La mezcla de reacción se diluyó con acetato de etilo y se lavó con agua, salmuera, se secó, y se concentró. El residuo oleoso se trató con fluoruro de tetrametil-amonio (1.0 equivalentes) en THF/MeOH (1:1, 0.02 M) a temperatura ambiente durante 1 hora. El solvente se removió bajo presión reducida, y el residuo se diluyó con acetato de etilo. La fase orgánica se lavó con agua, salmuera, se secó, y se concentró. El producto crudo se purificó mediante HPLC en fase inversa. La liofilización dio el producto deseado. ES/MS *m/z* 410 (MH^+).

Ejemplo 18: 2-(4-sulfamoil-fenil-amino)-quinazolin-6-carboxilato de metilo

El compuesto objeto se preparó de acuerdo con el siguiente

Esquema General 18:

Esquema 18



Paso 1: *3-formil-4-amino-benzoato de metilo,* ***18-1***

A una mezcla 1:1 de etanol y ácido acético se le agregó metil-3-formil-4-nitro-benzoato (1 equivalente), y se agregó polvo de Fe (3 equivalentes) en porciones. La reducción se completó en 1 hora. La mezcla de reacción se filtró, y entonces se concentró, y se dividió entre acetato de etilo y agua. La capa orgánica se lavó con bicarbonato de sodio saturado, y se secó y se concentró, para dar el 3-formil-4-amino-benzoato de metilo en un 85 por ciento de rendimiento. ES/MS *m/z* 180(MH^+).

Paso 2: *2-hidroxi-quinazolin-6-carboxilato de metilo*

Al 3-formil-4-amino-benzoato de metilo, **18-1** (1 equivalente), se le agregó urea (5 equivalentes), y la mezcla se calentó a 145°C durante 16 horas. Al producto crudo se le agregó agua y el sólido precipitado se filtró, para dar el 2-hidroxi-quinazolin-6-carboxilato de metilo en un rendimiento cuantitativo. ES/MS *m/z* 205(MH^+).

Paso 3: *2-cloro-quinazolin-6-carboxilato de metilo,* ***18-2***

Al 2-hidroxi-quinazolin-7-carboxilato se le agregó $POCL_3$ y la mezcla se agregó calentada a 100°C durante 20 minutos cuando la

reacción llegó a completarse. A la mezcla de reacción se le agregó hielo y agua, y el sólido precipitado se filtró y se secó sobre un alto vacío durante la noche para dar el 2-cloro-quinazolin-7-carboxilato de metilo en un 60 por ciento de rendimiento. ES/MS *m/z* 223(MH^+).

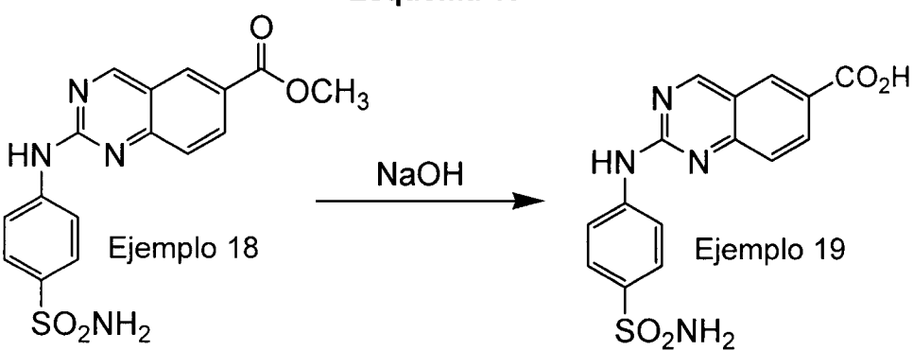
Paso 4: 2-(4-sulfamoil-fenil-amino)-quinazolin-6-carboxilato de metilo

Al 2-cloro-quinazolin-6-carboxilato de metilo (1 equivalente), se le agregaron sulfanil-amida (1 equivalente) e isopropanol, y la mezcla se calentó a 90°C durante 2 horas. La reacción llegó a completarse. La mezcla de reacción se enfrió a temperatura ambiente, y se filtró, para dar el 2-(4-sulfamoil-fenil-amino)-quinazolin-7-carboxilato de metilo en un rendimiento cuantitativo. ES/MS *m/z* 359(MH^+).

Ejemplo 19: Ácido metil-2-(4-sulfamoil-fenil-amino)-quinazolin-6-carboxílico

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 19:

Esquema 19

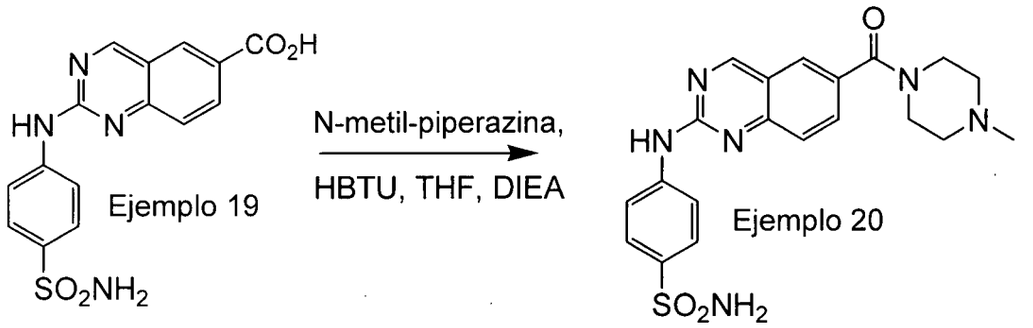


Al 2-(4-sulfamoil-fenil-amino)-quinazolin-7-carboxilato de metilo (el compuesto del Ejemplo 18), se le agregaron hidróxido de sodio 2N (4 equivalentes), y metanol, y la mezcla resultante se calentó a 80°C durante 10 minutos. La saponificación llegó a completarse. La mezcla de reacción se concentró, y se agregó HCl 1N para precipitar el ácido metil-2-(4-sulfamoil-fenil-amino)-quinazolin-7-carboxílico como la sal de HCl en un rendimiento cuantitativo. ES/MS *m/z* 344(MH^+).

Ejemplo 20: 4-(6-(4-metil-piperazin-1-carbonil)-quinazolin-2-il-amino-bencen-sulfonamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 20:

Esquema 20



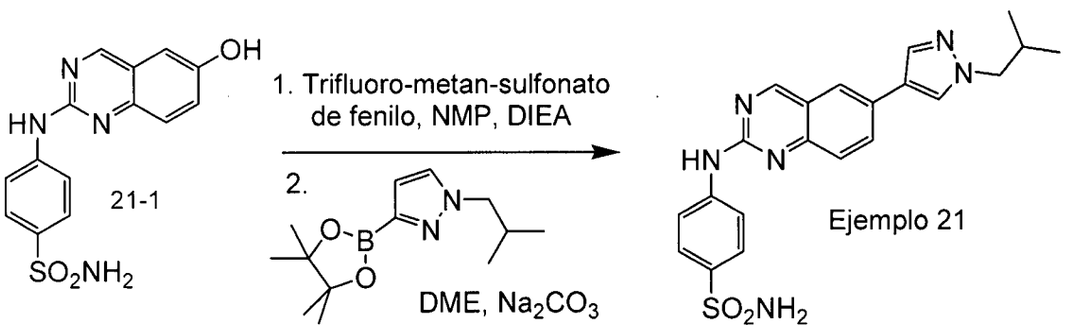
Al ácido 2-(4-sulfamoil-fenil-amino)-quinazolin-6-carboxílico (a partir del Ejemplo 19) (1 equivalente), se le agregaron *N*-metil-piperazina, tetrahidrofurano, di-isopropil-etil-amina (DIEA) (4

equivalentes), y HBTU (2 equivalentes), y la mezcla se agitó a temperatura ambiente durante la noche. El acoplamiento llegó a completarse, y la mezcla se concentró y se dividió entre acetato de etilo y agua. Las capas orgánicas se concentraron y se purificaron sobre la HPLC de preparación, para dar la 4-(6-(4-metil-piperazin-1-carbonil)-quinazolin-2-il-amino-bencen-sulfonamida en un 50 por ciento de rendimiento. ES/MS *m/z* 427(MH^+).

Ejemplo 21: 4-(6-(1-isobutil-1H-pirazol-4-il)-quinazolin-2-il-amino)-bencen-sulfonamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 21:

Esquema 21



Paso 1: Trifluoro-metan-sulfonato de 2-(4-sulfamoil-fenil-amino)-quinazolin-6-ilo

A una solución de 4-(6-hidroxi-quinazolin-2-il-amino)-bencen-sulfonamida, **21-1** (1 equivalente) en NMP, se le agregaron trifluoro-

metan-sulfonato de fenilo (1.2 equivalentes) y DIEA (2.5 equivalentes), y la mezcla de reacción se agitó durante la noche a temperatura ambiente. La mezcla de reacción se dividió entonces entre acetato de etilo y agua. Las capas orgánicas se lavaron con cloruro de sodio saturado, y se secaron y se concentraron. Al producto crudo se le agregó dicloro-metano y unas cuantas gotas de metanol. El sólido blanco así formado se filtró, para dar el trifluoro-metan-sulfonato de 2-(4-sulfamoil-fenil-amino)-quinazolin-6-ilo en un 80 por ciento de rendimiento. ES/MS *m/z* 447(MH^+).

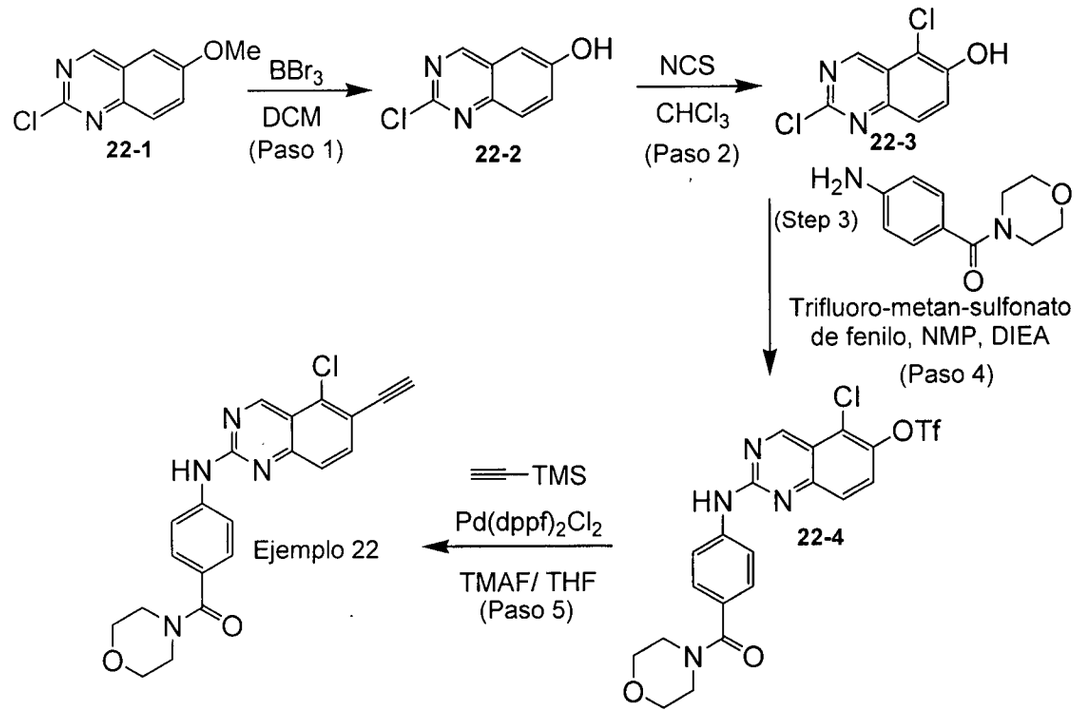
Paso 2: 4-(6-(1-isobutil-1H-pirazol-4-il)-quinazolin-2-il-amino)-bencen-sulfonamida

A una solución de trifluoro-metan-sulfonato de 2-(4-sulfamoil-fenil-amino)-quinazolin-7-ilo (1 equivalente) en DME, se le agregó una solución de carbonato de sodio 2 M y 1-isobutil-3-(4,4,5,5-tetrametil-1,3,2-dioxa-borolan-2-il)-1H-pirazol (3 equivalentes), y $Pd(dppf)_2$ $Cl_2 \cdot CH_2Cl_2$ (0.05 equivalentes), y la mezcla se pasó por microondas durante 10 minutos a 120°C. La mezcla de reacción se dividió entonces entre acetato de etilo y agua. La capa orgánica se concentró para proporcionar la 4-(6-(1-isobutil-1H-pirazol-4-il)-quinazolin-2-il-amino)-bencen-sulfonamida. ES/MS *m/z* 423(MH^+).

Ejemplo 22: (4-(5-cloro-6-etinil-quinazolin-2-il-amino)-fenil)-(morfolino)-metanona

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 22:

Esquema 22



Paso 1: 2-cloro-quinazolin-6-ol, ***22-2***

A la 2-cloro-6-metoxi-quinazolina, **22-1** en dicloro-metano, se le agregó tribromuro de boro (2 equivalentes), y la mezcla se calentó a 40°C durante 16 horas. La desprotección del metil-éter llegó a completarse mediante la LC/MS. La mezcla se concentró, y el sólido se filtró y se lavó con agua helada, y el sólido se secó sobre un alto vacío, para dar el 2-cloro-quinazolin-6-ol. ES/MS *m/z* 181(MH^+).

Paso 2: 2,5-dicloro-quinazolin-6-ol, ***22-3***

Al 2-cloro-quinazolin-6-ol, **22-2** (1 equivalente) en cloroformo, se le agregó N-cloro-succinimida (1 equivalente), y la mezcla se calentó a 40°C durante 16 horas. La reacción llegó a completarse para dar el 2,5-dicloro-quinazolin-6-ol que se observó mediante

LC/MS, y la estructura se confirmó mediante ^{1}H RMN. La mezcla se concentró y se purificó sobre gel de sílice, para dar el producto. ES/MS *m/z* 215(MH^+).

Paso 3: 2-cloro-5-bromo-quinazolin-6-ol

Al 2-cloro-quinazolin-6-ol, **22-2** (1 equivalente) en cloroformo, se le agregó *N*-bromo-succinimida (1 equivalente), y la mezcla se agitó a temperatura ambiente durante 1 hora. La reacción llegó a completarse para dar el 2-cloro-5-bromo-quinazolin-6-ol que se observó mediante LC/MS, y la estructura se confirmó mediante ^{1}H RMN. La mezcla se concentró y se pasó a través de un tapón de gel de sílice, para dar el producto en un rendimiento cuantitativo. ES/MS *m/z* 260(MH^+).

Paso 4: (4-(5-cloro-6-hidroxi-quinazolin-2-il-amino)-fenil)-(morfolino)-metanona

Al 2,5-dicloro-quinazolin-6-ol, **22-3** (1 equivalente) en isopropanol, se le agregó (4-amino-fenil)-(morfolino)-metanona (1 equivalente), y la mezcla de reacción se calentó a 90°C durante 1 hora. La reacción llegó a completarse mediante la LC/MS. La mezcla se concentró entonces, y se utilizó sin mayor purificación. ES/MS *m/z* 386(MH^+).

Paso 5: Trifluoro-metan-sulfonato de 5-cloro-2-(4-(morfolin-4-carbonil)-fenil-amino)-quinazolin-6-ilo, ***22-4***

A una solución de (4-(5-cloro-6-hidroxi-quinazolin-2-il-amino)-fenil)-(morfolino)-metanona (1 equivalente) en NMP, se le agregaron trifluoro-metan-sulfonato de fenilo (1.2 equivalentes) y DIEA (2.5

equivalentes), y la mezcla de reacción se agitó durante la noche a temperatura ambiente. La mezcla de reacción se dividió entonces entre acetato de etilo y agua. Las capas orgánicas se lavaron con cloruro de sodio saturado, y se secaron y se concentraron. Al producto crudo se le agregó cloruro de metileno y unas cuantas gotas de metanol. El sólido blanco así formado se filtró, para dar el trifluoro-metan-sulfonato de 5-cloro-2-(4-(morfolin-4-carbonil)-fenil-amino)-quinazolin-6-ilo en un 80 por ciento de rendimiento. ES/MS *m/z* 517(MH^+).

Paso 6: (4-(5-cloro-6-etinil-quinazolin-2-il-amino)-fenil)-(morfolino)-metanona

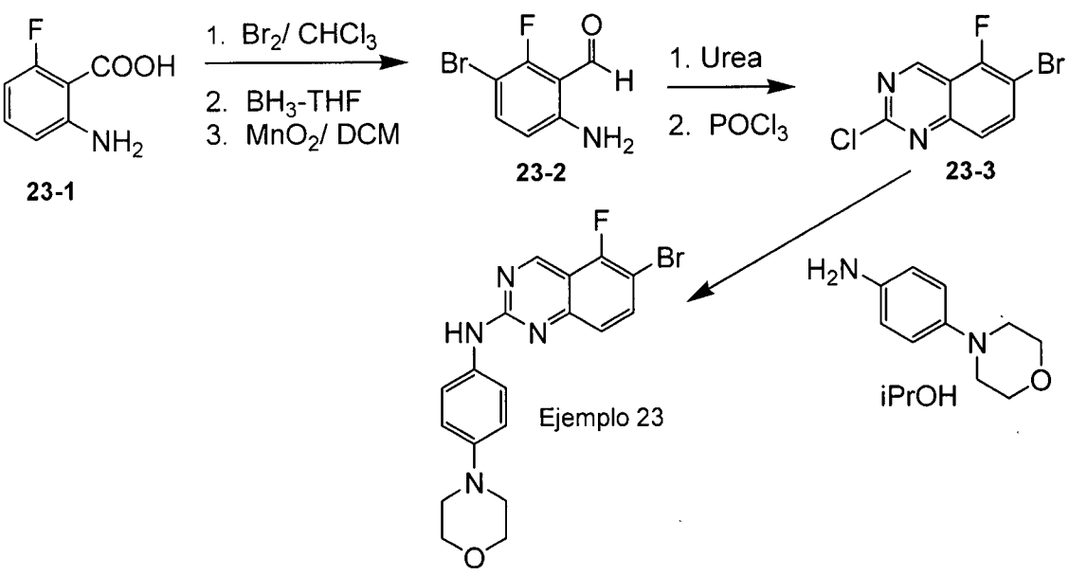
Al trifluoro-metan-sulfonato de 5-cloro-2-(4-(morfolin-4-carbonil)-fenil-amino)-quinazolin-6-ilo, **22-4** (1 equivalente) en 4:1 de dimetil-formamida y trietil-amina, se le agregaron TMS-acetileno (4 equivalentes), yoduro de cobre (0.2 equivalentes), y $Pd(dppf)_2Cl_2.CH_2Cl_2$ (0.2 equivalentes), y la mezcla se pasó por microondas durante 10 minutos a 120°C. La mezcla de reacción se dividió entonces entre acetato de etilo y agua. La capa orgánica se concentró para proporcionar la (4-(5-cloro-6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenil)-(morfolino)-metanona. ES/MS *m/z* 465(MH^+). Al producto crudo se le agregaron tetrahidrofurano y fluoruro de tetrametil-amonio (1 equivalente), y la mezcla se agitó a temperatura ambiente durante 1 hora. Se dividió entonces entre acetato de etilo y agua, y la capa orgánica se concentró y se purificó en una HPLC de preparación, para dar la (4-(5-cloro-6-etinil-

quinazolin-2-il-amino)-fenil)-(morfolino)-metanona. ES/MS *m/z* 393(MH^+).

Ejemplo 23: 6-bromo-5-fluoro-n-(4-morfolino-fenil)-quinazolin-2-amina

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 23:

Esquema 23



Paso 1: Ácido 6-amino-3-bromo-2-fluoro-benzoico

Al ácido 2-amino-6-fluoro-benzoico, **23-1** (1 equivalente) en cloroformo a 0°C, se le agregó bromo (1.2 equivalentes) por goteo, y la mezcla se agitó a temperatura ambiente durante 16 horas. Se observó la formación del ácido 6-amino-3-bromo-2-fluoro-benzoico (47 por ciento) mediante LC/MS, junto con el ácido 2-amino-3-bromo-

6-fluoro-benzoico (22 por ciento), el 20 por ciento del ácido 2-amino-3,5-dibromo-6-fluoro-benzoico, y el 9 por ciento del material de partida. La estructuras de los isómeros se confirmaron mediante ^{1}H RMN. La mezcla de reacción se concentró y se filtró, y el sólido se lavó con cloroformo, para dar un sólido grisáceo. La mezcla cruda se llevó adelante al siguiente paso sin purificación. ES/MS *m/z* 235(MH^+).

Paso 2: (6-amino-3-bromo-2-fluoro-fenil)-metanol

A la mezcla cruda a partir del Paso 1 en tetrahidrofurano a 0°C en un matraz secado con flama, se le agregó complejo de borano-tetrahidrofurano (4 equivalentes) por goteo. La mezcla se llevó hasta la temperatura ambiente, y se agitó durante 16 horas. La formación del (6-amino-3-bromo-2-fluoro-fenil)-metanol se observó mediante LC/MS. La mezcla de reacción se concentró, y el producto crudo se dividió entre agua y acetato de etilo. La capa orgánica se lavó con salmuera, y se secó (Na_2SO_4). El aceite amarillo crudo se purificó sobre gel de sílice, y la formación del (6-amino-3-bromo-2-fluoro-fenil)-metanol se confirmó mediante ^{1}H RMN. ES/MS *m/z* 218(MH^+).

Paso 3: 6-amino-3-bromo-2-fluoro-benzaldehído, ***23-2***

Al (6-amino-3-bromo-2-fluoro-fenil)-metanol (1 equivalente) en cloruro de metileno se le agregó dióxido de manganeso (8 equivalentes), y la mezcla se agitó a temperatura ambiente durante 16 horas. La formación del 6-amino-3-bromo-2-fluoro-benzaldehído se confirmó mediante LC/MS. La mezcla entonces se filtró, y el filtrado se concentró, para dar el 6-amino-3-bromo-2-fluoro-

benzaldehído. ES/MS *m/z* 218(MH^+).

Paso 4: 6-bromo-5-fluoro-quinazolin-2-ol

Al metil-6-amino-3-bromo-2-fluoro-benzaldehído, **23-2** (1 equivalente), se le agregó urea (8 equivalentes), y la mezcla se calentó a 180°C durante 1 hora. Al producto crudo se le agregó agua, y el sólido precipitado se filtró y se secó al vacío, para dar el 6-bromo-5-fluoro-quinazolin-2-ol. ES/MS *m/z* 242(MH^+).

Paso 5: 6-bromo-2-cloro-5-fluoro-quinazolina, ***23-3***

Al 6-bromo-5-fluoro-quinazolin-2-ol se le agregó $POCl_3$ y la mezcla se agregó calentada a 100°C durante 2 horas, cuando la reacción llegó a completarse. A la mezcla de reacción se le agregó hielo y agua, y el sólido precipitado se filtró y se secó sobre un alto vacío durante la noche, para dar la 6-bromo-2-cloro-5-fluoro-quinazolina. ES/MS *m/z* 260(MH^+).

Paso 6: 6-bromo-5-fluoro-N-(4-morfolino-fenil)-quinazolin-2-amina

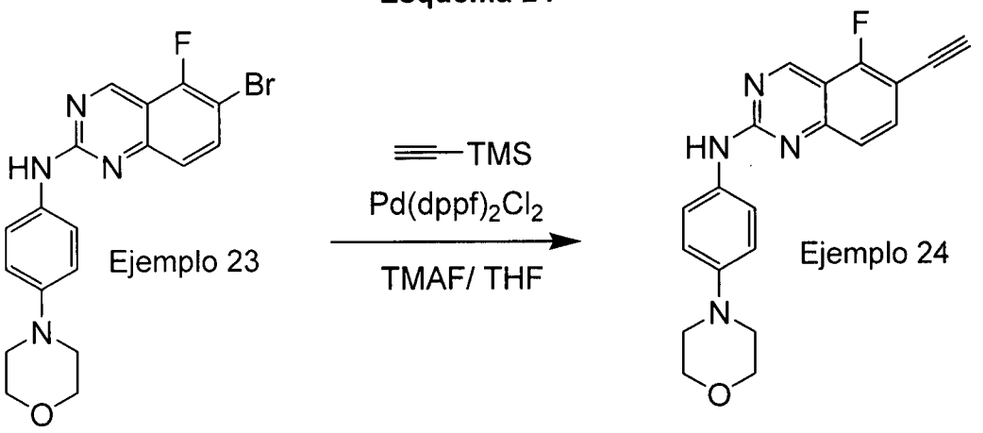
A una solución de la 6-bromo-2-cloro-5-fluoro-quinazolina, **23-3** (1 equivalente) en isopropanol, se le agregó 4-morfolino-anilina (1 equivalente), y la mezcla se calentó a 90°C durante 1 hora en un tubo sellado. La SNAR llegó a completarse mediante la LC/MS, y la purificación en la HPLC de preparación proporcionó la 6-bromo-5-fluoro-N-(4-morfolino-fenil)-quinazolin-2-amina en un rendimiento cuantitativo. ES/MS *m/z* 403(MH^+).

Ejemplo 24: 6-etinil-5-fluoro-N-(4-morfolino-fenil)-quinazolin-2-amina

El compuesto objeto se preparó de acuerdo con el siguiente

Esquema General 24:

Esquema 24



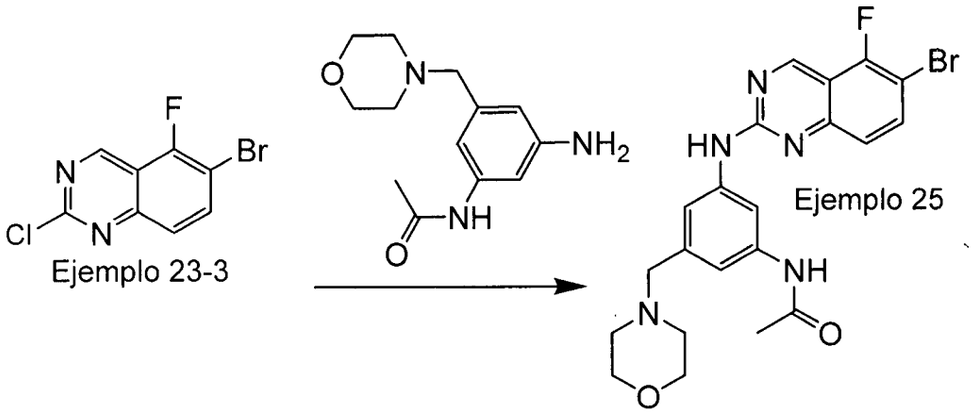
A la 6-bromo-5-fluoro-N-(4-morfolino-fenil)-quinazolin-2-amina (el compuesto del Ejemplo 20) (1 equivalente) en 4:1 de dimetil-formamida y trietil-amina, se le agregaron TMS-acetileno (4 equivalentes), yoduro de cobre (0.2 equivalentes), y $Pd(dppf)_2Cl_2.CH_2Cl_2$ (0.2 equivalentes), y la mezcla se pasó por microondas durante 10 minutos a 120°C. La mezcla de reacción se dividió entonces entre acetato de etilo y agua. La capa orgánica se concentró para proporcionar la 6-etinil-5-fluoro-N-(4-morfolino-fenil)-quinazolin-2-amina ES/MS *m/z* 420(MH^+). Al producto crudo se le agregaron tetrahidrofurano y fluoruro de tetrametil-amonio (1 equivalente), y la mezcla se agitó a temperatura ambiente durante 1 hora. Se dividió entonces entre acetato de etilo y agua, y la capa orgánica se concentró, y el residuo resultante se purificó en una HPLC de preparación, para dar la (4-(5-cloro-6-etinil-quinazolin-2-il-amino)-fenil)-(morfolino)-metanona. ES/MS *m/z* 349(MH^+).

Ejemplo 25: *N*-(3-(6-bromo-5-fluoro-quinazolin-2-il-amino)-5-

(morfolino-metil)-fenil)-acetamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 25:

Esquema 25

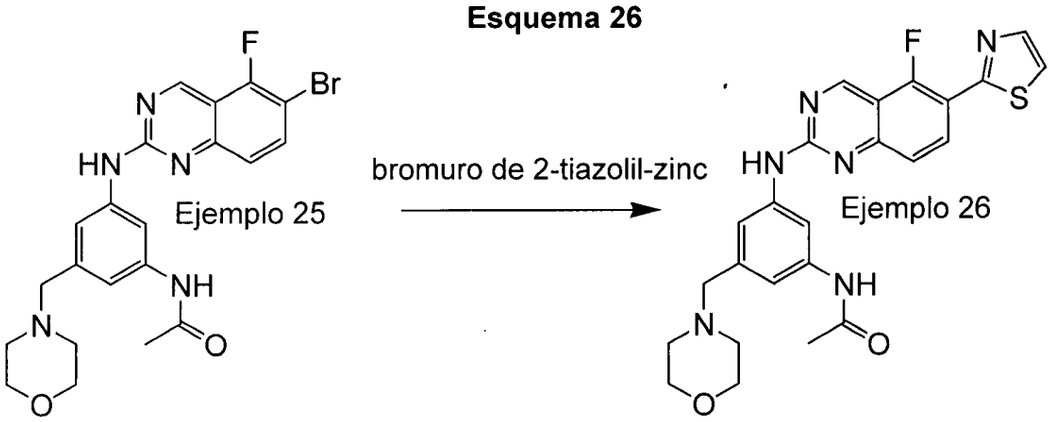


El compuesto de *N*-(3-(6-bromo-5-fluoro-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida se preparó mediante un procedimiento análogo al Ejemplo 23.

Ejemplo 26: *N*-(3-(5-fluoro-6-(tiazol-2-il)-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 26:

Esquema 26

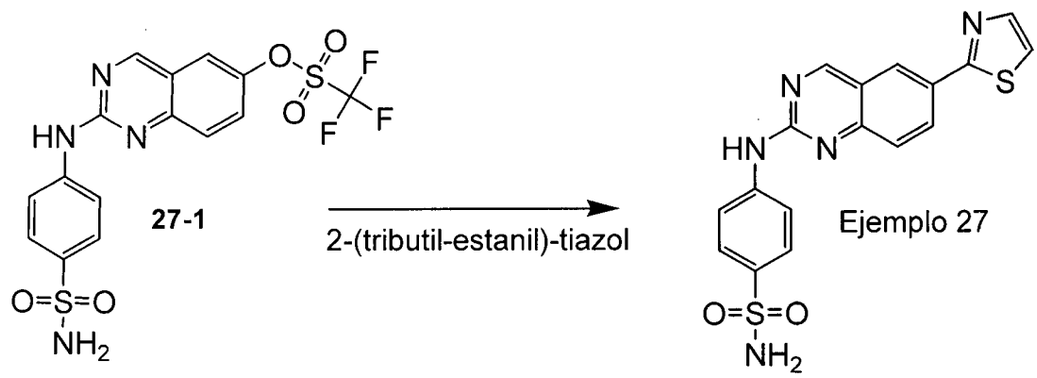


A la *N*-(3-(6-bromo-5-fluoro-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida (a partir del Ejemplo 25) (1 equivalente), se le agregó una solución de bromuro de 2-tiazolil-zinc en tetrahidrofurano, y la mezcla se pasó por microondas a 120°C durante 10 minutos. La formación de *N*-(3-(5-fluoro-6-(tiazol-2-il)-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida se confirmó mediante LC/MS. Entonces se concentró y se purificó mediante HPLC de preparación para dar el producto. ES/MS *m/z* 479(MH^+).

Ejemplo 27: 4-(6-(Tiazol-2-il)-quinazolin-2-il-amino)-bencen-sulfonamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 27:

Esquema 27



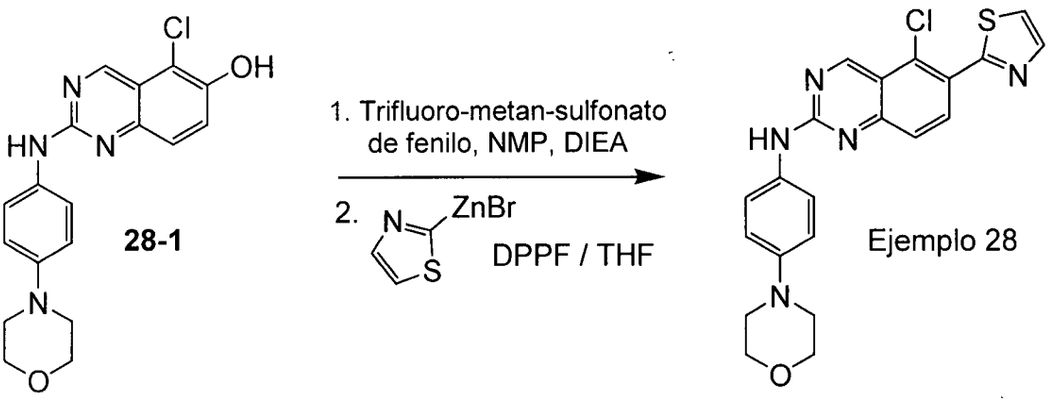
Al trifluoro-metan-sulfonato de 2-(4-sulfamoil-fenil-amino)-quinazolin-6-ilo (preparado siguiendo el Ejemplo 18, Paso 1) (1 equivalente) en N,N-dimetil-formamida se le agregaron 2-(tributil-

estanil)-tiazol (3 equivalentes) y trietil-amina (6 equivalentes). La mezcla se pasó por microondas a 120°C durante 10 minutos. La LC/MS mostró la formación de la 4-(6-(tiazol-2-il)-quinazolin-2-il-amino)-bencen-sulfonamida. Entonces, después del procesamiento, la mezcla cruda se purificó en una HPLC de preparación, para dar la 4-(6-(tiazol-2-il)-quinazolin-2-il-amino)-bencen-sulfonamida. ES/MS *m/z* 384(MH^+).

Ejemplo 28: 5-cloro-N-(4-morfolino-fenil)-6-(tiazol-2-il)-quinazolin-2-amina

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 28:

Esquema 28



Paso 1: Trifluoro-metan-sulfonato de 5-cloro-2-(4-(morfolino-fenil-amino)-quinazolin-6-ilo

Véase el Ejemplo 22 para la síntesis. ES/MS *m/z* 489.1(MH^+).

Paso 2: 5-cloro-N-(4-morfolino-fenil)-6-(tiazol-2-il)-quinazolin-2-

amina

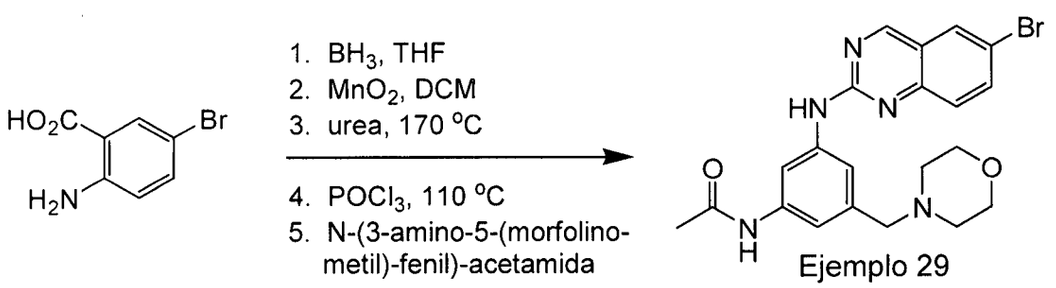
Una mezcla del trifluoro-metan-sulfonato de 5-cloro-2-(4-(morfolino-fenil-amino)-quinazolin-6-ilo (1 equivalente), bromuro de 2-tiazolil-zinc (5 equivalentes, solución 0.5 M en tetrahidrofurano), y Pd $(dppf)_2Cl_2.CH_2Cl_2$ (0.2 equivalentes) en tetrahidrofurano, se pasó por microondas durante 20 minutos a 120°C. La LC-MS mostró la formación de dos productos en una proporción de 1:1. La mezcla de reacción se concentró y se purificó mediante HPLC de semi-preparación, para proporcionar la 5-cloro-N-(4-morfolino-fenil)-6-(tiazol-2-il)-quinazolin-2-amina en un 25 por ciento de rendimiento. ES/MS *m/z* 424.1(MH^+).

El segundo producto de la reacción se identificó como: N-(4-morfolino-fenil)-5,6-di (tiazol-2-il)-quinazolin-2-amina. ES/MS *m/z* 473.0(MH^+).

Ejemplo 29: N-(3-(6-bromo-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 29:

Esquema 29



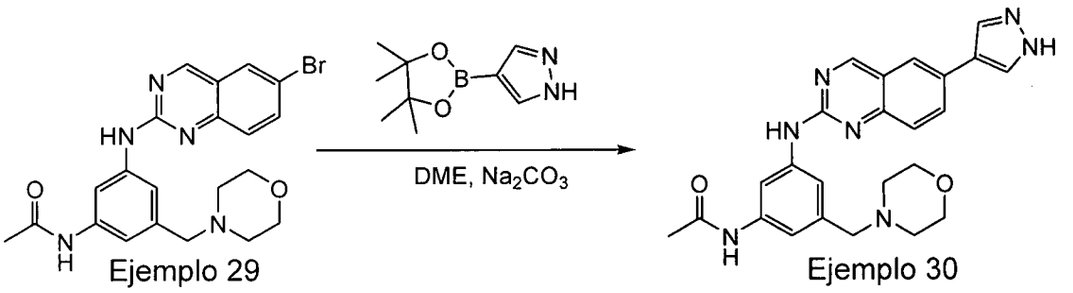
Ejemplo 29

El compuesto de *N*-(3-(6-bromo-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida se preparó mediante una síntesis análoga a la utilizada en el Ejemplo 9. ES/MS *m/z* 456.0 (MH^+).

Ejemplo 30: N-(3-(6-(1H-pirazol-4-il)-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 30:

Esquema 30



Ejemplo 29 Ejemplo 30

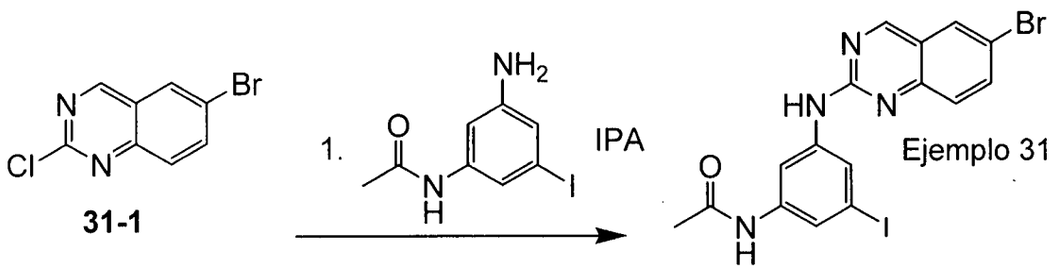
A una solución de la *N*-(3-(6-bromo-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida (a partir del Ejemplo 29) (1 equivalente) en DME, se le agregó una solución de carbonato de sodio 2 M, 4-(4,4,5,5,-tetrametil-1,3,2-dioxa-borolan-2-il)-1H-pirazol (3 equivalentes), y Pd $(dppf)_2Cl_2.CH_2Cl_2$ (0.05 equivalentes), y la mezcla se pasó por microondas durante 10 minutos a 120°C. La mezcla de reacción se dividió entonces entre acetato de etilo y agua. La capa orgánica se lavó con salmuera, se secó, se concentró, y se purificó mediante HPLC de semi-preparación, para proporcionar la *N*-

(3-(6-(1H-pirazol-4-il)-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida; 25 por ciento de rendimiento. ES/MS *m/z* 444.3 (MH^+). La *N*-(3-(morfolino-metil)-5-(quinazolin-2-il-amino)-fenil)-acetamida se aisló como un producto secundario. ES/MS *m/z* 378.2 (MH^+).

Ejemplo 31: *N*-(3-(6-bromo-quinazolin-2-il-amino)-5-yodo-fenil)-acetamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 31:

Esquema 31



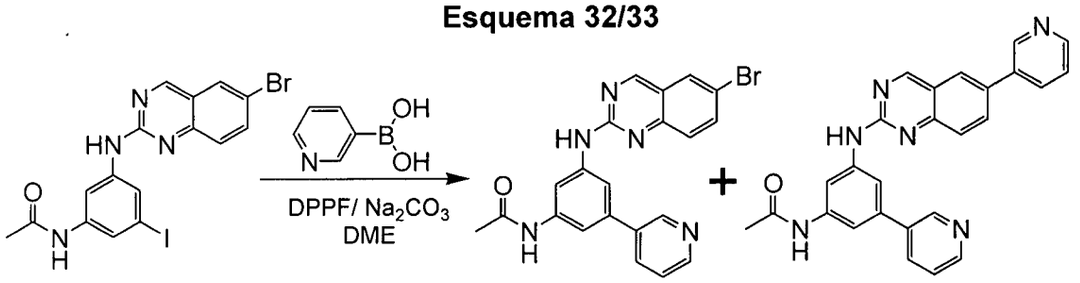
Una mezcla de la 6-bromo-2-cloro-quinazolina, **31-1** (1 equivalente), y N-(3-amino-5-yodo-fenil)-acetamida (1 equivalente) en 2-propanol se calentó a 110°C durante la noche. El producto se precipitó en la mezcla de reacción. El precipitado se filtró, se lavó, y se secó al vacío, para proporcionar el producto puro como un sólido amarillo en un 99 por ciento de rendimiento. ES/MS *m/z* 482.9(MH^+).

Ejemplo 32: *N*-(3-(6-bromo-quinazolin-2-il-amino)-5-(piridin-3-il)-fenil)-acetamida; y

Ejemplo 33: *N*-(3-(piridin-3-il)-5-(6-(piridin-3-il)-quinazolin-2-il-amino)-fenil)-acetamida

Los compuestos objeto se prepararon de acuerdo con el siguiente Esquema General 32/33:

Esquema 32/33



Ejemplo 31 | Ejemplo 32 | Ejemplo 33

Al compuesto del Ejemplo 26 (1 equivalente) en DME se le agregó una solución de carbonato de sodio 2 M, ácido 3-piridil-borónico (2 equivalentes), y $Pd(dppf)_2Cl_2.CH_2Cl_2$ (0.05 equivalentes), y la mezcla se pasó por microondas durante 10 minutos a 120°C. La LC-MS mostró la formación de dos productos. La mezcla de reacción se dividió entonces entre acetato de etilo y agua. La capa orgánica se lavó con salmuera, se secó, se concentró, y se purificó mediante HPLC de semi-preparación, para proporcionar la *N*-(3-(6-bromo-quinazolin-2-il-amino)-5-(piridin-3-il)-fenil)-acetamida en un 60 por ciento de rendimiento. ES/MS *m/z* 434.1 (MH^+).

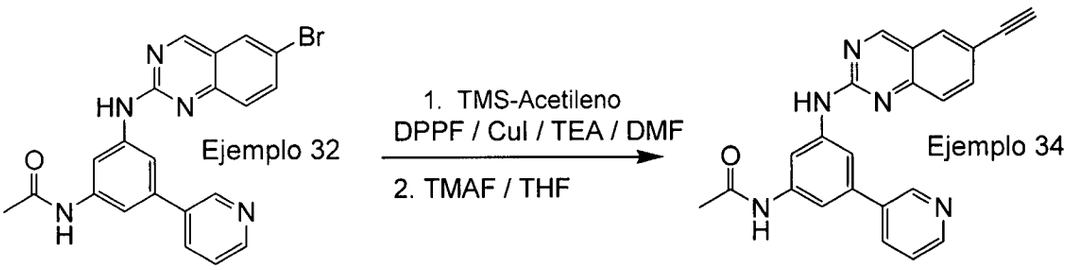
El segundo producto de esta reacción (Ejemplo 33), se identificó como: *N*-(3-(piridin-3-il)-5-(6-(piridin-3-il)-quinazolin-2-il-

amino)-fenil)-acetamida. ES/MS *m/z* 433.2 (MH^+).

Ejemplo 34: *N*-(3-(6-etinil-quinazolin-2-il-amino)-5-(piridin-3-il)-fenil)-acetamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 34:

Esquema 34



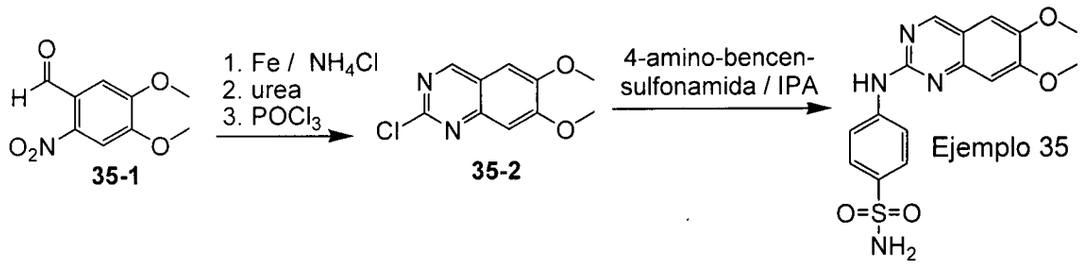
A la *N*-(3-(6-bromo-quinazolin-2-il-amino)-5-(piridin-3-il)-fenil)-acetamida (1 equivalente) en 4:1 de dimetil-formamida y trietil-amina, se le agregaron TMS-acetileno (4 equivalentes), yoduro de cobre (0.2 equivalentes), y $Pd(dppf)_2Cl_2.CH_2Cl_2$ (0.2 equivalentes), y la mezcla se pasó por microondas durante 10 minutos a 120°C. La mezcla de reacción se dividió entonces entre acetato de etilo y agua. La capa orgánica se concentró para proporcionar la *N*-(3-(piridin-3-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenil)-acetamida. ES/MS *m/z* 452.1(MH^+). Al producto crudo se le agregaron tetrahidrofurano y fluoruro de tetrametil-amonio (1 equivalente), y la mezcla se agitó a temperatura ambiente durante 1 hora. Se dividió entonces entre acetato de etilo y agua, y la capa orgánica se concentró y se purificó mediante HPLC de semi-preparación, para proporcionar la *N*-(3-(6-

etinil-quinazolin-2-il-amino)-5-(piridin-3-il)-fenil)-acetamida. ES/MS *m/z* 380.1(MH^+).

Ejemplo 35: 4-(6,7-dimetoxi-quinazolin-2-il-amino)-bencen-sulfonamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 35:

Esquema 35



Paso 1: 2-amino-4,5-dimetoxi-benzaldehído

A una solución del 4,5-dimetoxi-2-nitro-benzaldehído (1 equivalente) en etanol y agua (2:1), se le agregó cloruro de amonio (10 equivalentes). La solución se calentó a 90°C, seguida por la adición de polvo de hierro (4 equivalentes) en porciones. La mezcla de reacción se calentó a 90°C durante 30 minutos, se enfrió, se diluyó con dicloro-metano, y se filtró a través de tierra diatomácea. La capa orgánica se separó de la capa acuosa, se lavó con salmuera, y se secó sobre sulfato de sodio, se filtró, se concentró, y se secó al vacío, para proporcionar el producto en un 93 por ciento de rendimiento. ES/MS *m/z* 182.1 (MH^+).

Paso 2: 6,7-dimetoxi-quinazolin-2-ol

Una mezcla de 2-amino-4,5-dimetoxi-benzaldehído (1 equivalente) (obtenida a partir del Paso 1), y urea (15 equivalentes) se calentó a 175°C con agitación vigorosa durante 2 horas. La reacción se enfrió a temperatura ambiente, y se agregó agua. Se formó un precipitado sólido, se recolectó mediante filtración, y se secó al aire, para dar el 6,7-dimetoxi-quinazolin-2-ol como un sólido color café en un 40 por ciento de rendimiento. ES/MS *m/z* 207.0 (MH^+).

Paso 3: 2-cloro-6,7-dimetoxi-quinazolina, ***35-2***

El 6,7-dimetoxi-quinazolin-2-ol crudo se calentó en oxicloruro de fósforo puro ($POCl_3$) a 110°C durante 2 horas. La mezcla resultante se enfrió a temperatura ambiente, y se concentró al vacío hasta casi la sequedad. Se agregó agua helada, y el pH se ajustó a aproximadamente 6 utilizando bicarbonato de sodio. La extracción con dicloro-metano, seguida por secado con sulfato de sodio y concentración al vacío, proporcionó la 2-cloro-6,7-dimetoxi-quinazolina como un sólido color café. ES/MS *m/z* 225.0 (MH^+).

Paso 4: 4-(6,7-dimetoxi-quinazolin-2-il-amino)-bencen-sulfonamida

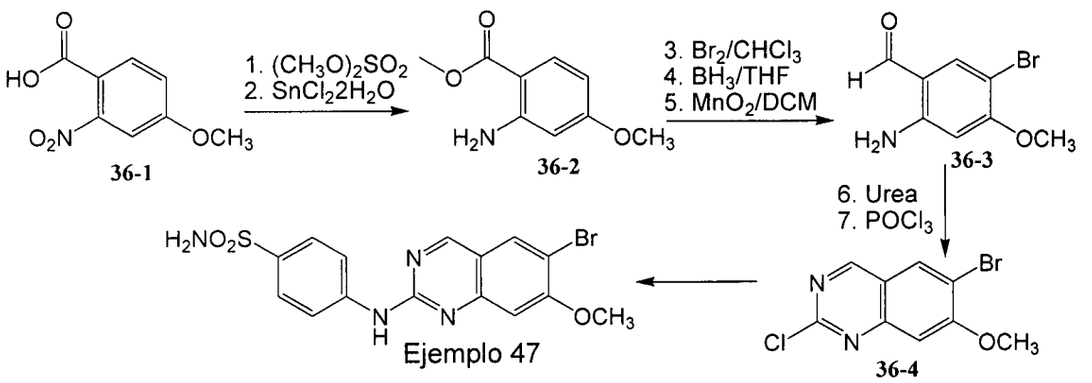
Una mezcla de la 2-cloro-6,7-dimetoxi-quinazolina (1 equivalente) y 4-amino-bencen-sulfonamida (1 equivalente) en isopropanol, se calentó a 90°C durante 16 horas. El producto se precipitó en la mezcla de reacción, y se separó mediante filtración, se lavó y se secó, para proporcionar el producto puro como un sólido

amarillo en un 87 por ciento de rendimiento. ES/MS *m/z* 361.0 (MH^+).

Ejemplo 47: 4-(6-bromo-7-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 36:

Esquema 36



Paso 1: 4-metoxi-2-nitro-benzoato de metilo

A una solución 0.4 M helada del ácido 4-metoxi-2-nitro-benzoico **36-1** en tetrahidrofurano, se le agregó trietil-amina (6.0 equivalentes), seguida por la adición de sulfato de dimetilo (4.0 equivalentes). La mezcla resultante se agitó a 0°C durante 1 hora, y luego a temperatura ambiente durante la noche. La LCMS mostró aproximadamente el 90 por ciento de conversión hasta el producto. El solvente se removió bajo presión reducida. El residuo resultante se diluyó con acetato de etilo, luego se lavó en secuencia con

bicarbonato de sodio saturado y salmuera, y entonces se secó sobre sulfato de sodio. La concentración de la solución secada proporcionó el producto deseado como un sólido grisáceo en un 94 por ciento de rendimiento. La estructura del producto se confirmó mediante espectro de RMN de protones.

Paso 2: *2-amino-4-metoxi-benzoato de metilo, 36-2*

A una solución 0.4 M del 4-metoxi-2-nitro-benzoato de metilo en N,N-dimetil-formamida en un baño de hielo, se le agregó dihidrato de cloruro de estaño(II) (7.0 equivalentes). La mezcla se agitó a temperatura ambiente durante la noche, y entonces se diluyó con acetato de etilo (40 mililitros de acetato de etilo por cada mM del compuesto de nitro). Se agregó trietil-amina (14 equivalentes), y la suspensión blanca resultante se agitó durante 1 hora, y entonces se filtró. La torta del filtro se enjuagó con acetato de etilo. La fase orgánica combinada se lavó con agua y luego con salmuera, y entonces se secó sobre sulfato de sodio. La concentración de la fase orgánica seca proporcionó el producto deseado en un 95 por ciento de rendimiento. ES/MS *m/z* 182 (MH^+).

Paso 3: *2-amino-5-bromo-4-metoxi-benzoato de metilo*

A una solución 0.06 M del 2-amino-4-metoxi-benzoato de metilo, **36-2** en cloroformo, se le agregó bromo (1.0 equivalente como una solución 0.05 M en cloroformo) por medio de un embudo adicional. La mezcla resultante se agitó a temperatura ambiente durante 3 horas. Los datos de LCMS mostraron que la reacción de bromación procedió hasta una conversión de aproximadamente el 72

por ciento. El precipitado blanco resultante se recolectó mediante filtración, se lavó completamente con dicloro-metano y entonces se secó al aire, para proporcionar el 2-amino-5-bromo-4-metoxi-benzoato de metilo como su sal de HBr. Rendimiento: 70 por ciento. ES/MS *m/z* 260/262 (MH^+).

Paso 4: (2-amino-5-bromo-4-metoxi-fenil)-metanol

A una suspensión 0.25 M del 2-amino-5-bromo-4-metoxi-benzoato de metilo en tetrahidrofurano en un baño de hielo, se le agregó lentamente borano (4.5 equivalentes como una solución en tetrahidrofurano 1.0 M). La mezcla de reacción se agitó a temperatura ambiente durante 48 horas. La mezcla entonces se volvió a enfriar hasta 0°C, se apagó con metanol, y se concentró para remover el solvente. El residuo resultante se disolvió en acetato de etilo y la fase orgánica resultante se lavó con agua y luego con salmuera, y entonces se secó sobre sulfato de sodio, y se concentró, para proporcionar el (2-amino-5-bromo-4-metoxi-fenil)-metanol, como un aceite color café. ES/MS *m/z* 214/216 (MH^+).

Paso 5: 2-amino-5-bromo-4-metoxi-benzaldehído, 36-3

Se agregó óxido de manganeso (IV) (8 equivalentes), a una solución 0.22 M de (2-amino-5-bromo-4-metoxi-fenil)-metanol en dicloro-metano. La suspensión resultante se agitó a temperatura ambiente bajo Argón durante 12 horas. La mezcla de reacción entonces se filtró a través de tierra diatomácea y la torta del filtro resultante se lavó con dicloro-metano. El filtrado combinado se concentró para proporcionar el producto como un sólido color café en

un 67 por ciento de rendimiento. ES/MS *m/z* 230/232 (MH^+).

Paso 6: 6-bromo-7-metoxi-quinazolin-2-ol

Una mezcla del 2-amino-5-bromo-4-metoxi-benzaldehído, **36-3**, (1 equivalente), y urea (14 equivalentes), se calentó a 180°C en un baño de aceite bajo argón durante 2 horas. Se agregó agua después de enfriar a temperatura ambiente. El sólido se recolectó mediante filtración, y se secó al aire, para dar el producto en un 90 por ciento de rendimiento. ES/MS *m/z* 255/257 (MH^+).

Paso 7: 6-bromo-2-cloro-7-metoxi-quinazolina, 36-4

Una suspensión 0.5 M de 6-bromo-7-metoxi-quinazolin-2-ol en oxicloruro de fósforo se calentó a 110°C en un baño de aceite durante 3 horas. La mezcla entonces se enfrió a temperatura ambiente. Los volátiles se removieron bajo presión reducida. El residuo resultante se trituró con agua helada. El sólido resultante se recolectó mediante filtración, y se secó al aire, para proporcionar el producto en un 55 por ciento de rendimiento. ES/MS *m/z* 273/275 (MH^+).

Paso 8: 4-(6-bromo-7-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida

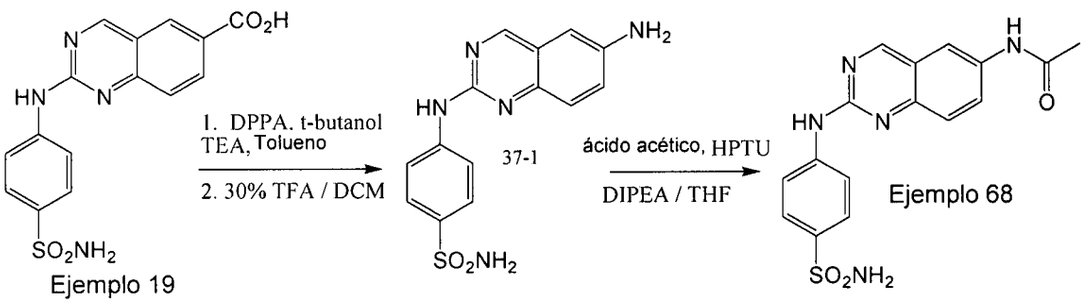
A una solución de 50 miligramos del **36-4** en 2-propanol (1 mililitro), se le agregó sulfanil-amida (1.0 equivalentes). La reacción se agitó a 90°C durante 18 horas. El clorhidrato se recolectó mediante filtración al vacío y se secó al aire, para dar un material crudo, el cual se puede utilizar para otras modificaciones químicas. El material puro se obtuvo mediante purificación con HPLC. ES/MS

m/z 409/411 (MH^+).

Ejemplo 68: *N*-(2-(4-Sulfamoil-fenil-amino)-quinazolin-6-il)-acetamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 37:

Esquema 37



Paso 1: Terbutil-carbamato de 2-(4-sulfamoil-fenil-amino)-quinazolin-6-ilo

Al ácido 2-(4-sulfamoil-fenil-amino)-quinazolin-6-carboxílico (1 equivalente) (preparado como en el Ejemplo 19) en tolueno, se le agregaron difenil-fosforil-azida (DPPA) (1.2 equivalentes), terbutanol (10 equivalentes), y trietil-amina (2 equivalentes). La mezcla resultante se calentó a 70°C durante 30 minutos, y entonces se calentó adicionalmente hasta 100°C, y se mantuvo a 100°C durante la noche. La mezcla de reacción se concentró entonces, y el residuo resultante se purificó mediante HPLC de semi-preparación, para proporcionar el producto puro.

Paso 2: 4-(6-amino-quinazolin-2-il-amino)-bencen-sulfonamida, 37-1

Una solución del terbutil-carbamato de 2-(4-sulfamoil-fenil-amino)-quinazolin-6-ilo en el 30 por ciento de ácido trifluoro-acético / dicloro-metano, se agitó a temperatura ambiente durante 30 minutos. El solvente entonces se evaporó, y el residuo crudo resultante se purificó mediante HPLC de semi-preparación, para proporcionar el producto.

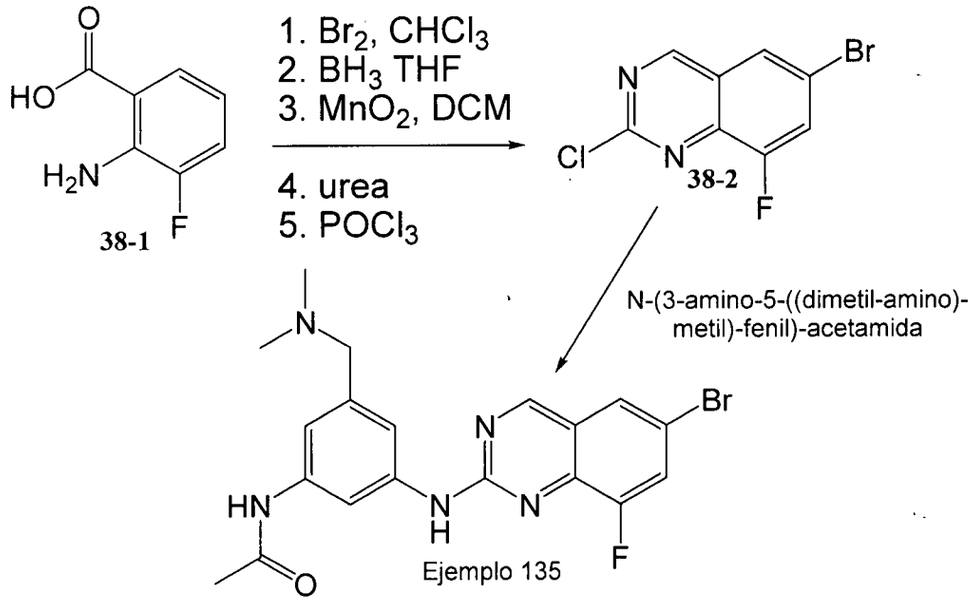
Paso 3: N-(2-(4-Sulfamoil-fenil-amino)-quinazolin-6-il)-acetamida

A una solución de la 4-(6-amino-quinazolin-2-il-amino)-bencen-sulfonamida, **37-1** (1 equivalente) en tetrahidrofurano, se le agregaron ácido acético (5 equivalentes), HBTU (4 equivalentes), y DIEA (10 equivalentes). La mezcla resultante se agitó a temperatura ambiente durante 48 horas. La reacción no llegó a completarse. La mezcla de reacción se diluyó con acetato de etilo, y la mezcla diluida resultante se lavó con agua y luego salmuera, y entonces se secó sobre sulfato de sodio. La mezcla seca se filtró, y entonces se concentró. El concentrado se purificó mediante HPLC de semi-preparación, para proporcionar la *N*-(2-(4-sulfamoil-fenil-amino)-quinazolin-6-il)-acetamida.

Ejemplo 135: *N*-(3-(6-bromo-8-fluoro-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-acetamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 38:

Esquema 38



Paso 1: Ácido 2-amino-5-bromo-3-fluoro-benzoico

A una suspensión del ácido 2-amino-3-fluoro-benzoico, **38-1**, (5 gramos, 32.2 milimoles) en cloroformo (200 mililitros), se le agregó por goteo una solución de bromo (1.1 equivalentes) en cloroformo (125 mililitros). La mezcla se agitó a temperatura ambiente durante 16 horas. El sólido blanco resultante se recolectó mediante filtración y se lavó completamente con dicloro-metano, hasta que el filtrado fue incoloro. El sólido se secó al aire, para dar 9.6 gramos de un polvo blanco como la sal de HBr del ácido 2-amino-5-bromo-3-fluoro-benzoico (95 por ciento de rendimiento). ES/MS *m/z* 234/236 (MH^+).

Paso 2:

Al intermediario anterior (30.6 milimoles) en tetrahidrofurano (100 mililitros) a 0°C, se le agregó una solución de complejo de boro-tetrahidrofurano (1 M en tetrahidrofurano, 129 mililitros, 4 equivalentes). La mezcla resultante se agitó a temperatura ambiente durante 40 horas. El solvente se removió al vacío, y el exceso de reactivo se apagó mediante la adición de agua (30 mililitros) lentamente. El pH (de aproximadamente 3) de la mezcla apagada se ajustó a un pH de 7 mediante la adición de bicarbonato de sodio (acuoso saturado). La mezcla se extrajo entonces con dicloro-metano. Los extractos orgánicos se combinaron, se lavaron con salmuera, se secaron con sulfato de sodio, y se concentraron, para proporcionar un material crudo como un sólido blanco. ES/MS *m/z* 220/222 (MH^+).

Paso 3: 2-amino-5-bromo-3-fluoro-fenil)-metanol

Al intermediario anterior (30.6 milimoles) en dicloro-metano (450 mililitros), se le agregó dióxido de manganeso (MnO_2, 22 gramos, 258 milimoles). La mezcla resultante se agitó a temperatura ambiente bajo argón durante 18 horas. La mezcla entonces se filtró a través de tierra diatomácea y se lavó completamente con dicloro-metano. El filtrado se concentró entonces al vacío, para proporcionar el producto crudo de (2-amino-5-bromo-3-fluoro-fenil)-metanol (5.6 gramos), el cual se utilizó para el siguiente paso sin mayor purificación. ES/MS *m/z* 218/220 (MH^+).

Paso 4: 2-hidroxi-quinazolina

Una mezcla del (2-amino-5-bromo-3-fluoro-fenil)-metanol (5.6 gramos, 23.7 milimoles, obtenido a partir del Paso 3), y urea (21 gramos, 15 equivalentes), se calentó a 175°C con agitación vigorosa durante 15 minutos. La reacción entonces se enfrió a temperatura ambiente, y se agregó agua. Se formó un precipitado sólido, se recolectó mediante filtración, y se secó al aire, para proporcionar la 2-hidroxi-quinazolina como un sólido color café claro.

Paso 5: 6-bromo-2-cloro-8-fluoro-quinazolina, 38-2

Al material crudo anterior se le agregó oxicloruro de fósforo ($POCl_3$, 20 mililitros), y esta mezcla se calentó a 110°C durante 30 minutos. La mezcla entonces se enfrió a temperatura ambiente, y se concentró al vacío hasta casi la sequedad. Se agregó agua helada al concentrado, y el pH de la mezcla resultante se ajustó a aproximadamente 6 utilizando bicarbonato de sodio. La mezcla con el pH ajustado se extrajo con dicloro-metano. El extracto se secó con sulfato de sodio, y se concentró al vacío, para proporcionar el producto deseado de 6-bromo-2-cloro-8-fluoro-quinazolina, como un polvo color café claro (1.63 gramos).

Paso 6: N-(3-(6-bromo-8-fluoro-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-acetamida

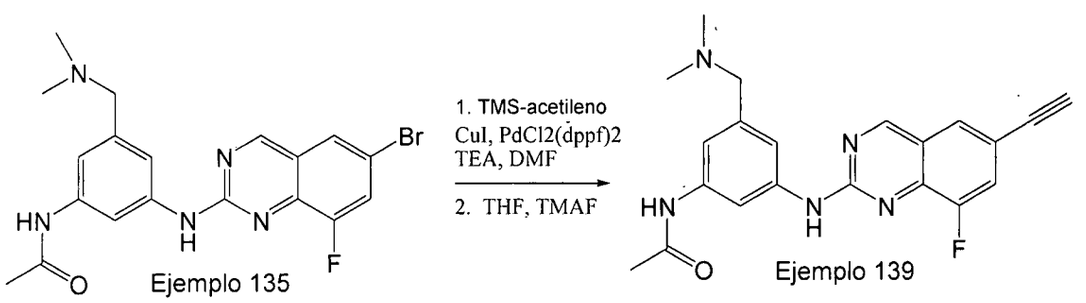
Una mezcla de la 6-bromo-2-cloro-8-fluoro-quinazolina, **38-2,** *N*-(3-amino-5-((dimetil-amino)-metil)-fenil)-acetamida (1 equivalente), y HCl en dioxano (1 equivalente) en isopropanol (2.5 mililitros), se

calentó a 75°C durante 16 horas. La mezcla resultante se diluyó con agua, se lavó con acetato de etilo para remover las impurezas orgánicas, se basificó la porción acuosa con bicarbonato de sodio (acuoso) a un pH de 9, y entonces se agregó salmuera. La solución acuosa basificada se extrajo con cloroformo (3 veces). Los extractos orgánicos se combinaron, se lavaron con salmuera, se secaron con sulfato de sodio, y se concentraron, para dar un material crudo, el cual se purificó mediante HPLC.

Ejemplo 139: *N*-(3-((dimetil-amino)-metil)-5-(6-etinil-8-fluoro-quinazolin-2-il-amino)-fenil)-acetamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General 39:

Esquema 39



Paso 1:

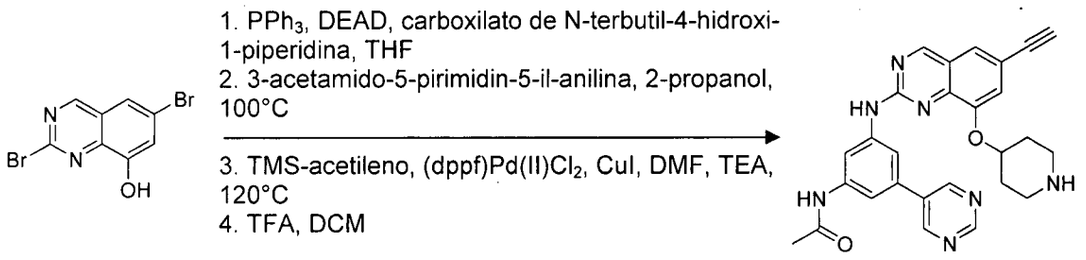
Una mezcla de la *N*-(3-(6-bromo-8-fluoro-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-acetamida, (a partir del Ejemplo 135), etinil-trimetil-silano, yoduro de cobre(I), 1,1'-bis-(difenil-fosfino)-ferroceno-dicloro-paladio(II), trietil-amina, y N,N-

dimetil-formamida, preparada de acuerdo con la misma estequiometría que se empleó en la reacción del Ejemplo 7, Paso 1, y se pasó por microondas a 120°C durante 8 minutos. La mezcla resultante se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó con sulfato de sodio, y se concentró, para proporcionar un residuo crudo.

Paso 2: N-(3-(8-fluoro-6-etinil-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-acetamida (Ejemplo 139)

Al intermediario a partir del Paso 1, se le agregan tetrahidrofurano, 2-propanol, y fluoruro de tetrametil-amonio, de acuerdo con la misma estequiometría que se empleó en la reacción del Ejemplo 7, Paso 2 . La mezcla se agitó a temperatura ambiente durante 20 minutos. La mezcla resultante se diluyó con agua, y se extrajo con acetato de etilo (3 veces). Los extractos orgánicos se combinaron, se lavaron con salmuera, se secaron con sulfato de sodio, y se concentraron, para proporcionar un material crudo, el cual se purificó mediante HPLC, para proporcionar el compuesto del título.

Ejemplo 216: N-(3-(6-etinil-8-(piperidin-4-iloxi)-quinazolin-2-il-amino)-5-(pirimidin-5-il)-fenil)-acetamida



Paso 1. Preparación de la 2,6-dibromo-8-(N-Boc-piperidin-4-iloxi)-quinazolina

A una solución 0.30 M de trifenil-fosfina (2.0 equivalentes) en tetrahidrofurano, se le agregó azodicarboxilato de dietilo (2.0 equivalentes). La mezcla se agitó durante 15 minutos a temperatura ambiente. Se agregó carboxilato de N-terbutil-4-hidroxi-1-piperidina (4.0 equivalentes). La mezcla se agitó durante 15 minutos a temperatura ambiente. Se agregó 2,6-dibromo-8-hidroxi-quinazolina (1.0 equivalentes). La mezcla se agitó durante 24 horas adicionales. La mezcla cruda se concentró, se purificó mediante cromatografía por evaporación instantánea (2:1 hexanos:EtOAc), y se concentró para dar el producto deseado.

Paso 2. Desplazamiento

A una solución 0.30 M de 2,6-dibromo-8-(N-Boc-piperidin-4-iloxi)-quinazolina en 2-propanol se le agregó 3-acetamido-5-pirimidin-5-il-anilina (1.0 equivalentes). La reacción se agitó a 100°C durante 14 horas. La mezcla cruda se concentró y se utilizó sin mayor purificación.

Paso 3. Sonogashira y destilación

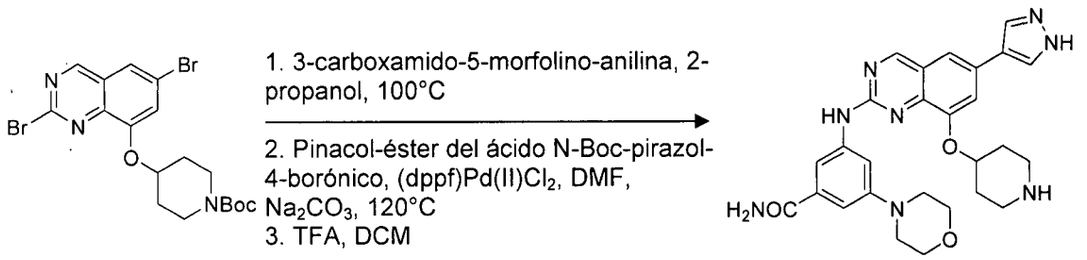
El producto a partir del Paso 2 se trató de una manera análoga al Ejemplo 281, Paso 2, y se llevó adelante al Paso 4 sin purificación.

Paso 4. Desprotección

El producto a partir del Paso 3 se disolvió en suficiente dicloro-metano:ácido trifluoro-acético, 1:1, para hacer una solución 0.20 M.

La mezcla se agitó durante 30 minutos a temperatura ambiente, y se concentró. El producto crudo se purificó mediante HPLC de fase inversa y se liofilizó, para dar el producto deseado como su sal de ácido trifluoro-acético. ES/MS *m/z* 480 (MH^+).

Ejemplo 220: 3-morfolino-5-(8-(piperidin-4-iloxi)-6-(1H-pirazol-4-il)-quinazolin-2-il-amino)-benzamida



Paso 1. Desplazamiento

A una solución 0.30 M del producto a partir del Ejemplo 283, Paso 1 en 2-propanol, se le agregó la 3-carboxamido-5-morfolino-anilina (1.0 equivalentes). La reacción se agitó a 100°C durante 14 horas. La mezcla cruda se concentró y se utilizó sin mayor purificación.

Paso 2. Suzuki

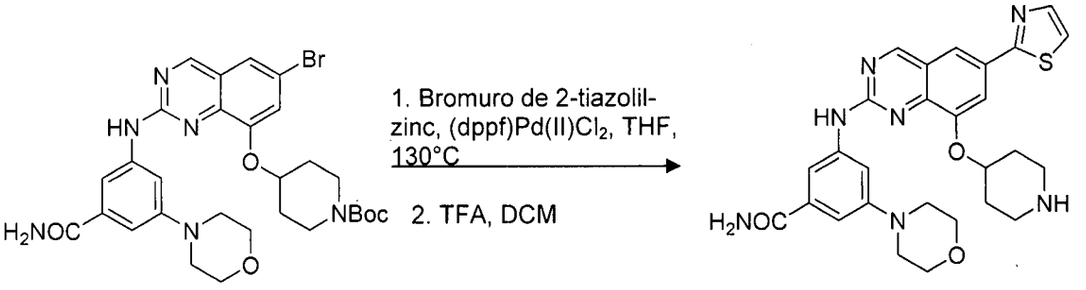
A una solución 0.10 M del producto a partir del Paso 1 (1.0 equivalentes) en DME, se le agregó pinacol-éster del ácido N-Boc-pirazol-4-borónico (4.0 equivalentes), complejo de [1,1'-bis-(difenil-fosfino)-ferroceno]-dicloro-paladio(II) con dicloro-metano (0.10 equivalentes), y carbonato de sodio acuoso 2.0M (5.0 equivalentes). La reacción se pasó por microondas a 120°C durante 10 minutos. La

mezcla se diluyó con tetrahidrofurano, se filtró, se concentró, y se llevó adelante al Paso 4 sin purificación.

Paso 3. Desprotección

El producto a partir del Paso 2 se disolvió en suficiente dicloro-metano:ácido trifluoro-acético, 1:1, para hacer una solución 0.20 M. La mezcla se agitó durante 30 minutos a temperatura ambiente, y se concentró. El producto crudo se purificó mediante HPLC de fase inversa y se liofilizó, para dar el producto deseado como su sal de ácido trifluoro-acético. ES/MS *m/z* 515 (MH^+).

Ejemplo 229: 3-morfolino-5-(8-(piperidin-4-iloxi)-6-(tiazol-2-il)-quinazolin-2-il-amino)-benzamida



Paso 1. Negishi

Al producto del Ejemplo 284, Paso 1, se le agregó cianuro de zinc(II) (4.0 equivalentes), y complejo de [1,1'-bis-(difenil-fosfino)-ferroceno]-dicloro-paladio(II) con dicloro-metano (0.10 equivalentes). La reacción se pasó por microondas a 130°C durante 10 minutos. La mezcla se diluyó con acetato de etilo, y se lavó con regulador de EDTA acuoso a un pH de aproximadamente 9. La fase orgánica se secó sobre sulfato de sodio, y se concentró, para dar el producto

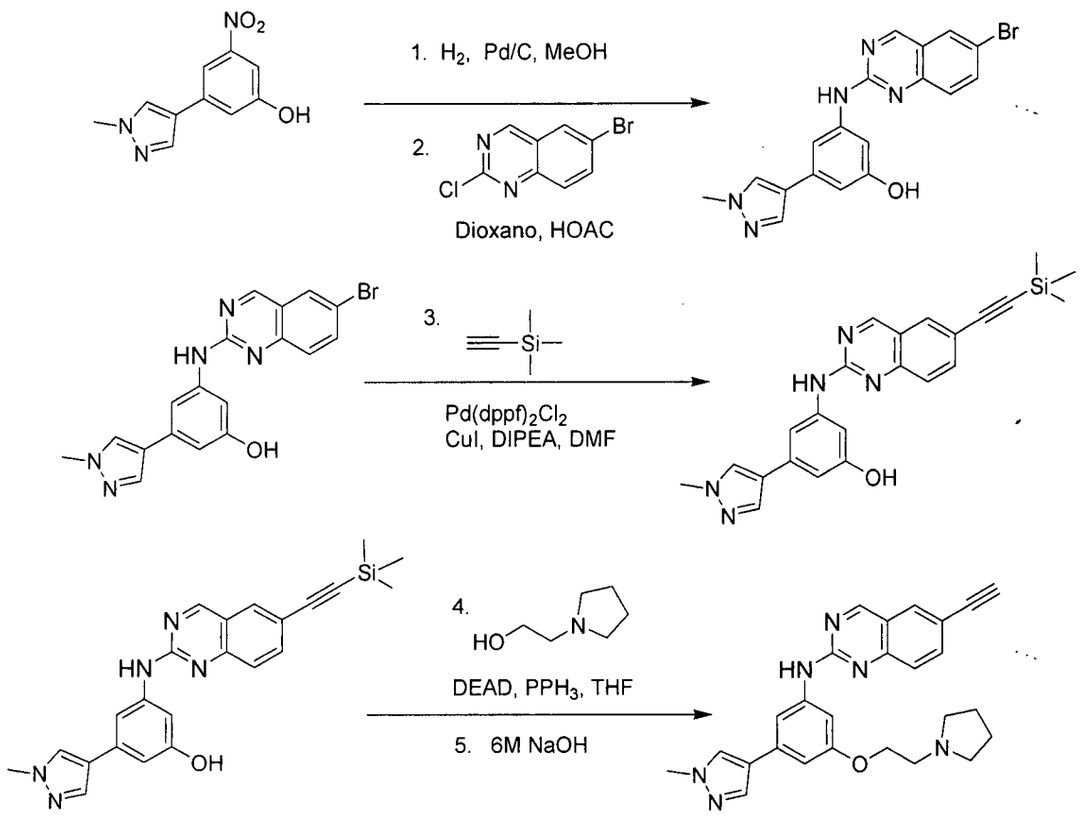
deseado.

Paso 2. Desprotección

El producto a partir del Paso 1 se disolvió en suficiente dicloro-metano:ácido trifluoro-acético, 1:1, para hacer una solución 0.20 M. La mezcla se agitó durante 30 minutos a temperatura ambiente, y se concentró. El producto crudo se purificó mediante HPLC de fase inversa y se liofilizó, para dar el producto deseado como su sal de ácido trifluoro-acético. ES/MS *m/z* 532 (MH^+).

Ejemplo 459: 6-etinil-N-(3-(1-metil-1H-pirazol-4-il)-5-(2-(pirrolidin-1-il)-etoxi)-fenil)-quinazolin-2-amina

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1: 3-amino-5-(1-metil-1H-pirazol-4-il)-fenol

Al material de partida del 3-(1-metil-1H-pirazol-4-il)-5-nitro-fenol crudo (7.04 gramos, 32 milimoles), se le agregó Pd al 10 por ciento sobre carbón (2.1 gramos, 30 por ciento en peso) bajo argón. Bajo argón, con una jeringa, se agregaron cuidadosamente 95 mililitros de metanol. A esta mezcla de reacción se le agregó un globo de hidrógeno y se evacuó y se rellenó 6 veces. La reacción se agitó a temperatura ambiente durante 22 horas o hasta que se consideró hecha mediante LC. A la mezcla de reacción se le agregó acetato de etilo, y se filtró bajo argón a través de Celite, y se lavó con una solución de 1:1 de acetato de etilo y metanol. El filtrado se concentró bajo presión reducida, para dar el 3-amino-5-(1-metil-1H-pirazol-4-il)-fenol, como el material crudo (8.0 gramos). ES/MS *m/z* 190(MH^+).

Paso 2: 3-(6-bromo-naftalen-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenol

A la mezcla de reacción del 3-amino-5-(1-metil-1H-pirazol-4-il)-fenol (2.6 gramos, 13.68 milimoles) en 20 mililitros de dioxano, se le agregaron 6-bromo-2-cloro-quinazolina (1.75 gramos, 7.20 milimoles) y ácido acético (1.73 mililitros, 28.8 milimoles). La solución de la reacción se agitó a 95-100°C durante 60 horas o hasta que se consideró hecha mediante LCMS. A la mezcla de reacción cruda se le agregaron 30 mililitros de dioxano, se dejó enfriar, se filtraron los sólidos, y el filtrado se concentró (producto). El residuo crudo se

purificó mediante cromatografía en columna de gel de sílice, y se concentró al vacío, para dar el 3-(6-bromo-naftalen-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenol, (1.13 gramos). ES/MS *m/z* 396/398(MH^+). Se puede hacer una purificación adicional mediante HPLC de preparación, y se liofilizó para hacer una sal del ácido trifluoro-acético.

Paso 3: 3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenol

A la mezcla de reacción del 3-(6-bromo-naftalen-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenol (1.13 gramos, 2.85 milimoles) en 7 mililitros de dimetil-formamida, se le agregaron $Pd(dppf)_2Cl_2$ (232 miligramos, 0.28 milimoles), CuI (119 miligramos, 0.622 milimoles), etinil-trimetil-silano (838 miligramos, 8.55 milimoles), y finalmente se agregó N-etil-N-isopropil-propan-2-amina (DIPEA) (1.5 mililitros, 8.55 milimoles). Esta mezcla de reacción se agitó a 95°C durante 1 hora o hasta que se consideró hecha mediante LCMS. La mayor parte de la dimetil-formamida se concentró, se agregaron 350 mililitros de acetato de etilo, 75 mililitros de bicarbonato de sodio saturado, y se agitaron brevemente. La mezcla formó una emulsión que se filtró a través de Celite, y se inundó con 100 mililitros de acetato de etilo. La capa orgánica se extrajo y se lavó con agua, NaCl saturado, se secó con Na_2SO_4, se filtró a través de un tapón de gel de sílice de 2" x 3" (5.08 x 7.62 centímetros), se inundó con acetato de etilo, y se concentró al vacío, para dar el 3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenol, (1.20 gramos).

ES/MS *m/z* 414(MH^+).

Paso 4: N-(3-(1-metil-1H-pirazol-4-il)-5-(2-(pirrolidin-1-il)-etoxi)-fenil)-6-((trimetil-silil)-etinil)-quinazolin-2-amina

A la mezcla de reacción de trifenil-fosfina (32 miligramos, 0.12 milimoles) en 0.5 mililitros de tetrahidrofurano, se le agregó 2-(pirrolidin-1-il)-etanol (17.3 miligramos, 0.15 milimoles), entonces se agregó DEAD (21 miligramos, 0.12 milimoles), y se agitó a temperatura ambiente durante 10 minutos. La mezcla de reacción anterior se agregó al 3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenol (24.8 miligramos, 0.06 milimoles), y se agitó a temperatura ambiente durante 20 horas o hasta que se consideró hecha mediante LCMS. La mezcla de reacción se concentró bajo presión reducida, para dar la N-(3-(1-metil-1H-pirazol-4-il)-5-(2-(pirrolidin-1-il)-etoxi)-fenil)-6-((trimetil-silil)-etinil)-quinazolin-2-amina como un residuo crudo utilizado en el siguiente paso. ES/MS *m/z* 511(MH^+).

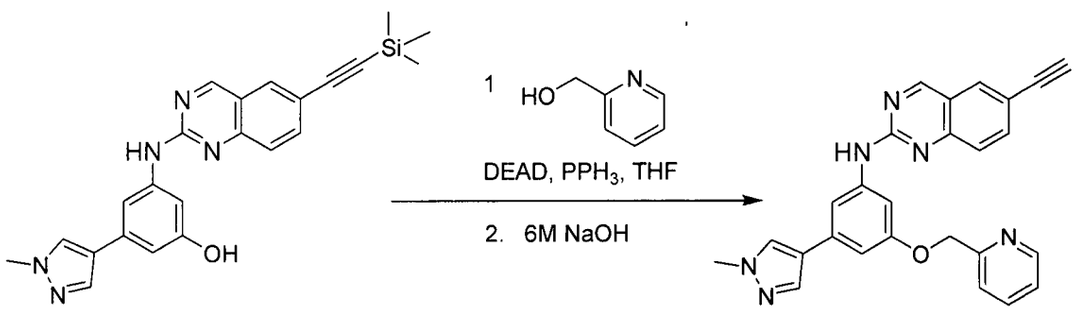
Paso 5: 6-etinil-N-(3-(1-metil-1H-pirazol-4-il)-5-(2-(pirrolidin-1-il)-etoxi)-fenil)-quinazolin-2-amina

A la mezcla de reacción cruda de la N-(3-(1-metil-1H-pirazol-4-il)-5-(2-(pirrolidin-1-il)-etoxi)-fenil)-6-((trimetil-silil)-etinil)-quinazolin-2-amina (0.06 milimoles) en 1 mililitro de dimetil-formamida, se le agregó NaOH 6M (0.06 mililitros, 0.36 milimoles), y se agitó a temperatura ambiente durante 10 minutos, y se verificó mediante LCMS. Si la desprotección quedó incompleta, se agregó más NaOH 6M y se volvió a verificar en 10 minutos. La mezcla de reacción

cruda se filtró, se purificó en la HPLC de preparación, y se liofilizó, para dar la 6-etinil-N-(3-(1-metil-1H-pirazol-4-il)-5-(2-(pirrolidin-1-il)-etoxi)-fenil)-quinazolin-2-amina como la sal de ácido trifluoro-acético (4.4 miligramos) . ES/MS *m/z* 439(MH^+).

Ejemplo 536: 6-etinil-N-(3-(1-metil-1H-pirazol-4-il)-5-(piridin-2-il-metoxi)-fenil)-quinazolin-2-amina

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1: N-(3-(1-metil-1H-pirazol-4-il)-5-(piridin-2-il-metoxi)-fenil)-6-((trimetil-silil)-etinil)-quinazolin-2-amina

A la mezcla de reacción del 3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenol (24.8 miligramos, 0.06 milimoles) en 0.4 mililitros de tetrahidrofurano, se le agregaron piridin-2-il-metanol (16.5 miligramos, 0.15 milimoles), trifenil-fosfina (32 miligramos, 0.12 milimoles), y luego DEAD (21 miligramos, 0.12 milimoles) al final. La mezcla de reacción se agitó a temperatura ambiente durante 20 horas o hasta que se consideró hecha mediante

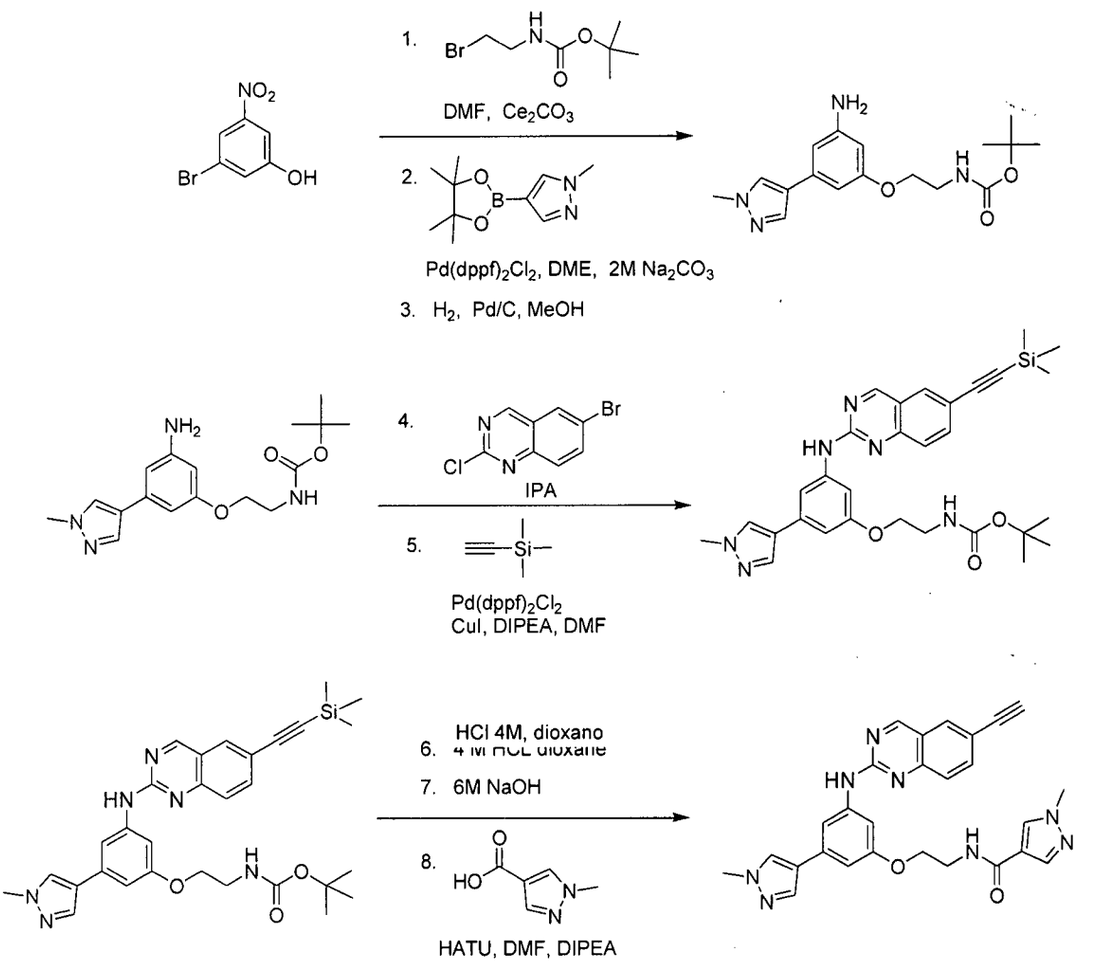
LCMS. Si la reacción no estuvo hecha, se agregó más DEAD (10.5 miligramos, 0.06 moles), y se agitó a temperatura ambiente durante 1 a 2 horas. La mezcla de reacción se concentró bajo presión reducida, para dar la N-(3-(1-metil-1H-pirazol-4-il)-5-(piridin-2-il-metoxi)-fenil)-6-((trimetil-silil)-etinil)-quinazolin-2-amina como un residuo crudo utilizado en el siguiente paso. ES/MS *m/z* 505(MH^+).

Paso 2: 6-etinil-N-(3-(1-metil-1H-pirazol-4-il)-5-(piridin-2-il-metoxi)-fenil)-quinazolin-2-amina

A la mezcla de reacción cruda de la N-(3-(1-metil-1H-pirazol-4-il)-5-(piridin-2-il-metoxi)-fenil)-6-((trimetil-silil)-etinil)-quinazolin-2-amina (0.06 milimoles) en 1.2 mililitros de dimetil-formamida, se le agregó NaOH 6M (0.125 mililitros, 0.75 milimoles), y se agitó a temperatura ambiente durante 10 minutos, y se verificó mediante LCMS. Si la desprotección quedó incompleta, se agregó más NaOH 6M y se volvió a verificar en 10 minutos. La mezcla de reacción cruda se filtró, se purificó en la HPLC de preparación, y se liofilizó, para dar la 6-etinil-N-(3-(1-metil-1H-pirazol-4-il)-5-(piridin-2-il-metoxi)-fenil)-quinazolin-2-amina como la sal de ácido trifluoro-acético (5.6 miligramos) . ES/MS *m/z* 433(MH^+).

Ejemplo 469: N-(2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil)-1-metil-1H-pirazol-4-carboxamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1: 2-(3-bromo-5-nitro-fenoxi)-etil-carbamato de terbutilo

A la mezcla de reacción del 3-bromo-5-nitro-fenol (4.0 gramos, 18.35 milimoles) en 40 mililitros de dimetil-formamida, se le agregó carbonato de cesio (12.0 gramos, 367. milimoles), y se agitó a temperatura ambiente durante 30 minutos. A la mezcla de reacción anterior se le agregó 2-bromo-etil-carbamato de terbutilo (6.16 gramos, 27.5 milimoles), se tapó con un globo de argón, y se agitó a

40°C durante 18 horas o hasta que se consideró hecha mediante LCMS. Se concentró aproximadamente la mitad de la dimetil-formamida, se agregaron 500 mililitros de acetato de etilo, se lavó la capa orgánica con NaOH 1M (3 veces), agua, NaCl saturado, se secó con Na_2SO_4, se filtró, y se concentró al vacío, para dar el 2-(3-bromo-5-nitro-fenoxi)-etil-carbamato de terbutilo crudo (6.6 gramos) utilizado en la siguiente reacción.

Paso 2: 2-(3-(1-metil-1H-pirazol-4-il)-5-nitro-fenoxi)-etil-carbamato de terbutilo

A la mezcla de reacción del 2-(3-bromo-5-nitro-fenoxi)-etil-carbamato de terbutilo crudo anterior (6.6 gramos, 18.28 milimoles) en 125 mililitros de DME, se le agregaron $Pd(dppf)_2Cl_2$ (1.2 gramos, 1.46 milimoles), 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxa-borolan-2-il)-1H-pirazol (5.7 gramos, 27.4 milimoles), y finalmente se agregó Na_2CO_3 2M (41.3 mililitros, 82.5 milimoles). Esta mezcla de reacción se agitó a 100°C durante 2 horas o hasta que se consideró hecha mediante LCMS. Se concentró la mayor parte del DME, se agregaron 600 mililitros de acetato de etilo, 100 mililitros de agua, y se agitaron brevemente. La mezcla formó una emulsión que se filtró. La capa orgánica se extrajo y se lavó con NaOH 1M (2 veces), agua, NaCl saturado, se secó con Na_2SO_4, se filtró, y se concentró al vacío, para dar el 2-(3-(1-metil-1H-pirazol-4-il)-5-nitro-fenoxi)-etil-carbamato de terbutilo, (6.2 gramos). ES/MS *m/z* 363(MH^+).

Paso 3: 2-(3-amino-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil-carbamato de terbutilo

De una manera análoga al Ejemplo 459, Paso 1, pero utilizando el 2-(3-(1-metil-1H-pirazol-4-il)-5-nitro-fenoxi)-etil-carbamato de terbutilo como material de partida. ES/MS *m/z* 333(MH^+).

Paso 4: 2-(3-(6-bromo-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil-carbamato de terbutilo

A la mezcla de reacción del 2-(3-amino-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil-carbamato de terbutilo (5.53 gramos, 16.66 milimoles) en 50 mililitros de alcohol isopropílico en una bomba de vidrio, se le agregó 6-bromo-2-cloro-quinazolina (3.9 gramos, 16.66 milimoles), y se tapó. La solución de la reacción se agitó a 95-100°C durante 22 horas o hasta que se consideró hecha mediante LCMS. A la mezcla de reacción cruda se le agregaron 20 mililitros de alcohol isopropílico, se dejó enfriar, se recolectaron los sólidos (producto), y se lavó 2 veces con alcohol isopropílico. El sólido crudo se secó al vacío, para dar el 2-(3-(6-bromo-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil-carbamato de terbutilo, (6.88 gramos). ES/MS *m/z* 539/541(MH^+). Se puede hacer una purificación adicional mediante HPLC de preparación, y se liofiliza para hacer la sal de ácido trifluoro-acético.

Paso 5: 2-(3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenoxi)-etil-carbamato de terbutilo

A la mezcla de reacción del 2-(3-(6-bromo-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil-carbamato de terbutilo (6.0 gramos, 11.13 milimoles) en 38 mililitros de dimetil-formamida, se le agregaron $Pd(dppf)_2Cl_2$ (1.09 gramos, 1.36 milimoles), CuI (529

miligramos, 2.78 milimoles), etinil-trimetil-silano (3.3 gramos, 33.4 milimoles), y finalmente se agregó di-isopropil-etil-amina (5.81 mililitros, 33.4 milimoles). Esta mezcla de reacción se agitó a 95°C durante 1 hora o hasta que se consideró hecha mediante LCMS. El grupo BOC puede llegar a extraerse parcialmente, y si fue así, se agregó dicarbonato de diterbutilo (1.5 gramos, 6.88 milimoles), y se agitó a temperatura ambiente durante 30 minutos, se volvió a verificar mediante LCMS, y se agregó más si fuera necesario. La mayor parte de la dimetil-formamida se concentró, se agregaron 750 mililitros de acetato de etilo, 200 mililitros de bicarbonato de sodio saturado, y se agitaron. La mezcla formó una emulsión que se filtró, como fue necesario. La capa orgánica se extrajo y se lavó con agua (2 veces), NaCl saturado, se secó con Na_2SO_4, se filtró a través de un tapón de gel de sílice de 3.5" x 3" (8.89 x 7.62 centímetros), se inundó con acetato de etilo, y se concentró al vacío, para dar el 2-(3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenoxi)-etil-carbamato de terbutilo (5.45 gramos). ES/MS *m/z* 557(MH^+).

Paso 6: N-(3-(2-amino-etoxi)-5-(1-metil-1H-pirazol-4-il)-fenil)-6-((trimetil-silil)-etinil)-quinazolin-2-amina

A la mezcla de reacción del 2-(3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenoxi)-etil-carbamato de terbutilo (1.3 gramos, 2.3 milimoles), se le agregó un exceso de HCl 4M en dioxano (20 mililitros, 80 milimoles). Esta mezcla de reacción se agitó a temperatura ambiente durante 1 hora o hasta que quedó

hecha mediante LCMS, y se concentró al vacío, para dar la N-(3-(2-amino-etoxi)-5-(1-metil-1H-pirazol-4-il)-fenil)-6-((trimetil-silil)-etinil)-quinazolin-2-amina cruda (1.49 gramos). ES/MS *m/z* 457(MH^+).

Paso 7: N-(3-(2-amino-etoxi)-5-(1-metil-1H-pirazol-4-il)-fenil)-6-etinil-quinazolin-2-amina

A la mezcla de reacción cruda anterior de la N-(3-(2-amino-etoxi)-5-(1-metil-1H-pirazol-4-il)-fenil)-6-((trimetil-silil)-etinil)-quinazolin-2-amina (2.33 milimoles) en 20 mililitros de tetrahidrofurano y 12 mililitros de metanol, se le agregó NaOH 6M (1.16 mililitros, 6.99 milimoles), se agitó a temperatura ambiente durante 15 minutos o hasta que quedó hecha mediante LCMS, y se agregó más NaOH 6M si fuera necesario. La mezcla de reacción se concentró al vacío hasta secarse, para dar la N-(3-(2-amino-etoxi)-5-(1-metil-1H-pirazol-4-il)-fenil)-6-etinil-quinazolin-2-amina cruda, (1.72 gramos). ES/MS *m/z* 385(MH^+).

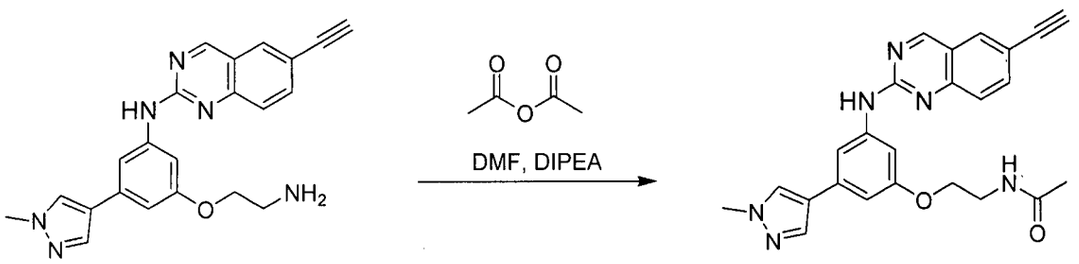
Paso 8: N-(2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil)-1-metil-1H-pirazol-4-carboxamida

A la mezcla de reacción del ácido 1-metil-1H-pirazol-4-carboxílico (11 miligramos, 0.0875 milimoles) en 0.65 mililitros de NMP, se le agregaron HATU (40 miligramos, 0.105 milimoles) y di-isopropil-etil-amina (0.031 mililitros, 0.175 milimoles), y se agitó a temperatura ambiente durante aproximadamente 3 minutos. A la mezcla de reacción anterior se le agregó la N-(3-(2-amino-etoxi)-5-(1-metil-1H-pirazol-4-il)-fenil)-6-etinil-quinazolin-2-amina (22.4 miligramos, 0.058 milimoles), y se agitó a temperatura ambiente durante

2 horas o hasta que se consideró hecha mediante LCMS. La mezcla de reacción cruda se filtró, se purificó en la HPLC de preparación, y se liofilizó, para dar la N-(2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil)-1-metil-1H-pirazol-4-carboxamida como la sal de ácido trifluoro-acético (2.9 miligramos). ES/MS *m/z* 493(MH^+).

Ejemplo 400: N-(2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil)-acetamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:

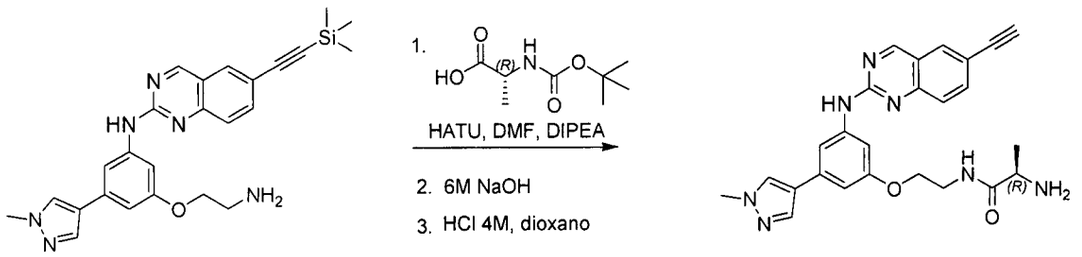


A la mezcla de reacción de la N-(3-(2-amino-etoxi)-5-(1-metil-1H-pirazol-4-il)-fenil)-6-etinil-quinazolin-2-amina (21 miligramos, 0.055 milimoles) en 0.65 mililitros de dimetil-formamida, se le agregaron di-isopropil-etil-amina (0.035 mililitros, 0.195 milimoles) y anhídrido acético (11.3 miligramos, 0.111 milimoles). La mezcla de reacción se agitó a temperatura ambiente durante aproximadamente 90 minutos o hasta que se consideró hecha mediante LCMS. La mezcla de reacción cruda se filtró, se purificó en la HPLC de preparación, y se liofilizó, para dar la N-(2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil)-acetamida como la sal

de ácido trifluoro-acético (4.3 miligramos). ES/MS *m/z* 427(MH^+).

Ejemplo 491: (R)-2-amino-N-(2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil)-propanamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1: (R)-1-(2-(3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenoxi)-etil-amino)-1-oxopropan-2-il-carbamato de terbutilo

A la mezcla de reacción del (R)-ácido 2-(terbutoxi-carbonil-amino)-propanoico (25.5 miligramos, 0.135 milimoles) en 0.15 mililitros de dimetil-formamida, se le agregaron HATU (55 miligramos, 0.144 milimoles), di-isopropil-etil-amina (0.028 mililitros, 0.16 milimoles), y se agitó a temperatura ambiente durante aproximadamente 10 minutos. A la mezcla de reacción anterior se le agregó una solución de N-(3-(2-amino-etoxi)-5-(1-metil-1H-pirazol-4-il)-fenil)-6-((trimetil-silil)-etinil)-quinazolin-2-amina (41 miligramos, 0.09 milimoles) en 0.5 mililitros de dimetil-formamida con di-isopropil-etil-amina (0.028 mililitros, 0.16 milimoles), y se agitó a temperatura ambiente durante 18 horas o hasta que se consideró hecha mediante LCMS. La solución de la reacción cruda con el

producto del (R)-1-(2-(3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenoxi)-etil-amino)-1-oxopropan-2-il-carbamato de terbutilo, se utilizó en el siguiente paso sin purificación. ES/MS *m/z* 628(MH^+).

Paso 2: (R)-1-(2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil-amino)-1-oxopropan-2-il-carbamato de terbutilo

Al material crudo anterior del (R)-1-(2-(3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenoxi)-etil-amino)-1-oxopropan-2-il-carbamato de terbutilo (0.09 milimoles) se le agregó NaOH 6M (0.120 mililitros, 0.72 milimoles), y se agitó a temperatura ambiente durante 10 minutos o hasta que se consideró hecha mediante LCMS. Si la reacción no estaba completa, se agregó más NaOH 6M como fue necesario. La mezcla de reacción cruda con el producto del (R)-1-(2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil-amino)-1-oxopropan-2-il-carbamato de terbutilo se utilizó en el siguiente paso sin purificación. ES/MS *m/z* 556(MH^+).

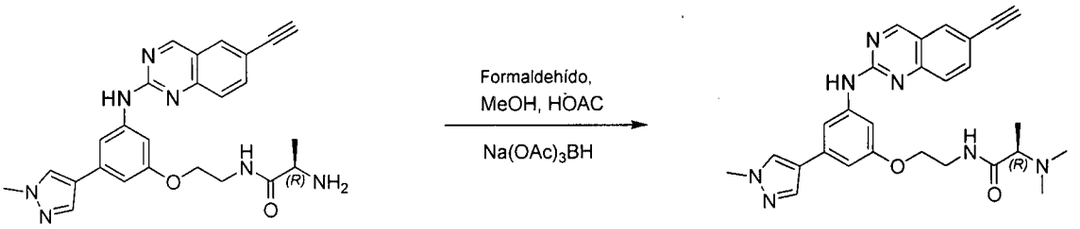
Paso 3: (R)-2-amino-N-(2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil)-propanamida

Al material crudo anterior del (R)-1-(2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil-amino)-1-oxopropan-2-il-carbamato de terbutilo (0.09 milimoles) se le agregó HCl 4M en dioxano (3 mililitros, 12 milimoles), y se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se concentró, se

agregó 1 mililitro de dimetil-formamida, se filtró, se purificó en la HPLC de preparación, y se liofilizó, para dar la (R)-2-amino-N-(2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil)-propanamida, como la sal de ácido trifluoro-acético (14.1 miligramos). ES/MS *m/z* 456(MH^+).

Ejemplo 495: (R)-2-(dimetil-amino)-N-(2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil)-propanamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:

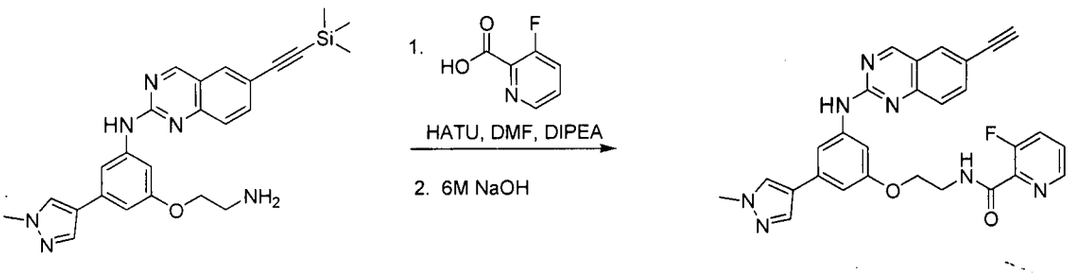


A la mezcla de reacción de la (R)-2-amino-N-(2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil)-propanamida (12 miligramos, 0.026 milimoles) en 1.2 mililitros de metanol, se le agregó ácido acético (0.08 mililitros, 1.3 milimoles), y una solución de formaldehído al 37 por ciento en agua (0.034 mililitros, 0.39 milimoles). La mezcla de reacción se agitó a temperatura ambiente durante aproximadamente 20 minutos. A esta solución de la reacción se le agregó triacetoxi-borohidruro de sodio (44 miligramos, 0.208 milimoles), y se agitó a temperatura ambiente durante 1 a 2 horas o hasta que se consideró hecha mediante LCMS. La mezcla de reacción cruda se concentró, se agregó 1 mililitro de dimetil-formamida, se filtró, se purificó en la HPLC de preparación, y

se liofilizó, para dar la (R)-2-(dimetil-amino)-N-(2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil)-propanamida como la sal de ácido trifluoro-acético (1.1 miligramos). ES/MS *m/z* 484(MH^+).

Ejemplo 523: N-(2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil)-3-fluoro-picolinamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1: 3-fluoro-N-(2-(3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenoxi)-etil)-picolinamida

De una manera análoga al Ejemplo 114, Paso 1, pero utilizando el ácido 3-fluoro-picolínico como material de partida.

ES/MS *m/z* 457(MH^+).

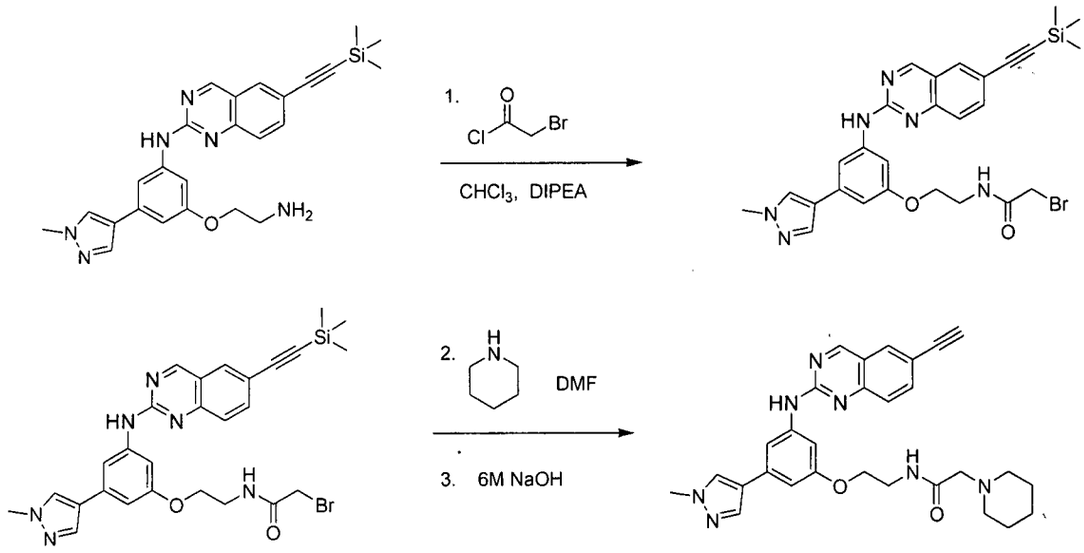
Paso 2: N-(2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil)-3-fluoro-picolinamida

Al producto crudo anterior a partir del Paso 1 (0.048 milimoles) se le agregó NaOH 6M (0.100 mililitros, 0.60 milimoles), y se agitó a temperatura ambiente durante 10 minutos o hasta que se consideró hecha mediante LCMS. Si la reacción no estaba completa, se agregó

más NaOH 6M como fue necesario. La mezcla de reacción cruda se purificó mediante la adición de dimetil-formamida (aproximadamente 0.7 mililitros), se filtró, se purificó en la HPLC de preparación, y se liofilizó, para dar la N-(2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil)-3-fluoro-picolinamida como la sal de ácido trifluoro-acético (6.3 miligramos). ES/MS *m/z* 508(MH^+).

Ejemplo 506: N-(2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil)-2-(piperidin-1-il)-acetamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1: 2-bromo-N-(2-(3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenoxi)-etil)-acetamida

A la mezcla de reacción de la N-(3-(2-amino-etoxi)-5-(1-metil-1H-pirazol-4-il)-fenil)-6-((trimetil-silil)-etinil)-quinazolin-2-amina (295 miligramos, 0.646 milimoles) en 9 mililitros de cloroformo, se le

agregó di-isopropil-etil-amina (0.394 mililitros, 2.26 milimoles), y se enfrió (a –5°C) con agitación. A la mezcla de reacción anterior (a –5°C) se le agregó por goteo una solución de cloruro de 2-bromo-acetilo (122.5 miligramos, 0.775 milimoles) en 2 mililitros de cloroformo . Esta mezcla de reacción se agitó (a –5°C) durante 20 minutos, y entonces se dejó calentar a temperatura ambiente durante 70 minutos o hasta que quedó hecha mediante LCMS. El cloroformo se concentró, se agregaron 300 mililitros de acetato de etilo, se lavó con $NaHCO_3$ saturado, agua, salmuera, se secó con Na_2SO_4, se filtró, y se concentró hasta obtener un residuo. El residuo crudo se purificó mediante cromatografía en columna de gel de sílice, y se concentró al vacío, para dar la 2-bromo-N-(2-(3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenoxi)-etil)-acetamida, (155 miligramos). ES/MS *m/z* 577/579(MH^+).

Paso 2: N-(2-(3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenoxi)-etil)-2-(piperidin-1-il)-acetamida

A la mezcla de reacción de la 2-bromo-N-(2-(3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenoxi)-etil)-acetamida (10.3 miligramos, 0.0178 milimoles) en 0.4 mililitros de dimetil-formamida, se le agregó piperidina (6 miligramos, 0.0712 milimoles), y se agitó a temperatura ambiente durante 4.5 horas o hasta que se consideró hecha mediante LCMS. La mezcla de reacción cruda con el producto de la N-(2-(3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenoxi)-etil)-2-(piperidin-1-il)-acetamida se utilizó en el siguiente paso sin

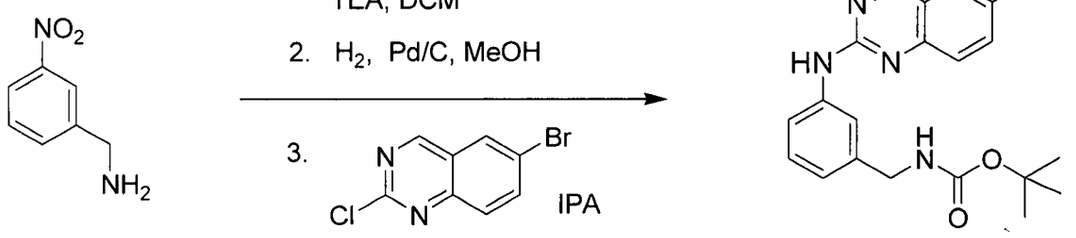
purificación. ES/MS *m/z* 582(MH^+).

Paso 3: N-(2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil)-2-(piperidin-1-il)-acetamida

Al material crudo anterior de la N-(2-(3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenoxi)-etil)-2-(piperidin-1-il)-acetamida (0.0178 milimoles) se le agregó NaOH 6M (0.03 mililitros, 0.18 milimoles), y se agitó a temperatura ambiente durante 10 minutos o hasta que se consideró hecha mediante LCMS. Si la reacción no estaba completa, se agregó más NaOH 6M como fue necesario. La mezcla de reacción cruda se purificó mediante la adición de 0.5 mililitros de N,N-dimetil-formamida, se filtró, se purificó en la HPLC de preparación, y se liofilizó, para dar la N-(2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil)-2-(piperidin-1-il)-acetamida como la sal de ácido trifluoro-acético (6.9 miligramos). ES/MS *m/z* 510(MH^+).

Ejemplo 379: 3-(6-bromo-quinazolin-2-il-amino)-bencil-carbamato de terbutilo

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1: *3-nitro-bencil-carbamato de terbutilo*

A la mezcla de reacción de (3-nitro-fenil)-metanamina HCl (2.00 gramos, 10.6 milimoles) en 15 mililitros de dicloro-metano se le agregaron trietil-amina (3.7 mililitros, 26.5 milimoles) y dicarbonato de diterbutilo (2.78 gramos, 12.72 milimoles) . La reacción se agitó a temperatura ambiente durante 90 minutos o hasta que se consideró hecha mediante LC. Se concentró la mayor parte del dicloro-metano, y se agregaron 200 mililitros de acetato de etilo, y se lavó con $NaHCO_3$ saturado (2 veces), agua (2 veces), salmuera, se secó con Na_2SO_4, se filtró, y se concentró al vacío, para dar el 3-nitro-bencil-carbamato de terbutilo como el material crudo utilizado en el siguiente paso. (2.96 gramos). ES/MS *m/z* 253(MH^+).

Paso 2: *3-amino-bencil-carbamato de terbutilo*

Al material de partida crudo del 3-nitro-bencil-carbamato de terbutilo (2.96 g crudo, 10.6 milimoles), se le agregó Pd al 10 por ciento sobre carbón (444 miligramos, 15 por ciento en peso) bajo argón. Bajo argón, con una jeringa, se agregaron cuidadosamente 19 mililitros de metanol. A esta mezcla de reacción se le agregó un globo de hidrógeno y se evacuó y se rellenó 5 veces. La reacción se agitó a temperatura ambiente durante 18 horas o hasta que se consideró hecha mediante LC. A la mezcla de reacción se le agregó acetato de etilo y se filtró bajo argón a través de Celite, y se lavó con una solución de 1:1 de acetato de etilo y metanol. El filtrado se concentró hasta obtener un residuo. Al residuo se le agregaron 150

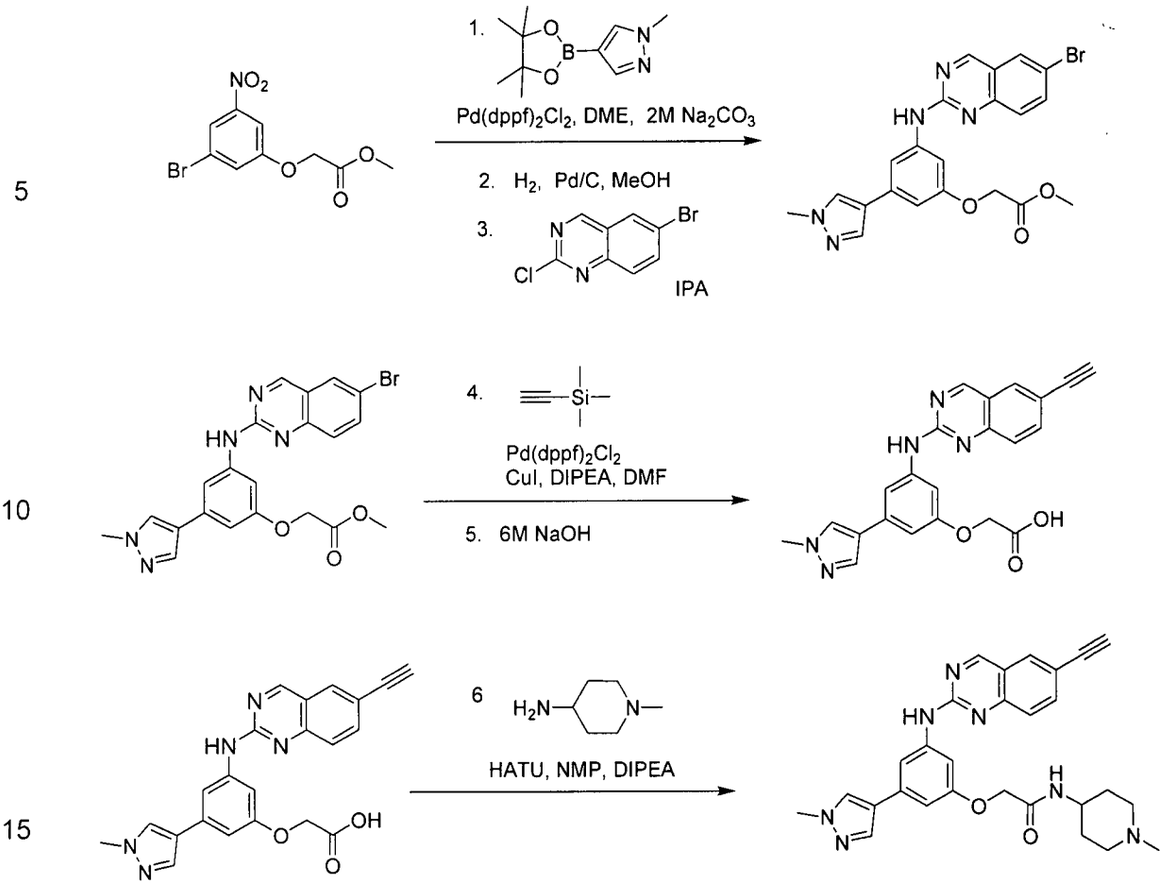
mililitros de acetato de etilo, y se lavó con $NaHCO_3$ saturado (2 veces), agua (2 veces), salmuera, se secó con Na_2SO_4, se filtró, y se concentró al vacío, para dar el 3-amino-bencil-carbamato de terbutilo como el material crudo utilizado en el siguiente paso. (2.45 gramos). ES/MS *m/z* 223(MH^+).

Paso 3: 3-(6-bromo-quinazolin-2-il-amino)-bencil-carbamato de terbutilo

A la mezcla de reacción del 3-amino-bencil-carbamato de terbutilo (840 miligramos, 3.76 milimoles) en 6 mililitros de alcohol isopropílico en una bomba de vidrio, se le agregó la 6-bromo-2-cloro-quinazolina (750 miligramos, 3.08 milimoles), y se tapó. La solución de la reacción se agitó a 95°C durante 20 horas o hasta que se consideró hecha mediante LCMS. A la mezcla de reacción cruda se le agregaron 6 mililitros de alcohol isopropílico, los sólidos se filtraron, y el filtrado se concentró (producto). El material crudo se purificó mediante cromatografía en columna de gel de sílice, y se concentró al vacío, para dar el 3-(6-bromo-quinazolin-2-il-amino)-bencil-carbamato de terbutilo (860 miligramos). ES/MS *m/z* 429/431(MH^+). Se puede hacer una purificación adicional mediante HPLC de preparación, se liofiliza y se convierte hasta una sal de amonio del ácido trifluoro-acético.

Ejemplo 340: 2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-N-(1-metil-piperidin-4-il)-acetamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1: 2-(3-(1-metil-1H-pirazol-4-il)-5-nitro-fenoxi)-acetato de metilo

A la mezcla de reacción del 2-(3-bromo-5-nitro-fenoxi)-acetato de metilo (1.65 gramos, 5.69 milimoles) en 35 mililitros de DME, se le agregaron $Pd(dppf)_2Cl_2$ (465 miligramos, 0.569 milimoles), 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxa-borolan-2-il)-1H-pirazol (2.4 gramos, 11.4 milimoles), y finalmente se agregó Na_2CO_3 2M (11.4 mililitros, 22.8 milimoles). Esta mezcla de reacción se agitó a 85°C durante 90 minutos o hasta que se consideró hecha mediante LCMS. Se

concentró aproximadamente la mitad del DME, se agregaron 350 mililitros de acetato de etilo y 50 mililitros de agua. La capa orgánica se extrajo y se lavó con Na_2CO_3 saturado, agua (2 veces), NaCl saturado, se secó con Na_2SO_4, se filtró, y se concentró hasta obtener un residuo. El material crudo se purificó mediante cromatografía en columna de gel de sílice, y se concentró al vacío, para dar el 2-(3-(1-metil-1H-pirazol-4-il)-5-nitro-fenoxi)-acetato de metilo, (480 miligramos). ES/MS *m/z* 292(MH^+).

Paso 2: 2-(3-amino-5-(1-metil-1H-pirazol-4-il)-fenoxi)-acetato de metilo

De una manera análoga al Ejemplo 459, Paso 1, pero utilizando el 2-(3-(1-metil-1H-pirazol-4-il)-5-nitro-fenoxi)-acetato de metilo como material de partida. ES/MS *m/z* 262(MH^+).

Paso 3: 2-(3-(6-bromo-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-acetato de metilo

De una manera análoga al Ejemplo 112, Paso 4, pero utilizando el 2-(3-amino-5-(1-metil-1H-pirazol-4-il)-fenoxi)-acetato de metilo como material de partida. ES/MS *m/z* 468/470(MH^+).

Paso 4: 2-(3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenoxi)-acetato de metilo

De una manera análoga al Ejemplo 459, Paso 3, pero utilizando el 2-(3-(6-bromo-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-acetato de metilo como material de partida. ES/MS *m/z* 486(MH^+).

Paso 5: Ácido 2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-

pirazol-4-il)-fenoxi)-acético

A la mezcla de reacción del 2-(3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenoxi)-acetato de metilo (740 miligramos, 1.52 milimoles) en 6 mililitros de tetrahidrofurano y 3 mililitros de metanol, se le agregó NaOH 6M (0.75 mililitros, 4.52 milimoles), se agitó a temperatura ambiente durante 1 hora o hasta que quedó hecha mediante LCMS, y se agregó más NaOH 6M si fuera necesario. La mezcla de reacción se concentró al vacío hasta secarse, para dar un residuo crudo. A este residuo se le agregó HCl 6M acuoso (0.91 mililitros, 5.48 milimoles), se agitó brevemente, y se concentró al vacío hasta secarse, para dar el ácido 2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-acético, como un sólido crudo utilizado en el siguiente paso (840 miligramos). ES/MS *m/z* 400(MH^+).

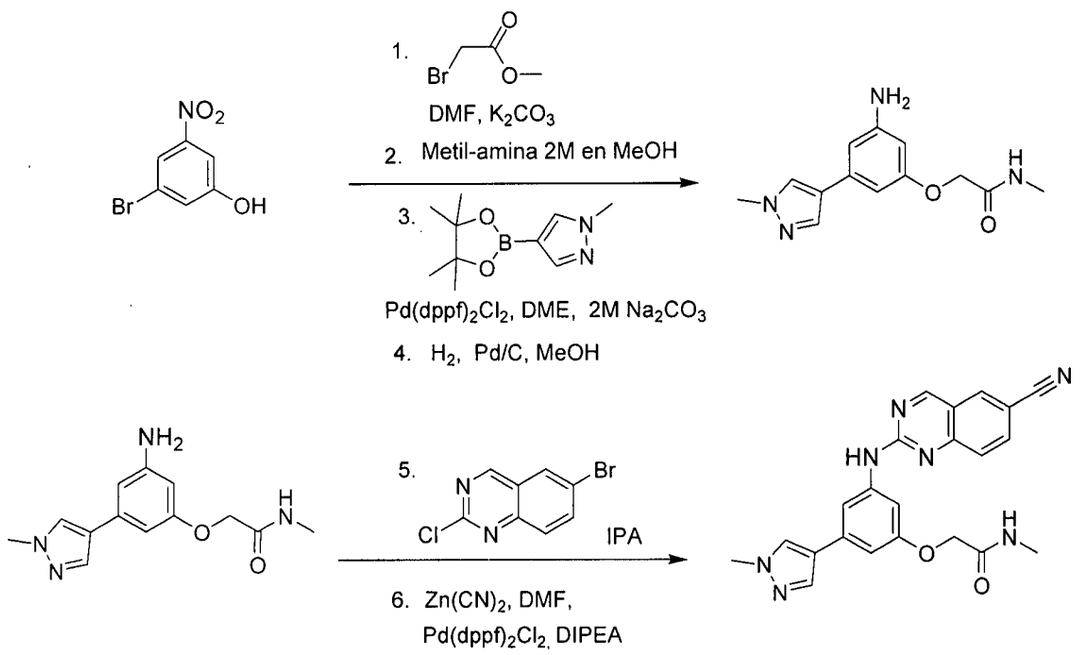
Paso 6: 2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-N-(1-metil-piperidin-4-il)-acetamida

A la mezcla de reacción del ácido 2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-acético (24 miligramos, 0.060 milimoles) en 0.5 mililitros de NMP, se le agregaron HATU (39 miligramos, 0.102 milimoles), di-isopropil-etil-amina (0.023 mililitros, 0.132 milimoles), y se agitó a temperatura ambiente durante aproximadamente 3 minutos. A la mezcla de reacción anterior se le agregó 1-metil-piperidin-4-amina (27 miligramos, 0.24 milimoles), y se agitó a temperatura ambiente durante 4 horas o hasta que se consideró hecha mediante LCMS. La mezcla de reacción cruda se

filtró, se purificó en la HPLC de preparación, y se liofilizó, para dar la 2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-N-(1-metil-piperidin-4-il)-acetamida como la sal de ácido trifluoro-acético (7.6 miligramos). ES/MS *m/z* 496(MH^+).

Ejemplo 356: 2-(3-(6-ciano-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-N-metil-acetamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1: 2-(3-bromo-5-nitro-fenoxi)-acetato de metilo

A la mezcla de reacción de 3-bromo-5-nitro-fenol (7.0 gramos, 32.1 milimoles) en 30 mililitros de dimetil-formamida, se le agregó K_2CO_3 (9.8 gramos, 70.6 milimoles), y se agitó durante 3 a 5 minutos. A la mezcla de reacción se le agregó 2-bromo-acetato de metilo (5.4 gramos, 35.3 milimoles), y se agitó a temperatura ambiente durante

18 horas o hasta que se consideró hecha mediante LC. A la reacción cruda se le agregaron 450 mililitros de acetato de etilo, y se lavó con Na_2CO_3 saturado, agua (3 veces), NaCl saturado, se secó con Na_2SO_4, se filtró, y se concentró al vacío, para dar el 2-(3-bromo-5-nitro-fenoxi)-acetato de metilo crudo, (9.0 gramos).

Paso 2: 2-(3-bromo-5-nitro-fenoxi)-N-metil-acetamida

Al producto crudo a partir del Paso 1 del 2-(3-bromo-5-nitro-fenoxi)-acetato de metilo (1.75 gramos, 6.0 milimoles) se le agregó metil-amina 2M en metanol (18 mililitros, 36 milimoles), y se agitó a temperatura ambiente durante 24 horas o hasta que se consideró hecha mediante LCMS. La mezcla de reacción cruda se concentró al vacío, para dar la 2-(3-bromo-5-nitro-fenoxi)-N-metil-acetamida cruda, (1.74 gramos). ES/MS *m/z 289/291*(MH^+).

Paso 3: N-metil-2-(3-(1-metil-1H-pirazol-4-il)-5-nitro-fenoxi)-acetamida

A la mezcla de reacción de la 2-(3-bromo-5-nitro-fenoxi)-N-metil-acetamida (800 miligramos, 2.77 milimoles) en 17 mililitros de DME, se le agregaron $Pd(dppf)_2Cl_2$ (226 miligramos, 0.277 milimoles), 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxa-borolan-2-il)-1H-pirazol (1.04 gramos, 5.0 milimoles), y finalmente se agregó Na_2CO_3 2M (5.5 mililitros, 11 milimoles). Esta mezcla de reacción se agitó a 85-90°C durante 18 horas o hasta que se consideró hecha mediante LCMS. Se concentró la mayor parte del DME, se agregaron aproximadamente 200 mililitros de acetato de etilo y 50 mililitros de agua, y se agitaron. Los sólidos (producto) se recolectaron mediante

filtración, se lavaron con agua (1 vez), y se secaron al vacío, para dar la N-metil-2-(3-(1-metil-1H-pirazol-4-il)-5-nitro-fenoxi)-acetamida cruda, (660 miligramos). ES/MS *m/z* 291(MH^+).

Paso 4: 2-(3-amino-5-(1-metil-1H-pirazol-4-il)-fenoxi)-N-metil-acetamida

Al material de partida crudo de la N-metil-2-(3-(1-metil-1H-pirazol-4-il)-5-nitro-fenoxi)-acetamida (660 miligramos, 2.27 milimoles), se le agregó Pd al 10 por ciento sobre carbón (132 miligramos, 20 por ciento en peso) bajo argón. Bajo argón, con una jeringa, se agregaron cuidadosamente 5 mililitros de metanol. A esta mezcla de reacción se le agregó un globo de hidrógeno y se evacuó y se rellenó 5 veces. La reacción se agitó a temperatura ambiente durante 22 horas o hasta que se consideró hecha mediante LC. A la mezcla de reacción se le agregó acetato de etilo y se filtró bajo argón a través de Celite, y se lavó con una solución de 1:1 de acetato de etilo y metanol. El filtrado se concentró al vacío, para dar la 2-(3-amino-5-(1-metil-1H-pirazol-4-il)-fenoxi)-N-metil-acetamida como el material crudo utilizado en el siguiente paso. (565 miligramos). ES/MS *m/z* 261(MH^+).

Paso5: 2-(3-(6-bromo-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-N-metil-acetamida

De una manera análoga al Ejemplo 112, Paso 4, pero utilizando la 2-(3-amino-5-(1-metil-1H-pirazol-4-il)-fenoxi)-N-metil-acetamida como material de partida. ES/MS *m/z* 467/469(MH^+).

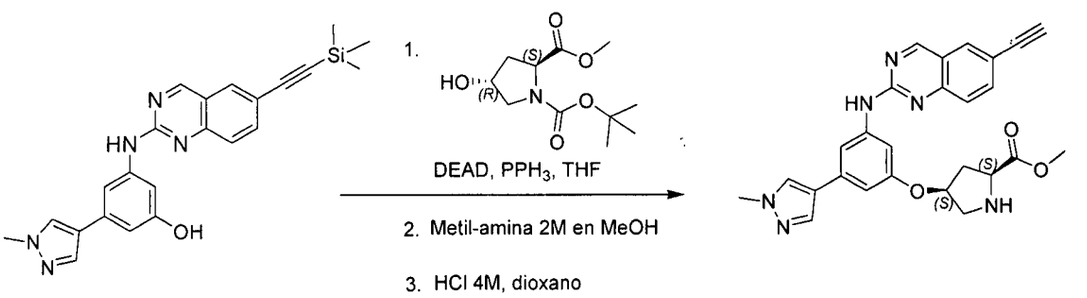
Paso 6: 2-(3-(6-ciano-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-

4-il)-fenoxi)-N-metil-acetamida

A la mezcla de reacción de la 2-(3-(6-bromo-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-N-metil-acetamida (30 miligramos, 0.064 milimoles) en 0.6 mililitros de dimetil-formamida, se le agregaron $Pd(dppf)_2Cl_2$ (10.5 miligramos, 0.0128 milimoles), $Zn(CN)_2$ (30 miligramos, 0.256 milimoles), y di-isopropil-etil-amina (34 microlitros, 0.192 milimoles). Esta mezcla de reacción se pasó por microondas a 170°C durante 800 segundos, y luego nuevamente a 210°C durante 800 segundos. La mezcla de reacción cruda se filtró, se purificó en la HPLC de preparación, y se liofilizó, para dar la 2-(3-(6-ciano-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-N-metil-acetamida como la sal de ácido trifluoro-acético (8.2 miligramos). ES/MS *m/z* 414(MH^+).

Ejemplo 543: ***(2S,4S)-4-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-pirrolidin-2-carboxilato de metilo***

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1: *(2S,4S)-4-(3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenoxi)-pirrolidin-1,2-dicarboxilato de 1-*

terbutil-2-metilo

De una manera análoga al Ejemplo 459, Paso 4, pero utilizando el (2S,4R)-4-hidroxi-pirrolidin-1,2-dicarboxilato de 1-terbutil-2-metilo como el material de partida (alcohol). ES/MS *m/z* 641(MH^+).

Paso 2: (2S,4S)-4-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-pirrolidin-1,2-dicarboxilato de 1-terbutil-2-metilo

A la mezcla de reacción del (2S,4S)-4-(3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenoxi)-pirrolidin-1,2-dicarboxilato de 1-terbutil-2-metilo (38 miligramos, 0.06 milimoles) en 0.375 mililitros de tetrahidrofurano, se le agregó metil-amina 2M en metanol (2.0 mililitros, 4.0 milimoles). La mezcla de reacción se agitó a temperatura ambiente durante 20 horas o hasta que se consideró hecha mediante LCMS. La mezcla de reacción cruda se concentró al vacío, hasta secarse, para dar un producto crudo utilizado en el siguiente paso, (2S,4S)-4-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-pirrolidin-1,2-dicarboxilato de 1-terbutil-2-metilo. ES/MS *m/z* 569(MH^+).

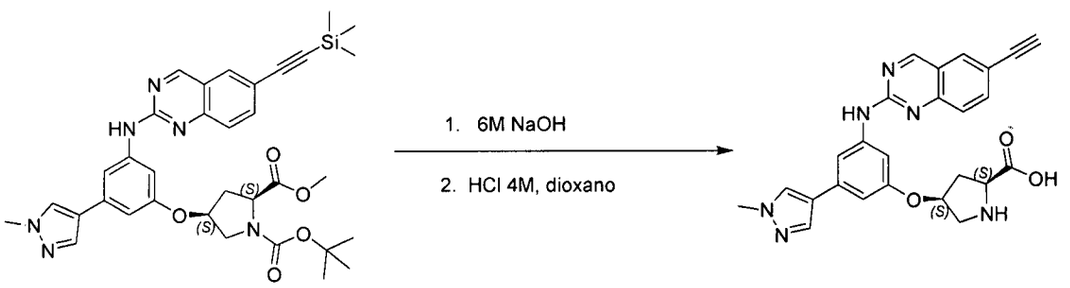
Paso 3: (2S,4S)-4-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-pirrolidin-2-carboxilato de metilo

A la mezcla de reacción del (2S,4S)-4-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-pirrolidin-1,2-dicarboxilato de 1-terbutil-2-metilo (0.06 milimoles), se le agregó HCl 4M en dioxano (3.5 mililitros, 14.0 milimoles). La mezcla de reacción se agitó a temperatura ambiente durante 1 hora o hasta que se

consideró hecha mediante LCMS. La mezcla de reacción cruda se concentró, se agregó aproximadamente 1 mililitro de dimetil-formamida, se filtró, se purificó en la HPLC de preparación, y se liofilizó para dar el (2S,4S)-4-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-pirrolidin-2-carboxilato de metilo como la sal de ácido trifluoro-acético (3.7 miligramos). ES/MS *m/z* *469*(MH^+).

Ejemplo 555: (2S,4S)-ácido 4-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-pirrolidin-2-carboxílico

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1: (2S,4S)-ácido 1-(terbutoxi-carbonil)-4-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-pirrolidin-2-carboxílico

A la mezcla de reacción del (2S,4S)-4-(3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenoxi)-pirrolidin-1,2-dicarboxilato de 1-terbutil-2-metilo (115 miligramos, 0.18 milimoles) en 0.75 mililitros de tetrahidrofurano, se le agregaron

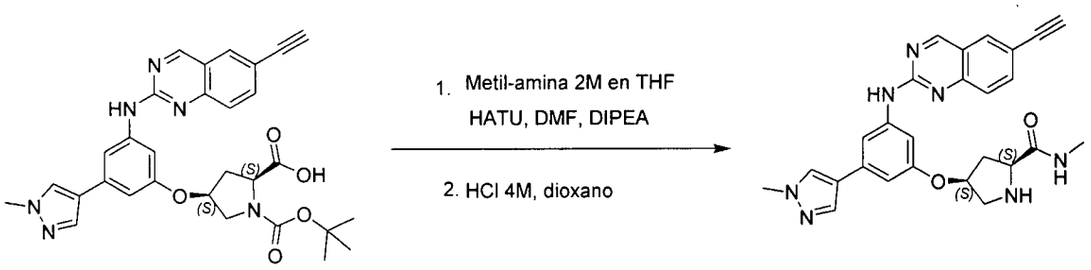
NaOH 6M (0.9 mililitros, 5.4 milimoles), y 1 mililitro de metanol. La mezcla de reacción se agitó a temperatura ambiente durante 1 hora o hasta que se consideró hecha mediante LCMS. La mezcla de reacción cruda se concentró al vacío, hasta solidificarse, se agregaron 2 mililitros de dimetil-formamida, se filtró, se purificó en la HPLC de preparación, y se liofilizó, para dar el (2S,4S)-ácido 1-(terbutoxi-carbonil)-4-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-pirrolidin-2-carboxílico como la sal de ácido trifluoro-acético (45 miligramos). ES/MS *m/z* 555(MH^+).

Paso 2: (2S,4S)-ácido 4-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-pirrolidin-2-carboxílico

A la mezcla de reacción del (2S,4S)-ácido 1-(terbutoxi-carbonil)-4-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-pirrolidin-2-carboxílico (15 miligramos, 0.027 milimoles), se le agregó HCl 4M en dioxano (1.5 mililitros, 6.0 milimoles). La mezcla de reacción se agitó a temperatura ambiente durante 1 hora o hasta que se consideró hecha mediante LCMS. La mezcla de reacción cruda se concentró, se agregó aproximadamente 1 mililitro de dimetil-formamida, se filtró, se purificó en la HPLC de preparación, y se liofilizó, para dar el (2S,4S)-ácido 4-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-pirrolidin-2-carboxílico como la sal de ácido trifluoro-acético (3.2 miligramos). ES/MS *m/z* 455(MH^+).

Ejemplo 557: (2S,4S)-4-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-N-metil-pirrolidin-2-carboxamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1: (2S,4S)-4-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-2-(metil-carbamoil)-pirrolidin-1-carboxilato de terbutilo

A la mezcla de reacción del (2S,4S)-ácido 1-(terbutoxi-carbonil)-4-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-pirrolidin-2-carboxílico (15 miligramos, 0.027 milimoles) en 0.5 mililitros de dimetil-formamida, se le agregaron HATU (31 miligramos, 0.081 milimoles), y di-isopropil-etil-amina (0.014 mililitros, 0.081 milimoles), y se agitó a temperatura ambiente durante aproximadamente 3 a 5 minutos. A la mezcla de reacción anterior se le agregó metil-amina 2M en tetrahidrofurano (0:081 mililitros, 0.162 milimoles), y se agitó a temperatura ambiente durante 20 horas o hasta que se consideró hecha mediante LCMS. La mezcla de reacción cruda con el producto de (2S,4S)-4-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-2-(metil-carbamoil)-pirrolidin-1-carboxilato de terbutilo se utilizó en el siguiente paso sin purificación. ES/MS *m/z* 568(MH^+).

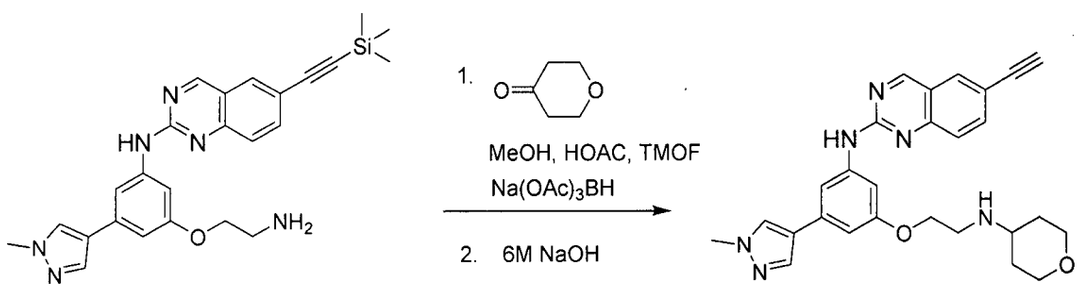
Paso 2: (2S,4S)-4-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-

1H-pirazol-4-il)-fenoxi)-N-metil-pirrolidin-2-carboxamida

A la mezcla de reacción del (2S,4S)-4-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-2-(metil-carbamoil)-pirrolidin-1-carboxilato de terbutilo (0.027 milimoles), se le agregó HCl 4M en dioxano (2.0 mililitros, 8.0 milimoles). La mezcla de reacción se agitó a temperatura ambiente durante 1 hora o hasta que se consideró hecha mediante LCMS. La mezcla de reacción cruda se concentró, se agregó aproximadamente 1 mililitro de dimetil-formamida, se filtró, se purificó en la HPLC de preparación, y se liofilizó, para dar la (2S,4S)-4-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-N-metil-pirrolidin-2-carboxamida como la sal de ácido trifluoro-acético (5.0 miligramos). ES/MS *m/z* 468(MH^+).

Ejemplo 552: 6-etinil-N-(3-(1-metil-1H-pirazol-4-il)-5-(2-(tetrahidro-2H-piran-4-il-amino)-etoxi)-fenil)-quinazolin-2-amina

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1: N-(3-(1-metil-1H-pirazol-4-il)-5-(2-(tetrahidro-2H-piran-4-il-amino)-etoxi)-fenil)-6-((trimetil-silil)-etinil)-quinazolin-2-amina

A la mezcla de reacción de la N-(3-(2-amino-etoxi)-5-(1-metil-1H-pirazol-4-il)-fenil)-6-((trimetil-silil)-etinil)-quinazolin-2-amina (41 miligramos, 0.09 milimoles) en 0.75 mililitros de metanol, se le agregaron ácido acético (0.162 mililitros, 2.7 milimoles), dihidro-2H-piran-4(3H)-ona (90 miligramos, 0.9 milimoles), y orto-formato de trimetilo (TMOF) (57 miligramos, 0.54 milimoles). La mezcla de reacción se agitó a temperatura ambiente durante aproximadamente 4 horas. A esta solución de la reacción se le agregó triacetoxi-borohidruro de sodio (76 miligramos, 0.36 milimoles), y se agitó a temperatura ambiente durante 20 horas. A la mezcla de reacción cruda se le agregó más triacetoxi-borohidruro de sodio (38 miligramos, 0.18 milimoles), y se agitó a temperatura ambiente durante otras 26 horas. La mezcla de reacción cruda con el producto de N-(3-(1-metil-1H-pirazol-4-il)-5-(2-(tetrahidro-2H-piran-4-il-amino)-etoxi)-fenil)-6-((trimetil-silil)-etinil)-quinazolin-2-amina se concentró hasta obtener un sólido, y se utilizó en el siguiente paso sin purificación. ES/MS *m/z* 541(MH^+).

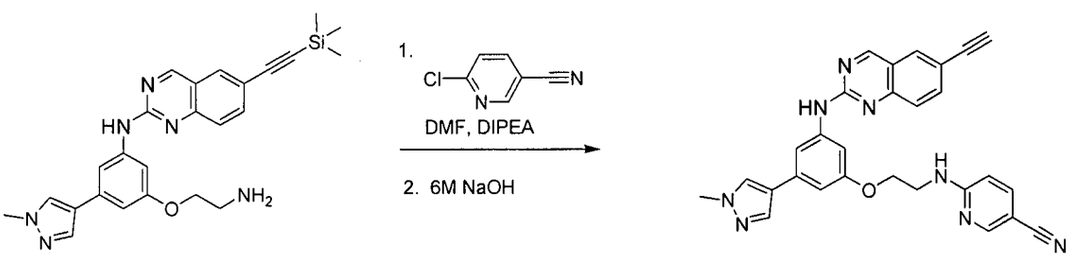
Paso 2: 6-etinil-N-(3-(1-metil-1H-pirazol-4-il)-5-(2-(tetrahidro-2H-piran-4-il-amino)-etoxi)-fenil)-quinazolin-2-amina

A la mezcla de reacción cruda de la N-(3-(1-metil-1H-pirazol-4-il)-5-(2-(tetrahidro-2H-piran-4-il-amino)-etoxi)-fenil)-6-((trimetil-silil)-etinil)-quinazolin-2-amina (0.09 milimoles) en 2 mililitros de metanol, se le agregó NaOH 6M (2.0 mililitros, 12.0 milimoles), y se agitó a temperatura ambiente durante 10 minutos, y se verificó mediante

LCMS. Si la desprotección quedó incompleta, se agregó más NaOH 6M y se volvió a verificar en 10 minutos. A la reacción cruda se le agregaron 100 mililitros de acetato de etilo, y se lavó con agua (2 veces), NaCl saturado, se secó con Na_2SO_4, se filtró, y se concentró hasta obtener un residuo. Al residuo crudo se le agregó N,N-dimetil-formamida, se filtró, se purificó en la HPLC de preparación, y se liofilizó, para dar la 6-etinil-N-(3-(1-metil-1H-pirazol-4-il)-5-(2-(tetrahidro-2H-piran-4-il-amino)-etoxi)-fenil)-quinazolin-2-amina como la sal de ácido trifluoro-acético (2.0 miligramos). ES/MS *m/z* 469(MH^+).

Ejemplo 530: 6-(2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil-amino)-nicotinonitrilo

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1: 6-(2-(3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenoxi)-etil-amino)-nicotinonitrilo

A la mezcla de reacción de la N-(3-(2-amino-etoxi)-5-(1-metil-1H-pirazol-4-il)-fenil)-6-((trimetil-silil)-etinil)-quinazolin-2-amina (26.7

miligramos, 0.0479 milimoles) en N,N-dimetil-formamida, se le agregó 6-cloro-nicotinonitrilo (13.2 miligramos, 0.096), y di-isopropil-etil-amina (0.025 mililitros, 0.144 milimoles). Esta mezcla de reacción se agitó a 105°C durante 20 horas. La mezcla de reacción cruda con el producto de 6-(2-(3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenoxi)-etil-amino)-nicotinonitrilo se utilizó en el siguiente paso sin purificación. ES/MS *m/z* 559(MH^+).

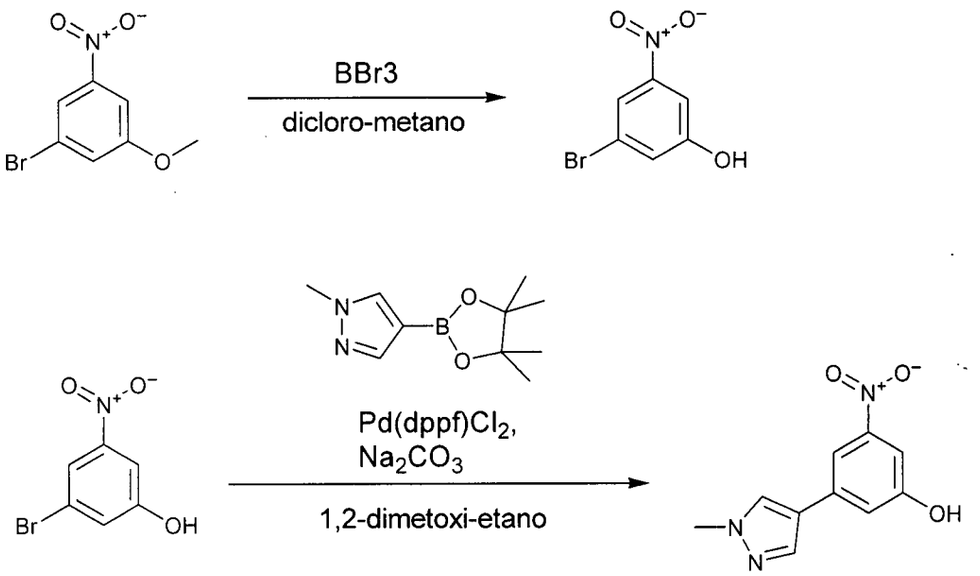
Paso 2: 6-(2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil-amino)-nicotinonitrilo

A la mezcla de reacción cruda del 6-(2-(3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenoxi)-etil-amino)-nicotinonitrilo (0.0479 milimoles), se le agregó NaOH 6M (0.08 mililitros, 0.48 milimoles), y se agitó a temperatura ambiente durante 10 minutos, y se verificó mediante LCMS. Si la desprotección quedó incompleta, se agregó más NaOH 6M, y se volvió a verificar en 10 minutos. A la mezcla de reacción cruda se le agregó N,N-dimetil-formamida, se filtró, se purificó en la HPLC de preparación, y se liofilizó para dar el 6-(2-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-etil-amino)-nicotinonitrilo como la sal de ácido trifluoro-acético (1.7 miligramos). ES/MS *m/z* 487(MH^+).

Ejemplo 606: (R)-2-(dimetil-amino)-N-(1-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-propan-2-il)-acetamida

3-(1-metil-1H-pirazol-4-il)-5-nitro-fenol

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso1: Preparación de 3-bromo-5-nitro-fenol

A la solución de 1-bromo-3-metoxi-5-nitro-benceno (13.5 gramos, 58.2 milimoles) en 50 mililitros de dicloro-metano, se le agregó la solución de 1 M de tribromuro de boro (163 mililitros, 163 milimoles) en dicloro-metano lentamente durante 10 minutos a 0°C. La mezcla de reacción se agitó a 0°C durante 20 minutos, y luego a temperatura ambiente durante 48 hora. La desprotección del metil-éter llegó a completarse y se monitoreó mediante LC/MS. La remoción de todo el solvente al vacío, seguido por apagado con agua y una solución diluida de $NaHCO_3$ a 0°C, y la extracción de la fase acuosa con acetato de etilo, y el secado de los extractos orgánicos

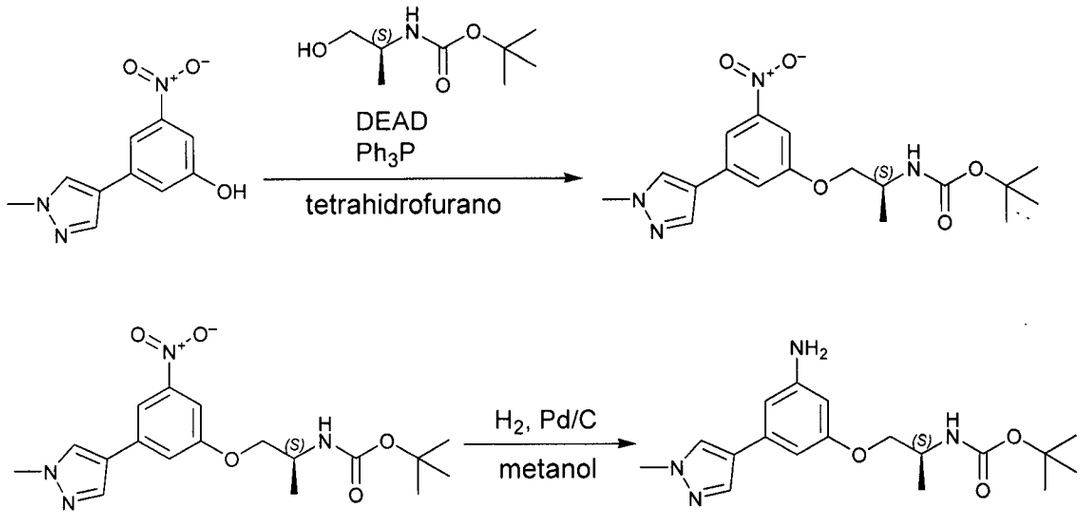
combinados sobre Na_2SO_4, y la remoción subsiguiente del acetato de etilo al vacío, proporcionó el producto deseado que se secó al vacío, para dar 12.3 gramos del 3-bromo-5-nitro-fenol como un sólido color púrpura.

Paso 2: Preparación de 3-(1-metil-1H-pirazol-4-il)-5-nitro-fenol

A la mezcla de reacción del 3-bromo-5-nitro-fenol (2.2 gramos, 10 milimoles), y 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxa-borolan-2-il)-1H-pirazol (2.7 gramos, 13 milimoles) en 37.5 mililitros de 1,2-dimetoxi-etano, se le agregaron $Pd(dppf)Cl_2$ (660 miligramos, 0.8 milimoles), y Na_2CO_3 acuoso 2M (12.5 mililitros, 25 milimoles). La mezcla de reacción se agitó a 85°C durante 24 horas o hasta que se consideró hecha mediante LC. La mezcla de reacción se diluyó con 250 mililitros de acetona, se filtró a través de Celite, y se lavó con una solución de 1:1 de acetato de etilo y metanol. El filtrado orgánico combinado se evaporó al vacío, para dar un sólido color café (4 gramos) que se purificó mediante un tapón de columna de gel de sílice, eluyendo con acetato de etilo, para dar el 3-(1-metil-1H-pirazol-4-il)-5-nitro-fenol como un polvo color café-amarillo (1.87 gramos). ES/MS *m/z* 220.0(MH^+).

(S)-1-(3-amino-5-(1-metil-1H-pirazol-4-il)-fenoxi)-propan-2-il-carbamato de terbutilo

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1: Preparación del (S)-1-(3-(1-metil-1H-pirazol-4-il)-5-nitro-fenoxi)-propan-2-il-carbamato de terbutilo

A la solución de la reacción del 3-(1-metil-1H-pirazol-4-il)-5-nitro-fenol (700 miligramos, 3.2 milimoles), y trifenil-fosfina (1.26 gramos, 4.84 milimoles) en 26 mililitros de tetrahidrofurano, se le agregaron (S)-1-hidroxi-propan-2-il-carbamato de terbutilo (848 miligramos, 4.84 milimoles), y azodicarboxilato de dietilo (860 microlitros, 5.46 milimoles). La solución resultante se agitó a 65°C durante 20 horas o hasta que se consideró hecha mediante LCMS. La solución de la reacción se concentró bajo presión reducida, para dar un pegamento color café oscuro (4 gramos) como un producto crudo que se purificó mediante cromatografía en columna sobre gel de sílice con acetato de etilo : hexano (60 : 40), para dar 1.08 gramos del (S)-1-(3-(1-metil-1H-pirazol-4-il)-5-nitro-fenoxi)-propan-2-

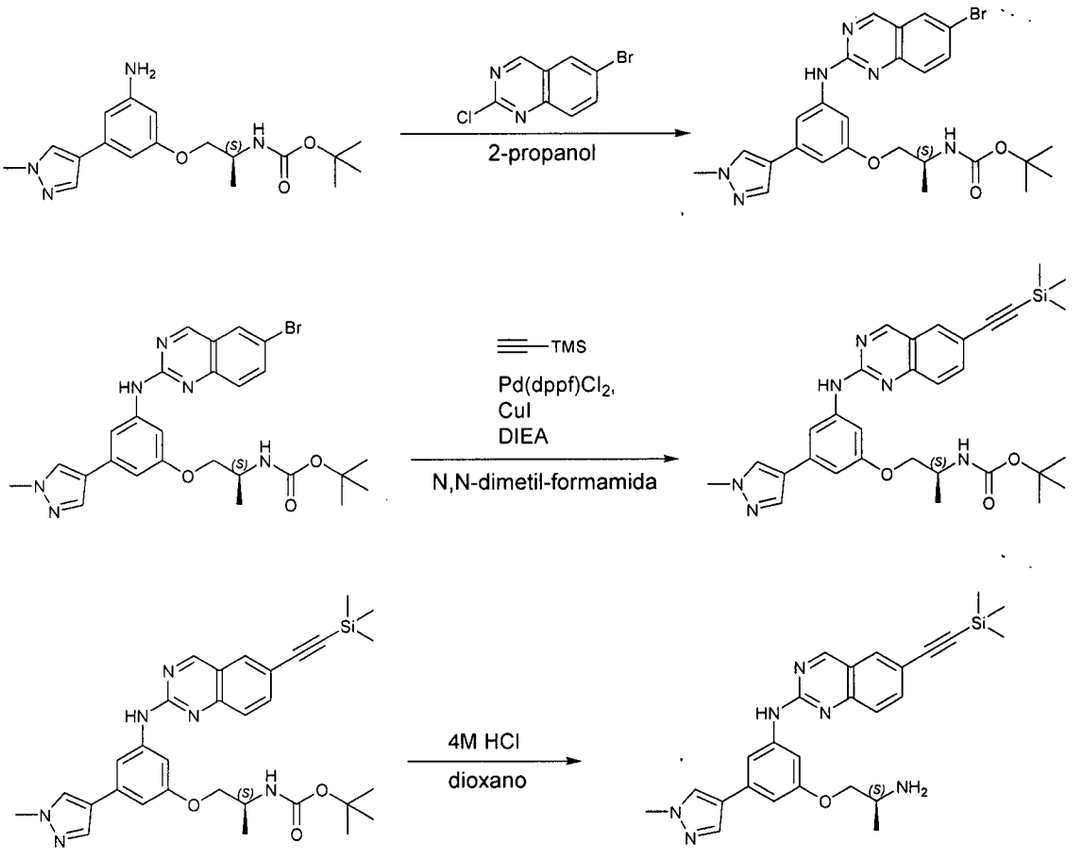
il-carbamato de terbutilo como un sólido amarillo. ES/MS *m/z* 377.2 (MH^+).

Paso 2: Preparación del (S)-1-(3-amino-5-(1-metil-1H-pirazol-4-il)-fenoxi)-propan-2-il-carbamato de terbutilo

Al material de partida crudo del (S)-1-(3-(1-metil-1H-pirazol-4-il)-5-nitro-fenoxi)-propan-2-il-carbamato de terbutilo (1.09 gramos, 2.89 milimoles), se le agregó Pd al 10 por ciento sobre carbón (1.02 gramos, 0.96 milimoles, 30 por ciento en peso) bajo argón. Bajo argón, se agregaron 11 mililitros de metanol con una jeringa cuidadosamente. A esta mezcla de reacción se le agregó un globo de hidrógeno, y se evacuó y se rellenó 6 veces. La mezcla de reacción se agitó a temperatura ambiente durante 22 horas o hasta que se consideró hecha mediante LC. A la mezcla de reacción se le agregó acetato de etilo y se filtró bajo argón a través de Celite, y se lavó con una solución de 1:1 de acetato de etilo y metanol. El filtrado se concentró bajo presión reducida, para dar el (S)-1-(3-amino-5-(1-metil-1H-pirazol-4-il)-fenoxi)-propan-2-il-carbamato de terbutilo como un polvo (945 miligramos). ES/MS *m/z* 347.1 (MH^+).

(S)-N-(3-(2-amino-propoxi)-5-(1-metil-1H-pirazol-4-il)-fenil)-6-((trimetil-silil)-etinil)-quinazolin-2-amina

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1: Preparación del (S)-1-(3-(6-bromo-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-propan-2-il-carbamato de terbutilo

A la mezcla de reacción del (S)-1-(3-amino-5-(1-metil-1H-pirazol-4-il)-fenoxi)-propan-2-il-carbamato de terbutilo (945 miligramos, 2.73 milimoles) en 25 mililitros de alcohol isopropílico en una bomba de vidrio, se le agregó 6-bromo-2-cloro-quinazolina (665 miligramos, 2.73 milimoles), y se selló. La solución de la reacción se agitó a 95°C durante 22 horas o hasta que se consideró hecha mediante LCMS. La solución de la reacción se concentró bajo

presión reducida, para dar un aceite color café rojizo que entonces se diluyó con 160 mililitros de acetato de etilo. La fase orgánica se lavó con una solución saturada de $NaHCO_3$ (60 mililitros, 2 veces), agua (30 mililitros), y salmuera (50 mililitros), entonces se secó sobre $MgSO_4$ y se evaporó al vacío, para dar un sólido color café rojizo. El sólido crudo se purificó mediante cromatografía en columna sobre gel de sílice con acetato de etilo : hexano (70 : 30), para dar el (S)-1-(3-(6-bromo-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-propan-2-il-carbamato de terbutilo (131 miligramos) como un sólido amarillo. ES/MS *m/z* 553.1/555.1 (MH^+).

Paso 2: Preparación del (S)-1-(3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenoxi)-propan-2-il-carbamato de terbutilo

A la mezcla de reacción del (S)-1-(3-(6-bromo-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-propan-2-il-carbamato de terbutilo (131 miligramos, 237 micromoles), $Pd(dppf)Cl_2$ (20 miligramos, 24 micromoles), CuI (10 miligramos, 47.4 micromoles), y di-isopropil-etil-amina (200 microlitros, 1.15 milimoles) en 2 mililitros de N,N-dimetil-formamida, se le agregó trimetil-silil-acetileno (99 microlitros, 710 micromoles). La mezcla de reacción se agitó a 60°C durante 2 horas. La mezcla de reacción cruda se dividió entre 80 mililitros de acetato de etilo y 20 mililitros de una solución saturada de $NaHCO_3$. La capa orgánica se lavó con agua (30 mililitros) y salmuera (50 mililitros), entonces se secó sobre Na_2SO_4 y se evaporó al vacío, para dar un sólido color café que se purificó

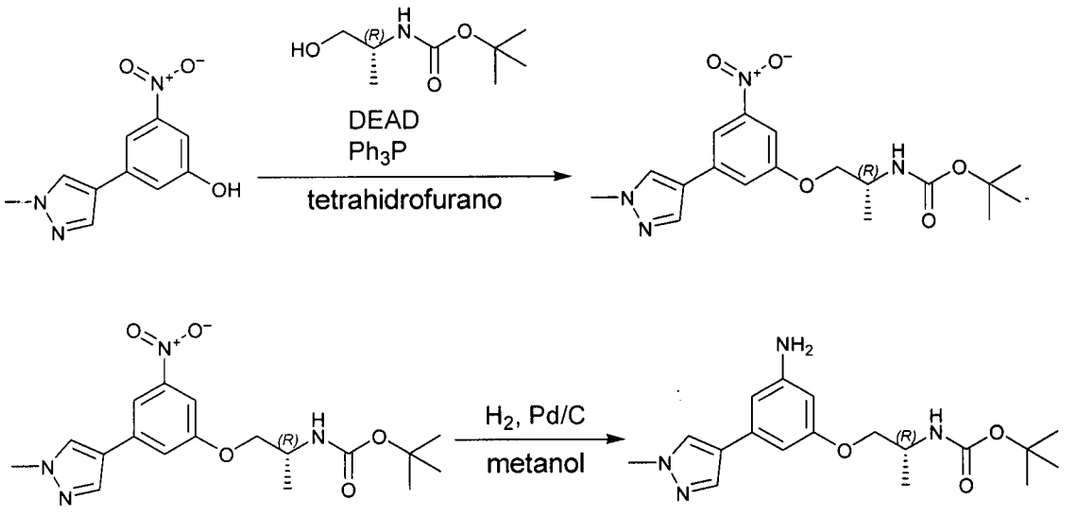
mediante cromatografía en columna sobre gel de sílice con acetato de etilo : hexano (50 : 50), para dar el (S)-1-(3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenoxi)-propan-2-il-carbamato de terbutilo (73 miligramos) como un sólido amarillo . ES/MS *m/z* 571.3 (MH^+).

Paso 3: Preparación de la (S)-N-(3-(2-amino-propoxi)-5-(1-metil-1H-pirazol-4-il)-fenil)-6-((trimetil-silil)-etinil)-quinazolin-2-amina

A la mezcla de reacción del (S)-1-(3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenoxi)-propan-2-il-carbamato de terbutilo (73 miligramos, 0.13 milimoles) se le agregó un exceso de HCl 4M en dioxano (4 mililitros, 16 milimoles). Esta mezcla de reacción se agitó a temperatura ambiente durante 1 hora o hasta que quedó hecha mediante LCMS, y se concentró al vacío, para dar un sólido amarillo que se disolvió con 60 mililitros de acetato de etilo. La fase orgánica se lavó con una solución de NaOH 1N (10 mililitros), agua (10 mililitros), y una solución de salmuera (20 mililitros), entonces se secó sobre Na_2SO_4 y se evaporó al vacío, para dar la (S)-N-(3-(2-amino-propoxi)-5-(1-metil-1H-pirazol-4-il)-fenil)-6-((trimetil-silil)-etinil)-quinazolin-2-amina como un polvo color café-amarillo (60 miligramos). ES/MS *m/z* 471.2 (MH^+).

(R)-1-(3-amino-5-(1-metil-1H-pirazol-4-il)-fenoxi)-propan-2-il-carbamato de terbutilo

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1: Preparación del (R)-1-(3-(1-metil-1H-pirazol-4-il)-5-nitro-fenoxi)-propan-2-il-carbamato de terbutilo

A la solución de la reacción del 3-(1-metil-1H-pirazol-4-il)-5-nitro-fenol (700 miligramos, 3.2 milimoles), y trifenil-fosfina (1.26 gramos, 4.84 milimoles) en 26 mililitros de tetrahidrofurano, se le agregaron (R)-1-hidroxi-propan-2-il-carbamato de terbutilo (848 miligramos, 4.84 milimoles), y azodicarboxilato de dietilo (790 microlitros, 5 milimoles). La solución resultante se agitó a 65°C durante 20 horas o hasta que se consideró hecha mediante LCMS. La solución de la reacción se concentró bajo presión reducida, para dar un pegamento color café (4 gramos) como un producto crudo que se purificó mediante cromatografía en columna sobre gel de sílice con acetato de etilo : hexano (60: 40), para dar 1.03 gramos del (R)-1-(3-(1-metil-1H-pirazol-4-il)-5-nitro-fenoxi)-propan-2-il-carbamato de

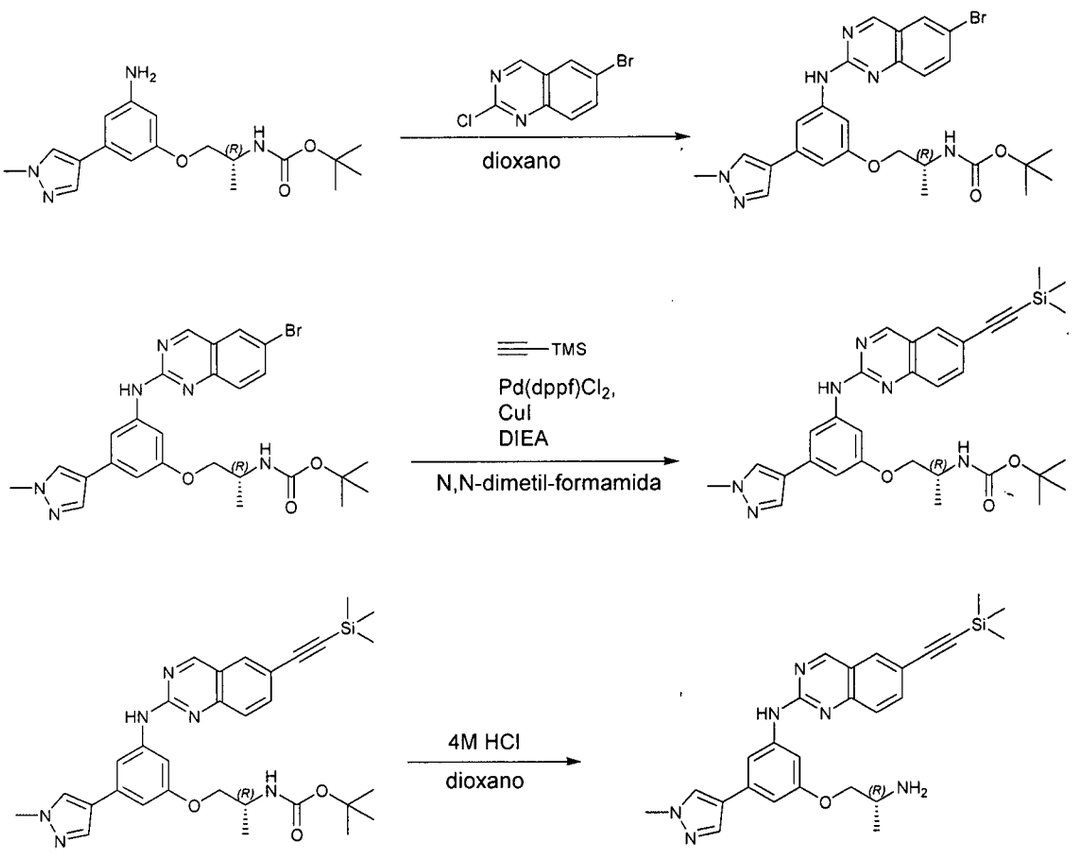
terbutilo como un pegamento amarillo. ES/MS *m/z* 377.1 (MH^+).

Paso 2: Preparación del (R)-1-(3-amino-5-(1-metil-1H-pirazol-4-il)-fenoxi)-propan-2-il-carbamato de terbutilo

Al material de partida crudo del (R)-1-(3-(1-metil-1H-pirazol-4-il)-5-nitro-fenoxi)-propan-2-il-carbamato de terbutilo (1.03 gramos, 2.73 milimoles), se le agregó Pd al 10 por ciento sobre carbón (968 miligramos, 0.91 milimoles, 30 por ciento en peso) bajo argón. Bajo argón, se agregaron 11 mililitros de metanol con una jeringa cuidadosamente. A esta mezcla de reacción se le agregó un globo de hidrógeno, y se evacuó y se rellenó 6 veces. La mezcla de reacción se agitó a temperatura ambiente durante 22 horas o hasta que se consideró hecha mediante LC. A la mezcla de reacción se le agregó acetato de etilo y se filtró bajo argón a través de Celite, y se lavó con una solución de 1:1 de acetato de etilo y metanol. El filtrado se concentró bajo presión reducida, para dar el (R)-1-(3-amino-5-(1-metil-1H-pirazol-4-il)-fenoxi)-propan-2-il-carbamato de terbutilo como un polvo (905 miligramos). ES/MS *m/z* 347.2 (MH^+).

(R)-N-(3-(2-amino-propoxi)-5-(1-metil-1H-pirazol-4-il)-fenil)-6-((trimetil-silil)-etinil)-quinazolin-2-amina

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1: Preparación del (R)-1-(3-(6-bromo-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-propan-2-il-carbamato de terbutilo

A la mezcla de reacción del (R)-1-(3-amino-5-(1-metil-1H-pirazol-4-il)-fenoxi)-propan-2-il-carbamato de terbutilo (905 miligramos, 2.35 milimoles), y 6-bromo-2-cloro-quinazolina (572 miligramos, 2.35 milimoles) en 11 mililitros de dioxano en una bomba de vidrio, se le agregó ácido acético (350 microlitros), y entonces se selló. La solución de la reacción se agitó a 92°C durante 22 horas o hasta que se consideró hecha mediante LCMS. La solución de la

reacción se concentró bajo presión reducida, para dar un sólido color café que entonces se diluyó con 180 mililitros de acetato de etilo. La fase orgánica se lavó con una solución saturada de $NaHCO_3$ (60 mililitros, 2 veces), agua (30 mililitros), y salmuera (50 mililitros), entonces se secó sobre Na_2SO_4 y se evaporó al vacío, para dar un sólido color café. El sólido crudo se purificó mediante cromatografía en columna sobre gel de sílice con acetato de etilo : hexano (70 : 30), para dar el (R)-1-(3-(6-bromo-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-propan-2-il-carbamato de terbutilo (405 miligramos) como un sólido amarillo. ES/MS *m/z* 553.1/555.1 (MH^+).

Paso 2: Preparación del (R)-1-(3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenoxi)-propan-2-il-carbamato de terbutilo

A la mezcla de reacción del (R)-1-(3-(6-bromo-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-propan-2-il-carbamato de terbutilo (408 miligramos, 737 micromoles), $Pd(dppf)Cl_2$ (90 miligramos, 111 micromoles), CuI (43 miligramos, 222 micromoles), y di-isopropil-etil-amina (500 microlitros, 2.87 milimoles) en 5 mililitros de N,N-dimetil-formamida, se le agregó trimetil-silil-acetileno (307 microlitros, 2.21 milimoles). La mezcla de reacción se agitó a 80°C durante 1.5 horas. La mezcla de reacción cruda se dividió entre 100 mililitros de acetato de etilo y 40 mililitros de una solución saturada de $NaHCO_3$. La capa orgánica se lavó con agua (30 mililitros) y salmuera (50 mililitros), entonces se secó sobre Na_2SO_4 y se evaporó al vacío, para dar un sólido color café que se purificó

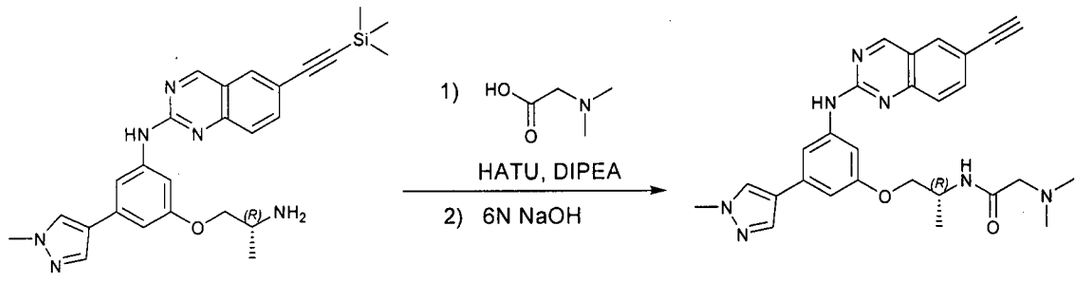
mediante cromatografía en columna sobre gel de sílice con acetato de etilo : hexano (60 : 40), para dar el (R)-1-(3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenoxi)-propan-2-il-carbamato de terbutilo (370 miligramos) como un sólido amarillo . ES/MS *m/z* 571.3 (MH^+).

Paso 3: Preparación de la (R)-N-(3-(2-amino-propoxi)-5-(1-metil-1H-pirazol-4-il)-fenil)-6-((trimetil-silil)-etinil)-quinazolin-2-amina

A la mezcla de reacción del (R)-1-(3-(1-metil-1H-pirazol-4-il)-5-(6-((trimetil-silil)-etinil)-quinazolin-2-il-amino)-fenoxi)-propan-2-il-carbamato de terbutilo (370 miligramos, 0.65 milimoles) se le agregó un exceso de HCl 4M en dioxano (16 mililitros, 64 milimoles). Esta mezcla de reacción se agitó a temperatura ambiente durante 1 hora o hasta que quedó hecha mediante LCMS, y se concentró al vacío, para dar un sólido amarillo que se disolvió con 100 mililitros de acetato de etilo. La fase orgánica se lavó con una solución de NaOH 1N (20 mililitros), agua (30 mililitros), y una solución de salmuera (40 mililitros), entonces se secó sobre Na_2SO_4 y se evaporó al vacío, para dar la (R)-N-(3-(2-amino-propoxi)-5-(1-metil-1H-pirazol-4-il)-fenil)-6-((trimetil-silil)-etinil)-quinazolin-2-amina como un polvo color café-amarillo (304 miligramos). ES/MS *m/z* 471.2 (MH^+).

(R)-2-(dimetil-amino)-N-(1-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-propan-2-il)-acetamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



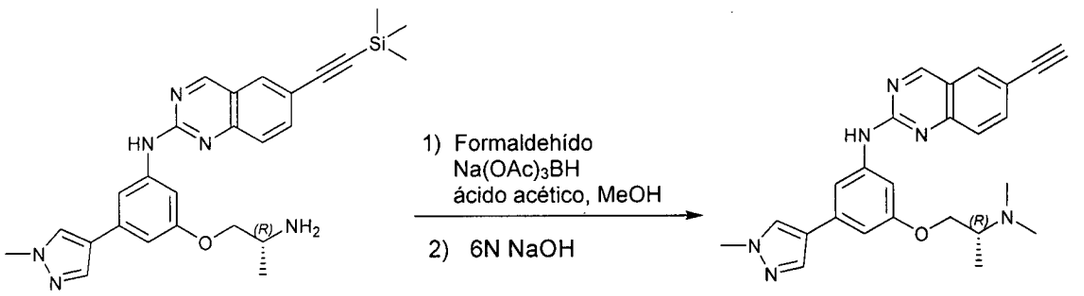
Paso 1: Preparación de la (R)-2-(dimetil-amino)-N-(1-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-propan-2-il)-acetamida

A la mezcla de reacción del ácido 2-(dimetil-amino)-acético (11 miligramos, 100 micromoles) en 0.7 mililitros de N,N-dimetil-formamida, se le agregaron HATU (38 miligramos, 100 micromoles), y di-isopropil-etil-amina (45 microlitros, 250 micromoles), y se agitó a temperatura ambiente durante aproximadamente 3 minutos. A la mezcla de reacción anterior se le agregó la (R)-N-(3-(2-amino-propoxi)-5-(1-metil-1H-pirazol-4-il)-fenil)-6-((trimetil-silil)-etinil)-quinazolin-2-amina (19 miligramos, 32 micromoles), y se agitó a temperatura ambiente durante 1 hora o hasta que se consideró hecha mediante LCMS. El producto crudo se desprotegió con 60 microlitros de una solución de NaOH 6N durante 5 minutos, y entonces se neutralizó con 60 microlitros de ácido acético. La mezcla de reacción cruda se filtró, se purificó en la HPLC de preparación, y se liofilizó, para dar la (R)-2-(dimetil-amino)-N-(1-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-propan-2-il)-acetamida

como la sal de ácido trifluoro-acético (10.3 miligramos). ES/MS *m/z* 483.2(MH^+).

Ejemplo 607: (R)-N-(3-(2-(dimetil-amino)-propoxi)-5-(1-metil-1H-pirazol-4-il)-fenil)-6-etinil-quinazolin-2-amina

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



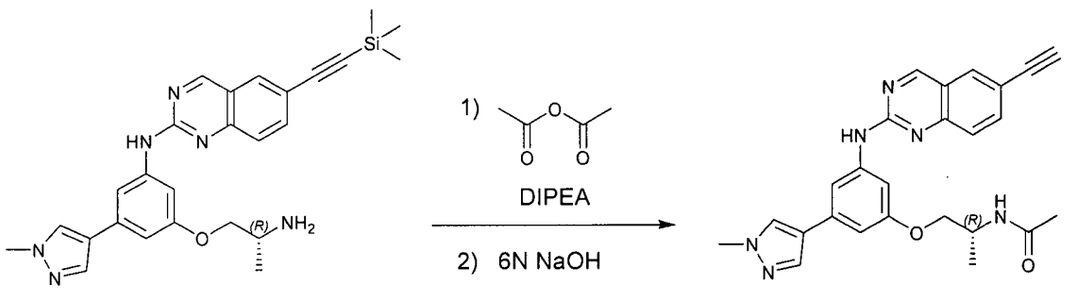
Paso 1: Preparación de la (R)-N-(3-(2-(dimetil-amino)-propoxi)-5-(1-metil-1H-pirazol-4-il)-fenil)-6-etinil-quinazolin-2-amina

A la mezcla de reacción de la (R)-N-(3-(2-amino-propoxi)-5-(1-metil-1H-pirazol-4-il)-fenil)-6-((trimetil-silil)-etinil)-quinazolin-2-amina (18.5 miligramos, 32 micromoles) en 0.6 mililitros de metanol, se le agregó ácido acético (36 microlitros, 600 micromoles), y una solución de formaldehído al 37 por ciento en agua (26 microlitros, 300 micromoles). La mezcla de reacción se agitó a temperatura ambiente durante aproximadamente 30 minutos. A esta solución de la reacción se le agregó triacetoxi-borohidruro de sodio (51 miligramos, 240 micromoles), y se agitó a temperatura ambiente durante 1 a 2 horas o hasta que se consideró hecha mediante LCMS. El producto crudo se desprotegió con 60 microlitros de una solución de NaOH 6N

durante 5 minutos, y entonces se neutralizó con 60 microlitros del ácido acético. La mezcla de reacción cruda se concentró, se agregó 1 mililitro de dimetil-formamida, se filtró, se purificó en la HPLC de preparación, y se liofilizó, para dar la (R)-N-(3-(2-(dimetil-amino)-propoxi)-5-(1-metil-1H-pirazol-4-il)-fenil)-6-etinil-quinazolin-2-amina como la sal de ácido trifluoro-acético (8 miligramos). ES/MS *m/z* 426.2(MH^+).

Ejemplo 618: (R)-N-(1-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-propan-2-il)-acetamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



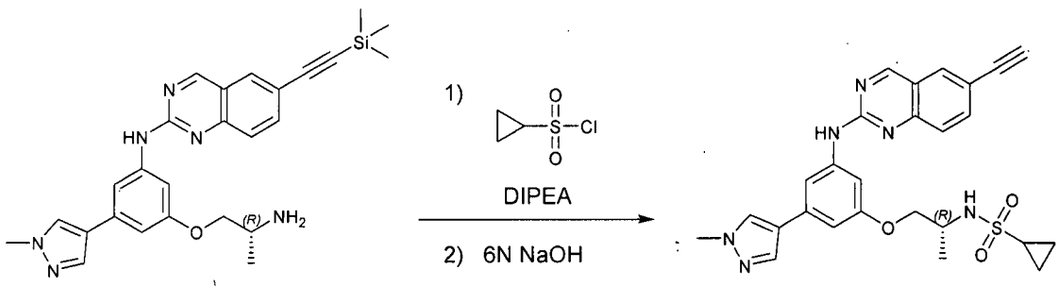
Paso 1: Preparación de la (R)-N-(1-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-propan-2-il)-acetamida

A la mezcla de reacción de la (R)-N-(3-(2-amino-propoxi)-5-(1-metil-1H-pirazol-4-il)-fenil)-6-((trimetil-silil)-etinil)-quinazolin-2-amina (15 miligramos, 30 micromoles) en 0.5 mililitros de N,N-dimetil-formamida, se le agregaron anhídrido acético (9 microlitros, 90 micromoles), y di-isopropil-etil-amina (17 microlitros, 100 micromoles). La solución de la reacción se agitó a temperatura

ambiente durante aproximadamente 90 minutos o hasta que se consideró hecha mediante LCMS. El producto crudo se desprotegió con 60 microlitros de una solución de NaOH 6N durante 5 minutos, y entonces se neutralizó con 60 microlitros del ácido acético. La mezcla de reacción cruda se filtró, se purificó en la HPLC de preparación, y se liofilizó, para dar la (R)-N-(1-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-propan-2-il)-acetamida como la sal de ácido trifluoro-acético (4.2 miligramos). ES/MS *m/z* 441.2(MH^+).

Ejemplo 619: (R)-N-(1-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-propan-2-il)-ciclopropan-sulfonamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



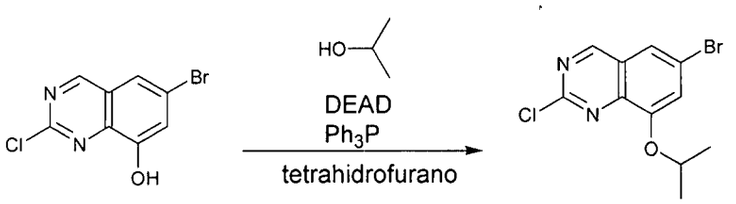
Paso 1: Preparación de la (R)-N-(1-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-propan-2-il)-ciclopropan-sulfonamida

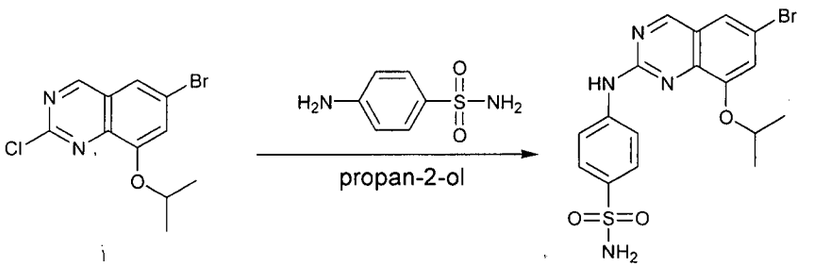
A la mezcla de reacción de la (R)-N-(3-(2-amino-propoxi)-5-(1-metil-1H-pirazol-4-il)-fenil)-6-((trimetil-silil)-etinil)-quinazolin-2-amina (15 miligramos, 30 micromoles) en 0.5 mililitros de N,N-dimetil-

formamida, se le agregaron cloruro de ciclopropan-sulfonilo (10 microlitros, 98 micromoles), y di-isopropil-etil-amina (35 microlitros, 200 micromoles). La solución de la reacción se agitó a temperatura ambiente durante 16 horas o hasta que se consideró hecha mediante LCMS. El producto crudo se desprotegió con 60 microlitros de una solución de NaOH 6N durante 5 minutos, y entonces se neutralizó con 60 microlitros del ácido acético. La mezcla de reacción cruda se filtró, se purificó en la HPLC de preparación, y se liofilizó, para dar la (R)-N-(1-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-1H-pirazol-4-il)-fenoxi)-propan-2-il)-ciclopropan-sulfonamida como la sal de ácido trifluoro-acético (4.3 miligramos). ES/MS *m/z* 503.2(MH^+).

Ejemplo 593: 4-(6-bromo-8-isopropoxi-quinazolin-2-il-amino)-bencen-sulfonamida y 4-(6-etinil-8-isopropoxi-quinazolin-2-il-amino)-bencen-sulfonamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:





Paso 1: Preparación de la 6-bromo-2-cloro-8-isopropoxi-quinazolina

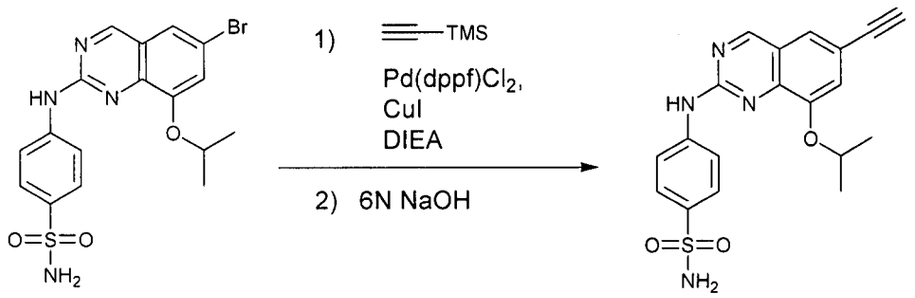
A la solución de la reacción de trifenil-fosfina (1.91 gramos, 7.3 milimoles), alcohol isopropílico (782 microlitros, 10.22 milimoles), y azodicarboxilato de dietilo (1.15 mililitros, 7.3 milimoles) en 18 mililitros de tetrahidrofurano, se le agregó 6-bromo-2-cloro-quinazolin-8-ol (928 miligramos, 3.64 milimoles) en 20 mililitros de tetrahidrofurano. La solución resultante se agitó a 65°C durante 24 horas o hasta que se consideró hecha mediante LCMS. La solución de la reacción se concentró bajo presión reducida, para dar un pegamento color café como un producto crudo que se purificó mediante cromatografía en columna sobre gel de sílice con acetato de etilo : hexano (15: 85), para dar 587 miligramos de la 6-bromo-2-cloro-8-isopropoxi-quinazolina como un sólido amarillo. ES/MS *m/z* 300.9/302.9 (MH^+).

Paso 2: Preparación de la 4-(6-bromo-8-isopropoxi-quinazolin-2-il-amino)-bencen-sulfonamida

A la mezcla de reacción de la 6-bromo-2-cloro-8-isopropoxi-quinazolina (45 miligramos, 150 micromoles) en 0.8 mililitros de alcohol isopropílico, se le agregó 4-amino-bencen-sulfonamida (51 miligramos, 300 micromoles), y se agitó a 82°C durante 20 horas o hasta que se consideró hecha mediante LCMS. La mezcla de reacción cruda se filtró, se purificó en la HPLC de preparación, y se liofilizó, para dar la 4-(6-bromo-8-isopropoxi-quinazolin-2-il-amino)-

bencen-sulfonamida como la sal de ácido trifluoro-acético (57 miligramos). ES/MS *m/z* 437.0/439.0(MH^+).

El compuesto de etinilo se preparó de acuerdo con el siguiente Esquema General:

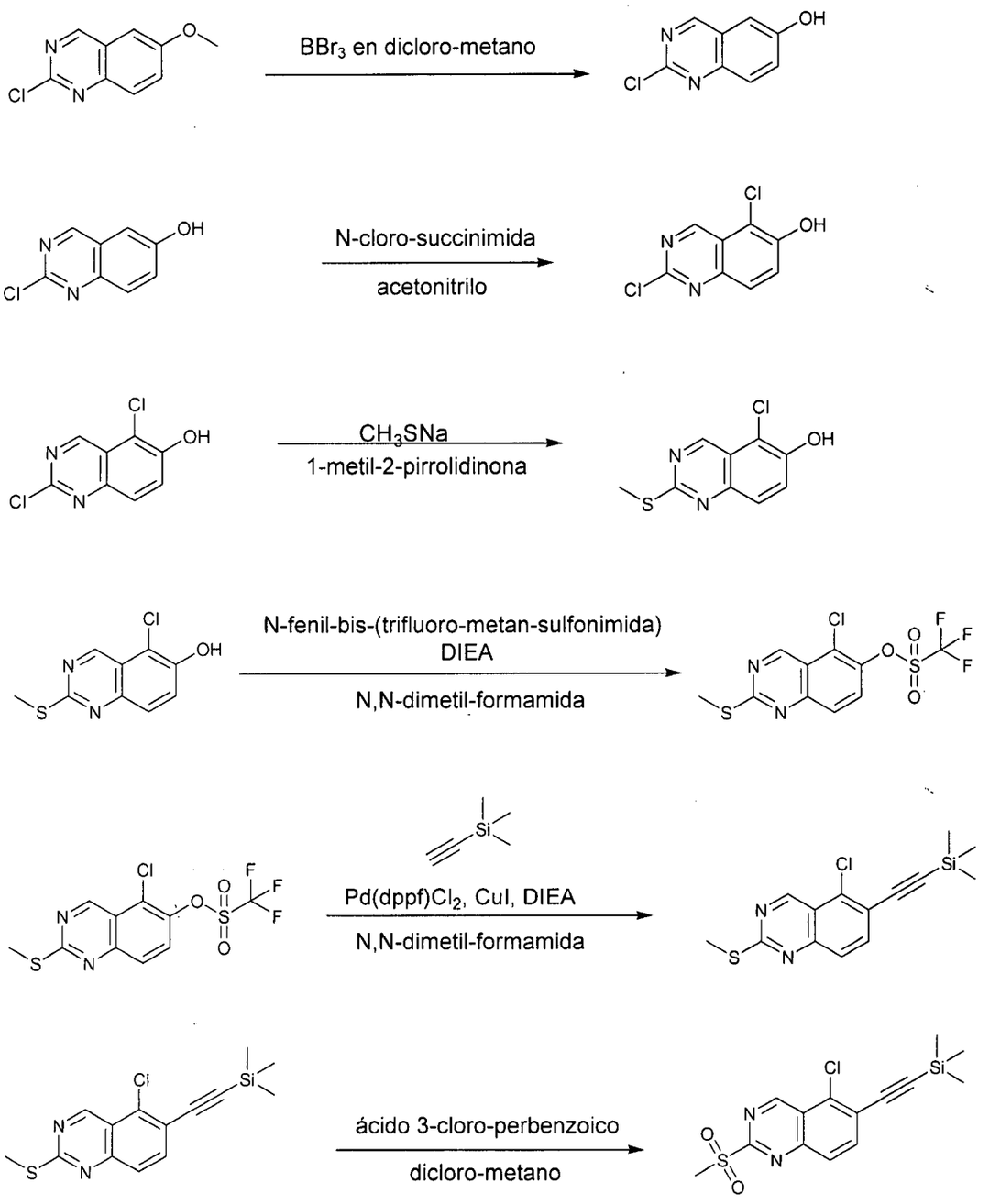


Paso 1: Preparación de la 4-(6-etinil-8-isopropoxi-quinazolin-2-il-amino)-bencen-sulfonamida

A la mezcla de reacción de la 4-(6-bromo-8-isopropoxi-quinazolin-2-il-amino)-bencen-sulfonamida (57 miligramos, 130 micromoles), $Pd(dppf)Cl_2$ (11 miligramos, 13 micromoles), CuI (5 miligramos, 26 micromoles), y di-isopropil-etil-amina (80 microlitros, 460 micromoles) en 0.8 mililitros de N,N-dimetil-formamida, se le agregó trimetil-silil-acetileno (55 microlitros, 390 micromoles). La mezcla de reacción se agitó a 55°C durante 2 horas o hasta que se consideró hecha mediante LCMS. El producto crudo se desprotegió con 50 microlitros de una solución de NaOH 6N durante 5 minutos, y entonces se neutralizó con 60 microlitros de ácido acético. La mezcla de reacción cruda se filtró, se purificó en la HPLC de preparación, y se liofilizó, para dar la 4-(6-etinil-8-isopropoxi-quinazolin-2-il-amino)-bencen-sulfonamida como la sal de ácido trifluoro-acético (22 miligramos). ES/MS *m/z* 383.1(MH^+).

Intermediario para los compuestos de 5-cloro: 5-cloro-2-(metil-sulfonil)-6-((trimetil-silil)-etinil)-quinazolina

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1: Preparación del 2-cloro-quinazolin-6-ol

A la solución de la 2-cloro-6-metoxi-quinazolina (1 equivalente) en dicloro-metano, se le agregó la solución 1 M de tribromuro de boro (2 equivalentes) en dicloro-metano lentamente durante 3 minutos a 0°C. La mezcla de reacción se agitó a 0°C durante 20 minutos, y se calentó a 40°C durante 16 horas. La desprotección del metil-éter llegó a completarse y se monitoreó mediante LC/MS. La remoción de todo el solvente al vacío, seguida por apagado con agua y una solución diluida de $NaHCO_3$ a 0°C, y la extracción de la fase acuosa con acetato de etilo, y el secado de los extractos orgánicos combinados sobre Na_2SO_4 y la remoción subsiguiente del acetato de etilo al vacío, proporcionaron el producto deseado, el cual se secó al vacío, para dar el 2-cloro-quinazolin- 6-ol como un sólido color café. ES/MS *m/z* 181.0(MH^+).

Paso 2: Preparación del 2,5-dicloro-quinazolin-6-ol

A la solución del 2-cloro-quinazolin-6-ol (3.61 gramos, 20 milimoles) en acetonitrilo, se le agregó N-cloro-succinimida (2.67 gramos, 20 milimoles), y la mezcla se agitó a temperatura ambiente, y se convirtió en una solución de reacción color café profundo. La reacción llegó a completarse en 30 minutos para dar el 2,5-dicloro-quinazolin-6-ol (85 por ciento del isómero deseado) que se observó mediante LC/MS, y la estructura se confirmó mediante ^1H RMN. La solución de la reacción se concentró y entonces se disolvió en 300 mililitros de acetato de etilo. La fase orgánica se lavó con ácido

clorhídrico diluido (70 mililitros, 2 veces), agua (50 mililitros, 2 veces), y salmuera (50 mililitros), entonces se secó sobre Na_2SO_4 y se evaporó al vacío, para dar un sólido color café (3.1 gramos) que se purificó mediante cromatografía en columna sobre gel de sílice con acetato de etilo : hexano (30 : 70), para dar un polvo amarillo como el 2,5-dicloro-quinazolin-6-ol (1.92 gramos). ES/MS *m/z* 215.0(MH^+).

Paso 3: Preparación del 5-cloro-2-(tiometil)-quinazolin-6-ol

A la solución del 2,5-dicloro-quinazolin-6-ol (1.75 gramos, 7.41 milimoles) en 23 mililitros de N-metil-2-pirrolidona, se le agregó tiometóxido de sodio (1.5 gramos, 22.23 milimoles). La mezcla de reacción se agitó a 60°C durante la noche. La mezcla de reacción se vertió en 100 mililitros de una solución saturada de $NaHCO_3$, y se extrajo con acetato de etilo (150 mililitros, 2 veces). Las capas orgánicas combinadas se lavaron con una solución diluida de $NaHCO_3$ (80 mililitros), agua (30 mililitros, 2 veces), y salmuera (40 mililitros), entonces se secó sobre Na_2SO_4 y se evaporó al vacío, para dar un pegamento color café que se recristalizó en hexano/dicloro-metano para dar el 5-cloro-2-(tiometil)-quinazolin-6-ol como un sólido color café. ES/MS *m/z* 227.0(MH^+).

Paso 4: Preparación del trifluoro-metan-sulfonato de 5-cloro-2-(tiometil)-quinazolin-6-ilo

A la solución del 5-cloro-2-(tiometil)-quinazolin-6-ol (1.98 gramos, 7.93 milimoles) en 30 mililitros de N, N-dimetil-formamida a 0°C se le agregaron N-fenil-bis-(trifluoro-metan-sulfonimida) (2.55

gramos, 7.13 milimoles), y di-isopropil-etil-amina (2.76 mililitros, 15.86 milimoles). La solución resultante se agitó a temperatura ambiente durante 2.5 horas, y se convirtió en una solución de reacción color café profundo. La solución de la reacción se dividió entre 250 mililitros de acetato de etilo y 80 mililitros de ácido clorhídrico diluido. La capa orgánica se lavó con ácido clorhídrico diluido (60 mililitros), agua (50 mililitros), y salmuera (50 mililitros), entonces se secó sobre Na_2SO_4 y se evaporó al vacío, para dar un sólido color café (4.72 gramos) que se purificó mediante cromatografía en columna sobre gel de sílice con acetato de etilo : hexano (10 : 90), para dar un sólido color beige como el trifluoro-metan-sulfonato de 5-cloro-2-(tiometil)-quinazolin-6-ilo (2.8 gramos). ES/MS *m/z* 358.8(MH^+).

Paso 5: Preparación de la 5-cloro-2-(tiometil)-6-((trimetil-silil)-etinil)-quinazolina

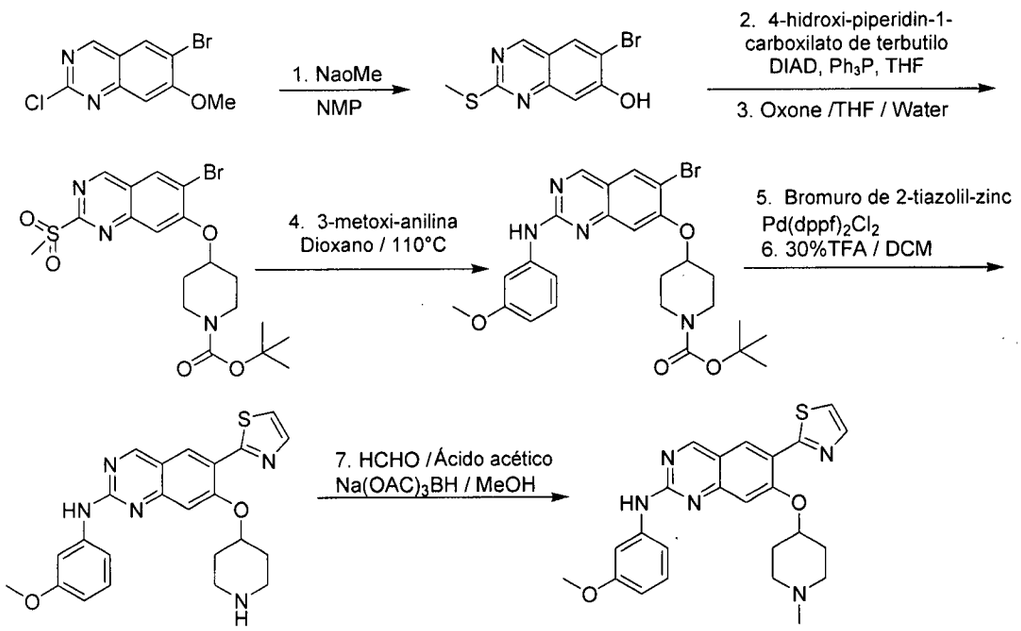
A la mezcla de reacción del trifluoro-metan-sulfonato de 5-cloro-2-(tiometil)-quinazolin-6-ilo (2.05 gramos, 5.39 milimoles), $Pd(dppf)Cl_2$ (440 miligramos, 0.539 milimoles), CuI (220 miligramos, 1.15 milimoles), y di-isopropil-etil-amina (3.6 mililitros, 20.7 milimoles) en 36 mililitros de N,N-dimetil-formamida, se le agregó trimetil-silil-acetileno (2.2 mililitros, 16.2 milimoles). La mezcla de reacción se agitó a 100°C durante 1.5 horas. La mezcla de reacción cruda se dividió entre 300 mililitros de acetato de etilo y 80 mililitros de ácido clorhídrico diluido. La capa orgánica se lavó con ácido clorhídrico diluido (60 mililitros), agua (50 mililitros), y salmuera (50

mililitros), entonces se secó sobre Na_2SO_4 y se evaporó al vacío, para dar un pegamento color café (aproximadamente 2.5 gramos) que se purificó mediante cromatografía en columna sobre gel de sílice con acetato de etilo : hexano (10 : 90), para dar la 5-cloro-2-(tiometil)-6-((trimetil-silil)-etinil)-quinazolina (723 miligramos) como un sólido amarillo . ES/MS *m/z* 351.0 (MH^+).

Paso 6: Preparación de la 5-cloro-2-(metil-sulfonil)-6-((trimetil-silil)-etinil)-quinazolina

A la solución de la 5-cloro-2-(tiometil)-6-((trimetil-silil)-etinil)-quinazolina (723 miligramos, 2.2 milimoles) en 20 mililitros de dicloro-metano a 0°C se le agregó la solución de ácido 3-cloro-perbenzoico (aproximadamente 77 por ciento puro, 926 miligramos, 4.13 milimoles) en 10 mililitros de dicloro-metano. La solución de la reacción se agitó a temperatura ambiente durante la noche y se monitoreó mediante LC/MS. Después de completarse, la solución de la reacción se diluyó con 200 mililitros de dicloro-metano. La fase orgánica se lavó con una solución saturada de $NaHCO_3$ (60 mililitros, 2 veces), agua (30 mililitros), y salmuera (50 mililitros), entonces se secó sobre Na_2SO_4 y se evaporó al vacío, para dar la 5-cloro-2-(metil-sulfonil)-6-((trimetil-silil)-etinil)-quinazolina como un polvo color café amarillento (732 miligramos) que se utilizó en el siguiente paso sin mayor purificación. ES/MS *m/z* 339.0(MH^+).

Ejemplo 1020: N-(3-metoxi-fenil)-7-(1-metil-piperidin-4-iloxi)-6-(tiazol-2-il)-quinazolin-2-amina



Paso 1. Preparación del 6-bromo-2-(tiometil)-quinazolin-7-ol

A una solución de la 6-bromo-2-cloro-7-metoxi-quinazolina (1 equivalente) (Véase el Ejemplo 11) en NMP (5 mililitros), se le agregó NaOMe (2 equivalentes). La mezcla de reacción se calentó a 80°C durante 2 horas. La mezcla de reacción se diluyó con agua, y el pH se ajustó a 5.5 con HCl 1N. El precipitado se filtró, se lavó, y se secó al vacío, para proporcionar el producto del título como un sólido amarillo (rendimiento del 60 por ciento). ES/MS *m/z* 271.0 / 273.0 (MH^+).

El 2,6-bis-(tiometil)-quinazolin-7-ol se formó como un producto secundario (40 por ciento).

Paso 2. Preparación del 4-(6-bromo-2-(tiometil)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo

A una solución de trifenil-fosfina (2 equivalentes) en tetrahidrofurano, se le agregó azodicarboxilato de dietilo (2 equivalentes). La mezcla se agitó durante 15 minutos a temperatura ambiente bajo una atmósfera de nitrógeno. A esto se le agregó el 4-hidroxi-piperidin-1-carboxilato de terbutilo (3 equivalentes). La mezcla se agitó durante 15 minutos a temperatura ambiente seguido por la adición de 6-bromo-2-(tiometil)-quinazolin-7-ol (1 equivalente). La mezcla se agitó durante la noche a temperatura ambiente. La mezcla de reacción se concentró y se purificó mediante cromatografía en columna por evaporación instantánea (10 por ciento de EtOAc / Hexano), para proporcionar el producto como un sólido blanco en un 70 por ciento de rendimiento. ES/MS *m/z* 454.0 / 456.0 (MH^+).

Paso 3. Preparación de 4-(6-bromo-2-(metilo sulfonil)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo

A una solución del 4-(6-bromo-2-(tiometil)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo (1 equivalente) en tetrahidrofurano (10 mililitros), se le agregó una solución de oxono en agua (10 mililitros) a 0°C. La mezcla de reacción se agitó durante 30 minutos a 0°C, entonces se calentó a temperatura ambiente, y se agitó durante la noche. La reacción se enfrió a 0°C y se apagó con una solución saturada de tiosulfato de sodio. El producto se extrajo en acetato de etilo. Los extractos de acetato de etilo se combinaron entre sí, se lavaron con salmuera, y se secaron sobre sulfato de sodio. Se filtraron, se evaporaron, y se secaron al vacío, para

proporcionar el producto en un 90 por ciento de rendimiento. ES/MS *m/z* 486.0 / 488.0(MH^+). Se utilizó para el siguiente paso sin mayor purificación.

Paso 4. Preparación del 4-(6-bromo-2-(3-metoxi-fenil-amino)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo

Una solución del 4-(6-bromo-2-(metilo sulfonil)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo (1 equivalente), y 3-metoxi-anilina (2 equivalentes) en dioxano, se calentó en un tubo sellado a 110°C durante 24 horas. El producto se purificó mediante HPLC de semi-preparación y se liofilizó, para proporcionar el producto puro como un sólido amarillo en un 50 por ciento de rendimiento. ES/MS *m/z* 529.0 / 531.0 (MH^+).

Paso 5. Preparación de 4-(2-(3-metoxi-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo

Una mezcla del 4-(6-bromo-2-(3-metoxi-fenil-amino)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo (1 equivalente), bromuro de 2-tiazolil-zinc (5 equivalentes, solución 0.5M en tetrahidrofurano), y $Pd(dppf)_2Cl_2$ (0.1 equivalentes) se calentó en microondas a 120°C durante 10 minutos. La mezcla de reacción se diluyó con acetato de etilo, y se lavó con agua y salmuera. Se secó sobre sulfato de sodio, se filtró, y se evaporó, para proporcionar el producto crudo en un rendimiento cuantitativo.

ES/MS *m/z* 534.2 (MH^+).

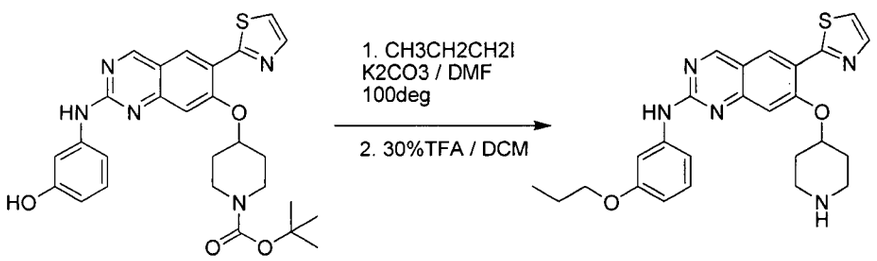
Paso 6. Preparación de la N-(3-metoxi-fenil)-7-(piperidin-4-iloxi)-6-(tiazol-2-il)-quinazolin-2-amina

Una solución del 4-(2-(3-metoxi-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo crudo en el 30 por ciento de ácido trifluoro-acético / dicloro-metano, se agitó a temperatura ambiente durante 30 minutos. El solvente se evaporó y el producto crudo se purificó mediante HPLC de semi-preparación, para proporcionar el producto puro en un 40 por ciento de rendimiento. ES/MS *m/z* 434.2 (MH^+).

Paso 7. Preparación de la N-(3-metoxi-fenil)-7-(1-metil-piperidin-4-iloxi)-6-(tiazol-2-il)-quinazolin-2-amina

A una solución de la N-(3-metoxi-fenil)-7-(piperidin-4-iloxi)-6-(tiazol-2-il)-quinazolin-2-amina (1 equivalente) en metanol, se le agregó HCHO (10 equivalentes), y una gota del ácido acético. Se agitó durante10 minutos a temperatura ambiente, seguido por la adición de $Na(OAc)_3BH$ (4 equivalentes). La mezcla de reacción se agitó durante 1 hora a temperatura ambiente. Se purificó mediante HPLC de semi-preparación, para proporcionar el producto como un sólido amarillo en un 70 por ciento de rendimiento. ES/MS *m/z* 448.2 (MH^+).

Ejemplo 1075: Síntesis de la 7-(piperidin-4-iloxi)-N-(3-propoxi-fenil)-6-(tiazol-2-il)-quinazolin-2-amina



Paso1. Preparación de 4-(2-(3-propoxi-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo

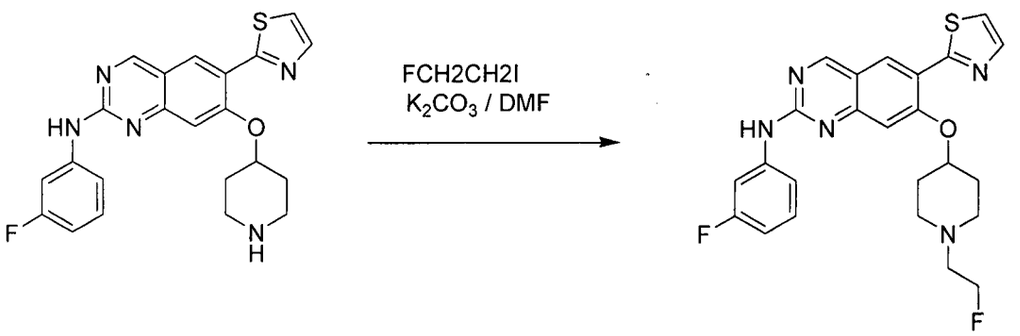
Al 4-(2-(3-hidroxi-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo (1 equivalente) (Para la síntesis, véase el Ejemplo 21) en N,N-dimetil-formamida (2 mililitros), se le agregaron K_2CO_3 (5 equivalentes), y yodo-propano (3 equivalentes). La mezcla de reacción se calentó a 100°C durante 48 horas.

La mezcla de reacción se dividió entre acetato de etilo y agua. La capa de acetato de etilo se separó y se lavó con agua, salmuera, y se secó sobre sulfato de sodio. Se filtró y se evaporó, para proporcionar el producto crudo. ES/MS *m/z* 562.2 (MH^+).

Paso 2. Preparación de la 7-(piperidin-4-iloxi)-N-(3-propoxi-fenil)-6-(tiazol-2-il)-quinazolin-2-amina

Para la síntesis, véase el Ejemplo 1020, Paso 6. ES/MS *m/z* 462.2 (MH^+).

Ejemplo 1082: 7-(1-(2-fluoro-metil-piperidin-4-iloxi)-N-(3-fluoro-fenil)-6-(tiazol-2-il)-quinazolin-2-amina

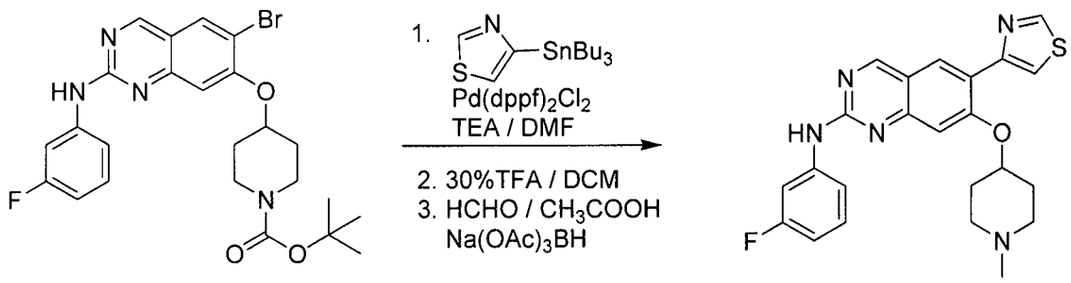


A la N-(3-fluoro-fenil)-7-(piperidin-4-iloxi)-6-(tiazol-2-il)-quinazolin-2-amina (1 equivalente) (Para la síntesis, véase el

Ejemplo 11) en N,N-dimetil-formamida, se le agregaron K_2CO_3 (5 equivalentes), y 1-fluoro-3-yodo-etano (1.2 equivalentes). La mezcla de reacción se agitó durante la noche a temperatura ambiente. El producto se purificó mediante HPLC de semi-preparación. ES/MS *m/z* 468.2 (MH^+).

EJEMPLO 1084

Síntesis de la N-(3-fluoro-fenil)-7-(1-metil-piperidin-4-iloxi)-6-(tiazol-4-il)-quinazolin-2-amina



Paso 1. Preparación de 4-(2-(3-fluoro-fenil-amino)-6-(tiazol-4-il)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo

Una mezcla del 4-(6-bromo-2-(3-fluoro-fenil-amino)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo (1 equivalente, véase el Ejemplo 11 para la síntesis), 4-tributil-estaño-tiazol (3 equivalentes), trietil-amina (3.5 equivalentes), y Pd $(dppf)_2Cl_2$ (0.1 equivalentes) en N,N-dimetil-formamida (1.5 mililitros), se calentó en microondas a 120°C durante 10 minutos. La mezcla de reacción se dividió entre acetato de etilo y agua. La capa de acetato de etilo se separó y se lavó con agua, salmuera, y se secó sobre sulfato de sodio. Se filtró, se evaporó y se purificó mediante HPLC de semi-preparación, para proporcionar el producto puro en un 50 por ciento de rendimiento

ES/MS *m/z* 522.1 (MH^+).

Paso 2. Preparación de la N-(3-fluoro-fenil)-7-(piperidin-4-iloxi)--6-(tiazol-4-il)-quinazolin-2-amina

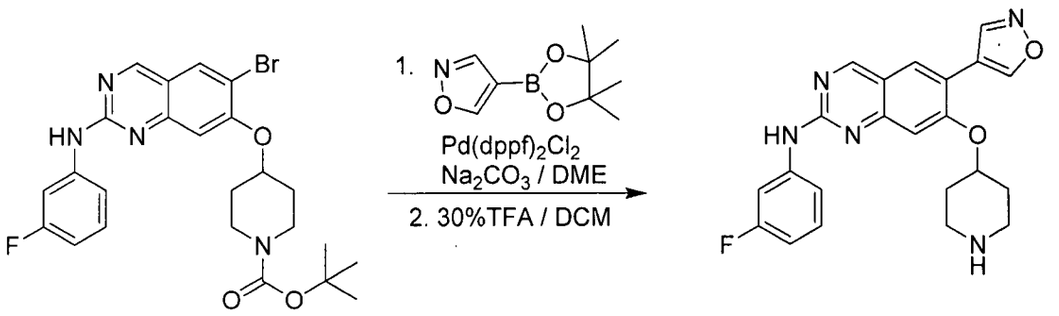
Para la síntesis véase el Ejemplo 21, Paso 6. ES/MS *m/z* 422.1 (MH^+).

Paso 3. Preparación de la N-(3-fluoro-fenil)-7-(1-metil-piperidin-4-iloxi)--6-(tiazol-4-il)-quinazolin-2-amina

Para la síntesis véase el Ejemplo 1020, Paso 7. ES/MS *m/z* 436.1 (MH^+).

EJEMPLO 1066

Síntesis de la N-(3-fluoro-fenil)-6-(isoxazol-4-ilo)-7-(piperidin-4-iloxi)-quinazolin-2-amina



Paso1. Preparación del 4-(2-(3-fluoro-fenil-amino)-6-(isoxazol-4-il)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo

Una mezcla del 4-(6-bromo-2-(3-fluoro-fenil-amino)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo (1 equivalente, véase el Ejemplo 11 para la síntesis), éster 4-isoxazol-borónico (3 equivalentes), 1,1'-bis-(difenil-fosfino)-ferroceno-dicloro-paladio(II) (0.1 equivalentes), y carbonato de sodio (0.5 mililitros de una

solución acuosa 2M) en DME (2 mililitros), se calentó en microondas a 120°C durante 10 minutos. La mezcla de reacción se dividió entre acetato de etilo y agua. La capa de acetato de etilo se separó y se lavó con agua, salmuera, y se secó sobre sulfato de sodio. Se filtró, se evaporó y se purificó mediante HPLC de semi-preparación, para proporcionar el producto puro en un 50 por ciento de rendimiento ES/MS *m/z* 506.1 (MH^+).

Nota: También se observó algo de producto desbromado en la reacción anterior.

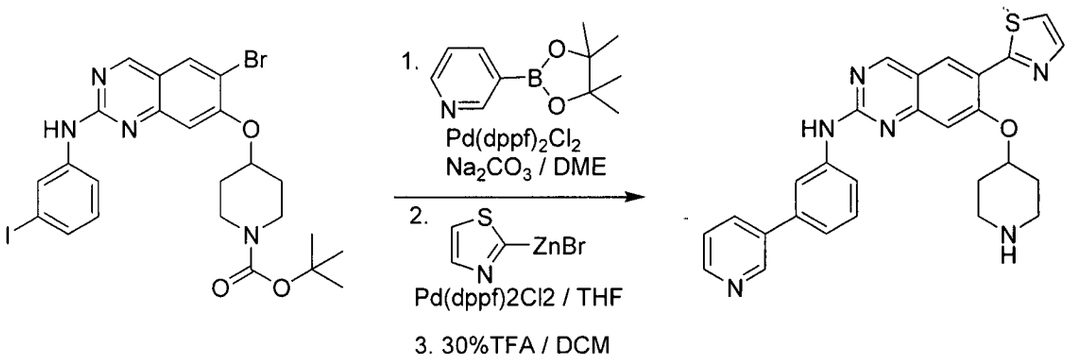
Paso 2. Preparación de la N-(3-fluoro-fenil)-6-(isoxazol-4-ilo)-7-(piperidin-4-iloxi)-quinazolin-2-amina

Para la síntesis véase el Ejemplo 1020, Paso 6. ES/MS *m/z* 406.1 (MH^+).

EJEMPLO 1135

Síntesis de la 7-(piperidin-4-iloxi)-N-(3-(piridin-3-il)-fenil)-6-(tiazol-2-il)-quinazolin-2-amina

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1. Preparación del 4-(6-bromo-2-(3-(piridin-3-il)-fenil-

amino)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo

Una mezcla de 4-(6-bromo-2-(3-yodo-fenil-amino)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo (1 equivalente, véase el Ejemplo 11 para la síntesis), éster 3-piridin-borónico (1.2 equivalentes), 1,1'-bis-(difenil-fosfino)-ferroceno-dicloro-paladio(II) (0.1 equivalentes), y carbonato de sodio (0.5 mililitros de una solución acuosa 2M) en DME (2 mililitros), se calentó en microondas a 120°C durante 10 minutos. La mezcla de reacción se dividió entre acetato de etilo y agua. La capa de acetato de etilo se separó y se lavó con agua, salmuera, y se secó sobre sulfato de sodio. Se filtró, se evaporó, y se purificó mediante HPLC de semi-preparación, para proporcionar el producto puro en un 50 por ciento de rendimiento ES/MS *m/z* 576.2 / 578.2.1 (MH^+).

Nota: También se aisló algo del producto bis-sustituido en la reacción anterior.

Paso 2. Preparación de 4-(2-(3-(piridin-3-il)-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo

Para la síntesis, véase el Ejemplo 1020, Paso 5. ES/MS m/z 581.2 (MH^+).

Paso 3. Preparación de la 7-(piperidin-4-iloxi)-N-(3-(piridin-3-il)-fenil)-6-(tiazol-2-il)-quinazolin-2-amina

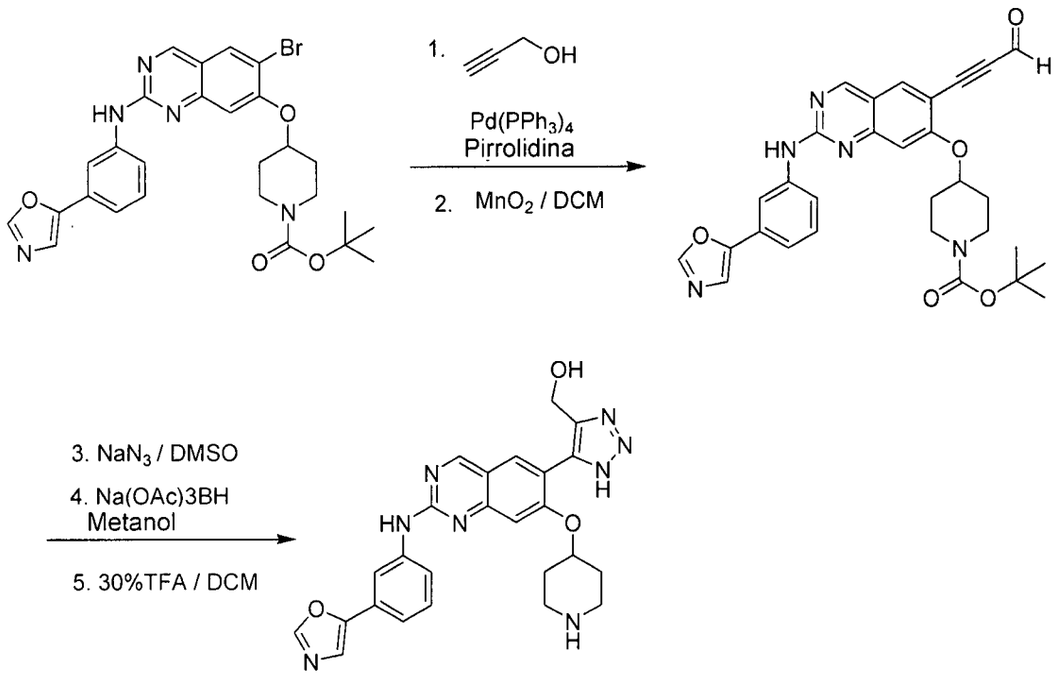
Para la síntesis, véase el Ejemplo 1020, Paso 6. ES/MS *m/z* 481.2 (MH^+).

EJEMPLO 1117

Síntesis del (5-(2-(3-(oxazol-5-il)-fenil-amino-(7-(piperidin-4-

iloxi)-quinazolin-6-il)-1H-1, 2, 3-triazol-4-il)-metanol

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1. Preparación de 4-(6-(3-hidroxi-prop-1-inil)-2-(3-(oxazol-5-il)-fenil-amino)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo

Al 4-(6-bromo-2-(3-(oxazol-5-il)-fenil-amino)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo (1 equivalente), y tetraquis-(PPH_3)Pd(0) (0.02 equivalentes) en pirrolidina (1.5 mililitros) a temperatura ambiente, se le agregó alcohol propargílico (2 equivalentes, en 1 mililitro de pirrolidina). La mezcla de reacción se calentó en un tubo sellado a 80°C durante 1 hora. La reacción se apagó con NH_4Cl saturado, y el producto se extrajo con dietil-éter. Los extractos de éter se lavaron con salmuera, se secaron sobre sulfato de sodio, se filtraron, y se evaporaron. Se purificó mediante

HPLC de semi-preparación, para proporcionar el producto puro como un sólido amarillo en un 40 por ciento de rendimiento. ES/MS *m/z* 542.2 (MH^+).

Paso 2. Preparación de 4-(2-(3-(oxazol-5-il)-fenil-amino)-6-(3-oxoprop-1-inil)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo

Una mezcla del 4-(6-(3-hidroxi-prop-1-inil)-2-(3-(oxazol-5-il)-fenil-amino)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo (1 equivalente), y MnO_2 (5 equivalentes) en dicloro-metano (5 mililitros) se agitó durante la noche a temperatura ambiente. El producto se filtró a través de Celite, y el solvente se evaporó, para proporcionar el producto puro en un 90 por ciento de rendimiento. ES/MS *m/z* 540.3 (MH^+).

Paso 3. Preparación de 4-(6-(4-formil-1H-1,2,3-triazol-5il)-2-(3-(oxazol-5-il)-fenil-amino)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo

A una solución agitada de azida de sodio (1.2 equivalentes) en sulfóxido de dimetilo (2 mililitros) en un baño de agua helada, se le agregó el 4-(2-(3-(oxazol-5-il)-fenil-amino)-6-(3-oxoprop-1-inil)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo en sulfóxido de dimetilo (1 mililitro). La mezcla de reacción se agitó durante 30 minutos a temperatura ambiente, y entonces se vertió a una solución bifásica vigorosamente agitada del 5 por ciento de KH_2PO_4 y dietil-éter. La capa de éter se separó, se lavó con salmuera, y se secó sobre sulfato de sodio. Se filtró, se evaporó y se secó al vacío, para proporcionar el producto como un sólido blanco en un 70 por ciento

de rendimiento. ES/MS *m/z* 583.31 (MH^+).

Paso 4. Preparación de 4-(6-(4-(hidroxi-metil)-1H-1,2,3-triazol-5il)-2-(3-(oxazol-5-il)-fenil-amino)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo

Al 4-(6-(4-formil-1H-1,2,3-triazol-5il)-2-(3-(oxazol-5-il)-fenil-amino)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo (1 equivalente) en metanol, se le agregó $Na(OAc)_3BH$ (5 equivalentes). La mezcla de reacción se agitó durante 1 hora a temperatura ambiente. Se purificó mediante HPLC de semi-preparación, para proporcionar el producto puro como un sólido amarillo en un 40 por ciento de rendimiento. ES/MS *m/z* 584.2 (MH^+).

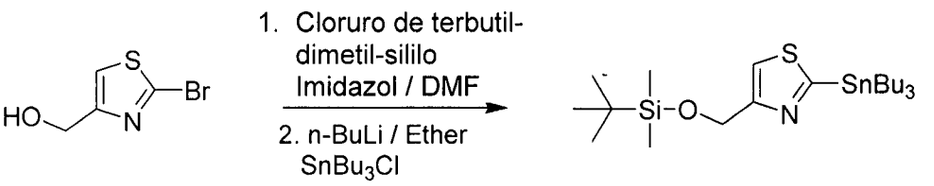
Paso 5. Preparación del (5-(2-(3-(oxazol-5-il)-fenil-amino-(7-(piperidin-4-iloxi)-quinazolin-6-il)-1H-1, 2, 3-triazol-4-il)-metanol

Para la síntesis, véase el Ejemplo 1020, Paso 6. ES/MS *m/z* 484.2 (MH^+).

EJEMPLO 1140: (2R,4S)-4-(2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-iloxi)-piperidin-2-carboxamida

Síntesis del 4-((terbutil-dimetil-sililoxi)-metil)-2-(tributil-estanil)-tiazol

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1. Preparación de 2-bromo-4-(terbutil-sililoxi)-metil)-tiazol

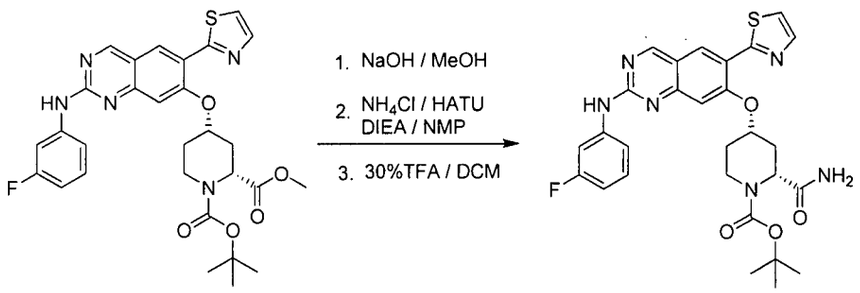
Una mezcla de 2-bromo-tiazol-4-il)-metanol (1 equivalente), imidazol (4 equivalentes), y cloruro de terbutil-dimetil-sililo (2 equivalentes) en N,N-dimetil-formamida (10 mililitros) se agitó durante 2 horas a temperatura ambiente. La mezcla de reacción se dividió entre acetato de etilo y agua. La capa de acetato de etilo se separó y se lavó con agua, salmuera, y se secó sobre sulfato de sodio. Se filtró, se evaporó y se purificó mediante cromatografía por evaporación instantánea (10 por ciento de EtOAc / Hexano), para proporcionar el producto puro como un líquido incoloro en un 95 por ciento de rendimiento ES/MS *m/z* 307.9 / 309.9 (MH^+).

Paso 2. Preparación del 4-((terbutil-dimetil-sililoxi)-metil)-2-(tributil-estanil)-tiazol

A un matraz secado en flama bajo nitrógeno a -78°C se le agregaron éter anhidro (10 mililitros), y n-butil-litio (1.5 equivalentes, solución 2.5M en Hexano), seguido por la adición de una solución de 2-bromo-4-(terbutil-sililoxi)-metil)-tiazol en éter (1 equivalente, 3 mililitros). Se agitó a -78°C durante 1 hora. Entonces se agregó por goteo una solución de cloruro de tributil-estaño en éter (1.5 equivalentes, 1 mililitro). Se agitó a esta temperatura durante 1 hora adicional La mezcla de reacción se apagó con bicarbonato de sodio saturado, y el compuesto se extrajo en éter. Los extractos de éter se combinaron, se lavaron con salmuera, y se secaron sobre sulfato de sodio. Se filtraron, se evaporaron, y se secaron al vacío, para proporcionar el producto como un líquido amarillo claro. Se utilizó sin mayor purificación.

Síntesis de la (2R,4S)-4-(2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-iloxi)-piperidin-2-carboxamida

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso1. Preparación del (2R,4S)-ácido 1-(terbutoxi-carbonil)-4-(2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-iloxi)-piperidin-2-carboxílico

Al (2R,4S)-2-metil-4-(2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-iloxi)-piperidin-1,2-dicarboxilato de 1-terbutilo (1 equivalente) en metanol (3 mililitros), se le agregó una solución acuosa de hidróxido de sodio (5 equivalentes). La mezcla de reacción se agitó durante la noche a temperatura ambiente. El solvente se evaporó; el residuo se absorbió en agua y se hizo ácido ccn 1NHCl. El producto se extrajo en acetato de etilo. Los extractos se combinaron, se lavaron con salmuera, y se secaron sobre sulfato de sodio. Se filtraron, se evaporaron, y se secaron al vacío, para proporcionar el producto como un sólido color café claro en un 70 por ciento de rendimiento. ES/MS *m/z* 566.1 (MH^+).

Paso 2. Preparación del (2R,4S)-2-carbamoil-4-(2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-iloxi)-piperidin-1-carboxilato de

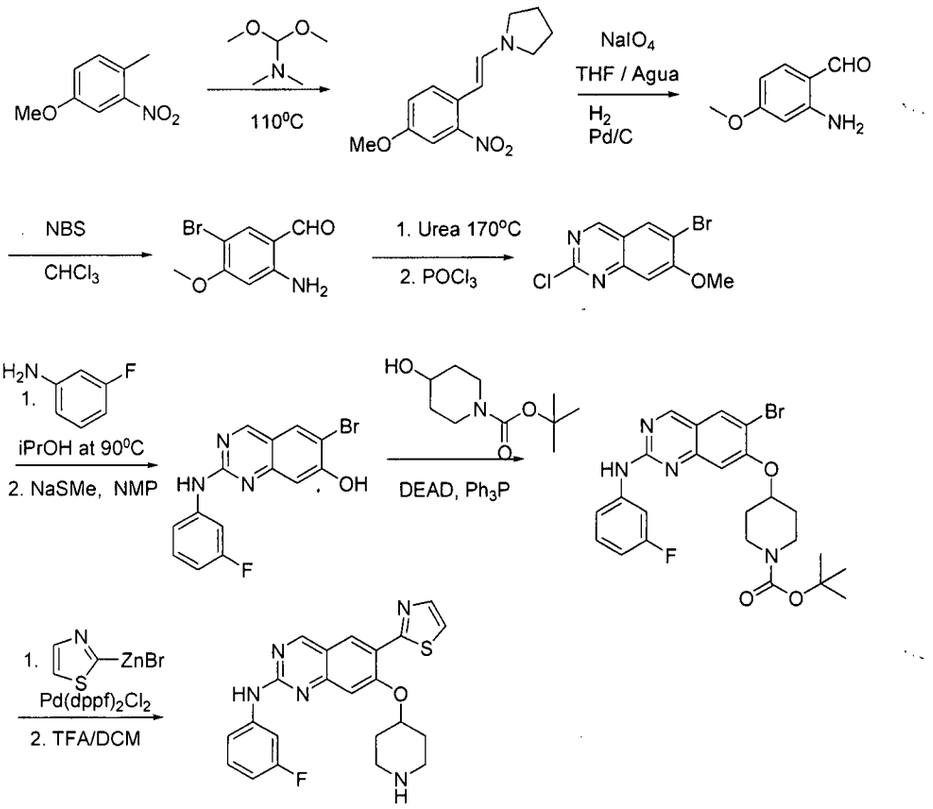
terbutilo

Una mezcla del (2R,4S)-ácido 1-(terbutoxi-carbonil)-4-(2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-iloxi)-piperidin-2-carboxílico (1 equivalente), NH_4Cl (10 equivalentes), HATU (1.75 equivalentes), y DIEA (5 equivalentes) en NMP (2 mililitros), se agitó durante la noche a temperatura ambiente. El producto se purificó mediante HPLC de semi-preparación. ES/MS *m/z* 565.1 (MH^+).

Paso 3. Preparación de la (2R,4S)-4-(2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-iloxi)-piperidin-2-carboxamida

Para la síntesis, véase Ejemplo 21, Paso 6. ES/MS *m/z* 465.1 (MH^+).

Ejemplo 997: Preparación de la N-(3-fluoro-fenil)-7-(piperidin-4-iloxi)-6-(tiazol-2-il)-quinazolin-2-amina



A. Preparación del 4-metoxi-2-amino-benzaldehído

A una mezcla de 4-metil-3-nitro-anisol en pirrolidina (1.9 equivalentes), se le agregó dimetil-acetal de N,N-dimetil-formamida, y la mezcla se calentó a 120°C durante 16 horas. La formación de la enaminona se confirmó mediante TLC. La mezcla se enfrió a temperatura ambiente, y se vertió en hielo, y se extrajo entonces con acetato de etilo, se secó (Na_2SO_4), y se concentró. A la enaminona cruda en tetrahidrofurano se le agregó $NaIO_4$ (2.5 equivalentes) disuelto en agua mientras que se mantenía la temperatura de la reacción a 40°C con un baño de hielo/agua. Después de la adición, la suspensión color amarillo pálido se agitó a 35°C durante 16 horas. La mezcla de reacción se concentró entonces, y la fase acuosa se extrajo luego con acetato de etilo, se secó (Na_2SO_4), y el 4-metoxi-2-nitro-benzaldehído crudo se obtuvo como un sólido color café. El sólido crudo color café se purificó sobre gel de sílice para obtener el producto. El 4-metoxi-2-nitro-benzaldehído así obtenido se hidrogenó en metanol con cantidades catalíticas del Pd/C al 10 por ciento para dar el 4-metoxi-2-amino-benzaldehído en un rendimiento cuantitativo. ES/MS *m/z* 152(MH^+).

B. Preparación del 5-bromo-4-metoxi-2-nitro-benzaldehído

Al 4-metoxi-2-amino-benzaldehído en cloroformo se le agregó NBS (1 equivalente), y la reacción llegó a completarse mediante la LC/MS y ^1H RMN. A la mezcla de reacción se le agregaron dicloro-metano y agua, y la capa orgánica separada se secó (Na_2SO_4), y se

concentró, para dar el 5-bromo-4-metoxi-2-nitro-benzaldehído. ES/MS *m/z* 229/231(MH^+).

C. Preparación de la 2-cloro-6-bromo-7-metoxi-quinazolina

El 5-bromo-4-metoxi-2-amino-benzaldehído (1.0 equivalentes), y urea (8.0 equivalentes) se agitaron a 170°C durante 1 hora. El sólido resultante se regresó hasta la temperatura ambiente, se agitó en agua durante 20 minutos, y se filtró. Esto se repitió por un total de tres lavados. El sólido se secó en un desecador, para dar el 6-bromo-7-metoxi-quinazolin-2-ol como el producto deseado. Una solución 0.50 M del 6-bromo-7-metoxi-quinazolin-2-ol en oxicloruro de fósforo se agitó a 110°C durante 1.5 horas. Los volátiles se removieron bajo presión reducida. Se agregó agua helada, y el precipitado se filtró, se enjuagó con agua, y se secó bajo un alto vacío, para proporcionar la 2-cloro-6-bromo-7-metoxi-quinazolina como un sólido amarillo. ES/MS *m/z* 272/274(MH^+).

D. Preparación del 6-bromo-2-(3-fluoro-fenil-amino)-quinazolin-7-ol

A una solución de la 2-cloro-6-bromo-7-metoxi-quinazolina en isopropanol se le agregó 3-fluoro-anilina (1.0 equivalentes). La reacción se agitó a 90°C durante 18 horas. El clorhidrato se recolectó mediante filtración al vacío, y se secó al aire, para dar un material crudo, el cual se puede utilizar para otras modificaciones químicas. El material puro se obtuvo mediante purificación con HPLC. Al producto crudo se le agregaron NMP y NaSMe (4 equivalentes), y la mezcla se calentó a 80°C durante 2 horas. La

conversión hasta el fenol se observó mediante LC/MS. La mezcla de reacción se enfrió, y se le agregaron acetato de etilo y HCl 1N para llevarla hasta un pH neutro. El 6-bromo-2-(3-fluoro-fenil-amino)-quinazolin-7-ol se exprimió como un sólido, el cual se filtró y se secó sobre un alto vacío, para dar el producto en un rendimiento cuantitativo. ES/MS *m/z* 333/335 (MH^+).

E. Preparación del 4-(6-bromo-2-(3-fluoro-fenil-amino)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo

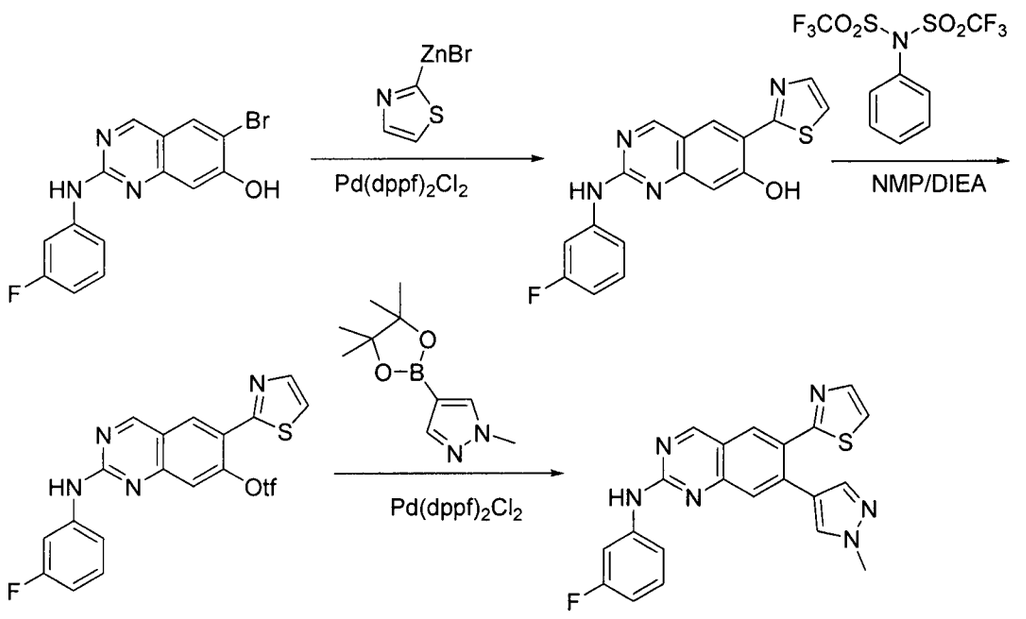
A una mezcla de DEAD (2 equivalentes), y trifenil-fosfina (2 equivalentes), se le agregó el 4-hidroxi-piperidin-1-carboxilato de terbutilo (4 equivalentes), y a la mezcla resultante se le agregó 6-bromo-2-(3-fluoro-fenil-amino)-quinazolin-7-ol, y se agitó durante 16 horas a temperatura ambiente. La formación del producto se observó en la LC/MS. La mezcla se concentró entonces y se purificó sobre gel de sílice para obtener el 4-(6-bromo-2-(3-fluoro-fenil-amino)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo como el producto. ES/MS *m/z* 517/519(MH^+).

F. Preparación de la N-(3-fluoro-fenil)-7-(piperidin-4-iloxi)-6-(tiazol-2-il)-quinazolin-2-amina

Al 4-(6-bromo-2-(3-fluoro-fenil-amino)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo (50 miligramos), se le agregó bromuro de 2-tiazolil-zinc 0.5M, y la mezcla se pasó por microondas a 120°C durante 10 minutos. La conversión completa hasta el producto se vio mediante LC/MS. La mezcla se concentró y se dividió entre acetato de etilo y agua. La capa orgánica se secó (Na_2SO_4), y

el producto se aisló. Al producto crudo se le agregó el 30 por ciento de ácido trifluoro-acético / dicloro-metano, y se agitó durante 2 horas para la desprotección del grupo terbutilo. La formación de la N-(3-fluoro-fenil)-7-(piperidin-4-iloxi)-6-(tiazol-2-il)-quinazolin-2-amina se observó mediante LC/MS. Entonces se purificó mediante cromatografía de preparación para dar el producto. ES/MS *m/z* 421(MH^+).

Ejemplo 889: Preparación de la N-(3-fluoro-fenil)-7-(1-metil-1H-pirazol-4-il)-6-(tiazol-2-il)-quinazolin-2-amina



A. Preparación del 2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-ol

Al 6-bromo-2-(3-fluoro-fenil-amino)-quinazolin-7-ol se le agregó bromuro de 2-tiazolil-zinc 0.5M, y la mezcla se pasó por microondas

a 120°C durante 10 minutos. La conversión completa hasta el producto se vio mediante LC/MS. La mezcla se concentró y se dividió entre acetato de etilo y agua. La capa orgánica se secó (Na_2SO_4), y el producto se aisló. ES/MS *m/z* 330(MH^+).

B. Preparación del trifluoro-metan-sulfonato de 2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-ilo

A una solución del 2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-ol (1 equivalente) en NMP sé le agregaron trifluoro-metan-sulfonato de fenilo (1.2 equivalentes), y DIEA (2.5 equivalentes), y la mezcla de reacción se agitó durante la noche a temperatura ambiente. La mezcla de reacción se dividió entonces entre acetato de etilo y agua. Las capas orgánicas se lavaron con cloruro de sodio saturado, y se secaron y se concentraron. Al producto crudo se le agregó cloruro de metileno y unas cuantas gotas de metanol. El sólido blanco así formado se filtró, para dar el trifluoro-metan-sulfonato de 2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-ilo en un 80 por ciento de rendimiento. ES/MS *m/z* 471(MH^+).

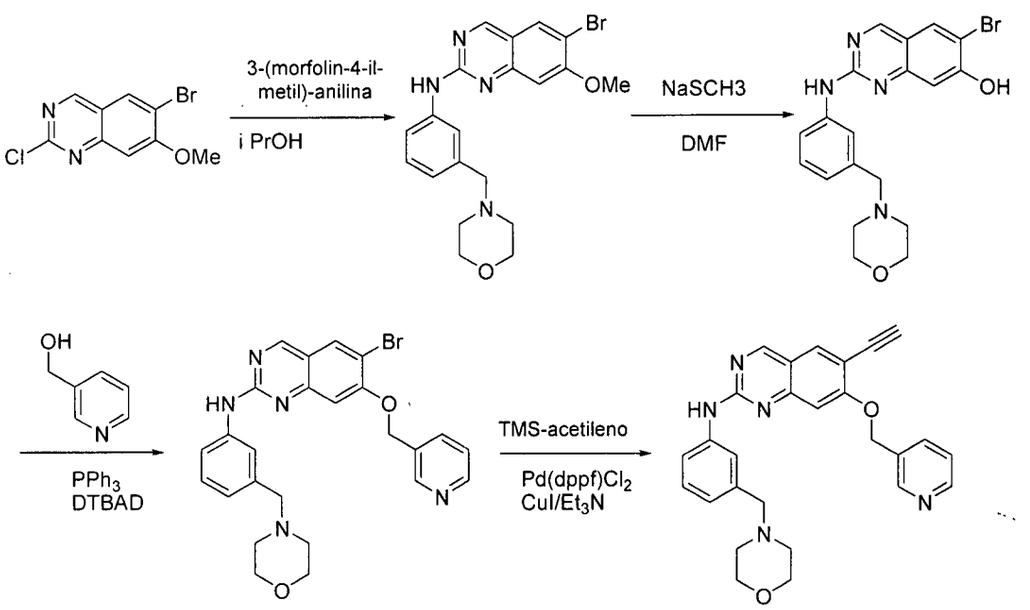
C. Preparación de la N-(3-fluoro-fenil)-7-(1-metil-1H-pirazol-4-il)-6-(tiazol-2-il)-quinazolin-2-amina

A una solución del trifluoro-metan-sulfonato de 2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-ilo (1 equivalente) en DME, se le agregó una solución de carbonato de sodio 2 M y 4-(4,4,5,5,-tetrametil-1,3,2-dioxa-borolan-2-il)-1metil-pirazol (3 equivalentes), y Pd $(dppf)_2Cl_2.CH_2Cl_2$ (0.05 equivalentes), y la mezcla se pasó por

microondas durante 10 minutos a 120°C. La mezcla de reacción se dividió entonces entre acetato de etilo y agua. La capa orgánica se lavó con salmuera, se secó, se concentró, y se purificó mediante HPLC de semi-preparación, para proporcionar la N-(3-fluoro-fenil)-7-(1-metil-1H-pirazol-4-il)-6-(tiazol-2-il)-quinazolin-2-amina ES/MS *m/z* 402 (MH^+).

Ejemplo 804: Preparación de la 6-etinil-N-(3-(morfolino-metil)-fenil)-7-(piridin-3-il-metoxi)-quinazolin-2-amina

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



A. Preparación de la 6-bromo-7-metoxi-N-(3-(morfolino-metil)-fenil)-quinazolin-2-amina

A una suspensión 0.25 M de 6-bromo-2-cloro-7-metoxi-

quinazolina en isopropanol, se le agregó 3-(morfolin-4-il-metil)-anilina (1.1 equivalentes), y cloruro de hidrógeno 4.0M en 1,4-dioxano (0.5 equivalentes). La mezcla de reacción se calentó a 95°C en un baño de aceite durante 15 horas. La mezcla de reacción se diluyó con acetato de etilo, y se filtró para recolectar el producto deseado. ES/MS *m/z* 429/431 (MH^+).

B. Preparación del 6-bromo-2-(3-(morfolino-metil)-fenil-amino)-quinazolin-7-ol

Una suspensión 0.2M de 6-bromo-7-metoxi-N-(3-(morfolino-metil)-fenil)-quinazolin-2-amina (1.0 equivalentes), y tiometóxido de sodio (4.0 equivalentes) en N,N-dimetil-formamida, se calentó a 90°C en un baño de aceite durante 10 horas. La mezcla se dividió entre acetato de etilo y agua. El pH de la fase acuosa se ajustó a 4 mediante la adición de clorhidrato de amonio saturado. La fase acuosa se extrajo con acetato de etilo, y la fase orgánica combinada se lavó con salmuera, se secó sobre sulfato de sodio, y se concentró para dar el producto deseado. ES/MS *m/z* 415/417 (MH^+).

C. Preparación de la 6-bromo-N-(3-(morfolino-metil)-fenil)-7-(piridin-3-il-metoxi)-quinazolin-2-amina

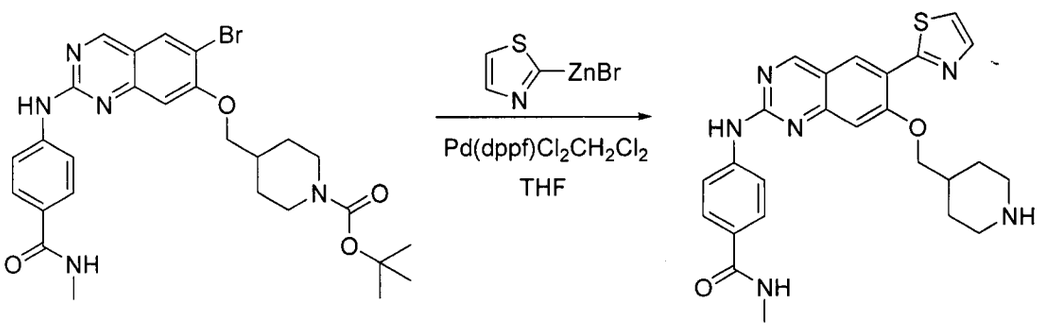
A una solución 0.55M de trifenil-fosfina (3.0 equivalentes) en tetrahidrofurano, se le agregó azodicarboxilato de diterbutilo (3.0 equivalentes). La mezcla se agitó durante 20 minutos a temperatura ambiente. Se agregó 3-piridil-carbinol (3.0 equivalentes), y la mezcla de reacción se agitó a temperatura ambiente durante otros 30 minutos. Entonces, se agregó 6-bromo-2-(3-(morfolino-metil)-fenil-

amino)-quinazolin-7-ol (1.0 equivalentes) al matraz de la reacción. La mezcla se agitó a temperatura ambiente durante 14 horas adicionales. El solvente se removió bajo presión reducida, y el residuo se trituró con acetato de etilo y se filtró. La torta del filtro se enjuagó con acetato de etilo frío y se secó al aire para dar la 6-bromo-N-(3-(morfolino-metil)-fenil)-7-(piridin-3-il-metoxi)-quinazolin-2-amina. ES/MS *m/z* 506/508 (MH^+).

D. Preparación de la 6-etinil-N-(3-(morfolino-metil)-fenil)-7-(piridin-3-il-metoxi)-quinazolin-2-amina

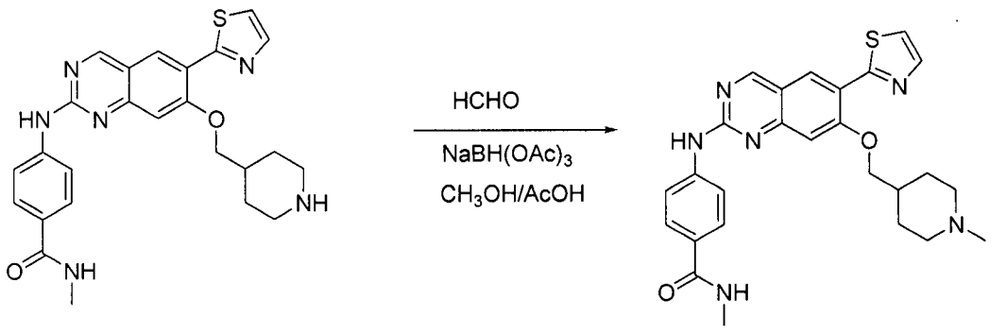
A una mezcla 0.05M de la 6-bromo-N-(3-(morfolino-metil)-fenil)-7-(piridin-3-il-metoxi)-quinazolin-2-amina (0.1 milimoles), trietil-amina (0.4 mililitros), $Pd(dppf)Cl_2CH_2Cl_2$ (0.1 equivalentes), y yoduro de cobre(I) (0.1 equivalentes) en N,N-dimetil-formamida, se le agregó trimetil-silil-acetileno (10 equivalentes). La mezcla se pasó por microondas a 120°C durante 15 minutos. La mezcla de reacción se diluyó con acetato de etilo y se lavó con agua, salmuera, se secó y se concentró. Sin mayor purificación, el compuesto crudo se trató con fluoruro de tetrametil-amonio (2.0 equivalentes) en tetrahidrofurano / isopropanol (10:1, 0.02M) a temperatura ambiente durante 15 minutos. El solvente se removió bajo presión reducida. El residuo se absorbió en acetato de etilo y se lavó con agua, salmuera, se secó y se concentró. El producto crudo se purificó mediante HPLC en fase inversa. La liofilización dio el producto deseado de la 6-etinil-N-(3-(morfolino-metil)-fenil)-7-(piridin-3-il-metoxi)-quinazolin-2-amina. ES/MS *m/z* 452 (MH^+).

Ejemplo 724: Preparación de la N-metil-4-(7-(piperidin-4-il-metoxi)-6-(tiazol-2-il)-quinazolin-2-il-amino)-benzamida



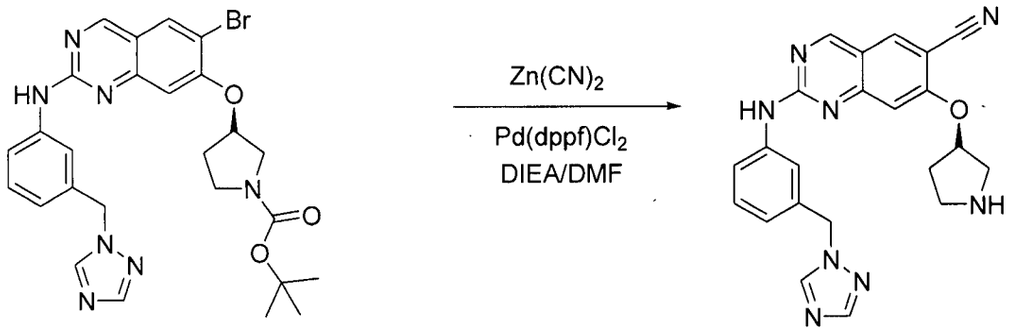
A una solución 0.05M del 4-((6-bromo-2-(4-(metil-carbamoil)-fenil-amino)-quinazolin-7-iloxi)-metil)-piperidin-1-carboxilato de terbutilo (0.12 milimoles) en tetrahidrofurano se le agregaron bromuro de 2-tiazolil-zinc 0.5M (3.0 equivalentes), y $Pd(dppf)Cl_2CH_2Cl_2$ (0.2 equivalentes). La mezcla se pasó por microondas a 120°C durante 15 minutos. La conversión completa hasta el producto se vio mediante LC/MS. La mezcla se concentró y se dividió entre acetato de etilo y agua. La capa orgánica se secó (Na_2SO_4), y se concentró. El residuo se trató con el 50 por ciento de ácido trifluoro-acético / dicloro-metano, y se agitó durante 10 minutos para remover el grupo carboxilato de terbutilo. El compuesto crudo entonces se purificó mediante HPLC en fase inversa, para dar el producto deseado de la N-metil-4-(7-(piperidin-4-il-metoxi)-6-(tiazol-2-il)-quinazolin-2-il-amino)-benzamida. ES/MS *m/z* 475 (MH^+).

Ejemplo 729: Preparación de la N-metil-4-(7-(piperidin-4-il-metoxi)-6-(tiazol-2-il)-quinazolin-2-il-amino)-benzamida



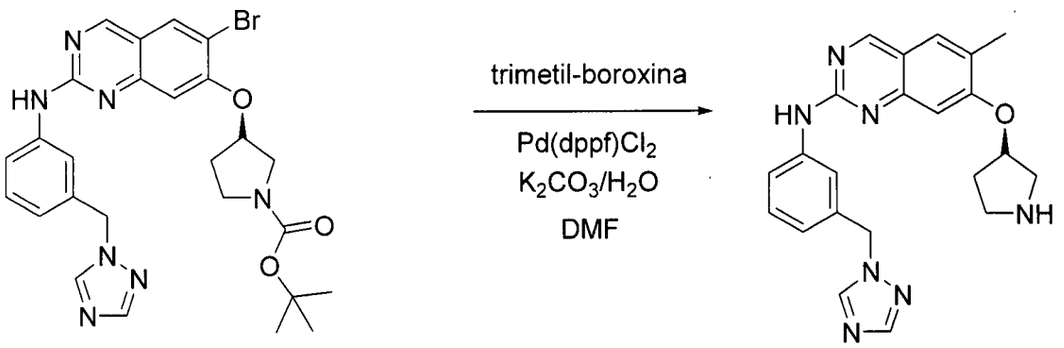
Una solución de la N-metil-4-(7-(piperidin-4-il-metoxi)-6-(tiazol-2-il)-quinazolin-2-il-amino)-benzamida (0.05 milimoles), formaldehído (10 equivalentes), y una cantidad catalítica de ácido acético en metanol (2.0 mililitros) se agitó a temperatura ambiente durante 1 hora. Entonces se agregó triacetoxi-borohidruro de sodio (2.0 equivalentes), y la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. Los datos de LCMS mostraron que la reacción estaba completa. El solvente se removió bajo presión reducida. El residuo se absorbió en acetato de etilo y se lavó con agua, salmuera, se secó y se concentró. La purificación mediante HPLC en fase inversa dio el producto deseado de la N-metil-4-(7-(piperidin-4-il-metoxi)-6-(tiazol-2-il)-quinazolin-2-il-amino)-benzamida. ES/MS *m/z* 489 (MH^+).

Ejemplo 767: Preparación del (S)-2-(3-((1H-1,2,4-triazol-1-il)-metil)-fenil-amino)-7-(pirrolidin-3-iloxi)-quinazolin-6-carbonitrilo



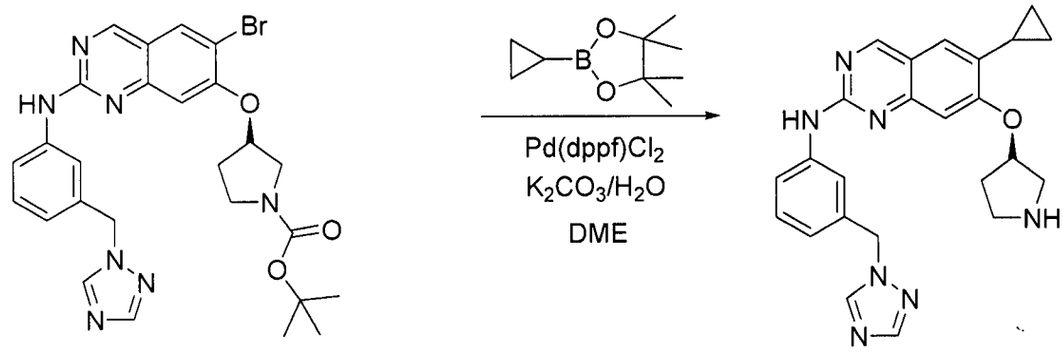
A una solución 0.1M de (S)-3-(2-(3-((1H-1,2,4-triazol-1-il)-metil)-fenil-amino)-6-bromo-quinazolin-7-iloxi)-pirrolidin-1-carboxilato de terbutilo (0.18 milimoles) en N,N-dimetil-formamida, se le agregaron cianuro de zinc (5.0 equivalentes), $Pd(dppf)Cl_2CH_2Cl_2$ (0.2 equivalentes), y di-isopropil-etil-amina (1.5 equivalentes). La mezcla se pasó por microondas a 150°C durante 20 minutos. La conversión completa hasta el producto se vio mediante LC/MS. La mezcla se dividió entre acetato de etilo y agua. La capa orgánica se secó (Na_2SO_4), y se concentró. El residuo se trató con el 50 por ciento de ácido trifluoro-acético / dicloro-metano, y se agitó durante 10 minutos para remover el grupo carboxilato de terbutilo. El compuesto crudo entonces se purificó mediante HPLC en fase inversa, para dar el producto deseado del (S)-2-(3-((1H-1,2,4-triazol-1-il)-metil)-fenil-amino)-7-(pirrolidin-3-iloxi)-quinazolin-6-carbonitrilo. ES/MS *m/z* 413 (MH^+).

Ejemplo 765: Preparación de la (S)-N-(3-((1H-1,2,4-triazol-1-il)-metil)-fenil)-6-metil-7-(pirrolidin-3-iloxi)-quinazolin-2-amina



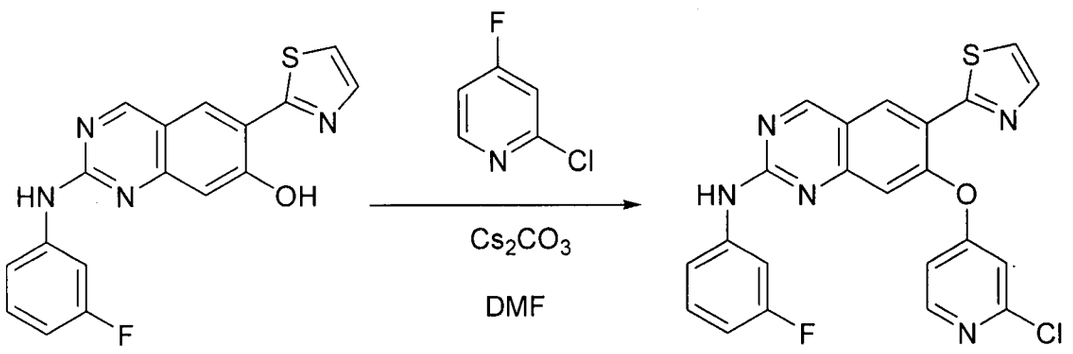
A una solución 0.06 M del (S)-3-(2-(3-((1H-1,2,4-triazol-1-il)-metil)-fenil-amino)-6-bromo-quinazolin-7-iloxi)-pirrolidin-1-carboxilato de terbutilo (0.11 milimoles) en N,N-dimetil-formamida, se le agregaron trimetil-boroxina (4.0 equivalentes), $Pd(dppf)Cl_2CH_2Cl_2$ (0.1 equivalentes), y una solución acuosa de carbonato de potasio 2.0 M (4.0 equivalentes). La mezcla se pasó por microondas a 120°C durante 20 minutos. La conversión completa hasta el producto se vio mediante LC/MS. La mezcla se dividió entre acetato de etilo y agua. La capa orgánica se secó (Na_2SO_4), y se concentró. El residuo se trató con el 50 por ciento de ácido trifluoro-acético / dicloro-metano, y se agitó durante 10 minutos para remover el grupo carboxilato de terbutilo. El compuesto crudo entonces se purificó mediante HPLC en fase inversa, para dar el producto deseado de la (S)-N-(3-((1H-1,2,4-triazol-1-il)-metil)-fenil)-6-metil-7-(pirrolidin-3-iloxi)-quinazolin-2-amina. ES/MS *m/z* 402 (MH^+).

Ejemplo 764: Preparación de la (S)-N-(3-((1H-1,2,4-triazol-1-il)-metil)-fenil)-6-ciclopropil-7-(pirrolidin-3-iloxi)-quinazolin-2-amina



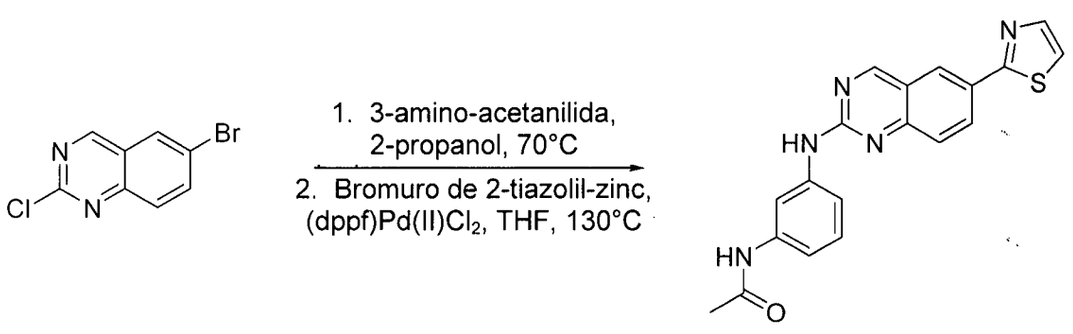
A una solución 0.06 M del (S)-3-(2-(3-((1H-1,2,4-triazol-1-il)-metil)-fenil-amino)-6-bromo-quinazolin-7-iloxi)-pirrolidin-1-carboxilato de terbutilo (0.13 milimoles) en DME, se le agregó 2-ciclopropil-4,4,5,5-tetrametil-1,3,2-dioxa-borolano (10 equivalentes), Pd(dppf) $Cl_2CH_2Cl_2$ (0.2 equivalentes), y una solución acuosa de carbonato de potasio 2.0 M (4.0 equivalentes). La mezcla se pasó por microondas a 120°C durante 20 minutos. La conversión completa hasta el producto se confirmó mediante LC/MS. La mezcla se dividió entre acetato de etilo y agua. La capa orgánica se secó (Na_2SO_4), y se concentró. El residuo se trató con el 50 por ciento de ácido trifluoro-acético / dicloro-metano, y se agitó durante 10 minutos para remover el grupo carboxilato de terbutilo. El compuesto crudo entonces se purificó mediante HPLC en fase inversa, para dar el producto deseado de la (S)-N-(3-((1H-1,2,4-triazol-1-il)-metil)-fenil)-6-ciclopropil-7-(pirrolidin-3-iloxi)-quinazolin-2-amina. ES/MS *m/z* 428 (MH^+).

Ejemplo 797: Preparación de la 7-(2-cloro-piridin-4-iloxi)-N-(3-fluoro-fenil)-6-(tiazol-2-il)-quinazolin-2-amina



Una suspensión 0.1 M del 2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-ol (0.15 milimoles), 2-cloro-4-fluoro-piridina (1.5 equivalentes), y carbonato de cesio (3.0 equivalentes) en N,N-dimetil-formamida, se calentó a 95°C en un baño de aceite durante 18 horas. Los datos de la LCMS indicaron la formación del producto deseado. La mezcla se dividió entre acetato de etilo y agua. La capa orgánica se secó (Na_2SO_4), y se concentró. El compuesto crudo entonces se purificó mediante HPLC en fase inversa, para dar el producto deseado de la 7-(2-cloro-piridin-4-iloxi)-N-(3-fluoro-fenil)-6-(tiazol-2-il)-quinazolin-2-amina. ES/MS *m/z* 450 (MH^+).

Ejemplo 902: N-(3-(6-(tiazol-2-il)-quinazolin-2-il-amino)-fenil)-acetamida



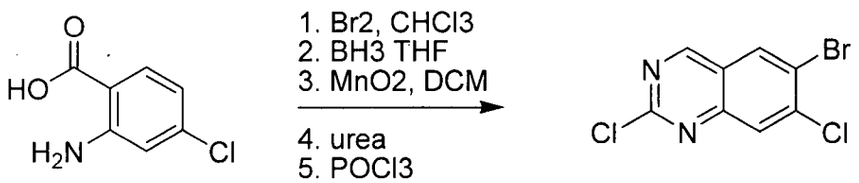
Paso 1. Desplazamiento

Una mezcla de la 6-bromo-2-cloro-quinazolina (1 equivalente), y 3-amino-acetanilida (0.9 equivalentes) en 2-propanol, se calentó a 70°C durante 16 horas, y se concentró para dar el producto crudo, el cual se utilizó sin mayor purificación.

Paso 2. Negishi

Al producto del Paso 1 se le agregó una solución en tetrahidrofurano 0.5 M de bromuro de 2-tiazolil-zinc (4.0 equivalentes), y complejo de [1,1'-bis-(difenil-fosfino)-ferroceno]-dicloro-paladio(II) con dicloro-metano (0.10 equivalentes). La reacción se pasó por microondas a 130°C durante 10 minutos. La mezcla se diluyó con acetato de etilo, y se lavó con regulador de EDTA acuoso a un pH de aproximadamente 9. La fase orgánica se secó sobre sulfato de sodio, y se concentró. La purificación mediante HPLC de fase inversa y la liofilización dio el producto deseado como su sal de ácido trifluoro-acético. ES/MS *m/z* 392 (MH^+).

6-bromo-2,7-dicloro-quinazolina



Paso 1: Bromación

A una suspensión del ácido 2-amino-4-cloro-benzoico (2 gramos, 11.6 milimoles) en cloroformo (120 mililitros), se le agregó por goteo una solución de bromo (1.1 equivalentes) en cloroformo

(12 mililitros). La mezcla se agitó a temperatura ambiente durante 16 horas. El sólido blanco resultante se recolectó mediante filtración, y se lavó completamente con dicloro-metano hasta que el filtrado fue incoloro. El sólido se secó al aire, para dar 3.35 gramos de un polvo blanco como la sal de HBr del ácido 2-amino-5-bromo-4-cloro-benzoico (87 por ciento de rendimiento). ES/MS *m/z* 250/252 (MH^+).

Paso 2: Reducción

Al intermediario anterior (3.35 gramos, 10.1 milimoles) en tetrahidrofurano (40 mililitros) a 0°C, se le agregó una solución de complejo de borano-tetrahidrofurano (1 M en tetrahidrofurano, 40 mililitros, 4 equivalentes). La mezcla se agitó a temperatura ambiente durante 18 horas. El exceso de reactivo se apagó mediante la adición de etanol (20 mililitros) lentamente. Se agregó agua y el pH (de aproximadamente 3) se ajustó mediante la adición de bicarbonato de sodio (acuoso saturado) a un pH de 7. Los volátiles se removieron bajo presión reducida. La mezcla resultante se extrajo con dicloro-metano. Los extractos orgánicos se combinaron, se lavaron con salmuera, se secaron con sulfato de sodio, y se concentraron, para dar el producto crudo como un sólido blanco. ES/MS *m/z* 236/238 (MH^+)

Paso 3: Oxidación

Al intermediario anterior (10.1 milimoles) en dicloro-metano (80 mililitros), se le agregó óxido de manganeso (IV) (MnO_2, 6 gramos, 70 milimoles). La mezcla se agitó a temperatura ambiente bajo argón durante 40 horas. La mezcla se filtró a través de tierra diatomácea y

se lavó completamente con dicloro-metano. El filtrado se concentró al vacío, para dar el alcohol 2-amino-5-bromo-4-cloro-bencílico crudo (3.3 gramos, sólido color naranja), el cual se utilizó para el siguiente paso sin mayor purificación. ES/MS *m/z* 234/236 (MH^+).

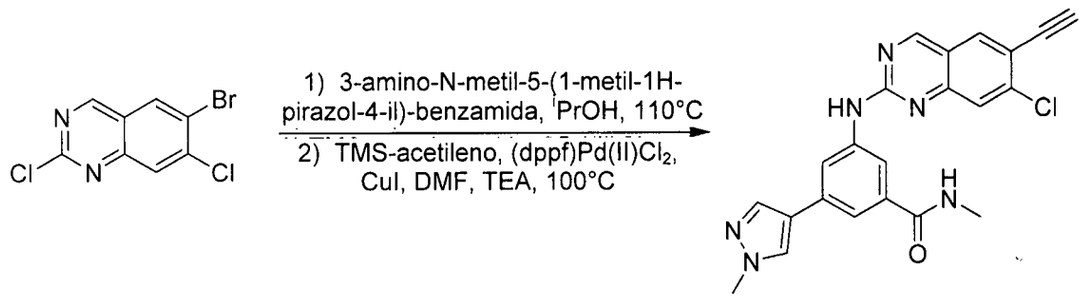
Paso 4: Ciclación

Una mezcla del alcohol 2-amino-5-bromo-4-cloro-bencílico crudo (3.3 gramos, obtenido a partir del Paso 3), y urea (10.5 gramos, 15 equivalentes), se calentó a 170°C con agitación vigorosa durante 1 hora. La reacción se enfrió a temperatura ambiente, y se agregó agua. El sólido se recolectó mediante filtración. El sólido filtrado se secó al aire, para dar el producto crudo como un polvo amarillo (2.18 gramos, crudo). ES/MS *m/z* 259/261 (MH^+).

Paso 5: Cloración

Al material crudo anterior se le agregó oxicloruro de fósforo ($POCl_3$, 25 mililitros), y se calentó a 110°C durante 30 minutos. La mezcla resultante se enfrió a temperatura ambiente, y se concentró al vacío hasta casi la sequedad. Se agregó agua helada, y el pH se ajustó a aproximadamente 8, utilizando bicarbonato de sodio. La mezcla se extrajo con dicloro-metano, y el extracto se secó con sulfato de sodio, y se concentró al vacío. La 6-bromo-2,7-dicloro-quinazolina cruda se purificó mediante cromatografía por evaporación instantánea sobre gel de sílice eluyendo con 2:1 de hexanos:acetato de etilo. ES/MS *m/z* 279 (MH^+).

Ejemplo 904: 3-(7-cloro-6-etinil-quinazolin-2-il-amino)-N-metil-5-(1-metil-1H-pirazol-4-il)-benzamida



Paso 1. Desplazamiento

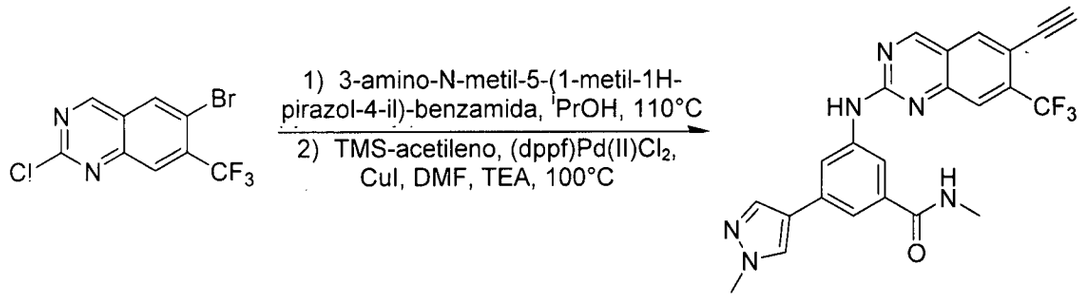
Una mezcla de la 6-bromo-2,7-dicloro-quinazolina (1 equivalente), y 3-amino-N-metil-5-(1-metil-1H-pirazol-4-il)-benzamida (1 equivalente) en 2-propanol, se calentó a 110°C durante 16 horas, y se concentró, para dar el producto crudo, el cual se utilizó sin mayor purificación.

Paso 2. Sonogashira y destilación

A una solución 0.15 M del producto del Paso 1 en 1:1 de N,N-dimetil-formamida : trietil-amina desgasificadas, se le agregaron TMS-acetileno (4.0 equivalentes), yoduro de cobre(I) (0.10 equivalentes), y complejo de [1,1'-bis-(difenil-fosfino)-ferroceno]-dicloro-paladio(II) con dicloro-metano (0.050 equivalentes). La reacción se agitó a 100°C durante 40 minutos. La mezcla se concentró y se volvió a disolver en 3:2 de tetrahidrofurano : metanol, para hacer una solución 0.15 M. Se agregó una solución acuosa 6M de hidróxido de sodio (2.5 equivalentes), y la mezcla se agitó durante 20 minutos. Los volátiles se removieron bajo presión reducida. El residuo se purificó mediante HPLC de fase inversa y se liofilizó, para dar el producto deseado como su sal de ácido trifluoro-

acético. ES/MS m/z 417.1 (MH^+).

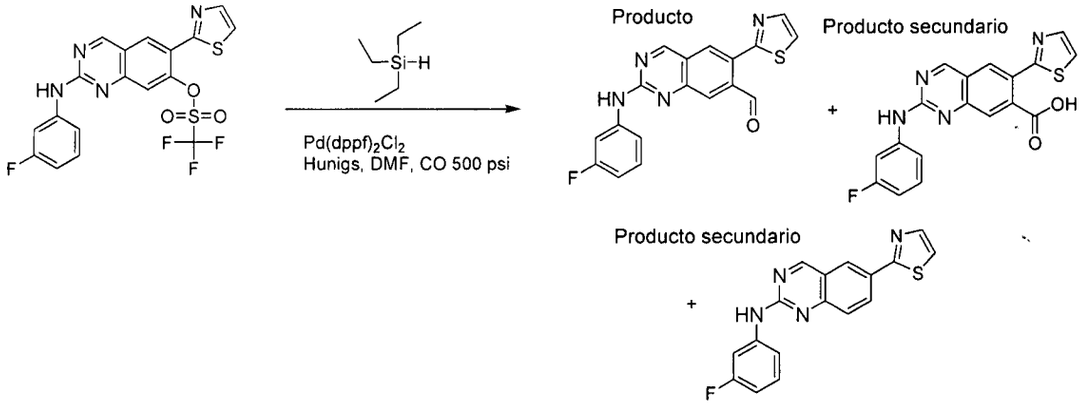
Ejemplo 905: 3-(6-etinil-7-(trifluoro-metil)-quinazolin-2-il-amino)-N-metil-5-(1-metil-1H-pirazol-4-il)-benzamida



La 3-(6-etinil-7-(trifluoro-metil)-quinazolin-2-il-amino)-N-metil-5-(1-metil-1H-pirazol-4-il)-benzamida se preparó siguiendo los Ejemplos 62 y 63. ES/MS *m/z* 451.0 (MH^+).

Ejemplo 907: 2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-carbaldehído

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-carbaldehído

A la mezcla de reacción del trifluoro-metan-sulfonato de 2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-ilo (50 miligramos, 0.106 milimoles) en 1.4 mililitros de dimetil-formamida en una bomba de acero, se le agregaron $Pd(dppf)_2Cl_2$ (8.7 miligramos, 0.0106 milimoles), trietil-silano (37 miligramos, 0.318 milimoles), y trietil-amina (0.037 mililitros, 0.265 milimoles). La bomba de acero se selló y se agregó cuidadosamente CO a 500 psi (35 kg/cm^2), y se liberó lentamente (3 veces en una campana), y entonces se volvió a cargar a 500 psi (35 kg/cm^2), y se agitó a 50-55°C durante 18 horas. Esta mezcla de reacción se enfrió y se ventiló en una campana. La mezcla de reacción cruda se filtró, se purificó en la HPLC de preparación, y se liofilizó, para dar el 2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-carbaldehído como la sal de ácido trifluoro-acético (6.0 miligramos) . ES/MS *m/z* 351(MH^+).

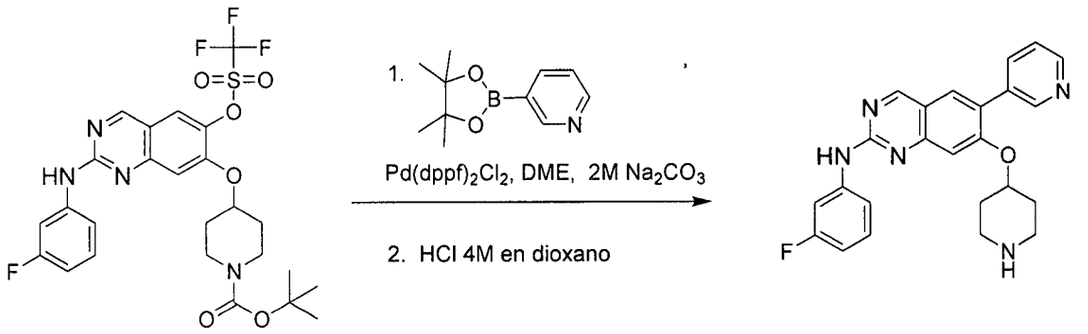
Productos Secundarios

En adición también se recolectaron dos productos secundarios en la HPLC de preparación, y se liofilizaron para dar el ácido 2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-carboxílico como la sal de ácido trifluoro-acético (8.0 miligramos) ES/MS *m/z* 367(MH^+), y la N-(3-fluoro-fenil)-6-(tiazol-2-il)-quinazolin-2-amina como la sal de ácido trifluoro-acético (3.3 miligramos) ES/MS *m/z* 323(MH^+).

Ejemplo 916: N-(3-fluoro-fenil)-7-(piperidin-4-iloxi)-6-(piridin-3-il)-quinazolin-2-amina

El compuesto objeto se preparó de acuerdo con el siguiente

Esquema General:



Paso 1: 4-(2-(3-fluoro-fenil-amino)-6-(piridin-3-il)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo

A la mezcla de reacción del 4-(2-(3-fluoro-fenil-amino)-6-(trifluoro-metil-sulfoniloxi)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo (30 miligramos, 0.058 milimoles) en 0.7 mililitros de DME, se le agregaron $Pd(dppf)_2Cl_2$ (9.5 miligramos, 0.0116 milimoles), 3-(4,4,5,5-tetrametil-1,3,2-dioxa-borolan-2-il)-piridina (36 miligramos, 0.174 milimoles), y finalmente se agregó Na_2CO_3 2M (0.2 mililitros, 0.4 milimoles). Esta mezcla de reacción se agitó a 100°C durante 3 horas o hasta que se consideró hecha mediante LCMS. A la mezcla de reacción cruda se le agregaron 1.5 mililitros de metanol, se transfirió la reacción y se concentró hasta obtener un sólido, para dar un producto crudo del 4-(2-(3-fluoro-fenil-amino)-6-(piridin-3-il)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo utilizado en el siguiente paso sin purificación. ES/MS *m/z* 516(MH^+).

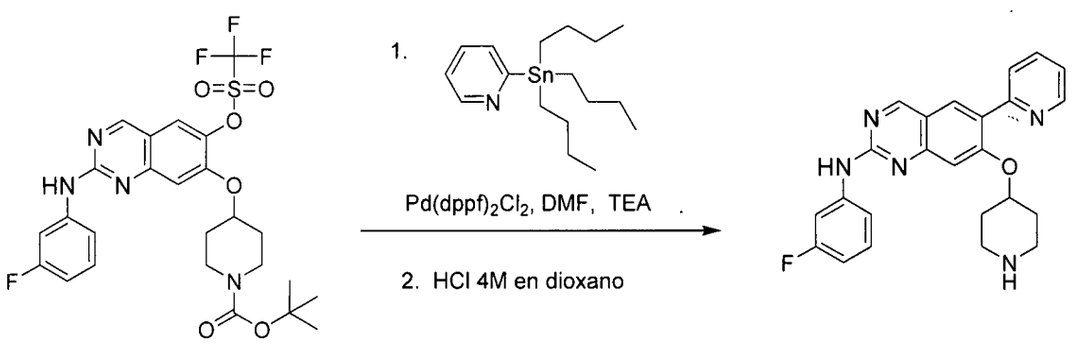
Paso 2: N-(3-fluoro-fenil)-7-(piperidin-4-iloxi)-6-(piridin-3-il)-quinazolin-2-amina

A la mezcla de reacción cruda del 4-(2-(3-fluoro-fenil-amino)-6-

(piridin-3-il)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo (0.058 milimoles), se le agregó HCl 4M en dioxano (4.0 mililitros, 16.0 milimoles). La mezcla de reacción se agitó a temperatura ambiente durante 1 hora o hasta que se consideró hecha mediante LCMS. La mezcla de reacción cruda se concentró, se agregó aproximadamente 1 mililitro de dimetil-formamida, se filtró, se purificó en la HPLC de preparación, y se liofilizó, para dar la N-(3-fluoro-fenil)-7-(piperidin-4-iloxi)-6-(piridin-3-il)-quinazolin-2-amina como la sal de ácido trifluoro-acético (8.3 miligramos). ES/MS *m/z* 416(MH^+).

Ejemplo 913: N-(3-fluoro-fenil)-7-(piperidin-4-iloxi)-6-(piridin-2-il)-quinazolin-2-amina

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1: 4-(2-(3-fluoro-fenil-amino)-6-(piridin-2-il)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo

A la mezcla de reacción del 4-(2-(3-fluoro-fenil-amino)-6-(trifluoro-metil-sulfoniloxi)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo (30 miligramos, 0.058 milimoles) en 0.5 mililitros de

dimetil-formamida, se le agregaron $Pd(dppf)_2Cl_2$ (9.5 miligramos, 0.0116 milimoles), 2-(tributil-estanil)-piridina (66 miligramos, 0.174 milimoles), y finalmente se agregó trietil-amina (0.021 mililitros, 0.145 milimoles). Esta mezcla de reacción se agitó a 105°C durante 1 hora o se pasó por microondas a 120°C durante 800 segundos hasta que se consideró hecha mediante LCMS. La mezcla de reacción cruda con el producto del 4-(2-(3-fluoro-fenil-amino)-6-(piridin-2-il)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo se utilizó en el siguiente paso sin purificación. ES/MS *m/z* 516(MH^+).

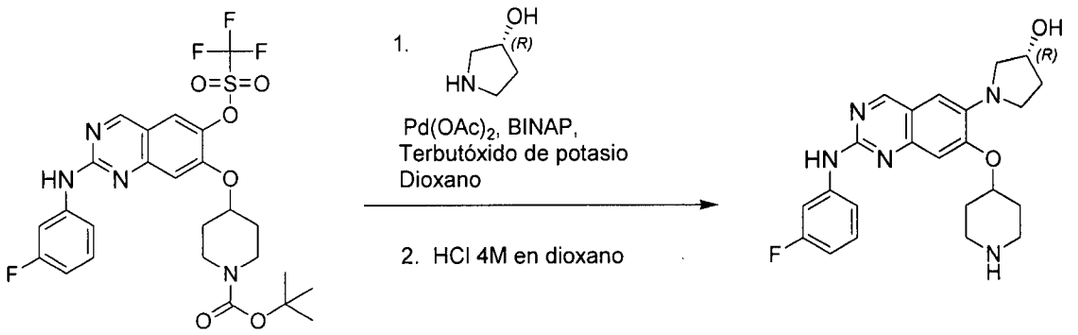
Paso 2: N-(3-fluoro-fenil)-7-(piperidin-4-iloxi)-6-(piridin-2-il)-quinazolin-2-amina

A la mezcla de reacción cruda del 4-(2-(3-fluoro-fenil-amino)-6-(piridin-3-il)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo (0.058 milimoles), se le agregó HCl 4M en dioxano (3.0 mililitros, 12.0 milimoles). La mezcla de reacción se agitó a temperatura ambiente durante 1 hora o hasta que se consideró hecha mediante LCMS. La mezcla de reacción cruda se concentró, se agregó aproximadamente 1 mililitro de dimetil-formamida, se filtró, se purificó en la HPLC de preparación, y se liofilizó para dar la N-(3-fluoro-fenil)-7-(piperidin-4-iloxi)-6-(piridin-2-il)-quinazolin-2-amina como la sal de ácido trifluoro-acético (4.6 miligramos). ES/MS *m/z* 416(MH^+).

Ejemplo 920: (R)-1-(2-(3-fluoro-fenil-amino)-7-(piperidin-4-iloxi)-quinazolin-6-il)-pirrolidin-3-ol

El compuesto objeto se preparó de acuerdo con el siguiente

Esquema General:



Paso 1: (R)-4-(2-(3-fluoro-fenil-amino)-6-(3-hidroxi-pirrolidin-1-il)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo

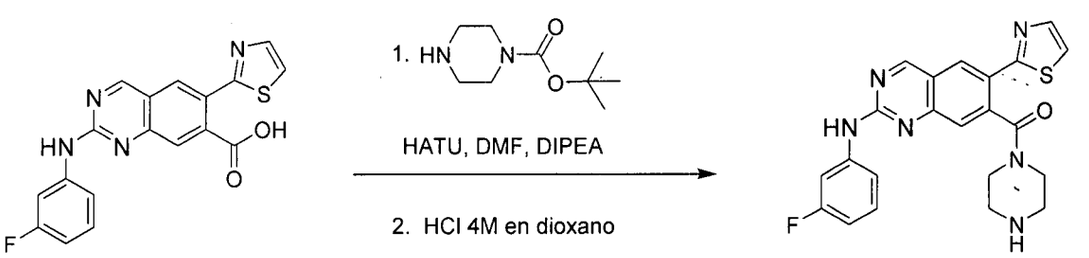
A la mezcla de reacción de $Pd(OAc)_2$ (9.5 miligramos, 0.0116 milimoles), y BINAP (10.8 miligramos, 0.0174 milimoles), se le agregaron 0.5 mililitros de dioxano, y se agitó durante 3 a 5 minutos a temperatura ambiente. A esta mezcla de reacción se le agregaron 4-(2-(3-fluoro-fenil-amino)-6-(trifluoro-metil-sulfoniloxi)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo (30 miligramos, 0.058 milimoles), (R)-pirrolidin-3-ol (20 miligramos, 0.232 milimoles), y entonces al final se agregó terbutóxido de potasio (19.5 miligramos, 0.174 milimoles). Esta mezcla de reacción se agitó a 90°C durante 5 horas o hasta que se consideró hecha mediante LCMS. La mezcla de reacción cruda con el producto de (R)-4-(2-(3-fluoro-fenil-amino)-6-(3-hidroxi-pirrolidin-1-il)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo se utilizó en el siguiente paso sin purificación. ES/MS *m/z* 524(MH^+).

Paso 2: (R)-1-(2-(3-fluoro-fenil-amino)-7-(piperidin-4-iloxi)-quinazolin-6-il)-pirrolidin-3-ol

A la mezcla de reacción cruda del (R)-4-(2-(3-fluoro-fenil-amino)-6-(3-hidroxi-pirrolidin-1-il)-quinazolin-7-iloxi)-piperidin-1-carboxilato de terbutilo (0.058 milimoles), se le agregó HCl 4M en dioxano (3.0 mililitros, 12.0 milimoles). La mezcla de reacción se agitó a temperatura ambiente durante 1 hora o hasta que se consideró hecha mediante LCMS. La mezcla de reacción cruda se concentró, se agregó aproximadamente 1 mililitro de dimetil-formamida (si fue necesario, se agregaron aproximadamente 0.2 mililitros de agua), se filtró, se purificó en la HPLC de preparación, y se liofilizó para dar el (R)-1-(2-(3-fluoro-fenil-amino)-7-(piperidin-4-iloxi)-quinazolin-6-il)-pirrolidin-3-ol como la sal de ácido trifluoro-acético (1.1 miligramos). ES/MS *m/z* 424(MH^+).

Ejemplo 909: (2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-il)-(piperazin-1-il)-metanona

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1: 4-(2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-carbonil)-piperazin-1-carboxilato de terbutilo

A la mezcla de reacción del ácido 2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-carboxílico (7 miligramos, 0.019 milimoles)

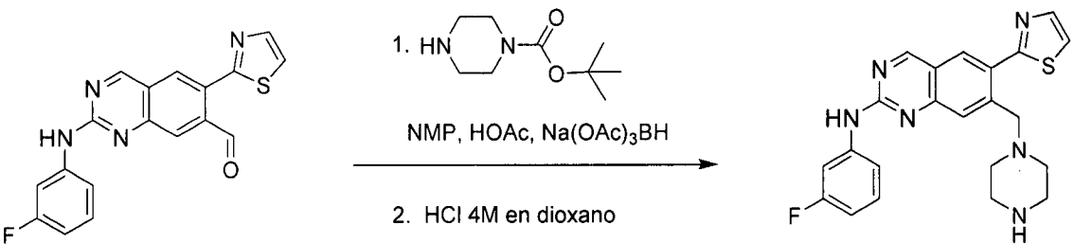
en 0.4 mililitros de dimetil-formamida, se le agregaron HATU (18.2 miligramos, 0.048 milimoles), y di-isopropil-etil-amina (0.014 mililitros, 0.076 milimoles), y se agitó a temperatura ambiente durante aproximadamente 3 a 5 minutos. A la mezcla de reacción anterior se le agregó piperazin-1-carboxilato de terbutilo (14 miligramos, 0.076 milimoles), y se agitó a temperatura ambiente durante 2 horas o hasta que se consideró hecha mediante LCMS. La mezcla de reacción cruda con el producto de 4-(2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-carbonil)-piperazin-1-carboxilato de terbutilo se utilizó en el siguiente paso sin purificación. ES/MS *m/z* 535(MH^+).

Paso 2: (2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-il)-(piperazin-1-il)-metanona

A la mezcla de reacción cruda del 4-(2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-carbonil)-piperazin-1-carboxilato de terbutilo (0.019 milimoles), se le agregó HCl 4M en dioxano (2.0 mililitros, 8.0 milimoles). La mezcla de reacción se agitó a temperatura ambiente durante 1 hora o hasta que se consideró hecha mediante LCMS. La mezcla de reacción cruda se concentró, se agregó aproximadamente 1 mililitro de dimetil-formamida, se filtró, se purificó en la HPLC de preparación, y se liofilizó para dar la (2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-il)-(piperazin-1-il)-metanona como la sal de ácido trifluoro-acético (2.1 miligramos). ES/MS *m/z* 435(MH^+).

Ejemplo 908: N-(3-fluoro-fenil)-7-(piperazin-1-il-metil)-6-(tiazol-2-il)-quinazolin-2-amina

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1: 4-((2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-il)-metil)-piperazin-1-carboxilato de terbutilo

A la mezcla de reacción del 2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-carbaldehído (12 miligramos, 0.034 milimoles) en 0.75 mililitros de NMP, se le agregó ácido acético (0.070 mililitros, 1.02 milimoles), y piperazin-1-carboxilato de terbutilo (65 miligramos, 0.35 milimoles). Esta mezcla de reacción se agitó a temperatura ambiente durante aproximadamente 16 horas. A esta solución de la reacción se le agregó triacetoxi-borohidruro de sodio (18 miligramos, 0.085 milimoles), y se agitó a temperatura ambiente durante 2 horas o hasta que se consideró hecha mediante LCMS. La mezcla de reacción cruda con el producto de 4-((2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-il)-metil)-piperazin-1-carboxilato de terbutilo se utilizó en el siguiente paso sin purificación. ES/MS *m/z* 521(MH^+).

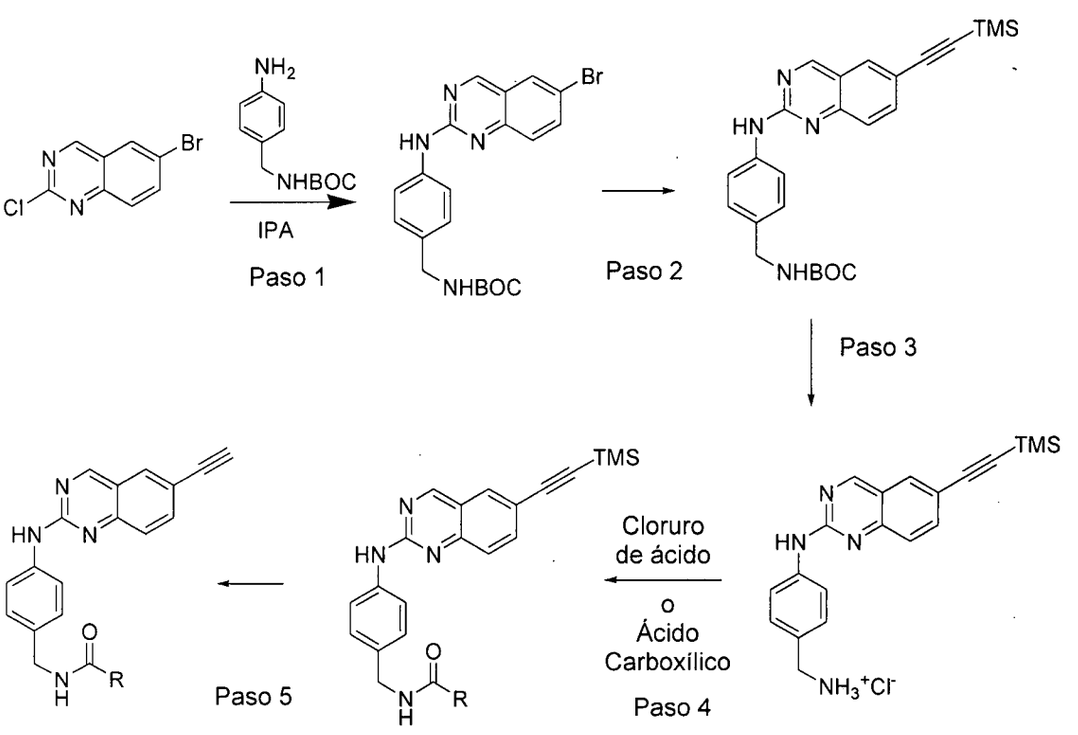
Paso 2: N-(3-fluoro-fenil)-7-(piperazin-1-il-metil)-6-(tiazol-2-il)-quinazolin-2-amina

A la mezcla de reacción cruda del 4-((2-(3-fluoro-fenil-amino)-6-(tiazol-2-il)-quinazolin-7-il)-metil)-piperazin-1-carboxilato de

terbutilo (0.034 milimoles), se le agregó HCl 4M en dioxano (4.0 mililitros, 16.0 milimoles). La mezcla de reacción se agitó a temperatura ambiente durante 1 hora o hasta que se consideró hecha mediante LCMS. La mezcla de reacción cruda se concentró, se agregó aproximadamente 1 mililitro de dimetil-formamida, se filtró, se purificó en la HPLC de preparación, y se liofilizó para dar la N-(3-fluoro-fenil)-7-(piperazin-1-il-metil)-6-(tiazol-2-il)-quinazolin-2-amina como la sal de ácido trifluoro-acético (1.7 miligramos). ES/MS *m/z* 421(MH^+).

Ejemplos 1161, 1165-1171, y 1174

Los compuestos objeto se prepararon de acuerdo con el siguiente Esquema General:



Paso 1:

Esta reacción se condujo de una manera similar a la descrita en el Ejemplo 9, Paso 5.

Paso 2:

Esta reacción se condujo de una manera similar a la descrita en el Ejemplo 10, Paso 1.

Paso 3:

La Boc-Amina se disolvió en dioxano, y se trató con HCl 4M / Dioxano (20 equivalentes). La reacción se agitó a temperatura ambiente durante 2 horas. La reacción se concentró hasta obtener un sólido blanco identificado como el producto deseado.

Paso 4:

Método A

La amina se disolvió en N,N-dimetil-formamida y Et_3N (3 equivalentes) a temperatura ambiente, y se trató con el cloruro de ácido apropiado (1.5 equivalentes). La reacción se agitó a temperatura ambiente durante 10 horas, y se purificó directamente mediante HPLC en fase inversa, para proporcionar los compuestos deseados.

Método B

La amina, HOAT (1.5 equivalentes), HATU (1.5 equivalentes), y Et_3N (3.0 equivalentes) se combinaron en N,N-dimetil-formamida. Se agregó el ácido carboxílico correspondiente (1.2 equivalentes), y las reacciones se agitaron a temperatura ambiente durante 10 horas, y

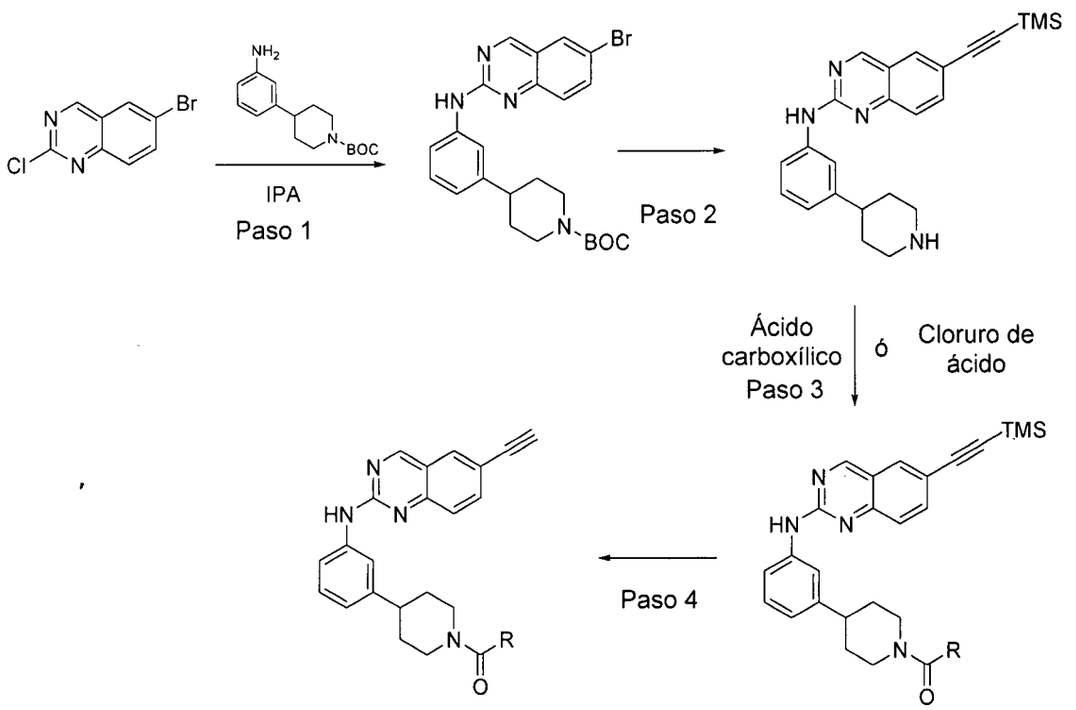
se purificaron directamente mediante HPLC en fase inversa, para proporcionar los compuestos deseados

Paso 5:

Esta reacción se condujo de una manera similar a la descrita en el Ejemplo 10, Paso 2.

Ejemplos 1153-1155, 1157, 1158, 1160, 1162-1164, 1172, y 1173

Los compuestos objeto se prepararon de acuerdo con el siguiente Esquema General:



Paso 1:

Esta reacción se condujo de una manera similar a la descrita en el Ejemplo 9, Paso 5.

Paso 2:

Esta reacción se condujo de una manera similar a la descrita en el Ejemplo 10, Paso 1.

Paso 3:

Método A

La amina se disolvió en N,N-dimetil-formamida y Et_3N (3 equivalentes) a temperatura ambiente, y se trató con el cloruro de ácido apropiado (1.5 equivalentes). Las reacciones se agitaron a temperatura ambiente durante 10 horas, y se purificaron directamente mediante HPLC en fase inversa, para proporcionar los compuestos deseados.

Método B

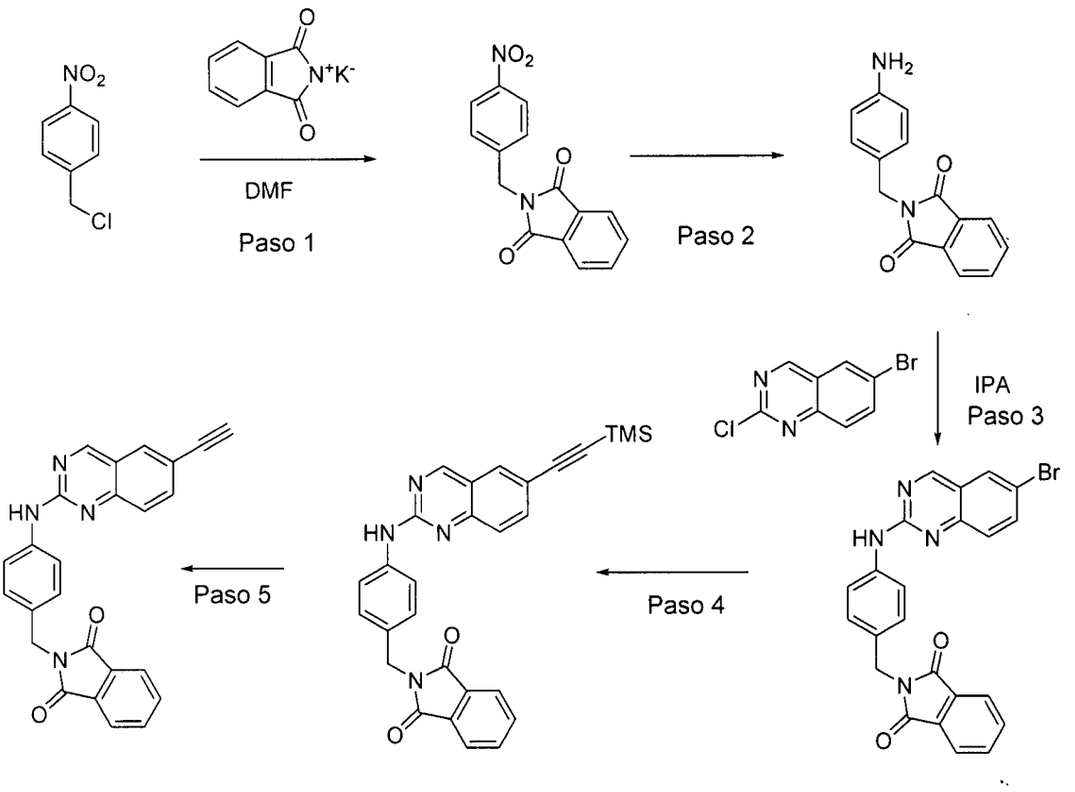
La amina, HOAT (1.5 equivalentes), HATU (1.5 equivalentes), y Et_3N (3.0 equivalentes) se combinaron en N,N-dimetil-formamida. Se agregó el ácido carboxílico correspondiente (1.2 equivalentes), y las reacciones se agitaron a temperatura ambiente durante 10 horas, y se purificaron directamente mediante HPLC en fase inversa, para proporcionar los compuestos deseados.

Paso 4:

Esta reacción se condujo de una manera similar a la descrita en el Ejemplo 10, Paso 2.

Ejemplos 1156 y 1159

Los compuestos objeto se prepararon de acuerdo con el siguiente Esquema General:



Paso 1:

El cloruro y la ftalamida de potasio (1.5 equivalentes) se combinaron en N,N-dimetil-formamida y se calentaron a 120°C durante 10 minutos en el reactor de microondas. La reacción se concentró y se purificó sobre sílice con un gradiente del 0 al 100 por ciento de EtOAc/Hexano, para proporcionar el compuesto deseado como un sólido blanco.

Paso 2:

Esta reacción se condujo de una manera similar a la descrita en el Ejemplo 459, Paso 1.

Paso 3:

Esta reacción se condujo de una manera similar a la descrita en el Ejemplo 9, Paso 5.

Paso 4:

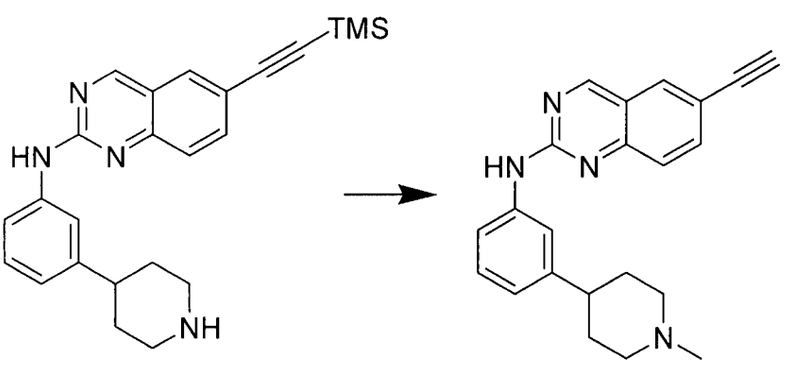
Esta reacción se condujo de una manera similar a la descrita en el Ejemplo 10, Paso 1.

Paso 5:

Esta reacción se condujo de una manera similar a la descrita en el Ejemplo 10, Paso 2.

Ejemplo 1175

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:

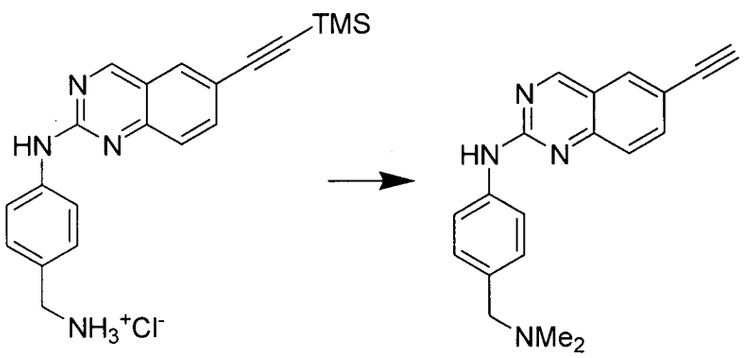


La amina (a partir del Ejemplo 1153 ó 1154), y formaldehído (5.0 equivalentes de una solución acuosa al 37 por ciento) se suspendieron en CH_2Cl_2 a temperatura ambiente. Se agregó triacetoxi-borohidruro de sodio a la vez, y la reacción se agitó durante 10 horas. Después de este tiempo, la reacción se apagó

mediante la adición de agua, seguida por concentración y purificación mediante HPLC en fase inversa. Las fracciones purificadas se combinaron y se trataron como en el Ejemplo 10, Paso 2, para proporcionar el compuesto deseado.

Ejemplo 1176

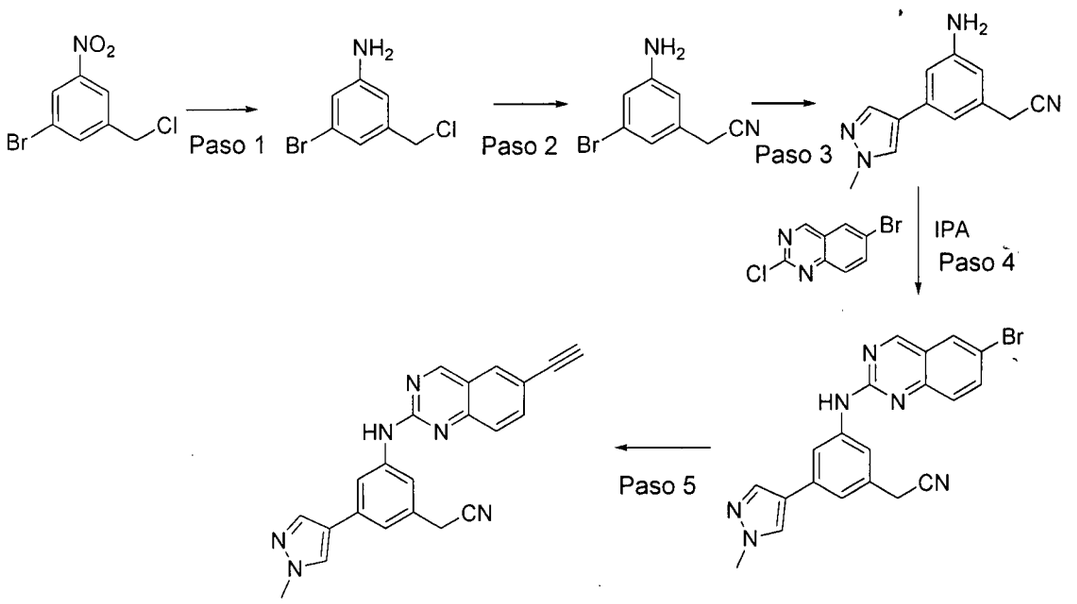
El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



La amina (a partir del Ejemplo 1161 ó 1165), y formaldehído (5.0 equivalentes de una solución acuosa al 37 por ciento) se suspendieron en CH_2Cl_2 a temperatura ambiente. Se agregó triacetoxi-borohidruro de sodio a la vez, y la reacción se agitó durante 10 horas. Después de este tiempo, la reacción se apagó mediante la adición de agua, seguida por concentración y purificación mediante HPLC en fase inversa. Las fracciones purificadas se combinaron y se trataron como en el Ejemplo 10, Paso 2, para proporcionar el compuesto deseado.

Ejemplo 1151

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1:

Se combinaron nitro y $SnCl_2$-$(H_2O)_2$ (10 equivalentes) en una solución de isopropanol y HCl 12 N. La reacción se calentó a 110°C durante 2 horas, y se concentró hasta el 25 por ciento del volumen original. La suspensión resultante se disolvió en una mezcla de 3:1 de EtOAc:CH_2Cl_2 y se neutralizó lentamente con $NaHCO_3$ (acuoso saturado) a un pH de 7. La mezcla resultante se filtró a través de un tapón de Celite, y las capas orgánicas se separaron. La capa acuosa se extrajo 3 veces con CH_2Cl_2 y los orgánicos combinados se secaron y se concentraron, para proporcionar 5.7 gramos de un sólido amarillo, el cual se utilizó sin mayor purificación.

Paso 2:

A una solución de amina en sulfóxido de dimetilo, se le agregó NaCN (2.0 equivalentes) a temperatura ambiente. La reacción se agitó durante 1 hora, se apagó con agua, y se extrajo 2 veces con EtOAc. Los orgánicos combinados se secaron sobre $MgSO_4$ y se concentraron hasta obtener un aceite amarillo. La purificación en gel de sílice con un gradiente del 0 a 80 por ciento proporcionó el producto deseado como un sólido blanco.

Paso 3:

Esta reacción se condujo de una manera similar a la descrita en el Ejemplo 469, Paso 2.

Paso 4:

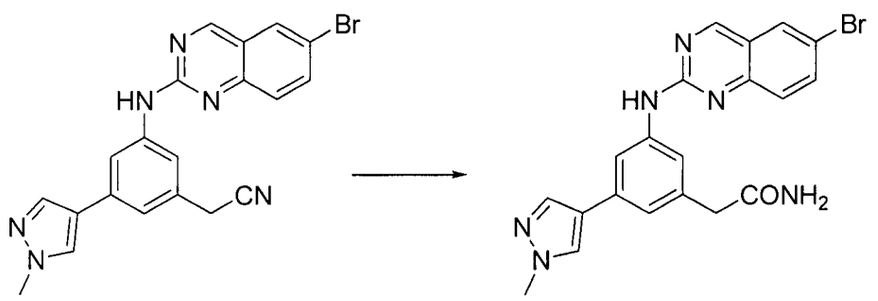
Esta reacción se condujo de una manera similar a la descrita en el Ejemplo 9, Paso 5.

Paso 5:

Esta conversión se logró de una manera similar a la descrita en el Ejemplo 10, Paso 1 y paso 2.

Ejemplo 1177

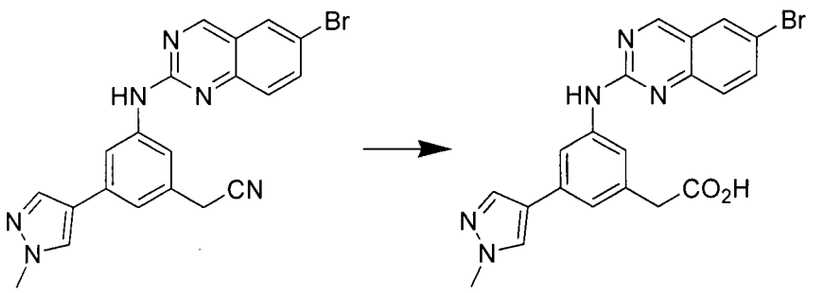
El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



El nitrilo (a partir del Ejemplo 1151) se trató con NaOH 1N (10 equivalentes) en microondas a 120°C durante 10 minutos. La reacción se purificó directamente mediante HPLC en fase inversa para proporcionar el producto deseado.

Ejemplo 1178

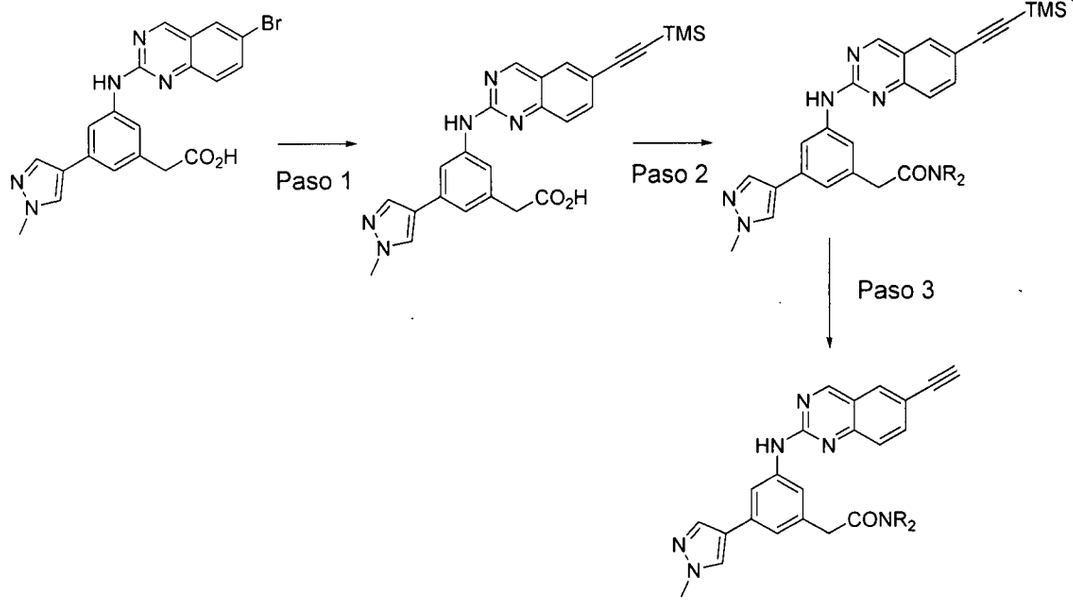
El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



El nitrilo (a partir del Ejemplo 1151) se trató con NaOH 1N (10 equivalentes) en una bomba de vidrio sellada a 110°C durante 12 horas. La reacción se enfrió a temperatura ambiente, y se concentró hasta el 20 por ciento del volumen original. Se agregó HCl 1N a un pH de 7, y el sólido amarillo resultante se recolectó y se secó, para proporcionar el producto deseado.

Ejemplos 1179 a 1184

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1:

Esta reacción se condujo de una manera similar a la descrita en el Ejemplo 10, Paso 1, utilizando el ácido a partir del Ejemplo 1178..

Paso 2:

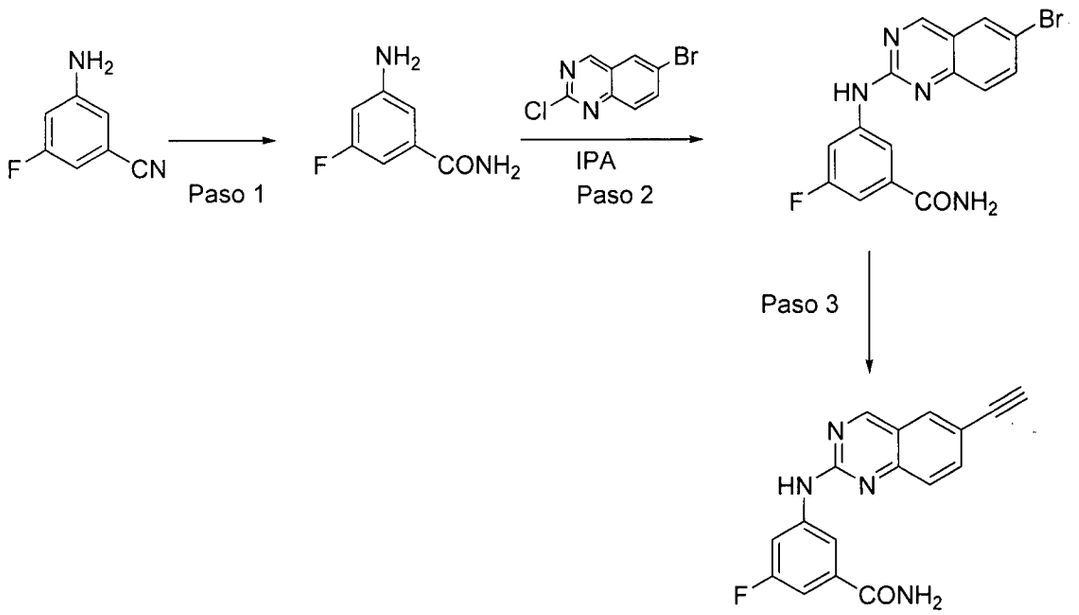
El ácido, HOAT (1.5 equivalentes), HATU (1.5 equivalentes), y Et_3N (3.0 equivalentes) se combinaron en N,N-dimetil-formamida. Se agregó la amina correspondiente, y la reacción se agitó a temperatura ambiente durante 10 horas, y se purificó directamente mediante HPLC en fase inversa, para proporcionar los compuestos deseados.

Paso 3:

Esta reacción se condujo de una manera similar a la descrita en el Ejemplo 10, Paso 2.

Ejemplo 1150

El compuesto objeto se preparó de acuerdo con el siguiente Esquema General:



Paso 1:

La amina se suspendió en NH_4OH y se calentó a 130°C durante 15 minutos en un reactor de microondas. La reacción se concentró hasta obtener un sólido amarillo, el cual se utilizó sin mayor purificación.

Paso 2:

Esta reacción se condujo de una manera similar a la descrita en el Ejemplo 9, Paso 5.

Paso 3:

Esta conversión se logró de una manera similar a la descrita en el Ejemplo 10, Paso 1 y Paso 2.

Ejemplos 1144-1149 y 1152

Los compuestos objeto se prepararon utilizando las aminas comercialmente disponibles de acuerdo con los Procedimientos Generales descritos en el Ejemplo 9, Paso 5, y en el Ejemplo 10, Paso 1 y Paso 2.

Ejemplos Biológicos

I. Ensayo de Rastreo de Cinasa Alfa PDK1

Reactivos/Concentraciones: El sustrato de péptido PDK1-4, biotina-GGGGRTWTLCG-NH_2, (SEQ ID NO: 1), se adquirió en la Tufts University Core Facility. La concentración final del sustrato de péptido PDK1-4 fue de 50 nM. El sustrato de ATP (5'-trifosfato de adenosina) se adquirió en Roche Diagnostics. La concentración final del sustrato de ATP fue de 10 µM. El anticuerpo de sustrato de Fosfo-(Ser/Thr) PKA se adquirió en Cell Signaling Technology. La concentración final del anticuerpo fue de 0.3 miligramos/mililitro. El kit de detección de Proteína A Alfa Screen que contenía las perlas donadoras y aceptoras, se adquirió en PerkinElmer Life Sciences. La concentración final de las perlas tanto donadoras como aceptoras fue de 25 microgramos/mililitro. Se utilizó Alfa Screen para la detección. El péptido PDK1-4 biotinilado se fosforiló mediante la cinasa PDK1 utilizando el sustrato de ATP. El sustrato de péptido PDK1-4 biotinilado se enlazó a la perla donadora recubierta de estreptavidina. El anticuerpo se enlazó a la perla aceptora recubierta con proteína A. El anticuerpo se enlazó a la forma fosforilada del sustrato de péptido PDK-1 biotinilado, poniendo en estrecha

proximidad las perlas donadoras y aceptoras. La irradiación con láser de la perla donadora a 680 nanómetros generó un flujo de moléculas de oxígeno singuletes de vida corta. Cuando las perlas donadoras y aceptoras estuvieron en estrecha proximidad, el oxígeno reactivo generado por la irradiación de las perlas donadoras inició una cascada de luminiscencia/fluorescencia en las perlas aceptoras. Este proceso condujo a una señal altamente amplificada con una salida en el intervalo de 530 a 620 nanómetros. Los ensayos se llevaron a cabo en Tris 50 mM, pH = 7.5, $MgCl_2$ 10 mM, albúmina de suero bovino al 0.1 por ciento, Tween-20 al 0.01 por ciento, ditioeritritol 2 mM, sulfóxido de dimetilo al 2.5 por ciento. Las reacciones se detuvieron mediante la adición de Tris 50 mM, pH = 7.5, EDTA 90 mM, albúmina de suero bovino al 0.1 por ciento, Tween-20 al 0.01 por ciento.

Procedimiento: A 10 microlitros del péptido PDK1-4, se les agregaron 0.5 microlitros del compuesto de prueba en sulfóxido de dimetilo. La cinasa PDK1 y el ATP se mezclaron, y se agregaron 10 microlitros de la mezcla de cinasa PDK1/ATP para iniciar la reacción. La reacción se dejó proceder durante 3 a 18 horas. Las reacciones se detuvieron entonces mediante la adición de 10 microlitros del regulador de paro que contenía EDTA. Las perlas se mezclaron con anticuerpos, y se agregaron entonces 25 microlitros de la mezcla de perlas/anticuerpos a las reacciones detenidas. Las placas se incubaron a temperatura ambiente durante la noche para permitir el desarrollo de la detección antes de leerse. El ensayo se ejecutó en

una placa de formato de 384 pozos.

Resultados: Como se muestra en la Tabla 1 de la presente, de los compuestos de ejemplo de la tabla, 140 compuestos demostraron IC_{50}s de menos de 25 µM en el rastreo anterior, y de éstos, 131 compuestos demostraron IC_{50}s de menos de 5 µM.

II. Ensayo de Rastreo *In Vitro* de la Inhibición de Cinasa CDK1 (CDC2)

Reactivos/Concentraciones: La Cdk1 de longitud completa humana se adquiere en Upstate (# 14-450) como una co-purificación con Ciclina B. La concentración final de la enzima en el ensayo es de 0.8 nM. El sustrato de péptido de histona H1 se adquiere en Research Genetics. El péptido, con la secuencia IcBiotina-GGCGPKTPKKAKKL[$CONH_2$], (SEQ ID NO: 2), se utiliza en el ensayo en una concentración final de 0.5 µM. El sustrato de ATP (5'-trifosfato de adenosina) se adquirió en Roche Diagnostics. La concentración final del sustrato de ATP es de 1 µM. El P^{33} γ-ATP se adquiere en NEN. El sustrato de péptido biotinilado se fosforila mediante la enzima de Cdk1/Ciclina B, en la presencia de diferentes concentraciones de los compuestos, utilizando el sustrato de ATP. Una fracción de ATP en la reacción se radiomarca para proporcionar una señal de fosforilación detectable. La reacción de fosforilación se detiene con la adición de EDTA 25 mM. Las soluciones se transfieren entonces a las placas de ensayo recubiertas con estreptavidina blancas BioBind, adquiridas en Thermo Electron Corporation. Después de lavar, se agrega a cada pozo el fluido de cintilación

Microscint 20, adquirido en Perkin Elmer, y se miden los conteos por minuto (cpm) utilizando un Contador de Microcintilación Packard TopCount. Los conteos por minuto más altos medidos indican la máxima fosforilación posible del sustrato bajo las condiciones del ensayo. Las reacciones ejecutadas sin enzima presente dan conteos por minuto que indican una inhibición completa de la enzima. Cada concentración del compuesto produjo un porcentaje de inhibición mensurable a partir de la máxima señal, basándose en estos valores. Los ensayos se llevaron a cabo en Tris-HCl 50 mM, pH de 7.5, $MgCl_2$ 10 mM, DTT 1 mM, EGTA 1 mM, ß-fosfato de glicerol 25 mM, NaF 1mM, BSA/PBS al 0.01 por ciento, sustrato de péptido 0.5 µM, y Cdk1 0.8 nM.

Procedimiento: En cada pozo se distribuyó el regulador de reacción (100 microlitros) que contenía Tris-HCl 50 mM, pH de 7.5, $MgCl_2$ 10 mM, BSA/PBS al 0.01 por ciento, DTT 1.5 mM, EGTA 1.5 mM, ß-fosfato de glicerol 37.5 mM, NaF 1.5 mM, sustrato de péptido 0.75 µM, y Cdk1 1.2 nM. Los pozos de control con el 100 por ciento de inhibición no contenían Cdk1. Los compuestos a probar se agregaron a los pozos en las concentraciones 10X deseadas, con sulfóxido de dimetilo al 10 por ciento, Tris-HCl 50 mM, pH de 7.5, $MgCl_2$ 10 mM, y BSA/PBS al 0.01 por ciento. Las reacciones se iniciaron mediante la adición de 15 microlitros de ATP concentrado a 10 µM, con P^{33} γ-ATP a < 10 nM como marca. Las reacciones se dejaron continuar durante cuatro horas a temperatura ambiente con agitación. Las placas recubiertas con estreptavidina se bloquearon

durante una hora con albúmina de suero bovino al 1 por ciento en suero regulado con fosfato. Se agregó EDTA (100 microlitros, 50 mM) a cada pozo de estreptavidina. Se transfirió una alícuota (100 microlitros) de cada solución de ensayo al pozo de estreptavidina correspondiente que contenía EDTA. Entonces se llevó a cabo la captura del sustrato radiomarcado mediante la agitación de la placa a temperatura ambiente durante una hora. Después del enlace, los pozos se lavaron 4 veces con suero regulado con fosfato, se agregaron 200 microlitros de Microscint 20 a cada pozo, y se midieron los conteos por minuto. El ensayo se ejecutó en un formato de 96 pozos.

Resultados: Muchos de los compuestos enlistados en la Tabla 1 se rastrearon de acuerdo con el método anterior, y exhibieron un valor de IC_{50} menor o igual a 25 µM, con respecto a la inhibición de Cdk1. Adicionalmente, muchos de los compuestos exhibieron una IC_{50} de menos de 10 µM, o de menos de 1 µM, o de menos de 0.1µM.

III. Ensayo de Rastreo *In Vitro* de Inhibición de Cinasa CDK2

Reactivos/Concentraciones: La Cdk2 de longitud completa humana se adquirió en Upstate (# 14-407) como una co-purificación con Ciclina A. La concentración final de la enzima en el ensayo fue de 5 nM. El sustrato de péptido de histona H1 se adquirió en Research Genetics. El péptido, con la secuencia lcBiotina-GGCGPKTPKKAKKL[$CONH_2$], (SEQ ID NO: 2), se utilizó en el ensayo en una concentración final de 0.5 µM. El sustrato de ATP (5'-trifosfato de adenosina) se adquirió en Roche Diagnostics. La

concentración final del sustrato de ATP fue de 1 µM. El P^{33} γ-ATP se adquirió en NEN. El sustrato de péptido biotinilado se fosforiló mediante la enzima de Cdk2/Ciclina A, en la presencia de diferentes concentraciones de los compuestos, utilizando el sustrato de ATP. Una fracción de ATP en la reacción se radiomarcó para proporcionar una señal de fosforilación detectable. La reacción de fosforilación se detuvo mediante la adición de EDTA 25 mM. Las soluciones se transfirieron entonces a las placas de ensayo recubiertas con estreptavidina blancas BioBind, adquiridas en Thermo Electron Corporation. Después de lavar, se agregó a cada pozo el fluido de cintilación Microscint 20, adquirido en Perkin Elmer, y se midieron los conteos por minuto (cpm) utilizando un Contador de Microcintilación Packard TopCount. Los conteos por minuto más altos medidos indican la máxima fosforilación posible del sustrato bajo las condiciones del ensayo. Las reacciones ejecutadas sin enzima presente dieron conteos por minuto que indican una inhibición completa de la enzima. Cada concentración del compuesto produjo un porcentaje de inhibición mensurable a partir de la máxima señal, basándose en estos valores. Los ensayos se llevaron a cabo en Tris-HCl 50 mM, pH de 7.5, $MgCl_2$ 10 mM, DTT 1 mM, EGTA 1 mM, ß-fosfato de glicerol 25 mM, NaF 1mM, BSA/PBS al 0.01 por ciento, sustrato de péptido 0.5 µM, y Cdk1 5 nM.

Procedimiento: En cada pozo se distribuyó el regulador de reacción (100 microlitros) que contenía Tris-HCl 50 mM, pH de 7.5, $MgCl_2$ 10 mM, BSA/PBS al 0.01 por ciento, DTT 1.5 mM, EGTA 1.5

mM, ß-fosfato de glicerol 37.5 mM, NaF 1.5 mM, sustrato de péptido 0.75 µM, y Cdk2 7.5 nM. Los pozos de control con el 100 por ciento de inhibición no contenían Cdk2. Los compuestos a probar se agregaron a los pozos en las concentraciones 10X deseadas, con sulfóxido de dimetilo al 10 por ciento, Tris-HCl 50 mM, pH de 7.5, $MgCl_2$ 10 mM, y BSA/PBS al 0.01 por ciento. Las reacciones se iniciaron mediante la adición de 15 microlitros de ATP concentrado a 10 µM, con P^{33} γ-ATP a < 10 nM como marca. Las reacciones se dejaron proceder durante cuatro horas a temperatura ambiente con agitación. Las placas recubiertas con estreptavidina se bloquearon durante una hora con albúmina de suero bovino al 1 por ciento en suero regulado con fosfato. Se agregó EDTA (100 microlitros, 50 mM) a cada pozo de estreptavidina. Se transfirió una alícuota (100 microlitros) de cada solución de ensayo a los pozos de estreptavidina correspondientes que contenían EDTA. Se capturó el sustrato radiomarcado mediante agitación en la placa a temperatura ambiente durante una hora. Después del enlace, los pozos se lavaron 4 veces con suero regulado con fosfato, se agregaron 200 microlitros de Microscint 20 a cada pozo, y se midieron los conteos por minuto. El ensayo se ejecutó en una placa de formato de 96 pozos.

Resultados: Muchos de los compuestos enlistados en la Tabla 1 se rastrearon de acuerdo con el método anterior, y exhibieron un valor de IC_{50} menor o igual a 25 µM, con respecto a la inhibición de Cdk2. Adicionalmente, muchos de los compuestos exhibieron una

IC_{50} de menos de 10 μM, o de menos de 1 μM, o de menos de 0.1μM. En las Tablas 2 y 3 se dan los valores de IC_{50} para compuestos adicionales.

IV. Protocolo de Ensayo de Proliferación Celular: A2780 de la Línea Celular PC-3

Las células A2780 o PC-3 se sembraron a 1,000 células/pozo en 100 microlitros/pozo (10,000 células/mililitro) del medio de cultivo, en placas de 96 pozos. Las células se dejaron adherirse al fondo de las placas durante 3 a 5 horas en una incubadora a 37°C con CO_2 al 5 por ciento. Los compuestos se disolvieron en sulfóxido de dimetilo, y entonces se transfirieron a las placas de células. Las células se incubaron con los compuestos durante 3 días en una incubadora a 37°C con CO_2 al 5 por ciento. Entonces se removió de las células el medio de cultivo que contenía los compuestos, y se agregó medio fresco, seguido por 100 microlitros de reactivo de ensayo Cell Titer Glo (Promega). Esta mezcla se agitó durante 1 minuto, y entonces se incubó sin agitación durante 10 minutos. Las determinaciones de actividad para los compuestos se hicieron mediante detección en un Instrumento Trilux. De los compuestos de ejemplo de la Tabla 1, 101 compuestos demostraron IC_{50}s de menos de 10 μM, y de éstos, 87 compuestos demostraron IC_{50}s de menos de 5 μM.

V. Protocolo de Ensayo de Proliferación Celular: Línea Celular PC-3

Las células PC-3 se sembraron a 1,000 células/pozo en 100 microlitros/pozo (10,000 células/mililitro), junto con el medio de

cultivo, en placas de 96 pozos de paredes negras y de fondo transparente. Las células se dejaron adherirse al fondo de la placa durante 3 a 5 horas en una incubadora a 37°C con CO_2 al 5 por ciento.

Los compuestos de prueba se diluyeron hasta 500 veces en sulfóxido de dimetilo. Las soluciones en sulfóxido de dimetilo de seis de los compuestos se transfirieron a las células en la placa de fondo redondo de 96 pozos, columna 2, filas B-F.

Se llevó a cabo una dilución en serie a 1:3 de cada compuesto. a dilución en serie comprendió la adición de 20microlitros de sulfóxido de dimetilo a los pozos que contenían los compuestos, y haciendo una dilución a 1:3 a través de la placa a partir de las columnas 2 a 10. La columna 11 contuvo solamente sulfóxido de dimetilo. La dilución en serie se llevó a cabo utilizando un protocolo BioMek 2000 "CP Serial Dilution using 250 µL tips" (Dilución en Serie CP usando puntas de 250 microlitros) o "Proliferation Compound" (Compuesto de Proliferación) (si se utilizaban las puntas de 20 microlitros).

A un boque de 96 pozos profundos, columnas 2 a 11, filas B a F, se transfirieron 500 microlitros del medio de cultivo. Empleando el protocolo FX "HH_CellAssay_2 µL to 500 µL" (Ensayo Celular HH de 2 microlitros a 500 microlitros), 2 microlitros del compuesto a partir de cada célula de la placa de compuestos se transfirieron a la célula correspondiente del bloque de 96 pozos profundos que contenía 500 microlitros de medio de cultivo. El instrumento se programó para

diluir el compuesto en el medio de cultivo y luego transferir 100 microlitros de esa mezcla a las placas que contenían células.

Las placas de células, a las cuales se habían agregado los compuestos de prueba, se incubaron durante 3 días a 37°C. En seguida de la incubación, el medio se removió y fue reemplazado con medio fresco. Se agregó Cell Titer Glo (100 microlitros) a cada pozo, y la placa se agitó durante 1 minuto, y entonces se incubó sin agitación durante 10 minutos. Las placas entonces se leyeron utilizando un Instrumento Trilux.

VI. El protocolo de Ensayo pAkt^{T308} ECL

En el Día 1, las células PC-3 se sembraron a 15,000 células/pozo en 100 microlitros/pozo (10,000 células/mililitro) del medio de cultivo en placas de paredes negras, de fondo transparente, recubiertas de poli-L-lisina. Las células se incubaron durante la noche en una incubadora a 37°C con CO_2 al 5 por ciento.

En el Día 2, una placa MSD ECL se bloqueó durante dos horas con 150 microlitros por pozo de Bloqueador A MSD al 3 por ciento.

Los compuestos de prueba se diluyeron 500 veces en sulfóxido de dimetilo, y entonces se sometieron a una dilución en serie adicional utilizando un instrumento BioMek 2000. Los compuestos diluidos en sulfóxido de dimetilo se diluyeron entonces en el medio de cultivo, y luego se agregaron a las placas de células.

Las placas de células se incubaron con los compuestos durante seis horas en una incubadora a 37°C con CO_2 al 5 por ciento, después de lo cual, se removió el medio de cultivo, y se agregaron

55 microlitros de regulador de lisis MSD a las placas de células sobre hielo. Las placas se lisaron sobre hielo durante cinco minutos, seguidos por 15 minutos de agitación vigorosa sobre un agitador de placas a 4°C. Las placas de ensayo MSD bloqueadas se lavaron dos veces con regulador de lavado MSD 1x, seguido por la adición del lisado celular como sigue: se agregaron 30 microlitros del lisado celular a las placas pAkt308, y se agregaron 13 microlitros del lisado + 12 microlitros del regulador de lisis a las placas tAkt. Las placas entonces se sellaron y se agitaron a 4°C durante la noche.

En el Día 3, las placas MSD se lavaron cuatro veces con regulador de lavado MSD 1x MSD, y luego se diluyeron 25 microlitros/pozo de anticuerpos MSD SULFO-TAG hasta una concentración final de 10 nM en Bloqueador al 1 por ciento. Se agregó un regulador al diluyente del anticuerpo que se agregó a las placas de ensayo. Las placas entonces se sellaron y se incubaron a temperatura ambiente durante 1.5 horas. Las placas luego se lavaron dos veces con regulador de lavado MSD 1x, seguido por la adición de 150 microlitros/pozo de regulador de lectura MSD 1.5x. Las placas se leyeron inmediatamente después de la adición del regulador de lectura utilizando un instrumento Trilux.

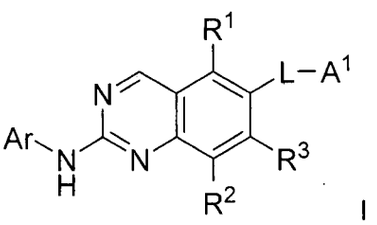
De los compuestos de ejemplo de la Tabla 1, 62 compuestos demostraron IC_{50}s de menos de 10 µM, y de éstos, 57 compuestos demostraron IC_{50}s de menos de 5 µM. Los valores IC_{50} específicos para los compuestos representativos también se proporcionan en las Tablas 2 y 3 (véanse las Figuras 1 y 2).

El contenido de cada una de las patentes, solicitudes de patente, y artículos de revistas citados anteriormente, se incorpora a la presente como referencia y para todos los propósitos como si se estipularan en su totalidad.

Se ha descrito un número de modalidades de la invención. No obstante, se entenderá que se pueden hacer diferentes modificaciones sin apartarse del espíritu y alcance de la invención. De conformidad con lo anterior, otras modalidades están dentro del alcance de las siguientes reivindicaciones.

REIVINDICACIONES

1. Un compuesto de la fórmula I:



I

o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde:

Ar es arilo, arilo sustituido, heteroarilo, o heteroarilo sustituido;

R^1 es H, alquilo de 1 a 3 átomos de carbono, halógeno, ciano, nitro, CF_3, imidazolilo, tiazolilo, oxazolilo, o amino;

R^2 se selecciona a partir del grupo que consiste en H, alcoxilo, alcoxilo sustituido, alquilo, alquilo sustituido, CN, heteroariloxilo, heteroariloxilo sustituido, hetero-cicliloxilo, heterocicliloxilo sustituido, y halógeno;

R^3 se selecciona a partir del grupo que consiste en H, halógeno, CN, carboxilo, alquilo, alquilo sustituido, alcoxilo, alcoxilo sustituido, ariloxilo, ariloxilo sustituido, cicloalquiloxilo, cicloalquiloxilo sustituido, heterociclil-alquiloxilo, heterociclil-alquiloxilo sustituido, heteroariloxilo, heteroariloxilo sustituido, heteroaril-alquiloxilo, heteroaril-alquiloxilo sustituido, aril-alquiloxilo, aril-alquiloxilo sustituido, heteroarilo, heteroarilo sustituido, heterociclilo, heterociclilo sustituido, heteroaril-alquilo, heteroaril-

alquilo sustituido, heterociclil-alquilo, y heterociclil-alquilo sustituido;

L es un enlace covalente, carbonilo, carbonil-amino, amino-carbonilo, -O-, -S-, -SO-, $-SO_2-$, -NH-, alquilo de 1 a 3 átomos de carbono, alquilo de 1 a 3 átomos de carbono sustituido, alquenilo de 2 a 3 átomos de carbono, alquinilo de 2 a 3 átomos de carbono, o un alquilo interrumpido con -O-, -S-, -SO-, o $-SO_2-$;

A^1 es alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, alcoxilo, alcoxilo sustituido, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, halógeno, hidroxilo, nitro, SO_3H, sulfonilo, sulfonilo sustituido, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, tioalquilo, tioalquilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, heterociclilo, o heterociclilo sustituido;

con las condiciones de que:

a) cuando R^1, R^2, y R^3 son cada uno H, y L es un enlace covalente, entonces A^1 es diferente de arilo o arilo sustituido;

b) cuando R^1, R^2, y R^3 son cada uno H, L es un enlace covalente, y A^1 es Br, fenilo sustituido, o piridinilo sustituido, entonces Ar es diferente de fenilo, fenilo sustituido con piperazinilo, o heterociclil-alquiloxilo, o piridinilo;

c) cuando R^1, R^2, y R^3 son cada uno H, L es un enlace

covalente, y A^1 es hidroxilo o alcoxilo, entonces Ar es diferente de fenilo sustituido con uno o más de alquilo o halógeno; y

d) cuando R^1, R^2, y R^3 son cada uno H, y L es O, entonces A^1 es diferente de piridinilo o piridinilo sustituido.

2. El compuesto de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde L es un enlace covalente.

3. El compuesto de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde L es carbonilo.

4. El compuesto de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde L es -NH-.

5. El compuesto de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde L es amino-carbonilo o carbonil-amino.

6. El compuesto de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde L es -O-.

7. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 6, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde A^1 es alquilo.

8. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 6, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde A^1 es alquinilo.

9. El compuesto de acuerdo con la reivindicación 8, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde A^1 es etinilo, propinilo, fenil-etinilo o piridil-etinilo.

10. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 6, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde A^1 es arilo o arilo sustituido.

11. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 6, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde A^1 es fenilo sustituido.

12. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 6, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde A^1 es heteroarilo o heteroarilo sustituido.

13. El compuesto de acuerdo con la reivindicación 12, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde este heteroarilo o heteroarilo sustituido se selecciona a partir del grupo que consiste en piridilo, pirazolilo, tiazolilo, pirimidilo, piridazinilo, oxazolilo, isoxazolilo, piridilo sustituido, pirazolilo sustituido, tiazolilo sustituido, pirimidilo sustituido, piridazinilo sustituido, oxazolilo sustituido, e isoxazolilo sustituido.

14. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 6, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde A^1 es heterociclilo o heterociclilo sustituido.

15. El compuesto de acuerdo con la reivindicación 14, o una

sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde este heterociclilo o heterociclilo sustituido se selecciona a partir del grupo que consiste en piperidinilo, piperazinilo, pirrolidinilo, tetrahidro-furanilo, tetrahidro-tiofenilo, morfolinilo, tiomorfolino, piperidinilo sustituido, piperazinilo sustituido, pirrolidinilo sustituido, tetrahidro-furanilo sustituido, tetrahidro-tiofenilo sustituido, morfolinilo sustituido, y tiomorfolino sustituido.

16. El compuesto de acuerdo con la reivindicación 2, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde A^1 es halógeno.

17. El compuesto de acuerdo con la reivindicación 2, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde A^1 es ciano.

18. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 17, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde R^1 es H o halógeno.

19. El compuesto de acuerdo con la reivindicación 18, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde R^2 y R^3 se seleccionan independientemente a partir del grupo que consiste en H, halógeno y alcoxilo.

20. El compuesto de acuerdo con la reivindicación 19, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde R^2 y R^3 se seleccionan independientemente a partir del grupo que consiste en H y metoxilo.

21. El compuesto de acuerdo con la reivindicación 20, o una

sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde cuando menos uno de R^2 y R^3 es H.

22. El compuesto de acuerdo con la reivindicación 19, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde R^2 y R^3 son ambos H.

23. El compuesto de cualquiera de las reivindicaciones 1 a 17, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde uno de R^2 y R^3 es H, y el otro de R^2 y R^3 es alcoxilo, alcoxilo sustituido, ariloxilo, ariloxilo sustituido, cicloalquiloxilo, cicloalquiloxilo sustituido, heterociclil-alquiloxilo, heterociclil-alquiloxilo sustituido, heteroariloxilo, heteroariloxilo sustituido, heteroaril-alquiloxilo, heteroaril-alquiloxilo sustituido, aril-alquiloxilo, o aril-alquiloxilo sustituido.

24. El compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 23, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde Ar es arilo sustituido o heteroarilo sustituido.

25. El compuesto de acuerdo con la reivindicación 24, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde Ar es arilo sustituido por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en alquilo, alquenilo, alquinilo, alcoxilo, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo,

ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino sustituido, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, hetero-cicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo sustituido, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, y tioalquilo;

en donde las fracciones de alquilo, alquenilo, alquinilo, arilo, cicloalquilo, cicloalquenilo, heterociclilo, y heteroarilo contenidas dentro de cualquiera de los grupos arilo sustituido enlistados, están opcionalmente sustituidas por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en alquenilo, alquinilo, alcoxilo, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, hetero-cicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, tioalquilo, y tioalquilo.

26. El compuesto de acuerdo con la reivindicación 25, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en

donde Ar es arilo sustituido por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en amino-sulfonilo, amino-carbonilo, arilo, heteroarilo, heterociclilo, amino, amino sustituido, alquilo, halógeno, y ciano;

en donde las fracciones de alquilo, arilo, y heteroarilo contenidas dentro de cualquiera de los grupos arilo sustituido enlistados, están opcionalmente sustituidas por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en alquenilo, alquinilo, alcoxilo, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, heterocicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, tioalquilo, y tioalquilo.

27. El compuesto de acuerdo con la reivindicación 25, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde Ar es fenilo sustituido.

28. El compuesto de acuerdo con la reivindicación 24, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde Ar es heteroarilo sustituido por 1, 2, 3, 4 ó 5 sustituyentes

seleccionados independientemente a partir del grupo que consiste en alquilo, alquenilo, alquinilo, alcoxilo, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino sustituido, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, hetero-cicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo sustituido, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, y tioalquilo;

en donde las fracciones de alquilo, alquenilo, alquinilo, arilo, cicloalquilo, cicloalquenilo, heterociclilo, y heteroarilo contenidas dentro de cualquiera de los grupos arilo sustituido enlistados, están opcionalmente sustituidas por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en alquenilo, alquinilo, alcoxilo, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino, halógeno, hidroxilo,

heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, heterocicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, tioalquilo, y tioalquilo.

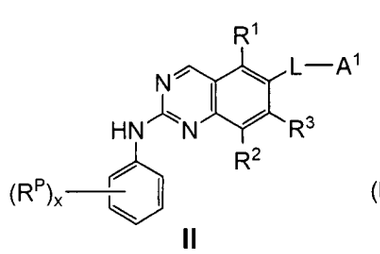
29. El compuesto de acuerdo con la reivindicación 28, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde Ar es heteroarilo sustituido por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en amino-sulfonilo, amino-carbonilo, arilo, heteroarilo, heterociclilo, amino, amino sustituido, alquilo, halógeno, y ciano;

en donde las fracciones de alquilo, arilo, y heteroarilo contenidas dentro de cualquiera de los grupos arilo sustituido enlistados, están opcionalmente sustituidas por 1, 2, 3, 4 ó 5 sustituyentes seleccionados independientemente a partir del grupo que consiste en alquenilo, alquinilo, alcoxilo, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, tioarilo, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquiloxilo, tiocicloalquilo, cicloalquenilo, cicloalqueniloxilo, tiocicloalquenilo, guanidino, guanidino, halógeno, hidroxilo, heteroarilo, heteroariloxilo, tioheteroarilo, heterocíclico, heterocicliloxilo, tioheterociclilo, nitro, SO_3H, sulfonilo, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, tioalquilo, y tioalquilo.

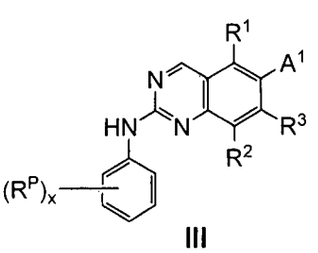
30. El compuesto de acuerdo con la reivindicación 29, o una

sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde Ar se selecciona a partir del grupo que consiste en piridilo sustituido, pirazolilo sustituido, tiazolilo sustituido, pirimidilo sustituido, piridazinilo sustituido, oxazolilo sustituido, e isoxazolilo sustituido.

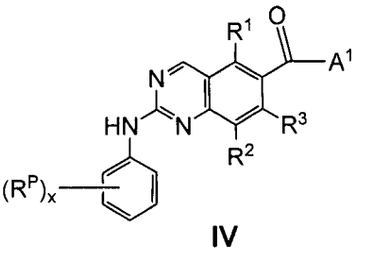
31. Un compuesto de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde el compuesto de la fórmula I es un compuesto de acuerdo con una de las fórmulas II a VII:



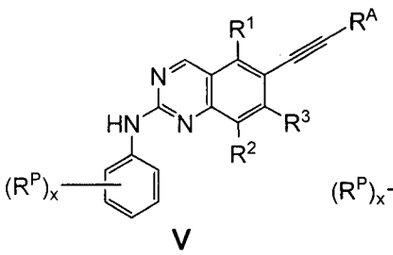
II



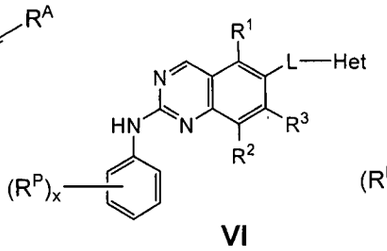
III



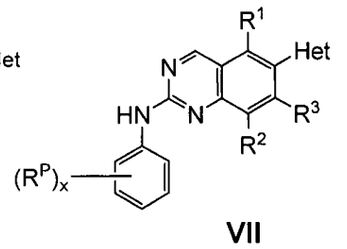
IV



V



VI



VII

en donde R^P se selecciona independientemente a partir del grupo que consiste en alquilo, alquilo sustituido, alquenilo, alquenilo sustituido, alquinilo, alquinilo sustituido, alcoxilo, alcoxilo sustituido, acilo, acil-amino, aciloxilo, amino, amino sustituido, amino-carbonilo, amino-tiocarbonilo, amino-carbonil-amino, amino-tiocarbonil-amino, amino-carboniloxilo, amino-sulfonilo, amino-sulfoniloxilo, amino-sulfonil-amino, amidino, arilo, ariloxilo, ariloxilo

sustituido, tioarilo, tioarilo sustituido, carboxilo, carboxil-éster, (carboxil-éster)amino, (carboxil-éster)oxilo, ciano, cicloalquilo, cicloalquilo sustituido, cicloalquiloxilo, cicloalquiloxilo sustituido, tiocicloalquilo, tiocicloalquilo sustituido, cicloalquenilo, cicloalquenilo sustituido, cicloalqueniloxilo, cicloalqueniloxilo sustituido, tiocicloalquenilo, tiocicloalquenilo sustituido, guanidino, guanidino sustituido, halógeno, hidroxilo, heteroarilo, heteroarilo sustituido, heteroariloxilo, heteroariloxilo sustituido, tioheteroarilo, tioheteroarilo sustituido, heterocíclico, heterocíclico sustituido, hetero-cicliloxilo, heterocicliloxilo sustituido, tioheterociclilo, tioheterociclilo sustituido, nitro, SO_3H, sulfonilo sustituido, sulfoniloxilo, sulfonil-amino, tioacilo, tiol, tioalquilo, y tioalquilo sustituido;

R^A se selecciona a partir del grupo que consiste en H, alquilo, alquilo sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, heterociclilo, y heterociclilo sustituido;

Het se selecciona a partir del grupo que consiste en heteroárilo, heteroarilo sustituido, heterociclilo, y heterociclilo sustituido; y

x es 1, 2, 3, 4 ó 5.

32. El compuesto de la reivindicación 27, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, en donde el fenilo sustituido mencionado está sustituido por 1, 2 ó 3 grupos que no están unidos al fenilo en *orto* en relación con el NH de la fórmula I.

33. Un compuesto de acuerdo con la reivindicación 1, seleccionado a partir del grupo que consiste en:

4-(6-bromo-8-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida;

4-(6-etinil-8-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida;

4-(6-etil-8-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida;

4-(6-ciano-8-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida;

4-(8-metoxi-6-metil-quinazolin-2-il-amino)-bencen-sulfonamida;

N-(3-(6-bromo-8-cloro-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-acetamida;

N-(3-(8-cloro-6-etinil-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-acetamida;

4-(8-bromo-6-(trifluoro-metil)-quinazolin-2-il-amino)-bencen-sulfonamida;

4-(6-bromo-quinazolin-2-il-amino)-bencen-sulfonamida;

4-(6-etinil-quinazolin-2-il-amino)-bencen-sulfonamida;

4-(6-bromo-quinazolin-2-il-amino)-*N*-*iso*propil-benzamida;

N-*iso*propil-4-(6-(tiazol-2-il)-quinazolin-2-il-amino)-benzamida;

4-(6-ciano-quinazolin-2-il-amino)-*N*-*iso*propil-benzamida;

N-(3-(6-bromo-5-cloro-8-metoxi-quinazolin-2-il-amino)-5-

((dimetil-amino)-metil)-fenil)-acetamida;

4-(8-bromo-6-fluoro-quinazolin-2-il-amino)-bencen-sulfonamida;

N-(3-(6-bromo-quinazolin-2-il-amino)-5-(1-metil-6-oxo-1,6-dihidro-piridin-3-il)-fenil)-acetamida;

N-(3-(6-etinil-quinazolin-2-il-amino)-5-(1-metil-6-oxo-1,6-dihidro-piridin-3-il)-fenil)-acetamida;

2-(4-sulfamoil-fenil-amino)-quinazolin-6-carboxilato de metilo;

ácido 2-(4-sulfamoil-fenil-amino)-quinazolin-6-carboxílico;

4-(6-(4-metil-piperazin-1-carbonil)-quinazolin-2-il-amino)-bencen-sulfonamida;

4-(6-(1-isobutil-1H-pirazol-4-il)-quinazolin-2-il-amino)-bencen-sulfonamida;

(4-(5-cloro-6-etinil-quinazolin-2-il-amino)-fenil)-(morfolino)-metanona;

6-bromo-5-fluoro-*N*-(4-morfolino-fenil)-quinazolin-2-amina;

6-etinil-5-fluoro-*N*-(4-morfolino-fenil)-quinazolin-2-amina;

N-(3-(6-bromo-5-fluoro-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida;

N-(3-(5-fluoro-6-(tiazol-2-il)-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida;

4-(6-(tiazol-2-il)-quinazolin-2-il-amino)-bencen-sulfonamida;

5-cloro-*N*-(4-morfolino-fenil)-6-(tiazol-2-il)-quinazolin-2-amina;

N-(3-(6-bromo-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida;

N-(3-(6-(1H-pirazol-4-il)-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida;

N-(3-(6-bromo-quinazolin-2-il-amino)-5-yodo-fenil)-acetamida;

N-(3-(6-bromo-quinazolin-2-il-amino)-5-(piridin-3-il)-fenil)-acetamida;

N-(3-(piridin-3-il)-5-(6-(piridin-3-il)-quinazolin-2-il-amino)-fenil)-acetamida;

N-(3-(6-etinil-quinazolin-2-il-amino)-5-(piridin-3-il)-fenil)-acetamida;

4-(6,7-dimetoxi-quinazolin-2-il-amino)-bencen-sulfonamida;

4-(6-metoxi-quinazolin-2-il-amino)-benzamida;

N-metil-2-(4-sulfamoil-fenil-amino)-quinazolin-6-carboxamida;

N-(1-metil-piperidin-4-il)-2-(4-sulfamoil-fenil-amino)-quinazolin-6-carboxamida;

4-(6-(4-isopropil-piperazin-1-carbonil)-quinazolin-2-il-amino)-bencen-sulfonamida;

N-*iso*propil-2-(4-sulfamoil-fenil-amino)-quinazolin-6-carboxamida;

4-(6-(pirrolidin-1-carbonil)-quinazolin-2-il-amino)-bencen-sulfonamida;

2-(4-sulfamoil-fenil-amino)-quinazolin-6-carboxamida;

N-ciclopropil-2-(4-sulfamoil-fenil-amino)-quinazolin-6-carboxamida;

4-(6-(2-fluoro-piridin-3-il)-quinazolin-2-il-amino)-bencen-sulfonamida;

4-(6-(2-(4-metil-piperazin-1-il)-piridin-4-il)-quinazolin-2-il-amino)-bencen-sulfonamida;

N-(3-benzamido-fenil)-2-(4-sulfamoil-fenil-amino)-quinazolin-6-carboxamida;

4-(6-bromo-7-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida;

6-bromo-7-metoxi-*N*-(4-(morfolino-sulfonil)-fenil)-quinazolin-2-amina;

4-(6-etinil-7-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida;

6-etinil-7-metoxi-*N*-(4-(morfolino-sulfonil)-fenil)-quinazolin-2-amina;

6-etinil-*N*-(3-morfolino-fenil)-quinazolin-2-amina;

4-(8-metoxi-6-(fenil-etinil)-quinazolin-2-il-amino)-bencen-sulfonamida;

4-(8-metoxi-6-(piridin-3-il-etinil)-quinazolin-2-il-amino)-bencen-sulfonamida;

4-(6-metil-quinazolin-2-il-amino)-bencen-sulfonamida;

4-(7-metoxi-6-(fenil-etinil)-quinazolin-2-il-amino)-bencen-sulfonamida;

4-(6-(1-metil-1H-pirazol-4-il)-quinazolin-2-il-amino)-bencen-sulfonamida;

6-etinil-*N*-(4-morfolino-fenil)-quinazolin-2-amina;

4-(6-etinil-quinazolin-2-il-amino)-benzamida;

3-(6-etinil-quinazolin-2-il-amino)-benzamida;

3-(6-etinil-quinazolin-2-il-amino)-bencen-sulfonamida;

N-(3-(6-etinil-quinazolin-2-il-amino)-fenil)-metan-sulfonamida;

4-(8-metoxi-6-(1-metil-1H-pirazol-4-il)-quinazolin-2-il-amino)-bencen-sulfonamida;

4-(8-metoxi-6-(tiazol-2-il)-quinazolin-2-il-amino)-bencen-sulfonamida;

4-(8-metoxi-6-(piridin-2-il-etinil)-quinazolin-2-il-amino)-bencen-sulfonamida;

4-(6-(3-hidroxi-3-metil-but-1-inil)-8-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida;

4-(6-(3-amino-3-metil-but-1-inil)-8-metoxi-quinazolin-2-il-amino)-bencen-sulfonamida;

4-(6-(1H-pirazol-3-il)-quinazolin-2-il-amino)-bencen-sulfonamida;

N-(2-(4-sulfamoil-fenil-amino)-quinazolin-6-il)-acetamida;

6-etinil-7-metoxi-*N*-(4-morfolino-fenil)-quinazolin-2-amina;

6-etinil-8-metoxi-*N*-(4-morfolino-fenil)-quinazolin-2-amina;

N-(3-((dimetil-amino)-metil)-fenil)-6-etinil-quinazolin-2-amina;

4-(6-etinil-quinazolin-2-il-amino)-*N*-*iso*propil-benzamida;

4-(6-etinil-7-metoxi-quinazolin-2-il-amino)-*N*-isopropil-benzamida;

(4-(6-etinil-7-metoxi-quinazolin-2-il-amino)-fenil)-(morfolino)-metanona;

4-(6-(tiazol-2-il)-quinazolin-2-il-amino)-benzamida;

2-(4-morfolino-fenil-amino)-quinazolin-6-carbonitrilo;

6-bromo-*N*-(4-morfolino-fenil)-quinazolin-2-amina;

4-(6-ciano-quinazolin-2-il-amino)-benzamida;

4-(6-bromo-quinazolin-2-il-amino)-benzamida;

6-etinil-8-metoxi-*N*-(3-morfolino-fenil)-quinazolin-2-amina;

(4-(6-etinil-quinazolin-2-il-amino)-fenil)-(morfolino)-metanona;

N-(3-((dimetil-amino)-metil)-4-morfolino-fenil)-6-etinil-quinazolin-2-amina;

N-(3-((dimetil-amino)-metil)-5-(6-etinil-quinazolin-2-il-amino)-fenil)-acetamida;

N-(3-((dimetil-amino)-metil)-5-(6-(tiazol-2-il)-quinazolin-2-il-amino)-fenil)-acetamida;

N-(3-((dimetil-amino)-metil)-5-(6-etinil-7-metoxi-quinazolin-2-il-amino)-fenil)-acetamida;

N-(3-((dimetil-amino)-metil)-5-(6-etinil-8-metoxi-quinazolin-2-il-amino)-fenil)-acetamida;

N-(3-((dimetil-amino)-metil)-5-(8-metoxi-6-(tiazol-2-il)-quinazolin-2-il-amino)-fenil)-acetamida;

N-(3-(5-cloro-6-etinil-8-metoxi-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-acetamida;

4-(6-bromo-5-cloro-8-metoxi-quinazolin-2-il-amino)-*N*-isopropil-benzamida;

N-(3-(5-cloro-6-etinil-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-acetamida;

N-(3-(5-cloro-6-(tiazol-2-il)-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-acetamida;

N-(3-((dimetil-amino)-metil)-5-(6-(pirimidin-5-il)-quinazolin-2-il-amino)-fenil)-acetamida;

N-(3-((dimetil-amino)-metil)-5-(6-(2-metoxi-piridin-3-il)-quinazolin-2-il-amino)-fenil)-acetamida;

N-(3-((dimetil-amino)-metil)-5-(8-metoxi-6-(2-metoxi-piridin-3-il)-quinazolin-2-il-amino)-fenil)-acetamida;

N-(3-((dimetil-amino)-metil)-5-(8-metoxi-6-(pirimidin-5-il)-quinazolin-2-il-amino)-fenil)-acetamida;

N-(4-(1H-tetrazol-5-il)-fenil)-6-etinil-7-metoxi-quinazolin-2-amina;

N-(4-(1H-tetrazol-1-il)-fenil)-6-etinil-7-metoxi-quinazolin-2-amina;

N-(3-(1H-tetrazol-5-il)-fenil)-6-etinil-7-metoxi-quinazolin-2-amina;

5-cloro-6-etinil-*N*-(4-morfolino-fenil)-quinazolin-2-amina;

N-(4-morfolino-fenil)-6-(tiazol-2-il)-quinazolin-2-amina;

5-cloro-6-etinil-8-metoxi-*N*-(4-morfolino-fenil)-quinazolin-2-amina;

(4-(6-bromo-7-metoxi-quinazolin-2-il-amino)-2-cloro-fenil)-(morfolino)-metanona;

N-(3-(1H-tetrazol-1-il)-fenil)-6-etinil-7-metoxi-quinazolin-2-amina;

(2-cloro-4-(7-metoxi-6-(tiazol-2-il)-quinazolin-2-il-amino)-fenil)-(morfolino)-metanona;

N,N'-(5-(6-etinil-quinazolin-2-il-amino)-1,3-fenileno)-diacetamida;

4-(5-cloro-6-etinil-quinazolin-2-il-amino)-*N-iso*propil-benzamida;

4-(5-cloro-6-etinil-quinazolin-2-il-amino)-*N-ciclo*propil-benzamida;

4-(5-cloro-6-(tiazol-2-il)-quinazolin-2-il-amino)-*N-iso*propil-benzamida;

N-(3-((dimetil-amino)-metil)-5-(6-metoxi-quinazolin-2-il-amino)-fenil)-acetamida;

N-(3-((dimetil-amino)-metil)-5-(8-metoxi-6-(6-metoxi-pirazin-2-il)-quinazolin-2-il-amino)-fenil)-acetamida;

N-(3-(6-(2-amino-4-metoxi-pirimidin-5-il)-8-metoxi-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-acetamida;

N-(3-(1H-tetrazol-1-il)-fenil)-7-metoxi-6-(tiazol-2-il)-quinazolin-2-amina;

(4-(5-cloro-6-etinil-8-metoxi-quinazolin-2-il-amino)-fenil)-(morfolino)-metanona;

4-(5-cloro-6-etinil-8-metoxi-quinazolin-2-il-amino)-N-isopropil-benzamida;

5-cloro-8-metoxi-N-(4-morfolino-fenil)-6-(tiazol-2-il)-quinazolin-2-amina;

6-bromo-5-cloro-8-metoxi-N-(4-morfolino-fenil)-quinazolin-2-amina;

(4-(5-cloro-8-metoxi-6-(tiazol-2-il)-quinazolin-2-il-amino)-fenil)-(morfolino)-metanona;

(4-(6-bromo-5-cloro-8-metoxi-quinazolin-2-il-amino)-fenil)-(morfolino)-metanona;

4-(5-cloro-8-metoxi-6-(tiazol-2-il)-quinazolin-2-il-amino)-N-isopropil-benzamida;

(2-cloro-4-(6-etinil-7-metoxi-quinazolin-2-il-amino)-fenil)-(morfolino)-metanona;

5-cloro-6-etinil-N-(3-morfolino-fenil)-quinazolin-2-amina;

N-(3-((dimetil-amino)-metil)-5-(7-metoxi-6-(tiazol-2-il)-quinazolin-2-il-amino)-fenil)-acetamida;

5-(6-bromo-quinazolin-2-il-amino)-2-morfolino-benzamida;

5-(6-etinil-quinazolin-2-il-amino)-2-morfolino-benzamida;

N-(3-(6-etinil-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida;

N-(3-(pirrolidin-1-il-metil)-5-(6-(tiazol-2-il)-quinazolin-2-il-amino)-fenil)-acetamida;

N-(3-(6-etinil-quinazolin-2-il-amino)-5-(pirrolidin-1-il-metil)-fenil)-acetamida;

N-(3-(6-bromo-8-cloro-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida;

N-(3-(8-cloro-6-etinil-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida;

N,N'-(5-(5-cloro-6-etinil-quinazolin-2-il-amino)-1,3-fenileno)-diacetamida;

N-(6-cloro-1H-indazol-4-il)-6-etinil-quinazolin-2-amina;

6-etinil-N-(6-fluoro-1H-indazol-4-il)-quinazolin-2-amina;

N-(3-(morfolino-metil)-5-(6-(tiazol-2-il)-quinazolin-2-il-amino)-fenil)-acetamida;

7-metoxi-N-(4-morfolino-fenil)-6-(tiazol-2-il)-quinazolin-2-amina;

N-(3-(6-bromo-8-fluoro-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-acetamida;

N-(3-(6-(isoxazol-4-il)-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida;

N-(3-(amino-metil)-5-(6-etinil-quinazolin-2-il-amino)-fenil)-acetamida;

6-etinil-N-fenil-quinazolin-2-amina;

N-(3-((dimetil-amino)-metil)-5-(6-etinil-8-fluoro-quinazolin-2-il-amino)-fenil)-acetamida;

N-(3-(7-metoxi-6-(tiazol-2-il)-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida;

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N-(3-(6-etinil-quinazolin-2-il-amino)-5-(piperazin-1-il-metil)-fenil)-acetamida;

N-(3-(6-etinil-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-isobutiramida;

N-(3-(6-etinil-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-metan-sulfonamida;

6-bromo-N-(3-(morfolino-metil)-5-(1H-tetrazol-5-il)-fenil)-quinazolin-2-amina;

N-(3-(6-bromo-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida;

N-(3-(6-etinil-quinazolin-2-il-amino)-5-(piridin-4-il)-fenil)-acetamida;

N-(3-(6-bromo-quinazolin-2-il-amino)-5-((dimetil-amino)-metil)-fenil)-acetamida;

N-(3-((dimetil-amino)-metil)-5-(6-(prop-1-inil)-quinazolin-2-il-amino)-fenil)-acetamida;

6-etinil-N-(3-(morfolino-metil)-5-(1H-tetrazol-5-il)-fenil)-quinazolin-2-amina;

7-metoxi-N-(4-morfolino-fenil)-6-(1H-pirazol-4-il)-quinazolin-2-amina;

3-(6-bromo-quinazolin-2-il-amino)-5-(morfolino-metil)-benzonitrilo;

3-(6-etinil-quinazolin-2-il-amino)-5-(morfolino-metil)-benzonitrilo;

N-(3-(6-bromo-quinazolin-2-il-amino)-5-(1H-pirazol-4-il)-

fenil)-acetamida;

6-bromo-N-(3-metoxi-5-(5-metil-1H-tetrazol-1-il)-fenil)-quinazolin-2-amina;

6-bromo-N-(3-metoxi-5-(1H-tetrazol-1-il)-fenil)-quinazolin-2-amina;

6-etinil-N-(3-metoxi-5-(5-metil-1H-tetrazol-1-il)-fenil)-quinazolin-2-amina;

6-etinil-N-(3-morfolino-5-(piridin-4-il)-fenil)-quinazolin-2-amina;

6-etinil-N-(3-morfolino-5-(1H-pirazol-4-il)-fenil)-quinazolin-2-amina;

6-etinil-N-(3-morfolino-5-(piridin-3-il)-fenil)-quinazolin-2-amina;

6-etinil-N-(3-(3-fluoro-piridin-4-il)-5-morfolino-fenil)-quinazolin-2-amina;

N-(3-(6-etinil-5-fluoro-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida;

N-(3-(6-etinil-5-fluoro-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-metan-sulfonamida;

3-(6-bromo-quinazolin-2-il-amino)-5-(morfolino-metil)-benzamida;

N-(3-(6-etinil-quinazolin-2-il-amino)-5-(1H-pirazol-4-il)-fenil)-acetamida;

N-(3-(6-etinil-quinazolin-2-il-amino)-5-(pirimidin-5-il)-fenil)-acetamida;

3-(6-etinil-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil-carbamato de metilo;

3-(6-bromo-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil-carbamato de metilo;

N-(4-morfolino-fenil)-5,6-di-(tiazol-2-il)-quinazolin-2-amina;

8-metoxi-N-(4-morfolino-fenil)-5,6-di-(tiazol-2-il)-quinazolin-2-amina;

(4-(8-metoxi-5,6-di-(tiazol-2-il)-quinazolin-2-il-amino)-fenil)-(morfolino)-metanona;

4-(5,6-di-(tiazol-2-il)-quinazolin-2-il-amino)-N-isopropil-benzamida;

6-etinil-7-metoxi-N-(3-metoxi-5-(5-metil-1H-tetrazol-1-il)-fenil)-quinazolin-2-amina;

6,7-dimetoxi-N-(4-morfolino-fenil)-quinazolin-2-amina;

N-(3-(6,7-dimetoxi-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida;

N-(3-(7-metoxi-6-(1H-pirazol-4-il)-quinazolin-2-il-amino)-5-(morfolino-metil)-fenil)-acetamida; y

N-(3-(7-metoxi-6-(1H-pirazol-4-il)-quinazolin-2-il-amino)-5-(1H-pirazol-4-il)-fenil)-acetamida;

o una sal farmacéuticamente aceptable, éster, o tautómero de uno de estos compuestos.

34. El compuesto de la reivindicación 1, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, el cual

se selecciona a partir de los compuestos en la Tabla 2 (Figura 1).

35. El compuesto de la reivindicación 1, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo, el cual se selecciona a partir de los compuestos en la Tabla 3 (Figura 2).

36. Una composición farmacéutica, la cual comprende un vehículo farmacéuticamente aceptable, y cuando menos un compuesto de acuerdo con cualquiera de las reivindicaciones anteriores, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo.

37. Un método para inhibir la PDK1 o una variante de PDK1 en un paciente, el cual comprende administrar a este paciente, una cantidad terapéuticamente efectiva de un compuesto de cualquiera de las reivindicaciones 1 a 31, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo.

38. El método de la reivindicación 37, el cual comprende un método para inhibir PDK1.

39. El método de la reivindicación 37, el cual comprende un método para inhibir una variante de PDK1.

40. El método de la reivindicación 37, en donde la variante de PDK1 mencionada es $PDK1^{T354M}$ o $PDK1^{D527E}$.

41. Un método para el tratamiento de una enfermedad caracterizada por una proliferación celular anormal en un paciente, el cual comprende administrar a este paciente, una cantidad terapéuticamente efectiva de un compuesto de cualquiera de las reivindicaciones 1 a 35, o una sal farmacéuticamente aceptable,

éster, o tautómero del mismo.

42. El método de la reivindicación 41, en donde la proliferación celular anormal es mediada por PDK1.

43. El método de la reivindicación 41, en donde la enfermedad es un cáncer.

44. El método de la reivindicación 43, en donde el cáncer se selecciona a partir del grupo que consiste en: cáncer de pulmón, cáncer bronquial, cáncer de próstata, cáncer de mama, cáncer pancreático, cáncer de colon, cáncer rectal, cáncer colo-rectal, cáncer de tiroides, cáncer de hígado, cáncer intrahepático del conducto biliar, cáncer hepatocelular, cáncer gástrico, glioma/ glioblastoma, cáncer endometrial, melanoma, cáncer de riñón, cáncer pélvico renal, cáncer de vejiga urinaria; cáncer de cuerpo uterino; cáncer cervical uterino, cáncer de ovario, mieloma múltiple, cáncer esofágico, leucemia mielógena aguda, leucemia mielógena crónica, leucemia linfocítica, leucemia mieloide, cáncer de cerebro, cáncer de la cavidad oral, y cáncer faríngeo, cáncer laríngeo, cáncer del intestino delgado, linfoma no de Hodgkin, y adenoma de colon velloso.

45. El método de la reivindicación 44, en donde el cáncer se selecciona a partir del grupo que consiste en cánceres de próstata, pulmón, colon, y mama.

46. El método de la reivindicación 41, en donde la enfermedad es un trastorno proliferativo que no es cáncer.

47. El método de la reivindicación 46, en donde la

enfermedad se selecciona a partir del grupo que consiste en neurofibromatosis, ateroesclerosis, fibrosis pulmonar, artritis, soriasis, glomerulonefritis, restenosis, retinopatía diabética proliferativa, formación de cicatriz hipertrófica, enfermedad inflamatoria del intestino, rechazo de trasplante, angiogénesis, y choque endotóxico.

48. Un método para inhibir el crecimiento tumoral en un paciente, comprendiendo el método administrar a este paciente, una cantidad terapéuticamente efectiva de un compuesto de cualquiera de las reivindicaciones 1 a 31, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo.

49. El método de la reivindicación 48, en donde el tumor mencionado se caracteriza por una actividad elevada de las cinasas de tirosina receptoras, Ras, PI3K, PDK1, AKT, RSK, PKC, 70S6K, o SGK.

50. Un método para el tratamiento de cáncer en un paciente, comprendiendo el método administrar a este paciente, una cantidad terapéuticamente efectiva de un compuesto de cualquiera de las reivindicaciones 1 a 31, o una sal farmacéuticamente aceptable, éster, o tautómero del mismo.

51. El método de la reivindicación 50, en donde el cáncer mencionado se caracteriza por un aumento de actividad de PDK1.

52. El método de la reivindicación 49, en donde el cáncer mencionado se caracteriza por la actividad de una variante de PDK1.

53. El método de la reivindicación 52, en donde la variante de PDK1 mencionada es $PDK1^{T354M}$ o $PDK1^{D527E}$.

RESUMEN

La invención proporciona compuestos novedosos que son inhibidores de PDK1. También se proporcionan composiciones farmacéuticas que incluyen a los compuestos, y métodos para el tratamiento de enfermedades proliferativas, tales como cánceres, con los compuestos o composiciones.

* * * * *

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Tabla 2

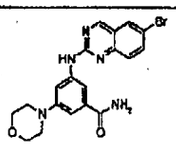
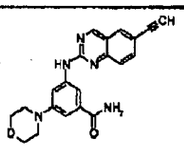
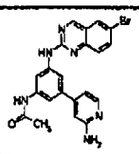
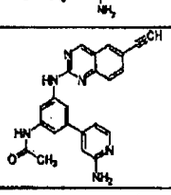
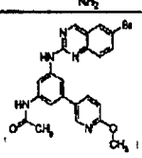
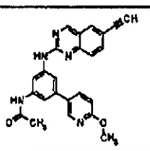
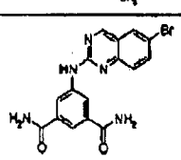
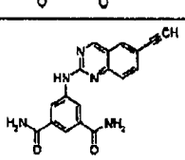
Ejemplo	Estructura	Actividad	Peso Molecular	LC/MS (ejecución 4.5 min) MS (M+1) m/z Rt (min)	LC/MS (ejecución 1.5 min) MS (M+1) m/z Rt (min)
177		*	428.2682	428/430 3.84	
178		***	373.4141	374.1 3.51	
179		**	449.3103	249/251 3.66	
180		***	394.4362	395.1 3.39	
181		*	464.3212	464/466 4.92	
182		***	409.4471	410.1 4.57	
183		*	386.2078	386/388 3.16	
184		**	331.3337	332.1 2.88	

FIG. 1
(Parte 1 de 59)

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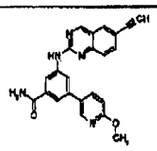
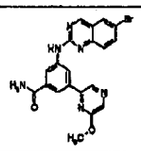
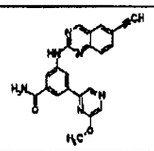
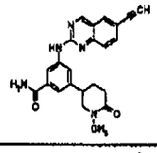
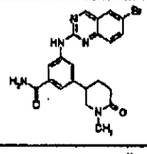
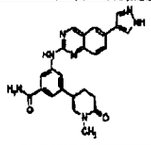
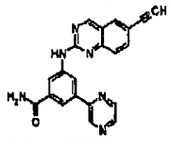
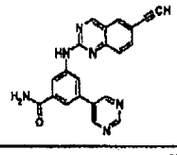
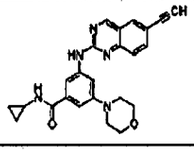
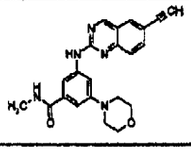
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186		*	451.2825	451/453 4.82	
187		*	396.4084	397.1 4.44	
188		****	399.4519	400.1 3.35	
189		**	454.326	454/456 3.64	
190		****	441.4927	442.1 2.51	
191		*	366.3826	367.1 3.77	
192		*	366.3826	367.1 3.56	
193		**	413.4787	414.1 4.14	
194		**	387.4409	388.1 3.74	

FIG. 1
(Parte 2 de 59)

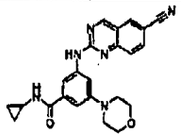
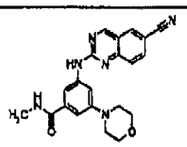
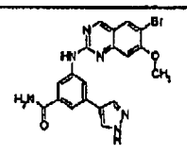
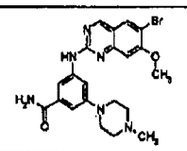
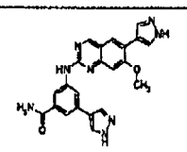
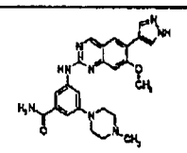
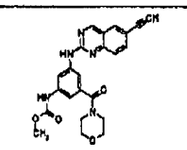
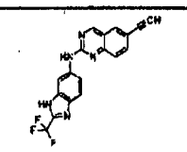
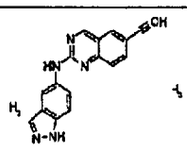
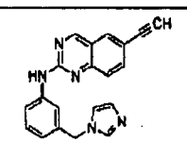
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196		*	388.429	389.1 3.49	
197		*	439.2715	438.9/441 2.2	
198		*	471.3567	471/473 1.9	
199		***	426.4382	427.1 1.7	
200		**	458.5234	459.1 1.6	
201		**	431.4499	432.1 2.4	
202		**	353.306	354.1 2.6	
203		**	285.3089	286.2 2.18	
204		*	325.3735	326.1 1.89	

FIG. 1
(Parte 3 de 59)

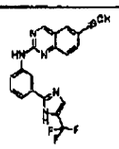
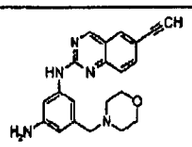
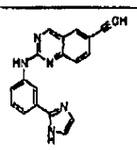
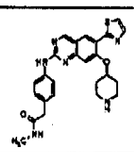
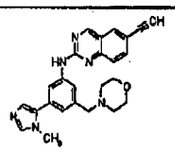
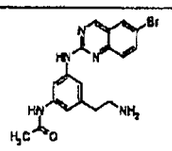
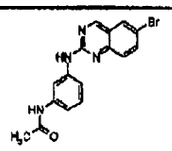
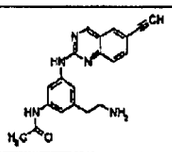
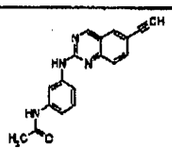
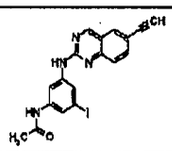
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206		****	359.4309	360.1 1.87	
207		*	311.3467	312 2.1	
208		****	474.5864	475.2 1.8	
209		*	424.5056	425.2 1.89	
210		***	400.2782	400/402 2.03	
211		***	357.2097	357/359 2.63	
212		****	345.4041	346 1.94	
213		****	302.3356	303 2.38	
214		***	428.2277	428.8 2.94	

FIG. 1
(Parte 4 de 59)

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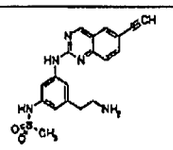
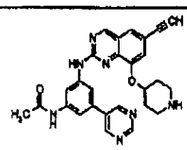
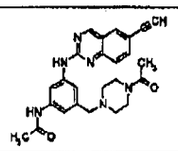
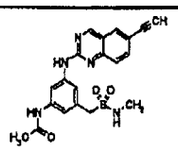
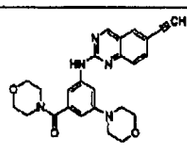
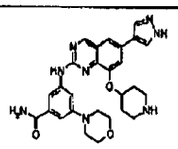
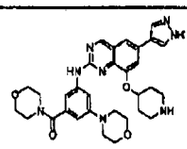
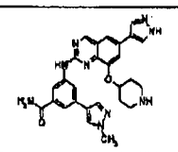
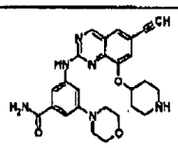
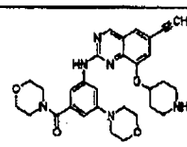
215		****	381.4581	381.9 2.03	
216		****	479.5415	480.0 2.05	
217		***	442.5204	443 1.98	
218		*	409.4681	410 2.26	
219		*	443.5045	444 2.42	
220		**	514.587	515 1.79	
221		**	584.6774	585 1.90	
222		**	509.5713	510 1.83	
223		***	472.5462	473 1.98	
224		*	542.6366	543 2.11	

FIG. 1
(Parte 5 de 59)

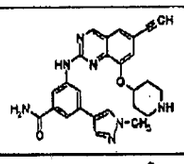
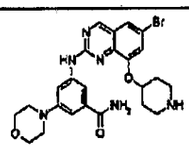
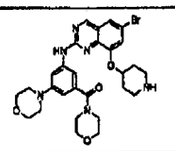
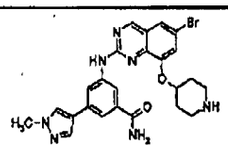
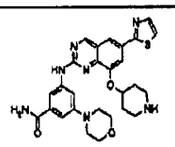
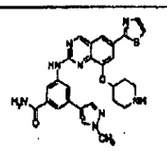
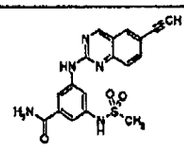
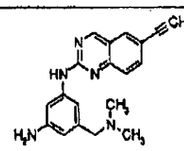
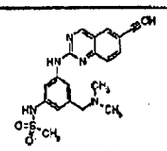
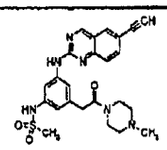
225		****	467.5305	468 2.01	
226		*	527.4203	527/529 2.03	
227		*	597.5107	597/599 2.16	
228		**	522.4046	522/524 2.07	
229		*	531.6381	532 2.09	
230		*	526.6224	527 2.13	
231		**	381.4145	381.9 2.18	
232		****	317.3941	318.1 1.74	
233		***	395.4849	396 2.03	
234		***	478.5744	479 2.01	

FIG. 1
(Parte 6 de 59)

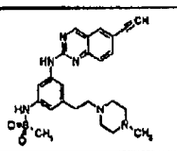
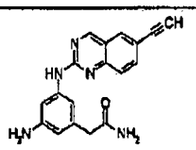
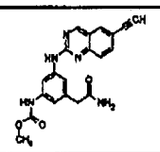
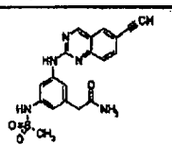
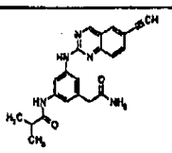
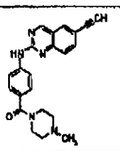
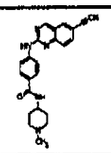
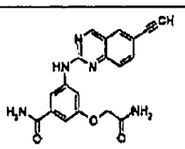
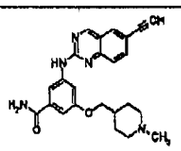
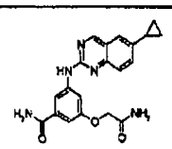
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236		****	317.3505	318 0.61	
237		****	375.3863	376 0.61	
238		****	395.4413	396 0.60	
239		****	387.4409	388 0.60	
240		*	371.4419	372 2.03	
241		**	385.4687	386.1 2.11	
242		****	361.3595	362.1 2.14	
243		**	415.4945	416.0 2.16	
244		**	377.4021	378.1 2.07	

FIG. 1
(Parte 7 de 59)

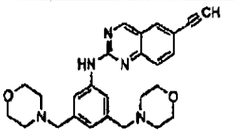
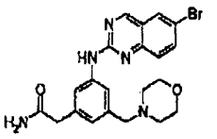
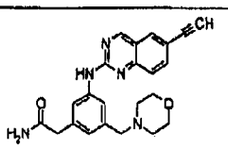
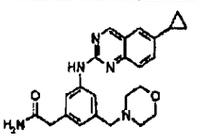
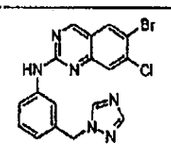
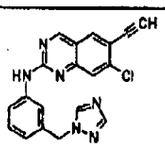
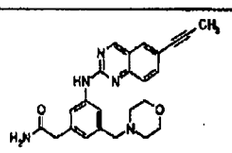
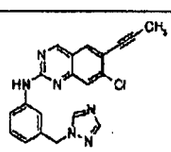
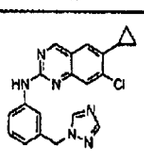
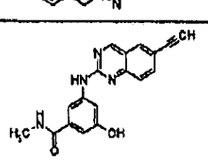
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246		**	456.3418	456/458 0.78	
247		****	401.4677	402.1 0.57	
248		*	417.5103	418.2 0.59	
249		*	415.6808	416.9 0.92	
250		***	360.8067	361.0 0.84	
251		****	415.4945	416.1 0.70	
252		**	374.8335	375.0 1.02	
253		*	376.8493	377.1 1.03	
254		***	318.3346	319.2 2.16	

FIG. 1
(Parte 8 de 59)

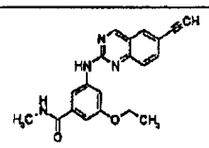
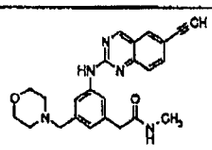
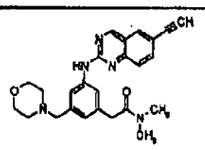
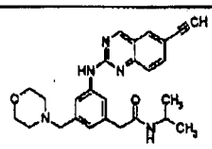
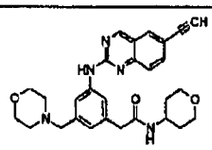
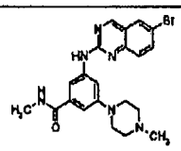
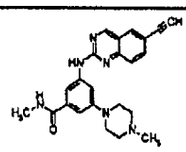
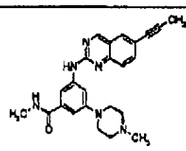
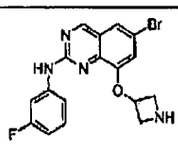
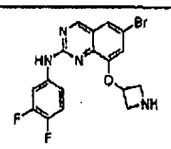
255		**	346.3882	347.2 2.72	
256		***	415.4945	416.2 2.01	
257		***	429.5213	430.2 2.17	
258		***	443.5481	444.1 2.27	
259		***	485.5849	486.2 2.14	
260		**	455.3577	455/457 0.61	
261		****	400.4836	401.2 0.56	
262		***	414.5104	415.2 0.61	
263		*	389.2266	389/391 0.71	
264		*	407.2167	407/409 0.73	

FIG. 1
(Parte 9 de 59)

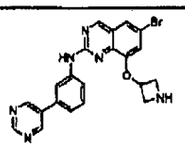
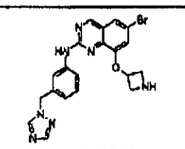
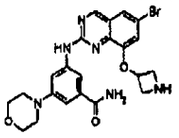
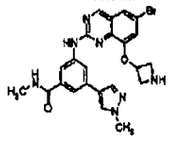
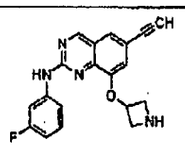
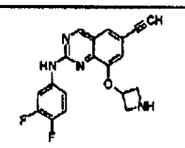
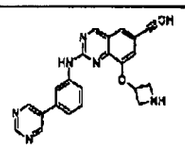
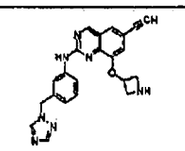
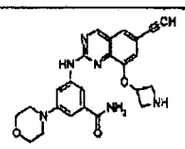
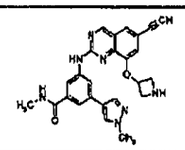
265		*	449.3103	449/451 0.63	
266		**	452.3142	452/454 0.58	
267		*	499.3667	499/501 0.56	
268		*	508.3778	508/510 0.60	
269		***	334.3525	335.1 0.67	
270		**	352.3426	353.1 0.69	
271		**	394.4362	395.1 0.60	
272		***	397.4401	398.2 0.54	
273		**	444.4926	445.2 0.52	
274		**	453.5037	454.2 0.57	

FIG. 1
(Parte 10 de 59)

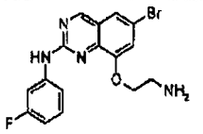
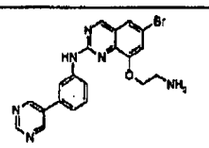
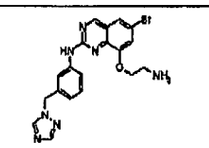
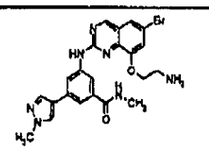
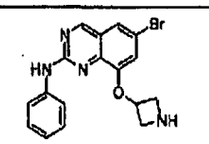
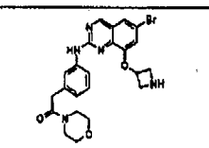
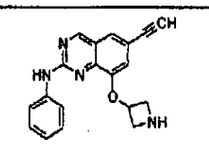
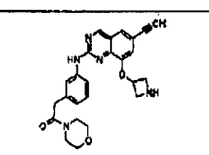
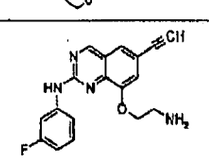
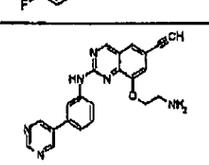
275		*	377.2156	377/379 0.73	
276		*	437.2993	437/439 0.66	
277		**	440.3032	440/442 0.60	
278		*	496.3668	496/498 0.62	
279		*	371.2365	371/373 0.70	
280		**	498.3786	498/500 0.62	
281		**	316.3624	317.1 0.67	
282		***	443.5045	444.1 0.61	
283		**	322.3415	323.1 0.70	
284		**	382.4252	383.1 0.63	

FIG. 1
(Parte 11 de 59)

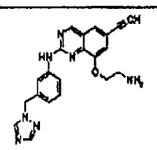
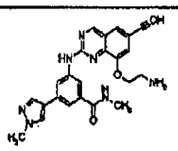
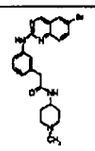
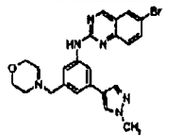
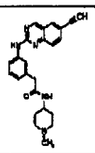
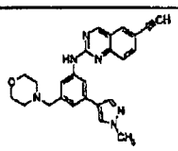
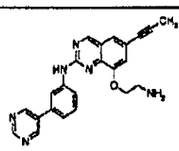
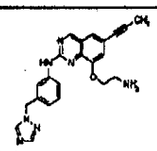
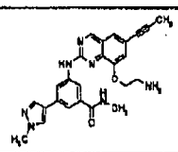
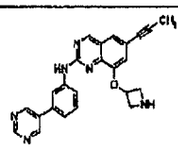
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286		**	441.4927	442.1 0.60	
287		*	454.3696	454/456 0.71	
288		**	479.3797	479/481 0.75	
289		*	399.4955	400.1 0.65	
290		***	424.5056	425.1 0.69	
291		*	396.452	397.1 0.71	
292		**	399.4559	400.1 0.65	
293		*	455.5195	456.1 0.67	
294		**	408.463	409.1 0.68	

FIG. 1
(Parte 12 de 59)

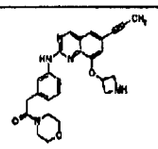
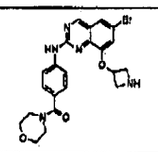
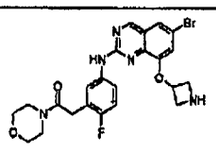
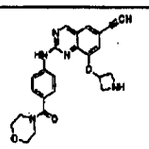
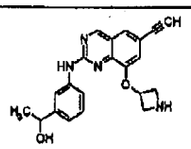
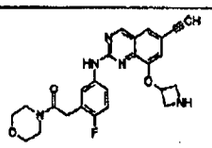
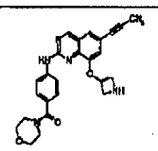
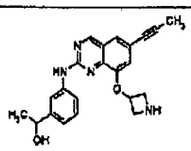
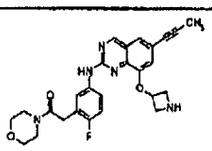
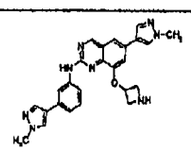
295		**	457.5313	458.1 0.65	
296		**	484.3518	484/486 0.66	
297		**	516.3687	516/518 0.68	
298		***	429.4777	430.1 0.60	
299		**	360.415	361.1 0.61	
300		***	461.4946	462.1 0.63	
301		**	443.5045	444.1 0.63	
302		N/A	374.4418	375.2 0.66	
303		**	475.5214	476.1 0.67	
304		*	452.5196	453.1 0.66	

FIG. 1
(Parte 13 de 59)

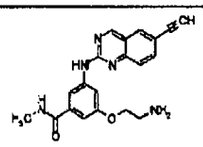
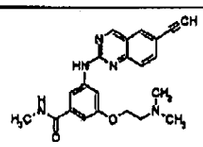
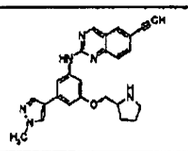
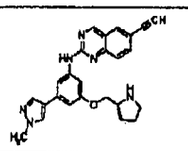
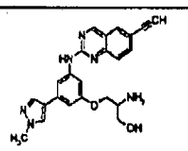
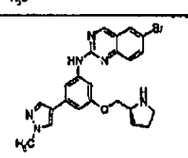
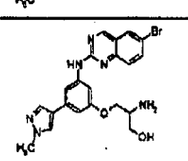
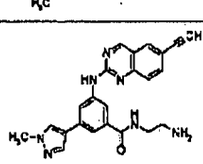
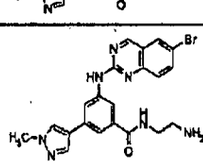
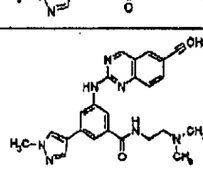
305		***	361.4031	362.0 0.59	
306		**	389.4567	390.1 0.60	
307		N/A	424.5056		
308		****	424.5056	425.1 0.68	
309		****	414.4668	415.1 0.62	
310		***	479.3797	479/481 0.73	
311		****	469.3409	469/471 0.68	
312		***	411.4669	412.1 0.62	
313		*	466.341	466/468 0.68	
314		****	439.5205	440.1 0.64	

FIG. 1
(Parte 14 de 59)

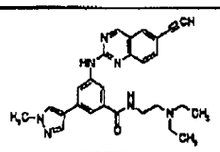
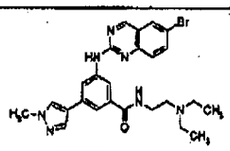
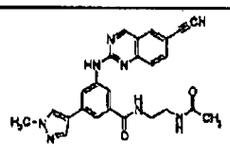
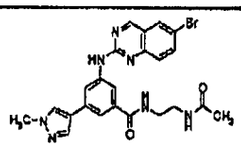
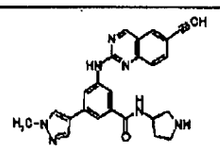
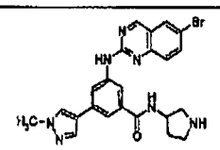
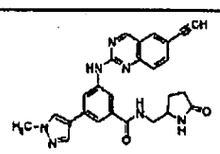
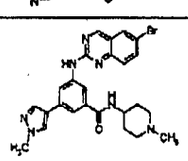
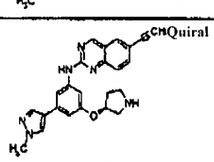
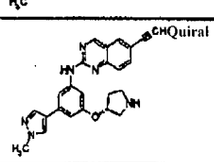
315		***	467.5741	468.2 0.68	
316		*	522.4482	522/524 0.73	
317		**	453.5037	454.1 0.68	
318		*	508.3778	508/510 0.74	
319		**	437.5047	438.1 0.64	
320		*	492.3788	492/494 0.69	
321		**	465.5147	466.2 0.68	
322		*	520.4324	520/522 0.70	
323		****	410.4788	411.1 0.67	
324		****	410.4788	411.1 0.67	

FIG. 1
(Parte 15 de 59)

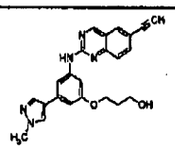
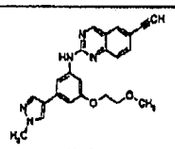
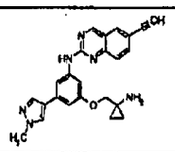
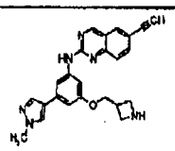
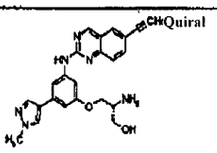
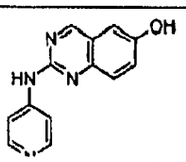
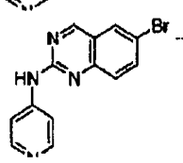
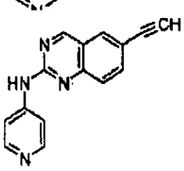
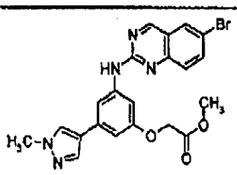
325		**	399.4519	400.1 0.78	
326		**	399.4519	400.0 0.88	
327		****	410.4788	411.1 0.67	
328		****	410.4788	411.1 0.67	
329		****	414.4668	415.1 0.62	
330		*	238.249	239.0 1.69	
331		*	301.1461	300.9/302.9 2.11	
332		*	246.272	247.1 2.03	
333		*	468.3092	468.0/470.0 3.00	

FIG. 1
(Parte 16 de 59)

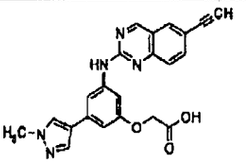
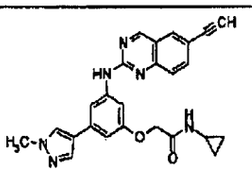
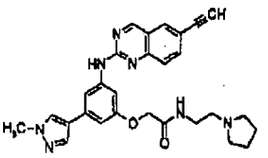
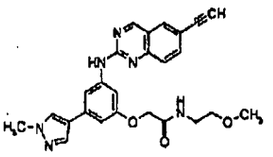
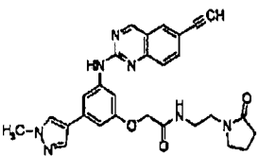
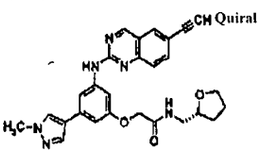
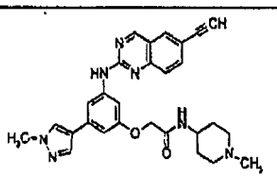
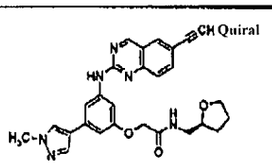
334		**	399.4083	400.1 2.48	
335		***	438.4888	439.2 2.62	
336		****	495.5841	496.2 2.28	
337		***	456.5036	457.2 2.54	
338		***	509.5673	510.2 2.39	
339		***	482.5414	483.2 2.63	
340		***	495.5841	496.2 2.22	
341		**	482.5414	483.2 2.62	

FIG. 1
(Parte 17 de 59)

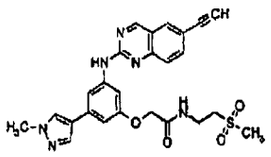
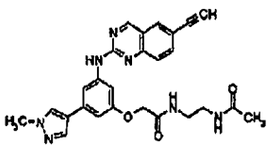
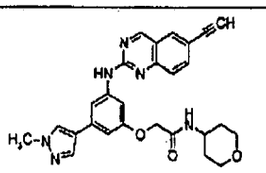
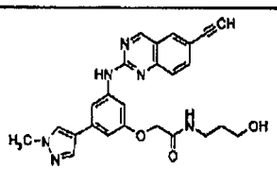
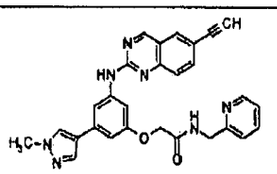
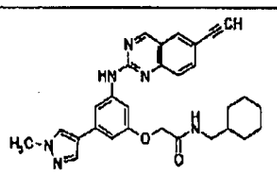
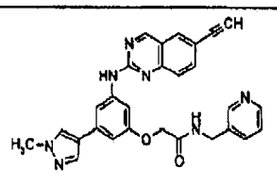
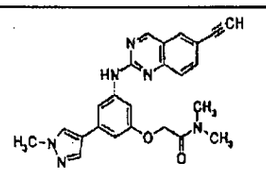
342		***	504.5686	505.2 2.41	
343		****	483.5295	484.2 2.30	
344		**	482.5414	483.2 2.53	
345		**	456.5036	457.2 2.36	
346		****	489.5367	490.2 2.26	
347		*	494.596	495.2 3.14	
348		****	489.5367	490.2 2.25	
349		**	426.4778	427.2 2.47	

FIG. 1
(Parte 18 de 59)

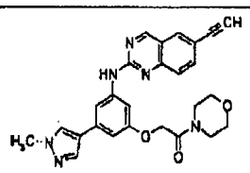
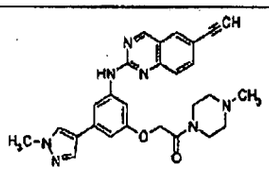
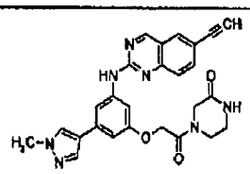
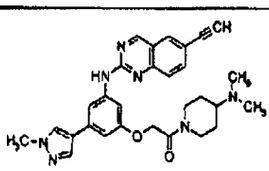
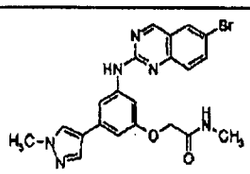
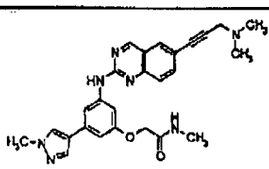
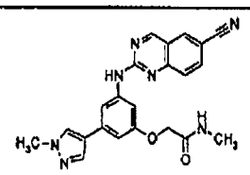
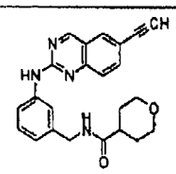
350		**	468.5146	469.2 2.47	
351		*	481.5573	482.2 2.18	
352		***	481.5137	482.2 2.23	
353		*	509.6109	510.3 2.21	
354		***	467.3251	467.1/469.1 2.61	
355		*	469.5463	470.2 1.96	
356		**	413.4391	414.2 2.33	
357		***	386.4528	387.2 2.41	

FIG. 1
(Parte 19 de 59)

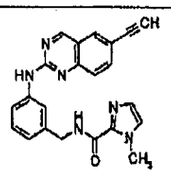
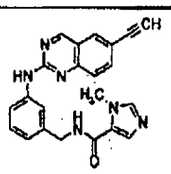
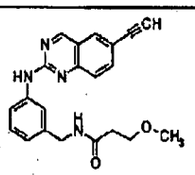
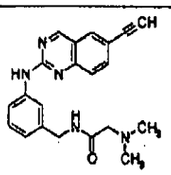
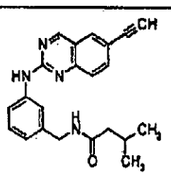
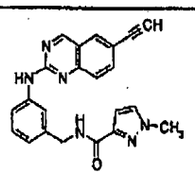
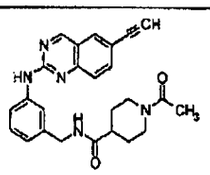
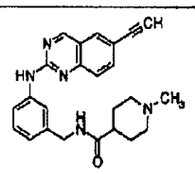
358		**	382.4252	383.2 2.34	
359		****	382.4252	383.2 2.21	
360		***	360.415	361.2 2.38	
361		****	359.4309	360.2 2.13	
362		**	358.4428	359.3 2.75	
363		**	382.4252	383.2 2.52	
364		***	427.5055	428.3 2.29	
365		**	399.4955	400.3 2.15	

FIG. 1
(Parte 20 de 59)

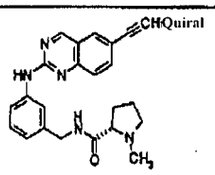
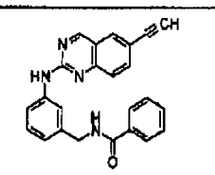
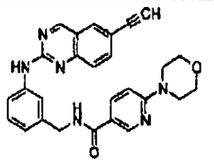
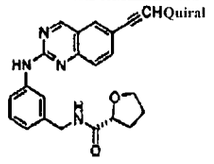
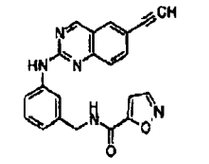
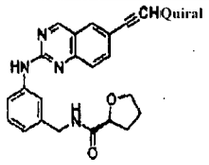
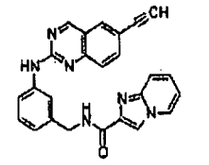
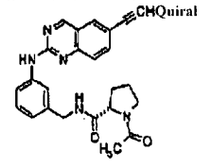
366		***	385.4687	386.3 2.19	
367		**	378.4332	379.2 2.83	
368		****	464.5266	465.2 2.30	
369		***	372.426	373.2 2.56	
370		***	369.3825	370.2 2.60	
371		**	372.426	373.2 2.55	
372		****	418.4582	419.2 2.31	
373		**	413.4787	414.2 2.30	

FIG. 1
(Parte 21 de 59)

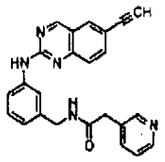
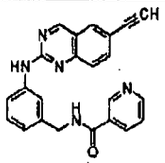
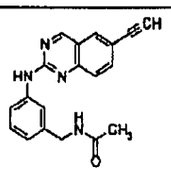
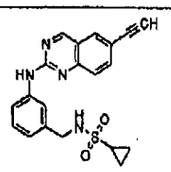
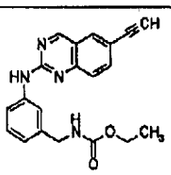
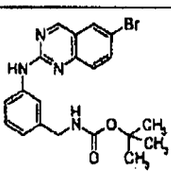
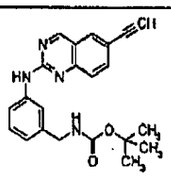
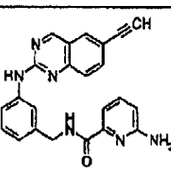
374		**	393.4481	394.2 2.17	
375		***	379.4213	380.2 2.26	
376		***	316.3624	317.2 2.29	
377		***	378.4542	379.2 2.71	
378		***	346.3882	347.1 2.78	
379		*	429.3159	429.1/431.2 3.41	
380		**	374.4418	375.2 3.20	
381		*	394.4362	395.2 2.36	

FIG. 1
(Parte 22 de 59)

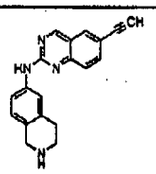
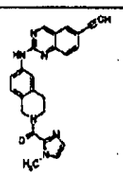
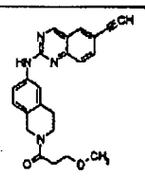
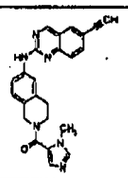
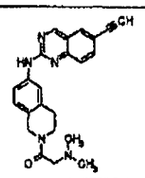
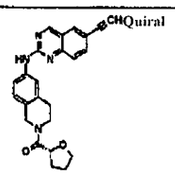
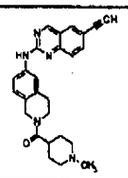
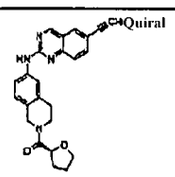
382		**	300.3634	301.2 2.05	
383		***	408.463	409.2 2.26	
384		***	386.4528	387.3 2.56	
385		**	408.463	409.2 2.24	
386		**	385.4687	386.3 2.17	
387		****	398.4638	399.2 2.61	
388		**	425.5333	426.3 2.20	
389		**	398.4638	399.2 2.61	

FIG. 1
(Parte 23 de 59)

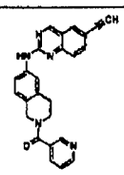
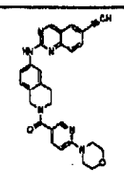
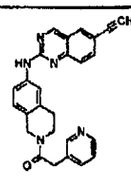
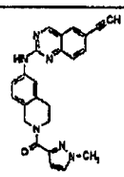
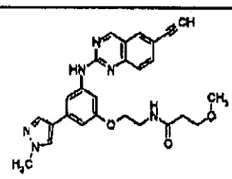
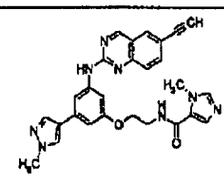
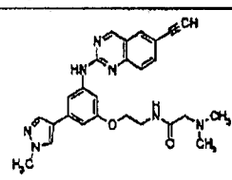
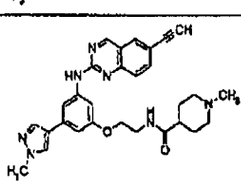
390		***	405.4591	406.2 2.27	
391		**	490.5644	491.2 2.37	
392		***	419.4859	420.2 2.21	
393		***	408.463	409.2 2.60	
394		***	470.5304	471.3 2.48	
395		***	492.5406	493.2 2.29	
396		***	469.5463	470.3 2.24	
397		****	509.6109	510.3 2.24	

FIG. 1
(Parte 24 de 59)

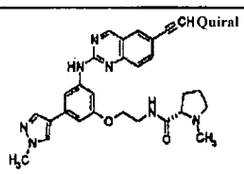
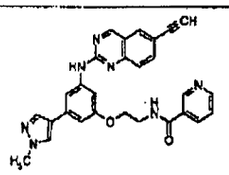
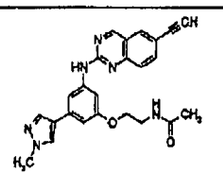
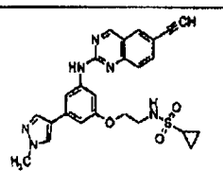
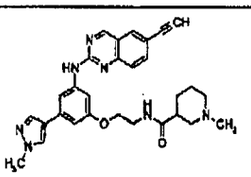
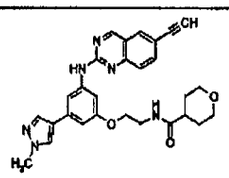
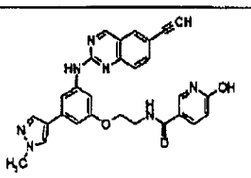
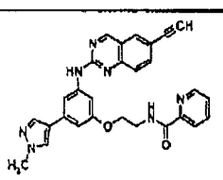
398		***	495.5841	496.3 2.28	
399		***	489.5367	490.2 2.32	
400		****	426.4778	427.3 2.42	
401		***	488.5696	489.2 2.72	
402		***	509.6109		510.3 0.66
403		***	496.5682		497.2 0.73
404		****	505.5357		506.1 0.67
405		***	489.5367		490.2 0.83

FIG. 1
(Parte 25 de 59)

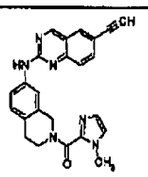
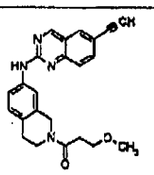
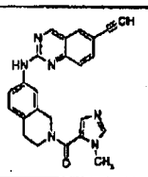
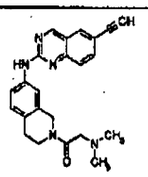
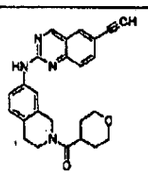
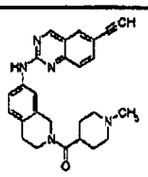
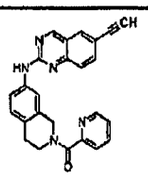
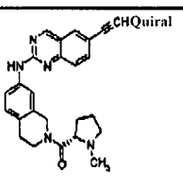
406		**	408.463		409.1 0.69
407		**	386.4528		387.2 0.81
408		**	408.463		409.2 0.68
409		**	385.4687		386.2 0.66
410		**	412.4906		413.2 0.82
411		**	425.5333		426.2 0.68
412		**	405.4591		406.1 0.80
413		**	411.5065		412.1 0.69

FIG. 1
(Parte 26 de 59)

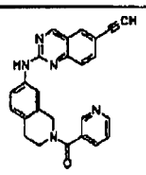
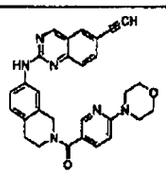
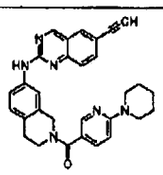
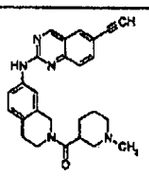
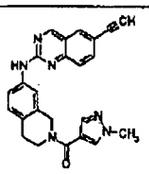
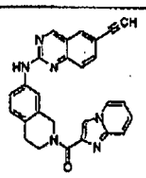
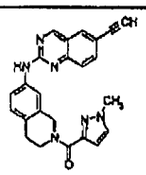
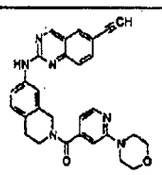
414		**	405.4591		406.1 0.69
415		*	490.5644		491.1 0.73
416		*	488.5922		489.1 0.77
417		**	425.5333		426.2 0.70
418		***	408.463		409.1 0.77
419		**	444.496		445.1 0.70
420		**	408.463		409.1 0.82
421		*	490.5644		491.1 0.72

FIG. 1
(Parte 27 de 59)

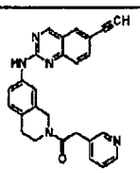
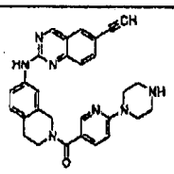
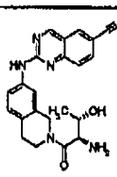
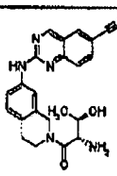
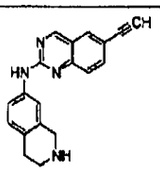
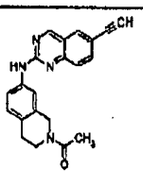
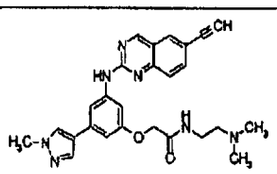
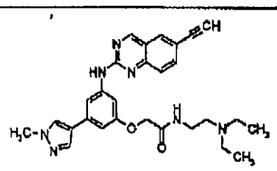
422		***	419.4859		420.1 0.68
423		**	489.5803		490.2 0.68
424		**	401.4677		402.2 0.64
425		**	401.4677		402.2 0.64
426		**	300.3634		301.1 0.59
427		**	342.4002		343.1 0.75
428		***	469.5463		470.2 0.68
429		***	497.5999		498.3 0.71

FIG. 1
(Parte 28 de 59)

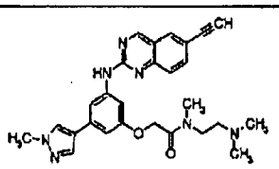
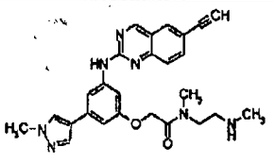
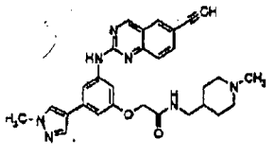
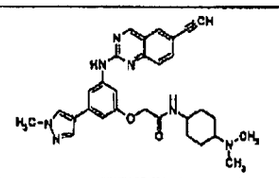
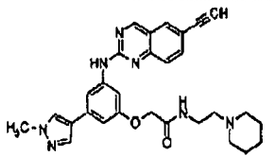
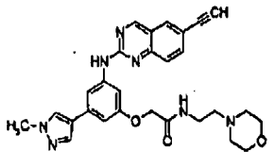
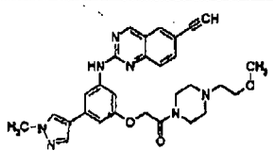
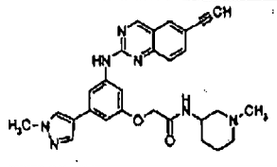
430		**	483.5731		484.3 0.68
431		**	469.5463		470.2 0.67
432		***	509.6109		510.3 0.69
433		**	523.6377		524.3 0.70
434		***	509.6109		510.3 0.72
435		***	511.5831		512.3 0.69
436		*	525.6099		526.3 0.69
437		**	495.5841		496.2 0.69

FIG. 1
(Parte 29 de 59)

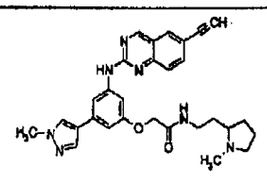
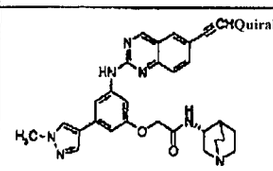
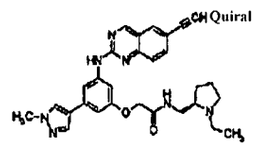
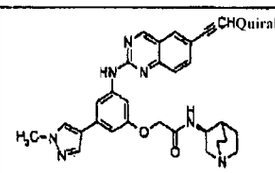
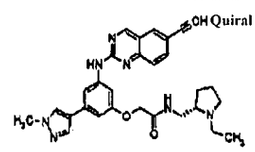
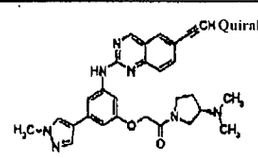
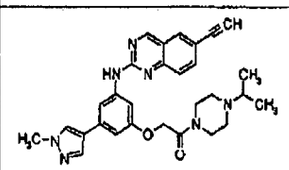
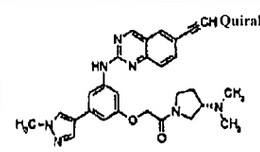
438		**	509.6109		510.3 0.70
439		**	507.5951		508.3 0.69
440		***	509.6109		510.3 0.72
441		**	507.5951		508.3 0.69
442		***	509.6109		510.3 0.72
443		*	495.5841		496.2 0.66
444		*	509.6109		510.3 0.70
445		*	495.5841		496.3 0.66

FIG. 1
(Parte 30 de 59)

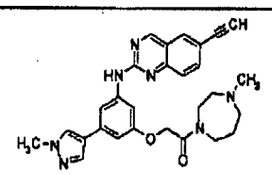
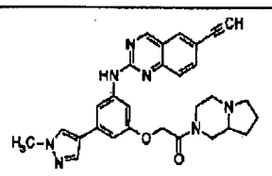
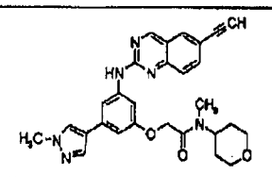
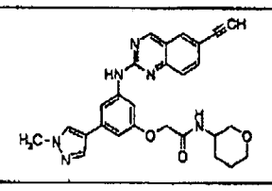
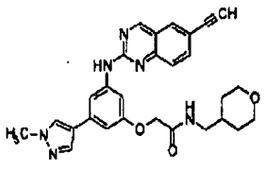
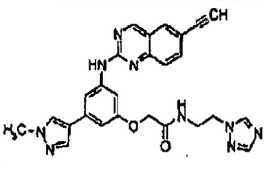
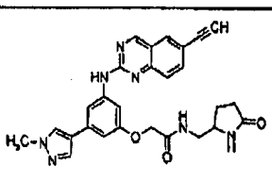
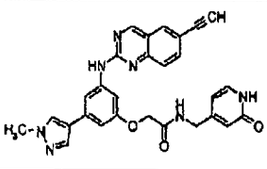
446		*	495.5841		496.2 0.67
447		*	507.5951		508.3 0.69
448		*	496.5682		497.2 0.81
449		**	482.5414		483.2 0.83
450		***	496.5682		497.2 0.81
451		***	493.5287		494.2 0.71
452		****	495.5405		496.2 0.71
453		****	505.5357		506.2 0.70

FIG. 1
(Parte 31 de 59)

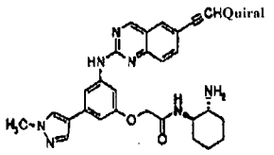
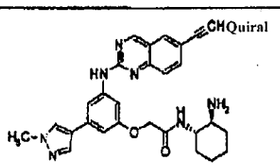
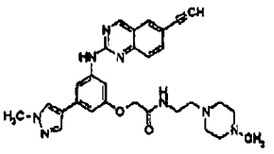
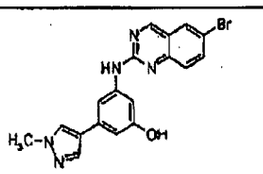
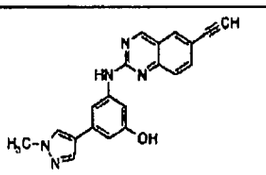
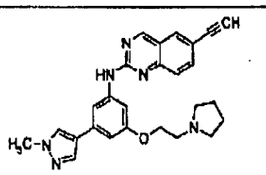
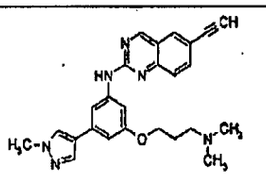
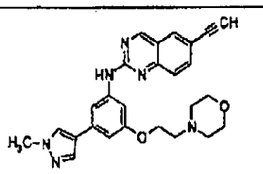
454		****	495.5841		496.2 0.73
455		**	495.5841		496.2 0.73
456		***	524.6258		525.3 0.66
457		**	396.2466		396.0/398.0 1.01
458		***	341.3725		342.1 0.72
459		****	438.5324		439.2 0.69
460		***	426.5214		427.2 0.68
461		**	454.5314		455.2 0.67

FIG. 1
(Parte 32 de 59)

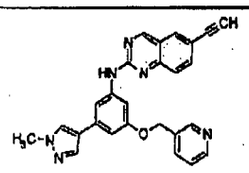
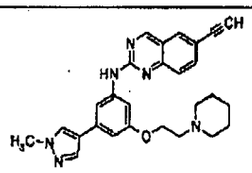
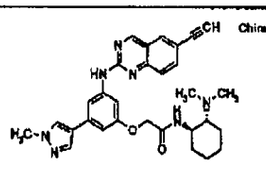
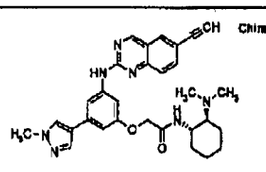
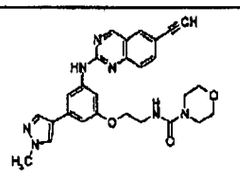
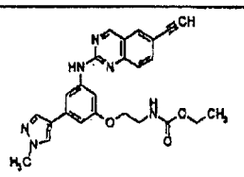
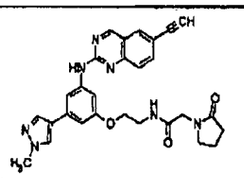
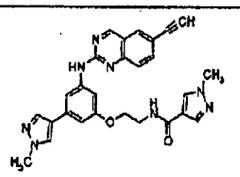
462		**	432.485		433.2 0.70
463		***	452.5592		453.2 0.71
464		****	523.6377		524.3 0.73
465		**	523.6377		524.3 0.73
466		**	497.5563		498.3 0.75
467		**	456.5036		457.2 0.87
468		***	509.5673		510.3 0.72
469		***	492.5406		493.2 0.74

FIG. 1
(Parte 33 de 59)

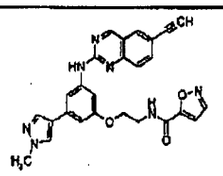
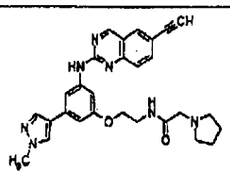
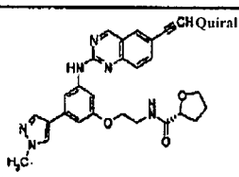
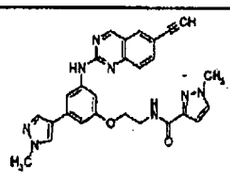
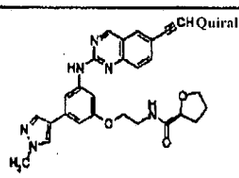
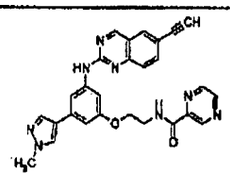
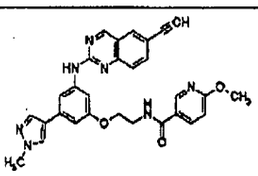
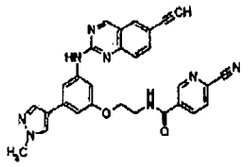
470		***	479.4979		480.2 0.80
471		***	495.5841		496.3 0.68
472		**	482.5414		483.1 0.81
473		**	492.5406		493.1 0.80
474		**	482.5414		483.1 0.81
475		**	490.5248		491.1 0.81
476		*	519.5625		520.2 0.84
477		***	514.5468		515.2 0.84

FIG. 1
(Parte 34 de 59)

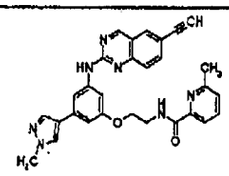
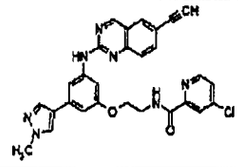
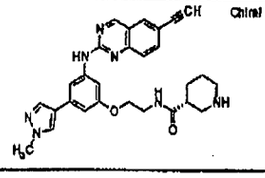
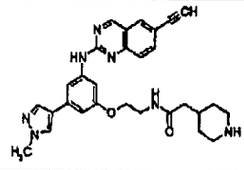
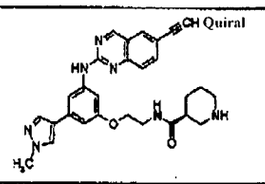
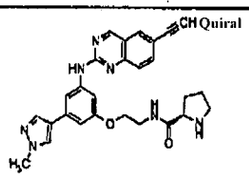
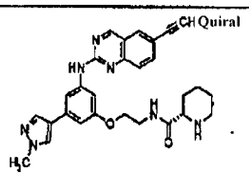
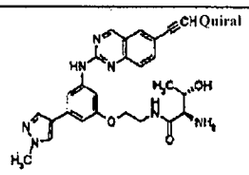
478		*	503.5635		504.2 0.88
479		*	523.9818		524.2 0.96
480		***	495.5841		496.2 0.69
481		***	509.6109		510.3 0.68
482		***	495.5841		496.2 0.69
483		***	481.5573		482.2 0.69
484		***	495.5841		496.2 0.70
485		***	485.5453		486.3 0.66

FIG. 1
(Parte 35 de 59)

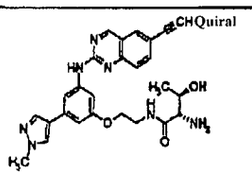
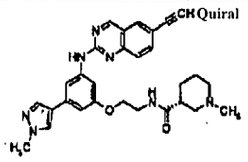
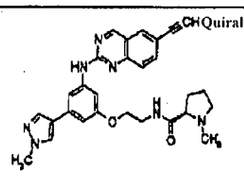
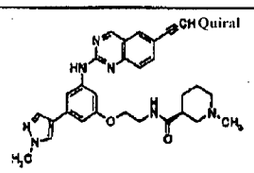
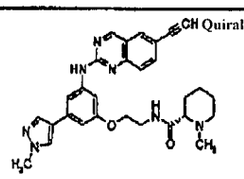
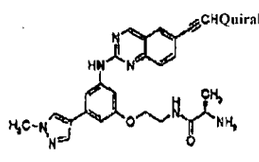
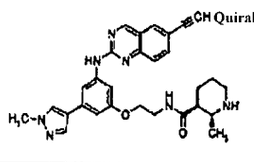
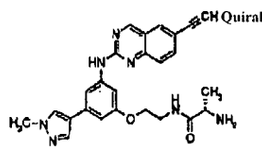
486		**	485.5453		486.3 0.66
487		***	509.6109		510.3 0.69
488		***	495.5841		496.2 0.69
489		***	509.6109		510.3 0.69
490		***	509.6109		510.3 0.70
491		***	455.5195		456.1 0.65
492		****	509.6109		510.2 0.68
493		***	455.5195		456.0 0.65

FIG. 1
(Parte 36 de 59)

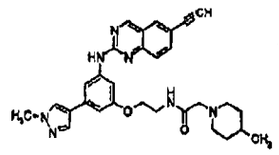
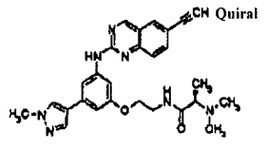
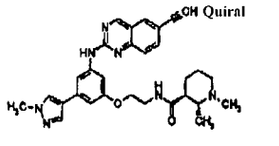
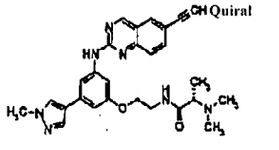
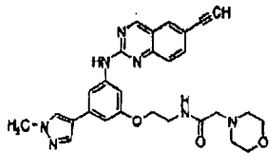
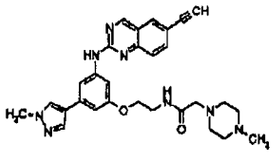
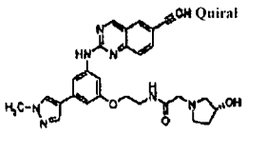
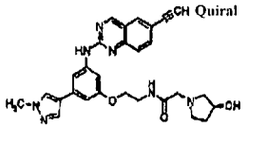
494		***	523.6377		524.2 0.72
495		**	483.5731		484.2 0.66
496		***	523.6377		524.3 0.67
497		***	483.5731		484.2 0.66
498		***	511.5831		512.3 0.65
499		**	524.6258		525.3 0.64
500		***	511.5831		512.2 0.64
501		***	511.5831		512.2 0.64

FIG. 1
(Parte 37 de 59)

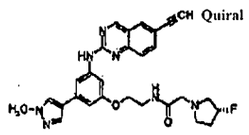
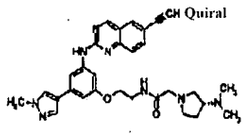
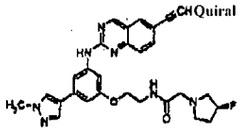
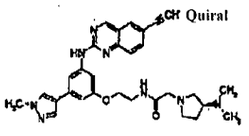
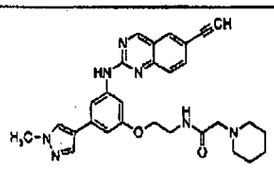
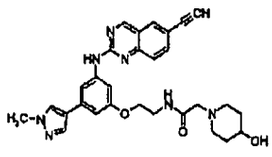
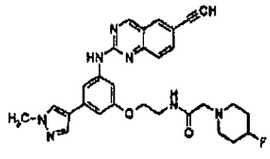
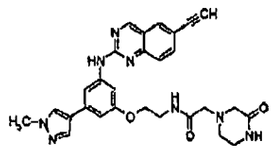
502		***	513.5742		514.2 0.66
503		**	538.6526		539.3 0.61
504		***	513.5742		514.3 0.66
505		***	538.6526		539.3 0.61
506		***	509.6109		510.3 0.68
507		***	525.6099		526.3 0.63
508		***	527.601		528.3 0.68
509		***	524.5822		525.3 0.62

FIG. 1
(Parte 38 de 59)

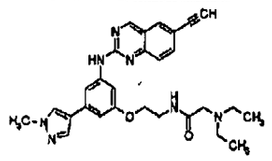
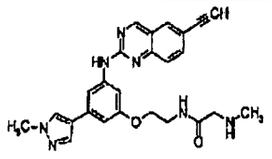
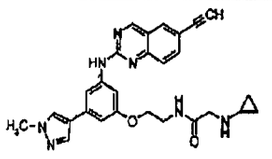
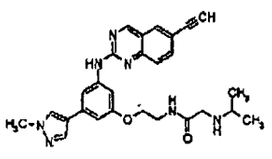
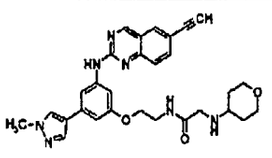
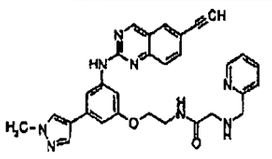
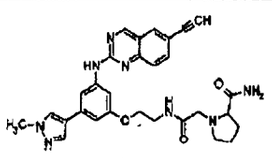
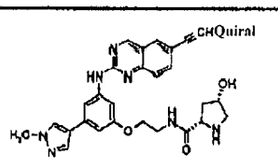
510		***	497.5999		498.3 0.67
511		***	455.5195		456.2 0.63
512		***	481.5573		482.2 0.66
513		***	483.5731		484.2 0.66
514		***	525.6099		526.3 0.65
515		***	532.6052		533.3 0.67
516		***	538.609		539.3 0.64
517		***	497.5563		498.2 0.63

FIG. 1
(Parte 39 de 59)

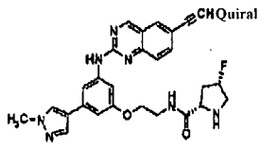
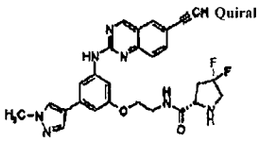
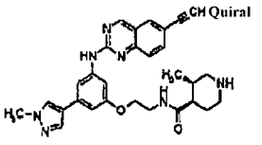
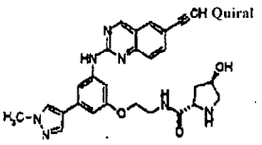
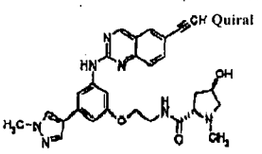
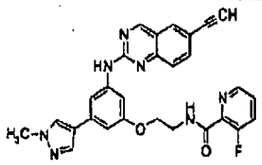
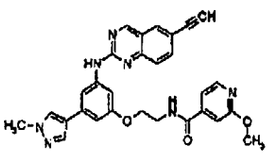
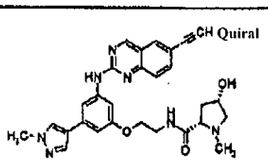
518		***	499.5474		500.2 0.66
519		***	517.5375		518.2 0.68
520		***	509.6109		510.3 0.66
521		****	497.5563		498.3 0.63
522		****	511.5831		512.3 0.64
523		***	507.5288		508.2 0.81
524		**	519.5625		520.2 0.81
525		***	511.5831		512.3 0.63

FIG. 1
(Parte 40 de 59)

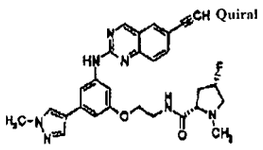
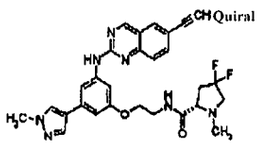
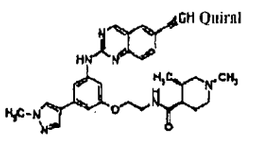
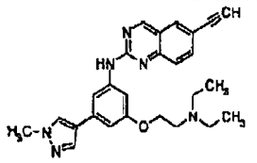
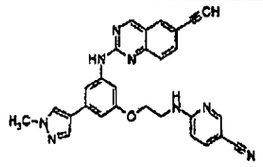
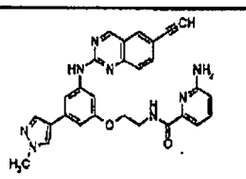
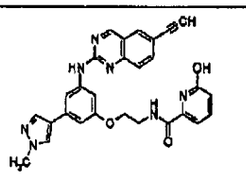
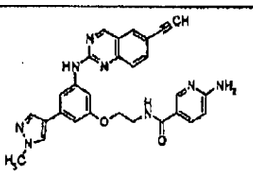
526		**	513.5742		514.3 0.66
527		**	531.5643		532.3 0.71
528		**	523.6377		524.4 0.68
529		***	440.5482		441.3 0.69
530		**	486.5368		487.2 0.82
531		**	504.5516		505.2 0.68
532		**	505.5357		506.2 0.71
533		***	504.5516		505.2 0.66

FIG. 1
(Parte 41 de 59)

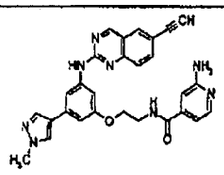
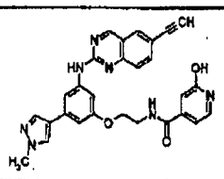
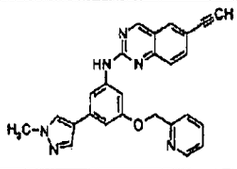
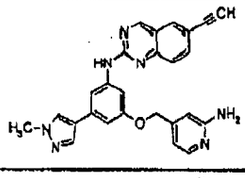
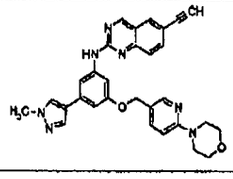
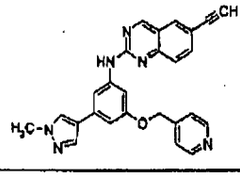
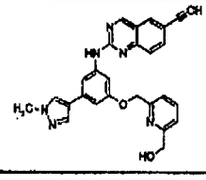
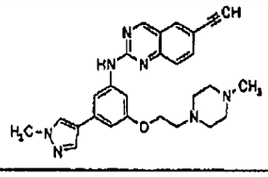
534		****	504.5516		505.2 0.67
535		***	505.5357		506.2 0.68
536		**	432.485		433.2 0.70
537		**	447.4999		448.2 0.70
538		*	517.5903		518.2 0.75
539		**	432.485		433.1 0.70
540		**	462.5108		463.1 0.71
541		***	467.5741		468.2 0.62

FIG. 1
(Parte 42 de 59)

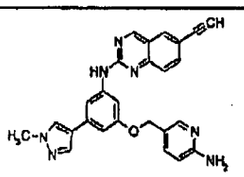
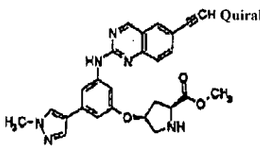
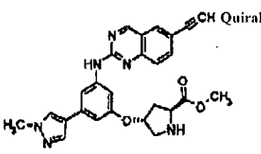
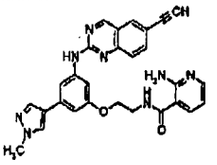
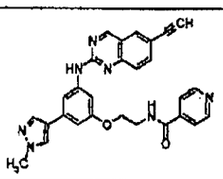
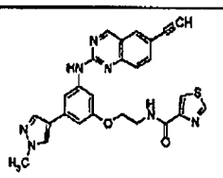
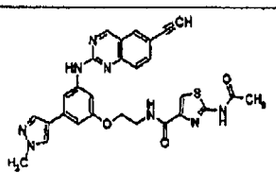
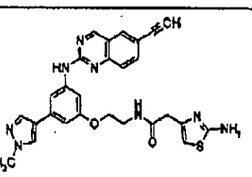
542		**	447.4999		448.2 0.69
543		**	468.5146		469.2 0.68
544		***	468.5146		496.2 0.68
545		***	504.5516		505.1 0.71
546		****	489.5367		490.1 0.70
547		***	495.5649		496.1 0.83
548		***	552.6166		553.2 0.76
549		***	524.6066		525.1 0.69

FIG. 1
(Parte 43 de 59)

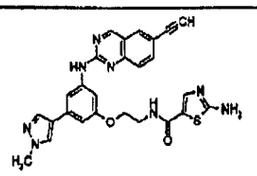
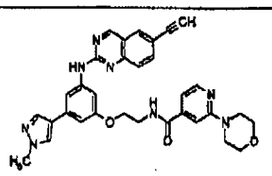
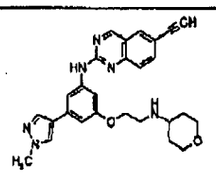
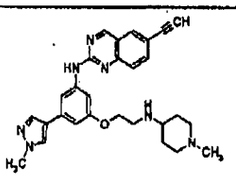
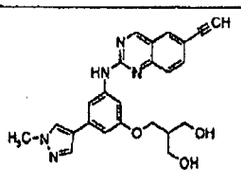
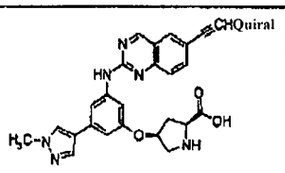
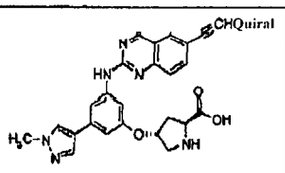
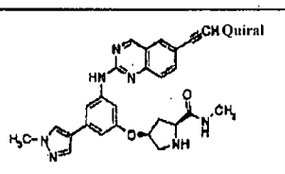
550		****	510.5798		511.1 0.71
551		*	574.642		575.2 0.73
552		****	468.5582		469.1 0.67
553		****	481.6009		482.1 0.61
554		***	429.4777		430.0 0.69
555		N/A	454.4878		455.2 0.62
556		N/A	454.4878		455.2 0.63
557		N/A	467.5305		468.2 0.64

FIG. 1
(Parte 44 de 59)

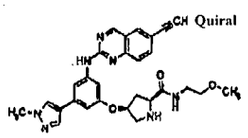
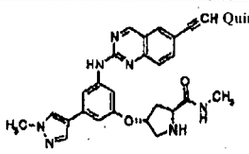
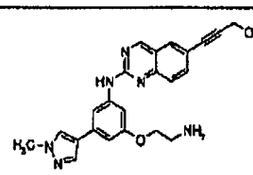
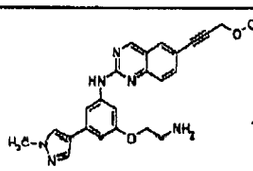
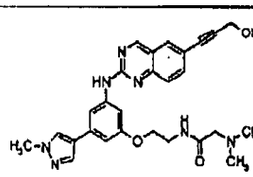
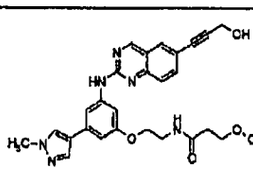
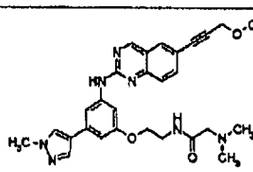
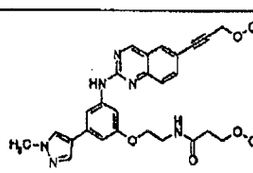
558		N/A	511.5831		512.2 0.66
559		N/A	467.5305		468.2 0.64
560		N/A	414.4668		415.2 0.52
561		N/A	428.4936		429.2 0.65
562		N/A	499.5721		500.3 0.55
563		N/A	500.5562		501.3 0.61
564		N/A	513.5989		514.3 0.67
565		N/A	514.583		515.3 0.75

FIG. 1
(Parte 45 de 59)

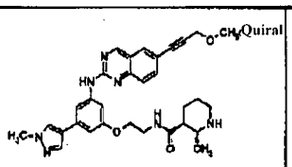
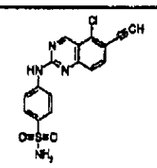
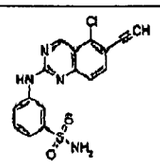
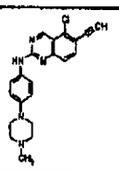
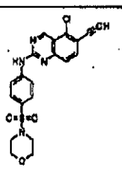
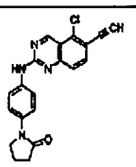
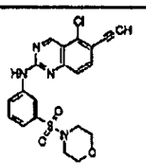
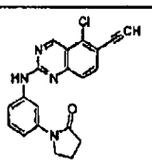
566		N/A	553.6635		554.3 0.69
567		**	358.8079	359.0 2.58	
568		***	358.8079	359.0 2.59	
569		***	377.877	378.1 2.22	
570		*	428.8983	429.1 3.04	
571		***	362.8185	363.1 2.81	
572		*	428.8983	429.1 3.05	
573		****	362.8185	363.1 2.88	

FIG. 1
(Parte 46 de 59)

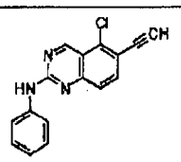
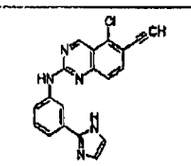
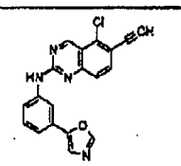
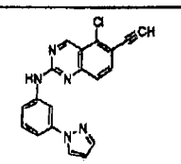
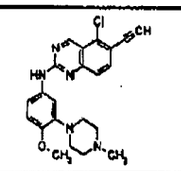
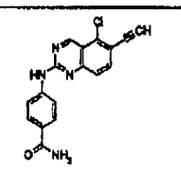
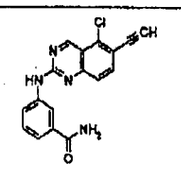
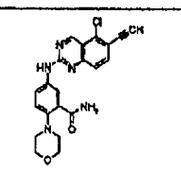
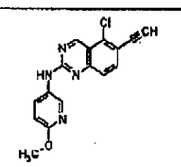
574		*	279.729	280.0 3.28	
575		*	345.7918		
576		*	346.7759	347.1 3.12	
577		*	345.7918	346.1 3.21	346.0 0.71
578		****	407.9028	408.1 2.26	
579		***	322.7539	323.1 2.45	
580		**	322.7539	323.1 2.45	
581		*	407.8592	408.1 2.33	
582		*	310.7429	311.01 2.73	

FIG. 1
(Parte 47 de 59)

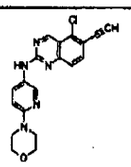
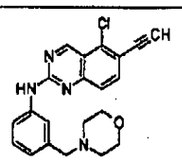
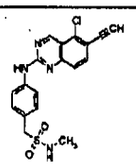
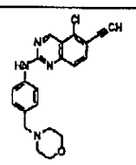
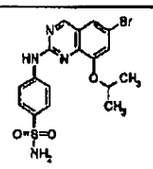
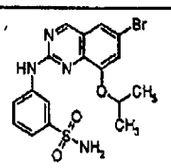
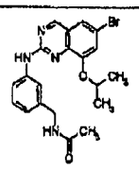
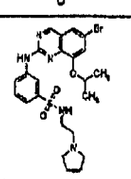
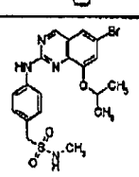
583		***	365.8224	366.0 2.19	
584		***	378.8611	379.1 2.25	
585		****	386.8615	387.1 2.79	
586		**	378.8611	379.1 2.41	
587		**	437.3163	437.0/439.0 2.89	
588		*	437.3163	437.0/439.0 2.88	
589		**	429.3159	429.1/431.1 2.90	
590		*	534.4762	534.1/536.1 2.75	
591		**	465.3699	465.0/467.0 3.13	

FIG. 1
(Parte 48 de 59)

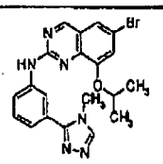
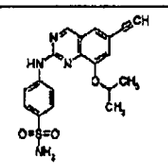
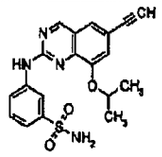
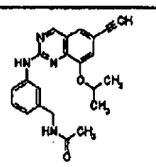
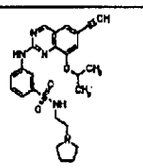
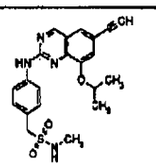
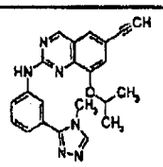
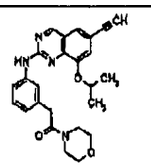
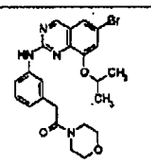
592		*	439.3151	439.1/441.1 2.68	
593		****	382.4422	383.1 2.57	
594		***	382.4422	383.1 2.57	
595		***	374.4418		375.2 0.79
596		*	479.6021		480.2 0.77
597		***	410.4958		411.2 0.86
598		*	384.441		385.2 0.74
599		**	430.5054		431.2 0.85
600		*	485.3795		485.1/487.2 0.92

FIG. 1
(Parte 49 de 59)

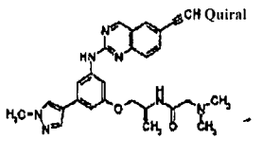
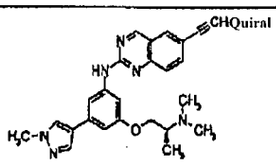
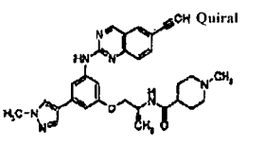
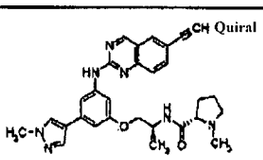
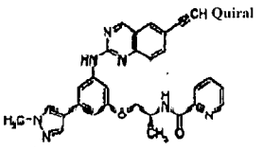
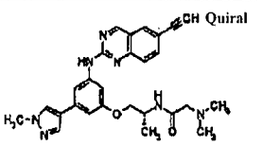
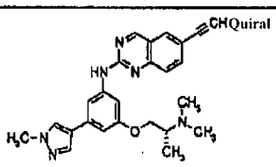
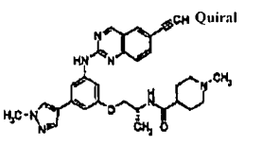
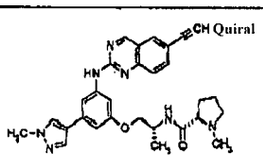
601		**	483.5731	484.2 2.1	
602		****	426.5214	427.2 2.07	
603		**	523.6377	524.3 2.15	
604		**	509.6109	510.2 2.17	
605		*	503.5635	504.2 2.75	
606		***	483.5731		484.3 0.67
607		****	426.5214		427.2 0.66
608		***	523.6377		524.2 0.69
609		***	509.6109		510.2 0.71

FIG. 1
(Parte 50 de 59)

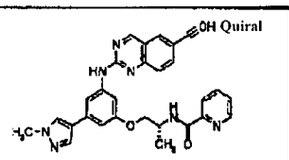
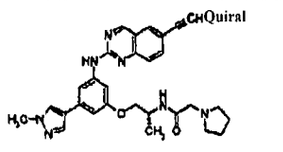
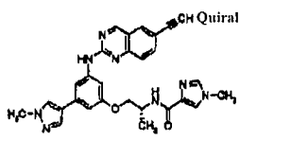
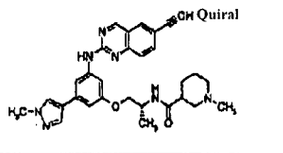
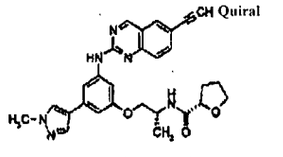
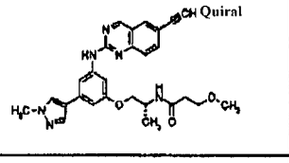
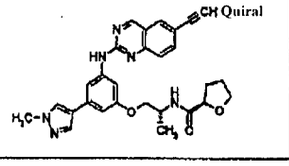
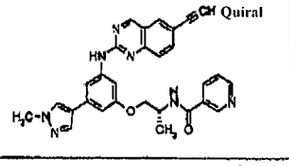
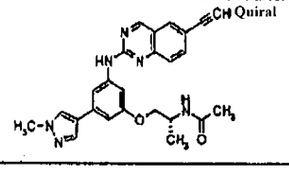
610		***	503.5635		504.2 0.90
611		***	509.6109		510.2 0.70
612		***	506.5674		507.2 0.70
613		***	523.6377		524.2 0.70
614		***	496.5682	497.2 2.48	
615		***	484.5572	485.2 2.36	
616		****	496.5682		497.2 0.82
617		****	503.5635		504.2 0.71
618		****	440.5046		441.2 0.75

FIG. 1
(Parte 51 de 59)

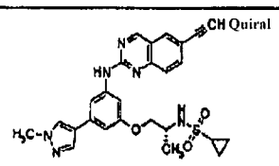
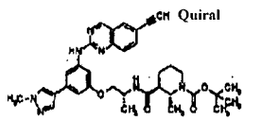
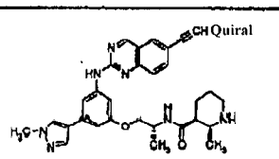
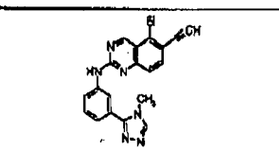
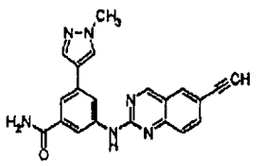
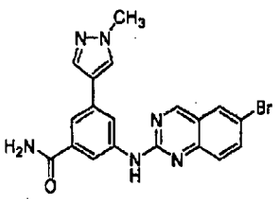
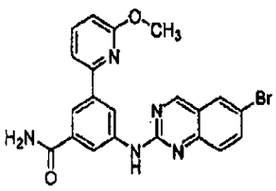
619		***	502.5964		503.2 0.86
620		**	623.7539	624.3 2.98	
621		****	523.6377		524.3 0.69
622		****	360.8067	361.1 2.290	
623		***	368.3984	369	
624		*	423.2725	424	
625		*	450.2944	451	

FIG. 1
(Parte 52 de 59)

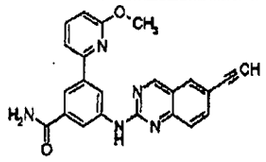
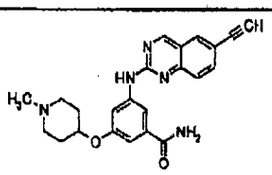
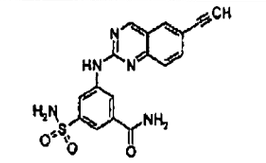
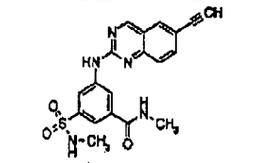
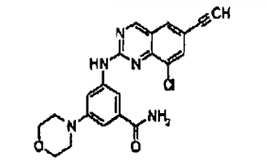
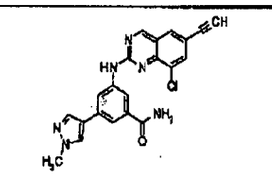
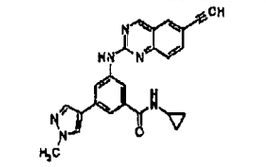
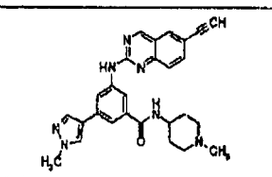
626		*	395.4203	396	
627		**	401.4677	402	
628		**	367.3877	368	
629		*	395.4413	396	
630		***	407.8592	409	
631		***	402.8435	404	
632		**	408.463	409	
633		*	465.5583	466	

FIG. 1
(Parte 53 de 59)

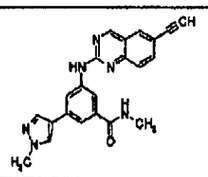
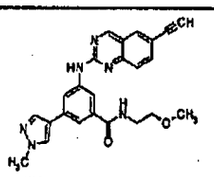
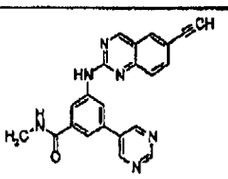
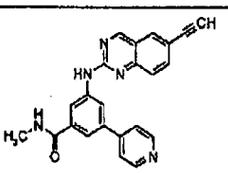
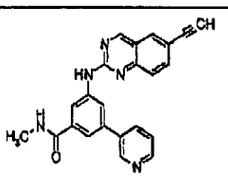
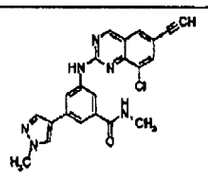
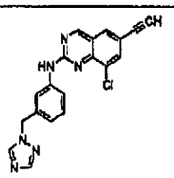
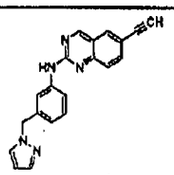
634		***	382.4252	383	
635		**	426.4778	427	
636		*	380.4094	381	
637		*	379.4213	380	
638		*	379.4213	380	
639		***	416.8703	418	
640		****	360.8067	362	
641		***	325.3735	326	

FIG. 1
(Parte 54 de 59)

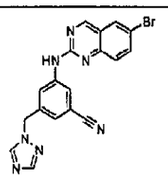
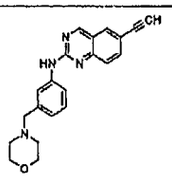
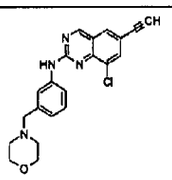
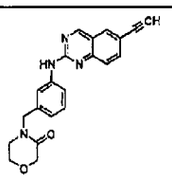
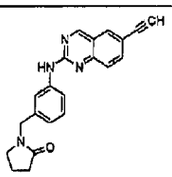
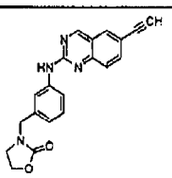
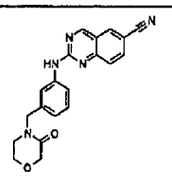
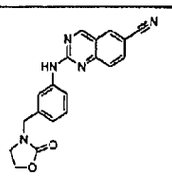
642		*	406.2458	407	
643		**	344.416	345	
644		****	378.8611	380	
645		****	358.3992	359	
646		****	342.4002	343	
647		***	344.3724	345	
648		*	359.3873	360	
649		*	345.3605	346	

FIG. 1
(Parte 55 de 59)

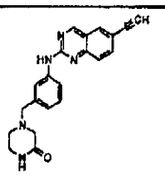
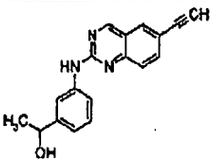
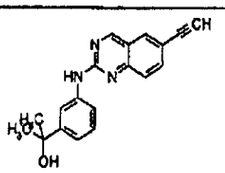
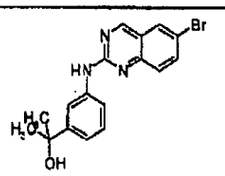
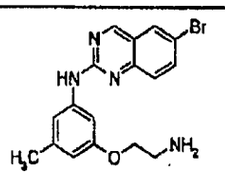
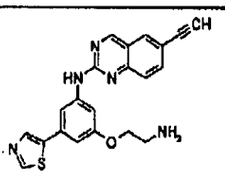
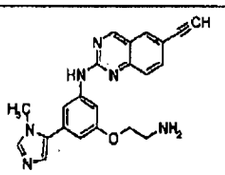
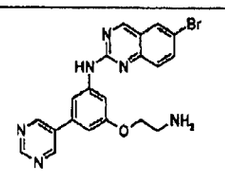
650		**	357.4151	358	
651		**	289.3365	290	
652		*	303.3633	304	
653		*	358.2374	359	
654		*	373.2523	374	
655		****	387.4653	388	
656		***	384.441	385	
657		**	437.2993	438	

FIG. 1
(Parte 56 de 59)

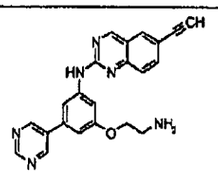
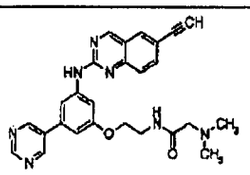
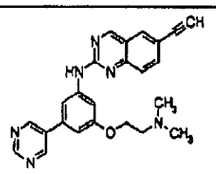
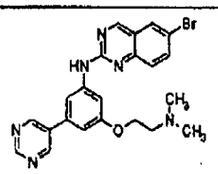
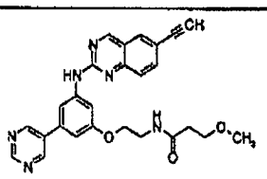
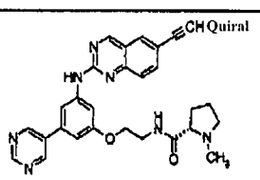
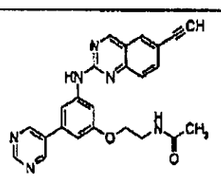
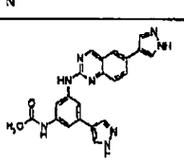
658		***	382.4252	383	
659		***	467.5305	468	
660		**	410.4788	411	
661		**	465.3529	465/467	
662		**	468.5146	469	
663		**	493.5683	494	
664		***	424.462	425	
665		****	410.4392	411.1 1.77	

FIG. 1
(Parte 57 de 59)

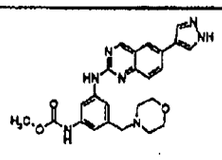
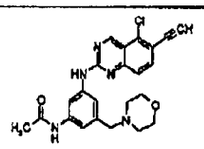
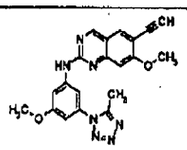
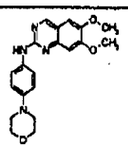
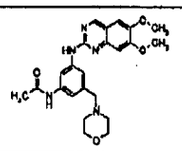
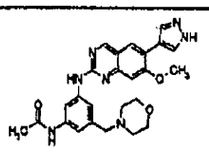
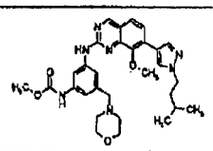
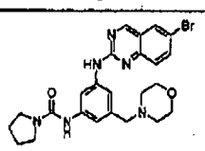
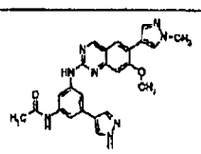
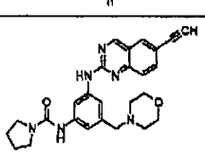
666		***	459.5075	460.2 1.83	
667		****	435.9128	436.1 2.23	
668		*	387.4013	388.1 2.75	
669		*	366.4188	367.1 1.92	
670		*	437.4973	438.1 1.73	
671		****	473.5343	474.2 1.72	
672		****	559.6673	560.2 2.51	
673		**	511.4213	511.1 / 513.1 2.29	
674		**	454.4918	455.1 1.94	
675		***	456.5472	457.1 2.18	

FIG. 1
(Parte 58 de 59)

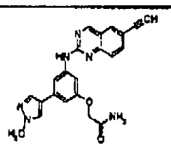
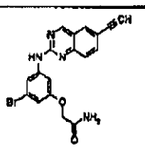
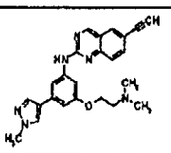
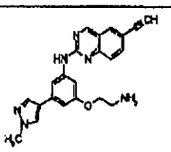
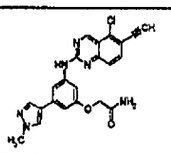
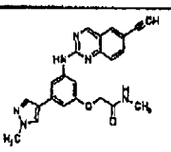
676		****	398.4242	399.0 2.34	
677		**	397.2307	396.9 / 398.9 2.77	
678		****	412.4946	413.1 2.21	
679		***	384.441	385.1 2.16	
680		***	432.8693	433.0 2.62	
681		****	412.451	413.1 2.47	

FIG. 1
(Parte 59 de 59)

Tabla 3

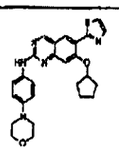
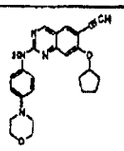
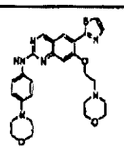
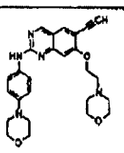
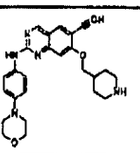
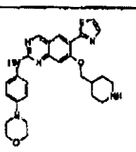
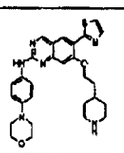
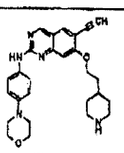
Ejemplo	Estructura	Actividad	LC/MS (ejecución 4.5 min) MS (M+1) m/z Rt (min)	LC/MS (ejecución 1.5 min) MS (M+1) m/z Rt (min)
682		*	474.1 4.82	
683		***	415.0 4.71	
684		*	519.0 2.78	
685		***	460.1 2.68	
686		****	444.0 2.90	
687		***	503.1 2.96	
688		***	517.1 3.16	
689		***	458.1 3.08	

FIG. 2
(Parte 1 de 55)

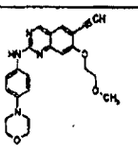
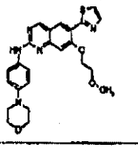
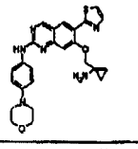
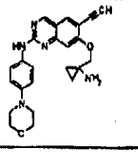
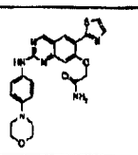
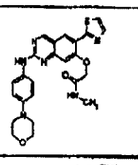
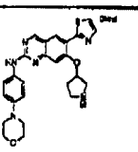
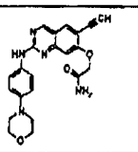
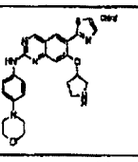
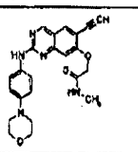
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691		*	464.0 3.69	
692		**	475.0 2.91	
693		***	416.1 2.73	
694		*	463.1 2.93	
695		*	477.0 0.60	
696		****	475.1 2.80	
697		**	404.1 2.86	
698		***	475.0 2.78	
699		**	418.1 3.05	

FIG. 2
(Parte 2 de 55)

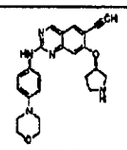
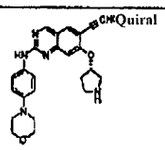
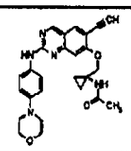
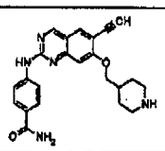
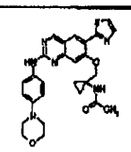
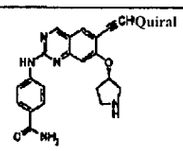
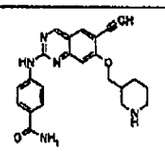
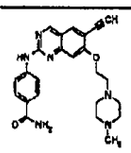
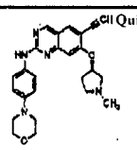
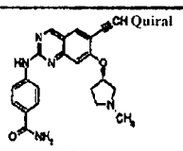
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701		****	416.1 1.83	
702		***	458.1 3.20	
703		****	402.0 2.85	
704		**	517.0 3.31	
705		****	374.0 2.59	
706		****	402.1 2.88	
707		**	431.0 2.44	
708		***	430.1 2.68	
709		****	388. 2.66	

FIG. 2
(Parte 3 de 55)

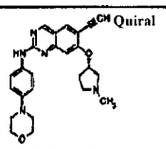
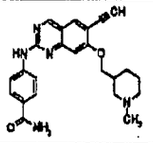
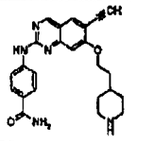
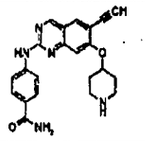
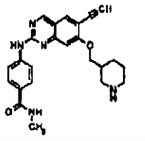
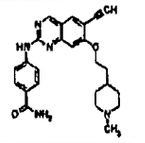
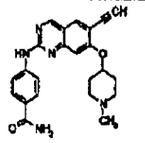
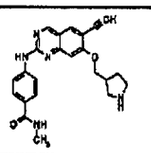
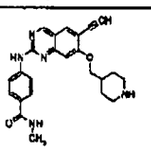
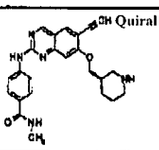
710		***	430.1 2.64	
711		****	416.0 2.90	
712		****	416.0 3.01	
713		****	388.0 2.76	
714		****	416.0 3.07	
715		***	430.1 3.12	
716		****	402.1 2.83	
717		****	402.2 2.94	
718		****	416.0 3.12	
719		****	416.0 2.96	

FIG. 2
(Parte 4 de 55)

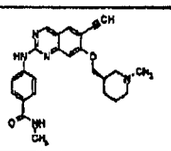
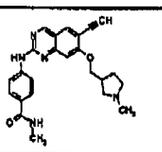
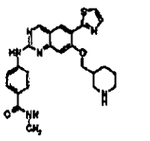
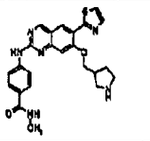
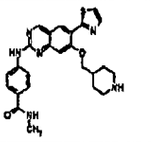
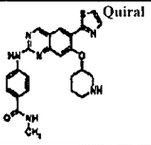
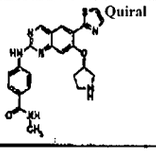
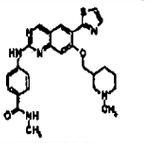
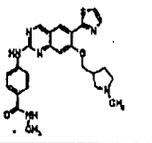
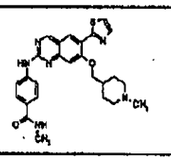
720		***	430.3 2.99	
721		***	416.0 2.86	
722		****	475.1 3.05	
723		****	461.0 2.92	
724		****	475.0 3.01	
725	 Quiral	**	461.0 3.10	
726	 Quiral	****	447.2 2.85	
727		**	489.2 3.09	
728		**	475.2 2.98	
729		**	489.2 3.03	

FIG. 2
(Parte 5 de 55)

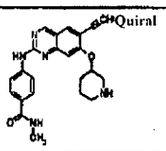
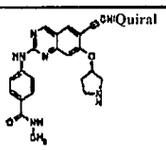
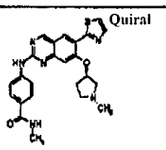
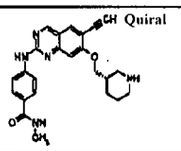
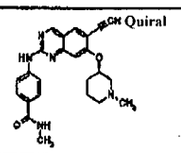
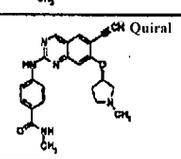
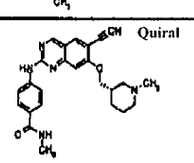
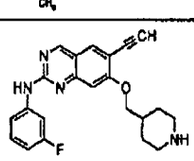
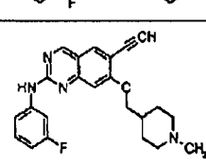
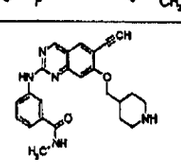
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731		****	388.0 2.72	
732		***	461.2 2.88	
733		****	416.2 0.54	
734		**	416.2 0.52	
735		****	402.2 0.50	
736		***	430.2 0.55	
737		***	377.1 0.74	
738		**	391.2 0.73	
739		***	416.2 0.54	

FIG. 2
(Parte 6 de 55)

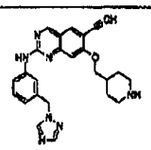
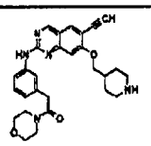
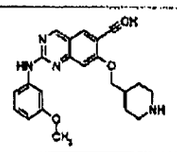
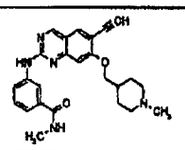
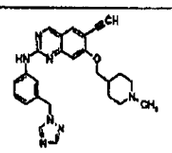
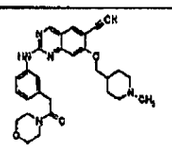
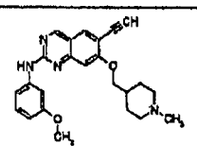
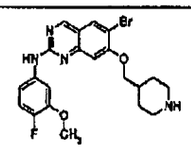
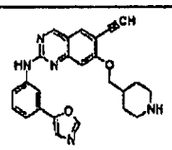
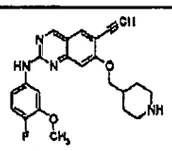
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741		****	486.3 0.58	
742		****	389.0 0.69	
743		**	430.2 0.57	
744		***	454.2 0.59	
745		***	500.3 0.59	
746		**	403.2 0.70	
747		***	461/463 0.76	
748		**	426.2 0.69	
749		****	407.2 0.71	

FIG. 2
(Parte 7 de 55)

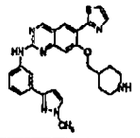
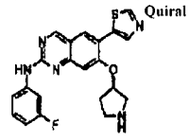
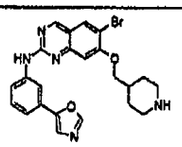
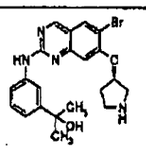
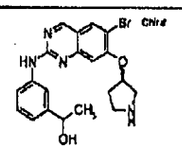
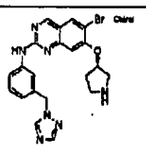
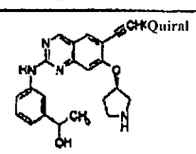
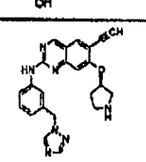
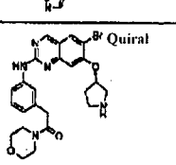
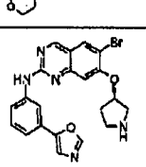
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751		*	408.1 0.68	
752		**	480/482 0.75	
753		**	443/445 0.75	
754		**	429/431 0.71	
755		***	466/468 0.69	
756		****	375.2 0.54	
757		****	412.2 0.53	
758		***	512/514 0.56	
759		**	452/454 0.67	

FIG. 2
(Parte 8 de 55)

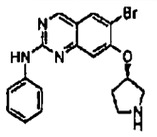
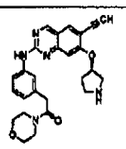
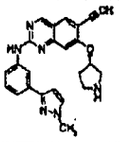
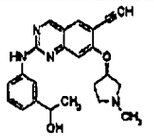
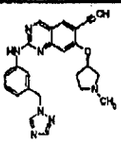
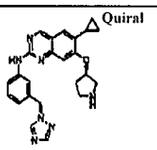
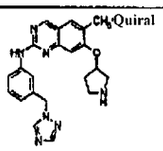
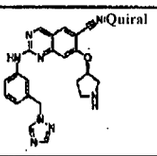
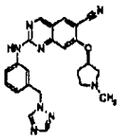
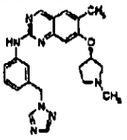
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761		****	458.2 0.66	
762		****	411.2 0.65	
763		***	389.2 0.57	
764		****	426.1 0.56	
765		*	428.2 0.54	
766		**	402.2 0.47	
767		****	413.1 0.51	
768		***	427.1 0.52	
769		**	416.1 0.48	

FIG. 2
(Parte 9 de 55)

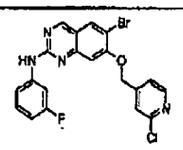
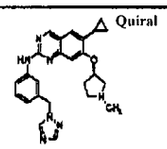
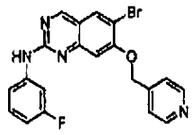
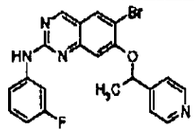
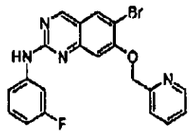
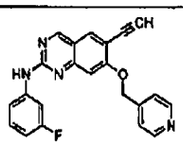
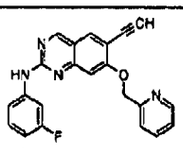
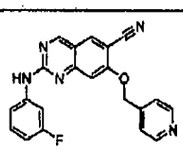
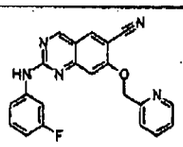
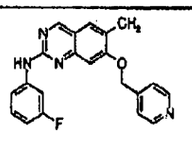
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771		*	442.2 0.54	
772		*	425/427 0.76	
773		*	439/441 0.79	
774		*	425/427 0.87	
775		**	371.0 0.74	
776		**	371.0 0.80	
777		**	372.0 0.69	
778		*	372.0 0.77	
779		*	361.1 0.68	

FIG. 2
(Parte 10 de 55)

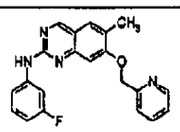
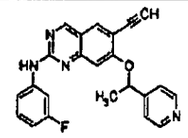
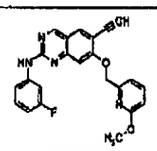
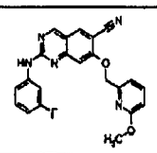
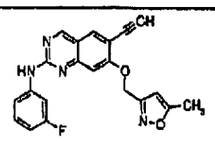
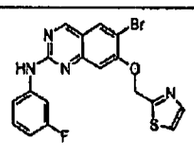
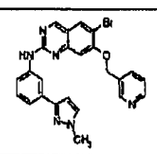
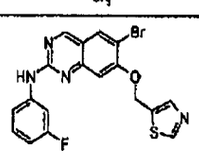
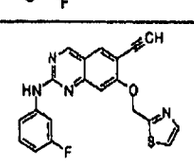
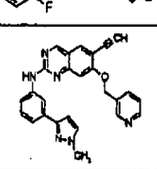
780		*	361.1 0.75	
781		**	385.2 0.74	
782		*	401.1 1.14	
783		*	402.1 1.12	
784		*	375.1 1.02	
785		*	431/433 1.06	
786		**	487/489 0.69	
787		*	431/433 0.97	
788		**	377.0 0.98	
789		****	433.1 0.68	

FIG. 2
(Parte 11 de 55)

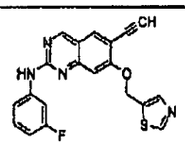
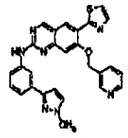
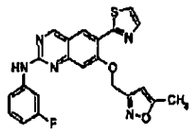
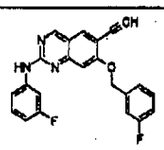
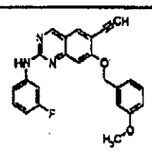
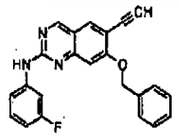
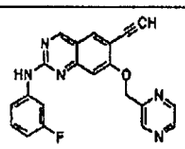
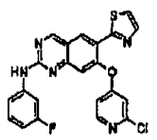
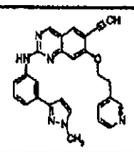
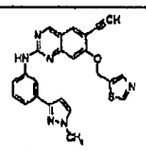
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791		*	492.1 0.67	
792		*	434.1 1.03	
793		*	388.0 1.18	
794		*	400.1 1.15	
795		*	370.1 1.16	
796		****	372.0 0.93	
797		*	450.0 1.14	
798		**	447.1 0.70	
799		***	439.1 0.81	

FIG. 2
(Parte 12 de 55)

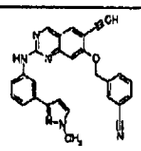
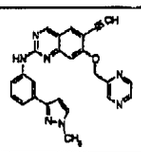
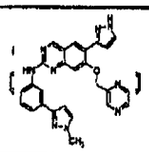
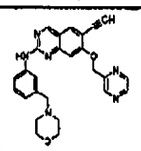
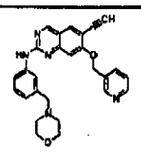
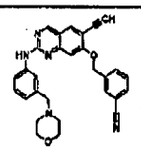
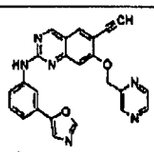
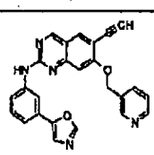
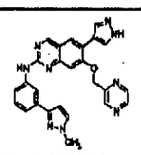
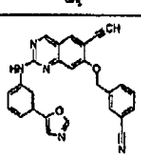
800		***	457.1 0.97.	
801		*	434.1 0.81	
802		***	476.2 0.68	
803		***	453.1 0.62	
804		****	452.1 0.49	
805		****	476.1 0.78	
806		***	421.0 0.84	
807		****	420.0 0.68	
808		****	476.0 0.64	
809		***	444.0 1.01	

FIG. 2
(Parte 13 de 55)

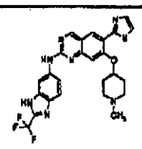
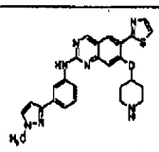
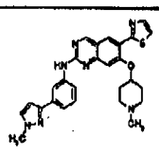
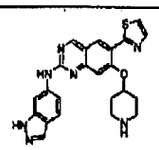
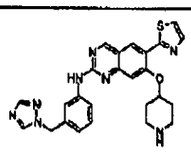
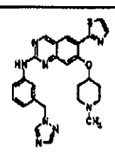
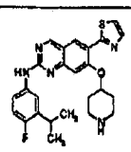
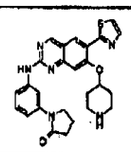
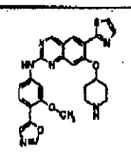
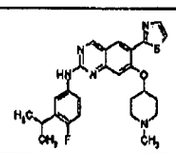
810		**	526.1 2.16	
811		****	484.1 2.2	
812		***	498.1 2.2	
813		****	444.1 1.92	
814		****	485.2 1.9	
815		****	499.2 1.9	
816		****		464.1 0.78
817		****		487.2 0.5
818		****		501.2 0.6
819		***		478.2 0.81

FIG. 2
(Parte 14 de 55)

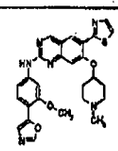
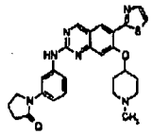
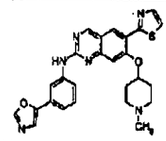
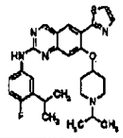
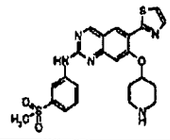
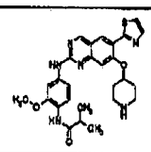
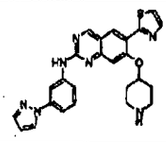
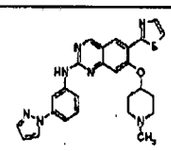
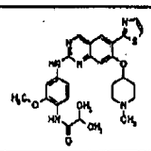
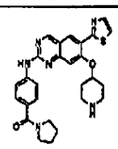
820		****		515.2 0.69
821		****		501.2 0.61
822		***	485.1 2.2	
823		*	506.2 3.3	
824		**		482.2 0.6
825		****		519.2 0.58
826		****		470.2 0.6
827		****		484.2 0.6
828		****	533.2 2.2	
829		****		501.1 0.56

FIG. 2
(Parte 15 de 55)

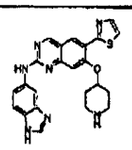
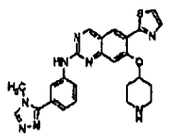
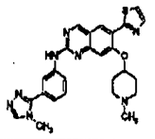
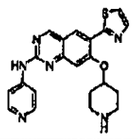
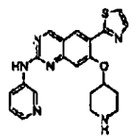
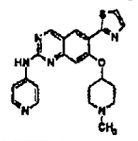
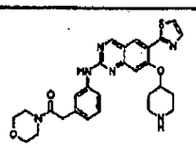
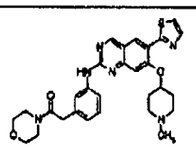
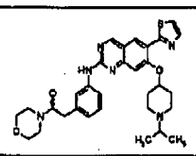
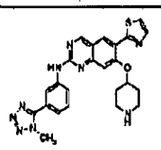
830		****	444.1 1.7	
831		****	485.1 1.9	
832		***	499.2 1.9	
833		*	405.2 1.7	
834		*	405.2 1.7	
835		*	419.2 1.79	
836		****	531.2 1.97	
837		****	545.2 1.9	
838		***	573.2 2.1	
839		****	486.2 2.1	

FIG. 2
(Parte 16 de 55)

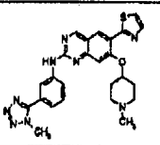
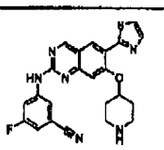
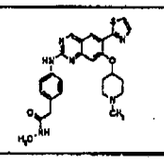
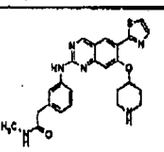
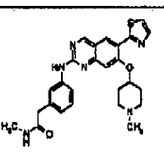
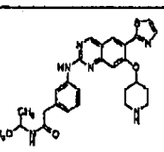
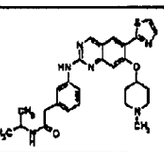
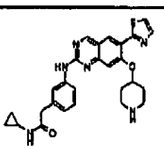
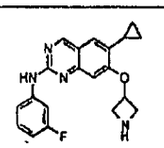
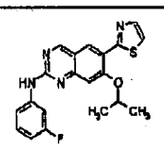
840		***	500.2 2.1	
841		***	447.2 2.35	
842		***	489.2 2.01	
843		****	475.1 1.86	
844		****	489.2 1.9	
845		****	503.3 2.01	
846		****	517.3 2.07	
847		****	501.3 1.95	
848		*		351.1 0.66
849		*	381.1 1.07	

FIG. 2
(Parte 17 de 55)

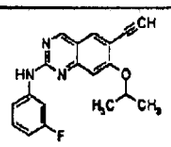
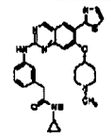
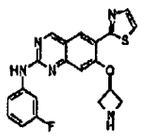
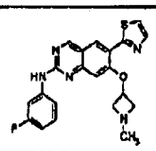
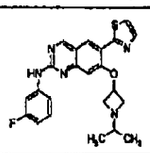
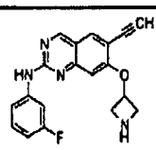
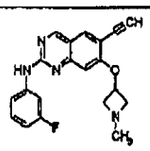
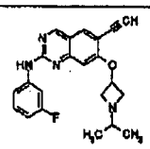
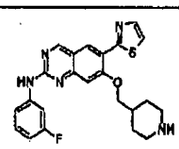
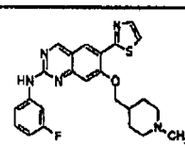
850		*	322.1 1.04	
851		****	515.2 1.99	
852		*		394 0.64
853		*		408.1 0.65
854		*		436.1 0.7
855		****		335.2 0.64
856		***	349.2 2.7	
857		*		377.2 0.73
858		**		436.1 0.73
859		*		450.2 0.72

FIG. 2
(Parte 18 de 55)

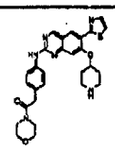
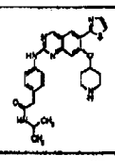
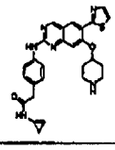
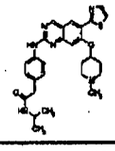
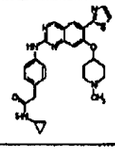
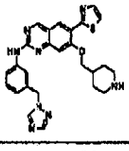
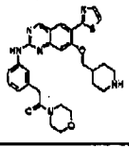
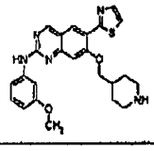
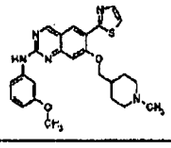
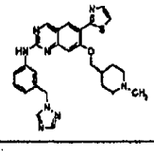
860		****		531.3 0.54
861		****		503.2 0.57
862		****		501.2 0.55
863		***		517.2 0.58
864		**		515.2 0.55
865		***		499.2 0.57
866		***		545.3 0.57
867		**		448.2 0.68
868		**		462.2 0.69
869		**		513.3 0.59

FIG. 2
(Parte 19 de 55)

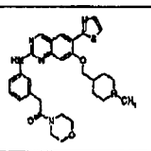
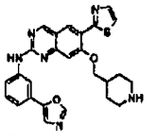
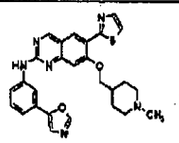
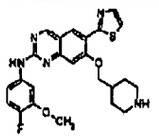
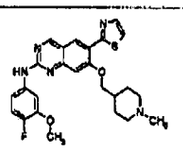
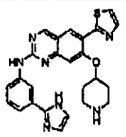
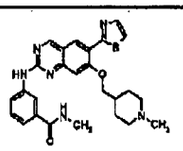
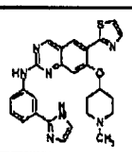
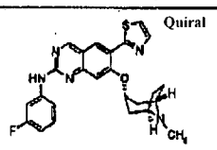
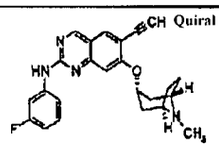
870		**		559.3 0.59
871		*	485.2 2.5	
872		*	499.2 2.69	
873		**		466.2 0.7
874		**		480.2 0.73
875		****		470.2 0.53
876		*	489.2 2.1	
877		***		484.2 0.66
878		****		462.3 0.74
879		****		403.2 0.73

FIG. 2
(Parte 20 de 55)

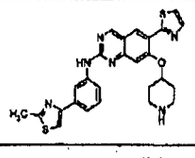
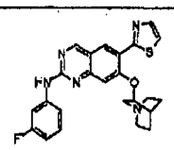
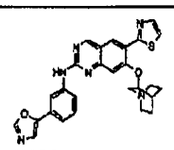
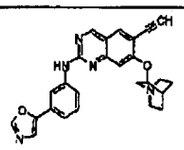
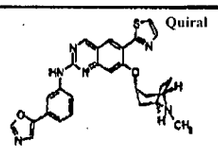
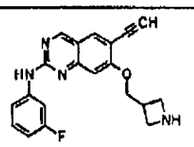
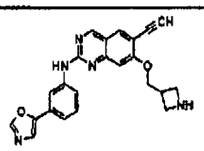
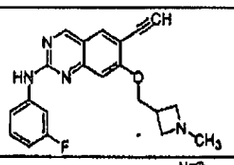
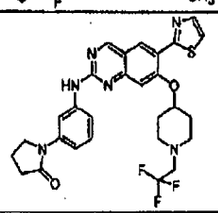
880		***		501.2 '0.74
881		*		448.2 0.74
882		*		497.2 0.69
883		*		438.2 0.71
884		*		511.2 0.83
885		**		349.1 0.70
886		**		398.2 0.64
887		*		363.1 0.73
888		*		569.2 0.79

FIG. 2
(Parte 21 de 55)

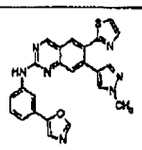
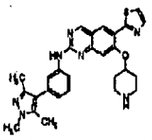
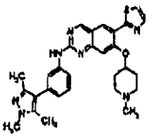
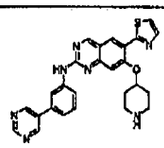
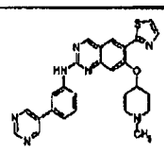
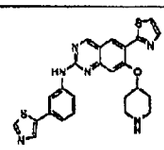
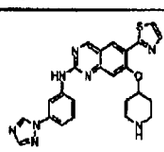
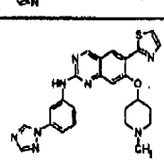
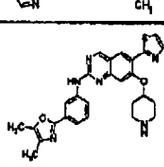
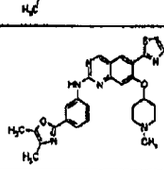
889		*		452.1 0.76
890		***		512.2 0.61
891		***		526.2 0.6
892		****		482.2 0.58
893		****		496.2 0.6
894		**		487.2 0.66
895		****		471.2 0.57
896		***		485.2 0.59
897		**		499.2 0.72
898		*		513.3 0.72

FIG. 2
(Parte 22 de 55)

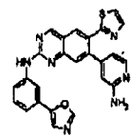
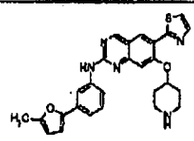
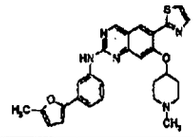
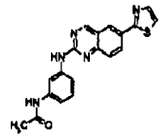
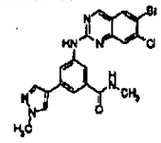
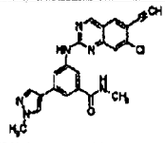
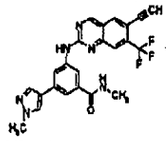
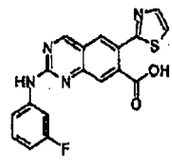
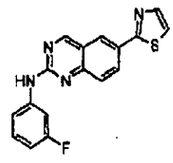
899		*		464.2 0.64
900		**		484.2 0.85
901		*		498.2 0.82
902		**	392 2.31	
903		*	472.8 0.89	
904		**	417.1 0.80	
905		*	451.0 0.86	
906		N/A		367.1 0.78
907		N/A		323.1 1.01

FIG. 2
(Parte 23 de 55)

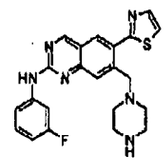
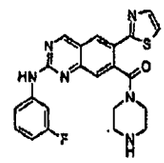
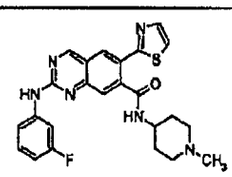
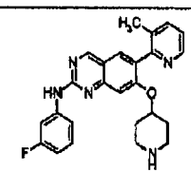
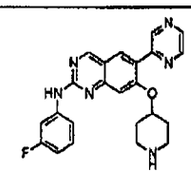
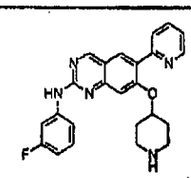
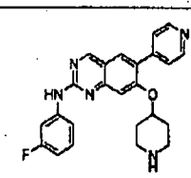
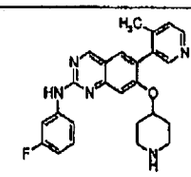
908		N/A		421.1 0.61
909		N/A		435.0 0.65
910		N/A		463.1 0.64
911		N/A		430.1 0.57
912		N/A		417.1 0.65
913		N/A		416.1 0.55
914		N/A		416.1 0.56
915		N/A		430.2 0.57

FIG. 2
(Parte 24 de 55)

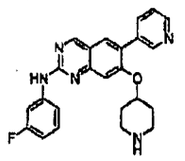
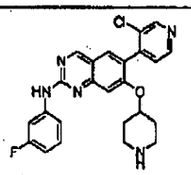
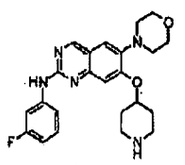
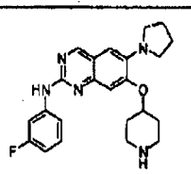
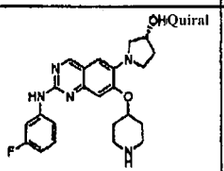
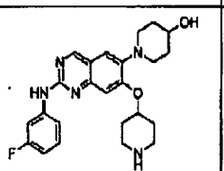
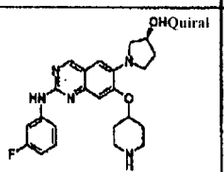
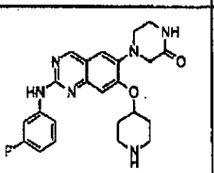
916		N/A		416.2 0.55
917		N/A		450.1 0.71
918		N/A		424.1 0.61
919		N/A		408.1 0.57
920		N/A		424.1 0.56
921		N/A		438.1 0.53
922		N/A		424.1 0.55
923		N/A		437.1 0.55

FIG. 2
(Parte 25 de 55)

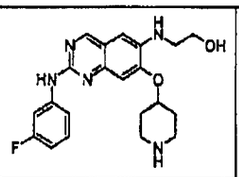
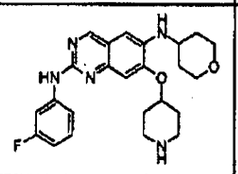
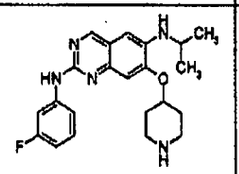
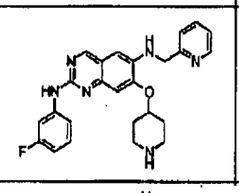
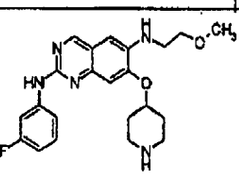
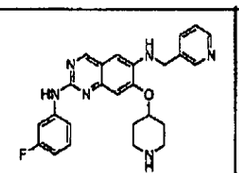
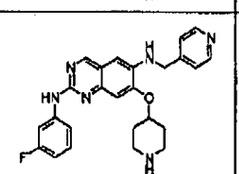
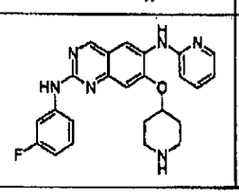
924		N/A		398.1 0.55
925		N/A		438.1 0.63
926		N/A		396.1 0.64
927		N/A		445.1 0.52
928		N/A		412.1 0.62
929		N/A		445.2 0.51
930		N/A		445.1 0.51
931		N/A		431.1 0.54

FIG. 2
(Parte 26 de 55)

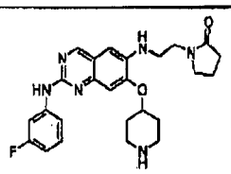
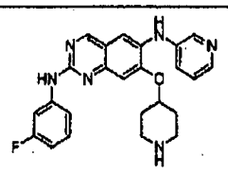
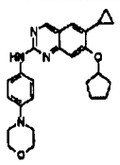
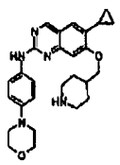
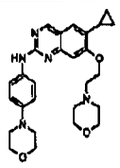
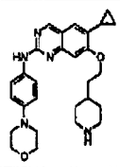
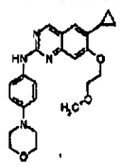
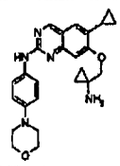
932		N/A		465.1 0.60
933		N/A		431.1 0.53
934		*	431	
935		**	460	
936		*	476	
937		*	474	
938		*	421	
939		*	432	

FIG. 2
(Parte 27 de 55)

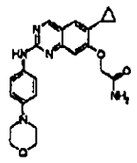
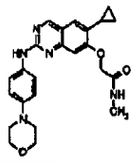
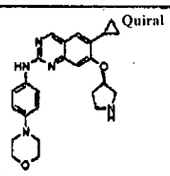
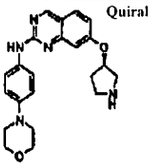
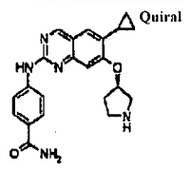
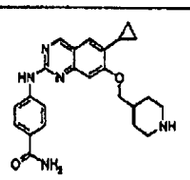
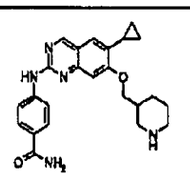
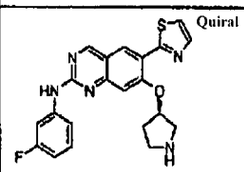
940		*	420	
941		*	434	
942		*	432	
943		**	392	
944		**	390	
945		**	418	
946		**	418	
947		***	408	

FIG. 2
(Parte 28 de 55)

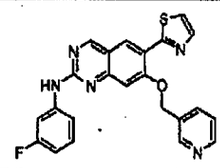
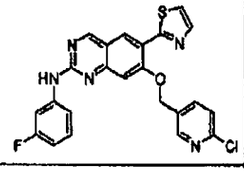
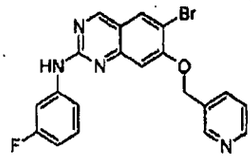
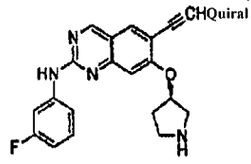
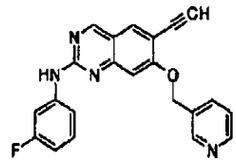
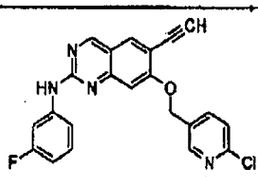
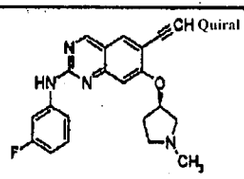
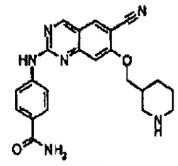
948		*	430	
949		*	465	
950		**	426	
951		***	349	
952		***	371	
953		***	405	
954		**	363	
955		****	403	

FIG. 2
(Parte 29 de 55)

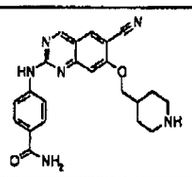
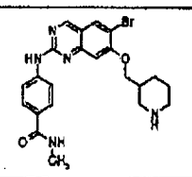
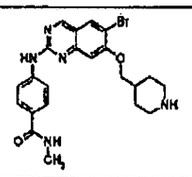
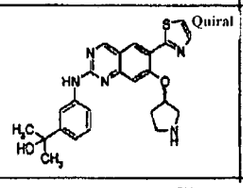
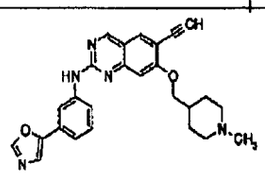
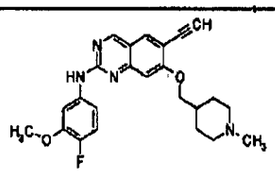
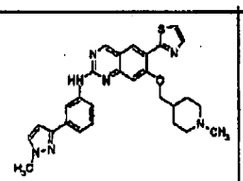
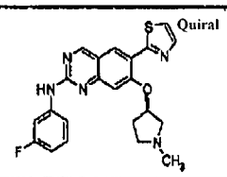
956		****	403	
957		****	470/472	
958		****	470/472	
959		**	448	
960		**	440	
961		***	421	
962		*	512	
963		**	422	

FIG. 2
(Parte 30 de 55)

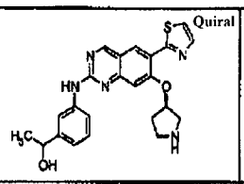
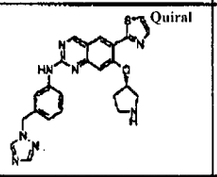
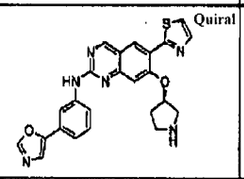
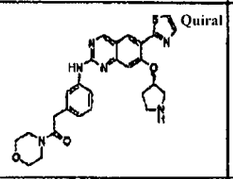
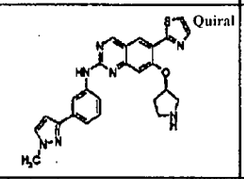
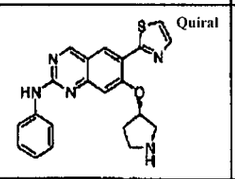
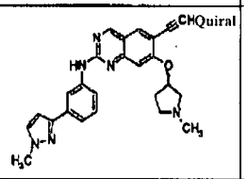
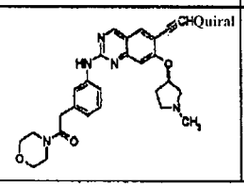
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965		****	471	
966		***	457	
967		****	518	
968		****	470	
969		****	390	
970		***	425	
971		****	472	

FIG. 2
(Parte 31 de 55)

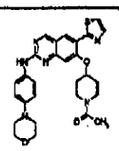
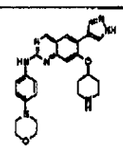
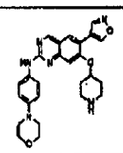
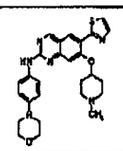
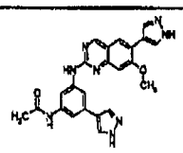
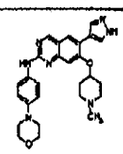
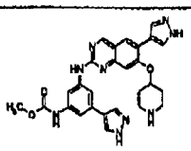
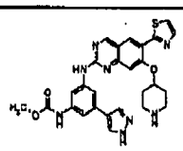
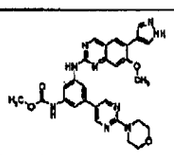
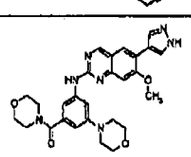
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973		****	472.1 1.55	
974		****	473.1 1.68	
975		****	503.1 1.97	
976		****	441.1 1.79	
977		****	486.1 1.73	
978		****	526.1 1.79	
979		****	543.2 2.03	
980		*	554.1 2.27	
981		**	516.1 1.94	

FIG. 2
(Parte 32 de 55)

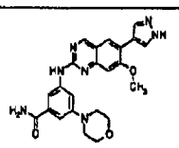
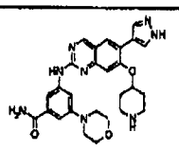
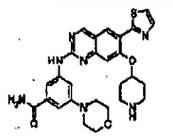
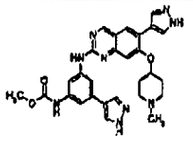
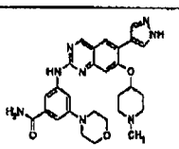
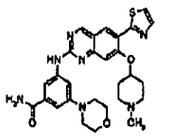
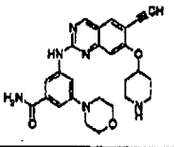
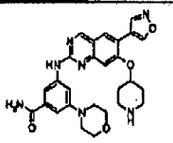
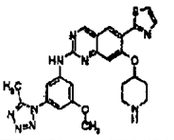
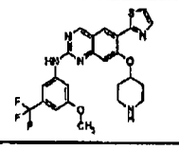
982		**	446.0 1.81	
983		****	515.2 1.77	
984		****	532.2 1.94	
985		****	540.1 1.83	
986		***	529.2 1.71	
987		***	546.1 1.90	
988		****	473.0 1.86	
989		***	516.1 1.84	
990		****	516.1 2.21	
991		**	502.0 2.58	

FIG. 2
(Parte 33 de 55)

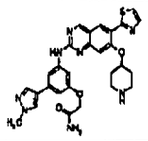
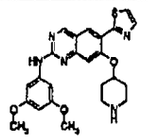
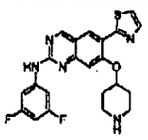
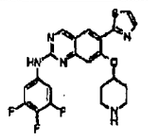
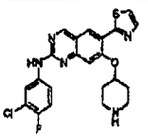
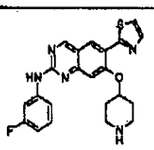
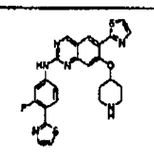
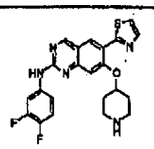
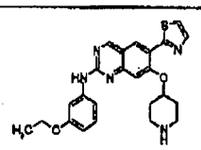
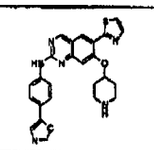
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993		*	464.3 2.11	
994		***	440.0 2.42	
995		***	458.0 2.47	
996		****	456.1 2.47	
997		****	422.1 2.34	
998		****	505.2 2.36	
999		****	440.1 2.40	
1000		****	448.1 2.38	
1001		****	471.1 2.19	

FIG. 2
(Parte 34 de 55)

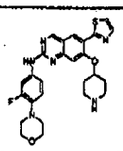
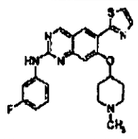
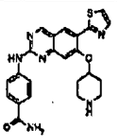
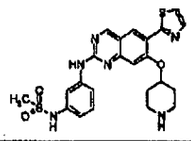
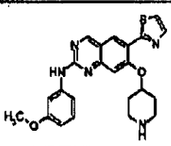
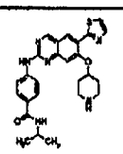
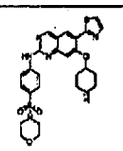
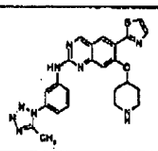
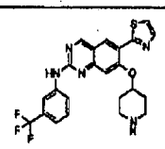
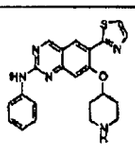
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1003		****	436.1 2.32	
1004		****	447.1 1.90	
1005		****	497.1 2.05	
1006		****	434.2 2.21	
1007		****	489.3 2.14	
1008		****	553.2 2.23	
1009		****	486.1 2.14	
1010		***	472.1 2.56	
1011		****	404.1 2.16	

FIG. 2
(Parte 35 de 55)

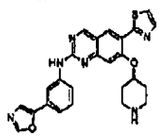
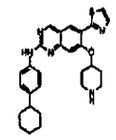
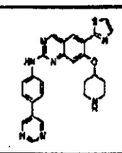
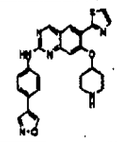
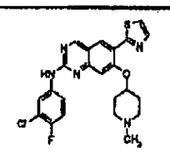
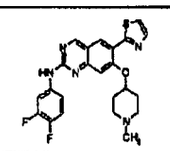
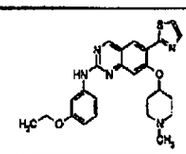
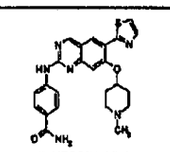
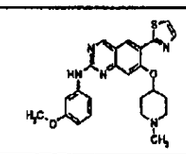
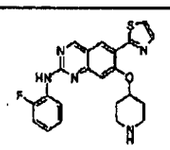
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1013		*	486.1 2.80	
1014		****	482.1 2.08	
1015		****	471.1 2.25	
1016		***	470.0 2.47	
1017		***	454.1 2.38	
1018		**	462.2 2.34	
1019		****	461.1 1.92	
1020		****	448.1 2.23	
1021		*	422.1 2.23	

FIG. 2
(Parte 36 de 55)

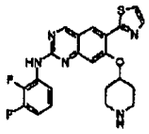
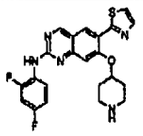
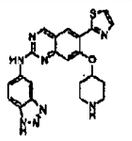
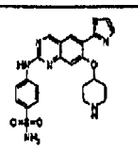
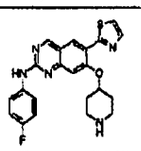
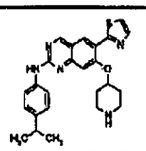
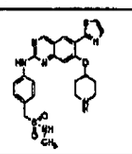
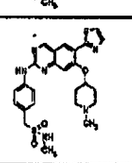
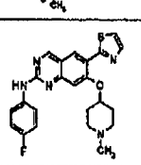
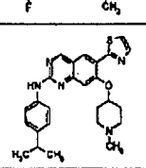
1022		*	440.0 2.34	
1023		*	440.0 2.25	
1024		****	445.1 1.94	
1025		****	483.1 1.95	
1026		****	422.1 2.18	
1027		****	446.1 2.49	
1028		****	511.1 2.01	
1029		****	525.1 2.03	
1030		****	436.2 2.21	
1031		****	460.2 2.53	

FIG. 2
(Parte 37 de 55)

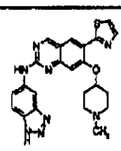
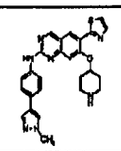
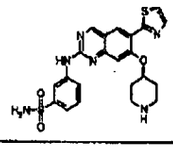
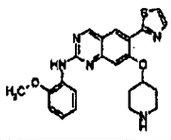
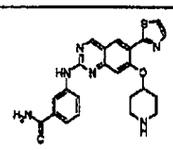
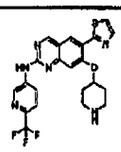
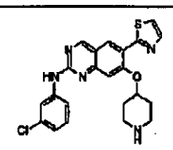
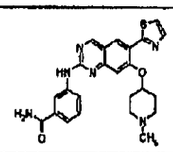
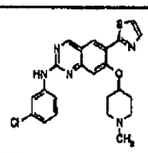
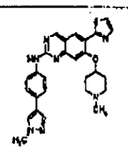
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1033		****	484.1 2.12	
1034		****	483.1 1.97	
1035		*	434.2 2.19	
1036		****	447.2 1.88	
1037		****	473.0 2.32	
1038		****	438.2 2.40	
1039		****	461.2 1.90	
1040		**	452.1 2.47	
1041		****	498.2 2.16	

FIG. 2
(Parte 38 de 55)

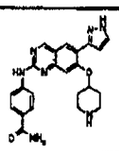
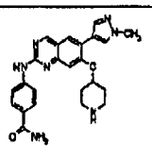
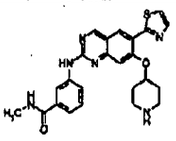
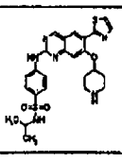
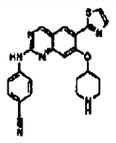
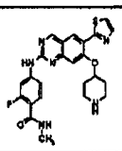
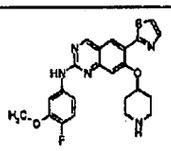
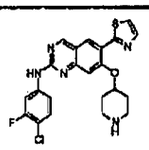
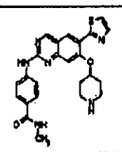
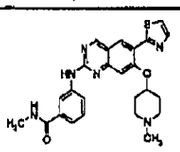
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1043		***	444.2 1.77	
1044		****	461.1 1.94	
1045		****	525.1 2.27	
1046		****	429.1 2.25	
1047		****	479.2 2.07	
1048		****	452.1 2.21	
1049		****	456.1 2.51	
1050		****	461.2 2.01	
1051		***	475.2 2.03	

FIG. 2
(Parte 39 de 55)

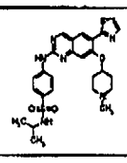
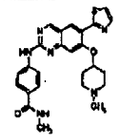
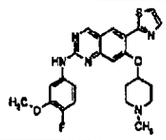
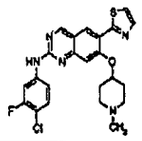
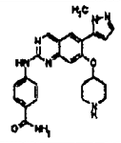
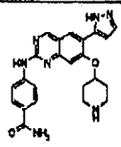
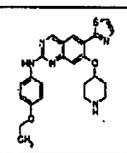
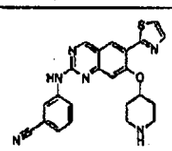
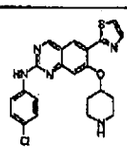
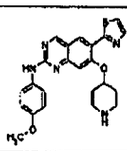
1052		****	539.2 2.38	
1053		****	475.2 2.05	
1054		****	466.2 2.34	
1055		**	470.1 2.64	
1056		*	444.2 1.81	
1057		****	430.2 1.73	
1058		****	448.2 2.19	
1059		****	429.2 2.23	
1060		****	438.2 2.38	
1061		****	434.2 2.07	

FIG. 2
(Parte 40 de 55)

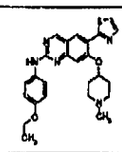
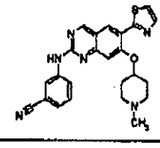
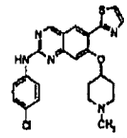
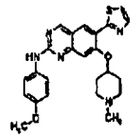
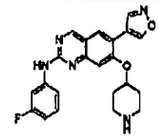
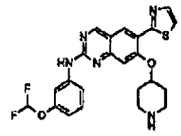
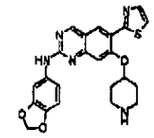
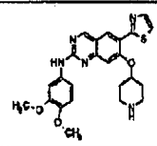
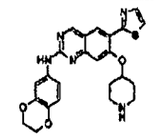
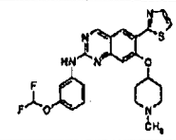
1062		****	462.2 2.27	
1063		**	443.2 2.32	
1064		***	452.2 2.47	
1065		***	448.2 2.14	
1066		***	406.2 2.25	
1067		****	470.1 2.38	
1068		****	448.2 2.07	
1069		****	464.2 2.015	
1070		****	462.2 2.08	
1071		***	484.2 0.711	

FIG. 2
(Parte 41 de 55)

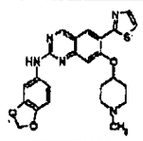
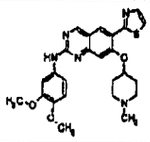
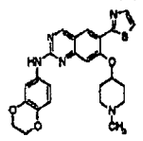
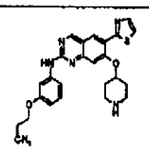
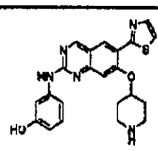
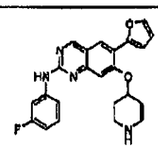
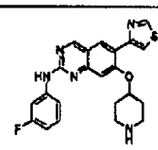
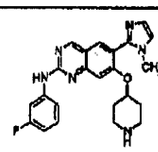
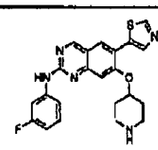
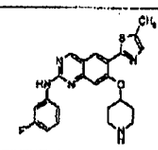
1072		***	462.1 0.58	
1073		****	478.2 0.55	
1074		**	476.2 0.59	
1075		****	462.2 0.75	
1076		****	420.2 0.55	
1077		****	405.2 0.76	
1078		****	422.1 0.68	
1079		*	419.2 0.55	
1080		***	422.1 0.67	
1081		*	436.1 0.73	

FIG. 2
(Parte 42 de 55)

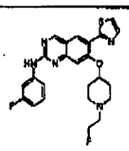
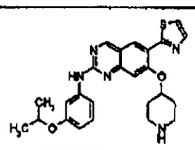
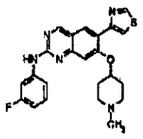
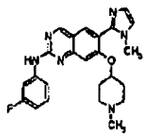
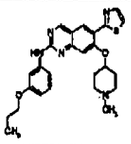
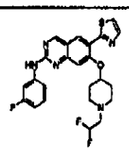
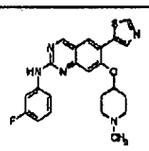
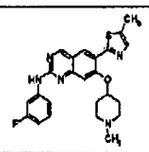
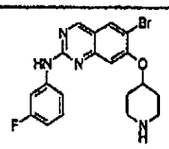
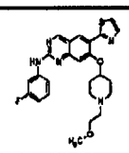
1082		**	468.2 0.73	
1083		***	462.2 0.75	
1084		**	436.2 0.69	
1085		*	433.2 0.55	
1086		***	476.2 0.76	
1087		*	486.1 0.74	
1088		*	436.1 0.66	
1089		*	450.1 0.73	
1090		***	417.1 / 419.1 0.72	
1091		*	480.2, 0.79	

FIG. 2
(Parte 43 de 55)

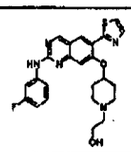
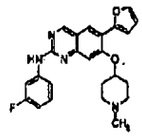
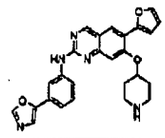
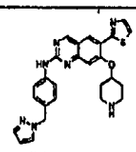
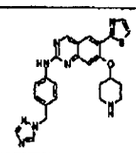
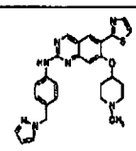
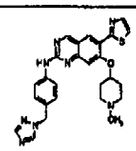
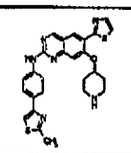
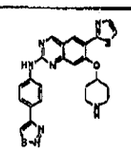
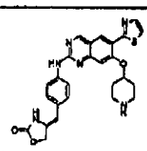
1092		***	486.2 0.73	
1093		****	419.2 0.82	
1094		****	454.2 0.76	
1095		****	484.1 0.64	
1096		****	485.0 0.56	
1097		****	498.2 0.63	
1098		***	499.1 0.54	
1099		****	501.0 0.68	
1100		****	488.0 0.68	
1101		****	503.0 0.55	

FIG. 2
(Parte 44 de 55)

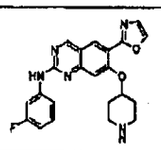
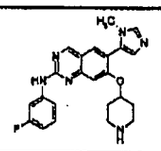
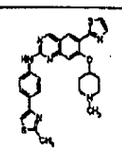
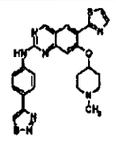
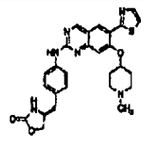
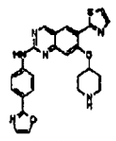
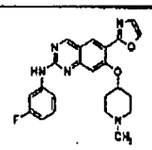
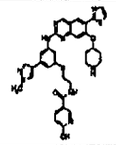
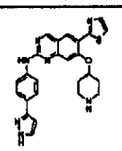
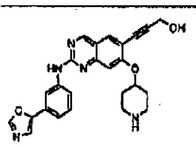
1102		***	406.1 0.68	
1103		*	419.1 0.55	
1104		**	515.1 0.70	
1105		****	502.1 0.71	
1106		****	517.1 0.56	
1107		****	471.1 0.67	
1108		**	420.0 0.69	
1109		****	664.2 0.55	
1110		****	470.1 0.59	
1111		****	442.1 0.60	

FIG. 2

(Parte 45 de 55)

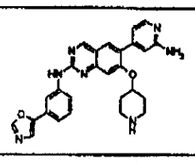
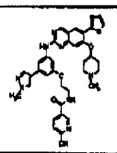
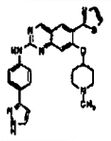
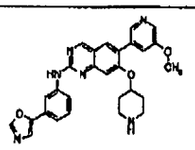
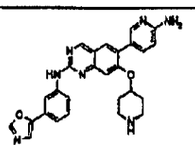
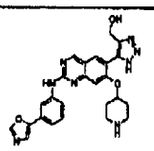
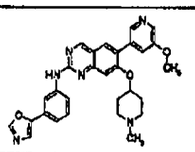
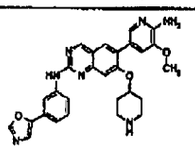
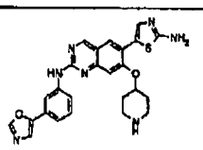
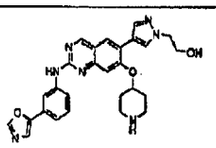
1112		*	480.0 0.54	
1113		***	678.3 0.56	
1114		****	464.1 0.59	
1115		*	495.0 0.55	
1116		*	480.0 0.53	
1117		*	485.2 0.52	
1118		*	509.2 0.58	
1119		*	510.2 0.55	
1120		***	486.1 0.55	
1121		**	498.2 0.57	

FIG. 2
(Parte 46 de 55)

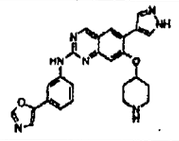
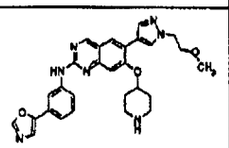
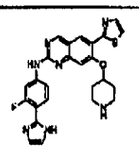
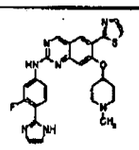
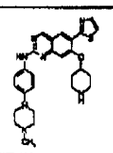
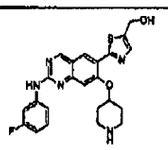
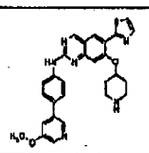
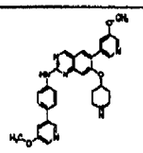
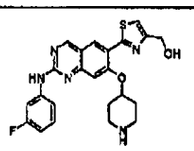
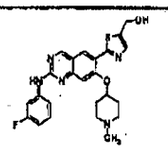
1122		****	454.1 0.57	
1123		*	512.2 0.62	
1124		****	488.1 0.50	
1125		***	502.1 0.52	
1126		****	502.1 0.48	
1127		**	452.1 0.65	
1128		****	511.0 0.57	
1129		**	535.1 0.48	
1130		***	452.1 0.64	
1131		**	466.1 0.66	

FIG. 2
(Parte 47 de 55)

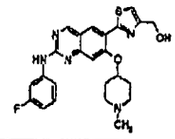
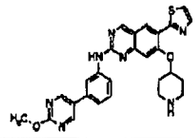
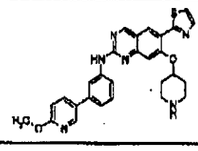
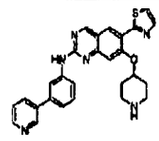
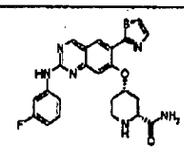
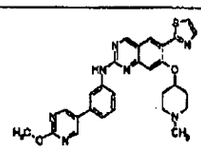
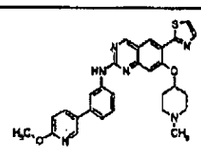
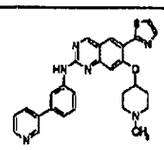
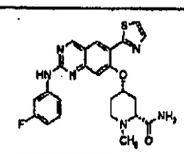
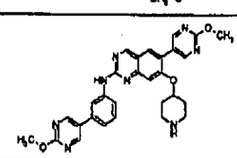
1132		**	466.1 0.65	
1133		****	512.1 0.68	
1134		***	511.1 0.73	
1135		****	481.1 0.53	
1136		*	465.1 0.66	
1137		***	526.1 0.69	
1138		**	525.1 0.75	
1139		****	495.1 0.54	
1140		*	479.0 0.68	
1141		*	537.0 0.66	

FIG. 2
(Parte 48 de 55)

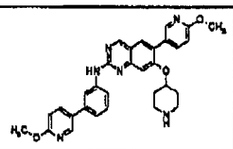
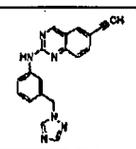
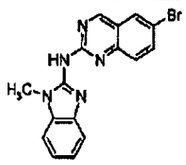
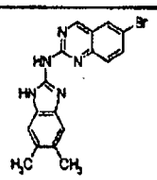
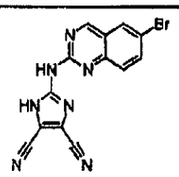
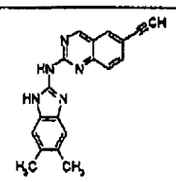
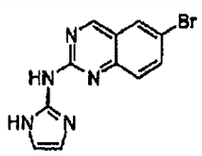
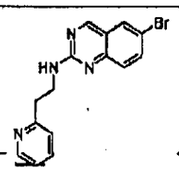
1142		*	535.1 0.74	
1143		****	327.1	
1144		*	354.9 2.57	
1145		*	368.9 2.86	
1146		*	339.9 2.94	
1147		*	314.0 2.63	
1148		*	289.9 2.20	
1149		*	328.9 1.78	

FIG. 2
(Parte 49 de 55)

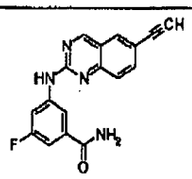
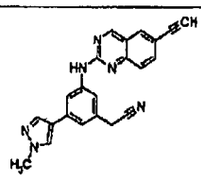
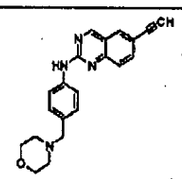
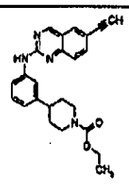
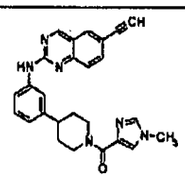
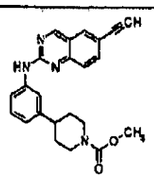
1150		**	307.0 2.58	
1151		***	365.3 0.84	
1152		*	345.2 2.15	
1153		*	387.1 0.98	
1154		**	437.2 0.72	
1155		*	387.2 0.99	

FIG. 2
(Parte 50 de 55)

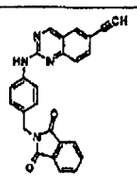
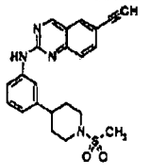
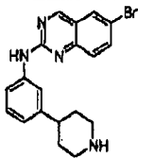
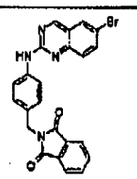
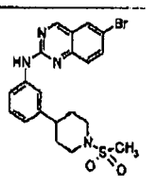
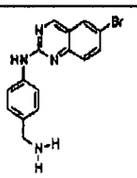
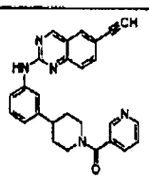
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FIG. 2
(Parte 51 de 55)

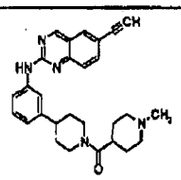
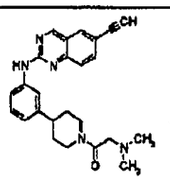
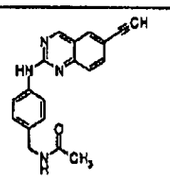
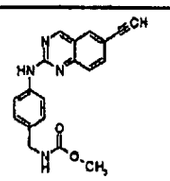
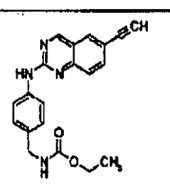
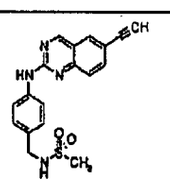
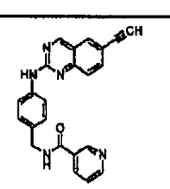
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1165		**	317.1 0.69	
1166		*	333.2 0.69	
1167		*	347.2 0.86	
1168		**	353.1 0.76	
1169		*	380.1 0.65	

FIG. 2
(Parte 52 de 55)

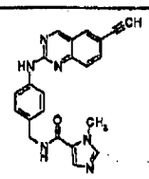
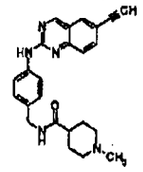
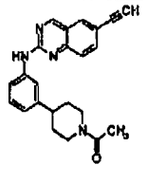
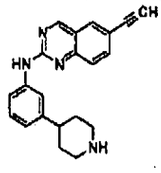
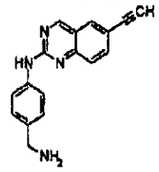
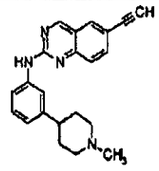
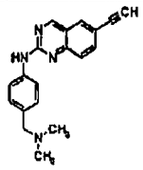
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1173		**	329.2 0.71	
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FIG. 2
(Parte 53 de 55)

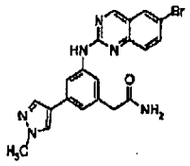
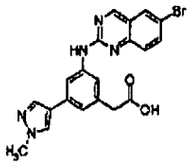
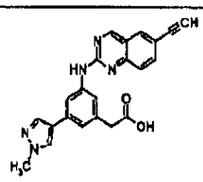
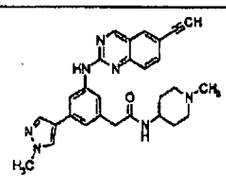
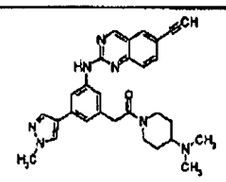
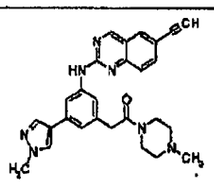
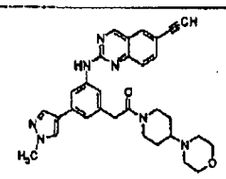
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1179		*	384.2 0.70	
1180		**	480.2 0.63	
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1182		****	466.3 0.62	
1183		**	536.4 0.63	

FIG. 2
(Parte 54 de 55)

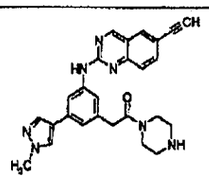
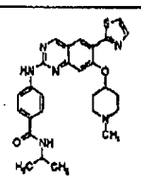
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FIG. 2
(Parte 55 de 55)

LISTADO DE SECUENCIAS

<110> Novartis Vaccines & Diagnostics, Inc.

<120> QUINAZOLINAS PARA LA INHIBICIÓN DE PDK1

<130> 20366-161WO1

<150> US 60/876,972

<151> 2006-12-22

<160> 2

<170> FastSEQ para Windows Versión 4.0

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<211> 11

<212> PRT

<213> Secuencia Artificial

<220>

<223> Péptido sintéticamente generado

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1 5 10

<210> 2

<211> 14

<212> PRT

<213> Secuencia Artificial

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<223> Péptido sintéticamente generado

<400> 2

Gly Gly Cys Gly Pro Lys Thr Pro Lys Lys Ala Lys Lys Leu

1 5 10

PATENT COOPERATION TREATY PCT/US2007/088392

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

NOVARTIS PHARMA AG
Patent Department
Postfach
CH-4002 Basel
SUISSE

Date of mailing *(day/month/year)*
10 June 2009 (10.06.2009)

Applicant's or agent's file reference
52100-WO-PCT

IMPORTANT NOTIFICATION

International application No.
PCT/US2007/088392

International filing date *(day/month/year)*
20 December 2007 (20.12.2007)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address

NOVARTIS VACCINES & DIAGNOSTICS, INC.
P.O. Box 8097
Emeryville, California 94602-8097
United States of America

State of Nationality: US
State of Residence: US
Telephone No.: 510-923-2585
Facsimile No.: 510-655-3542
E-mail address:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address

NOVARTIS AG
Lichtstrasse 35
CH-4056 Basel
Switzerland

State of Nationality: CH
State of Residence: CH
Telephone No.:
Facsimile No.:
E-mail address:
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 70 90

Authorized officer
Baechler Francois
e-mail pt12.pct@wipo.int
Telephone No. +41 22 338 74 12

Form PCT/IB/306 (January 2009) 1/D250DND70

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

(19) World Intellectual Property Organization
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(43) International Publication Date
3 July 2008 (03.07.2008)

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C07D 401/08 (2006.01)	*C07D 411/04* (2006.01)
C07D 401/12 (2006.01)	*C07D 413/14* (2006.01)
C07D 401/14 (2006.01)	*C07D 417/04* (2006.01)
C07D 403/04 (2006.01)	*A61K 31/517* (2006.01)
C07D 403/06 (2006.01)	*A61P 35/00* (2006.01)

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(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

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60/999,170	15 October 2007 (15.10.2007)	US

(71) Applicant *(for all designated States except US)*: **NOVARTIS VACCINES & DIAGNOSTICS, INC.** [US/US]; P.O. Box 8097, Emeryville, California 94602-8097 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **RAMURTHY, Savithri** [US/US]; 4560 Horton Street, Emeryville, California 94608-2916 (US). **LIN, Xiaodong** [US/US]; 4560 Horton Street, Emeryville, California 94608-2916 (US). **SUBRAMANIAN, Sharada** [US/US]; 4560 Horton Street, Emeryville, California 94608-2916 (US). **RICO, Alice, C.** [US/US]; 4560 Horton Street, Emeryville, California 94608-2916 (US). **WANG, Xiaojing, M.** [US/US]; 4560 Horton Street, Emeryville, California 94608-2916 (US). **JAIN, Rama** [US/US]; 4560 Horton Street, Emeryville, California 94608-2916 (US). **MURRAY, Jeremy, M.** [GB/US]; 4560 Horton Street, Emeryville, California 94608-2916 (US). **BASHAM, Steven, E.** [US/US]; 4560 Horton Street, Emeryville, California 94608-2916 (US). **WARNE, Robert, L.** [US/US]; 4560 Horton Street, Emeryville, California 94608-2916 (US). **SHU, Wei** [CN/US]; 4560 Horton Street, Emeryville, California 94608-2916 (US). **ZHOU, Yasheen** [US/US]; 4560 Horton Street, Emeryville, California 94608-2916 (US). **DOVE, Jeffrey** [US/US]; 4560 Horton Street, Emeryville,

[Continued on next page]

(54) Title: QUINAZOLINES FOR PDK1 INHIBITION

(57) Abstract: The invention provides novel compounds that are inhibitors of PDK1. Also provided are pharmaceutical compositions including the compounds, and methods of treating proliferative diseases, such as cancers, with the compounds or compositions.

Table 2

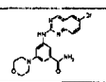
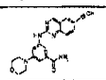
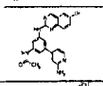
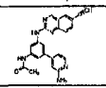
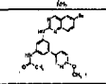
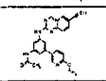
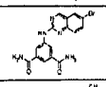
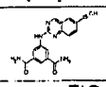
Example	Structure	Activity	Molecular Weight	LC/MS (4.5min run) MS (M+1) m/z Rt (min)	LC/MS (1.5min run) MS (M+1) m/z Rt (min)
177		*	428.2882	428/430 3.84	
178		***	373.4141	374.1 3.51	
179		**	448.3103	249/251 3.66	
180		***	394.4362	395.1 3.39	
181		*	464.3212	464/466 4.92	
182		***	409.4471	410.1 4.57	
183		*	386.2078	386/388 3.16	
184		**	331.3337	332.1 2.88	

FIG. 1 (PART 1 of 59)

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California 94608-2916 (US). **AIKAWA, Mina** [US/US]; 4560 Horton Street, Emeryville, California 94608-2916 (US). **AMIRI, Payman** [US/US]; 4560 Horton Street, Emeryville, California 94608-2916 (US).

(74) **Agents: GODDARD, Christine A.** et al.; Fish & Richardson P.C., P. O. Box 1022, Minneapolis, Minnesota 55440-1022 (US).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, 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.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, 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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— *with sequence listing part of description published separately in electronic form and available upon request from the International Bureau*

(88) **Date of publication of the international search report:**
16 October 2008

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/088392

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D239/84 C07D401/08 C07D401/12 C07D401/14 C07D403/04
C07D403/06 C07D403/12 C07D411/04 C07D413/14 C07D417/04
C07D417/14 A61K31/517 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/118256 A (KYOWA HAKKO KOGYO KK [JP]; KISHIKAWA KUNIYUKI; IMASE HIDETOMO; KASHIMA) 9 November 2006 (2006-11-09) examples 140,141,175-180,300-307,316-320,391	1-53
P,X	WO 2007/117607 A (NOVARTIS VACCINES & DIAGNOSTIC [US]; RAMURTHY SAVITHRI [US]; LIN XIADO) 18 October 2007 (2007-10-18) the whole document	1-53
E	WO 2008/068507 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; AQUILA BRIAN [US]; COOK) 12 June 2008 (2008-06-12) the whole document	1-53

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 August 2008	29/08/2008
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Bourghida, E

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/088392

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2008/020203 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; AQUILA BRIAN [US]; COOK) 21 February 2008 (2008-02-21) the whole document	1-53

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/088392

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

   a. type of material

   [X] a sequence listing

   [ ] table(s) related to the sequence listing

   b. format of material

   [ ] on paper

   [X] in electronic form

   c. time of filing/furnishing

   [ ] contained in the international application as filed

   [X] filed together with the international application in electronic form

   [ ] furnished subsequently to this Authority for the purpose of search

2. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/088392

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 37-53 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/088392

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006118256 A	09-11-2006	EP 1878727 A1	16-01-2008
WO 2007117607 A	18-10-2007	AR 060358 A1	11-06-2008
WO 2008068507 A	12-06-2008	NONE	
WO 2008020203 A	21-02-2008	UY 30547 A1	31-03-2008

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
NOVARTIS AG

REFERENCIA	Radicación No.	9 62868
	Solicitud internacional	PCT/US2007/088392
	Fecha inicio fase nacional	22/07/2009
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	9305

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de quince reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del titulo primero de la Circular Única Nº 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 14 AGO. 2009
adpa11