OPS

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

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Industria y Comercio

SUPERINTENDENCIA

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

08-74670

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: DERIVADOS DE PIRIMIDINA UTILIZADOS COMO INHIBIDORES DE CINASA PI-3

SOLICITANTE: NOVARTIS AG

DIRECCIÓN: Lichtstrasse 35, CH- 4056 Basel, Suiza

APODERADO: CARLOS R. OLARTE

BOGOTÁ: 18 de Julio de 2008

OLARTERAISBECK

1

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-074670- -00000-0000
Fecha: 2008-07-18 17:48:39 Dep: 2020 NUECREACIONE
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 611

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2008/000132**

SOLICITUD DE:

(1) [X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

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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

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TP 74.295

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(5) **PCT (86)**

Solicitud Internacional No. PCT/US2007/001708 Fecha Enero 22, 2007

Publicación Internacional No. WO 2007/084786 Fecha Julio 26, 2007

(6) **Título (54)** **DERIVADOS DE PIRIMIDINA UTILIZADOS COMO INHIBIDORES DE CINASA PI-3**

Clasificación Internacional (51) C07D 401/04, C07D 401/14, C07D 405/12, C07D 405/14, C07D 417/12, A61K 31/506, A61P 35/00

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

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US	Enero 20, 2006	60/760,789

(9) **Comprobante de pago No.** 08-57,450 **Fecha** Julio 18 de 2008

ANEXOS

2

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [ ] 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
- [ ] 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.
- [ ] 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.

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Nacionalidad: China

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Act: 411 PRESENTACION Folios: 611

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 57,450
FECHA : JULIO 18 DE 2008

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	4807180	18/07/2008	3,821,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	501,000.00
		TOTAL : $	501,000.00

SON: QUINIENTOS UN MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

TRADUCCIÓN OFICIAL DE UN DOCUMENTO QUE ESTÁ ORIGINALMENTE EN INGLÉS

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.

Traductor Ofic
JORGE E. SIERRA
Licencia 376 - 1993

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 Oficial
JORGE E. SIERRA F
Licencia N°6

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

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10

OLARTE RAISBECK

OLARTE RAISBECK & FRIERI LTDA.

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

Zayde Chahín
Jacqueline Chaparro
José Luis Londoño
Felipe Mendoza
Simón Salinas

Of Counsel
Guillermo Chahín
Graciela Mele

Power of Attorney

Poder

The undersigned,

El suscrito,

NOVARTIS AG

domiciled in

domiciliado en

Lichtstrasse 35, CH-4056 Basel / Switzerland

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.

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 Thaub

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

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

12

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 4 AUG. 2006

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

Heidi Fischer

STATE CHANCERY BASEL-CITY

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
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60/760,789 20 January 2006 (20.01.2006) US

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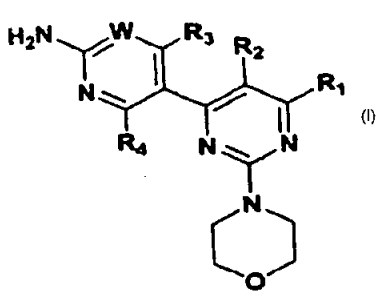
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[Continued on next page]

(54) Title: PYRIMIDINE DERIVATIVES USED AS PI-3 KINASE INHIBITORS



(I)

(57) **Abstract:** Phosphatidylinositol (PI) 3-kinase inhibitor compounds (I), their pharmaceutically acceptable salts, and prodrugs thereof ; compositions of the new compounds, either alone or in combination with at least one additional therapeutic agent, with a pharmaceutically acceptable carrier; and uses of the new compounds, either alone or in combination with at least one additional therapeutic agent, in the prophylaxis or treatment of proliferative diseases characterized by the abnormal activity of growth factors, protein serine/threonine kinases, and phospholipid kinases.

WO 2007/084786 A1

WO 2007/084786 A1



(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, 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, 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).

Published:

— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

PYRIMIDINE DERIVATIVES USED AS PI-3 KINASE INHIBITORS

FIELD OF THE INVENTION

[0001] The present invention relates to new phosphatidylinositol (PI) 3-kinase inhibitor compounds, their pharmaceutically acceptable salts, and prodrugs thereof; compositions of the new compounds, either alone or in combination with at least one additional therapeutic agent, with a pharmaceutically acceptable carrier; and uses of the new compounds, either alone or in combination with at least one additional therapeutic agent, in the prophylaxis or treatment of a number of diseases, in particular, those characterized by the abnormal activity of growth factors, receptor tyrosine kinases, protein serine/threonine kinases, G protein coupled receptors and phospholipid kinases and phosphatases.

BACKGROUND OF THE INVENTION

[0002] Phosphatidylinositol 3-kinases (PI3Ks) comprise a family of lipid and serine/threonine kinases that catalyze the transfer of phosphate to the D-3' position of inositol lipids to produce phosphoinositol-3-phosphate (PIP), phosphoinositol-3,4-diphosphate (PIP_2) and phosphoinositol-3,4,5-triphosphate (PIP_3) that, in turn, act as second messengers in signaling cascades by docking proteins containing pleckstrin-homology, FYVE, Phox and other phospholipid-binding domains into a variety of signaling complexes often at the plasma membrane ((Vanhaesebroeck et al., *Annu. Rev. Biochem* 70:535 (2001); Katso et al., *Annu. Rev. Cell Dev. Biol.* 17:615 (2001)). Of the two Class 1 PI3Ks, Class 1A PI3Ks are heterodimers composed of a catalytic p110 subunit (α, β, δ isoforms) constitutively associated with a regulatory subunit that can be p85α, p55α, p50α, p85β or p55γ. The Class 1B sub-class has one family member, a

heterodimer composed of a catalytic p110γ subunit associated with one of two regulatory subunits, p101 or p84 (Fruman et al., *Annu Rev. Biochem.* 67:481 (1998); Suire et al., *Curr. Biol.* 15:566 (2005)). The modular domains of the p85/55/50 subunits include Src Homology (SH2) domains that bind phosphotyrosine residues in a specific sequence context on activated receptor and cytoplasmic tyrosine kinases, resulting in activation and localization of Class 1A PI3Ks. Class 1B PI3K is activated directly by G protein-coupled receptors that bind a diverse repertoire of peptide and non-peptide ligands (Stephens et al., *Cell* 89:105 (1997)); Katso et al., *Annu. Rev. Cell Dev. Biol.* 17:615-675 (2001)). Consequently, the resultant phospholipid products of class I PI3K link upstream receptors with downstream cellular activities including proliferation, survival, chemotaxis, cellular trafficking, motility, metabolism, inflammatory and allergic responses, transcription and translation (Cantley et al., *Cell* 64:281 (1991); Escobedo and Williams, *Nature* 335:85 (1988); Fantl et al., *Cell* 69:413 (1992)).

[0003] In many cases, PIP2 and PIP3 recruit Akt, the product of the human homologue of the viral oncogene *v-Akt*, to the plasma membrane where it acts as a nodal point for many intracellular signaling pathways important for growth and survival (Fantl et al., *Cell* 69:413-423(1992); Bader et al., *Nat Rev. Cancer* 5:921 (2005); Vivanco and Sawyer, *Nat. Rev. Cancer* 2:489 (2002)). Aberrant regulation of PI3K, which often increases survival through Akt activation, is one of the most prevalent events in human cancer and has been shown to occur at multiple levels. The tumor suppressor gene *PTEN*, which dephosphorylates phosphoinositides at the 3' position of the inositol ring and in so doing antagonizes PI3K activity, is functionally deleted in a variety of tumors. In other tumors, the genes for the p110α isoform, *PIK3CA*, and for *Akt* are amplified and increased protein expression of their gene products has been demonstrated in several human cancers. Furthermore, mutations and translocation of p85α that serve to up-regulate the p85-p110 complex have been described in a few human cancers. Finally, somatic missense mutations in *PIK3CA* that activate downstream signaling pathways

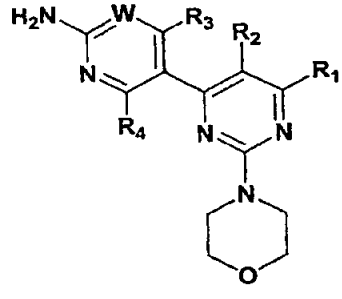
have been described at significant frequencies in a wide diversity of human cancers (Kang at el., *Proc. Natl. Acad. Sci. USA* 102:802 (2005); Samuels et al., *Science* 304:554 (2004); Samuels et al., *Cancer Cell* 7:561-573(2005)). These observations show that deregulation of phosphoinositol-3 kinase and the upstream and downstream components of this signaling pathway is one of the most common deregulations associated with human cancers and proliferative diseases (Parsons et al., *Nature* 436:792(2005); Hennessey at el., *Nature Rev. Drug Dis.* 4:988-1004 (2005)).

SUMMARY OF THE INVENTION

[0004] The present invention provides new phosphatidylinositol 3-kinase (PI3K) inhibitor compounds, pharmaceutical formulations that include the compounds, methods of inhibiting phosphatidylinositol 3-kinase (PI3K), and methods of treating proliferative diseases.

[0005] In one aspect of the present invention, new phosphatidylinositol 3-kinase (PI3K) inhibitor compounds that are pyrimidine-based compounds, their pharmaceutically acceptable salts, and prodrugs thereof are provided. The pyrimidine compounds, pharmaceutically acceptable salts, and prodrugs are PI3K inhibitors and are useful in the treatment of cellular proliferative diseases.

[0006] One embodiment of the invention provides a compound having Formula I:



I

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein,

W is CR_w or N, wherein R_w is selected from the group consisting of

(1) hydrogen,

(2) cyano,

(3) halogen,

(4) methyl,

(5) trifluoromethyl,

(6) sulfonamido;

R_1 is selected from the group consisting of

(1) hydrogen,

(2) cyano,

(3) nitro,

(4) halogen,

(5) substituted and unsubstituted alkyl,

(6) substituted and unsubstituted alkenyl,

(7) substituted and unsubstituted alkynyl,

(8) substituted and unsubstituted aryl,

(9) substituted and unsubstituted heteroaryl,

(10) substituted and unsubstituted heterocyclyl,

(11) substituted and unsubstituted cycloalkyl,

(12) $-COR_{1a}$,

(13) $-CO_2R_{1a}$,

(14) $-CONR_{1a}R_{1b}$,

(15) $-NR_{1a}R_{1b}$,

(16) $-NR_{1a}COR_{1b}$,

(17) $-NR_{1a}SO_2R_{1b}$,

(18) $-OCOR_{1a}$,

(19) $-OR_{1a}$,

(20) $-SR_{1a}$,

(21) $-SOR_{1a}$,

(22) $-SO_2R_{1a}$, and

(23) $-SO_2NR_{1a}R_{1b}$,

wherein R_{1a}, and R_{1b} are independently selected from the group consisting of

(a) hydrogen,

(b) substituted or unsubstituted alkyl,

(c) substituted and unsubstituted aryl,

(d) substituted and unsubstituted heteroaryl,

(e) substituted and unsubstituted heterocyclyl, and

(f) substituted and unsubstituted cycloalkyl;

R_2 is selected from the group consisting

(1) hydrogen,

(2) cyano,

(3) nitro,

(4) halogen,

(5) hydroxy,

(6) amino,

(7) substituted and unsubstituted alkyl,

(8) $-COR_{2a}$, and

(9) $-NR_{2a}COR_{2b}$,

wherein R_{2a}, and R_{2b} are independently selected from the group consisting of

(a) hydrogen, and

(b) substituted or unsubstituted alkyl;

R_3 is selected from the group consisting of

(1) hydrogen,

(2) cyano,

(3) nitro,

(4) halogen,

(5) substituted and unsubstituted alkyl,

(6) substituted and unsubstituted alkenyl,

(7) substituted and unsubstituted alkynyl,

(8) substituted and unsubstituted aryl,

(9) substituted and unsubstituted heteroaryl,

(10) substituted and unsubstituted heterocyclyl,

(11) substituted and unsubstituted cycloalkyl,

(12) $-COR_{3a}$,

(13) $-NR_{3a}R_{3b}$,

(14) $-NR_{3a}COR_{3b}$,

(15) $-NR_{3a}SO_2R_{3b}$,

(16) $-OR_{3a}$,

(17) $-SR_{3a}$,

(18) $-SOR_{3a}$,

(19) $-SO_2R_{3a}$, and

(20) $-SO_2NR_{3a}R_{3b}$,

wherein R_{3a}, and R_{3b} are independently selected from the group consisting of

(a) hydrogen,

(b) substituted or unsubstituted alkyl,

(c) substituted and unsubstituted aryl,

(d) substituted and unsubstituted heteroaryl,

(e) substituted and unsubstituted heterocyclyl, and

(f) substituted and unsubstituted cycloalkyl; and

R_4 is selected from the group consisting of

(1) hydrogen, and

(2) halogen.

[0007] In another embodiment thereof, R_1 comprises substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, or substituted or unsubstituted heterocyclylalkyl.

[0008] In a more particular embodiment, W is CH.

[0009] In another embodiment, W is N. In a more particular embodiment thereof, R_3 is =O.

[0010] In another embodiment, R_1 is selected from the group consisting of

(1) substituted and unsubstituted alkyl,

(2) substituted and unsubstituted aryl,

(3) substituted and unsubstituted heteroaryl,

(4) substituted and unsubstituted heterocyclyl,

(5) substituted and unsubstituted cycloalkyl,

(6) $-OR_{1a}$, and

(7) $-NR_{1a}R_{1b}$,

wherein R_{1a} and R_{1b} are independently selected from the group consisting of

(a) substituted and unsubstituted heteroaryl, and

(b) substituted and unsubstituted heterocyclyl.

[0011] In another embodiment R_1 is substituted or unsubstituted heterocyclyl, or substituted or unsubstituted -O-heterocyclyl. In another embodiment, R_1 is substituted or unsubstituted morpholinyl; more particular still, R_1 is unsubstituted N-linked morpholinyl.

[0012] In another embodiment thereof, R_1 comprises substituted or unsubstituted heterocyclylalkyl, or substituted or unsubstituted heteroarylalkyl. In another embodiment, R_1 comprises substituted or unsubstituted morpholinyl; more particular still, morpholinyl comprises N-linked morpholinyl.

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[0013] In another embodiment, R_1 is substituted or unsubstituted tetrahydropyran or substituted or unsubstituted tetrahydropyranyloxy. More particular still, R_1 is unsubstituted 4-tetrahydropyranyloxy.

[0014] In another embodiment thereof, R_1 comprises substituted or unsubstituted tetrahydropyran. In a more particular embodiment, tetrahydropyran comprises 4-tetrahydropyranyloxy.

[0015] In another embodiment, R_1 is substituted or unsubstituted tetrahydrofuran or substituted or unsubstituted tetrahydrofuranyloxy. More particular still, R_1 is unsubstituted 3-tetrahydrofuranyloxy.

[0016] In another embodiment embodiment, R_1 comprises substituted or unsubstituted tetrahydrofuran. In another embodiment thereof, tetrahydrofuran comprises 3-tetrahydrofuranyloxy.

[0017] In another embodiment, R_2 is selected from the group consisting

(1) hydrogen,
(2) cyano,
(3) hydroxy,
(4) halogen,
(5) amino,
(6) methyl, and
(7) trifluoromethyl.

[0018] In another embodiment, R_2 is hydrogen or halogen. In a more particular embodiment, R_2 is hydrogen.

[0019] In another embodiment, R_3 is selected from the group consisting of

(1) cyano,
(2) nitro,

(3) halogen,

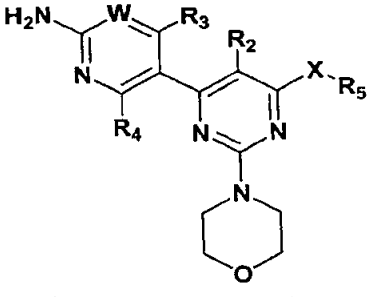
(4) hydroxy,

(5) amino, and

(6) trifluoromethyl.

[0020] In another embodiment, R_3 is trifluoromethyl. In another embodiment, R_3 is cyano.

[0021] Another embodiment of the invention provides a compound having Formula II:



II

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein,

W is CR_w or N, wherein R_w is selected from the group consisting of

(1) hydrogen,

(2) cyano,

(3) halogen,

(4) methyl,

(5) trifluoromethyl, and

(6) sulfonamido;

X is O, S, NH, or a direct bond;

R_2 is selected from the group consisting

(1) hydrogen,

(2) cyano,

(3) nitro,

(4) halogen,

(5) hydroxy,

(6) amino,

(7) substituted and unsubstituted alkyl,

(8) $-COR_{2a}$, and

(9) $-NR_{2a}COR_{2b}$,

wherein R_{2a}, and R_{2b} are independently selected from the group consisting of

(a) hydrogen, and

(b) substituted or unsubstituted alkyl;

R_3 is selected from the group consisting of

(1) hydrogen,

(2) cyano,

(3) nitro,

(4) halogen,

(5) substituted and unsubstituted alkyl,

(6) substituted and unsubstituted alkenyl,

(7) substituted and unsubstituted alkynyl,

(8) substituted and unsubstituted aryl,

(9) substituted and unsubstituted heteroaryl,

(10) substituted and unsubstituted heterocyclyl,

(11) substituted and unsubstituted cycloalkyl,

(12) $-COR_{3a}$,

(13) $-NR_{3a}R_{3b}$,

(14) $-NR_{3a}COR_{3b}$,

(15) $-NR_{3a}SO_2R_{3b}$,

(16) $-OR_{3a}$,

(17) $-SR_{3a}$,

(18) $-SOR_{3a}$,

(19) $-SO_2R_{3a}$, and

(20) $-SO_2NR_{3a}R_{3b}$,

wherein R_{3a}, and R_{3b} are independently selected from the group consisting of

(a) hydrogen,

(b) substituted or unsubstituted alkyl,

(c) substituted and unsubstituted aryl,

(d) substituted and unsubstituted heteroaryl,

(e) substituted and unsubstituted heterocyclyl, and

(f) substituted and unsubstituted cycloalkyl;

R_4 is selected from the group consisting of

(1) hydrogen, and

(2) halogen; and

R_5 is selected from the group consisting of

(1) substituted and unsubstituted cycloalkyl,

(2) substituted and unsubstituted heterocyclyl,

(3) substituted and unsubstituted aryl, and

(4) substituted and unsubstituted heteroaryl.

In another embodiment of Formula II, R_2 is selected from the group consisting of

(1) hydrogen,

(2) cyano,

(3) hydroxy,

(4) amino,

(5) halogen, and

(6) substituted and unsubstituted C_{1-3} alkyl.

In another embodiment of Formula II, R_3 is selected from the group consisting of

(1) hydrogen,

(2) cyano,

(3) thio,

(4) halogen,

(5) nitro,

(6) substituted and unsubstituted alkyl,

(7) substituted and unsubstituted alkenyl,

(8) substituted and unsubstituted alkynyl,

(9) $-OR_{3a}$,

(10) $-NR_{3a}R_{3b}$,

(11) $-COR_{3a}$, and

(12) $-NR_{3a}COR_{3b}$,

wherein R_{3a}, and R_{3b} are independently selected from the group consisting of

(a) hydrogen, and

(b) substituted or unsubstituted alkyl.

[0022] In another embodiment of Formula II, R_3 is trifluoromethyl. In another embodiment, W is CH. In another embodiment, R_2 is H.

[0023] In another embodiment of Formula II, R_5 is selected from the group consisting of

(1) substituted or unsubstituted morpholinyl,

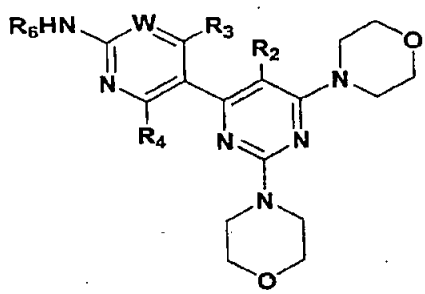
(2) substituted or unsubstituted tetrahydropyranyl, and

(3) substituted or unsubstituted tetrahydrofuranyl.

[0024] In a more particular embodiment thereof, R_5 is N-linked morpholinyl; more particular still, X is a direct link. In another more particular embodiment, R_5 is 4-tetrahydropyranyl; more particular still, X is O. In another embodiment, R_5 is 3-tetrahydrofuranyl; more particular still, X is O.

[0025] In another embodiment, W is N. In a more particular embodiment thereof, R_3 is =O.

[0026] Another embodiment of the invention provides a compound having Formula III:



III

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein,

W is CR_w or N, wherein R_w is selected from the group consisting of

(1) hydrogen,

(2) cyano,

(3) halogen,

(4) methyl,

(5) trifluoromethyl, and

(6) sulfonamido;

R_2 is selected from the group consisting

(1) hydrogen,

(2) cyano,

(3) nitro,

(4) halogen,

(5) hydroxy,

(6) amino,

(7) substituted and unsubstituted alkyl,

(8) $-COR_{2a}$, and

(9) $-NR_{2a}COR_{2b}$,

wherein R_{2a}, and R_{2b} are independently selected from the group consisting of

(a) hydrogen, and

(b) substituted or unsubstituted alkyl;

R_3 is selected from the group consisting of

(1) hydrogen,

(2) cyano,

(3) nitro,

(4) halogen,

(5) substituted and unsubstituted alkyl,

(6) substituted and unsubstituted alkenyl,

(7) substituted and unsubstituted alkynyl,

(8) substituted and unsubstituted aryl,

(9) substituted and unsubstituted heteroaryl,

(10) substituted and unsubstituted heterocyclyl,

(11) substituted and unsubstituted cycloalkyl,

(12) $-COR_{3a}$,

(13) $-NR_{3a}R_{3b}$,

(14) $-NR_{3a}COR_{3b}$,

(15) $-NR_{3a}SO_2R_{3b}$,

(16) $-OR_{3a}$,

(17) $-SR_{3a}$,

(18) $-SOR_{3a}$,

(19) $-SO_2R_{3a}$, and

(20) $-SO_2NR_{3a}R_{3b}$,

wherein R_{3a}, and R_{3b} are independently selected from the group consisting of

(a) hydrogen,

(b) substituted or unsubstituted alkyl,

(c) substituted and unsubstituted aryl,

(d) substituted and unsubstituted heteroaryl,

(e) substituted and unsubstituted heterocyclyl, and

(f) substituted and unsubstituted cycloalkyl;

R_4 is selected from the group consisting of

(1) hydrogen, and

(2) halogen; and

R_6 is selected from the group consisting of

(1) hydrogen,

(2) substituted and unsubstituted alkyl, and

(3) substituted and unsubstituted cycloalkyl.

[0027] In another embodiment of Formula III, R_2 is selected from the group consisting

(1) hydrogen,

(2) cyano,

(3) hydroxy,

(4) halogen,

(5) amino,

(6) methyl, and

(7) trifluoromethyl.

[0028] In another embodiment of Formula III, R_3 is selected from the group consisting of

(1) cyano,

(2) nitro,

(3) halogen,

(4) hydroxy,

(5) amino, and

(6) trifluoromethyl.

[0029] In another embodiment of Formula III, R_6 is selected from the group consisting

(1) hydrogen,

(2) methyl, and

(3) ethyl.

[0030] Another embodiment provides a method for inhibiting phosphorylation of Akt in a human or animal subject, comprising administering to a human or animal subject an effective amount of a compound of any one of the embodiments provided herein.

[0031] Another embodiment provides a composition, comprising a pharmaceutically acceptable carrier and an amount of a compound of any one of the embodiments provided herein effective to inhibit PI3-K activity in a human or animal subject when administered thereto. In a more particular embodiment thereof, the composition is effective to inhibit PI3-K alpha activity in a human or animal subject when administered thereto.

[0032] Another embodiment provides a composition, comprising a pharmaceutically acceptable carrier, an amount of a compound of any one of the embodiments provided herein effective to inhibit PI3-K activity in a human or animal subject when administered thereto, and at least one additional agent for the treatment of cancer. In a more particular embodiment thereof, at least one additional agent for the treatment of cancer is vatalanib (PTK-787), imatinib or gefitinib. Alternatively, the at least one additional agent for the treatment of cancer is selected from the kinase inhibitors, anti-estrogens, anti-androgens, other inhibitors, cancer chemotherapeutic drugs, alkylating agents, chelating agents, biological response modifiers, cancer vaccines, or antisense therapies (groups A-J) listed below. Further, the at least one additional agent

for the treatment of cancer is selected from radiation, nucleoside analogues, or antimitotic agents.

[0033] Another embodiment provides a method for treating a condition by modulation of PI3-K activity comprising administering to a human or animal subject in need of such treatment an effective amount of a compound of any one of the embodiments provided herein. In a more particular embodiment, the compound has an IC_{50} value of less than about 1 μM with respect to inhibition of PI3K. In another more particular embodiment, the condition is cancer.

[0034] Another embodiment provides a method for inhibiting PI3-K activity in a human or animal subject, comprising administering to the human or animal subject a composition comprising an amount of a compound of any one of the embodiments provided herein effective to inhibit PI3-K activity the human or animal subject.

[0035] Another embodiment provides a method for treating a cancer disorder in a human or animal subject, comprising administering to the human or animal subject a composition comprising an amount of a compound of any one of the embodiments provided herein effective to inhibit PI3-K activity the human or animal subject. A more particular embodiment further comprises administering to the human or animal subject at least one additional agent for the treatment of cancer. In another embodiment, the at least one additional agent for the treatment of cancer is vatalanib, imatinib or gefitinib. Alternatively, the at least one additional agent for the treatment of cancer is selected from the kinase inhibitors, anti-estrogens, anti-androgens, other inhibitors, cancer chemotherapeutic drugs, alkylating agents, chelating agents, biological response modifiers, cancer vaccines, or antisense therapies (groups A-J) listed below.

[0036] In another embodiment of any of the aforementioned, the cancer is breast cancer, bladder cancer, colon cancer, glioma, glioblastoma, lung cancer, hepatocellular cancer, gastric cancer, melanoma, thyroid cancer, endometrial cancer, renal cancer,

cervical cancer, pancreatic cancer, esophageal cancer, prostate cancer, brain cancer, or ovarian cancer.

[0037] Another embodiment provides a method for modulating phosphorylation of Akt comprising contacting a compound of any one of the embodiments described herein with a cell. Another embodiment provides a method for modulating phosphorylation of Akt comprising contacting a cell with a compound of any one of the embodiments described herein. In a more particular embodiment thereof, said modulation is inhibiting. In a more particular embodiment, the compound has an EC_{50} value of less than about 1 μM with respect to inhibition of pAKT. In a more particular embodiment still, the compound has an EC_{50} value of less than about 0.5 μM with respect to inhibition of pAKT. In an even more particular embodiment, the compound has an EC_{50} value of less than about 0.1 μM with respect to inhibition of pAKT.

[0038] Another embodiment provides a compound of any one of the embodiments described herein for use in the treatment of cancer.

[0039] Another embodiment provides for the use of a compound of any one of the embodiments described herein in the manufacture of a medicament for the treatment for cancer.

[0040] Another embodiment provides a method of modulating phosphorylation of Akt comprising contacting a compound of the present invention with a cell. In a more particular embodiment thereof, the compound has an EC_{50} value of less than about 1 μM with respect to inhibition of pAKT.

[0041] Another embodiment provides a compound of any one of the embodiments described herein, and a package insert or other labeling including directions for treating a cellular proliferative disease by administering a PI3-K inhibitory amount of the compound.

[0042] The invention further provides compositions, kits, methods of use, and methods of manufacture as described in the detailed description of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0043] The foregoing aspects and many of the attendant advantages of this invention will become more readily appreciated as the same become better understood by reference to the following detailed description, when taken in conjunction with the accompanying drawings, wherein:

FIGURE 1 is a graph illustrating tumor growth inhibition for a representative compound of the invention at two dosages compared to a control vehicle;

FIGURE 2 is a graph illustrating tumor growth inhibition for a representative compound of the invention at three dosages compared to a control vehicle;

FIGURE 3 is a graph illustrating tumor growth inhibition for a representative compound of the invention at two dosages compared to a control vehicle;

FIGURE 4 is a graph illustrating tumor growth inhibition for a representative compound of the invention at two dosages compared to a control vehicle; and

FIGURE 5 is a graph illustrating tumor growth inhibition for a representative compound of the invention compared to a control vehicle.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0044] Phosphotidylinositol-3-kinase (PI3K) mediates the signal from various growth factors to regulate cell proliferation and survival. A Serine/Threonine (Ser/Thr, or S/T) protein kinase, termed Akt, is identified as a downstream target of PI 3-kinase. This protein kinase is recruited to the cell membrane by interaction of its pleckstrin homology domain with PI3K products, phosphatidylinositol-3,4,5-triphosphate (PIP_3), and phosphatidylinositol-3,4-biphosphate (PIP_2), where it is activated by phosphorylation of its catalytic domain by 3-Phosphoinositide-dependent Kinase-1 (PDK-1). Akt is further activated by phosphorylation of a serine in its C-terminal hydrophobic motif by another

candidate kinase (PDK-2). The activation of Akt acts downstream to regulate additional kinases many of which are implicated in cellular processes that control survival, proliferation, metabolism and growth translation. PI3K can also drive cellular processes that impact transformation, cellular proliferation, cytoskeletal rearrangement and survival through a parallel pathway that does not involve Akt (Hennessy et al., *Nat. Rev. Drug Disc.* 4:988-1004 (2005)). Two of these pathways are activation of the small GTP-binding proteins Cdc42 and Rac1 and activation of the serum and glucocorticoid-inducible kinase (SGK). Cdc42 and Rac1, which regulate cytoskeletal movement and cell motility and can function as oncogenes when over-expressed, are also linked to the RAS pathway. Thus, PI3K activity generates 3'-phosphatidylinositol lipids that act as a nodal point to stimulate a diversity of downstream signaling pathways.

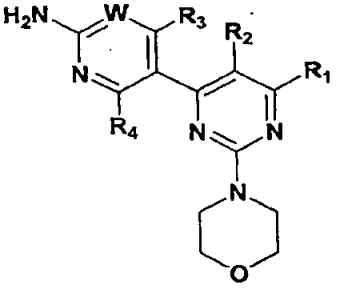
[0045] That these pathways impact cellular properties proliferation, survival, motility and morphology that are often disrupted in cancer, proliferative diseases, thrombotic diseases and inflammation, among others, suggests that compounds inhibiting PI3K (and isoforms thereof) have utility, either as a single agent or in combination, in the treatment of these diseases. In cancer, deregulation of the PI3K/Akt pathway is extensively documented, including overexpression of the *PIK3CA* gene, activating mutations of the *PIK3CA* gene, overexpression of Akt, mutations of *PDK-1*, and deletions/inactivation of *PTEN* (Parsons et al., *Nature* 436:792 (2005); Hennessy et al., *Nat. Rev. Drug Disc.* 4:988 (2005); Stephens et al., *Curr. Opin. Pharmacol.* 5:1 (2005); Bonneau and Longy, *Human Mutation* 16:109 (2000) and Ali et al., *J. Natl. Can. Inst.* 91:1922 (1999)). Recent findings indicate that *PIK3CA* is frequently mutated (>30%) in various solid tumors in humans (Samuels and Ericson, *Curr. Opin. Oncology* 18:77 (2005)) and the most frequent of these mutations promote cell growth and invasion (Samuels et al., *Cancer Cell* 7:561 (2005), and are transforming (Kang et al., *Proc. Natl. Acad. Sci. USA* 102:802 (2005), Zhao et al., *Proc. Natl. Acad. Sci. USA* 102:18443 (2005)). Thus, inhibitors of PI3K, particularly of the p110α isoform encoded by

PIK3CA and its mutations, will be useful in the treatment of cancers driven by these mutations and deregulations.

[0046] The present invention provides novel compounds that act as inhibitors of serine threonine kinases, lipid kinases, and, more particularly, as inhibitors of phosphatidylinositol 3-kinase (PI3K) function. The compounds provided herein can be formulated into pharmaceutical formulations that are useful in treating patients with a need for an inhibitor of PI3K, especially, in particular embodiments, to provide compositions and methods for reducing cellular proliferation and increasing cell death in the treatment of cancer.

[0047] In one aspect of the present invention, new phosphatidylinositol 3-kinase (PI3K) inhibitor compounds, their pharmaceutically acceptable salts, and prodrugs thereof are provided. The PI3K inhibitor compounds are pyrimidine-based compounds. The pyrimidine compounds, pharmaceutically acceptable salts, and prodrugs are PI3K inhibitors and are useful in the treating cellular proliferative diseases.

[0048] In one embodiment, the phosphatidylinositol 3-kinase (PI3K) inhibitor compounds of the invention have the formula (I):



I

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein,

W is CR_w or N, wherein R_w is selected from the group consisting of

(1) hydrogen,

(2) cyano,

(3) halogen,

(4) methyl,

(5) trifluoromethyl, and

(6) sulfonamido;

R_1 is selected from the group consisting of

(1) hydrogen,

(2) cyano,

(3) nitro,

(4) halogen,

(5) substituted and unsubstituted alkyl,

(6) substituted and unsubstituted alkenyl,

(7) substituted and unsubstituted alkynyl,

(8) substituted and unsubstituted aryl,

(9) substituted and unsubstituted heteroaryl,

(10) substituted and unsubstituted heterocyclyl,

(11) substituted and unsubstituted cycloalkyl,

(12) $-COR_{1a}$,

(13) $-CO_2R_{1a}$,

(14) $-CONR_{1a}R_{1b}$,

(15) $-NR_{1a}R_{1b}$,

(16) $-NR_{1a}COR_{1b}$,

(17) $-NR_{1a}SO_2R_{1b}$,

(18) $-OCOR_{1a}$,

(19) $-OR_{1a}$,

(20) $-SR_{1a}$,

(21) $-SOR_{1a}$,

(22) $-SO_2R_{1a}$, and

(23) $-SO_2NR_{1a}R_{1b}$,

wherein R_{1a}, and R_{1b} are independently selected from the group consisting of

(a) hydrogen,

(b) substituted or unsubstituted alkyl,

(c) substituted and unsubstituted aryl,

(d) substituted and unsubstituted heteroaryl,

(e) substituted and unsubstituted heterocyclyl, and

(f) substituted and unsubstituted cycloalkyl;

R_2 is selected from the group consisting

(1) hydrogen,

(2) cyano,

(3) nitro,

(4) halogen,

(5) hydroxy,

(6) amino,

(7) substituted and unsubstituted alkyl,

(8) $-COR_{2a}$, and

(9) $-NR_{2a}COR_{2b}$,

wherein R_{2a}, and R_{2b} are independently selected from the group consisting of

(a) hydrogen, and

(b) substituted or unsubstituted alkyl;

R_3 is selected from the group consisting of

(1) hydrogen,

(2) cyano,

(3) nitro,

(4) halogen,

(5) substituted and unsubstituted alkyl,

(6) substituted and unsubstituted alkenyl,

(7) substituted and unsubstituted alkynyl,

(8) substituted and unsubstituted aryl,

(9) substituted and unsubstituted heteroaryl,

(10) substituted and unsubstituted heterocyclyl,

(11) substituted and unsubstituted cycloalkyl,

(12) $-COR_{3a}$,

(13) $-NR_{3a}R_{3b}$,

(14) $-NR_{3a}COR_{3b}$,

(15) $-NR_{3a}SO_2R_{3b}$,

(16) $-OR_{3a}$,

(17) $-SR_{3a}$,

(18) $-SOR_{3a}$,

(19) $-SO_2R_{3a}$, and

(20) $-SO_2NR_{3a}R_{3b}$,

wherein R_{3a}, and R_{3b} are independently selected from the group consisting of

(a) hydrogen,

(b) substituted or unsubstituted alkyl,

(c) substituted and unsubstituted aryl,

(d) substituted and unsubstituted heteroaryl,

(e) substituted and unsubstituted heterocyclyl, and

(f) substituted and unsubstituted cycloalkyl; and

R_4 is selected from the group consisting of

(1) hydrogen, and

(2) halogen.

[0049] Substituted R_1 comprises substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, or substituted or unsubstituted heterocyclylalkyl.

[0050] In one embodiment, W is CH.

[0051] In another embodiment, W is N. In a more particular embodiment thereof, R_3 is =O.

[0052] In one embodiment, R_1 is selected from the group consisting of

(1) substituted and unsubstituted alkyl,

(2) substituted and unsubstituted aryl,

(3) substituted and unsubstituted heteroaryl,

(4) substituted and unsubstituted heterocyclyl,

(5) substituted and unsubstituted cycloalkyl,

(6) $-OR_{1a}$, and

(7) $-NR_{1a}R_{1b}$,

wherein R_{1a} and R_{1b} are independently selected from the group consisting of

(a) substituted and unsubstituted heteroaryl, and

(b) substituted and unsubstituted heterocyclyl.

[0053] In another embodiment R_1 is substituted or unsubstituted heterocyclyl, or substituted or unsubstituted -O-heterocyclyl. In another embodiment, R_1 is substituted or unsubstituted morpholinyl; more particular still, R_1 is unsubstituted N-linked morpholinyl.

[0054] In another embodiment, R_1 is substituted or unsubstituted tetrahydropyran or substituted or unsubstituted tetrahydropyranyloxy. More particular still, R_1 is unsubstituted 4-tetrahydropyranyloxy.

[0055] In another embodiment, R_1 is substituted or unsubstituted tetrahydrofuran or substituted or unsubstituted tetrahydrofuranyloxy. More particular still, R_1 is unsubstituted 3-tetrahydrofuranyloxy.

[0056] In one embodiment, R_1 comprises substituted or unsubstituted heterocyclylalkyl, or substituted or unsubstituted heteroarylalkyl. In one embodiment, R_1 comprises substituted or unsubstituted morpholinyl. In one embodiment, morpholinyl comprises N-linked morpholinyl. In one embodiment, R_1 comprises substituted or unsubstituted tetrahydropyran. In one embodiment, tetrahydropyran comprises

4-tetrahydropyranyloxy. In one embodiment, tetrahydropyran comprises 3-tetrahydropyranyloxy. In one embodiment, R_1 comprises substituted or unsubstituted tetrahydrofuran. In one embodiment, tetrahydrofuran comprises 3-tetrahydrofuranyloxy. In one embodiment, R_1 comprises substituted or unsubstituted piperidine. In one embodiment, piperidine comprises 4-piperidinyloxy. In another embodiment, piperidine comprises 3-piperidinyloxy. In one embodiment, R_1 comprises substituted or unsubstituted pyrrolidine. In one embodiment, pyrrolidine comprises 3-pyrrolidinyloxy.

[0057] In one embodiment, R_2 is selected from the group consisting

(1) hydrogen,

(2) cyano,

(3) hydroxy,

(4) halogen,

(5) amino,

(6) methyl, and

(7) trifluoromethyl.

In one embodiment, R_3 is selected from the group consisting of

(1) cyano,

(2) nitro,

(3) halogen,

(4) hydroxy,

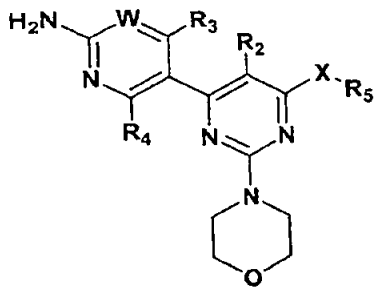
(5) amino, and

(6) trifluoromethyl.

[0058] In one embodiment, R_3 is trifluoromethyl. In one embodiment, R_3 is cyano.

[0059] In one embodiment, the phosphatidylinositol 3-kinase (PI3K) inhibitor compounds of the invention have the formula (II):

41



II

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein,

W is CR_w or N, wherein R_w is selected from the group consisting of

(1) hydrogen,

(2) cyano,

(3) halogen,

(4) methyl,

(5) trifluoromethyl, and

(6) sulfonamido;

X is O, S, NH, or a direct bond;

R_2 is selected from the group consisting

(1) hydrogen,

(2) cyano,

(3) nitro,

(4) halogen,

(5) hydroxy,

(6) amino,

(7) substituted and unsubstituted alkyl,

(8) $-COR_{2a}$, and

(9) $-NR_{2a}COR_{2b}$,

wherein R_{2a}, and R_{2b} are independently selected from the group consisting of

(a) hydrogen, and

(b) substituted or unsubstituted alkyl;

R_3 is selected from the group consisting of

(1) hydrogen,

(2) cyano,

(3) nitro,

(4) halogen,

(5) substituted and unsubstituted alkyl,

(6) substituted and unsubstituted alkenyl,

(7) substituted and unsubstituted alkynyl,

(8) substituted and unsubstituted aryl,

(9) substituted and unsubstituted heteroaryl,

(10) substituted and unsubstituted heterocyclyl,

(11) substituted and unsubstituted cycloalkyl,

(12) $-COR_{3a}$,

(13) $-NR_{3a}R_{3b}$,

(14) $-NR_{3a}COR_{3b}$,

(15) $-NR_{3a}SO_2R_{3b}$,

(16) $-OR_{3a}$,

(17) $-SR_{3a}$,

(18) $-SOR_{3a}$,

(19) $-SO_2R_{3a}$, and

(20) $-SO_2NR_{3a}R_{3b}$,

wherein R_{3a}, and R_{3b} are independently selected from the group consisting of

(a) hydrogen,

(b) substituted or unsubstituted alkyl,

(c) substituted and unsubstituted aryl,

(d) substituted and unsubstituted heteroaryl,

(e) substituted and unsubstituted heterocyclyl, and

(f) substituted and unsubstituted cycloalkyl;

R_4 is selected from the group consisting of

(1) hydrogen, and

(2) halogen; and

R_5 is selected from the group consisting of

(1) substituted and unsubstituted cycloalkyl,

(2) substituted and unsubstituted heterocyclyl,

(3) substituted and unsubstituted aryl, and

(4) substituted and unsubstituted heteroaryl.

[0060] In one embodiment, W is CH.

[0061] In one embodiment, W is N. In a more particular embodiment thereof, R_3 is =O.

[0062] In one embodiment, R_2 is selected from the group consisting of

(1) hydrogen,

(2) cyano,

(3) hydroxy,

(4) amino,

(5) halogen, and

(6) substituted and unsubstituted C_{1-3} alkyl.

[0063] In one embodiment, R_3 is selected from the group consisting of

(1) hydrogen,

(2) cyano,

(3) $-SR_{3a}$

(4) halogen,

(5) nitro,

(6) substituted and unsubstituted alkyl,

(7) substituted and unsubstituted alkenyl,

(8) substituted and unsubstituted alkynyl,

(9) $-OR_{3a}$,

(10) $-NR_{3a}R_{3b}$,

(11) $-COR_{3a}$, and

(12) $-NR_{3a}COR_{3b}$,

wherein R_{3a}, and R_{3b} are independently selected from the group consisting of

(a) hydrogen, and

(b) substituted or unsubstituted alkyl.

[0064] In one embodiment, R_3 is trifluoromethyl.

[0065] In one embodiment, R_5 is selected from the group consisting of

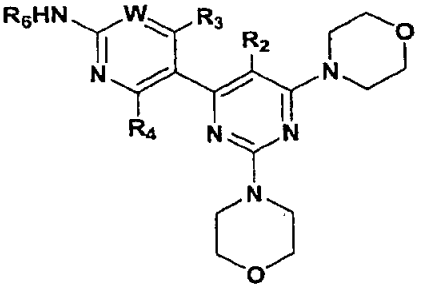
(1) substituted or unsubstituted morpholinyl,

(2) substituted or unsubstituted tetrahydropyranyl, and

(3) substituted or unsubstituted tetrahydrofuranyl.

[0066] In a more particular embodiment thereof, R_5 is N-linked morpholinyl; more particular still, X is a direct link. In another more particular embodiment, R_5 is 4-tetrahydropyranyl; more particular still, X is O. In another embodiment, R_5 is 3-tetrahydrofuranyl; more particular still, X is O.

[0067] In one embodiment, the phosphatidylinositol 3-kinase (PI3K) inhibitor compounds of the invention have the formula (III):



III

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein,

W is CR_w or N, wherein R_w is selected from the group consisting of

(1) hydrogen,

(2) cyano,

(3) halogen,

(4) methyl,

(5) trifluoromethyl, and

(6) sulfonamido;

R_2 is selected from the group consisting

(1) hydrogen,

(2) cyano,

(3) nitro,

(4) halogen,

(5) hydroxy,

(6) amino,

(7) substituted and unsubstituted alkyl,

(8) $-COR_{2a}$, and

(9) $-NR_{2a}COR_{2b}$,

wherein R_{2a}, and R_{2b} are independently selected from the group consisting of

(a) hydrogen, and

(b) substituted or unsubstituted alkyl;

R_3 is selected from the group consisting of

(1) hydrogen,

(2) cyano,

(3) nitro,

(4) halogen,

(5) substituted and unsubstituted alkyl,

(6) substituted and unsubstituted alkenyl,

(7) substituted and unsubstituted alkynyl,

(8) substituted and unsubstituted aryl,

(9) substituted and unsubstituted heteroaryl,

(10) substituted and unsubstituted heterocyclyl,

(11) substituted and unsubstituted cycloalkyl,

(12) $-COR_{3a}$,

(13) $-NR_{3a}R_{3b}$,

(14) $-NR_{3a}COR_{3b}$,

(15) $-NR_{3a}SO_2R_{3b}$,

(16) $-OR_{3a}$,

(17) $-SR_{3a}$,

(18) $-SOR_{3a}$,

(19) $-SO_2R_{3a}$, and

(20) $-SO_2NR_{3a}R_{3b}$,

wherein R_{3a}, and R_{3b} are independently selected from the group consisting of

(a) hydrogen,

(b) substituted or unsubstituted alkyl,

(c) substituted and unsubstituted aryl,

(d) substituted and unsubstituted heteroaryl,

(e) substituted and unsubstituted heterocyclyl, and

(f) substituted and unsubstituted cycloalkyl;

R_4 is selected from the group consisting of

(1) hydrogen, and

(2) halogen; and

R_6 is selected from the group consisting of

(1) hydrogen,

(2) substituted and unsubstituted alkyl, and

(3) substituted and unsubstituted cycloalkyl.

In one embodiment, R_2 is selected from the group consisting

(1) hydrogen,

(2) cyano,

(3) hydroxy,

(4) halogen,

(5) amino,

(6) methyl, and

(7) trifluoromethyl..

[0068] In one embodiment, R_3 is selected from the group consisting of

(1) cyano,

(2) nitro,

(3) halogen,

(4) hydroxy,

(5) amino, and

(6) trifluoromethyl.

[0069] In one embodiment, R_5 is selected from the group consisting

(1) hydrogen,

(2) methyl, and

(3) ethyl.

[0070] It should be understood that the inhibitor compounds according to the invention may exhibit the phenomenon of tautomerism. As the chemical structures within this specification can only represent one of the possible tautomeric forms, it should be understood that the invention encompasses any tautomeric form of the drawn structure.

[0071] For the compounds of formulas (I)-(III), representative substituted alkyl groups include arylalkyl, heteroarylalkyl, heterocyclyalkyl, aminoalkyl, alkylaminoalkyl, dialkyaminoalkyl, and sulfonamidoalkyl groups. Representative substituted aryl groups include sulfonamidoaryl groups. Representative substituted heteroaryl groups include alkylheteroaryl groups.

[0072] The syntheses of representative PI3K inhibitor compounds of the invention are described in the methods presented in the Examples Section below and the preparation of representative compounds are described in Examples 1-31.

[0073] Representative PI3K inhibitor compounds of the invention are shown in Table 1.

[0074] In other aspects, the present invention provides methods for manufacture of PI3K inhibitor compounds. It is further contemplated that, in addition to the compounds of formulas (I)-(III), intermediates, and their corresponding methods of syntheses are included within the scope of the invention.

[0075] Another embodiment provides a method of inhibiting phosphorylation of Akt comprising administering a compound of Formula I, II, or III to a human in need thereof. Another embodiment provides a method of treating cancer responsive to inhibition of phosphorylation of Akt, comprising administering a compound of Formula I, II, or III. Another embodiment provides a method of inhibiting phosphorylation of Akt comprising contacting a cell with a compound of Formula I, II, or III.

[0076] Another embodiment provides a method of inhibiting phosphorylation of Akt comprising orally administering a compound of Formula I, II, or III to a human in need thereof. In a more particular embodiment the human is suffering from cancer. In a more particular embodiment the cancer is responsive to treatment with a compound that inhibits phosphorylation of Akt. In another embodiment the compound is orally bioavailable.

[0077] Another embodiment provides a method of treating cancer comprising orally administering a compound of Formula I, II, or III, wherein said compound is capable of inhibiting activity of pAkt.

[0078] In some embodiments of the method of inhibiting PI3K using a PI3K inhibitor compound of the invention, the IC_{50} value of the compound is less than or equal to 1 mM with respect to PI3K. In other such embodiments, the IC_{50} value is less than or equal to 100 μM, is less than or equal to 25 μM, is less than or equal to 10 μM, is less

than or equal to 1 μM, is less than or equal to 0.1 μM, is less than or equal to 0.050 μM, or is less than or equal to 0.010 μM.

[0079] The compounds of the present invention are also useful in assays evaluating relative activity of PI3 kinase inhibition. In such assays a compound of the present invention can be used to determine relative inhibitory activity of a compound in comparison to a second compound. When so employed, the compound of the present invention is employed in an amount sufficient to allow the skilled artisan to detect inhibition of PI3 kinase. Such an amount is sometimes referred to herein as an "effective inhibitory amount." In a preferred embodiment the inhibitory amount is an amount that will reduce PI3 kinase activity by approximately 50% as compared to the activity in the absence of a compound. Other compounds can then be evaluated as providing greater or lesser inhibition at the same concentration so as to provide a ranking of relative activity. Such information is useful in determining structural changes and other modifications to the test compound to improve its activity. Accordingly the present invention provides a method for inhibiting the activity of PI3 kinase which method comprises contacting said PI3 kinase with an effective inhibitory amount of a compound of the present invention as disclosed herein. Also provided is a method for inhibiting the activity of PI3 kinase activity in a cell, which method comprises contacting said cell with an effective inhibitory amount of a compound as claimed herein.

[0080] Some embodiments provide methods of inhibiting phosphorylation of Akt using a compound of the the invention having an EC_{50} value of less than about 10 μM with respect to inhibition of pAKT. In another more particular embodiment, the compound has an EC_{50} value of less than about 1 μM with respect to inhibition of pAKT. In a more particular embodiment still, the compound has an EC_{50} value of less than about 0.5 μM with respect to inhibition of pAKT. In an even more particular embodiment, the compound has an EC_{50} value of less than about 0.1 μM with respect to inhibition of pAKT.

[0081] In certain embodiments, components of the present invention are capable of inhibition of phosphorylation of Akt. In certain embodiments, components of the invention are capable of inhibition of phosphorylation of Akt in a human or animal subject (i.e., *in vivo*).

[0082] In one embodiment, a method of reducing pAkt activity in a human or animal subject is provided. In the method, a compound of the invention is administered in an amount effective to reduce pAkt activity.

[0083] In some embodiments of the method of inhibiting PI3K using a PI3K inhibitor compound of the invention, the EC_{50} value of the compound is between 1 nM to 10 nM. In other such embodiments, the EC_{50} value is between 10 nM to 50 nM, between 50 nM to 100 nM, between 100 nM to 1 μM, between 1 μM to 25 μM, or is between 25 μM to 100 μM.

[0084] The compounds of the present invention are also useful in assays evaluating relative activity of inhibition of phosphorylation of AKT. In such assays a compound of the present invention can be used to determine relative inhibitory activity of a compound in comparison to a second compound. When so employed, the compound of the present invention is employed in an amount sufficient to allow the skilled artisan to detect inhibition AKT phosphorylation. Such an amount is sometimes referred to herein as an "effective inhibitory amount." In a preferred embodiment the inhibitory amount is an amount that will reduce phosphorylation of AKT activity by approximately 50% as compared to the activity in the absence of a compound. Other compounds can then be evaluated as providing greater or lesser inhibition at the same concentration so as to provide a ranking of relative activity. Such information is useful in determining structural changes and other modifications to the test compound to improve its activity. Accordingly the present invention provides a method for inhibiting the AKT phosphorylation which method comprises contacting a cell with an effective inhibitory amount of a compound of the present invention, as discribed herein. Also provided is a

method for inhibiting the activity of PI3 kinase activity in a cell, which method comprises contacting said cell with an effective inhibitory amount of a compound as claimed herein.

[0085] In another embodiment, the invention provides methods of treating a PI3K-mediated disorder. In one method, an effective amount of a PI3K inhibitor compound is administered to a patient (e.g., a human or animal subject) in need thereof to mediate (or modulate) PI3K activity.

[0086] The compounds of the present invention are useful in pharmaceutical compositions for human or veterinary use where inhibition of PI3K is indicated, for example, in the treatment of cellular proliferative diseases such as tumor and/or cancerous cell growth mediated by PI3K. In particular, the compounds are useful in the treatment of human or animal (e.g., murine) cancers, including, for example, lung and bronchus; prostate; breast; pancreas; colon and rectum; thyroid; liver and intrahepatic bile duct; hepatocellular; gastric; glioma/glioblastoma; endometrial; melanoma; kidney and renal pelvis; urinary bladder; uterine corpus; uterine cervix; ovary; multiple myeloma; esophagus; acute myelogenous leukemia; chronic myelogenous leukemia; lymphocytic leukemia; myeloid leukemia; brain; oral cavity and pharynx; larynx; small intestine; non-Hodgkin lymphoma; melanoma; and villous colon adenoma.

[0087] Agents of the invention, in particular, those which have selectivity for PI3 kinase gamma inhibition, are particularly useful in the treatment of inflammatory or obstructive airways diseases, resulting, for example, in reduction of tissue damage, airways inflammation, bronchial hyperreactivity, remodeling or disease progression. Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type of genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma, mild asthma, moderate asthma, severe asthma, bronchitic asthma, exercise-induced asthma, occupational asthma and asthma induced following bacterial infection. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major

medical concern and now often identified as incipient or early-phase asthmatics ("wheezy infant syndrome").

[0088] Compounds of the invention that are selective for one PI3 Kinase isoform (α, β, γ, δ) over a different isoform are compounds that preferentially inhibit one isoform. For example, a compound may preferentially inhibit the alpha isoform over the gamma isoform. Alternatively, a compound may preferentially inhibit the gamma isoform over the alpha isoform. To determine a compound's selectivity, the compound's activity is determined according to the Biological Methods described herein. For example, the IC_{50} value, or the EC_{50} value, of a compound is determined for two or more PI3 Kinase isoforms, e.g, alpha and gamma, according to Biological Methods 1 and 2, respectively. The obtained values are then compared to determine the selectivity of the tested compound. Preferably, the compounds of the invention are selective for one isoform over a second isoform by at least two-fold, five-fold or ten-fold. Even more preferably, the compounds of the invention are selective for one isoform over a second isoform by at least fifty-fold or 100-fold. Even more preferably, the compounds of the invention are selective for one isoform over a second isoform by at least 1000-fold.

[0089] Other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include acute lung injury (ALI), adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD), including pulmonary fibrosis, chronic bronchitis or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy. The invention is also applicable to the treatment of bronchitis of whatever type or genesis including, e.g., acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for

example, aluminosis, anthracosis, abestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

[0090] Having regard to their anti-inflammatory activity, in particular in relation to inhibition of eosinophil activation, agents of the invention are also useful in the treatment of eosinophil related disorders, e.g. eosinophilia, in particular eosinophil related disorders of the airways (e.g. involving morbid eosinophilic infiltration of pulmonary tissues) including hypereosinophilia as it effects the airways and/or lungs as well as, for example, eosinophil-realted disorders of the airways consequential or concomitant to Loffler's syndrome, eosinophilic pneumonia, parasitic (in particular metazoan) infestation (including tropical eosinophilia), bronchopulmonary aspergillosis, polyarteritis nodosa (including Churg-Strauss syndrome), eosinophilic granuloma and eosinophil-related disorders affecting the airways occasioned by drug-reaction.

[0091] Agents of the invention are also useful in the treatment of inflammatory or allergic conditions of the skin, for example psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforme, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, pemphisus, epidermolysis bullosa acquisita, and other inflammatory or allergic conditions of the skin.

[0092] Agents of the invention may also be used for the treatment of other diseases or conditions, in particular diseases or conditions having an inflammatory component, for example, treatment of diseases and conditions of the eye such as conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis, diseases affecting the nose including allergic rhinitis, and inflammatory disease in which autoimmune reactions are implicated or having an autoimmune component or aetiology, including autoimmune haematogical disorders (e.g. haemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, scleroderma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, autoimmune

inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease), endocrine opthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary biliary cirrhosis, uveitis (anterior and posterior), interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephritic syndrome, e.g. including idiopathic nephritic syndrome or minal change nephropathy).

[0093] In another embodiment, the invention is a method for inhibiting leucocytes, in particular neutrophils and B and T lymphocytes. Exemplary medical conditions that can be treated include those conditions characterized by an undesirable neutrophil function selected from the group consisting of stimulated superoxide release, stimulated exocytosis, and chemotactic migration, preferably without inhibiting phagocytic activity or bacterial killing by the neutrophils.

[0094] In another embodiment the invention is a method for disrupting the function of osteoclasts and ameliorating a bone resorption disorder, such as osteoporosis.

[0095] In another embodiment, diseases or conditions which may be treated with agents of the invention include septic shock, allograft rejection following transplantation, bone disorders such as but not limited to rheumatoid arthritis, ankylosing spondylitis osteoarthritis, obesity, restenosis, diabetes, e.g. diabetes mellitus type I (juvenile diabetes) and diabetes mellitus type II, diarrheal diseases.

[0096] In other embodiments, the PI3K-mediated condition or disorder is selected from the group consisting of: cardiovascular diseases, atherosclerosis, hypertension, deep venous thrombosis, stroke, myocardial infarction, unstable angina, thromboembolism, pulmonary embolism, thrombolytic diseases, acute arterial ischemia, peripheral thrombotic occlusions, and coronary artery disease, reperfusion injuries, retinopathy, such as diabetic retinopathy or hyperbaric oxygen-induced retinopathy, and conditions characterized by elevated intraocular pressure or secretion of ocular aqueous humor, such as glaucoma.

[0097] As describeed above, since PI3K serves as a second messenger node that integrates parallel signaling pathways, evidence is emerging that the combination of a PI3K inhibitor with inhibitors of other pathways will be useful in treating cancer and proliferative diseases in humans:

[0098] Approximately 20-30% of human breast cancers overexpress Her-2/neu-ErbB2, the target for the drug trastuzumab. Although trastuzumab has demonstrated durable responses in some patients expressing Her2/neu-ErbB2, only a subset of these patients respond. Recent work has indicated that this limited response rate can be substantially improved by the combination of trastuzumab with inhibitors of PI3K or the PI3K/AKT pathway (Chan et al., *Breast Can. Res. Treat.* 91:187 (2005), Woods Ignatoski et al., *Brit. J. Cancer* 82:666 (2000), Nagata et al., *Cancer Cell* 6:117 (2004)).

[0099] A variety of human malignancies express activitating mutations or increased levels of Her1/EGFR and a number of antibody and small molecule inhibitors have been developed against this receptor tyrosine kinase including tarceva, gefitinib and erbitux. However, while EGFR inhibitors demonstrate anti-tumor activity in certain human tumors (e.g., NSCLC), they fail to increase overall patient survival in all patients with EGFR-expressing tumors. This may be rationalized by the fact that many downstream targets of Her1/EGFR are mutated or deregulated at high frequencies in a variety of malignancies, including the PI3K/Akt pathway. For example, gefitinib inhibits the growth of an adenocarcinoma cell line in *in vitro* assays. Nonetheless, sub-clones of these cell lines can be selected that are resistant to gefitinib that demonstrate increased activation of the PI3/Akt pathway. Down-regulation or inhibition of this pathway renders the resistant sub-clones sensitive to gefitinib (Kokubo et al., *Brit. J. Cancer* 92:1711 (2005)). Furthermore, in an *in vitro* model of breast cancer with a cell line that harbors a PTEN mutation and over-expresses EGFR inhibition of both the PI3K/Akt pathway and EGFR produced a synergistic effect (She et al., *Cancer Cell* 8:287-297(2005)). These results indicate that the combination of gefitinib and PI3K/Akt pathway inhibitors would be an attractive therapeutic strategy in cancer.

[0100] The combination of AEE778 (an inhibitor of Her-2/neu/ErbB2, VEGFR and EGFR) and RAD001 (an inhibitor of mTOR, a downstream target of Akt) produced greater combined efficacy that either agent alone in a glioblastoma xenograft model (Goudar et al., *Mol. Cancer. Ther.* 4:101-112 (2005)).

[0101] Anti-estrogens, such as tamoxifen, inhibit breast cancer growth through induction of cell cycle arrest that requires the action of the cell cycle inhibitor p27Kip. Recently, it has been shown that activation of the Ras-Raf-MAP Kinase pathway alters the phosphorylation status of p27Kip such that its inhibitory activity in arresting the cell cycle is attenuated, thereby contributing to anti-estrogen resistance (Donovan, et al, *J. Biol. Chem. 276*:40888, 2001). As reported by Donovan et al., inhibition of MAPK signaling through treatment with MEK inhibitor reversed the aberrant phosphorylation status of p27 in hormone refractory breast cancer cell lines and in so doing restored hormone sensitivity. Similarly, phosphorylation of p27Kip by Akt also abrogates its role to arrest the cell cycle (Viglietto et al., *Nat Med.* 8:1145 (2002)). Accordingly, in one aspect, the compounds of formula (I) may be used in the treatment of hormone dependent cancers, such as breast and prostate cancers, to reverse hormone resistance commonly seen in these cancers with conventional anticancer agents.

[0102] In hematological cancers, such as chronic myelogenous leukemia (CML), chromosomal translocation is responsible for the constitutively activated BCR-Abl tyrosine kinase. The afflicted patients are responsive to imatinib, a small molecule tyrosine kinase inhibitor, as a result of inhibition of Abl kinase activity. However, many patients with advanced stage disease respond to imatinib initially, but then relapse later due to resistance-conferring mutations in the Abl kinase domain. *In vitro* studies have demonstrated that BCR-Abl employs the Ras-Raf kinase pathway to elicit its effects. In addition, inhibiting more than one kinase in the same pathway provides additional protection against resistance-conferring mutations. Accordingly, in another aspect of the invention, the compounds of formula (I) are used in combination with at least one additional agent, such as Gleevec®, in the treatment of hematological cancers, such as

chronic myelogenous leukemia (CML), to reverse or prevent resistance to at least one additional agent.

[0103] Because activation of the PI3K/Akt pathway drives cell survival, inhibition of the pathway in combination with therapies that drive apoptosis in cancer cells, including radiotherapy and chemotherapy, will result in improved responses (Ghobrial et al., *CA Cancer J. Clin* 55:178-194 (2005)). As an example, combination of PI3 kinase inhibitor with carboplatin demonstrated synergistic effects in both *in vitro* proliferation and apoptosis assays as well as in *in vivo* tumor efficacy in a xenograft model of ovarian cancer (Westfall and Skinner, Mol. Cancer Ther 4:1764-1771 (2005)).

[0104] In addition to cancer and proliferative diseases, there is accumulating evidence that inhibitors of Class 1A and 1B PI3 kinases would be therapeutically useful in others disease areas. The inhibition of p110□, the PI3K isoform product of the PIK3CB gene, has been shown to be involved in shear-induced platelet activation (Jackson et al., *Nature Medicine* 11:507-514 (2005)). Thus, a PI3K inhibitor that inhibits p110□ would be useful as a single agent or in combination in anti-thrombotic therapy. The isoform p110□, the product of the PIK3CD gene, is important in B cell function and differentiation (Clayton et al., *J. Exp. Med.* 196:753-763 (2002)), T-cell dependent and independent antigen responses (Jou et al., *Mol. Cell. Biol.* 22:8580-8590 (2002)) and mast cell differentiation (Ali et al., *Nature* 431:1007-1011 (2004)). Thus, it is expected that p110□-inhibitors would be useful in the treatment of B-cell driven autoimmune diseases and asthma. Finally, the inhibition of p110□, the isoform product of the PI3KCG gene, results in reduced T, but not B cell, response (Reif et al., J. Immunol. 173:2236-2240 (2004)) and its inhibition demonstrates efficacy in animal models of autoimmune diseases (Camps et al., Nature Medicine 11:936-943 (2005), Barber et al., Nature Medicine 11:933-935 (2005)).

[0105] The present invention provides pharmaceutical compositions comprising at least one PI3K inhibitor compound (e.g., a compound of formulas (I)-(III)) together

with a pharmaceutically acceptable carrier suitable for administration to a human or animal subject, either alone or together with other anticancer agents.

[0106] In one embodiment, the present invention provides methods of treating human or animal subjects suffering from a cellular proliferative disease, such as cancer. The present invention provides methods of treating a human or animal subject in need of such treatment, comprising administering to the subject a therapeutically effective amount of a PI3K inhibitor compound (e.g., a compound of formulas (I)-(III)), either alone or in combination with other anticancer agents.

[0107] In particular, compositions will either be formulated together as a combination therapeutic or administered separately. Anticancer agents for use with the invention include, but are not limited to, one or more of the following set forth below:

A. Kinase Inhibitors

[0108] Kinase inhibitors for use as anticancer agents in conjunction with the compositions of the present invention include inhibitors of Epidermal Growth Factor Receptor (EGFR) kinases such as small molecule quinazolines, for example gefitinib (US 5457105, US 5616582, and US 5770599), ZD-6474 (WO 01/32651), erlotinib (Tarceva®, US 5,747,498 and WO 96/30347), and lapatinib (US 6,727,256 and WO 02/02552); Vascular Endothelial Growth Factor Receptor (VEGFR) kinase inhibitors, including SU-11248 (WO 01/60814), SU 5416 (US 5,883,113 and WO 99/61422), SU 6668 (US 5,883,113 and WO 99/61422), CHIR-258 (US 6,605,617 and US 6,774,237), vatalanib or PTK-787 (US 6,258,812), VEGF-Trap (WO 02/57423), B43-Genistein (WO-09606116), fenretinide (retinoic acid p-hydroxyphenylamine) (US 4,323,581), IM-862 (WO 02/62826), bevacizumab or Avastin® (WO 94/10202), KRN-951, 3-[5-(methylsulfonylpiperadine methyl)-indolyl]-quinolone, AG-13736 and AG-13925, pyrrolo[2,1-f][1,2,4]triazines, ZK-304709, Veglin®, VMDA-3601, EG-004, CEP-701 (US 5,621,100), Cand5 (WO 04/09769); Erb2 tyrosine kinase inhibitors such as pertuzumab (WO 01/00245), trastuzumab, and rituximab; Akt protein kinase inhibitors, such as RX-0201; Protein Kinase C (PKC) inhibitors, such as LY-317615 (WO

95/17182), and perifosine (US 2003171303); Raf/Map/MEK/Ras kinase inhibitors including sorafenib (BAY 43-9006), ARQ-350RP, LErafAON, BMS-354825 AMG-548, and others disclosed in WO 03/82272; Fibroblast Growth Factor Receptor (FGFR) kinase inhibitors; Cell Dependent Kinase (CDK) inhibitors, including CYC-202 or roscovitine (WO 97/20842 and WO 99/02162); Platelet-Derived Growth Factor Receptor (PGFR) kinase inhibitors such as CHIR-258, 3G3 mAb, AG-13736, SU-11248 and SU6668; and Bcr-Abl kinase inhibitors and fusion proteins such as STI-571 or Gleevec® (imatinib).

B. Anti-Estrogens

[0109] Estrogen-targeting agents for use in anticancer therapy in conjunction with the compositions of the present invention include Selective Estrogen Receptor Modulators (SERMs) including tamoxifen, toremifene, raloxifene; aromatase inhibitors including Arimidex® or anastrozole; Estrogen Receptor Downregulators (ERDs) including Faslodex® or fulvestrant.

C. Anti-Androgens

[0110] Androgen-targeting agents for use in anticancer therapy in conjunction with the compositions of the present invention include flutamide, bicalutamide, finasteride, aminoglutethamide, ketoconazole, and corticosteroids.

D. Other Inhibitors

[0111] Other inhibitors for use as anticancer agents in conjunction with the compositions of the present invention include protein farnesyl transferase inhibitors including tipifarnib or R-115777 (US 2003134846 and WO 97/21701), BMS-214662, AZD-3409, and FTI-277; topoisomerase inhibitors including merbarone and diflomotecan (BN-80915); mitotic kinesin spindle protein (KSP) inhibitors including SB-743921 and MKI-833; protease modulators such as bortezomib or Velcade® (US 5,780,454), XL-784; and cyclooxygenase 2 (COX-2) inhibitors including non-steroidal antiinflammatory drugs I (NSAIDs).

E. Cancer Chemotherapeutic Drugs

[0112] Particular cancer chemotherapeutic agents for use as anticancer agents in conjunction with the compositions of the present invention include anastrozole (Arimidex®), bicalutamide (Casodex®), bleomycin sulfate (Blenoxane®), busulfan (Myleran®), busulfan injection (Busulfex®), capecitabine (Xeloda®), N4-pentoxycarbonyl-5-deoxy-5-fluorocytidine, carboplatin (Paraplatin®), carmustine (BiCNU®), chlorambucil (Leukeran®), cisplatin (Platinol®), cladribine (Leustatin®), cyclophosphamide (Cytoxan® or Neosar®), cytarabine, cytosine arabinoside (Cytosar-U®), cytarabine liposome injection (DepoCyt®), dacarbazine (DTIC-Dome®), dactinomycin (Actinomycin D, Cosmegan), daunorubicin hydrochloride (Cerubidine®), daunorubicin citrate liposome injection (DaunoXome®), dexamethasone, docetaxel (Taxotere®, US 2004073044), doxorubicin hydrochloride (Adriamycin®, Rubex®), etoposide (Vepesid®), fludarabine phosphate (Fludara®), 5-fluorouracil (Adrucil®, Efudex®), flutamide (Eulexin®), tezacitibine, Gemcitabine (difluorodeoxycitidine), hydroxyurea (Hydrea®), Idarubicin (Idamycin®), ifosfamide (IFEX®), irinotecan (Camptosar®), L-asparaginase (ELSPAR®), leucovorin calcium, melphalan (Alkeran®), 6-mercaptopurine (Purinethol®), methotrexate (Folex®), mitoxantrone (Novantrone®), mylotarg, paclitaxel (Taxol®), phoenix (Yttrium90/MX-DTPA), pentostatin, polifeprosan 20 with carmustine implant (Gliadel®), tamoxifen citrate (Nolvadex®), teniposide (Vumon®), 6-thioguanine, thiotepa, tirapazamine (Tirazone®), topotecan hydrochloride for injection (Hycamptin®), vinblastine (Velban®), vincristine (Oncovin®), and vinorelbine (Navelbine®).

F. Alkylating Agents

[0113] Alkylating agents for use in conjunction with the compositions of the present invention for anticancer therapeutics include VNP-40101M or cloretizine, oxaliplatin (US 4,169,846, WO 03/24978 and WO 03/04505), glufosfamide,

mafosfamide, etopophos (US 5,041,424), prednimustine; treosulfan; busulfan; irofluven (acylfulvene); penclomedine; pyrazoloacridine (PD-115934); O6-benzylguanine; decitabine (5-aza-2-deoxycytidine); brostallicin; mitomycin C (MitoExtra); TLK-286 (Telcyta®); temozolomide; trabectedin (US 5,478,932); AP-5280 (Platinate formulation of Cisplatin); porfiromycin; and clearazide (meclorethamine).

G. Chelating Agents

[0114] Chelating agents for use in conjunction with the compositions of the present invention for anticancer therapeutics include tetrathiomolybdate (WO 01/60814); RP-697; Chimeric T84.66 (cT84.66); gadofosveset (Vasovist®); deferoxamine; and bleomycin optionally in combination with electorporation (EPT).

H. Biological Response Modifiers

[0115] Biological response modifiers, such as immune modulators, for use in conjunction with the compositions of the present invention for anticancer therapeutics include staurosprine and macrocyclic analogs thereof, including UCN-01, CEP-701 and midostaurin (see WO 02/30941, WO 97/07081, WO 89/07105, US 5,621,100, WO 93/07153, WO 01/04125, WO 02/30941, WO 93/08809, WO 94/06799, WO 00/27422, WO 96/13506 and WO 88/07045); squalamine (WO 01/79255); DA-9601 (WO 98/04541 and US 6,025,387); alemtuzumab; interferons (e.g. IFN-a, IFN-b etc.); interleukins, specifically IL-2 or aldesleukin as well as IL-1, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, and active biological variants thereof having amino acid sequences greater than 70% of the native human sequence; altretamine (Hexalen®); SU 101 or leflunomide (WO 04/06834 and US 6,331,555); imidazoquinolines such as resiquimod and imiquimod (US 4,689,338, 5,389,640, 5,268,376, 4,929,624, 5,266,575, 5,352,784, 5,494,916, 5,482,936, 5,346,905, 5,395,937, 5,238,944, and 5,525,612); and SMIPs, including benzazoles, anthraquinones, thiosemicarbazones, and tryptanthrins (WO 04/87153, WO 04/64759, and WO 04/60308).

I. Cancer Vaccines:

[0116] Anticancer vaccines for use in conjunction with the compositions of the present invention include Avicine® (Tetrahedron Letters **26**, 1974 2269-70); oregovomab (OvaRex®); Theratope® (STn-KLH); Melanoma Vaccines; GI-4000 series (GI-4014, GI-4015, and GI-4016), which are directed to five mutations in the Ras protein; GlioVax-1; MelaVax; Advexin® or INGN-201 (WO 95/12660); Sig/E7/LAMP-1, encoding HPV-16 E7; MAGE-3 Vaccine or M3TK (WO 94/05304); HER-2VAX; ACTIVE, which stimulates T-cells specific for tumors; GM-CSF cancer vaccine; and Listeria monocytogenes-based vaccines.

J. Antisense Therapy:

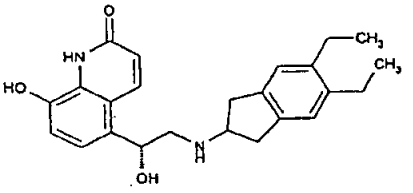
[0117] Anticancer agents for use in conjunction with the compositions of the present invention also include antisense compositions, such as AEG-35156 (GEM-640); AP-12009 and AP-11014 (TGF-beta2-specific antisense oligonucleotides); AVI-4126; AVI-4557; AVI-4472; oblimersen (Genasense®); JFS2; aprinocarsen (WO 97/29780); GTI-2040 (R2 ribonucleotide reductase mRNA antisense oligo) (WO 98/05769); GTI-2501 (WO 98/05769); liposome-encapsulated c-Raf antisense oligodeoxynucleotides (LErafAON) (WO 98/43095); and Sirna-027 (RNAi-based therapeutic targeting VEGFR-1 mRNA).

[0118] The compounds of the invention can also be combined in a pharmaceutical composition with bronchiodilatory or antihistamine drugs substances. Such bronchiodilatory drugs include anticholinergic or antimuscarinic agents, in particular ipratropium bromide, oxitropium bromide, and tiotropium bromide, and □-2-adrenoreceptor agonists such as salbutamol, terbutaline, salmeterol and, especially, formoterol. Co-therapeutic antihistamine drug substances include cetirizine hydrochloride, clemastine fumarate, promethazine, loratadine, desloratadine diphenhydramine and fexofenadine hydrochloride.

[0119] The effectiveness of an agent of the invention in inhibiting inflammatory conditions, for example in inflammatory airways diseases, may be demonstrated in an animal model, e.g. a mouse or rat model, of airways inflammation or other inflammatory

conditions, for example as described by Szarka et al, J. Immunol. Methods (1997) 202:49-57; Renzi et al, Am. Rev. Respir. Dis. (1993) 148:932-939; Tsuyuki et al., J. Clin. Invest. (1995) 96:2924-2931; and Cernadas et al (1999) Am. J. Respir. Cell Mol. Biol. 20:1-8.

[0120] The agents of the invention are also useful as co-therapeutic agents for use in combination with other drug substances such as anti-inflammatory, bronchodilatory or antihistamine drug substances, particularly in the treatment of obstructive or inflammatory airways diseases such as those mentioned hereinbefore, for example as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs. An agent of the invention may be mixed with the other drug substance in a fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the other drug substance. Accordingly the invention includes a combination of an agent of the invention as hereinbefore described with an anti-inflammatory, bronchodilatory or antihistamine drug substance, said agent of the invention and said drug substance being in the same or different pharmaceutical composition. Such anti-inflammatory drugs include steroids, in particular glucocorticosteroids such as budesonide, beclamethasone, fluticasone, ciclesonide or mometasone, LTB4 antagonists such as those described in US5451700, LTD4 antagonists such as montelukast and zafirlukast, dopamine receptor agonists such as cabergoline, bromocriptine, ropinirole and 4-hydroxy-7-[2-[[2-[[3-(2-phenylethoxy)propyl]-sulfonyl]ethyl]-amino]ethyl]-2(3H)-benzothiazolone and pharmaceutically acceptable salts thereof (the hydrochloride being Viozan® - AstraZeneca), and PDE4 inhibitors such as Ariflo® (GlaxoSmith Kline), Roflumilast (Byk Gulden),V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), Arofylline (Almirall Prodesfarma) and PD189659 (Parke-Davis). Such bronchodilatory drugs include anticholinergic or antimuscarinic agents, in particular ipratropium bromide, oxitropium bromide and tiotropium bromide, and beta-2 adrenoceptor agonists such as salbutamol, terbutaline, salmeterol and, especially, formoterol and pharmaceutically acceptable salts thereof, and compounds (in free or salt or solvate form) of formula I of PCT International patent publication No. WO 00/75114, which document is incorporated herein by reference, preferably compounds of the Examples thereof, especially a compound of formula



and pharmaceutically acceptable salts thereof. Co-therapeutic antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine hydrochloride. Combinations of agents of the invention and steroids, beta-2 agonists, PDE4 inhibitors or LTD4 antagonists may be used, for example, in the treatment of COPD or, particularly, asthma. Combinations of agents of the invention and anticholinergic or antimuscarinic agents, PDE4 inhibitors, dopamine receptor agonists or LTB4 antagonists may be used, for example, in the treatment of asthma or, particularly, COPD.

[0121] Other useful combinations of agents of the invention with anti-inflammatory drugs are those with antagonists of chemokine receptors, e.g. CCR-1, CCR-2, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CCR-9 and CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, particularly CCR-5 antagonists such as Schering-Plough antagonists SC-351125, SCH-55700 and SCH-D, Takeda antagonists such as N-[[4-[[[6,7-dihydro-2-(4-methylphenyl)-5H-benzocyclohepten-8-yl]carbonyl]amino]phenyl]-methyl]tetrahydro-N,N-dimethyl-2H-pyran-4-aminium chloride (TAK-770), and CCR-5 antagonists described in US 6166037 (particularly claims 18 and 19), WO 00/66558 (particularly claim 8), and WO 00/66559 (particularly claim 9).

[0122] The compounds of the invention can also be combined in a pharmaceutical composition with compounds that are useful for the treatment of a thrombolytic disease, heart disease, stroke, etc., (e.g., aspirin, streptokinase, tissue plasminogen activator, urokinase, anticoagulants, antiplatelet drugs (e.g, PLAVIX; clopidogrel bisulfate), a statin (e.g., LIPITOR or Atorvastatin calcium), ZOCOR (Simvastatin), CRESTOR (Rosuvastatin), etc.), a Beta blocker (e.g., Atenolol), NORVASC (amlodipine besylate), and an ACE inhibitor (e.g., lisinopril).

[0123] The compounds of the invention can also be combined in a pharmaceutical composition with compounds that are useful for the treatment of antihypertension agents such as, ACE inhibitors, lipid lowering agents such as statins, LIPITOR (Atorvastatin calcium), calcium channel blockers dush as NORVASC (amlodipine besylate). The compound s of the present invention may also be used in combination with fibrates, beta-blockers, NEPI inhibitors, Angiotensin-2 receptor antagonists and platelet aggregation inhibitors.

[0124] For the treatment of inflammatory diseases, including rheumatoid arthritis, the compounds of the invention may be combined with agents such as TNF-□ inhibitors such as anti-TNF-□ monoclonal antibodies (such as REMICADE, CDP-870) and D2E7 (HUMIRA) and TNF receptor immunoglobulin fusion molecules (such as ENBREL), IL-1 inhibitors, receptor antagonists or soluble IL-1R□(e.g. KINERET or ICE inhibitors), nonsterodial anti-inflammatory agents (NSAIDS), piroxicam, diclofenac, naproxen, flurbiprofen, fenoprofen, ketoprofen ibuprofen, fenamates, mefenamic acid, indomethacin, sulindac, apazone, pyrazolones, phenylbutazone, aspirin, COX-2 inhibitors (such as CELEBREX (celecoxib), PREXIGE (lumiracoxib)), metalloprotease inhibitors (preferably MMP-13 selective inhibitors), p2x7 inhibitors, □□□inhibitors, NEUROTIN, pregabalin, low dose methotrexate, leflunomide, hydroxyxchloroquine, d-penicillamine, auranofin or parenteral or oral gold.

[0125] The compounds of the invention can also be used in combination with the existing therapeutic agents for the treatment of osteoarthritis. Suitable agents to be used in combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as naproxen, flurbiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, COX-2 inhibitors such as celecoxib, valdecoxib, lumiracoxib and etoricoxib, analgesics and intraarticular therapies such as corticosteroids and hyaluronic acids such as hyalgan and synvisc.

[0126] The compounds of the invention may also be used in combination with antiviral agents such as Viracept, AZT, acyclovir and famciclovir, and antisepsis compounds such as Valant.

[0127] The compounds of the present invention may also be used in combination with CNS agents such as antidepressants (sertraline), anti-Parkinsonian drugs (such as deprenyl, L-dopa, Requip, Mirapex, MAOB inhibitors such as selegine and rasagiline, comP inhibitors, such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, Nicotine agonists, Dopamine agonists, and inhibitors of neuronal nitric oxide synthase), and anti-Alzheimer's drugs such as donepezil, tacrine, □□□inhibitors, NEUROTIN, pregabalin, COX-2 inhibitors, propentofylline or metryfonate.

[0128] The compounds of the present invention may also be used in combination with osteoporosis agents such as EVISTA (raloxifene hydrochloride), droloxifene, lasofoxifene or fosomax and immunosuppressant agents such as FK-506 and rapamycin.

[0129] In another aspect of the invention, kits that include one or more compounds of the invention are provided. Representative kits include a PI3K inhibitor compound of the invention (e.g., a compound of formulas (I)-(III)) and a package insert or other labeling including directions for treating a cellular proliferative disease by administering an PI3K inhibitory amount of the compound.

[0130] The following definitions are provided to better understand the invention.

[0131] "Alkyl" refers to alkyl groups that do not contain heteroatoms. Thus the phrase includes straight chain alkyl groups such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl and the like. The phrase also includes branched chain isomers of straight chain alkyl groups, including but not limited to, the following which are provided by way of example: $-CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-CH(CH_2CH_3)_2$, $-C(CH_3)_3$, $-C(CH_2CH_3)_3$, $-CH_2CH(CH_3)_2$, $-CH_2CH(CH_3)(CH_2CH_3)$, $-CH_2CH(CH_2CH_3)_2$, $-CH_2C(CH_3)_3$, $-CH_2C(CH_2CH_3)_3$, $-CH(CH_3)-CH(CH_3)(CH_2CH_3)$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH(CH_3)(CH_2CH_3)$, $-CH_2CH_2CH(CH_2CH_3)_2$, $-CH_2CH_2C(CH_3)_3$, $-CH_2CH_2C(CH_2CH_3)_3$, $-CH(CH_3)CH_2-CH(CH_3)_2$,

-$CH(CH_3)CH(CH_3)CH(CH_3)_2$, -$CH(CH_2CH_3)CH(CH_3)CH(CH_3)(CH_2CH_3)$, and others. Thus the phrase "alkyl groups" includes primary alkyl groups, secondary alkyl groups, and tertiary alkyl groups. Preferred alkyl groups include straight and branched chain alkyl groups having 1 to 12 carbon atoms or 1 to 6 carbon atoms.

[0132] "Alkylene" refers to the same residues as noted above for "alkyl," but having two points of attachment. Exemplary alkylene groups include ethylene (-CH_2CH_2-), propylene (-$CH_2CH_2CH_2$-), dimethylpropylene (-$CH_2C(CH_3)_2CH_2$-), and cyclohexylpropylene (-$CH_2CH_2CH(C_6H_{13})$-).

[0133] "Alkenyl" refers to straight chain, branched, or cyclic groups from 2 to about 20 carbon atoms such as those described with respect to alkyl groups as defined above, except having one or more carbon-carbon double bonds. Examples include, but are not limited to vinyl, -$CH=C(H)(CH_3)$, -$CH=C(CH_3)_2$, -$C(CH_3)=C(H)_2$, -$C(CH_3)=C(H)(CH_3)$, -$C(CH_2CH_3)=CH_2$, cyclohexenyl, cyclopentenyl, cyclohexadienyl, butadienyl, pentadienyl, and hexadienyl among others. Preferred alkenyl groups include straight chain and branched alkenyl groups and cyclic alkenyl groups having 2 to 12 carbon atoms or 2 to 6 carbon atoms.

[0134] "Alkynyl" refers to straight chain, branched, or cyclic groups from 2 to about 20 carbon atoms such as those described with respect to alkyl groups as defined above, except having one or more carbon-carbon triple bonds. Examples include, but are not limited to -$C\equiv C(H)$, -$C\equiv C(CH_3)$, -$C\equiv C(CH_2CH_3)$, -$C(H_2)C\equiv C(H)$, -$C(H)_2C\equiv C(CH_3)$, and -$C(H)_2C\equiv C(CH_2CH_3)$ among others. Preferred alkynyl groups include straight chain and branched alkynyl groups having 2 to 12 carbon atoms or 2 to 6 carbon atoms.

[0135] Alkyl, alkenyl, and alkynyl groups may be substituted. "Substituted alkyl" refers to an alkyl group as defined above in which one or more bonds to a carbon(s) or hydrogen(s) are replaced by a bond to non-hydrogen and non-carbon atoms such as, but not limited to, a halogen atom such as F, Cl, Br, and I; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, aryloxy groups, and ester groups; a sulfur atom in

groups such as thiol groups, alkyl and aryl sulfide groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as amines, amides, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, N-oxides, imides, and enamines; a silicon atom in groups such as in trialkylsilyl groups, dialkylarylsilyl groups, alkyldiarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups. Substituted alkyl groups also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom is replaced by a higher-order bond (e.g., a double- or triple-bond) to a heteroatom such as oxygen in oxo, carbonyl, carboxyl, and ester groups; nitrogen in groups such as imines, oximes, hydrazones, and nitriles. Substituted alkyl groups further include alkyl groups in which one or more bonds to a carbon(s) or hydrogen(s) atoms is replaced by a bond to an aryl, heteroaryl, heterocyclyl, or cycloalkyl group. Preferred substituted alkyl groups include, among others, alkyl groups in which one or more bonds to a carbon or hydrogen atom is/are replaced by one or more bonds to fluoro, chloro, or bromo group. Another preferred substituted alkyl group is the trifluoromethyl group and other alkyl groups that contain the trifluoromethyl group. Other preferred substituted alkyl groups include those in which one or more bonds to a carbon or hydrogen atom is replaced by a bond to an oxygen atom such that the substituted alkyl group contains a hydroxyl, alkoxy, or aryloxy group. Other preferred substituted alkyl groups include alkyl groups that have an amine, or a substituted or unsubstituted alkylamine, dialkylamine, arylamine, (alkyl)(aryl)amine, diarylamine, heterocyclylamine, diheterocyclylamine, (alkyl)(heterocyclyl)amine, or (aryl)(heterocyclyl)amine group. Still other preferred substituted alkyl groups include those in which one or more bonds to a carbon(s) or hydrogen(s) atoms is replaced by a bond to an aryl, heteroaryl, heterocyclyl, or cycloalkyl group. Examples of substituted alkyl are: $-(CH_2)_3NH_2$, $-(CH_2)_3NH(CH_3)$, $-(CH_2)_3NH(CH_3)_2$, $-CH_2C(=CH_2)CH_2NH_2$, $-CH_2C(=O)CH_2NH_2$, $-CH_2S(=O)_2CH_3$, $-CH_2OCH_2NH_2$, $-CO_2H$. Examples of substituents of substituted alkyl are: $-CH_3$, $-C_2H_5$, $-CH_2OH$, $-OH$, $-OCH_3$, $-OC_2H_5$, $-OCF_3$, $-OC(=O)CH_3$, $-OC(=O)NH_2$, $-OC(=O)N(CH_3)_2$, $-CN$, $-NO_2$, $-C(=O)CH_3$, $-CO_2H$,

$-CO_2CH_3$, $-CONH_2$, $-NH_2$,$-N(CH_3)_2$, $-NHSO_2CH_3$, $-NHCOCH_3$, $-NHC(=O)OCH_3$, $-NHSO-_2CH_3$, $-SO_2CH_3$, $-SO_2NH_2$, Halo.

[0136] "Substituted alkenyl" has the same meaning with respect to alkenyl groups that substituted alkyl groups had with respect to unsubstituted alkyl groups. A substituted alkenyl group includes alkenyl groups in which a non-carbon or non-hydrogen atom is bonded to a carbon double bonded to another carbon and those in which one of the non-carbon or non-hydrogen atoms is bonded to a carbon not involved in a double bond to another carbon.

[0137] "Substituted alkynyl" has the same meaning with respect to alkynyl groups that substituted alkyl groups had with respect to unsubstituted alkyl groups. A substituted alkynyl group includes alkynyl groups in which a non-carbon or non-hydrogen atom is bonded to a carbon triple bonded to another carbon and those in which a non-carbon or non-hydrogen atom is bonded to a carbon not involved in a triple bond to another carbon.

[0138] "Alkoxy" refers to RO- wherein R is alkyl. Representative examples of alkoxy groups include methoxy, ethoxy, t-butoxy, trifluoromethoxy, and the like.

[0139] "Halogen" or "halo" refers to chloro, bromo, fluoro, and iodo groups. The term "haloalkyl" refers to an alkyl radical substituted with one or more halogen atoms. The term "haloalkoxy" refers to an alkoxy radical substituted with one or more halogen atoms.

[0140] "Amino" refers herein to the group $-NH_2$. The term "alkylamino" refers herein to the group –NRR' where R is alkyl and R' is hydrogen or alkyl. The term "arylamino" refers herein to the group –NRR' where R is aryl and R' is hydrogen, alkyl, or aryl. The term "aralkylamino" refers herein to the group –NRR' where R is aralkyl and R' is hydrogen, alkyl, aryl, or aralkyl.

[0141] "Alkoxyalkyl" refers to the group $-alk_1-O-alk_2$ where alk_1 is alkyl or alkenyl, and alk_2 is alkyl or alkenyl. The term "aryloxyalkyl" refers to the group -alkyl O-aryl. The term "aralkoxyalkyl" refers to the group -alkylenyl-O-aralkyl.

[0142] "Alkoxyalkylamino" refers herein to the group –NR-(alkoxyalkyl), where R is typically hydrogen, aralkyl, or alkyl.

[0143] "Aminocarbonyl" refers herein to the group $-C(O)-NH_2$. "Substituted aminocarbonyl" refers herein to the group –C(O)-NRR' where R is alkyl and R' is hydrogen or alkyl. The term "arylaminocarbonyl" refers herein to the group -C(O)-NRR' where R is aryl and R' is hydrogen, alkyl or aryl. "Aralkylaminocarbonyl" refers herein to the group -C(O)-NRR' where R is aralkyl and R' is hydrogen, alkyl, aryl, or aralkyl.

[0144] "Aminosulfonyl" refers herein to the group $-S(O)_2-NH_2$. "Substituted aminosulfonyl" refers herein to the group $-S(O)_2-NRR'$ where R is alkyl and R' is hydrogen or alkyl. The term "aralkylaminosulfonlyaryl" refers herein to the group -aryl-$S(O)_2$–NH-aralkyl.

[0145] "Carbonyl" refers to the divalent group –C(O)-.

[0146] "Carbonyloxy" refers generally to the group –C(O)-O. Such groups include esters, -C(O)-O-R, where R is alkyl, cycloalkyl, aryl, or aralkyl. The term "carbonyloxycycloalkyl" refers generally herein to both a "carbonyloxycarbocycloalkyl" and a "carbonyloxyheterocycloalkyl," i.e., where R is a carbocycloalkyl or heterocycloalkyl, respectively. The term "arylcarbonyloxy" refers herein to the group -C(O)-O-aryl, where aryl is a mono- or polycyclic, carbocycloaryl or heterocycloaryl. The term "aralkylcarbonyloxy" refers herein to the group –C(O)-O-aralkyl.

[0147] "Sulfonyl" refers herein to the group $-SO_2-$. "Alkylsulfonyl" refers to a substituted sulfonyl of the structure $-SO_2R-$ in which R is alkyl. Alkylsulfonyl groups employed in compounds of the present invention are typically alkylsulfonyl groups having from 1 to 6 carbon atoms in its backbone structure. Thus, typical alkylsulfonyl groups employed in compounds of the present invention include, for example, methylsulfonyl (i.e., where R is methyl), ethylsulfonyl (i.e., where R is ethyl), propylsulfonyl (i.e., where R is propyl), and the like. The term "arylsulfonyl" refers herein to the group $-SO_2$-aryl. The term "aralkylsulfonyl" refers herein to the group $-SO_2$-aralkyl. The term "sulfonamido" refers herein to $-SO_2NH_2$.

[0148] "Carbonylamino" refers to the divalent group -NH-C(O)- in which the hydrogen atom of the amide nitrogen of the carbonylamino group can be replaced alkyl, aryl, or aralkyl group. Such groups include moieties such as carbamate esters (-NH-C(O)-O-R) and amides –NH-C(O)-R, where R is a straight or branched chain alkyl, cycloalkyl, or aryl or aralkyl. The term "alkylcarbonylamino" refers to alkylcarbonylamino where R is alkyl having from 1 to about 6 carbon atoms in its backbone structure. The term "arylcarbonylamino" refers to group –NH-C(O)-R where R is an aryl. Similarly, the term "aralkylcarbonylamino " refers to carbonylamino where R is aralkyl.

[0149] "Guanidino" or "guanidyl" refers to moieties derived from guanidine, H_2N-C(=NH)-NH_2. Such moieties include those bonded at the nitrogen atom carrying the formal double bond (the "2"-position of the guanidine, e.g., diaminomethyleneamino, $(H_2N)_2C$=NH-)) and those bonded at either of the nitrogen atoms carrying a formal single bond (the "1-" and/or "3"-positions of the guanidine, e.g., H_2N-C(=NH)-NH-)). The hydrogen atoms at any of the nitrogens can be replaced with a suitable substituent, such as alkyl, aryl, or aralkyl.

[0150] "Amidino" refers to the moieties R-C(=N)-NR'- (the radical being at the "N^1" nitrogen) and R(NR')C=N- (the radical being at the "N^2" nitrogen), where R and R' can be hydrogen, alkyl, aryl, or aralkyl.

[00151] "Cycloalkyl" refers to a mono- or polycyclic, heterocyclic or carbocyclic alkyl substituent. Representative cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl and such rings substituted with straight and branched chain alkyl groups as defined above. Typical cycloalkyl substituents have from 3 to 8 backbone (i.e., ring) atoms in which each backbone atom is either carbon or a heteroatom. The term "heterocycloalkyl" refers herein to cycloalkyl substituents that have from 1 to 5, and more typically from 1 to 4 heteroatoms in the ring structure. Suitable heteroatoms employed in compounds of the present invention are nitrogen, oxygen, and sulfur. Representative heterocycloalkyl

moieties include, for example, morpholino, piperazinyl, piperadinyl, and the like. Carbocycloalkyl groups are cycloalkyl groups in which all ring atoms are carbon. When used in connection with cycloalkyl substituents, the term "polycyclic" refers herein to fused and non-fused alkyl cyclic structures.

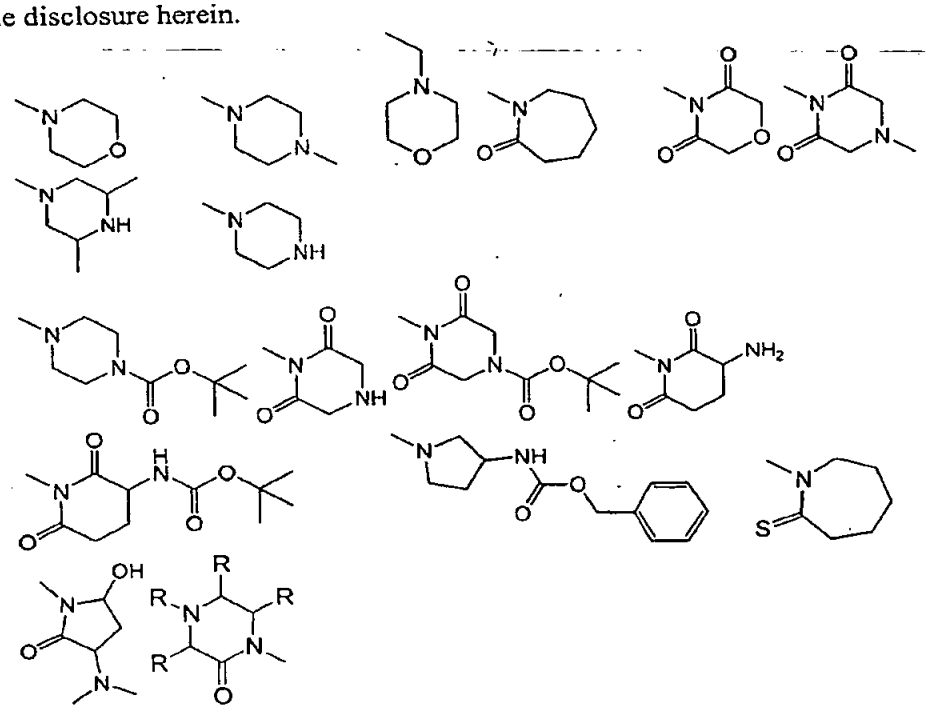
[0152] "Substituted heterocycle," "heterocyclic group," "heterocycle," or "heterocyclyl," as used herein refers to any 3- or 4-membered ring containing a heteroatom selected from nitrogen, oxygen, and sulfur or a 5- or 6-membered ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, or sulfur; wherein the 5-membered ring has 0-2 double bonds and the 6-membered ring has 0-3 double bonds; wherein the nitrogen and sulfur atom maybe optionally oxidized; wherein the nitrogen and sulfur heteroatoms maybe optionally quarternized; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another 5- or 6-membered heterocyclic ring independently defined above. Examples of heterocyclyl groups include, but are not limited to: unsaturated 3- to 8-membered rings containing 1 to 4 nitrogen atoms such as, but not limited to pyrrolyl, dihydropyridyl, pyrimidyl, pyrazinyl, tetrazolyl, (e.g., 1H-tetrazolyl, 2H-tetrazolyl); condensed unsaturated heterocyclic groups containing 1 to 4 nitrogen atoms such as, but not limited to, isoindolyl, indolinyl, indolizinyl, quinolyl, indazolyl; unsaturated 3- to 8-membered rings containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms such as, but not limited to, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl); saturated 3- to 8-membered rings containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms such as, but not limited to, morpholinyl; unsaturated condensed heterocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, benzoxadiazolyl, benzoxazinyl (e.g., 2H-1,4-benzoxazinyl); unsaturated 3- to 8-membered rings containing 1 to 3 sulfur atoms and 1 to 3 nitrogen atoms such as, but not limited to, thiadiazolyl (e.g., 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,-thiadiazolyl); saturated 3- to 8-membered rings containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms such as, but not limited to, thiazolodinyl; saturated

and unsaturated 3- to 8-membered rings containing 1 to 2 sulfur atoms such as, but not limited to, dihydrodithienyl, dihydrodithionyl, tetrahydrothiophene, tetra-hydrothiopyran; unsaturated condensed heterocyclic rings containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms such as, but not limited to, benzothiadiazolyl, benzothiazinyl (e.g., 2H-1,4-benzothiazinyl), dihydrobenzothiazinyl (e.g., 2H-3,4-dihydrobenzothiazinyl), unsaturated 3- to 8-membered rings containing oxygen atoms such as, but not limited to furyl; unsaturated condensed heterocyclic rings containing 1 to 2 oxygen atoms such as benzodioxoyl (e.g., 1,3-benzodioxoyl); unsaturated 3- to 8-membered rings containing an oxygen atom and 1 to 2 sulfur atoms such as, but not limited to, dihydrooxathienyl; saturated 3- to 8-membered rings containing 1 to 2 oxygen atoms and 1 to 2 sulfur atoms such as 1,4-oxathiane; unsaturated condensed rings containing 1 to 2 sulfur atoms such as benzodithienyl; and unsaturated condensed heterocyclic rings containing an oxygen atom and 1 to 2 oxygen atoms such as benzoxathienyl. Preferred heterocycles include, for example: diazapinyl, pyrryl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazoyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, pyrazinyl, piperazinyl, N-methyl piperazinyl, azetidinyl, N-methylazetidinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, triazolyl, and benzothienyl. Heterocyclyl groups also include those described above in which one or more S atoms in the ring is double-bonded to one or two oxygen atoms (sulfoxides and sulfones). For example, heterocyclyl groups include tetrahydrothiophene, tetrahydrothiophene oxide, and tetrahydrothiophene 1,1-dioxide. Preferred heterocyclyl groups contain 5 or 6 ring members. More preferred heterocyclyl groups include piperazine, 1,2,3-triazole, 1,2,4-triazole, tetrazole, thiomorpholine, homopiperazine, oxazolidin-2-one, pyrrolidin-2-one, quinuclidine, and tetrahydrofuran.

[0153] Heterocyclic moieties can be unsubstituted or monosubstituted or disubstituted with various substituents independently selected from hydroxy, halo, oxo

(C=O), alkylimino (RN=, wherein R is alkyl or alkoxy group), amino, alkylamino, dialkylamino, acylaminoalkyl, alkoxy, thioalkoxy, polyalkoxy, alkyl, cycloalkyl or haloalkyl. "Unsubstituted heterocyclyl" includes condensed heterocyclic rings such as benzimidazolyl, it does not include heterocyclyl groups that have other groups such as alkyl or halo groups bonded to one of the ring members as compounds such as 2-methylbenzimidazolyl are substituted heterocyclyl groups.

[0154] The heterocyclic groups may be attached at various positions as will be apparent to those having skill in the organic and medicinal chemistry arts in conjunction with the disclosure herein.



where R is H or a heterocyclic substituent, as described herein.

[0155] Representative heterocyclics include, for example, imidazolyl, pyridyl, piperazinyl, azetidinyl, thiazolyl, furanyl, triazolyl benzimidazolyl, benzothiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, indolyl, naphthpyridinyl, indazolyl, and quinolizinyl.

[0156] "Aryl" refers to optionally substituted monocyclic and polycyclic aromatic groups having from 3 to 14 backbone carbon or hetero atoms, and includes both

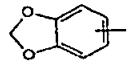
carbocyclic aryl groups and heterocyclic aryl groups. The term refers to, but is not limited to, groups such as phenyl, biphenyl, anthracenyl, naphthenyl by way of example. Carbocyclic aryl groups are aryl groups in which all ring atoms in the aromatic ring are carbon. The term "heteroaryl" refers herein to aryl groups having from 1 to 4 heteroatoms as ring atoms in an aromatic ring with the remainder of the ring atoms being carbon atoms.

[0157] "Unsubstituted aryl" includes groups containing condensed rings such as naphthalene. It does not include aryl groups that have other groups such as alkyl or halo groups bonded to one of the ring members, as aryl groups such as tolyl are considered herein to be substituted aryl groups as described below. A preferred unsubstituted aryl group is phenyl. Unsubstituted aryl groups may be bonded to one or more carbon atom(s), oxygen atom(s), nitrogen atom(s), and/or sulfur atom(s) in the parent compound, however.

[0158] "Substituted aryl group" has the same meaning with respect to unsubstituted aryl groups that substituted alkyl groups had with respect to unsubstituted alkyl groups. However, a substituted aryl group also includes aryl groups in which one of the aromatic carbons is bonded to one of the non-carbon or non-hydrogen atoms described above and also includes aryl groups in which one or more aromatic carbons of the aryl group is bonded to a substituted and/or unsubstituted alkyl, alkenyl, or alkynyl group as defined herein. This includes bonding arrangements in which two carbon atoms of an aryl group are bonded to two atoms of an alkyl, alkenyl, or alkynyl group to define a fused ring system (e.g., dihydronaphthyl or tetrahydronaphthyl). Thus, the phrase "substituted aryl" includes, but is not limited to tolyl, and hydroxyphenyl among others.

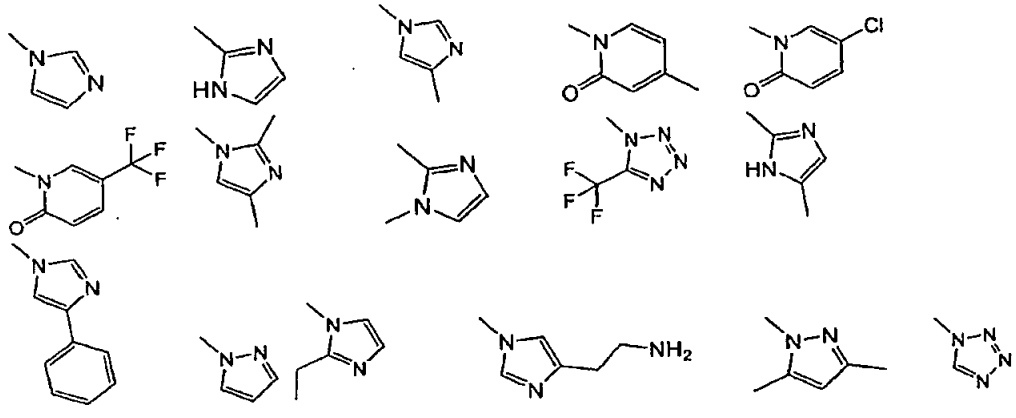
[0159] "Substituted heteroaryl" as used herein refers to a heteroaryl group as defined herein substituted by independent replacement of one, two or three of the hydrogen atoms thereon with Cl, Br, F, I, -OH, -CN, C_1-C_3-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy substituted with aryl, haloalkyl, thioalkoxy, amino, alkylamino, dialkylamino, mercapto, nitro, carboxaldehyde, carboxy, alkoxycarbonyl and

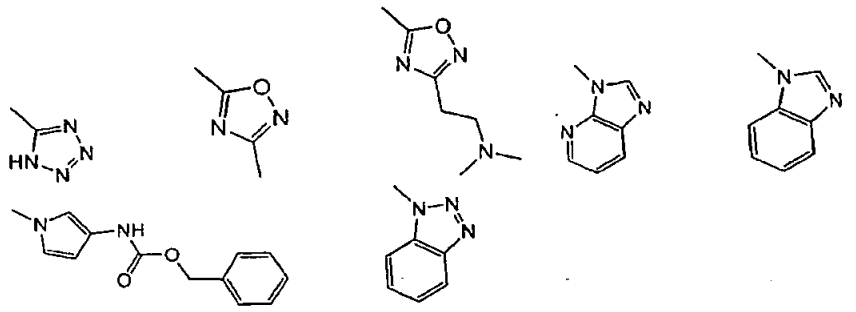
carboxamide. In addition, any one substituent may be an aryl, heteroaryl, or heterocycloalkyl group.

[0160] When used in connection with aryl substituents, the term "polycyclic aryl" refers herein to fused and non-fused cyclic structures in which at least one cyclic structure is aromatic, such as, for example, benzodioxole (which has a heterocyclic structure fused to a phenyl group, i.e.,  ,) naphthyl, and the like. Exemplary aryl or heteroaryl moieties employed as substituents in compounds of the present invention include phenyl, pyridyl, pyrimidinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl, triazolyl, thiophenyl, furanyl, quinolinyl, purinyl, naphthyl, benzothiazolyl, benzopyridyl, and benzimidazolyl, and the like.

[0161] "Aralkyl" or "arylalkyl" refers to an alkyl group substituted with an aryl group. Typically, aralkyl groups employed in compounds of the present invention have from 1 to 6 carbon atoms incorporated within the alkyl portion of the aralkyl group. Suitable aralkyl groups employed in compounds of the present invention include, for example, benzyl, picolyl, and the like.

[0162] Representative heteroaryl groups include, for example, those shown below. These heteroaryl groups can be further substituted and may be attached at various positions as will be apparent to those having skill in the organic and medicinal chemistry arts in conjunction with the disclosure herein.





[0163] Representative heteroaryls include, for example, imidazolyl, pyridyl, thiazolyl, triazolyl benzimidazolyl, benzothiazolyl, and benzoxazolyl.

[0164] "Biaryl" refers to a group or substituent to which two aryl groups, which are not condensed to each other, are bound. Exemplary biaryl compounds include, for example, phenylbenzene, diphenyldiazene, 4-methylthio-1-phenylbenzene, phenoxybenzene, (2-phenylethynyl)benzene, diphenyl ketone, (4-phenylbuta-1,3-diynyl)benzene, phenylbenzylamine, (phenylmethoxy)benzene, and the like. Preferred optionally substituted biaryl groups include: 2-(phenylamino)-N-[4-(2-phenylethynyl)-phenyl]acetamide, 1,4-diphenylbenzene, N-[4-(2-phenylethynyl)phenyl]-2-[benzyl-amino]-acetamide, 2-amino-N-[4-(2-phenylethynyl)phenyl]propanamide, 2-amino-N-[4-(2-phenyl-ethynyl)phenyl]acetamide, 2-(cyclopropylamino)-N-[4-(2-phenylethynyl)-phenyl]-acetamide, 2-(ethylamino)-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-[(2-methyl-propyl)amino]-N-[4-(2-phenylethynyl)phenyl]acetamide, 5-phenyl-2H-benzo-[d]1,3-dioxolene, 2-chloro-1-methoxy-4-phenylbenzene, 2-[(imidazolylmethyl)-amino]-N-[4-(2-phenylethynyl)phenyl]acetamide, 4-phenyl-1-phenoxybenzene, N-(2-amino-ethyl)-[4-(2-phenylethynyl)phenyl]carboxamide, 2-{[(4-fluorophenyl)methyl]-amino}-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-{[(4-methylphenyl)methyl]amino}-N-[4-(2-phenyl-ethynyl)phenyl]acetamide, 4-phenyl-1-(trifluoromethyl)benzene, 1-butyl-4-phenyl-benzene, 2-(cyclohexylamino)-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-(ethyl-methyl-amino)-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-(butylamino)-N-[4-(2-phenyl-ethynyl)-phenyl]acetamide, N-[4-(2-phenylethynyl)phenyl]-2-(4-pyridylamino)-

acetamide, N-[4-(2-phenylethynyl)phenyl]-2-(quinuclidin-3-ylamino)acetamide, N-[4-(2-phenyl-ethynyl)phenyl]pyrrolidin-2-ylcarboxamide, 2-amino-3-methyl-N-[4-(2-phenyl-ethynyl)-phenyl]butanamide, 4-(4-phenylbuta-1,3-diynyl)phenylamine, 2-(dimethyl-amino)-N-[4-(4-phenylbuta-1,3-diynyl)phenyl]acetamide, 2-(ethylamino)-N-[4-(4-phenylbuta-1,3-diynyl)-phenyl]acetamide, 4-ethyl-1-phenylbenzene, 1-[4-(2-phenyl-ethynyl)-phenyl]ethan-1-one, N-(1-carbamoyl-2-hydroxypropyl)[4-(4-phenylbuta-1,3-diynyl)-phenyl]-carbox-amide, N-[4-(2-phenylethynyl)phenyl]propanamide, 4-methoxy-phenyl phenyl ketone, phenyl-N-benzamide, (tert-butoxy)-N-[(4-phenylphenyl)-methyl]-carboxamide, 2-(3-phenyl-phenoxy)ethanehydroxamic acid, 3-phenylphenyl propanoate, 1-(4-ethoxyphenyl)-4-methoxybenzene, and [4-(2-phenylethynyl)phenyl]pyrrole.

[0165] "Heteroarylaryl" refers to a biaryl group where one of the aryl groups is a heteroaryl group. Exemplary heteroarylaryl groups include, for example, 2-phenylpyridine, phenylpyrrole, 3-(2-phenylethynyl)pyridine, phenylpyrazole, 5-(2-phenyl-ethynyl)-1,3-dihydropyrimidine-2,4-dione, 4-phenyl-1,2,3-thiadiazole, 2-(2-phenylethynyl)pyrazine, 2-phenylthiophene, phenylimidazole, 3-(2-piperazinyl-phenyl)-furan, 3-(2,4-dichlorophenyl)-4-methylpyrrole, and the like. Preferred optionally substituted heteroarylaryl groups include: 5-(2-phenylethynyl)pyrimidine-2-ylamine, 1-methoxy-4-(2-thienyl)benzene, 1-methoxy-3-(2-thienyl)benzene, 5-methyl-2-phenyl-pyridine, 5-methyl-3-phenylisoxazole, 2-[3-(trifluoromethyl)phenyl]furan, 3-fluoro-5-(2-furyl)-2-methoxy-1-prop-2-enylbenzene, (hydroxyimino)(5-phenyl(2-thienyl))-methane, 5-[(4-methylpiperazinyl)methyl]-2-phenylthiophene, 2-(4-ethylphenyl)-thio-phene, 4-methyl-thio-1-(2-thienyl)benzene, 2-(3-nitrophenyl)thiophene, (tert-butoxy)-N-[(5-phenyl-(3-pyridyl))methyl]carboxamide, hydroxy-N-[(5-phenyl(3-pyridyl))methyl]-amide, 2-(phenyl-methylthio)pyridine, and benzylimidazole.

[0166] "Heteroarylheteroaryl" refers to a biaryl group where both of the aryl groups is a heteroaryl group. Exemplary heteroarylheteroaryl groups include, for example, 3-pyridylimidazole, 2-imidazolylpyrazine, and the like. Preferred optionally substituted heteroarylheteroaryl groups include: 2-(4-piperazinyl-3-pyridyl)furan, diethyl-

(3-pyrazin-2-yl(4-pyridyl))amine, and dimethyl{2-[2-(5-methylpyrazin-2-yl)ethynyl](4-pyridyl)}amine.

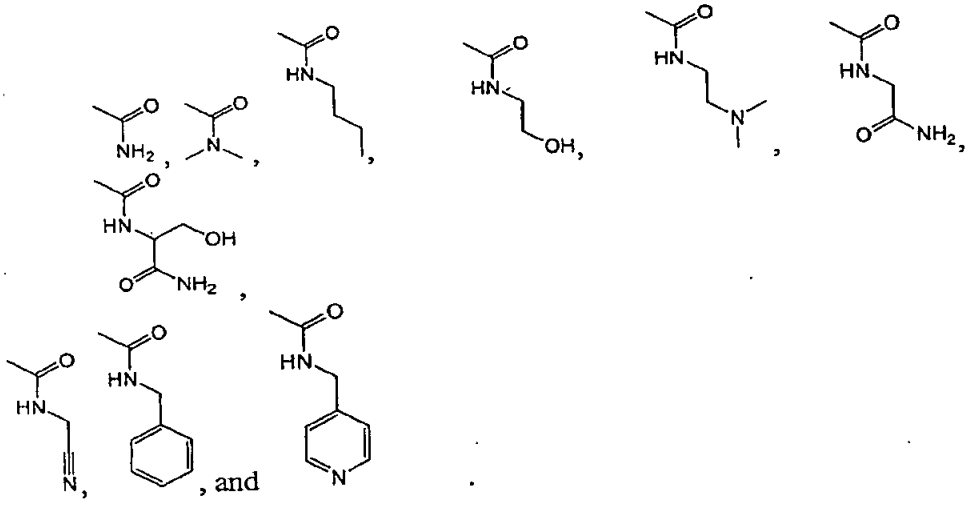
[0167] "Optionally substituted" or "substituted" refers to the replacement of hydrogen with one or more monovalent or divalent radical. Suitable substitution groups include, for example, hydroxyl, nitro, amino, imino, cyano, halo, thio, sulfonyl, thioamido, amidino, imidino, oxo, oxamidino, methoxamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, alkyl, substituted alkyl, haloalkyl, alkyamino, haloalkylamino, alkoxy, haloalkoxy, alkoxy-alkyl, alkylcarbonyl, aminocarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteroaralkyl-carbonyl, alkylthio, aminoalkyl, cyanoalkyl, aryl, benzyl, pyridyl, pyrazolyl, pyrrole, thiophene, imidazolyl, and the like.

[0168] The substitution group can itself be substituted. The group substituted onto the substitution group can be carboxyl, halo, nitro, amino, cyano, hydroxyl, alkyl, alkoxy, aminocarbonyl, -SR, thioamido, $-SO_3H$, $-SO_2R$, or cycloalkyl, where R is typically hydrogen, hydroxyl or alkyl.

[0169] When the substituted substituent includes a straight chain group, the substitution can occur either within the chain (e.g., 2-hydroxypropyl, 2-aminobutyl, and the like) or at the chain terminus (e.g., 2-hydroxyethyl, 3-cyanopropyl, and the like). Substituted substituents can be straight chain, branched or cyclic arrangements of covalently bonded carbon or heteroatoms.

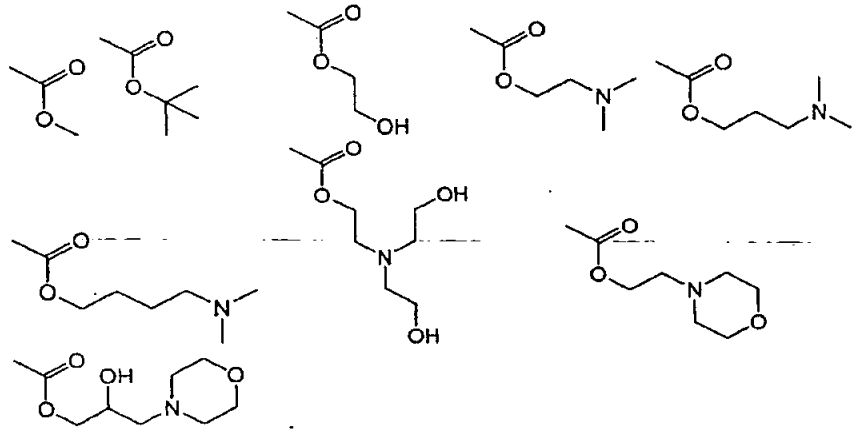
[0170] Representative substituted aminocarbonyl groups include, for example, those shown below. These can be further substituted by heterocyclyl groups and heteroaryl groups as will be apparent to those having skill in the organic and medicinal chemistry arts in conjunction with the disclosure herein. Preferred aminocarbonyl groups include: N-(2-cyanoethyl)carboxamide, N-(3-methoxypropyl)carboxamide, N-cyclopropylcarboxamide, N-(2-hydroxy-isopropyl)carboxamide, methyl 2-carbonylamino-3-hydroxypropanoate, N-(2-hydroxypropyl)carboxamide, N-(2-hydroxy-isopropyl)carboxamide, N-[2-hydroxy-1-

(hydroxymethyl)ethyl]carboxamide, N-(2-carbonylaminoethyl)acetamide, N-(2-(2-pyridyl)ethyl)carboxamide, N-(2-pyridylmethyl)carboxamide, N-(oxolan-2-ylmethyl)-carboxamide, N-(4-hydroxypyrrolidin-2-yl)carboxamide, N-[2-(2-hydroxyethoxy)ethyl]-carboxamide, N-(4-hydroxycyclohexyl)carboxamide, N-[2-(2-oxo-4-imidazolinyl)ethyl]-carboxamide, N-(carbonylaminomethyl)acetamide, N-(3-pyrrolidinylpropyl)carboxamide, N-[1-(carbonylaminomethyl)pyrrolidin-3-yl]acetamide, N-(2-morpholin-4-ylethyl)carboxamide, N-[3-(2-oxopyrrolidinyl)propyl]carboxamide, 4-methyl-2-oxopiperazinecarbaldehyde, N-(2-hydroxy-3-pyrrolidinylpropyl)carboxamide, N-(2-hydroxy-3-morpholin-4-ylpropyl)carboxamide, N-{2-[(5-cyano-2-pyridyl)amino]ethyl}carboxamide, 3-(dimethylamino)pyrrolidinecarbaldehyde, N-[(5-methylpyrazin-2-yl)methyl]carboxamide, 2,2,2-trifluoro-N-(1-formylpyrrolidin-3-yl)acetamide,



[0171] Representative substituted alkoxycarbonyl groups include, for example, those shown below. These alkoxycarbonyl groups can be further substituted as will be apparent to those having skill in the organic and medicinal chemistry arts in conjunction with the disclosure herein.

[0172] Representative substituted alkoxycarbonyl groups include, for example, those shown below. These alkoxycarbonyl groups can be further substituted as will be apparent to those having skill in the organic and medicinal chemistry arts in conjunction with the disclosure herein.



[0173] The term "protected" with respect to hydroxyl groups, amine groups, and sulfhydryl groups refers to forms of these functionalities which are protected from undesirable reaction with a protecting group known to those skilled in the art such as those set forth in *Protective Groups in Organic Synthesis*, Greene, T.W.; Wuts, P. G. M., John Wiley & Sons, New York, NY, (3rd Edition, 1999) which can be added or removed using the procedures set forth therein. Examples of protected hydroxyl groups include, but are not limited to, silyl ethers such as those obtained by reaction of a hydroxyl group with a reagent such as, but not limited to, t-butyldimethyl-chlorosilane, trimethylchlorosilane, triisopropylchlorosilane, triethylchlorosilane; substituted methyl and ethyl ethers such as, but not limited to methoxymethyl ether, methythiomethyl ether, benzyloxymethyl ether, t-butoxymethyl ether, 2-methoxyethoxymethyl ether, tetrahydropyranyl ethers, 1-ethoxyethyl ether, allyl ether, benzyl ether; esters such as, but not limited to, benzoylformate, formate, acetate, trichloroacetate, and trifluoroacetate. Examples of protected amine groups include, but are not limited to, amides such as,

formamide, acetamide, trifluoroacetamide, and benzamide; imides, such as phthalimide, and dithiosuccinimide; and others. Examples of protected sulfhydryl groups include, but are not limited to, thioethers such as S-benzyl thioether, and S-4-picolyl thioether; substituted S-methyl derivatives such as hemithio, dithio and aminothio acetals; and others.

[0173] "Carboxy-protecting group" refers to a carbonyl group which has been esterified with one of the commonly used carboxylic acid protecting ester groups employed to block or protect the carboxylic acid function while reactions involving other functional sites of the compound are carried out. In addition, a carboxy protecting group can be attached to a solid support whereby the compound remains connected to the solid support as the carboxylate until cleaved by hydrolytic methods to release the corresponding free acid. Representative carboxy-protecting groups include, for example, alkyl esters, secondary amides and the like.

[0174] Certain compounds of the invention comprise asymmetrically substituted carbon atoms. Such asymmetrically substituted carbon atoms can result in the compounds of the invention comprising mixtures of stereoisomers at a particular asymmetrically substituted carbon atom or a single stereoisomer. As a result, racemic mixtures, mixtures of diastereomers, as well as single diastereomers of the compounds of the invention are included in the present invention. The terms "S" and "R" configuration, as used herein, are as defined by the IUPAC 1974 "RECOMMENDATIONS FOR SECTION E, FUNDAMENTAL STEREOCHEMISTRY," *Pure Appl. Chem. 45*:13-30, 1976. The terms α and β are employed for ring positions of cyclic compounds. The α-side of the reference plane is that side on which the preferred substituent lies at the lower numbered position. Those substituents lying on the opposite side of the reference plane are assigned β descriptor. It should be noted that this usage differs from that for cyclic stereoparents, in which "α" means "below the plane" and denotes absolute configuration. The terms α and β configuration, as used herein, are as defined by the "Chemical Abstracts Index Guide," Appendix IV, paragraph 203, 1987.

[0175] As used herein, the term "pharmaceutically acceptable salts" refers to the nontoxic acid or alkaline earth metal salts of the pyrimidine compounds of the invention. These salts can be prepared *in situ* during the final isolation and purification of the pyrimidine compounds, or by separately reacting the base or acid functions with a suitable organic or inorganic acid or base, respectively. Representative salts include, but are not limited to, the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemi-sulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphth-alenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproionate, picrate, pivalate, propionate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl, and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

[0176] Examples of acids that may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, hydroboric acid, nitric acid, sulfuric acid and phosphoric acid and such organic acids as formic acid, acetic acid, trifluoroacetic acid, fumaric acid, tartaric acid, oxalic acid, maleic acid, methanesulfonic acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, and p-toluenesulfonic acid, citric acid, and acidic amino acids such as aspartic acid and glutamic acid.

[0177] Basic addition salts can be prepared *in situ* during the final isolation and purification of the pyrimidine compounds, or separately by reacting carboxylic acid moieties with a suitable base such as the hydroxide, carbonate or bicarbonate of a

pharmaceutically acceptable metal cation or with ammonia, or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, aluminum salts and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. Other representative organic amines useful for the formation of base addition salts include diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, pyridine, picoline, triethanolamine and the like, and basic amino acids such as arginine, lysine and ornithine.

[0178] As used herein, the term "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.

[0179] The term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compound of the above formula, for example by hydrolysis in blood. A thorough discussion is provided in Higuchi, T., and V. Stella, "Pro-drugs as Novel Delivery Systems," *A.C.S. Symposium Series 14*, and in "Bioreversible Carriers in Drug Design,"

in Edward B. Roche (ed.), *American Pharmaceutical Association*, Pergamon Press, 1987, both of which are incorporated herein by reference.

[0180] "Treating" within the context of the instant invention, means an alleviation of symptoms associated with a disorder or disease, or halt of further progression or worsening of those symptoms, or prevention or prophylaxis of the disease or disorder. For example, within the context of treating patients in need of an inhibitor of PI3K, successful treatment may include a reduction in the proliferation of capillaries feeding a tumor or diseased tissue, an alleviation of symptoms related to a cancerous growth or tumor, proliferation of capillaries, or diseased tissue, a halting in capillary proliferation, or a halting in the progression of a disease such as cancer or in the growth of cancerous cells. Treatment may also include administering the pharmaceutical formulations of the present invention in combination with other therapies. For example, the compounds and pharmaceutical formulations of the present invention may be administered before, during, or after surgical procedure and/or radiation therapy. The compounds of the invention can also be administered in conjunction with other anti-cancer drugs including those used in antisense and gene therapy.

[0181] As used herein, "limit", "treat" and "treatment" are interchangeable terms as are "limiting" and "treating" and, as used herein, include preventative (e.g., prophylactic) and palliative treatment or the act of providing preventative or palliative treatment.

[0182] The term "PI3K-mediated disorder" refers to a disorder that can be beneficially treated by the inhibition of PI3K.

[0183] The term "cellular proliferative diseases" refers to diseases including, for example, cancer, tumor, hyperplasia, restenosis, cardiac hypertrophy, immune disorder and inflammation.

[0184] The term "cancer" refers to cancer diseases that can be beneficially treated by the inhibition of PI3K, including, for example, lung and bronchus; prostate; breast; pancreas; colon and rectum; thyroid; liver and intrahepatic bile duct; hepatocellular;

gastric; glioma/glioblastoma; endometrial; melanoma; kidney and renal pelvis; urinary bladder; uterine corpus; uterine cervix; ovary; multiple myeloma; esophagus; acute myelogenous leukemia; chronic myelogenous leukemia; lymphocytic leukemia; myeloid leukemia; brain; oral cavity and pharynx; larynx; small intestine; non-Hodgkin lymphoma; melanoma; and villous colon adenoma.

[0185] The PI3K inhibitors of this invention, as described herein, can be administered in the form of acid addition salts. The salts are conveniently formed by reacting a compound, if basic, with a suitable acid, such as have been described above. The salts are quickly formed in high yields at moderate temperatures, and often are prepared by merely isolating the compound from a suitable acidic wash as the final step of the synthesis. The salt-forming acid is dissolved in an appropriate organic solvent, or aqueous organic solvent, such as an alkanol, ketone or ester. On the other hand, if the compound of this invention is desired in the free base form, it is isolated from a basic final wash step, according to the usual practice. A preferred technique for preparing hydrochlorides is to dissolve the free base in a suitable solvent and dry the solution thoroughly, as over molecular sieves, before bubbling hydrogen chloride gas through it. It will also be recognized that it is possible to administer amorphous forms of the PI3K inhibitors.

[0186] The invention also provides isotopically-labeled PI3K inhibitors, which are structurally identical to those disclosed above, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. 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, prodrugs thereof, and pharmaceutically acceptable salts of said compounds and of said prodrugs which 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.

[0187] The compounds of the invention are useful *in vitro* or *in vivo* in inhibiting the growth of cancer cells. The compounds may be used alone or in compositions together with a pharmaceutically acceptable carrier or excipient. Pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a phosphatidylinositol 3-kinase inhibitor compound described herein formulated together with one or more pharmaceutically acceptable carriers. As used herein, the term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring

agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator. Other suitable pharmaceutically acceptable excipients are described in "Remington's Pharmaceutical Sciences," Mack Pub. Co., New Jersey, 1991, incorporated herein by reference.

[0188] The compounds of the present invention may be administered to humans and other animals orally, parenterally, sublingually, by aerosolization or inhalation spray, rectally, intracisternally, intravaginally, intraperitoneally, bucally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve 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.

[0189] Methods of formulation are well known in the art and are disclosed, for example, in Remington: *The Science and Practice of Pharmacy*, Mack Publishing Company, Easton, Pa., 19th Edition (1995). Pharmaceutical compositions for use in the present invention can be in the form of sterile, non-pyrogenic liquid solutions or suspensions, coated capsules, suppositories, lyophilized powders, transdermal patches or other forms known in the art.

[0190] 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, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-propanediol or 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. 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

di-glycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables. The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[0191] In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form may be accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations may also be prepared by entrapping the drug in liposomes or microemulsions, which are compatible with body tissues.

[0192] Compositions—for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[0193] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example,

carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, acetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[0194] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[0195] The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[0196] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. 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 comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may

also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[0197] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, EtOAc, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0198] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulations, ear drops, and the like are also contemplated as being within the scope of this invention.

[0199] The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[0200] Compositions of the invention may also be formulated for delivery as a liquid aerosol or inhalable dry powder. Liquid aerosol formulations may be nebulized

predominantly into particle sizes that can be delivered to the terminal and respiratory bronchioles.

[0201] Aerosolized formulations of the invention may be delivered using an aerosol forming device, such as a jet, vibrating porous plate or ultrasonic nebulizer, preferably selected to allow the formation of an aerosol particles having with a mass medium average diameter predominantly between 1 to 5 μm. Further, the formulation preferably has balanced osmolarity ionic strength and chloride concentration, and the smallest aerosolizable volume able to deliver effective dose of the compounds of the invention to the site of the infection. Additionally, the aerosolized formulation preferably does not impair negatively the functionality of the airways and does not cause undesirable side effects.

[0202] Aerosolization devices suitable for administration of aerosol formulations of the invention include, for example, jet, vibrating porous plate, ultrasonic nebulizers and energized dry powder inhalers, that are able to nebulize the formulation of the invention into aerosol particle size predominantly in the size range from 1-5 μm. Predominantly in this application means that at least 70% but preferably more than 90% of all generated aerosol particles are within 1-5 μm range. A jet nebulizer works by air pressure to break a liquid solution into aerosol droplets. Vibrating porous plate nebulizers work by using a sonic vacuum produced by a rapidly vibrating porous plate to extrude a solvent droplet through a porous plate. An ultrasonic nebulizer works by a piezoelectric crystal that shears a liquid into small aerosol droplets. A variety of suitable devices are available, including, for example, AERONEB and AERODOSE vibrating porous plate nebulizers (AeroGen, Inc., Sunnyvale, California), SIDESTREAM nebulizers (Medic-Aid Ltd., West Sussex, England), PARI LC and PARI LC STAR jet nebulizers (Pari Respiratory Equipment, Inc., Richmond, Virginia), and AEROSONIC (DeVilbiss Medizinische Produkte (Deutschland) GmbH, Heiden, Germany) and ULTRAAIRE (Omron Healthcare, Inc., Vernon Hills, Illinois) ultrasonic nebulizers.

[0203] Compounds of the invention may also be formulated for use as topical powders and sprays that can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

[0204] Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel. The compounds 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 multi-lamellar 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 can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art. See, for example, Prescott (ed.), "Methods in Cell Biology," Volume XIV, Academic Press, New York, 1976, p. 33 *et seq*.

[0205] Effective amounts of the compounds of the invention generally include any amount sufficient to detectably inhibit PI3K activity by any of the assays described herein, by other PI3K activity assays known to those having ordinary skill in the art, or by detecting an inhibition or alleviation of symptoms of cancer. 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 the 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.

[0206] According to the methods of treatment of the present invention, tumor growth is reduced or prevented in a patient such as a human or lower mammal by administering to the patient a therapeutically effective amount of a compound of the invention, in such amounts and for such time as is necessary to achieve the desired result. By a "therapeutically effective amount" of a compound of the invention is meant a sufficient amount of the compound to treat tumor growth, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

[0207] For purposes of the present invention, a therapeutically effective dose will generally be a total daily dose administered to a host in single or divided doses may be in amounts, for example, of from 0.001 to 1000 mg/kg body weight daily and more preferred from 1.0 to 30 mg/kg body weight daily. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose. In general, treatment regimens according to the present invention comprise administration to a

patient in need of such treatment from about 10 mg to about 2000 mg of the compound(s) of this invention per day in single or multiple doses.

[0208] In another aspect of the invention, kits that include one or more compounds of the invention are provided. Representative kits include a PI3K inhibitor compound of the invention (e.g., a compound of formulas (I)-(III)) and a package insert or other labeling including directions for treating a cellular proliferative disease by administering an PI3K inhibitory amount of the compound.

[0209] The term "kit" as used herein comprises a container for containing the pharmaceutical compositions and may also include divided containers such as a divided bottle or a divided foil packet. The container can be in any conventional shape or form as known in the art which is made of a pharmaceutically acceptable material, for example a paper or cardboard box, a glass or plastic bottle or jar, a resealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual doses for pressing out of the pack according to a therapeutic schedule. The container employed can depend on the exact dosage form involved, for example a conventional cardboard box would not generally be used to hold a liquid suspension. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle which is in turn contained within a box.

[0210] An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process, recesses are formed in the plastic foil. The recesses have the size and shape of individual tablets or capsules to be packed or may have the size and shape to accommodate multiple tablets and/or capsules to be packed. Next, the tablets or capsules are placed in the recesses accordingly and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is

opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are individually sealed or collectively sealed, as desired, in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

[0211] It maybe desirable to provide a written memory aid, where the written memory aid is of the type containing information and/or instructions for the physician, pharmacist or other health care provider, or subject, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested or a card which contains the same type of information. Another example of such a memory aid is a calendar printed on the card, e.g., as follows "First Week, Monday, Tuesday," "Second Week, Monday, Tuesday, . . ." Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several tablets or capsules to be taken on a given day. When the kit contains separate compositions, a daily dose of one or more compositions of the kit can consist of one tablet or capsule while a daily dose of another one or more compositions of the kit can consist of several tablets or capsules.

[0212] Another specific embodiment of a kit is a dispenser designed to dispense the daily doses one at a time in the order of their intended use. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter, which indicates the number of daily doses that has been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

[0213] The kits of the present invention may also comprise, in addition to a PI3K inhibitor, one or more additional pharmaceutically active compounds. Preferably, the

additional compound is another PI3K inhibitor or another compound useful to treat cancer, angiogenesis, or tumor growth. The additional compounds may be administered in the same dosage form as the PI3K inhibitor or in different dosage forms. Likewise, the additional compounds can be administered at the same time as the PI3K inhibitor or at different times.

[0214] The present invention will be understood more readily by reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present invention.

EXAMPLES

[0215] Referring to the examples that follow, compounds of the present invention were synthesized using the methods described herein, or other methods, which are known in the art.

[0216] 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 Alltima C-18 reversed phase, 4.6 x 50 mm, flow 2.5 mL/min, from Alltech (Deerfield, IL). A gradient elution was used, typically starting with 5% acetonitrile/95% water and progressing to 100% acetonitrile over a period of 40 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.

[0217] Mass spectrometric analysis was performed on one of two LCMS instruments: a Waters System (Alliance HT HPLC and a Micromass ZQ mass spectrometer; Column: Eclipse XDB-C18, 2.1 x 50 mm; solvent system: 5-95% (or

35-95%, or 65-95% or 95-95%) acetonitrile in water with 0.05% TFA; flow rate 0.8 mL/min; molecular weight range 200-1500; cone Voltage 20 V; column temperature 40 °C) or a Hewlett Packard System (Series 1100 HPLC; Column: Eclipse XDB-C18, 2.1 x 50 mm; solvent system: 1-95% acetonitrile in water with 0.05% TFA; 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.

[0218] GCMS analysis is 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).

[0219] 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 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.

[0220] The purity of some of the invention compounds is assessed by elemental analysis (Desert Analytics, Tucson, AZ).

[0221] Melting points are determined on a Laboratory Devices Mel-Temp apparatus (Holliston, MA).

[0222] 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 were dichloromethane, methanol, ethyl acetate, hexane, acetone, aqueous ammonia (or ammonium hydroxide), and triethyl amine. Typical solvents employed for the reverse phase HPLC were varying concentrations of acetonitrile and water with 0.1% trifluoroacetic acid.

[0223] It should be understood that the organic compounds according to the invention may exhibit the phenomenon of tautomerism. As the chemical structures within this specification can only represent one of the possible tautomeric forms, it should be understood that the invention encompasses any tautomeric form of the drawn structure.

[0224] It is understood that the invention is not limited to the embodiments set forth herein for illustration, but embraces all such forms thereof as come within the scope of the above disclosure.

Abbreviations

ACN	Acetonitrile
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binapthyl
DIEA	diisopropylethylamine
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DPPF	1,1'-bis(diphenylphosphino)ferrocene
EtOAc	ethyl acetate
EtOH	ethanol
MCPBA	*meta*-chloroperoxybenzoic acid
NBS	N-bromosuccinimide
NMP	N-methyl-2-pyrrolidone
RT	room temperature
THF	tetrahydrofuran

General Methods for Synthesizing PI3K Inhibitor Compounds

[0225] Methods for preparing compounds of Formula I and/or II are provided. The methods include: reacting a 4-halo-2-morpholinopyrimidine with a substituted pyridinyl or pyrimidinyl group containing a reactive boronic ester substituent, in the presence of a palladium catalyst. In one embodiment, the substituted pyridinyl or

pyrimidinyl group containing a reactive boronic ester substituent has an $-NH_2$ group positioned *para* to the boronic ester. In another embodiment, the substituted pyridinyl or pyrimidinyl group containing a reactive boronic ester substituent has an $-NH_2$ group positioned *para* to the boronic ester and another non-hydrogen substituent positioned *ortho* to the boronic ester. In certain embodiments, the non-hydrogen substituent is $-CF_3$, -CN, $-NH_2$, halo, or substituted or unsubstituted C_{1-3} alkyl.

[0226] In another embodiment, the 4-halo-2-morpholinopyrimidine group is a 4-halo-6-heterocyclyl-2-morpholinopyrimidine group. In another embodiment, the 4-halo-2-morpholinopyrimidine group is a 4-halo-6-heterocyclyloxy-2-morpholinopyrimidine group. In another embodiment, the 4-halo-2-morpholinopyrimidine group is a 4-halo-6-heteroarylamino-2-morpholinopyrimidine group. In another embodiment, the 4-halo-2-morpholinopyrimidine group is 4-chloro-2,6-dimorpholinopyrimidine.

[0227] In another embodiment, the pyridinyl boronic ester is 4-(trifluoromethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine. In another embodiment, the palladium catalyst is $Pd(dppf)Cl_2$ dichloromethane adduct.

[0228] In another embodiment, the 4-halo-6-heterocyclyl-2-morpholinopyrimidine group is prepared by reacting a heterocyclyl group with a 4,6-dihalo-2-morpholinopyrimidine group. In another embodiment, the 4-chloro-2,6-dimorpholinopyrimidine group is prepared by reacting 4,6-dichloro-2-morpholinopyrimidine with morpholine. In another embodiment, the 4,6-dichloro-2-morpholinopyrimidine group is prepared by reacting 2-morpholinopyrimidine-4,6-diol with $POCl_3$. In another embodiment, the 2-morpholinopyrimidine-4,6-diol is prepared by reacting morpholine-4-carboxamidine with diethyl malonate in the presence of a base, such as sodium ethoxide.

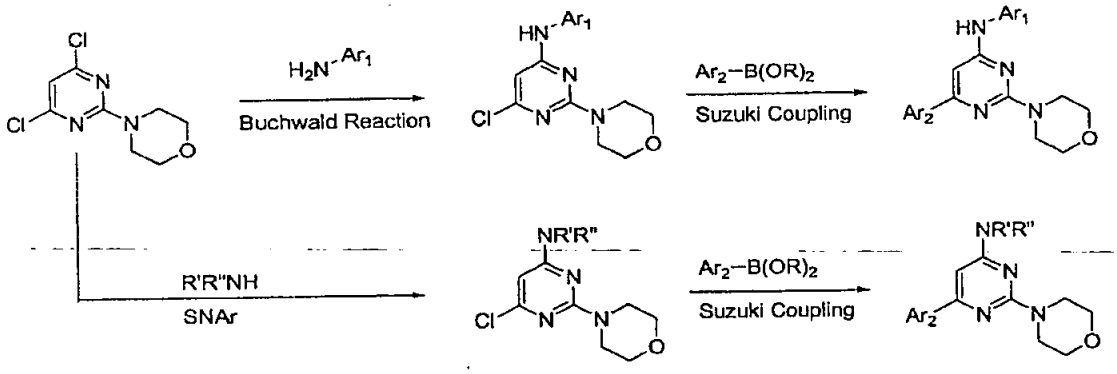
[0229] In another embodiment, the substituted pyridinyl or pyrimidinyl group containing a reactive boronic ester substituent is prepared by reacting a substituted pyridinyl or pyrimidinyl group containing a bromo substituent with a diboronic ester, such as 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-

dioxaborolane. In another embodiment, the substituted pyridinyl or pyrimidinyl group containing a bromo substituent is prepared by reacting the substituted pyridinyl or pyrimidinyl group with N-bromosuccinimide (NBS).

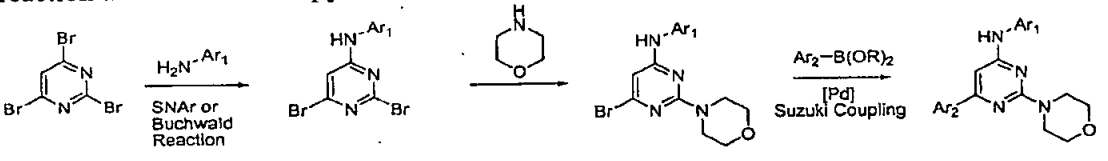
[0230] Another embodiment of the present invention provides a method of preparing a 4-chloro-2,6-dimorpholinopyrimidine comprising reacting morpholine with 2,4,6-trichloropyrimidine in a suitable solvent. In a more particular embodiment, the solvent is a polar aprotic solvent. More particular still the solvent is THF. In another more particular embodiment, the 4-chloro-2,6-dimorpholinopyrimidine is added over a period of at least 10 minutes, or at least 20 minutes, or 30 minutes to a solution comprising morpholine. Alternatively, the morpholine is added to a solution comprising 4-chloro-2,6-dimorpholinopyrimidine. More particular still, the solution is cooled below 20°C, or below 10°C, or below 5°C, or below 0°C. More particularly, during or after addition of the 4-chloro-2,6-dimorpholinopyrimidine, the solution is allowed to warm to greater than 20°C, or greater than 25°C, or greater than 30°C. In another embodiment, after the morpholine and 4-chloro-2,6-dimorpholinopyrimidine are combined, the solution is quenched by addition of an aqueous solution. More particularly, at least 10 hours, or at least 20 hours, or at least 30 hours, or at least 40 hours, or at least 50 hours, or about 64 hours after the morpholine and 4-chloro-2,6-dimorpholinopyrimidine are combined, the solution is quenched by addition of an aqueous solution. More particularly, after quenching, the solution is purified by column chromatography. More particular still, the column is silica gel. In another embodiment, the 4-chloro-2,6-dimorpholinopyrimidine is reacted with a 2-aminopyridyl or 2-aminopyrimidyl moiety to form a compound of Formula III.

[0231] Compounds of the invention containing a pyrimidine core, such as those of Formula I, may be prepared using a number of methods familiar to one of skill in the art. In one method, suitably functionalized amines may be coupled with 4,6-dichloro-2-morpholinopyrimidine by nucleophilic aromatic substitution reactions or by a Buchwald-Hartwig cross-coupling reaction (Hartwig et al., Tetrahedron Letters 36, (1995) 3609),

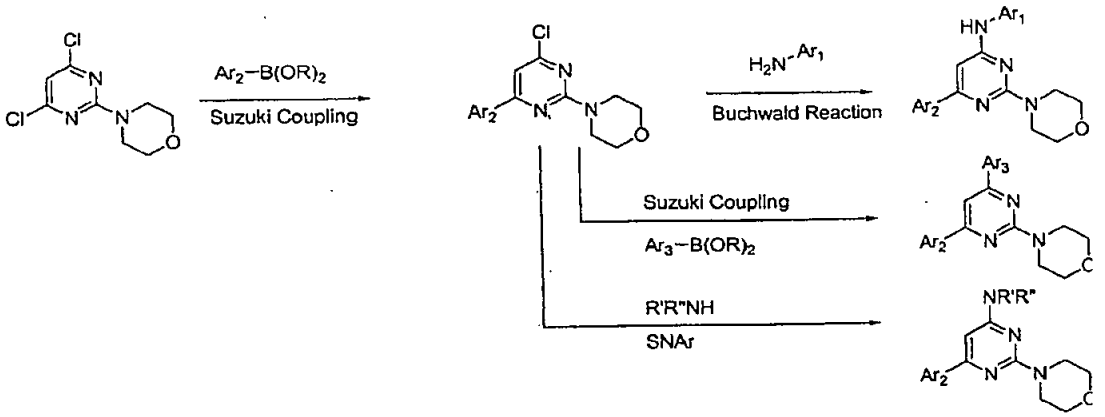
wherein Ar represents aryl or heteroaryl moieties. Subsequently, Suzuki coupling (Suzuki et al., Chem. Commun. (1979) 866) to form the final product may be effected under known conditions such as by treatment with functionalized boronic esters as in the following schemes:



[0232] From 2,4,6-tribromopyrimidine: SNAr (or Buchwald) reaction of functionalized arylamines with 2,4,6-tribromopyrimidine gave preferentially 4-substitituted products. Morpholine substitution at 2-position followed with Suzuki reaction affords the final pyrimidine analogs:



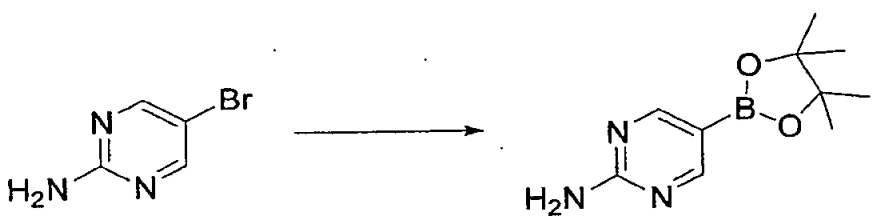
[0233] Alternatively, multiple Suzuki couplings can be used to afford aryl or heteroaryl groups appended directly to the pyrimidine core at the 4 and 6 positions; or an initial Suzuki coupling can be performed followed by a nucleophilic aromatic substitution reaction or a Buchwald-Hartwig cross-coupling reaction, as shown in the following scheme:



[0234] More particular syntheses of compounds of the present invention, particularly those of Formula I, II, and III, are provided in the following Methods and Examples:

Method 1

[0235] Synthesis of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine-2-ylamine

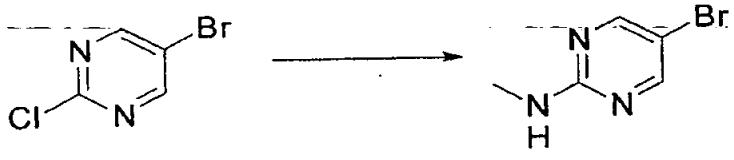


[0236] To a dry 500-mL flask was added 2-amino-5-bromopyrimidine (10 g, 57.5 mmol), potassium acetate (16.9 g, 172 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2yl)-1,3,2-dioxaborolane (16.1 g, 63.0 mmol) and dioxane (300 mL). Argon was bubbled through the solution for 15 minutes, at which time dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium (II) dichloromethane adduct ($Pd(dppf)Cl_2$ CH_2Cl_2) (2.34 g, 2.87 mmol) was added. The reaction mixture was refluxed in a 115 °C oil bath for 4 hours under argon. After cooling to room temperature, EtOAc (500 mL) was added and the resulting slurry was sonicated and filtered. Additional EtOAc (500 mL) was used to wash the solid. The combined organic extracts

were washed with H_2O (2x300 mL), $NaCl_{(sat.)}$ (300 mL), dried over Na_2SO_4, and filtered through a 5 cm pad of silica gel. Additional EtOAc was used to flush product. After the solvent was concentrated, the crude was treated with a mixture of 1:3 dichloromethane and hexane (40 mL), filtered and washed with hexane yielding a light yellow solid (8.5 g, 75%). LCMS (*m/z*): 140 (MH^+ of boronic acid, deriving from product hydrolysis on LC). ^1H NMR ($CDCl_3$): δ 8.58 (s, 2H), 5.74 (s, 2H), 1.32 (s, 12H).

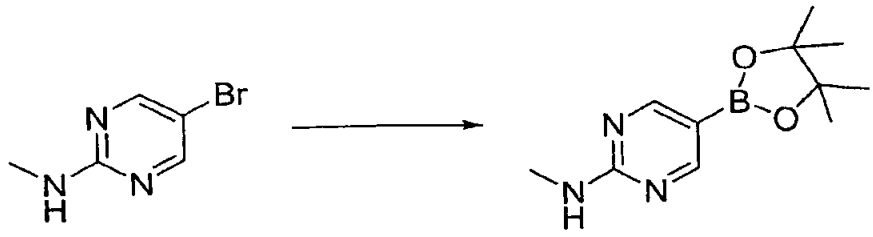
Method 2

[0237] Synthesis of 2-Aminomethyl-5-bromopyrimidine



[0238] Methylamine (2.0 M in methanol, 40 mL, 80 mmol) was added to 5-bromo-2-chloropyrimidine (5.6 g, 29.0 mmol) in a sealable reaction vessel. After allowing to vent for a few minutes, the vessel was sealed, placed behind a safety shield and heated in a 115 °C oil bath for 48 hours. Upon cooling the volatiles were removed *in vacuo*. The material was dissolved in CH_2Cl_2 (200 mL) and washed with 1M NaOH (40 mL). The aqueous layer was extracted further with CH_2Cl_2 (2x50 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated yielding an off white solid (5.1 g, 93%). LCMS (*m/z*): 188.0/190.0 (MH^+).

[0239] Synthesis of methyl[5-(4,4,5,5-tetramethyl(1,3,2-dioxaborolan-2-yl))pyrimidin-2-yl]amine



[0240] To a dry 500 mL flask was added 2-methylamino-5-bromopyrimidine (9.5 g, 50.5 mmol), potassium acetate (15.1 g, 154.4 mmol), 4,4,5,5,-tetramethyl-2-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (14.1 g, 55.5 mmol) and dioxane (280 mL). Argon was bubbled through the solution for 15 minutes, at which time 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride dichloromethane adduct (2.05 g, 2.51 mmol) was added. The reaction was refluxed in a 115 °C oil bath for 4 hours under argon. After cooling to room temperature, EtOAc (500 mL) was added and the resulting slurry was sonicated and filtered. Additional EtOAc (500 mL) was used to wash the solid. The combined organics were washed with H_2O (2x300 mL), $NaCl_{(sat.)}$, (300 mL), dried over Na_2SO_4, filtered and the solvents were removed *in vacuo*. Purification by SiO_2 chromatography (50% EtOAc/hexanes) yielded an off white solid (7.66 g, 64%). LCMS (*m/z*): 154 (MH^+ of boronic acid, deriving from *in situ* product hydrolysis on LC). ^1H NMR ($CDCl_3$): δ 8.58 (s, 2H), 5.56 (s, 1H), 3.02 (d, 3H), 1.32 (s, 12H).

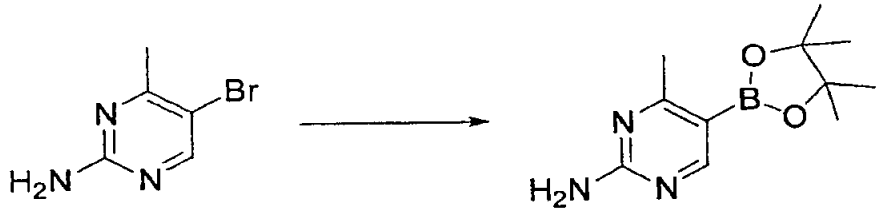
Method 3

[0241] Synthesis of 5-bromo-4-methylpyrimidine-2-ylamine



[0242] To a solution of 4-methylpyrimidine-2-ylamine (10.9 g, 100 mmol) in chloroform (400 mL) was added N-bromosuccinimide (17.8 g, 100 mmol). The solution was stirred in the dark for 15 hours, at which time it was added to CH_2Cl_2 (1400 mL), washed with 1N NaOH (3x200 mL) and $NaCl_{(sat.)}$ (100 mL), dried over Na_2SO_4, filtered and concentrated, yielding 5-bromo-4-methylpyrimidine-2-ylamine (18.8 g, 99%). LCMS (*m/z*): 188.0/190.0 (MH^+). ^1H NMR ($CDCl_3$): δ 8.22 (s, 1H), 5.02 (bs, 2H), 2.44 (s, 3H).

[0243] Synthesis of 4-methyl-5-(4,4,5,5-tetramethyl(1,3,2-dioxaborolan-2-yl))pyrimidine-2-ylamine

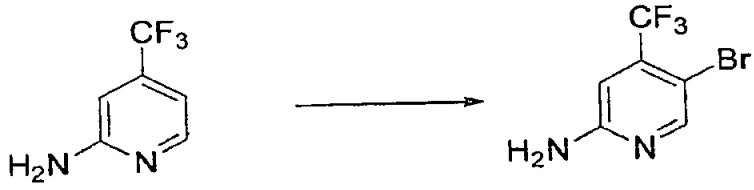


[0244] To a dry 1 L flask was added 5-bromo-4-methylpyrimidine-2-ylamine (18.8 g, 100 mmol), potassium acetate (29.45 g, 300 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (26.7 g, 105 mmol) and dioxane (500 mL). Argon was bubbled through the solution for 15 minutes, at which time 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride dichloromethane adduct (4.07 g, 5 mmol) was added. The reaction was refluxed in a 115 °C oil bath for 18 hours under argon. After cooling to room temperature, EtOAc (500 mL) was added and the resulting slurry was sonicated and filtered. Additional EtOAc (500 mL) was used to wash the solid. The combined organic extracts were washed with H_2O (2x300 mL), $NaCl_{(sat.)}$ (300 mL), dried over Na_2SO_4, concentrated and purified by SiO_2 chromatography (EtOAc eluent) yielding 18.1 g of an off-white solid. By ^1H NMR the material was a 5:1 mixture of boronate ester and 4-methylpyrimidine-2-ylamine as a

byproduct. The material was used as is in subsequent Suzuki reactions. LCMS (*m/z*): 154 (MH^+ of boronic acid, deriving from *in situ* product hydrolysis on LC). ^1H NMR ($CDCl_3$): δ 8.52 (s, 1H), 5.14 (bs, 2H), 2.56 (d, 3H), 1.32 (s, 12H).

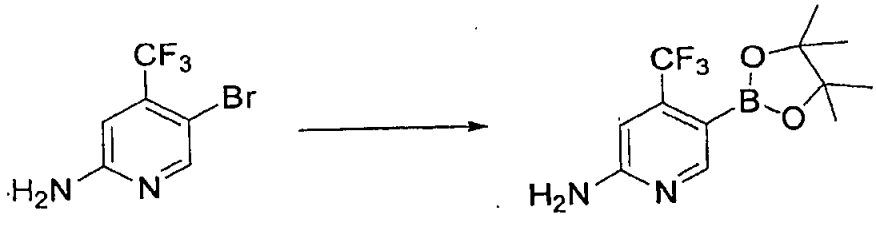
Method 4

[0245] Synthesis of 5-bromo-4-(trifluoromethyl)-2-pyridylamine



[0246] To a solution of 2-amino-4-trifluoromethylpyridine (10.0 g, 62.1 mmol) in chloroform (200 mL) was added N-bromosuccinimide (12.0 g, 67.4 mmol). The solution was stirred in the dark for 2 hours, at which time it was added to CH_2Cl_2 (200 mL) and 1N NaOH (200 mL). Upon mixing, the layers were separated and the organic layer was washed with $NaCl_{(sat.)}$ (100 mL), dried over Na_2SO_4, filtered and concentrated. The crude material was purified by SiO_2 chromatography (0-5% EtOAc/ CH_2Cl_2) yielding 12.0 g (80%) of 5-bromo-4-(trifluoromethyl)-2-pyridylamine LCMS (*m/z*): 241/243 (MH^+). ^1H NMR ($CDCl_3$): δ 8.28(s, 1H), 6.77(s, 1H), 4.78(bs, 2H).

[0247] Synthesis of 5-(4,4,5,5-tetramethyl(1,3,2-dioxaborolan-2-yl))-4-(trifluoromethyl)-2-pyridylamine



[0248] To a dry 500 mL flask was added 5-bromo-4-(trifluoromethyl)-2-pyridylamine (11.8 g, 49.0 mmol), potassium acetate (14.4 g, 146.9 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (13.6 g, 53.9 mmol) and dioxane (300 mL). Argon was bubbled through the solution for 15 minutes, at which time 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride dichloromethane adduct (2.0 g, 2.45 mmol) was added. The reaction was refluxed in a 115 °C oil bath for 8 hours under argon. After cooling to room temperature, the dioxane was removed *in vacuo*. EtOAc (500 mL) was added, and the resulting slurry was sonicated and filtered. Additional EtOAc (500 mL) was used to wash the solid. The combined organic extracts were concentrated and the crude material was partially purified by SiO_2 chromatography (30-40% EtOAc/Hexanes). Upon removal of solvent, hexanes (75 mL) was added; after sonication, the resulting solid was filtered and dried on a high vacuum for 3 days yielding 2.4 g of an off-white solid. By ^1H NMR the material was a 5:1 mixture of boronate ester and 2-amino-4-trifluoromethyl pyridine byproduct. The material was used as is in subsequent Suzuki reactions. LCMS (*m/z*): 207 (MH^+ of boronic acid, deriving from *in situ* product hydrolysis on LC). ^1H NMR ($CDCl_3$): δ 8.50 (s, 1H), 6.72 (s, 1H), 4.80 (bs, 2H), 1.34 (s, 12H).

Method 5

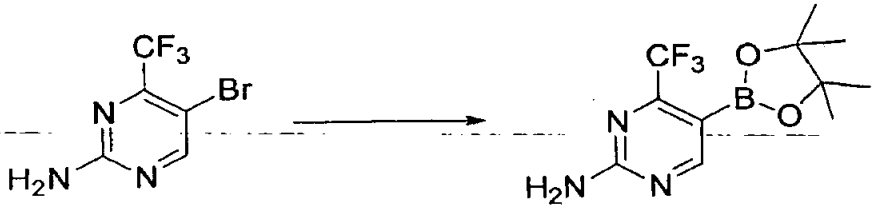
[0249] Synthesis of 5-bromo-4-(trifluoromethyl)pyrimidin-2-amine



[0250] To a solution of 2-amino-4-trifluoromethylpyrimidine (8.0 g, 49.1 mmol) in chloroform (300 mL) was added N-bromosuccinimide (8.9 g, 50 mmol). The solution was stirred in the dark for 16 hours, at which time additional N-bromosuccinimide (4.0 g, 22.5 mmol) was added. After stirring for an additional 4 hours the solution was added to CH_2Cl_2 (200 mL) and 1N NaOH (200 mL). Upon mixing, the layers were separated and

the organic layer was washed with $NaCl_{(sat.)}$ (100 mL), dried over Na_2SO_4, filtered and concentrated, yielding 10.9 g (82%) of 5-bromo-4-(trifluoromethyl)-2-pyrimidylamine. LCMS (*m/z*): 242/244 (MH^+). ^1H NMR ($CDCl_3$): δ 8.52 (s, 1H), 5.38 (bs, 2H).

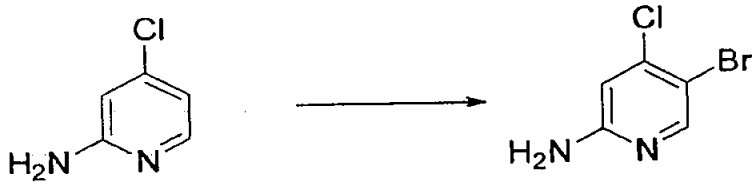
[0251] Synthesis of 5-(4,4,5,5-tetramethyl(1,3,2-dioxaborolan-2-yl))-4-(trifluoromethyl)pyrimidine-2-ylamine



[0252] To a dry 500 mL flask was added 5-bromo-4-(trifluoromethyl)-2-pyrimidylamine (10.1 g, 41.7 mmol), potassium acetate (12.3 g, 125.2 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (11.6 g, 45.9 mmol) and dioxane (150 mL). Argon was bubbled through the solution for 15 minutes, at which time 1,1'-bis(diphenylphosphino)ferrocene palladium (II) chloride (1.7 g, 2.1 mmol) was added. The reaction was refluxed in a 115 °C oil bath for 6 hours under argon. After cooling to room temperature, the dioxane was removed *in vacuo*. EtOAc (500 mL) was added and the resulting slurry was sonicated and filtered. Additional EtOAc (500 mL) was used to wash the solid. The combined organic extracts were concentrated and the crude material was purified by SiO_2 chromatography (30-40% EtOAc/hexanes) yielding 4.40 g of an off white solid. By ^1H NMR the material was a 1:1 mixture of boronate ester and 2-amino-4-trifluoromethylpyrimidine byproduct. The material was used as is in subsequent Suzuki reactions. LCMS (*m/z*): 208 (MH^+ of boronic acid, deriving from *in situ* product hydrolysis on LC). ^1H NMR ($CDCl_3$): δ 8.72 (s, 1H), 5.50 (bs, 2H), 1.34 (s, 12H).

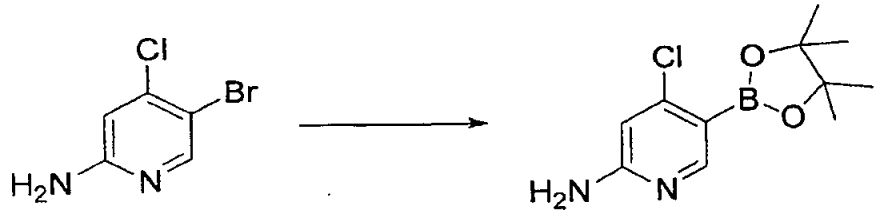
Method 6

[0253] Synthesis of 5-bromo-4-chloro-2-pyridylamine



[0254] To a solution of 4-chloro-2-pyridylamine (6.0 g, 46.7 mmol) in chloroform (180 mL) was added N-bromosuccinimide (8.3 g, 46.7 mmol). The solution was stirred in the dark for 2 hours, at which time it was added to CH_2Cl_2 (800 mL) and 1N NaOH (100 mL). Upon mixing, the layers were separated and the organic layer was washed with $NaCl_{(sat.)}$ (100 mL), dried over Na_2SO_4, filtered and concentrated. The crude material was purified by SiO_2 chromatography (25-35% EtOAc/hexanes) yielding 3.63 g (38%) of 5-bromo-4-chloro-2-pyridylamine. LCMS (*m/z*): 206.9/208.9 (MH^+). ^1H NMR ($CDCl_3$): δ 8.18 (s, 1H), 6.62 (s, 1H), 4.52 (bs, 2H).

[0255] Synthesis of 4-chloro-5-(4,4,5,5-tetramethyl(1,3,2-dioxaborolan-2-yl))-2-pyridylamine



[0256] To a dry 500-mL flask was added 5-bromo-4-chloro 2-pyridylamine (7.3 g, 35.8 mmol), potassium acetate (10.3 g, 105 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (10.1 g, 39.8 mmol) and dioxane (150 mL). Argon was bubbled through the solution for 15 minutes, at which

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time 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride dichloromethane adduct (0.85 g, 1.04 mmol) was added. The reaction was refluxed in a 115 °C oil bath for 6 hours under argon. After cooling to room temperature, the dioxane was removed *in vacuo*. EtOAc (500 mL) was then added and the resulting slurry was sonicated and filtered. Additional EtOAc (500 mL) was used to wash the solid. The combined organic extracts were concentrated and the crude material was purified by SiO_2 chromatography (EtOAc as eluent). Upon removal of solvent, 3:1 hexanes/CH_2Cl_2 was added (100 mL). After sonication, the resulting solid was filtered and concentrated *in vacuo* yielding 2.8 g of a white solid. By ^{1}H NMR the material was a 10:1 mixture of boronate ester and 2-amino-4-chloropyridine byproduct. The material was used as is in subsequent Suzuki reactions. LCMS (*m/z*): 173 (MH^+ of boronic acid, deriving from *in situ* product hydrolysis on LC). ^{1}H NMR ($CDCl_3$): δ 8.36 (s, 1H), 6.46 (s, 1H), 4.70 (bs, 2H), 1.38 (s, 12H).

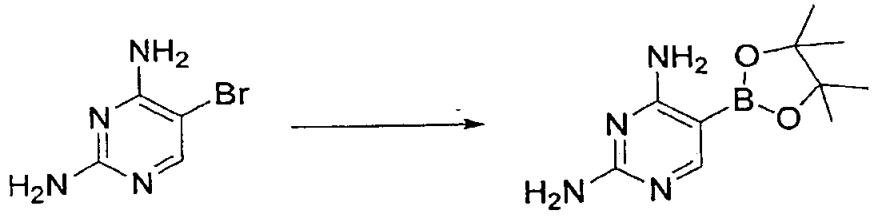
Method 7

[0257] Synthesis of 5-bromopyrimidine-2,4-diamine



[0258] To a solution of 2,4-diaminopyrimidine (1.0 g, 9.1 mmol) in chloroform (30 mL) was added N-bromosuccinimide (1.62 g, 9.08 mmol). The solution was stirred in the dark for 12 hours, at which time it was added to CH_2Cl_2 (150 mL) and 1N NaOH (50 mL). The solid that formed was filtered, rinsed with water and concentrated *in vacuo*, yielding 1.4 g (74%) of 5-bromopyrimidine-2,4-diamine. LCMS (*m/z*): 189/191 (MH^+). ^{1}H NMR (DMSO-d_6): δ 7.78 (s, 1H), 6.58 (bs, 2H), 6.08 (bs, 2H).

[0259] Synthesis of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine-2,4-diamine



[0260] To a dry 1 L flask was added 5-bromopyrimidine-2,4-diamine (30.0 g, 158.7 mmol), potassium acetate (45.8 g, 466.7 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (51.2 g, 202.2 mmol) and dioxane (500 mL). Argon was bubbled through the solution for 15 minutes, at which time 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride (2.5 g, 3.11 mmol) was added. The reaction was refluxed in a 115 °C oil bath for 16 hours under argon. After cooling to room temperature, the solid inorganic material was filtered, rinsed with EtOAc (1 L). The organic filtrate was concentrated *in vacuo* and to the resulting solid was added dichloromethane (1 L). After sonication the solid was filtered. The solid was the debrominated 2,4-diaminopyrimidine. The filtrate containing desired boronate ester was concentrated *in vacuo*. To this residue was added diethyl ether (100 mL). After sonication, the solution was filtered, rinsed with additional diethyl ether (50 mL) and the solid obtained was dried under high vacuum to yield the desired 2,4-diaminopyrimidyl-5-boronate ester (10.13 g, 27%). By ^{1}H NMR the material was a 4:1 mixture of 2,4-diaminopyrimidyl-5-boronate ester and 2,4-diaminopyrimidine byproduct. The material was used as is in subsequent Suzuki reactions. LCMS (*m/z*): 155 (MH^+ of boronic acid, deriving from *in situ* product hydrolysis on LC). ^{1}H NMR ($CDCl_3$+CD_3OD): δ 8.16 (s, 1H), 1.34 (s, 12H).

Method 8

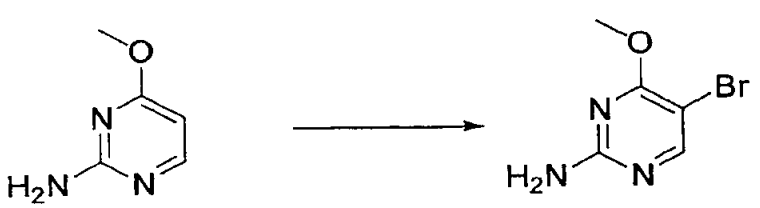
[0261] Synthesis of 4-methoxypyrimidine-2-ylamine



[0262] To a solution of 4,6-dichloro-2-amino pyrimidine (5.0 g, 30.5 mmol) in methanol (100 mL) was added 25% sodium methoxide (6.59 g, 30.5 mmol). The solution was refluxed for 20 hours, at which time the methanol was removed *in vacuo*. The residue was dissolved in EtOAc (350 mL), washed with H_2O (100 mL) and with $NaCl_{(sat.)}$ (100 mL), dried over Na_2SO_4, filtered and concentrated yielding 4.4 g (90%) of 4-chloro-6-methoxypyrimidine-2-ylamine.

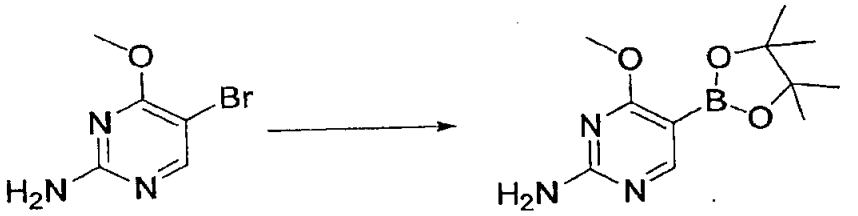
[0263] To a solution of 4-chloro-6-methoxypyrimidine-2-ylamine (4.4 g, 27.7 mmol) in EtOAc (200 mL) and ethanol (150 mL), was added diisopropylethylamine (9.6 mL, 55.3 mmol) and 10% palladium on carbon (2.9 g, 2.77 mmol). The heterogeneous solution was stirred under a balloon atmosphere of H_2 for 14 hours, at which time the solution was filtered through a Celite pad and the volatiles were removed *in vacuo*. The residue was dissolved in EtOAc (200 mL), washed with $Na_2CO_{3(sat.)}$ (100 mL) and with $NaCl_{(sat.)}$ (100 mL), dried over Na_2SO_4, filtered and concentrated yielding 3.1 g (90%) of 4-methoxypyrimidine-2-ylamine. LCMS (*m/z*): 126 (MH^+). ^1H NMR ($CDCl_3$): δ 8.00 (d, *J* = 5.7 Hz, 1H), 6.08 (d, *J* = 5.7 Hz, 1H), 4.98 (bs, 2H), 3.84 (s, 3H).

[0264] Synthesis of 5-bromo-4-methoxypyrimidine-2-ylamine



[0265] To a solution of 4-methoxypyrimidine-2-ylamine (1.84 g, 14.7 mmol) in chloroform (600 mL) was added N-bromosuccinimide (2.62 g, 14.7 mmol). After stirring in the dark for 5 hours, the solution was added to CH_2Cl_2 (200 mL) and 1N NaOH (100 mL). Upon mixing, the layers were separated and the organic layer was washed with $NaCl_{(sat.)}$ (100 mL), dried over Na_2SO_4, filtered and concentrated yielding 2.88 g (96%) of 5-bromo-4-methoxypyrimidine-2-ylamine. LCMS (*m/z*): 204/206 (MH^+). ^1H NMR ($CDCl_3$): δ 8.10 (s, 1H), 4.93 (bs, 2H), 3.96 (s, 3H).

[0266] Synthesis of 4-methoxy-5-(4,4,5,5-tetramethyl(1,3,2-dioxaborolan-2-yl))pyrimidine-2-ylamine

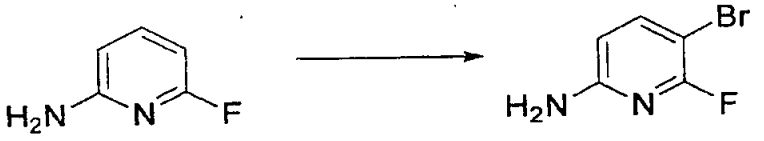


[0267] To a dry 200-mL flask was added 5-bromo-4-methoxypyrimidine-2-ylamine (2.88 g, 14.1 mmol), potassium acetate (4.16 g, 42.4 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (3.76 g, 14.8 mmol) and dioxane (75 mL). Argon was bubbled through the solution for 15 minutes, at which time 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride dichloromethane adduct (0.58 g, 0.71 mmol). The reaction was refluxed in a 115 °C oil bath for 21 hours under argon. After cooling to room temperature, the dioxane was removed *in vacuo*. EtOAc (500 mL) was added and the resulting slurry was sonicated and filtered. Additional EtOAc (500 mL) was used to wash the solid. The combined organics were concentrated and the crude material was purified by SiO_2 chromatography (EtOAc as eluent) yielding 2.4 g of an off white solid. By ^1H NMR the material was a 1:1 mixture of boronate ester and 4-methoxypyrimidine-2-ylamine. The material was used as is in subsequent Suzuki

reactions. LCMS (*m/z*): 170 (MH^+ of boronic acid, deriving from *in situ* product hydrolysis on LC). ^1H NMR ($CDCl_3$): δ 8.42 (s, 1H), 5.22 (bs, 2H), 3.90 (s, 3H), 1.34 (s, 12H).

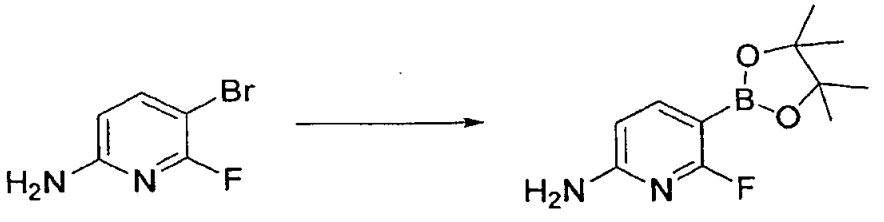
Method 9

[0268] Synthesis of 5-bromo-6-fluoro-2-pyridylamine



[0269] To a solution of 6-fluoro-2-pyridylamine (1.0 g, 8.93 mmol) in chloroform (55 mL) was added N-bromosuccinimide (1.59 g, 8.93 mmol). The solution was stirred in the dark for 15 hours, at which time it was added to CH_2Cl_2 (200 mL) and 1N NaOH (50 mL). Upon mixing, the layers were separated and the organic layer was washed with $NaCl_{(sat.)}$ (50 mL), dried over Na_2SO_4, filtered and concentrated. The crude material was purified by SiO_2 chromatography (25% EtOAc/ hexanes) yielding 5-bromo-6-fluoro-2-pyridylamine (386 mg, 22%). LCMS (*m/z*): 190.9/192.9 (MH^+); ^1H NMR ($CDCl_3$): δ 7.59 (t, J = 8.7 Hz, 1H), 6.25 (dd, J = 8.1, 1.2 Hz, 1H), 4.58 (bs, 1H).

[0270] Synthesis of 6-fluoro-5-(4,4,5,5-tetramethyl(1,3,2-dioxaborolan-2-yl))-2-pyridylamine

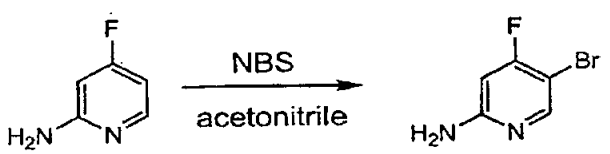


[0271] To a dry 50-mL flask was added 5-bromo-6-fluoro-2-pyridylamine (370 mg, 1.93 mmol), potassium acetate (569 mg, 5.8 mmol), 4,4,5,5-tetramethyl-2-

(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (538 mg, 2.12 mmol) and dioxane (15 mL). Argon was bubbled through the solution for 15 minutes, at which time 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride dichloromethane adduct (79 mg, 0.09 mmol). The reaction was refluxed in a 115 °C oil bath for 4 hours under argon. After removal of the volatiles *in vacuo*, EtOAc (150 mL) was added and the solution was washed with H_2O (3x40 mL), with $NaCl_{(sat.)}$ (300 mL), dried over Na_2SO_4, filtered and concentrated. Purification by SiO_2 chromatography (30% EtOAc/hexanes) yielded boronate ester (161 mg, 35%). LCMS (*m/z*): 157 (MH^+ of boronic acid, deriving from *in situ* product hydrolysis on LC) ^1H NMR ($CDCl_3$): δ 7.86 (t, J = 8.4 Hz, 1H), 6.29 (dd, J = 8.1, 2.7 Hz, 1H), 4.70 (bs, 1H), 1.32 (s, 12H).

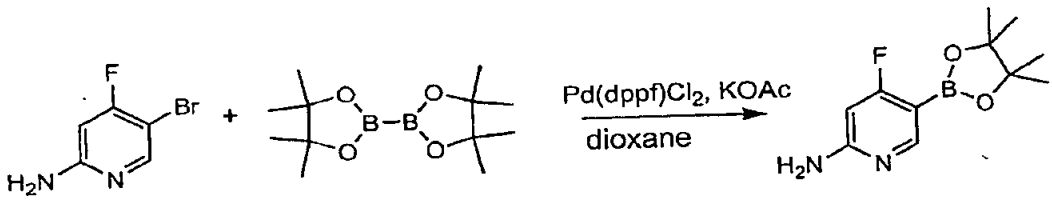
Method 10

[0272] Synthesis of 5-bromo-4-fluoropyridin-2-amine



[0273] *N*-Bromosuccinimide (126 mg, 0.71 mmol) was added to a solution of 4-fluoropyridin-2-amine TFA salt (162 mg, 0.72 mmol) in acetonitrile (4 mL) in an aluminum foil-wrapped flask in a darkened hood. The reaction solution was stirred at room temperature in darkness for 2 hours. After evaporation of the solvent, the crude product was purified on a silica gel column eluting with EtOAc to give 5-bromo-4-fluoropyridin-2-amine as an ivory solid (92 mg, 67%). LC/MS (*m/z*): 190.9/192.9 (MH^+), R_t 1.02 minutes.

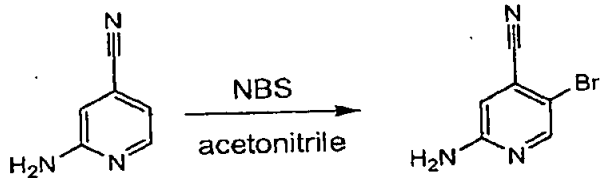
[0274] Synthesis of 4-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine



[0275] In a sealable Pyrex pressure vessel, a mixture of 5-bromo-4-fluoropyridin-2-amine (25 mg, 0.13 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (40 mg, 0.16 mmol), potassium acetate (51 mg, 0.52 mmol) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II)-dichloromethane adduct (16 mg, 0.019 mmol) was suspended in dioxane (1.7 mL) under argon. The pressure vessel was sealed and the reaction mixture was stirred at 110 °C for 2 hours. After the reaction was complete as judged by LCMS, the reaction mixture was cooled to room temperature and the 4-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine was used in subsequent reactions without further purification, assuming a quantitative yield (0.13 mmol). LC/MS (*m/z*): 157.0 (MH^+ of the boronic acid formed by product hydrolysis on LC), R_t 0.34 minutes.

Method 11

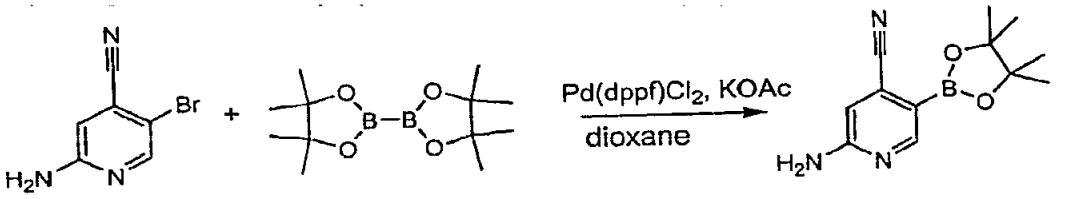
[0276] Synthesis of 2-amino-5-bromo-isonicotinonitrile



[0277] In an aluminum foil-covered flask in a darkened hood, 2-amino-isonicotinonitrile TFA salt (125 mg, 0.54 mmol) was dissolved in acetonitrile (3.5 mL). Solid *N*-bromosuccinimide (89.2 mg, 0.501 mmol) was added to the stirred solution in one portion at RT. The reaction solution was stirred at room temperature in darkness for

90 minutes. After evaporation of the solvent, the crude material was further purified by silica gel chromatography to give 2-amino-5-bromo-isonicotinonitrile (53 mg, 49%). LC/MS (*m/z*): 197.9 (MH^+), R_t 2.92 minutes.

[0278] Synthesis of 2-amino-5-boronic ester-isonicotinonitrile

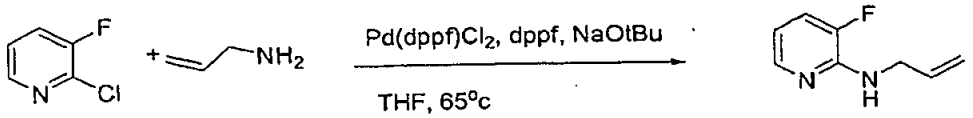


[0279] In a glass pressure vessel, a mixture of 2-amino-5-bromo-isonicotinonitrile (25 mg, 0.126 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (38 mg, 0.151 mmol) and potassium acetate (49 mg, 0.504 mmol) were suspended in dioxane (1.8 mL). After purging the mixture with argon for 1-2 min, dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium(II) dichloromethane adduct (16 mg, 0.019 mmol) was added in one portion. The reaction vessel was sealed and heated at 120 °C with stirring for 2 hours. The crude reaction solution was cooled to room temperature and used without further purification assuming a quantitative yield of the boronic ester (0.126 mmol). LC/MS (*m/z*): 164.0 (MH^+ of the boronic acid formed by product hydrolysis on LC), R_t 0.37 minutes.

Method 12

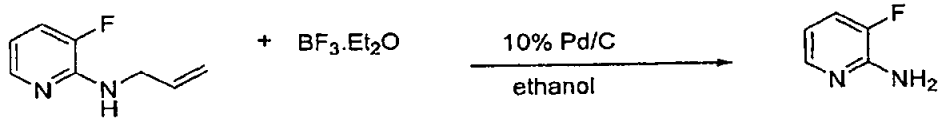
[0280] Synthesis of 3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine

[0281] Synthesis of *N*-allyl-3-fluoropyridin-2-amine



[0282] To a preformed bright-yellow complex of $Pd(dppf)Cl_2$ CH_2Cl_2 (41 mg, 0.05 mmol), dppf (83 mg, 0.15 mmol) and NaO*t*-Bu (1.4 g, 15 mmol) in THF (20 mL) was added 2-chloro-3-fluoropyridine (1.32 g, 10 mmol) and allylamine (1.2 mL, 15 mmol). The mixture was sparged with nitrogen and the pressure vessel was capped and sealed. The reaction was heated at 65-70 °C for 16 hours. The cooled reaction was filtered through a plug of Celite and the pad was washed with EtOAc (30 mL). The solvent was removed under reduced pressure to give a brown thick oil. The crude product was purified by silica gel chromatography eluting with 5% MeOH in EtOAc. The product-containing fractions were diluted with EtOAc (100 mL) and extracted with 1 M HCl (2x50 mL). The aqueous acidic product was lyophilized to a light brown solid giving *N*-allyl-3-fluoropyridin-2-amine as an HCl salt (1.6 g, 85%). LC/MS (*m/z*): 153.1 (MH^+), R_t 0.5 minutes.

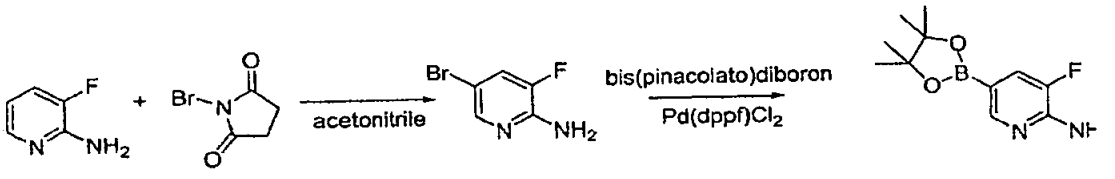
[0283] Synthesis of 3-fluoropyridin-2-amine



[0284] In one portion, 10% Pd/C (1.23 g) was added to a solution of *N*-allyl-3-fluoropyridin-2-amine (1.62 g, 7.18 mmol) and $BF_3 \cdot Et_2O$ (900 uL, 7.18 mmol) in EtOH (20 mL) at RT under nitrogen. After stirring at 80 °C for 2 days, the reaction mixture was filtered through a plug of Celite and the pad was washed with EtOH (20 mL). 6 N HCl was added to the light yellow filtrate until the solution was acidic. The HCl salt of 3-fluoropyridin-2-amine is much less volatile than the free base. The filtrate was concentrated under reduced pressure. The salt residue was dried *in vacuo* to give 3-

fluoropyridin-2-amine as a light yellow glassy solid (1.66 g, quant. yield). LC/MS (*m*/z): 113.0 (MH^+), R_t 0.41 minutes.

[0285] Synthesis of 5-bromo-3-fluoropyridin-2-amine and 3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine



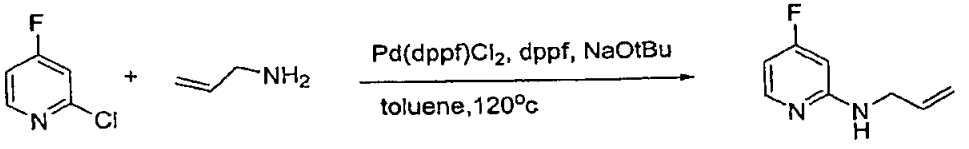
[0286] Solid NBS (750 mg, 4.2 mmol) was added to a solution of 3-fluoropyridin-2-amine HCl salt (1.66 g, 7.18 mmol) in ACN (30 mL) at RT with stirring. The reaction was shielded from light and stirred under nitrogen. After 1 h, an additional amount of NBS (250 mg, 1.4 mmol) was added to the reaction. After 1 h, the solvent was removed under reduced pressure and the residue purified by silica gel flash chromatography eluting with 70% EtOAc/hexane followed by 100% EtOAc to afford 5-bromo-3-fluoropyridin-2-amine as a yellow-brown solid (1.26 g, 92% yield). LC/MS (*m*/z): 191.0/193.0 (MH^+), R_t 1.18 minutes.

[0287] The bromide was converted to the pinacolborane ester under conditions described in Method 1. LC/MS (*m*/z): 157.0 (MH^+), R_t 0.36 minutes.

Method 13

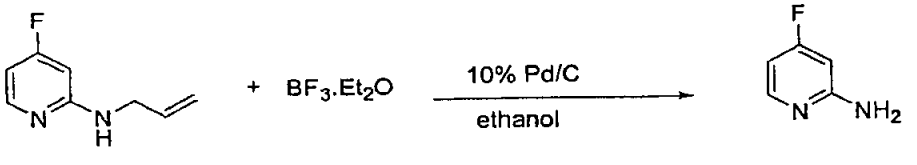
[0288] Synthesis of 4-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine

[0289] Synthesis of *N*-allyl-4-fluoropyridin-2-amine



[0290] To a preformed red-brown complex of $Pd(dppf)Cl_2$ (817 mg, 1.0 mmol), dppf (1.66 g, 3.0 mmol) and NaO*t*Bu (2.9 g, 30 mmol) in toluene (30 mL) was added 2-chloro-4-fluoropyridine (2.16 g, 20 mmol) and allylamine (1.2 mL, 15 mmol). The mixture was sparged with nitrogen and the pressure vessel was capped and sealed. The reaction was heated at 120-125 °C for 18 hours. The cooled dark brown reaction was filtered through a plug of Celite and the pad was washed with EtOAc (60 mL). The solvent was gently removed under reduced pressure to give a brown thick oil which can sublime under vacuum. The crude mixture was acidified with 6 N HCl (10 mL) and lyophilized to dryness to give a brown powder as the HCl salt. The crude product was partitioned between EtOAc (100 mL) and sat. $NaHCO_3$ (80 mL). The layers were separated and the aqueous layer was extracted again with EtOAc (100 mL). The combined organic layers are washed with brine (100 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a brown solid *N*-allyl-4-fluoropyridin-2-amine (690 mg, 25%). LC/MS (*m/z*): 153.0 (MH^+), R_t 1.13 minutes.

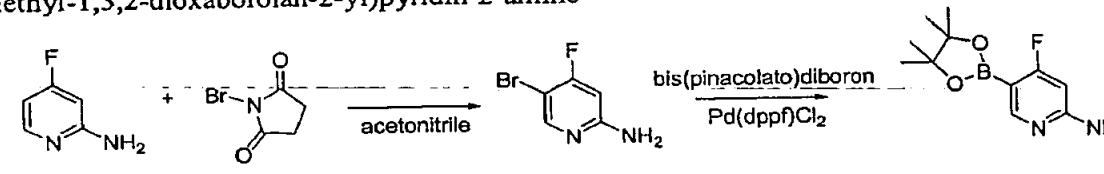
[0291] Synthesis of *N*-allyl-4-fluoropyridin-2-amine



[0292] In one portion, 10% Pd/C (552 mg) was added to a solution of *N*-allyl-4-fluoropyridin-2-amine (690 mg, 3.07 mmol) and BF_3•Et_2O (0.386 mL, 3.07 mmol) in abs. EtOH (12 mL) at RT under nitrogen. After stirring at 80 °C for 24 h, reaction mixture was filtered through a plug of Celite and the pad was washed with MeOH (100 mL).

6 N HCl (2 mL) was added to the dark filtrate until the solution was acidic. The HCl salt of 4-fluoropyridin-2-amine is much less volatile than the free base. The filtrate was concentrated under reduced pressure and dried *in vacuo*. The crude product was purified by preparative HPLC to give 4-fluoropyridin-2-amine as a brown powder TFA salt (162 mg, 23%). LC/MS (*m/z*): 113.0 (MH^+), R_t 0.40 minutes.

[0293] Synthesis of 5-bromo-4-fluoropyridin-2-amine and 4-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine

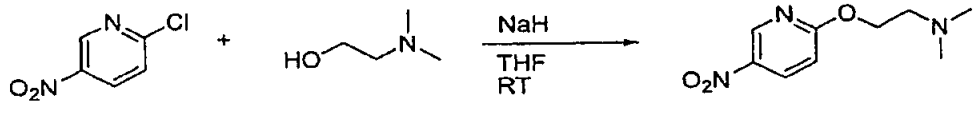


[0294] Solid NBS (78 mg, 0.43 mmol) was added to a solution of 3-fluoropyridin-2-amine HCl salt (162 mg, 0.72 mmol) in ACN (4 mL) at RT with stirring. The reaction was shielded from light and stirred under nitrogen. After 1.5 h, an additional amount of NBS (15 mg, 0.084 mmol) was added to the reaction. Checking the reaction again after 1.5 h, an additional amount of NBS (15 mg, 0.084 mmol) was added to the reaction until the starting material had been consumed by LCMS. After 1 h, the solvent was removed under reduced pressure and the residue purified by silica flash chromatography eluting with 50% ethyl acetate/hexane to afford 5-bromo-4-fluoropyridin-2-amine as a ivory solid (92 mg, 68%). LC/MS (*m/z*): 190.9/192.9 (MH^+), R_t 1.02 minutes.

[0295] The bromide was converted to the pinacolborane under conditions described in Method 1. LC/MS (*m/z*): 157.0 (MH^+), R_t 0.34 minutes.

Method 14

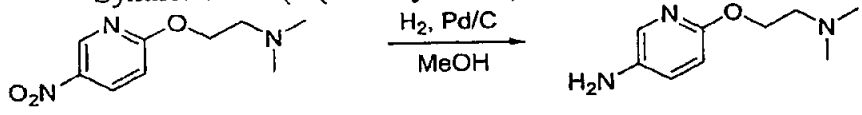
[0296] Synthesis of 2-(5-nitropyridin-2-yloxy)-N,N-dimethylethanamine



[0297] Microwave heating. To a solution of 2-(dimethylamino)ethanol (339 mg, 3.80 mmol) in DMF (5 mL) was added sodium bis(trimethylsilyl)amide (4.75 mL, 1M solution in THF, 4.75 mmol). The mixture was stirred at room temperature for 15 min. 2-Chloro-5-nitropyridine (500 mg, 3.16 mmol) was then added. The vial was capped and subjected to microwave irradiation (150 °C for 10 minutes). The mixture was diluted with water (250 mL) and EtOAc (250 mL). The two layers were separated, and the aqueous layer extracted two more times with EtOAc. The organic extracts were combined, washed with water and brine, dried over sodium sulfate and evaporated to give the crude material as brown oil. Purification by column chromatography on silica gel using 5% methanol/methylene chloride yielded 2-(5-nitropyridin-2-yloxy)-N,N-dimethylethanamine as a light yellow solid (295 mg, 44%).

[0298] Sodium hydride and oil bath heating. To a mixture of sodium hydride (189 mg, 4.73 mmol) in anhydrous tetrahydrofuran (2 mL) at 0 °C a solution of 2-chloro-5-nitropyridine (500 mg, 3.16 mmol) and 2-(dimethylamino)ethanol (353 mg, 3.96 mmol) in anhydrous tetrahydrofuran (4 mL) was added dropwise. The reaction was warmed to room temperature and stirred for 16 h. The THF was evaporated, and water (100 mL) and EtOAc (200 mL) were added. The aqueous layer was extracted with EtOAc (200 mL), and the organic layers combined, washed with brine, dried over sodium sulfate and concentrated to give a brown oil. Purification column chromatography on silica gel using 5% methanol/methylene chloride yielded 2-(5-nitropyridin-2-yloxy)-N,N-dimethylethanamine as a light yellow solid (233 = mg, 35%). LC/MS (*m*/z): 212.2 (MH^+), R_t 1.28 minutes.

[0299] Synthesis of 6-(2-(dimethylamino)ethoxy)pyridin-3-amine

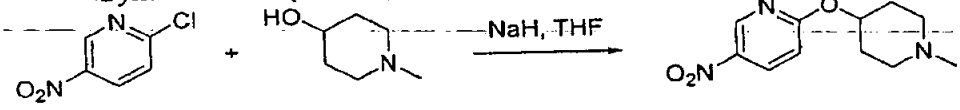


[0300] 2-(5-Nitropyridin-2-yloxy)-N,N-dimethylethanamine (295 mg, 1.40 mmol) was dissolved in 5 mL of methanol and placed under a nitrogen atmosphere.

A catalytic amount of 10% palladium on carbon was added and a hydrogen balloon was connected to the reaction flask. The flask was flushed five times with hydrogen and stirred at room temperature under hydrogen atmosphere for 16 hours. The solid was filtered and washed with methanol. The filtrate was evaporated under reduced pressure yielding 6-[2-(dimethylamino)ethoxy]pyridin-3-amine as a brown oil (250 mg, 99%). LC/MS (*m*/z): 182.1 (MH^+), R_t 0.36 minutes.

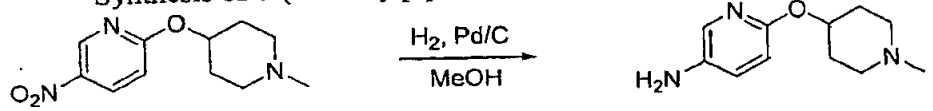
Method 15

[0301] Synthesis of 2-(1-methylpiperidin-4-yloxy)-5-nitropyridine



[0302] To a mixture of sodium hydride (189 mg, 4.73 mmol) in anhydrous tetrahydrofuran (2 mL) at 0 °C, a solution of 2-chloro-5-nitropyridine (500 mg, 3.16 mmol) and 1-methylpiperidin-4-ol (455 mg, 3.96 mmol) in anhydrous tetrahydrofuran (4 mL) was added dropwise. The reaction was heated reflux for 16 h. The THF was evaporated and water (100 mL) and EtOAc (200 mL) were added. The aqueous layer was extracted with EtOAc (200 mL). The organic layers were combined, washed with brine, dried over sodium sulfate and concentrated to give a brown oil. Purification by silica gel column chromatography using 3% methanol/methylene chloride yielded 2-(1-methylpiperidin-4-yloxy)-5-nitropyridine as a yellow solid, (367 mg, 49%). LC/MS (*m*/z): 238.0 (MH^+), R_t 1.59 minutes.

[0303] Synthesis of 6-(1-methylpiperidin-4-yloxy)pyridin-3-amine

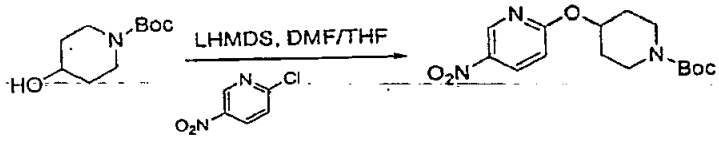


[0304] 2-(1-Methylpiperidin-4-yloxy)-5-nitropyridine (100 mg, 0.42 mmol) was dissolved in 5 mL of methanol and placed under a nitrogen atmosphere. A catalytic amount of 10% palladium on carbon was added and a hydrogen balloon connected to the reaction flask. The flask was flushed five times with hydrogen and stirred at room

temperature under hydrogen atmosphere. The solid was filtered and washed with methanol. The filtrate was evaporated under reduced pressure to yield 6-(1-methylpiperidin-4-yloxy)pyridin-3-amine as a brown solid (85 mg, 98%). LC/MS (*m*/z): 208.2 (MH^+), R_t 0.34 minutes.

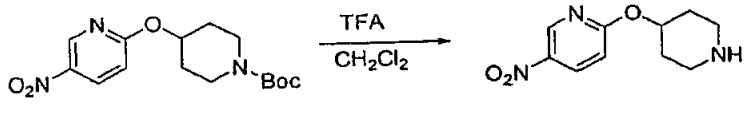
Method 16

[0305] Synthesis of *tert*-butyl 4-(5-nitropyridin-2-yloxy)piperidine-1-carboxylate



[0306] To a solution of *tert*-butyl 4-hydroxypiperidine-1-carboxylate (1 eq) in DMF was added potassium bis-trimethylsilylamide (1.5 eq, 1M solution in tetrahydrofuran). The solution was stirred at room temperature for 10 minutes, and 2-chloro-5-nitropyridine (1.2 eq) was added. The reaction mixture was submitted to microwave irradiation for 600 seconds at 145 °C. EtOAc and water were added to the reaction and the layers separated. The organic layer was washed with water, brine, dried over sodium sulfate and evaporated to give brown crude material. Purification by silica gel column chromatography using 10% EtOAc/hexane afforded the product as a light yellow solid. LC/MS (*m*/z): 324.3 (MH^+), R_t 3.33 minutes

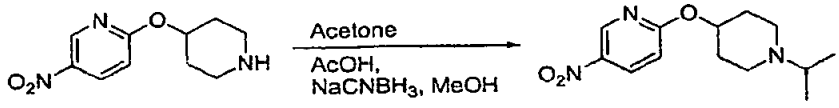
[0307] Synthesis of 5-nitro-2-(piperidin-4-yloxy)pyridine



[0308] Trifluoroacetic acid (5 eq) was added to a solution of *tert*-butyl 4-(5-nitropyridin-2-yloxy)piperidine-1-carboxylate (1 eq) in dichloromethane, stirring at room

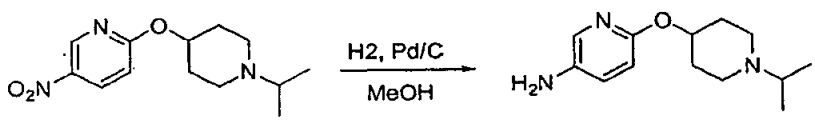
temperature for 1 hour. The solvent was then evaporated, the residue brought to pH = 10 with sat. aq. Na_2CO_3 solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and evaporated to afford the product as a light yellow crystalline solid. LC/MS (*m/z*): 224.3 (MH^+), R_t 1.64 minutes

[0309] Synthesis of 2-(1-isopropylpiperidin-4-yloxy)-5-nitropyridine



[0310] To a solution of 10% acetic acid in methanol was added 5-nitro-2-(piperidin-4-yloxy)pyridine (1 eq) and anhydrous acetone (5 eq). The solution was stirred at room temperature for 1 hour. The reaction mixture was cooled to 0 °C on an ice bath and sodium cyanoborohydride (1.5 eq) was added. The reaction mixture was then warmed to room temperature and stirred for 5 hours. The solvent was evaporated, the residue brought to pH = 10 with sodium carbonate and extracted with EtOAc. The organic layer was washed with water, brine, dried over sodium sulfate, and evaporated to give the crude material. Purification by silica gel column chromatography using 2% methanol/dichloromethane afforded the product as a yellow solid. LC/MS (*m/z*): 266.3 (MH^+), R_t 1.85 minutes.

[0311] Synthesis of 6-(1-isopropylpiperidin-4-yloxy)pyridin-3-amine

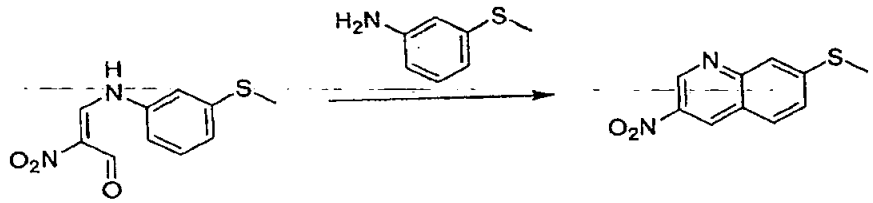


[0312] 2-(1-Isopropylpiperidin-4-yloxy)-5-nitropyridine (1 eq) was dissolved in methanol and laced under a nitrogen atmosphere. A catalytic amount of 10% palladium

on carbon was added and a hydrogen balloon connected to the reaction flask. The flask was flushed five times with hydrogen and stirred at room temperature for 4 hours under hydrogen atmosphere. The solid was filtered and washed with methanol. The filtrate was evaporated under reduced pressure yielding the product as a brown oil. LC/MS (*m/z*): 236.3 (MH^+), R_t 0.38 minutes.

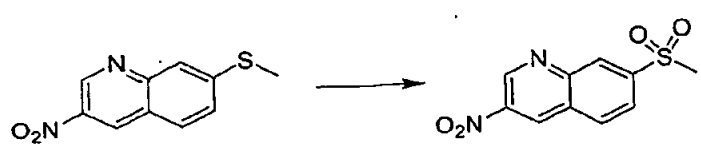
Method 17

[0313] Synthesis of 7-methylthio-3-nitroquinoline



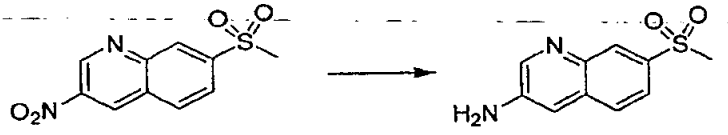
[0314] To a refluxing mixture of 3-[(3-methylthiophenyl)amino]-2-nitroprop-2-enal (2.3 g, 9.6 mmol) and the HCl salt of 3-methylthiophenylamine (2.7 g, 19.3 mmol) in acetic acid (25 mL) was added thiophenol (0.2 g, 1.9 mmol). After being refluxed for 18 h, the mixture was cooled to room temperature and the acetic acid was removed under reduced pressure. To the remaining dark colored solid EtOAc (50 mL) was added with stirring. Filtration gave a yellow/green solid and a dark filtrate. The product crystallized from the EtOAc solution upon standing. Filtration and rinsing with cold EtOAc gave 330 mg crystalline product. The yellow/green solid was washed with 3x250 mL portions of dichloromethane. The dichloromethane washes were concentrated to give an additional 150 mg of product (23%). LC/MS (*m/z*): 221.1 (MH^+), R_t 2.54 minutes.

[0315] Synthesis of 7-(methylsulfonyl)-3-nitroquinoline



[0316] To an ice-bath chilled solution of 7-methylthio-3-nitroquinoline (141 mg, 0.6 mmol) in dichloromethane (6 mL) was added MCPBA (221 mg, 1.3 mmol) in dichloromethane (3 mL). After warming to room temperature, the white precipitate formed was filtered and rinsed with an additional 10 mL of dichloromethane to yield the pure product (85 mg, 53%). LC/MS (*m/z*): 252.9 (MH^+), R_t 1.82 minutes.

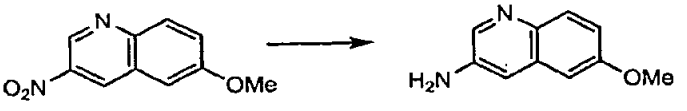
[0317] Synthesis of 7-(methylsulfonyl)-3-quinolylamine



[0318] To a suspension of 7-(methylsulfonyl)-3-nitroquinoline (85 mg, 0.4 mmol) in EtOAc (6 mL,) under argon, was added 10% Pd/C (22 mg, 0.04 mmol). A H_2 balloon was connected to the reaction flask, the flask was purged with H_2 three times and the reaction mixture was allowed to stir under H_2 atmosphere for 18 h. Unreacted starting material could be seen settling to the bottom of the flask together with the catalyst. The solids were removed from the EtOAc solution by filtration. Evaporation of EtOAc under reduced pressure yielded 7-(methylsulfonyl)-3-quinolylamine (22 mg, 30%). LC/MS (*m/z*): 223.0 (MH^+), R_t 1.10 minutes.

Method 18

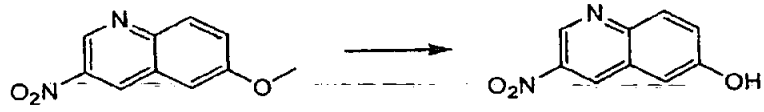
[0319] Synthesis of 6-methoxyquinolin-3-amine



[0320] A mixture of 6-methoxy-3-nitroquinoline (Magnus, P. et al., *J. Am. Chem. Soc. 119*, 5591, 1997; 0.17 g, 0.83 mmol) and Pd/C (10%, 80 mg) in EtOAc (15 mL) was hydrogenated with a hydrogen balloon to give 6-methoxyquinolin-3-amine in quantitative yield. LC/MS (*m/z*): 175.1 (MH+), R_t 1.54 minutes.

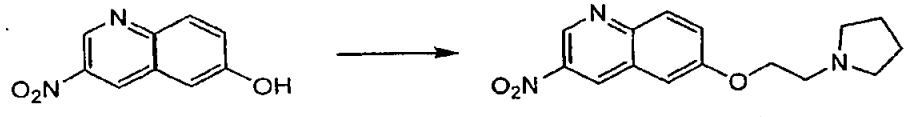
Method 19

[0321] Synthesis 6-hydroxy-3-nitroquinoline



[0322] 6-Methoxy-3-nitroquinoline (Magnus, P. et al., *J. Am. Chem. Soc. 119*, 5591, 1997; 100 mg, 0.49 mmol) was dissolved in hydrogen bromide solution (47% aq, 2.5 mL, 0.2 M), heated and stirred at 120 °C for 16 hours. The reaction mixture was cooled to room temperature, neutralized with 6N NaOH, then extracted with EtOAc (150 mL). The organic layer was dried over Na_2SO_4 and purified by flash chromatography (SiO_2, 40-50% EtOAc/hexanes), obtaining 73 mg (78%) of 6-hydroxy-3-nitroquinoline. LC/MS (*m/z*): 190.9 (MH^+), R_t 1.97 minutes.

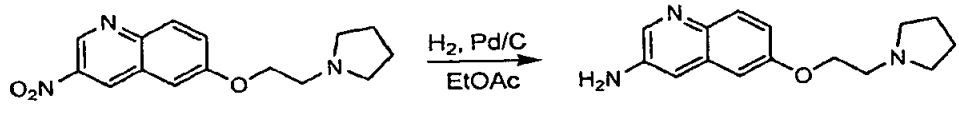
[0323] Synthesis of 3-nitro-6-(2-(pyrrolidin-1-yl)ethoxy)quinoline



[0324] 6-Hydroxy-3-nitroquinoline (148 mg, 0.78 mmol) was dissolved in THF (18 mL). 2-(Pyrrolidin-1-yl)ethanol (0.091 mL, 0.78 mmol) and triphenylphosphine (306 mg, 1.17 mmol) were added. Lastly, diethyl azodicarboxylate (0.184 mL, 1.17 mmol) was added and the reaction mixture was allowed to stir at room temperature

for 2 hours. The solvent was then concentrated *in vacuo* and the residue was purified by flash chromatography (SiO_2) to yield 134 mg (60%) of 3-nitro-6-(2-(pyrrolidin-1-yl)ethoxy)quinoline. LC/MS (*m/z*): 288.1 (MH^+), R_t 1.80 minutes.

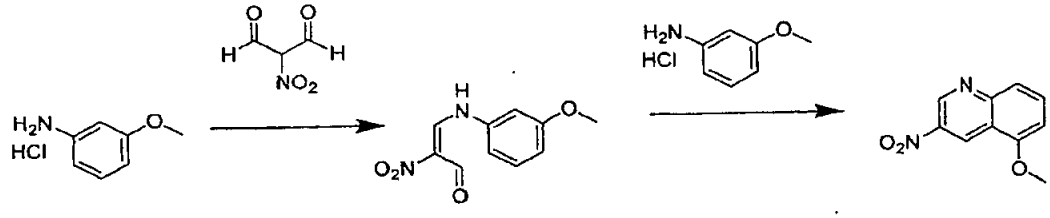
[0335] Synthesis of 3-amino-6-(2-(pyrrolidin-1-yl)ethoxy)quinoline



[0326] 3-Nitro-6-(2-(pyrrolidin-1-yl)ethoxy)quinoline (134 mg, 0.46 mmol) was dissolved in EtOAc (10 mL) and the solution was sparged with N_2 for several minutes. Triethylamine (0.065 mL, 0.46 mmol) was then added followed by a catalytic amount of 10% Pd/C. Sparging with N_2 was repeated after each addition. A balloon of H_2 was connected to the reaction flask and the reaction mixture was stirred at room temperature under H_2 atmosphere for 48 hours. The mixture was then filtered through a Celite pad and concentrated to obtain crude 3-amino-6-(2-(pyrrolidin-1-yl)ethoxy)quinoline, which was used as is in the next reaction. LC/MS (*m/z*): 258.1 (MH^+), R_t 0.33 minutes.

Method 20

[0327] Synthesis of 5-methoxy-3-nitro-quinoline



[0328] Synthesis of 3-(3-methoxy-phenylamino)-2-nitro-propenal

[0329] To the HCl salt of 3-methoxy-phenylamine (4.6 g, 28.9 mmol) in 1N HCl (300 mL) was added a solution of 2-nitro-malonaldehyde (2.7 g, 19.3 mmol) in 150 mL water. After 30 min, the precipitate was filtered and rinsed with 0.1 N HCl. Air-drying in a Büchner funnel for 18 h gave 3.36 g (78%) of a light yellow/green powder. LC/MS (*m/z*): 245.1 (MH^+ +Na), R_t 2.21 minutes.

[0330] Synthesis of 5-methoxy-3-nitroquinoline and 7-methoxy-3-nitroquinoline

[0331] To the HCl salt of 3-methoxy-phenylamine (4.7 g, 29.7 mmol) in 30 mL acetic acid was added 3-(3-methoxy-phenylamino)-2-nitro-propenal (3.3 g, 14.9 mmol). The reaction mixture was heated to reflux, and thiophenol (0.3 mL, 2.98 mmol) was added. After 22 h, the reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. Addition of 70 mL EtOAc and filtration gave solid byproduct, 7-methoxy-3-nitro-quinoline, and a filtrate, which contained impure 5-methoxy-3-nitro-quinoline. The filtrate was loaded on to silica column and eluted from 5% to 25% EtOAc in hexanes at 85 mL/min for 30 minutes. The product-enriched fractions were concentrated and taken on to the next step as a mixture of 5- and 7-methoxy substituted 3-nitroquinolines. LC/MS (*m/z*): 205.1 (MH^+), R_t 2.26 minutes.

[0332] Synthesis of 5-methoxyquinolin-3-amine

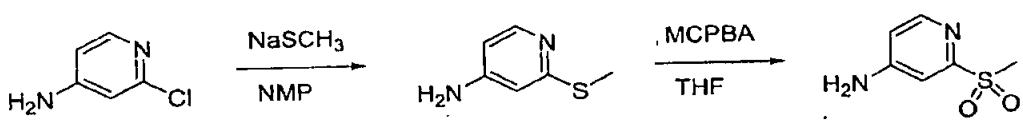


[0333] A mixture of 5- and 7-methoxy substituted 3-nitroquinolines (780 mg, 3.82 mmol) was dissolved in EtOAc (75 mL) and the reaction mixture sparged with N_2 for several minutes. 10% Pd/C (54 mg) was then added and a H_2 balloon was connected to the reaction flask. The reaction mixture was sparged with H_2 and stirred at room

temperature under H_2 atmosphere overnight. Solvent removal *in vacuo* and purification by column chromatography on silicagel (100% EtOAc) afforded the two separated isomers 5-methoxyquinolin-3-amine and 7-methoxyquinolin-3-amine. The desired product 5-methoxyquinolin-3-amine (80 mg, 12%) was obtained as a yellow powder. The structure was assigned by ^{1}H NMR (CD_3OD): δ 8.40 (d, 1H), 7.69 (d, 1H), 7.40 (d, 1H), 7.30 (t, 1H), 6.85 (d, 1H). LC/MS (desired isomer) (*m/z*): 175.0 (MH^+), R_t 1.54 minutes; LC/MS (undesired isomer) (*m/z*): 175.0 (MH^+), R_t 1.53 minutes.

Method 21

[0334] Synthesis of 2-(methylsulfonyl)pyridin-4-amine



[0335] Synthesis of 2-(methylthio)pyridin-4-amine

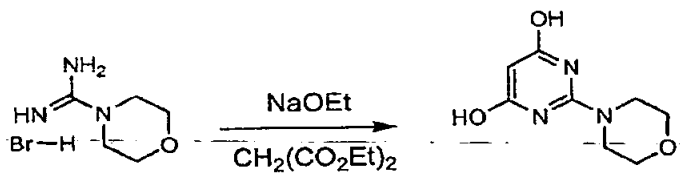
[0336] Sodium thiomethoxide (140 mg, 1.98 mmol) was added to a solution of 2-chloropyridin-4-amine (150 mg, 1.17 mmol) in NMP (0.65 mL) in a pressure vessel. The vessel was sealed and heated in a microwave to 200 °C for 800 sec. Purification by silica flash chromatography eluting with 8% MeOH/DCM afforded 2-(methylthio)pyridin-4-amine (435 mg, 50% yield). LC/MS (*m/z*): 140.9 (MH^+), R_t 0.59 minutes.

[0337] Solid MCPBA (780 mg, 2-3 mmol) was slowly added in small portions to a solution of 2-(methylthio)pyridin-4-amine (435 mg, 1.17 mmol) in THF (7 mL) at RT, with stirring. The reaction was followed by LCMS as the starting material was consumed by titrating with MCPBA. Silica was added to the reaction mixture, which was then concentrated to dryness under reduced pressure. Silica supported crude was purified by

silica flash chromatography, eluting with 5% MeOH/DCM, to afford 2-(methylsulfonyl)pyridin-4-amine (220 mg, quant. yield). LC/MS (*m/z*): 173.0 (MH^+), R_t 0.34 minutes.

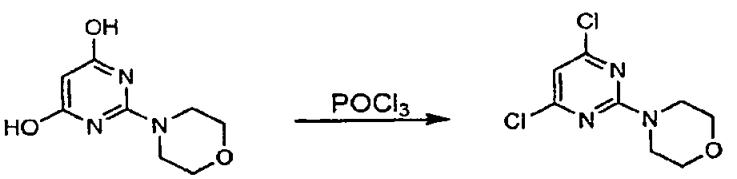
Method 22

[0338] Synthesis of 2-morpholinopyrimidine-4,6-diol



[0339] Sodium (17.25 g, 150 mmol) was cut into small pieces and slowly added to EtOH (500 mL) in a 1-L round bottom flask under N_2 and cooled with water. After all the sodium was dissolved, morpholinoformamidine hydrobromide (52.5 g, 50 mmol) and diethyl malonate (40 g, 50 mmol) were added. The mixture was heated to reflux for three hours. The reaction mixture was cooled to room temperature, and the ethanol was removed *in vacuo*. Aqueous HCl (1N, 800 mL) was added to the white solid, at room temperature. The solid initially dissolved, giving a clear solution, then the product crashed out as a white solid. After 1 h at room temperature, the solid was filtered, washed with water (3x), dried (air and then over P_2O_5) to give 2-morpholinopyrimidine-4,6-diol (42.5 g, 86%). LC/MS (*m/z*): 198.1 (MH^+), R_t 0.51 minutes.

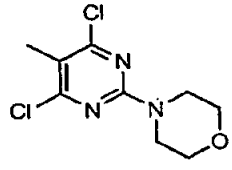
[0340] Synthesis of 4,6-dichloro-2-morpholinopyrimidine



[0341] A mixture of 2-morpholinopyrimidine-4,6-diol (30 g, 0.15 mol) and $POCl_3$ (150 mL, 1.61 mol) was heated at 120 °C for 16 h, then cooled to RT. Excess $POCl_3$ was removed to give a semi-solid. The solid was gradually transferred to a stirring solution of water (700 mL) and EtOH (100 mL) occasionally cooled with water. White solid formed and was subsequently filtered, washed with water, 10% EtOH in water, and dried over P_2O_5 to give 4,6-dichloro-2-morpholinopyrimidine (17.82 g, 50%). LC/MS (*m/z*): 233.9 (MH^+), R_t 2.95 minutes.

Method 23

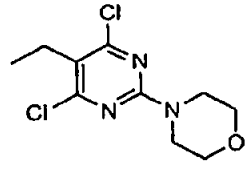
[0342] Synthesis of 4,6-dichloro-5-methyl-2-morpholinopyrimidine



[0343] 4,6-Dichloro-5-methyl-2-morpholinopyrimidine was prepared by similar procedure as 4,6-dichloro-2-morpholinopyrimidine (in Method 22) using dimethyl 2-methylmalonate in place of diethyl malonate. LC/MS (*m/z*): 248.1 (MH^+).

Method 24

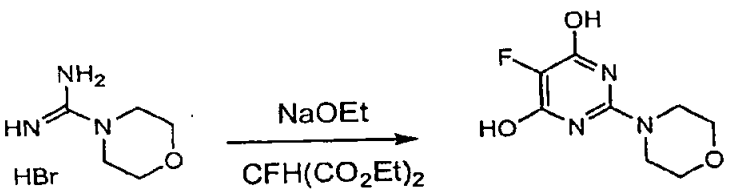
[0344] Synthesis of 4,6-dichloro-5-ethyl-2-morpholinopyrimidine



[0345] 4,6-Dichloro-5-ethyl-2-morpholinopyrimidine was prepared by similar procedure as 4,6-dichloro-2-morpholinopyrimidine (in Method 22) using dimethyl 2-ethylmalonate in place of diethyl malonate. LC/MS (*m/z*): 262.1 (MH^+), R_t 3.59 minutes.

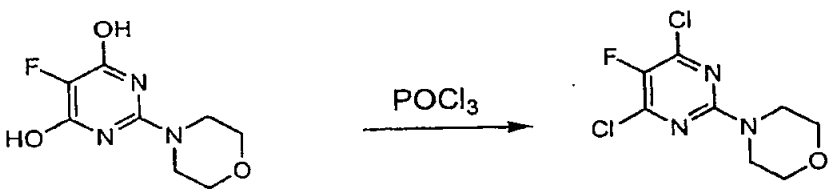
Method 25

[0346] Synthesis of 5-fluoro-2-morpholinopyrimidine-4,6-diol



[0347] Sodium hydride (60% in oil, 3.9 g, 96.5 mmol) was washed with hexanes in a round bottom flask under argon and cooled with an ice water bath. EtOH (100 mL) was slowly added. The resulting mixture was warmed to RT and stirred for 30 minutes. To the base mixture, diethyl 2-fluoromalonate (5.7 g, 32.2 mmol) was added, followed by morpholinoformamidine hydrobromide (6.8 g, 32.2 mmol). The mixture was heated to 90-95 °C with stirring under argon. After 12 hours, the reaction was cooled to room temperature and the EtOH was removed *in vacuo*. The resulting white solid was dissolved in water (25 mL) and acidified with conc. HCl to pH = 3-4. A white precipitate formed which was collected on a Büchner filter, washed with water (2x50 mL), air dried on the filter, and dried *in vacuo* to give 5-fluoro-2-morpholinopyrimidine-4,6-diol (0.87 g, 12%). LC/MS (*m/z*): 216.0 (MH^+), R_t 0.63 minutes.

[0348] Synthesis of 4-(4,6-dichloro-5-fluoropyrimidin-2-yl)morpholine

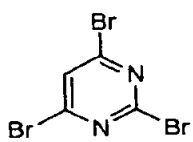


[0349] A mixture of 5-fluoro-2-morpholinopyrimidine-4,6-diol (0.87 g, 4.0 mmol) and $POCl_3$ (10 mL) was heated at 120 °C for 16 hours, then cooled to RT.

Excess of $POCl_3$ was removed under reduced pressure to give a semi-solid which was dried further *in vacuo*. After 12 h of vacuum drying, the solid was diluted in EtOAc (150 mL) and washed with sat. $NaHCO_3$ (60 mL). A solid formed during the wash and was discarded with the aqueous layer. The organic layer was washed again with sat. $NaHCO_3$ (2x30 mL), brine (30 mL), dried with Na_2SO_4, filtered and evaporated under reduced pressure to give a crude product. The product was purified by flash chromatography eluting with 25% EtOAc/hexane to give 4-(4,6-dichloro-5-fluoropyrimidin-2-yl)morpholine (418 mg, 42%). LC/MS (*m/z*): 251.9 (MH^+), R_t 3.22 minutes.

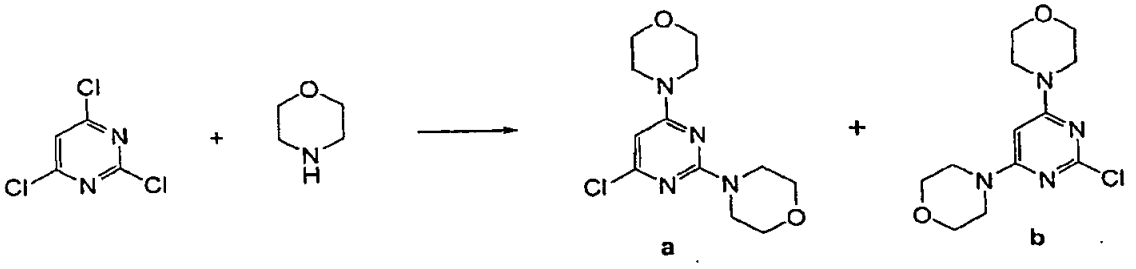
Method 26

[0350] Synthesis of 2,4,6-tribromopyrimidine



[0351] To a mixture of pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (2.66 g, 20.87 mmol) and $POBr_3$ (25 g, 87.2 mmol) in toluene (35 mL) in a 200 mL flask, *N*,*N*-dimethylaniline (4.52 mL, 35.7 mmol) was added. The brick-red slurry was heated to reflux for 3 hours. During the process a biphasic solution formed with a red gum at the bottom of the flask and a clear yellow liquid above. The reaction mixture was cooled to room temperature and the yellow organic layer decanted off. The red gum was rinsed once with EtOAc. The combined organic extracts were washed with saturated $NaHCO_3$ (3x, or until CO_2 evolution ceased), H_2O (3x), brine (2x) and dried over Na_2SO_4. The solution was then concentrated and dried under high vacuum to yield 2,4,6-tribromopyrimidine (5.40 g, 82%), which was used without further purification. LC/MS (*m/z*): 316.8/318.7 (MH^+), R_t 2.78 minutes.

Method 27



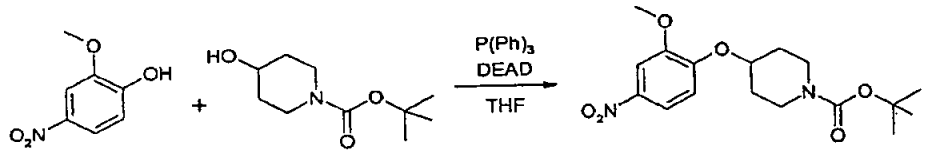
[0352] A solution of morpholine (100 g; 1.15 moles; 5.3 equivalents) in THF (450 mL) was cooled with an ice bath. A solution of 2,4,6-trichloropyrimidine (39.9 g; 217 mmoles; 1.0 equivalents) in THF (100 mL) was added over a period of 30 minutes. A copious white precipitate formed upon addition of 2,4,6-trichloropyrimidine and the reaction mixture rapidly thickened. The mixture was allowed to warm to ambient temperature and mechanically stirred for 64 hours (heating the reaction mixture at reflux following the addition of 2,4,6-trichloropyrimidine leads to complete reaction in 60 min. The ratio of **a** to **b** was unchanged). The mixture was then filtered and the filter cake washed with additional THF (2 x 100 mL). The filtrate was concentrated on the rotavap. Water (600 mL) was added and the resulting slurry was stirred for 30 minutes. The solids were isolated by filtration, washed with additional water (2 x 100 mL) and dried overnight under vacuum. Yield **a** + **b**: 61.3 g (99%). Product was 87% **a** by hplc area percent; remainder is **b**.

[0353] 31 g of the crude solid was dissolved in 200 mL of CH_2Cl_2 and applied to 600 g of dry silica in a fritted glass funnel. The silica was eluted with 1 : 1 hexane : EtOAc and 300 mL fractions were collected. TLC analysis shows **a** to be present in fractions 1-7 and 4,6-dimorpholino-2-chloropyrimidine in fractions 6-10. Fractions 1-5 were pooled and concentrated to provide a white solid. Yield: 28.2 g (Product was 98% **a** by hplc area percent).

Method 28

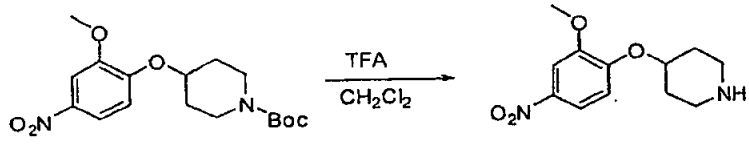
SYNTHESIS OF 4-(1-ISOPROPYLPIPERIDIN-4-YLOXY)ANILINE

SYNTHESIS OF *T*-BUTYL 4-(2-METHOXY-4-NITROPHENOXY)PIPERIDINE-1-CARBOXYLATE



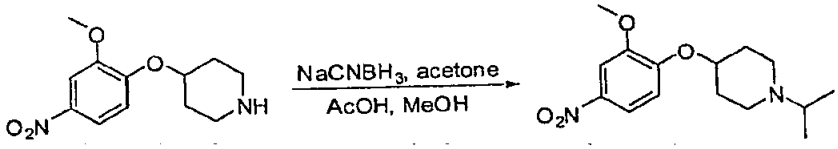
[0354] To a mixture of triphenylphosphine (3.10 g, 11.8 mmol) and diethylazodicarboxylate (2.06 g, 11.8 mmol) under N_2 in THF (40 mL) was added *t*-butyl 4-hydroxypiperidine-1-carboxylate (2.00g, 9.94 mmol). After stirring 10 min, 2-methoxy-4-nitrophenol (1.00 g, 5.91 mmol) was added. The reaction was stirred for 16 h and the solvent was evaporated under reduced pressure to give orange oil. The crude product was purified by column chromatography on silica gel using 25% EtOAc/hexane yielding *t*-butyl 4-(2-methoxy-4-nitrophenoxy)piperidine-1-carboxylate as a beige solid (1.70 g, 82%). LC/MS (*m*/z): 353.2 (MH^+), R_t 3.23 minutes

SYNTHESIS OF 4-(2-METHOXY-4-NITROPHENOXY)PIPERIDINE



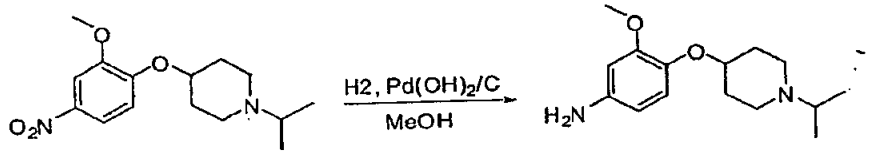
[0355] Trifluoroacetic acid (5 eq) was added to a solution of tert-butyl 4-(2-methoxy-4-nitrophenoxy)piperidine-1-carboxylate (200 mg, 0.57 mmol, 1 eq) in dichloromethane, stirring at room temperature for 1 hour. The solvent was then evaporated, the residue was brought to pH 10 with sat. aq. Na2CO3 solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and evaporated to afford the product 4-(2-methoxy-4-nitrophenoxy)piperidine as a light yellow solid (137.3 mg, 96%). LC/MS (m/z): 253.2(MH+), Rt 1.81 minutes.

SYNTHESIS OF 1-ISOPROPYL-4-(2-METHOXY-4-NITROPHENOXY)PIPERIDINE



[0356] To a solution of 10% acetic acid in methanol was added 4-(2-methoxy-4-nitrophenoxy)piperidine (148 mg, 0.59 mmol, 1 eq), anhydrous acetone (5 eq), and sodium cyanoborohydride (1.5 eq). The solution was stirred at room temperature for 24 h. Additional anhydrous acetone (5 eq) and sodium cyanoborohydride (1.5 eq) were added and the reaction was stirred for 24 h. The solvent was evaporated, the residue was brought to pH 10 with aqueous sodium carbonate and extracted with EtOAc. The organic layer was washed with water, brine, dried with magnesium sulfate and evaporated to afford 1-isopropyl-4-(2-methoxy-4-nitrophenoxy)piperidine as a yellow oil (163 mg, 97%). LC/MS (*m*/z): 295.2 (MH^+), R_t 1.96 minutes.

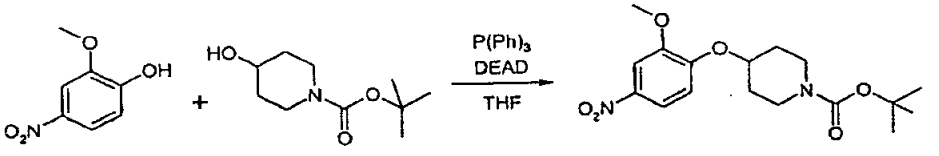
SYNTHESIS OF 4-(1-ISOPROPYLPIPERIDIN-4-YLOXY)-3-METHOXYANILINE



[0357] 1-isopropyl-4-(2-methoxy-4-nitrophenoxy)piperidine (167 mg, 0.57 mmol) was dissolved in methanol (20 mL) and placed under a nitrogen atmosphere. A catalytic amount of 20% palladium hydroxide on carbon was added and a hydrogen balloon was connected to the reaction flask. The flask was flushed five times with hydrogen and stirred at room temperature under hydrogen atmosphere for 16 hours. The reaction mixture was filtered and washed with methanol. The filtrate was evaporated under reduced pressure. Acetonitrile (10 mL) was added to the residue, swirled for 10 min, and decanted away from white film. The acetonitrile layer was evaporated under reduced pressure yielding 4-(1-isopropylpiperidin-4-yloxy)aniline as a brown oil (131 mg, 87%). LC/MS (*m*/z): 265.2 (MH^+), R_t 0.33 minutes.

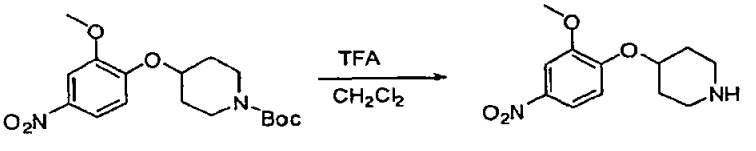
Method 29

SYNTHESIS OF 4-(1-ISOPROPYLPIPERIDIN-4-YLOXY)-3-METHOXYANILINE; SYNTHESIS OF TERT-BUTYL 4-(2-METHOXY-4-NITROPHENOXY)PIPERIDINE-1-CARBOXYLATE



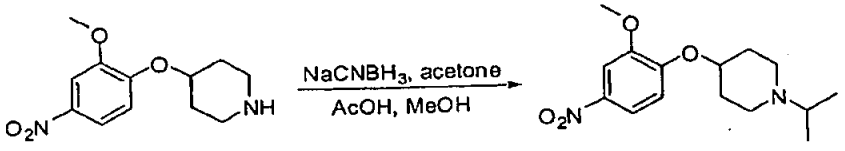
[0358] To a mixture under N_2 of triphenylphosphine (3.10g, 11.825 mmol) and diethylazodicarboxylate (2.06g, 11.825 mmol) in THF (40 mL) was added tert-butyl 4-hydroxypiperidine-1-carboxylate (2.00g, 9.937 mmol). After stirring 10 min, 2-methoxy-4-nitrophenol (1.00 g, 5.912 mmol) was added. The reaction stirred 16 h and evaporated under reduced pressure to give an orange oil. The crude product was purified by column chromatography on silica gel using 25% EtOAc/hexane yielding tert-butyl 4-(2-methoxy-4-nitrophenoxy)piperidine-1-carboxylate as a beige solid (1.70g, 82%). LC/MS (*m/z*): 353.2 (MH^+), R_t 3.23 minutes

SYNTHESIS OF 4-(2-METHOXY-4-NITROPHENOXY)PIPERIDINE



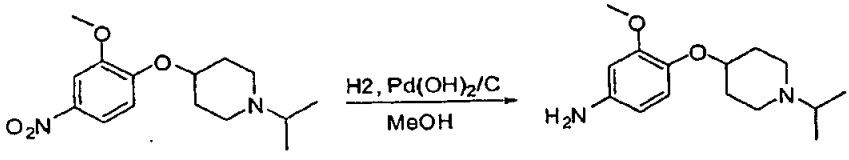
[0359] Trifluoroacetic acid (5 eq) was added to a solution of *tert*-butyl 4-(2-methoxy-4-nitrophenoxy)piperidine-1-carboxylate (200 mg, 0.5676 mmol, 1 eq) in dichloromethane, stirring at room temperature for 1 hour. The solvent was then evaporated, the residue brought to pH = 10 with sat. aq. Na_2CO_3 solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and evaporated to afford the product 4-(2-methoxy-4-nitrophenoxy)piperidine as a light yellow solid (137.3 mg, 96%). LC/MS (*m/z*): 253.2(MH^+), R_t 1.81 minutes.

SYNTHESIS OF 1-ISOPROPYL-4-(2-METHOXY-4-NITROPHENOXY)PIPERIDINE



[0360] To a solution of 10% acetic acid in methanol was added 4-(2-methoxy-4-nitrophenoxy)piperidine (148 mg, 0.59 mmol, 1 eq), anhydrous acetone (5 eq), and sodium cyanoborohydride (1.5 eq). The solution was stirred at room temperature for 24 h. Reaction is 85% complete. Charged additional anhydrous acetone (5 eq) and sodium cyanoborohydride (1.5 eq) and stirred for 24 h. The solvent was evaporated, the residue brought to pH = 10 with sodium carbonate and extracted with EtOAc. The organic layer was washed with water, brine, dried with magnesium sulfate and evaporated to afford 1-isopropyl-4-(2-methoxy-4-nitrophenoxy)piperidine as a yellow oil (163 mg, 97%). LC/MS (*m*/z): 295.2 (MH^+), R_t 1.96 minutes.

SYNTHESIS OF 4-(1-ISOPROPYLPIPERIDIN-4-YLOXY)-3-METHOXYANILINE

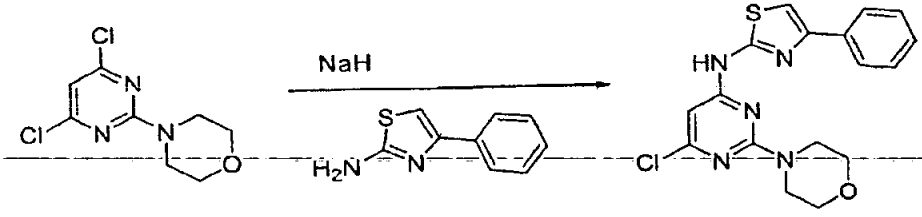


[0361] 1-isopropyl-4-(2-methoxy-4-nitrophenoxy)piperidine (167 mg, 0.57 mmol) was dissolved in 20 mL of methanol and placed under a nitrogen atmosphere. A catalytic amount of 20% palladium hydroxide on carbon was added and a hydrogen balloon was connected to the reaction flask. The flask was flushed five times with hydrogen and stirred at room temperature under hydrogen atmosphere for 16 hours. The reaction mixture was filtered and washed with methanol. The filtrate was evaporated under reduced pressure. Acetonitrile (10 mL) was added to the residue, swirled for 10 min, and decanted away from white film. The acetonitrile layer was evaporated under

reduced pressure yielding 4-(1-isopropylpiperidin-4-yloxy)aniline as a brown oil (131 mg, 87%). LC/MS (*m/z*): 265.2 (MH^+), R_t 0.33 minutes.

Method 30

SYNTHESIS OF N-(6-CHLORO-2-MORPHOLINOPYRIMIDIN-4-YL)-4-PHENYLTHIAZOL-2-AMINE

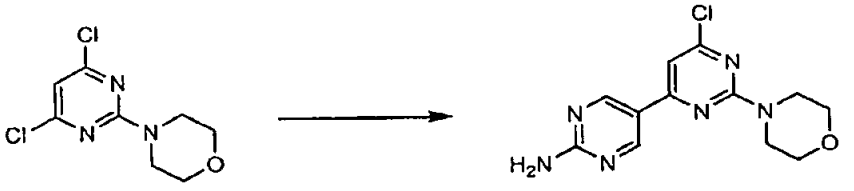


[0362] To a solution of the 4-phenylthiazol-2-amine (374 mg, 2.1 mmol) in 10 mL of N,N-dimethylacetamide was added sodium hydride (50 mg, 2.1 mmol) at room temperature. After the mixture was stirred at that temperature for 10 minutes, the dichloride (470 mg, 2.0 mmol) was added to the reaction mixture. After being stirred at room temperature for 1 hour, additional sodium hydride (50 mg, 2.1 mmol) was added to the reaction mixture. The mixture was stirred for 1 hour and quenched with 5 mL of aq. ammonium chloride. The resulting mixture was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), then dried over MgSO4, filtered, and evaporated under reduced pressure to give crude product, which was purified by silica gel column eluted with ethyl acetate and hexane to give N-(6-chloro-2-morpholinopyrimidin-4-yl)-4-phenylthiazol-2-amine. LC/MS (m/z): 374 and 376 (MH+), Rt 3.40 minutes.

Example 1

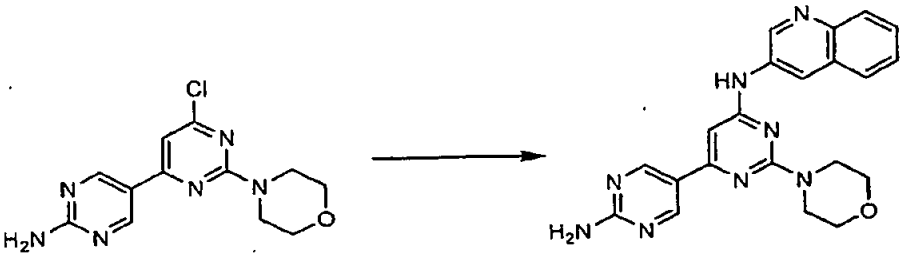
Preparation of N-(6-(2-aminopyrimidin-5-yl)-2-morpholinopyrimidin-4-yl)quinolin-3-amine

143



[0363] 4,6-Dichloro-2-morpholinopyrimidine (prepared as in Method 22; 3.0 g, 12.9 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-amine (3.43 g, 15.5 mmol) were dissolved in DME (130 mL). Aqueous Na_2CO_3 (2 M, 32 mL, 64 mmol) was then added and the reaction mixture was sparged with N_2 for several minutes. $Pd(OAc)_2$ (145 mg, 0.65 mmol) and PPh_3 (339 mg, 1.29 mmol) were then added and the reaction mixture was heated at 95 °C for 1 h. The reaction mixture was allowed to cool to room temperature, the solution was decanted away from the solid residue and concentrated. The solid thus formed was separated from the water phase. The water extracted with EtOAc and this organic layer was combined with the precipitate. Removal of the solvent *in vacuo* gave a solid residue which was triturated with about 20 mL of EtOAc, filtered and evaporated under reduced pressure to give the desired product. Additional product was obtained by concentrating the mother liquor and purifying the solid crash out by trituration with EtOAc. The two crops were combined obtaining 1.98 g (52%) of the desired product. LC/MS (*m/z*): 293.1 (MH^+), R_t 1.92 minutes

[0364] N-(6-(2-aminopyrimidin-5-yl)-2-morpholinopyrimidin-4-yl)quinolin-3-amine

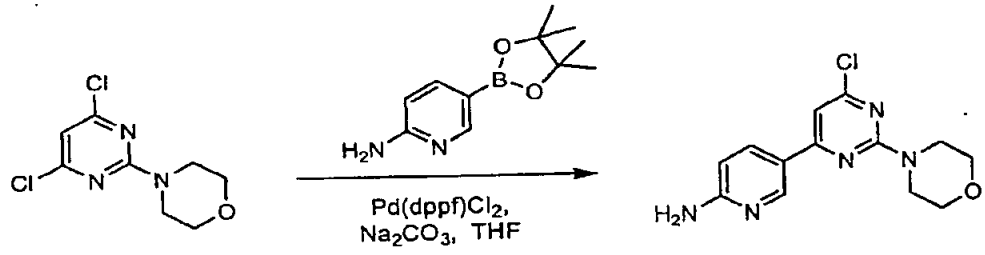


[0365] $Pd(OAc)_2$, BINAP, cesium carbonate, THF (0.8 mL) were mixed with 5-(6-chloro-2-morpholinopyrimidin-4-yl)pyrimidin-2-amine (1 eq) and quinolin-3-amine (2 eq). The mixture was heated under microwave irradiation for 10 minutes at 110 °C. The solution was filtered and concentrated under reduced pressure. LC/MS (*m*/z): 401.4 (MH^+).

Example 2

Preparation of N-(6-(6-aminopyridin-3-yl)-2-morpholinopyrimidin-4-yl)quinolin-3-amine

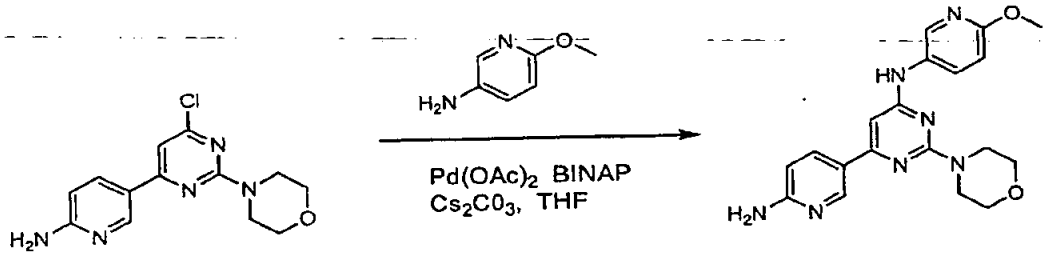
[0366] 5-(6-Chloro-2-morpholin-4-yl-pyrimidin-4-yl)pyridin-2-ylamine



[0367] THF (130 mL) and aq. Na_2CO_3 (2M, 40 mL, 80 mmol) were added to a glass pressure vessel containing 4,6-dichloro-2-morpholinopyrimidine (prepared as in Method 22; 4.5 g, 19.2 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (4.7 g, 21.2 mmol). The resulting mixture was stirred and sparged with argon for 1-2 minutes. The catalyst, dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium (II) dichloromethane adduct (1.26 g, 1.54 mmol), was then added in one portion. After sealing the reaction vessel, the reaction was heated at 85 °C for 1 hour with stirring. Upon cooling to RT, the THF was removed under reduced pressure to leave a viscous residue. EtOAc (450 mL) and water (50 mL) were added. After vigorously stirring for 1-2 minutes, the solids were filtered off and washed with EtOAc (100 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc

(100 mL). The combined organic layers were washed with saturated NaCl solution (1 x 50 mL), dried with Na_2SO_4, filtered and evaporated under reduced pressure. The crude material was further purified by silica gel chromatography to give 5-(6-chloro-2-morpholin-4-yl-pyrimidin-4-yl)-pyridin-2-ylamine (2.48 g, 44%). LC/MS (*m/z*): 292.1 (MH^+), R_t 2.06 minutes.

[0368] [6-(6-amino-pyridin-3-yl)-2-morpholin-4-yl-pyrimidin-4-yl]-(6-methoxy-pyridin-3-yl)-amine

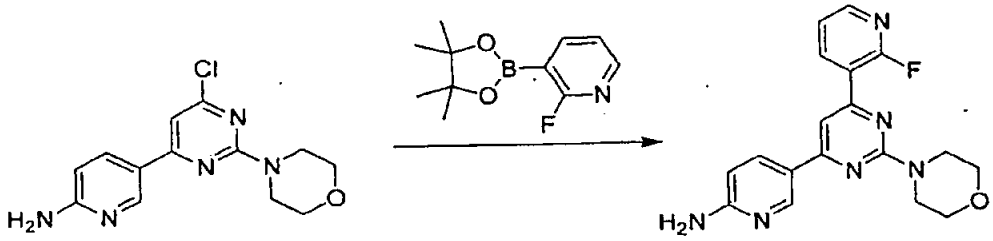


[0369] In a glass pressure vessel, $Pd(OAc)_2$ (2.0 mg, 0.0082 mmol), BINAP (6.4 mg, 0.0102 mmol), cesium carbonate (20.0 mg, 0.0615 mmol) and THF (0.8 mL) were mixed and stirred at room temperature for 1-3 minutes. To the resulting mixture was added 5-(6-chloro-2-morpholin-4-yl-pyrimidin-4-yl)-pyridin-2-ylamine (12.0 mg, 0.041 mmol) followed by 6-methoxypyridin-3-ylamine (10.2 mg, 0.082 mmol). The glass pressure vessel was sealed and stirred at 95 °C for 90 minutes. The reaction mixture was filtered and concentrated under reduced pressure. The product was purified by preparative reverse phase HPLC to give [6-(6-amino-pyridin-3-yl)-2-morpholin-4-yl-pyrimidin-4-yl]-(6-methoxy-pyridin-3-yl)-amine (5.0 mg, 32%). LC/MS (*m/z*): 380.1 (MH^+), R_t 1.82 minutes.

Example 3

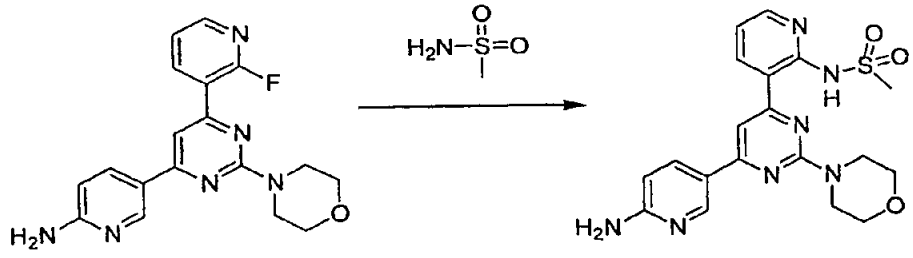
Preparation of 5-(6-[2-(methylsulfonamide)pyridin]-3-yl)-2-morpholino-pyrimidin-4-yl)pyridin-2-amine

[0370] 5-[6-(2-fluoro-pyridin-3-yl)-2-morpholin-4-yl-pyrimidin-4-yl]-pyridin-2-ylamine



[0371] To a solution of 5-(6-chloro-2-morpholin-4-yl-pyrimidin-4-yl)pyridin-2-ylamine, prepared as in Example 2, (252 mg, 0.87 mmol) and 2-fluoro-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)pyridine (183 mg, 1.30 mmol) in DME (4 mL) was added an aqueous solution of Na_2CO_3 (2 M, 1 mL), followed by dichloro[1,1'-bis(diphenylphosphino) ferrocene]palladium(II)-dichloromethane (71 mg, 0.087 mmol). The mixture was heated in a microwave for 20 min at 120 °C. The aqueous phase was separated from DME, and extracted with EtOAc. The combined organic phases were washed with brine, dried, filtered, and concentrated to give crude desired product which was carried on to the next step without further purification. LC/MS (*m/z*): 353.3 (MH^+), 1.84 minutes.

[0372] N-{3-[6-(6-Amino-pyridin-3-yl)-2-morpholin-4-yl-pyrimidin-4-yl]pyridin-2-yl}-methanesulfonamide

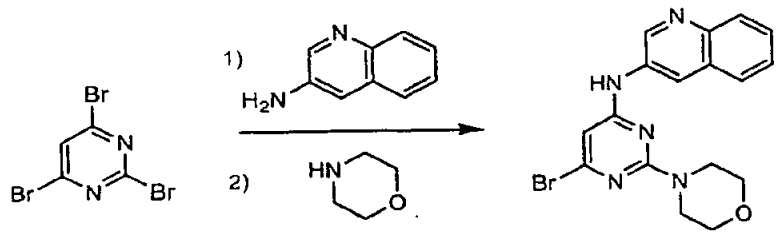


[0373] To a solution of 5-[6-(2-fluoro-pyridin-3-yl)-2-morpholin-4-yl-pyrimidin-4-yl]-pyridin-2-ylamine (200 mg, 0.57 mmol) and methanesulfonamide (216 mg, 2.3 mmol) in NMP (8 mL) was added Cs_2CO_3 (372 mg, 1.1 mmol). The solution was heated at 125 °C for 4 hours. The reaction mixture was cooled to room temperature, filtered and purified by reverse phase preparatory HPLC to give the title compound. LC/MS (*m/z*): 428.3 (MH^+), R_t 1.80 minutes.

Example 4

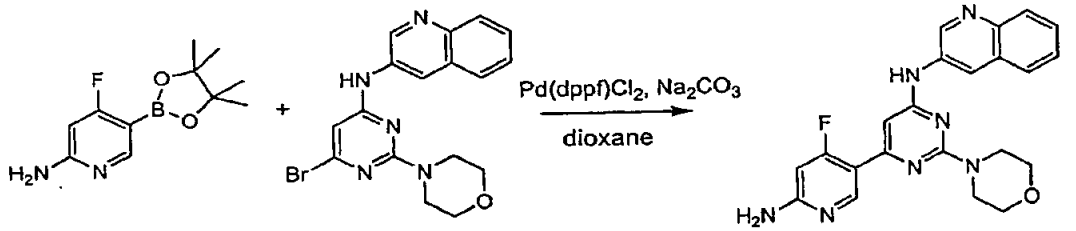
Preparation of N-(6-(6-amino-4-fluoropyridin-3-yl)-2-morpholinopyrimidin-4-yl)quinolin-3-amine

[0374] *N*-(6-bromo-2-morpholinopyrimidin-4-yl)quinolin-3-amine



[0375] To a solution of 2,4,6-tribromopyrimidine (5.40 g, 17.2 mmol) in acetonitrile (60 mL) was added quinolin-3-amine, followed by DIEA (8.99 mL, 51.6 mmol). The reaction mixture was heated to 45 °C overnight. Morpholine (1.50 mL, 17.2 mmol) was then added, and the reaction mixture continued heating for 4 h. The reaction mixture was then cooled to room temperature, concentrated and dissolved in EtOAc (about 500 mL), the organic solution was washed with saturated $NaHCO_3$ (3x), H_2O (2x), brine (1x) and dried over Na_2SO_4. The solution was then evaporated in the presence of silica gel and purified by column chromatography (SiO_2, 15-25% EtOAc/Hexanes) to yield *N*-(6-bromo-2-morpholinopyrimidin-4-yl)quinolin-3-amine. LC/MS (*m/z*): 386.1 (MH^+).

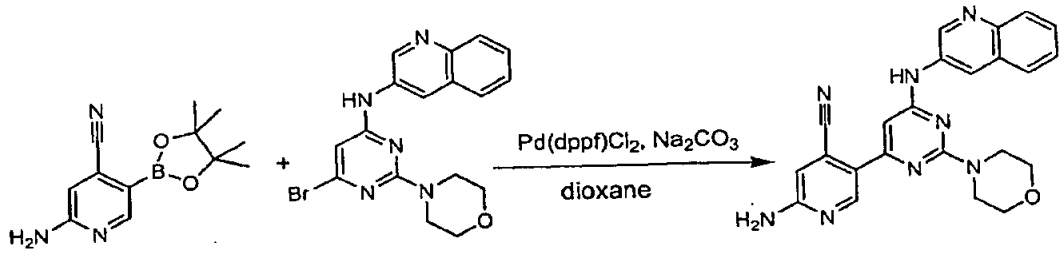
[0376] N-(6-(6-amino-4-fluoropyridin-3-yl)-2-morpholinopyrimidin-4-yl)quinolin-3-amine



[0377] To a solution of 4-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (prepared as shown in Method 10) in dioxane (1.7 mL, 0.13 mmol), *N*-(6-bromo-2-morpholinopyrimidin-4-yl)quinolin-3-amine (20 mg, 0.052 mmol), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II)-dichloromethane adduct (11 mg, 0.013 mmol) and 2 M aqueous sodium carbonate solution (0.6 mL, 1.2 mmol) were added under argon. The pressure vessel was sealed and the reaction mixture was heated in a microwave reactor at 120 °C for 15 minutes. The crude product was partitioned between EtOAc (30 mL) and saturated sodium bicarbonate (10 mL). The organic layer was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure. The product was purified by reverse phase preparative HPLC to give *N*-(6-(6-amino-4-fluoropyridin-3-yl)-2-morpholinopyrimidin-4-yl)quinolin-3-amine as yellow powder (14 mg, 26%). LC/MS (*m/z*): 418.0 (MH^+), R_t 2.31 minutes.

Example 5

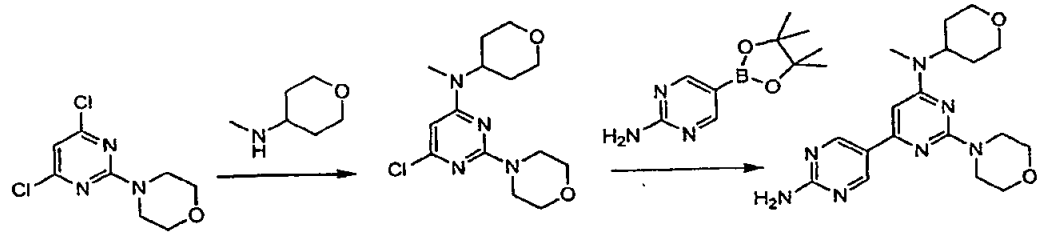
Preparation of 2-amino-5-[2-morpholin-4-yl-6-(quinolin-3-ylamino)-pyrimidin-4-yl]-isonicotinonitrile



[0378] To the crude 2-amino-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-4-carbonitrile (prepared as in Method 11) (25 mg, 0.13 mmol) solution in dioxane (1.8 mL) in a pressure vessel, was added (6-bromo-2-morpholin-4-yl-pyrimidin-4-yl)-quinolin-3-yl-amine (19.4 mg, 0.05 mmol) and aq. Na_2CO_3 (2 M, 0.6 mL, 1.2 mmol). After purging the reaction mixture with argon, dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium(II) dichloromethane adduct (10.3 mg, 0.01 mmol) was added in one portion. The pressure vessel was sealed and the mixture was heated in a microwave at 120 °C for 900 seconds. The crude mixture was filtered and concentrated under reduced pressure. The crude product was purified by reverse phase preparative HPLC to give 2-amino-5-[2-morpholin-4-yl-6-(quinolin-3-ylamino)-pyrimidin-4-yl]-isonicotinonitrile (4.4 mg, 20%). LC/MS (*m/z*): 425.0 (MH^+), R_t 2.03 minutes.

Example 6

Preparation of N^6-methyl-2-morpholino-N^6-(tetrahydro-2H-pyran-4-yl)-4,5'-bipyrimidine-2',6-diamine



[0379] *N*-Methyltetrahydro-2*H*-pyran-4-amine

[0380] Tetrahydro-2*H*-pyran-4-amine (90 mg, 0.9 mmol) was added to a solution of formaldehyde (37% solution in water, 0.091 mL, 1.13 mmol) and acetic acid (0.162 mL) in ACN (0.8 mL). After stirring for 5 minutes, $Na(CN)BH_3$ (60 mg, 1.13 mmol) was added in one portion at RT. After 1 hour, excess Cs_2CO_3 was added to the reaction until made alkaline. After stirring for 15 minutes, the reaction was filtered to remove solids and the solvent evaporated under reduced pressure. The crude product, *N*-methyltetrahydro-2*H*-pyran-4-amine, was used for the following displacement without further purification. LC/MS (*m/z*): 116.1 (MH^+), R_t 0.34 minutes.

[0381] 6-chloro-*N*-methyl-2-morpholino-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrimidin-4-amine

[0382] The crude *N*-methyltetrahydro-2*H*-pyran-4-amine (104 mg, 0.9 mmol) was dissolved in NMP (0.8 mL). To the solution, Cs_2CO_3 (366 mg, 1.13 mmol) and 4-(4,6-dichloropyrimidin-2-yl)morpholine (prepared as in Method 22) (80 mg, 0.34 mmol) were added at room temperature. The reaction mixture was heated to 95 °C. After 90 minutes, the reaction mixture was cooled to room temperature, filtered and purified by reverse phase preparative HPLC yielding 24 mg (23%) of pure 6-chloro-*N*-methyl-2-morpholino-*N*-(tetrahydro-2*H*-pyran-4-yl)pyrimidin-4-amine. LC/MS (*m/z*): 313.2 (MH^+), R_t 2.61 minutes.

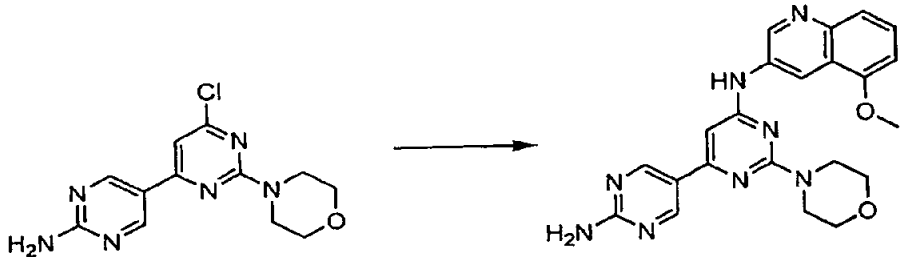
[0383] N^6-methyl-2-morpholino-N^6-(tetrahydro-2H-pyran-4-yl)-4,5'-bipyrimidine-2',6-diamine

[0384] To an argon flushed mixture of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-amine (42 mg, 0.19 mmol), 6-chloro-*N*-methyl-2-morpholino-*N*-

(tetrahydro-2*H*-pyran-4-yl)pyrimidin-4-amine (12 mg, 0.038 mmol) in THF (0.8 mL), and aq. Na_2CO_3 (2M, 0.27 mL) in a pressure vessel, was added dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium (II) dichloromethane adduct (8 mg, 0.0095 mmol) in one portion. The pressure vessel was sealed and the mixture was heated in a microwave at 120 °C for 600 seconds. The crude mixture was filtered, concentrated under reduced pressure and purified by reverse phase preparative HPLC to give N^6-methyl-2-morpholino-N^6-(tetrahydro-2H-pyran-4-yl)-4,5'-bipyrimidine-2',6-diamine (4.6 mg, 32%). LC/MS (*m/z*): 372.2 (MH^+), R_t 1.76 minutes.

Example 7

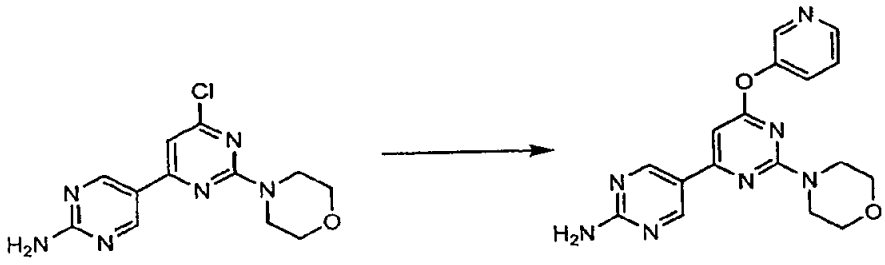
Preparation of N-(6-(2-aminopyrimidin-5-yl)-2-morpholinopyrimidin-4-yl)-5-methoxyquinolin-3-amine



[0385] The desired compound was prepared as described in Example 2: $Pd(OAc)_2$, BINAP, cesium carbonate, THF (0.8 mL) were mixed with 5-(6-chloro-2-morpholinopyrimidin-4-yl)pyrimidin-2-amine (1 eq.) and 5-methoxyquinolin-3-amine (2 eq), which was prepared as shown in Method 20. The mixture was heated under microwave irradiation for 10 minutes at 110 °C. The solution was filtered and concentrated under reduced pressure. The crude product was purified by preparative reverse phase HPLC. LC/MS (*m/z*): 431.2 (MH^+), R_t 2.03 minutes.

Example 8

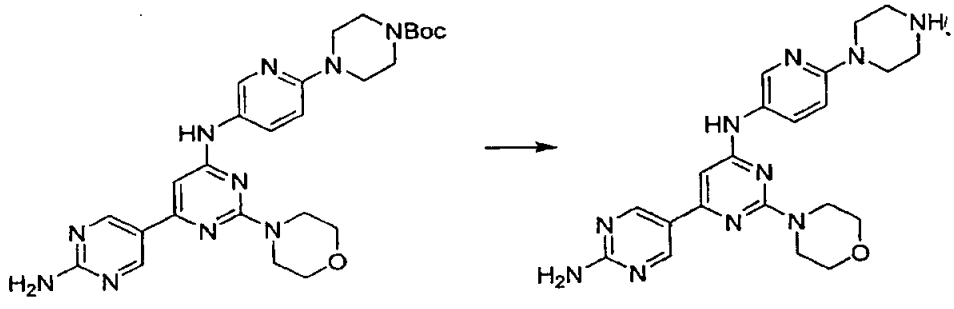
Preparation of 5-(2-morpholino-6-(pyridin-3-yloxy)pyrimidin-4-yl)pyrimidin-2-amine



[0386] 5-(6-chloro-2-morpholinopyrimidin-4-yl)pyrimidin-2-amine (10 mg, 0.034 mmol, prepared as in example 1), potassium *tert*-butoxide (6 mg, 0.051 mmol), pyridin-3-ol (5 mg, 0.051 mmol) and DMSO (0.5 mL) were all combined together and heated at 110 °C for 2 days. The crude product was purified directly by preparative reverse phase HPLC to give 5-(2-morpholino-6-(pyridin-3-yloxy)pyrimidin-4-yl)pyrimidin-2-amine (5.1 mg, 32%). LC/MS (*m/z*): 352.1 (MH^+), R_t 1.83 minutes.

Example 9

Preparation of 6-(2-aminopyrimidin-5-yl)-2-morpholino-N-(6-(piperazin-1-yl)pyridin-3-yl)pyrimidin-4-amine

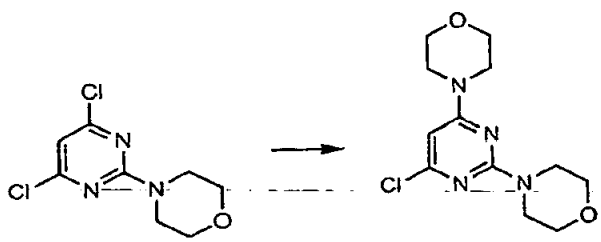


[0387] To *tert*-butyl 4-(5-(6-(2-aminopyrimidin-5-yl)-2-morpholinopyrimidin-4-ylamino) pyridin-2-yl)piperazine-1-carboxylate (prepared as described in Example 1 from 5-(6-chloro-2-morpholinopyrimidin-4-yl)pyrimidin-2-amine and commercially available *tert*-butyl 4-(5-aminopyridin-2-yl)piperazine-1-carboxylate, 30 mg, 0.06 mmol) were added 5 mL of 4N HCl in dioxane. After stirring for one hour, the solution was

concentrated *in vacuo*. The residue was dissolved in a 3:1 acetonitrile and water and lyophilized to afford the desired product LC/MS (*m/z*): 435.2 (MH^+), R_t 1.52 minutes.

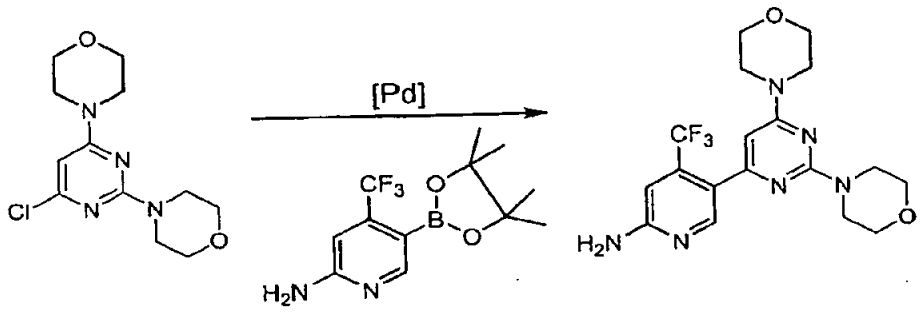
Example 10

Preparation of 4-(trifluoromethyl)-5-(2,6-dimorpholinopyrimidin-4-yl)pyridin-2-amine



[0388] To a slurry of 2-morpholino-4,6-dichloropyrimidine (prepared as in Method 22, 2.0 g, 8.54 mmol) in NMP (14 mL), triethylamine (1.43 mL, 10.25 mmol) was added. The heterogeneous mixture was stirred for 15 minutes, then treated with morpholine (0.75 mL, 8.54 mmol). Upon refluxing at 85 °C under argon for 2 hours, the solution was cooled, then added to EtOAc (160 mL). The organic solution was washed with 25 mL of $NaHCO_{3(sat.)}$ (2 x), water (2 x) and brine, dried over Na_2SO_4, filtered and concentrated. The crude material was dissolved in 200 mL EtOAc and filtered through a SiO_2 pad, further eluting with EtOAc, yielding 2.2 g (93%) of 2,4-dimorpholino-6-chloropyrimidine as an off-white solid. LCMS (*m/z*): 285.0 (MH^+), ^1H NMR ($CDCl_3$): δ 5.86 (s, 1H), 3.71-3.76(m, 12H), 3.52-3.56(m, 4H).

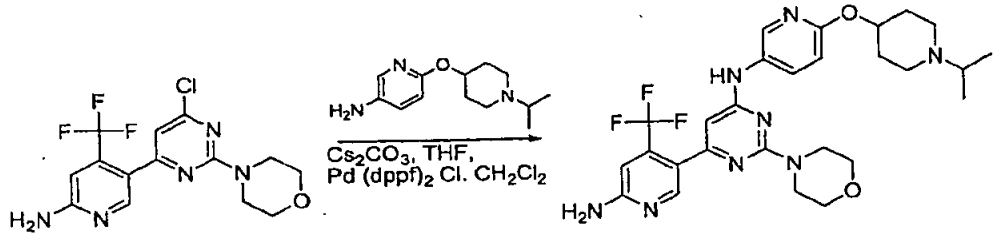
[0389] 4-(trifluoromethyl)-5-(2,6-dimorpholinopyrimidin-4-yl)pyridin-2-amine



[0390] Argon gas was bubbled through a heterogeneous mixture of 2,4-dimorpholino-6-chloropyrimidine (4.1 g, 14.3 mmol) and 4-(trifluoromethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (16.5 g, 57.3 mmol) in 1,2-dimethoxyethane and 2M Na_2CO_3 (3:1) for 20 minutes. 1,1'-Bis(diphenylphosphino)ferrocene palladium (II) chloride (292 mg, 0.36 mmol) was added and the high pressure glass vessel containing the mixture was sealed. The reaction mixture was then heated at 90 °C for 15 hours, cooled and diluted with EtOAc (300 mL). The organic solution was washed with 300 mL of a mixture of water: $Na_2CO_{3(sat.)}$:$NH_4OH_{(conc.)}$ = 5:4:1, then $NH_4Cl_{(sat.)}$, and brine (2x), dried over Na_2SO_4, filtered and concentrated. The crude material was purified by SiO_2 chromatography (50-90% EtOAc/hexanes with 0.1% TEA) resulting in 5.62 g (95%) of 4-(trifluoromethyl)-5-(2,6-dimorpholinopyrimidin-4-yl)pyridin-2-amine as an off-white solid. LCMS (*m/z*): 411.3 (MH^+); ^1H NMR ($CDCl_3$): δ 8.27 (s, 1H), 6.78 (s, 1H), 5.97 (s, 1H), 4.77 (bs, 2H), 3.59-3.80(m, 12H), 3.58-3.61(m, 4H).

Example 11

Preparation of N-(6-(1-isopropylpiperidin-4-yloxy)pyridin-3-yl)-6-(6-amino-4-(trifluoromethyl)pyridin-3-yl)-2-morpholinopyrimidin-4-amine

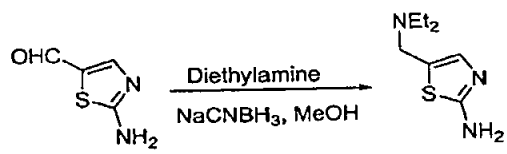


[0391] N-(6-(1-isopropylpiperidin-4-yloxy)pyridin-3-yl)-6-(6-amino-4-(trifluoromethyl)-pyridin-3-yl)-2-morpholinopyrimidin-4-amine was synthesized according to the general procedure for the Buchwald reaction in Example 2 by reacting 6-(1-isopropylpiperidin-4-yloxy)pyridin-3-amine (prepared as in Method 16) with 5-(6-chloro-2-morpholinopyrimidin-4-yl)-4-(trifluoromethyl)pyridin-2-amine. LC/MS (*m/z*): 559.2 (MH^+), R_t 1.92 minutes. ^1H NMR (DMSO): δ 10.27 (1H, bs, NH); 8.41 (1H, bs); 8.17 (1H, s); 7.98 and 7.94 (1H, 2 **b** doublets, *J*= 9.0 Hz, 2 conformers); 6.97 (1H, s); 6.90 and 6.84 (1H, 2 doublets, *J*= 9.0 Hz, 2 conformers); 6.23 (1H, bs); 5.25 and 5.15 (1H, 2 multiplets, 2 conformers); 3.66 (8H, bs); 3.44 (1H, m); 3.35 (2H, m); 3.10 (2H, m); 2.22 (2H, m); 2.03 (2H, m); 1.27 (6H, overlapping doublets because of conformers, app. triplet, *J*= 5.7 Hz).

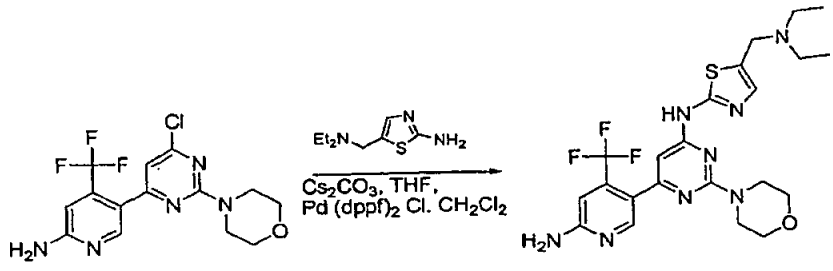
Example 12

Preparation of N-(5-((diethylamino)methyl)thiazol-2-yl)-6-(6-amino-4-(trifluoromethyl)pyridin-3-yl)-2-morpholinopyrimidin-4-amine

[0392] 5-((diethylamino)methyl)thiazol-2-amine



[0393] 2-Aminothiazole-5-carbaldehyde (1 eq) was added to a stirring solution of diethylamine (4 eq) in anhydrous MeOH at 0 °C. Sodium cyanoborohydride (1.5 eq) was then added in portions at 0 °C. The reaction mixture was stirred at 70 °C for 10 hours. After this time, the solution was quenched with H_2O and extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated to afford a viscous brown oil. LC/MS (*m/z*): 186.2 (MH^+), R_t 0.33 minutes.

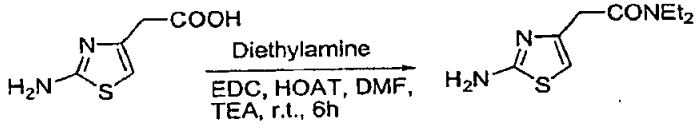


[0394] The title compound was synthesized according to the general procedure shown in Example 2. LC/MS (*m/z*): 509.2 (MH^+), R_t 1.98 minutes. ^1H NMR (DMSO): δ 11.0, (2H, bs, NH2), 8.17 (1H, s); 7.63 (1H, s); 7.08 (1H, bs), 6.40 (1H, s); 4.48 (2H, bd, *J*= 4.2 Hz); 3.80 (4H, m); 3.68 (4H, m); 3.03 (4H, bq, *J*= 6.9 Hz); 1.30 (6H, t, *J*= 6.9 Hz).

Example 13

Synthesis of 6-(6-amino-4-(trifluoromethyl)pyridin-3-yl)-N-(4-(2-(diethylamino)ethyl)thiazol-2-yl)-2-morpholinopyrimidin-4-amine

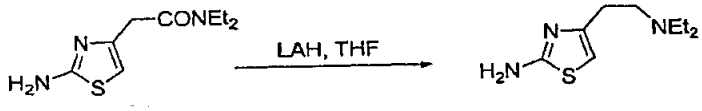
[0395] 2-(2-aminothiazol-4-yl)-N,N-diethylacetamide



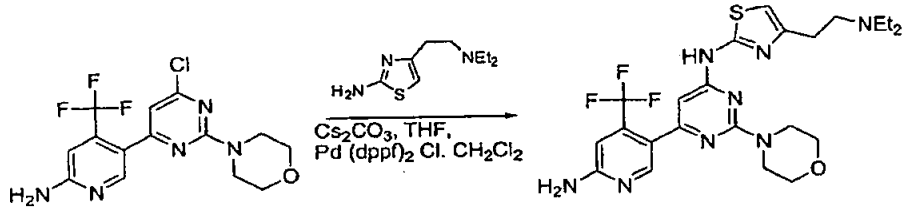
[0396] A mixture of 2-(2-aminothiazol-4-yl)acetic acid (1 eq), HOAT (1 eq), EDC (1.1 eq), TEA (1 eq) and $HNEt_2$ (1 eq) in DMA was stirred at room temperature for 6 hours. The reaction mixture was then quenched with H_2O and concentrated. The residue was dissolved in a stirred 4:1 mixture of EtOAc and $NaHCO_{3(sat.)}$. The two phases were separated and the organic solution was washed with brine, dried over Na_2SO_4 and concentrated to dryness. The resulting solid was washed twice with Et_2O and dried to yield the desired product as a white solid. LC/MS (*m/z*): 214.0 (MH^+), R_t 1.13 minutes.

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[0397] 4-(2-(diethylamino)ethyl)thiazol-2-amine



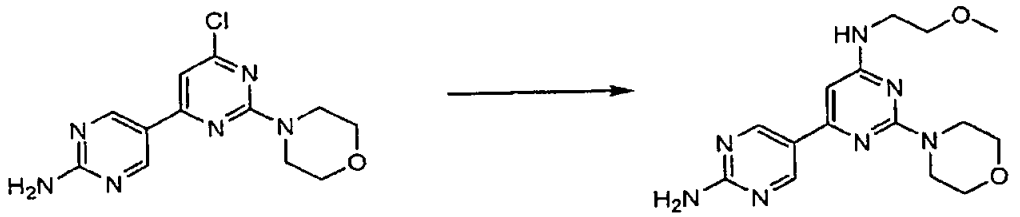
[0398] A suspension of 2-(2-aminothiazol-4-yl)-N,N-diethylacetamide (1 eq) in THF was added dropwise to a vigorously stirred suspension of LAH (1 eq) in THF at 0 °C. The mixture was stirred at room temperature for 2 hours. At this time, the resulting mixture was cooled to 0 °C and 1 part H_2O, followed by 1 part 10% NaOH and lastly 3 parts H_2O, were added dropwise. The mixture was stirred for 10 minutes, filtered, and the solid residue washed with THF. The filtrate was collected and concentrated to dryness. The resulting crude material was washed with Et_2O twice and dried to afford a viscous brown oil. LC/MS (*m/z*): 200.1, (MH^+), R_t 0.34 minutes.



[0399] The title compound was synthesized according to the general procedure shown in Example 2. LC/MS (*m/z*): 523.1 (MH^+), R_t 2.11 minutes. ^{1}H-NMR (DMSO): δ 8.15 (1H, s); 7.08 (1H, s); 6.96 (1H, s); 6.38 (1H, s); 3.78 (4H, m); 3.65 (4H, m); 3.31 (2H, m); 3.13 (4H, q, J = 7.2 Hz); 3.02 (2H, m); 1.20 (6H, t, J = 7.2 Hz).

Example 14

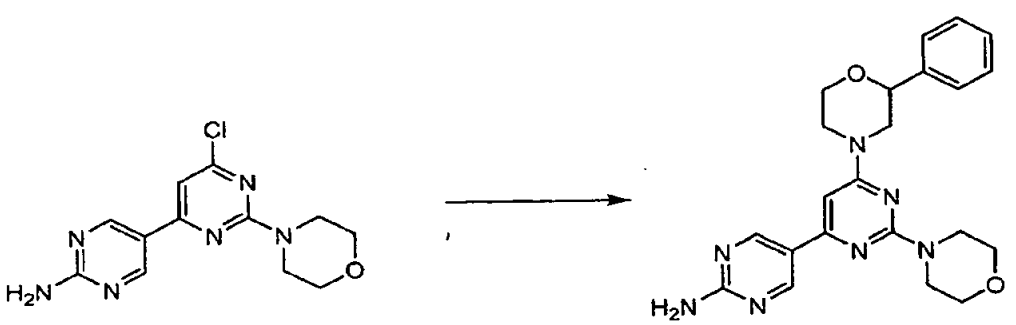
Preparation of N^6-(2-methoxyethyl)-2-morpholino-4,5'-bipyrimidine-2',6-diamine



[0400] An argon sparged mixture of 6-chloro-2-morpholino-4,5'-bipyrimidin-2'-amine (10 mg, 0.03 mmol) and 2-methoxyethanamine (0.018 mL, 0.20 mmol) in NMP (0.8 mL) contained in a sealed pressure vessel was heated in a microwave at 155 °C for 1000 seconds. The reaction mixture was filtered and purified by reverse phase preparative HPLC to give N^6-(2-methoxyethyl)-2-morpholino-4,5'-bipyrimidine-2',6-diamine as the TFA salt (4.0 mg, 30%). LC/MS (*m/z*): 332.2 (MH^+), R_t 1.44 minutes.

Example 15

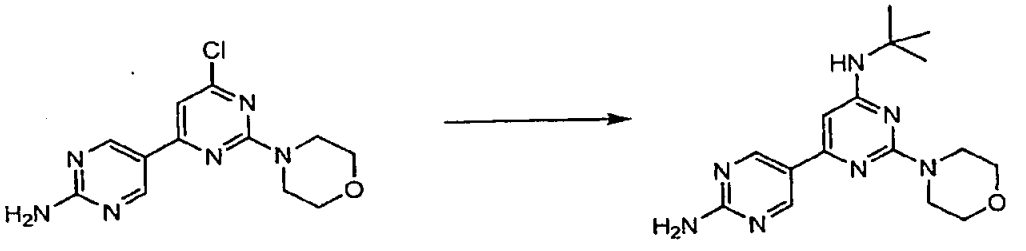
Preparation of 2-morpholino-6-(2-phenylmorpholino)-4,5'-bipyrimidin-2'-amine



[0401] An argon sparged mixture of 6-chloro-2-morpholino-4,5'-bipyrimidin-2'-amine (10 mg, 0.03 mmol), Cs_2CO_3 (27 mg, 0.09 mmol) and 2-phenylmorpholine (11 mg, 0.068 mmol) in NMP (0.5 mL) contained in a sealed pressure vessel, was heated in a microwave at 170 °C for 600 seconds. The reaction mixture was filtered and purified by reverse phase preparative HPLC to give 2-morpholino-6-(2-phenylmorpholino)-4,5'-bipyrimidin-2'-amine as the TFA salt (7.2 mg, 45%). LC/MS (*m/z*): 420.1 (MH^+), R_t 2.20 minutes.

Example 16

Preparation of N^6-tert-butyl-2-morpholino-4,5'-bipyrimidine-2',6-diamine

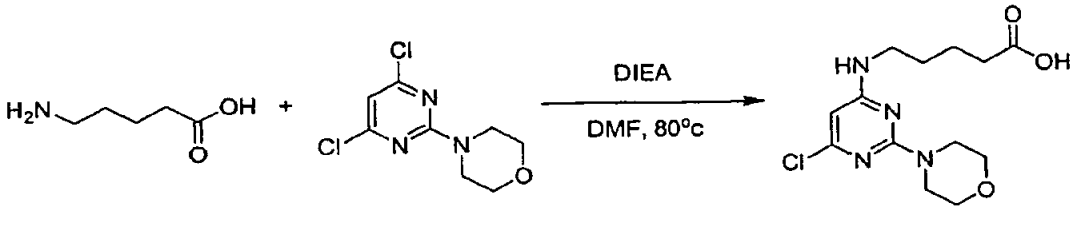


[0402] An argon sparged mixture of 6-chloro-2-morpholino-4,5'-bipyrimidin-2'-amine (10 mg, 0.03 mmol) and *tert*-butylamine (12.5 mg, 0.17 mmol) in NMP (0.5 mL) contained in a sealed pressure vessel, was heated in a microwave at 175 °C for 800 seconds. An additional amount of *tert*-butylamine (50 mg, 0.68 mmol) was added to the reaction. The reaction was again heated in a microwave at 175 °C for 800 seconds and again at 175 °C for 800 seconds until disappearance of the starting material. The crude mixture was filtered. The crude product was purified by reverse phase preparative HPLC to give N^6-*tert*-butyl-2-morpholino-4,5'-bipyrimidine-2',6-diamine as the TFA salt (0.9 mg, 7%). LC/MS (*m/z*): 330.2 (MH^+), R_t 1.96 minutes.

Example 17

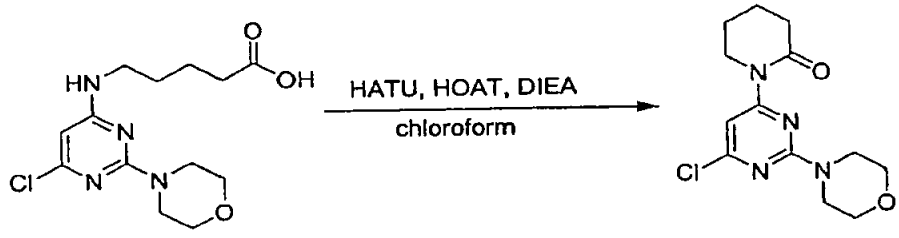
Preparation of 1-(2-(6-amino-4-(trifluoromethyl)pyridin-3-yl)-6-morpholino-pyrimidin-4-yl)piperidin-2-one

[0403] 5-(2-chloro-6-morpholinopyrimidin-4-ylamino)pentanoic acid



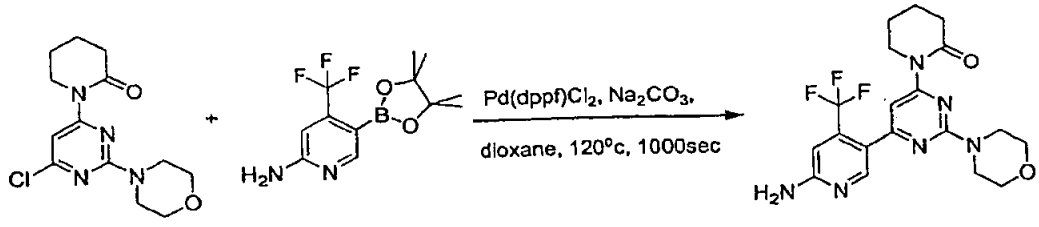
[0404] 5-Aminopentanoic acid (140 mg, 1.19 mmol), 4-(2,6-dichloropyrimidin-4-yl)morpholine (prepared as in Method 22; 234 mg, 1.0 mmol) and DIEA (0.530 mL, 3.0 mmol) were dissolved in N,N-dimethylformamide (6 mL). The reaction solution was stirred at 40 °C for 40 hours. The reaction was diluted with EtOAc (100 mL) and washed with 0.5 M HCl (40 mL), water (40 mL), brine (40 mL), dried with Na_2SO_4, filtered and evaporated to give a solid. The crude product was chromatographed on a silica gel column by eluting with 80% EtOAc in hexane to give 5-(2-chloro-6-morpholinopyrimidin-4-ylamino)pentanoic acid as a white solid (190 mg, 60%). LC/MS (*m/z*): 315.0 (MH^+), R_t 1.79 minutes.

[0405] 1-(2-chloro-6-morpholinopyrimidin-4-yl)piperidin-2-one



[0406] To a solution of HATU (304 mg, 0.8 mmol), HOAT (82 mg, 0.6 mmol) and DIEA (0.209 mL, 1.2 mmol) in chloroform (20 mL) under argon, a solution of 5-(2-chloro-6-morpholinopyrimidin-4-ylamino)pentanoic acid (190 mg, 0.6 mmol) in chloroform (10 mL) was slowly added. The reaction solution was stirred at room temperature for 5 hours. After the reaction was complete, the solution was evaporated to dryness to give a white solid which was chromatographed on a silica gel column by eluting with 40% EtOAc/hexane to give 1-(2-chloro-6-morpholinopyrimidin-4-yl)piperidin-2-one as a white solid (62 mg, 35%). LC/MS (*m/z*): 297.0 (MH^+), R_t 2.74 minutes.

[0407] 1-(2-(6-amino-4-(trifluoromethyl)pyridin-3-yl)-6-morpholinopyrimidin-4-yl)piperidin-2-one

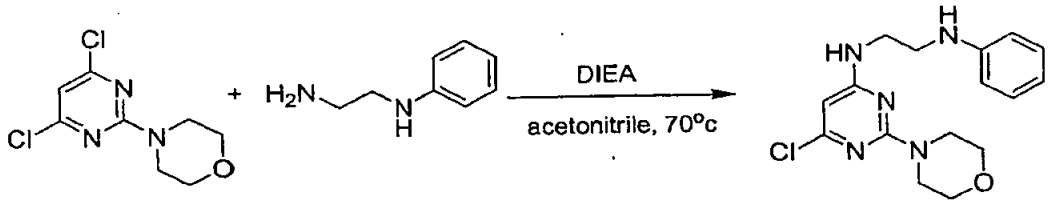


[0408] To a suspension of 1-(2-chloro-6-morpholinopyrimidin-4-yl)piperidin-2-one (16 mg, 0.05 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)pyridin-2-amine (prepared as in Method 4; 23 mg, 0.08 mmol) and dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium (II) dichloromethane adduct (8 mg, 0.009 mmol) in dioxane (1.1 mL), 2 M aqueous sodium carbonate solution (0.4 mL, 0.8 mmol) was added under argon. The reaction mixture was heated in a microwave at 120 °C for 1000 seconds. The crude product was partitioned between EtOAc (30 mL) and saturated sodium bicarbonate (10 mL). The organic layer was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by preparative reverse phase HPLC to give 1-(2-(6-amino-4-(trifluoromethyl)pyridin-3-yl)-6-morpholinopyrimidin-4-yl)piperidin-2-one as a yellow powder (8.8 mg, 42%). LC/MS (*m/z*): 423.0 (MH^+), R_t 2.25 minutes.

Example 18

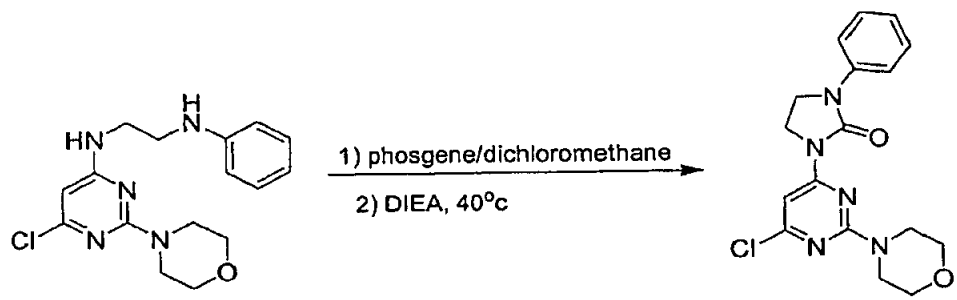
Preparation of 1-(6-(6-amino-4-(trifluoromethyl)pyridin-3-yl)-2-morpholinopyrimidin-4-yl)-3-phenylimidazolidin-2-one

[0409] N^1-(6-chloro-2-morpholinopyrimidin-4-yl)-N^2-phenylethane-1,2-diamine



[0410] To a solution of 4-(4,6-dichloropyrimidin-2-yl)morpholine (prepared as described in Method 22; 932 mg, 4.0 mmol) and DIEA (0.7 mL, 4.0 mmol) in ACN (40 mL), neat N^1-phenyl-ethane-1,2-diamine (0.523 mL, 4.0 mmol) was slowly added. The reaction mixture was stirred at 70-80 °C under nitrogen. After 20 hours, the reaction mixture was cooled down, and the solvent was removed under reduced pressure. The crude product was partitioned between EtOAc (120 mL) and 0.1 M $NaHCO_3$ (50 mL). The organic layer was washed with additional 0.1 M $NaHCO_3$ (2x50 mL), brine (50 mL), dried, filtered and concentrated to give N^1-(6-chloro-2-morpholinopyrimidin-4-yl)-N^2-phenylethane-1,2-diamine, as an off-white solid (1.29 g, 96%). LC/MS (*m/z*): 334.0 (MH^+), R_t 1.94 minutes.

[0411] 1-(6-chloro-2-morpholinopyrimidin-4-yl)-3-phenylimidazolidin-2-one

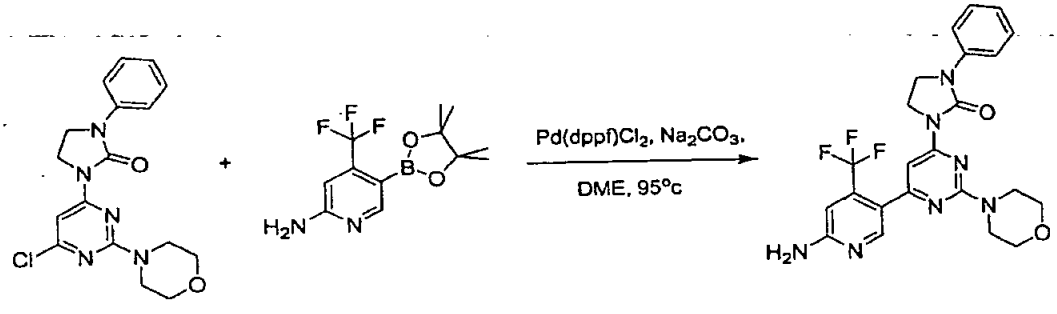


[0412] To a solution of N^1-(6-chloro-2-morpholinopyrimidin-4-yl)-N^2-phenylethane-1,2-diamine (100 mg, 0.3 mmol) in DCM (15 mL) at 0 °C under nitrogen, a solution of phosgene in toluene (1.89 M, 0.32 mL, 0.6 mmol) was slowly added. After 20 minutes, the reaction was allowed to warm to RT. After 18 hours, DIEA (0.42 mL,

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2.4 mmol) was added and the reaction solution was heated to 40-50 °C for 40 hours. The reaction mixture was evaporated under reduced pressure and the crude product was purified by silica gel chromatography eluting with 70% EtOAc /hexane to give 1-(6-chloro-2-morpholinopyrimidin-4-yl)-3-phenylimidazolidin-2-one as a white solid (94 mg, 87%). LC/MS (*m/z*): 360.1 (MH^+), R_t 3.41 minutes.

[0413] 1-(6-(6-amino-4-(trifluoromethyl)pyridin-3-yl)-2-morpholinopyrimidin-4-yl)-3-phenylimidazolidin-2-one



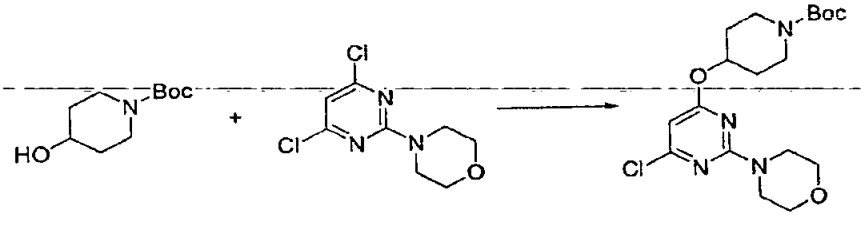
[0414] To a suspension of 1-(6-chloro-2-morpholinopyrimidin-4-yl)-3-phenylimidazolidin-2-one (18 mg, 0.05 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)pyridin-2-amine (prepared as described in Method 4; 18 mg, 0.06 mmol) and dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium (II) dichloromethane adduct (3.2 mg, 0.004 mmol) in DME (1.2 mL), 2 M aqueous sodium carbonate solution (0.4 mL, 0.8 mmol) was added under argon. The reaction mixture was stirred at 95 °C for 5 hours. The crude product was partitioned between EtOAc (30 mL) and saturated sodium bicarbonate (10 mL). The organic layer was separated, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by preparative HPLC to give 1-(6-(6-amino-4-(trifluoromethyl)pyridin-3-yl)-2-morpholinopyrimidin-4-yl)-3-phenylimidazolidin-2-one

as a pale yellow powder (8.4 mg, 35% overall yield). LC/MS (*m/z*): 448.1 (MH^+), R_t 3.29 minutes.

Example 19

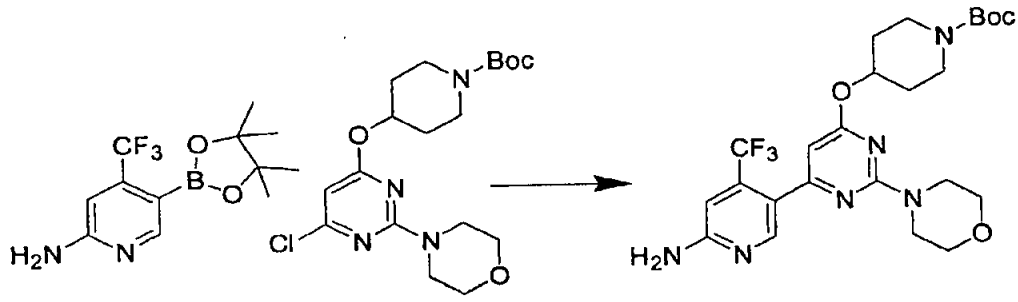
Preparation of 1-(4-(6-(6-amino-4-(trifluoromethyl)pyridin-3-yl)-2-morpholinopyrimidin-4-yloxy)piperidin-1-yl)ethanone

[0415] Step 1: Alkoxylation of 2-morpholino- 4,6-dichloropyrimidine



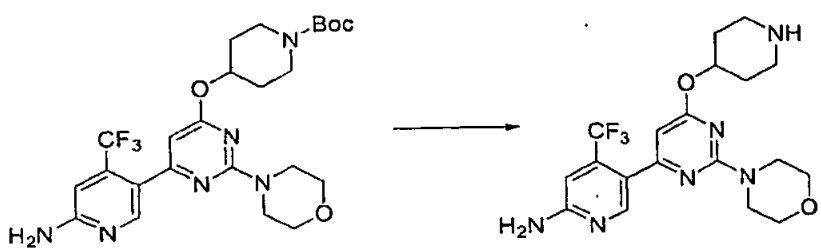
[0416] To a solution of N-Boc-4-hydroxy piperidine (2.58 g, 12.81 mmol) in tetrahydrofuran at 0 °C under argon, was added sodium hydride (60%, 512 mg, 12.81 mmol). After stirring for 20 minutes, a solution of 2-morpholino-4,6-dichloropyrimidine (2.0 g, 8.54 mmol) in tetrahydrofuran (20 mL) was added through a syringe. The solution was stirred for 14 hours as the ice bath warmed to room temperature. At this time, the reaction mixture was quenched with water (2 mL), and was partitioned between EtOAc (350 mL) and Na_2CO_3(sat.) (75 mL). The organic layer was separated, washed with brine (50 mL), dried over Na_2SO_4, filtered, concentrated and the residue was purified by SiO_2 chromatography (15-20% EtOAc in hexanes) to yield *tert*-butyl 4-(6-chloro-2-morpholinopyrimidin-4-yloxy)piperidine-1-carboxylate as a white solid (2.64 g, 77%). LCMS (*m/z*): 399.1 (MH^+). ^1H NMR ($CDCl_3$): δ 6.00 (s, 1H), 5.18 (m, 1H), 3.74 (s, 8H), 3.64-3.74 (m, 2H), 3.28-3.38 (m, 2H), 1.86-1.96 (m, 2H), 1.68-1.78 (m, 2H), 1.44 (s, 9H).

[0417] Step 2: Suzuki reaction of 2-morpholino-4-alkoxy-substituted-6-chloropyrimidine



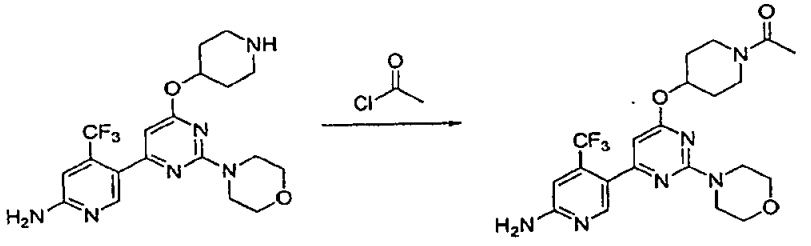
[0418] A mixture of *tert*-butyl 4-(6-chloro-2-morpholinopyrimidin-4-yloxy)piperidine-1-carboxylate (250 mg, 0.63 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)-4-(trifluoromethyl)pyridine-2-amine (prepared as in method 4, 325 mg, 1.13 mmol) and $Pd(dppf)Cl_2$-CH_2Cl_2 (25.6 mg, 0.031 mmol) in dimethoxyethane/2 M Na_2CO_3 (3:1, 8 mL) was heated under microwave irradiation for 15 minutes at 120 °C. The reaction mixture was partitioned between EtOAc (200 mL) and $Na_2CO_{3(sat.)}$ (50 mL), the organic layer was separated, washed with brine (50 mL), dried over Na_2SO_4, filtered, concentrated and purified by SiO_2 chromatography (50-75% EtOAc/hexanes) to yield the product as a white solid (207 mg, 63%). LCMS (*m/z*): 525.2 (MH^+).

[0419] Step 3: Hydrolysis of N-Boc protecting group



[0420] A mixture of tert-butyl 4-(6-(6-amino-4-(trifluoromethyl)pyridin-3-yl)-2-morpholinopyrimidin-4-yloxy)piperidine-1-carboxylate (649 mg, 1.24 mmol) and 4 M HCl/dioxane (15 mL, 60 mmol) was allowed to stand at room temperature for 14 hours. Upon removal of volatiles *in vacuo*, diethyl ether (50 mL) was added, the material was sonicated and concentrated yielding the bis HCl salt of the desired product as an off white solid. LCMS (*m/z*): 425.1 (MH^+).

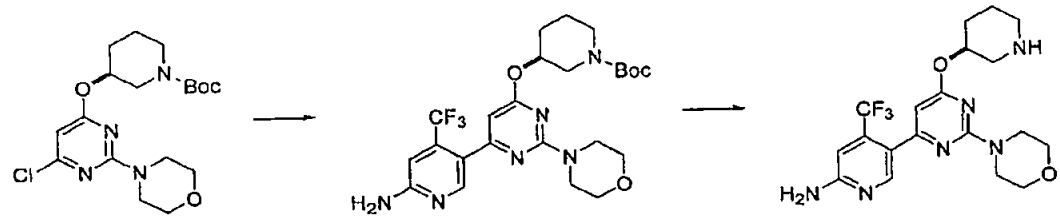
[0421] Step 4: Acylation



[0422] To a solution of 4-(trifluoromethyl)-5-(2-morpholino-6-(piperidin-4-yloxy)pyrimidin-4-yl)pyridin-2-amine in NMP, was added diisopropylethylamine (5 eq) and acetyl chloride (1.5 eq). The reaction mixture was stirred at room temperature for 2 h and then was purified directly by reverse-phase HPLC and lyophilized yielding the TFA salt of the product. Alternatively, after reverse phase HPLC the free base of the product could be isolated after extraction into EtOAc upon basifying, followed by drying over Na_2SO_4 and removal of volatiles *in vacuo*. LCMS (m/z): 467.1 (MH^+).

Example 20

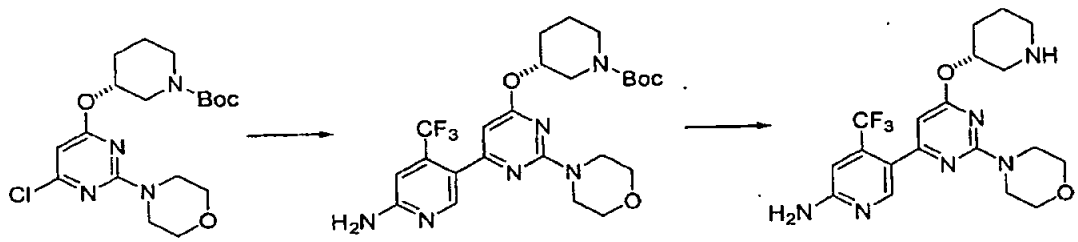
Preparation of 5-(6-((S)-piperidin-3-yloxy)-2-morpholinopyrimidin-4-yl)-4-(trifluoromethyl)pyridin-2-amine



[0423] (*S*)-*tert*-butyl 3-(6-chloro-2-morpholinopyrimidin-4-yloxy)piperidine-1-carboxylate was prepared as in Example 19, Step 1, for the alkoxylation of 2-morpholino-4,6-dichloropyrimidine (87%). LCMS (*m/z*): 399.1(MH^+). The Boc protected intermediate was prepared by Suzuki reaction as shown in Step 2 of Example 19 and was purified by SiO_2 chromatography (30-60% EtOAc/hexanes; 78%). LCMS (*m/z*): 526.0 (MH^+). The title compound was prepared by cleaving the N-Boc protecting group as shown in Step 3 of Example 19. LCMS (*m/z*): 425.1 (MH^+).

Example 21

Preparation of 5-(6-((R)-piperidin-3-yloxy)-2-morpholino pyrimidin-4-yl)-4-(trifluoromethyl)pyridin-2-amine

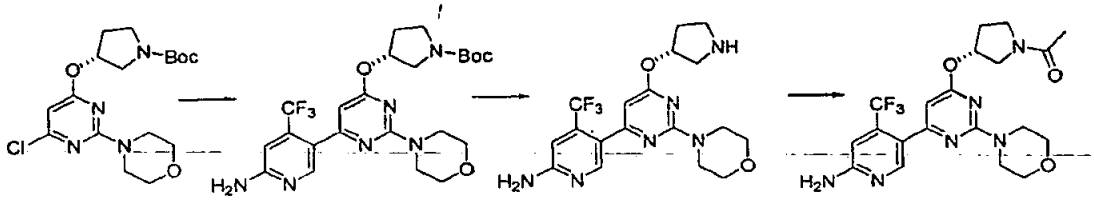


[0424] (*R*)-*tert*-butyl 3-(6-chloro-2-morpholinopyrimidin-4-yloxy)piperidine-1-carboxylate was prepared as in Example 19, Step 1, for the alkoxylation of 2-morpholino-4,6-dichloropyrimidine (82%). LCMS (*m/z*): 399.1 (MH^+). The Boc protected intermediate was prepared by Suzuki reaction as shown in Step 2 of Example 19 and was purified by silica gel chromatography (30-60% EtOAc/hexanes, 54%). LCMS (*m/z*):

526.0 (MH^+). The title compound was prepared by cleaving the N-Boc protecting group as shown in Step 3 of Example 19. LCMS (*m/z*): 425.1 (MH^+).

Example 22

Preparation of 1-((R)-3-(6-(6-amino-4-(trifluoromethyl)pyridin-3-yl)-2-morpholinopyrimidin-4-yloxy)pyrrolidin-1-yl)ethanone

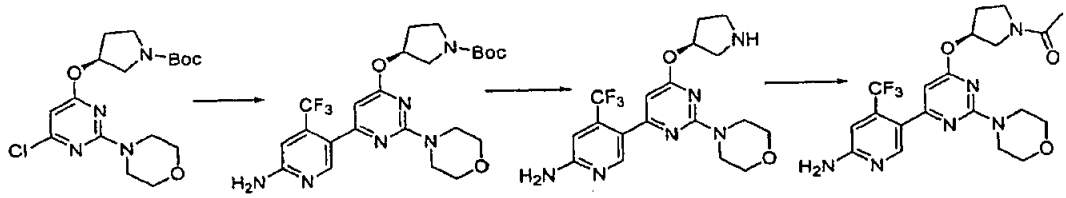


[0425] (*R*)-*tert*-butyl 3-(6-chloro-2-morpholinopyrimidin-4-yloxy)pyrrolidine-1-carboxylate was prepared as in Example 19, Step 1, for the alkoxylation of 2-morpholino-4,6-dichloropyrimidine (41%). LCMS (*m/z*): 385.0 (MH^+).

[0426] The Boc protected intermediate was prepared by Suzuki reaction as shown in Step 2 of Example 19 and was purified by reverse phase HPLC and isolated as free base after extraction into EtOAc upon basifying (71%). LCMS (*m/z*): 511.0 (MH^+). Cleavage of the N-Boc protecting group was performed as shown in Step 3 of Example 19. LCMS (*m/z*): 411.0 (MH^+). The title compound was prepared as in Step 4 of Example 19. LCMS (*m/z*): 453.1 (MH^+), R_t 2.18.

Example 23

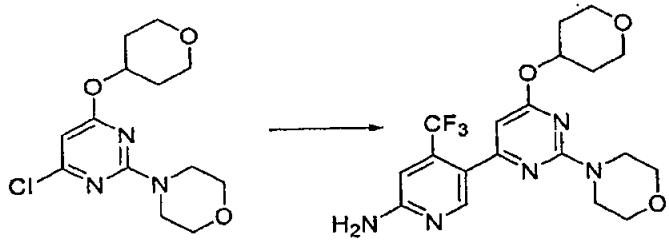
Preparation of 1-((S)-3-(6-(6-amino-4-(trifluoromethyl)pyridin-3-yl)-2-morpholinopyrimidin-4-yloxy)pyrrolidin-1-yl)ethanone



[0427] (*S*)-tert-butyl 3-(6-chloro-2-morpholinopyrimidin-4-yloxy)pyrrolidine-1-carboxylate was prepared according to Example 19, Step 1, for the alkoxylation of 2-morpholino-4,6-dichloropyrimidine (99%). LCMS (*m/z*): 385.0 (MH^+). The Boc protected intermediate was prepared by Suzuki reaction as shown in Step 2 of Example 19, purified by reverse phase HPLC and isolated as free base after extraction into EtOAc upon basifying (72%). LCMS (*m/z*): 511.0 (MH^+). The N-Boc protecting group was cleaved as shown in Step 3 of Example 19. LCMS (*m/z*): 411.0 (MH^+). The title compound was prepared as in step 4 of Example 19. LCMS (*m/z*): 453.1 (MH^+), R_t 2.18.

Example 24

Preparation of 4-(trifluoromethyl)-5-(2-morpholino-6-(tetrahydro-2H-pyran-4-yloxy)pyrimidin-4-yl)pyridin-2-amine



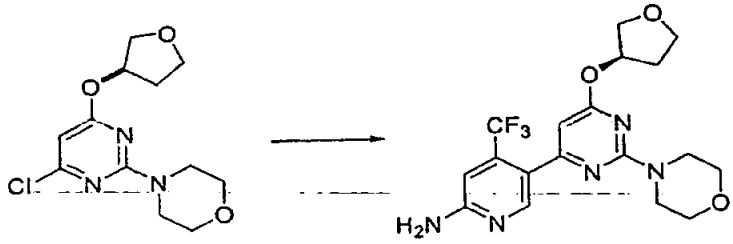
[0428] 4-(4-chloro-6-(tetrahydro-2H-pyran-4-yloxy)pyrimidin-2-yl)morpholine was prepared according to Example 19, Step 1, for the alkoxylation of 2-morpholino-4,6-dichloropyrimidine with 4-hydroxytetrahydropyran (80%). LCMS (*m/z*): 300.1 (MH^+).

120

The title compound was prepared by Suzuki reaction as shown in Step 2 of Example 19. LC/MS (*m/z*): 426.1 (MH+), R_t 2.26 minutes.

Example 25

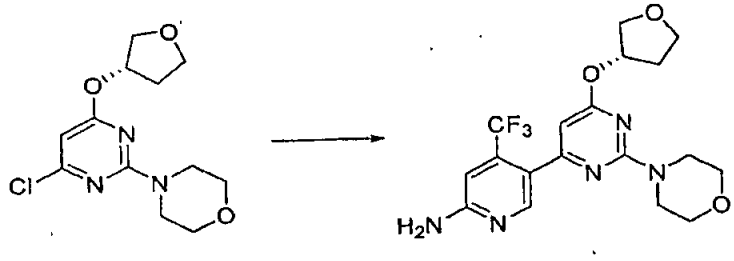
Preparation 5-(6-((R)-tetrahydrofuran-3-yloxy)-2-morpholino pyrimidin-4-yl)-4-(trifluoromethyl)pyridin-2-amine



[0429] (R)-4-(4-chloro-6-(tetrahydrofuran-3-yloxy)pyrimidin-2-yl)morpholine was prepared according to Example 19, Step 1, for the alkoxylation of 2-morpholino-4,6-dichloropyrimidine with (R)-3-hydroxytetrahydrofuran (81%). LCMS (*m/z*): 286.1 (MH^+). The title compound was prepared by Suzuki reaction as shown in Step 2 of Example 19. LC/MS (*m/z*): 412.1 (MH^+).

Example 26

Preparation of 5-(6-((S)-tetrahydrofuran-3-yloxy)-2-morpholino pyrimidin-4-yl)-4-(trifluoromethyl)pyridin-2-amine

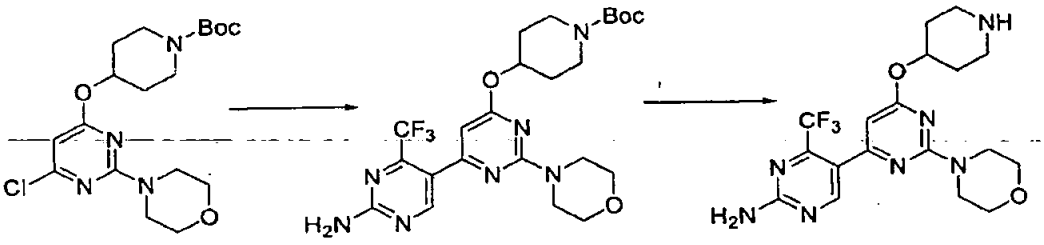


[0430] (S)-4-(4-chloro-6-(tetrahydrofuran-3-yloxy)pyrimidin-2-yl)morpholine was prepared according to Example 19, Step 1, for alkoxylation of 2-morpholino-4,6-

dichloropyrimidine with (S)-3-hydroxytetrahydrofuran (85%). LCMS (*m/z*): 286.1 (MH^+). The title compound was prepared by Suzuki reaction as shown in Step 2 of Example 19. LC/MS (*m/z*): 412.1 (MH^+).

Example 27

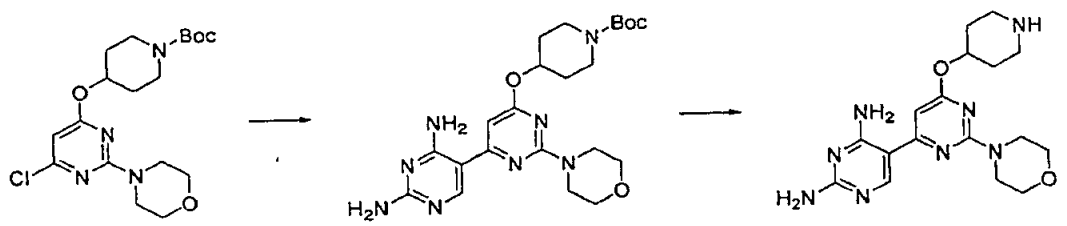
Preparation of 4-(trifluoromethyl)-5-(2-morpholino-6-(piperidin-4-yloxy)pyrimidin-4-yl)pyrimidin-2-amine



[0431] *tert*-butyl 4-(6-(2-amino-4-(trifluoromethyl)pyrimidin-5-yl)-2-morpholinopyrimidin-4-yloxy)piperidine-1-carboxylate was prepared by Suzuki reaction of tert-butyl 4-(6-chloro-2-morpholinopyrimidin-4-yloxy)piperidine-1-carboxylate, as shown in Step 2 of Example 19, with 5-(4,4,5,5-tetramethyl(1,3,2-dioxaborolan-2-yl))-4-(trifluoromethyl)pyrimidine-2-ylamine (prepared as in Method 5). The crude product was purified by silica gel chromatography (30-50% EtOAc/hexanes) (63%). LCMS (*m/z*): 526.0 (MH^+). The title compound was prepared by cleaving the N-Boc protecting group as shown in Step 3 of Example 19. LCMS (*m/z*): 426.0 (MH^+).

Example 28

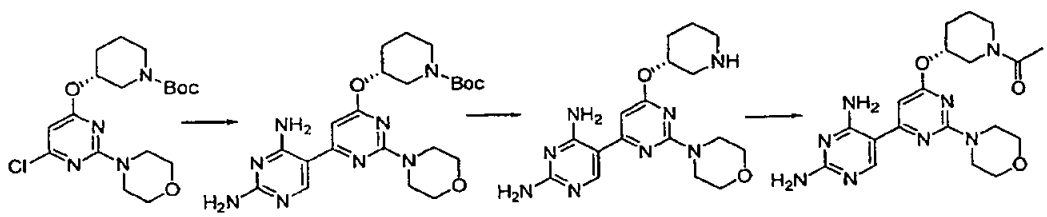
Preparation of 5-(2-morpholino-6-(piperidin-4-yloxy)pyrimidin-4-yl)pyrimidine-2,4-diamine



[0432] *tert*-butyl 4-(6-(2,4-diaminopyrimidin-5-yl)-2-morpholinopyrimidin-4-yloxy)piperidine-1-carboxylate was prepared by Suzuki reaction tert-butyl 4-(6-chloro-2-morpholinopyrimidin-4-yloxy)piperidine-1-carboxylate, as shown in Step 2 of Example 19, with 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine-2,4-diamine (prepared as in Method 7). The crude product was purified by reverse phase HPLC and isolated as the free base after extraction into EtOAc upon basifying (70%). LCMS (*m/z*): 473.1 (MH^+). The title compound was prepared by cleaving the N-Boc protecting group as shown in Step 3 of Example 19. LCMS (*m/z*): 373.0 (MH^+).

Example 29

Preparation of 1-((R)-3-(6-(2,4-diaminopyrimidin-5-yl)-2-morpholinopyrimidin-4-yloxy)piperidin-1-yl)ethanone

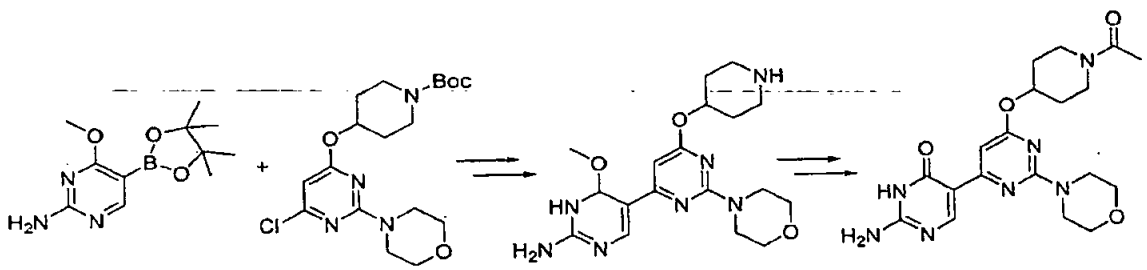


[0433] (R)-*tert*-butyl 3-(6-(2,4-diaminopyrimidin-5-yl)-2-morpholinopyrimidin-4-yloxy)piperidine-1-carboxylate was prepared by Suzuki reaction of 4-(6-chloro-2-morpholinopyrimidin-4-yloxy)piperidine-1-carboxylate, as shown in Step 2 of Example 19, with 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine-2,4-diamine. The crude product was purified by reverse phase HPLC and isolated as the free

base after extraction into EtOAc upon basifying (77%). LCMS (*m/z*): 473.1 (MH^+). The N-Boc protecting group was cleaved as shown in Step 3 of Example 19. LCMS (*m/z*): 373.0 (MH^+). The title compound was synthesized as shown in step 4 of Example 19. LCMS (*m/z*): 460.1 (MH^+), R_t 2.51.

Example 30

Preparation of 2-amino-5-(2-morpholino-6-(N-acyl-piperidin-4-yloxy)pyrimidin-4-yl)pyrimidin-4(3H)-one

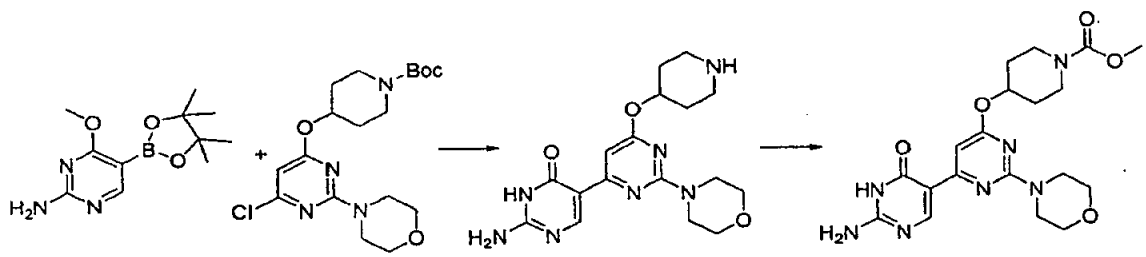


[0434] A mixture of tert-butyl 4-(6-chloro-2-morpholinopyrimidin-4-yloxy)piperidine-1-carboxylate (500 mg, 1.26 mmol), 4-methoxy-2-aminopyrimidyl boronate ester (prepared as in Method 8, 630 mg, 2.51 mmol) and $Pd(dppf)Cl_2$-CH_2Cl_2 (51 mg, 0.063 mmol) in dimethoxyethane and 2 M Na_2CO_3 (3:1, 12 mL) was heated under microwave irradiation for 15 minutes at 120 °C. The reaction mixture was partitioned between EtOAc (200 mL) and $Na_2CO_{3(sat.)}$ (50 mL), the organic layer was separated and washed with brine (50 mL). The combined aqueous layers were extracted further with EtOAc (2x100 mL), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. To this material was added 4 M HCl/dioxane (20 mL) to remove the Boc group. After standing for 12 hours, the volatiles were removed *in vacuo*, and the residue was partitioned between CH_2Cl_2 (200 mL) and 1N NaOH (50 mL). Upon separating, the aqueous layer was extracted further with CH_2Cl_2 (200 mL) and then $CHCl_3$ (2x150 mL). The combined organic layers were concentrated yielding 1,6-

dihydro-6-methoxy-5-(2-morpholino-6-(piperidin-4-yloxy)pyrimidin-4-yl)pyrimidin-2-amine (464 mg). The crude compound and morpholine (0.9 mL, 10.45 mmol) in NMP (10 mL) were heated under microwave irradiation for 15 minutes at 200 °C to convert the methoxy pyrimidine to the pyrimidone. Additional morpholine (0.9 mL, 10.45 mmol) was added and the solution was heated under microwave irradiation for 15 minutes and than 10 minutes at 200 °C. Upon cooling the material was directly purified by reverse-phase HPLC. After lyophilization, the bis TFA salt of the 2-amino-5-(2-morpholino-6-(piperidin-4-yloxy)pyrimidin-4-yl)pyrimidin-4(3H)-one was isolated as an off-white solid (325 mg, 45%). LCMS (*m/z*): 374.1 (MH^+). The title compound was prepared by acylation of the secondary amino group as shown in Example 19, step 4. LCMS (*m/z*): 416.0 (MH^+), R_t 1.67.

Example 31

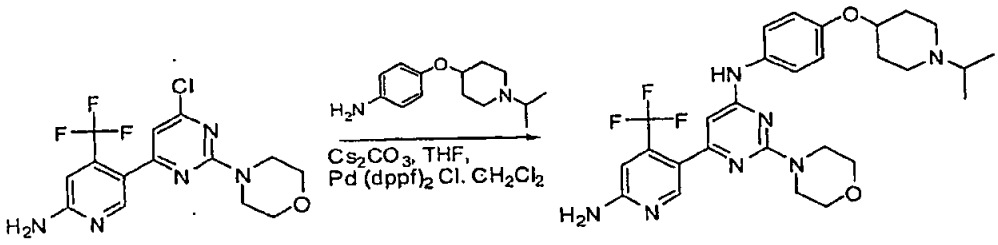
Preparation of 2-amino-5-(2-morpholino-6-(N-methoxycarbonyl-piperidin-4-yloxy)pyrimidin-4-yl)pyrimidin-4(3H)-one



[0435] The title compound was prepared as in Example 30, except utilizing methylchloroformate instead of acetyl chloride in the last step. LCMS (*m/z*): 432.0 (MH^+), R_t 2.05.

Example 32

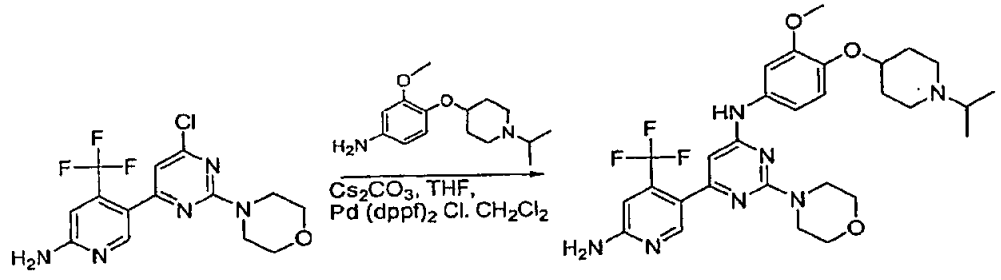
Preparation of 6-[6-amino-4-(trifluoromethyl)pyridin-3-yl]-N-[4-(1-isopropylpiperidin-4-yloxy)phenyl]-2-morpholinopyrimidin-4-amine



[0436] In a glass pressure vessel, $Pd(OAc)_2$ (5.0 mg, 0.022 mmol), BINAP (17.0 mg, 0.028 mmol), cesium carbonate (72.0 mg, 0.22 mmol) and THF (2.0 mL) were mixed and stirred at room temperature for 1-3 minutes. To the resulting mixture was added 5-(6-chloro-2-morpholin-4-yl-pyrimidin-4-yl)-pyridin-2-ylamine (40.0 mg, 0.11 mmol) followed by 4-(1-isopropylpiperidin-4-yloxy) aniline (37.0 mg, 0.16 mmol). The glass pressure vessel was sealed, stirred, and heated in microwave under irradiation at 110 °C for 10 minutes. The reaction mixture was filtered and concentrated under reduced pressure. The product was purified by preparative reverse phase HPLC to give 6-[6-amino-4-(trifluoromethyl)pyridin-3-yl]-N-[4-(1-isopropylpiperidin-4-yloxy)phenyl]-2-morpholinopyrimidin-4-amine (3.0 mg, 5%). LC/MS (*m/z*): 558.3(MH^+), R_t 1.90 minutes.

Example 33

Preparation of 6-(6-amino-4-(trifluoromethyl)pyridin-3-yl)-N-(4-(1-isopropylpiperidin-4-yloxy)-3-methoxyphenyl)-2-morpholinopyrimidin-4-amine

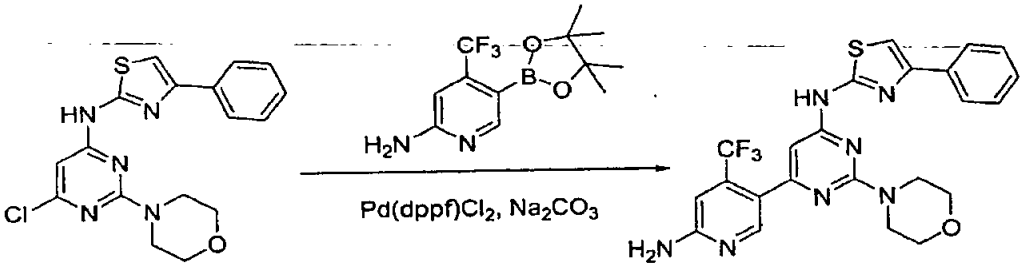


[0437] In a glass pressure vessel, $Pd(OAc)_2$ (5.0 mg, 0.02 mmol), BINAP (17.0 mg, 0.028 mmol), cesium carbonate (72.0 mg, 0.22 mmol) and THF (2.0 mL) were mixed and stirred at room temperature for 1-3 minutes. To the resulting mixture was added 5-(6-chloro-2-morpholin-4-yl-pyrimidin-4-yl)-pyridin-2-ylamine (40.0 mg, 0.11 mmol) followed by 4-(1-isopropylpiperidin-4-yloxy)-3-methoxyaniline (46.6 mg,

0.16 mmol). The glass pressure vessel was sealed, stirred, and heated in microwave under irradiation at 120 °C for 10 minutes. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by preparative reverse phase HPLC to give 6-(6-amino-4-(trifluoromethyl)pyridin-3-yl)-N-(4-(1-isopropylpiperidin-4-yloxy)-3-methoxyphenyl)-2-morpholinopyrimidin-4-amine (6.6 mg, 10%). LC/MS (*m/z*): 588.3(MH^+), R_t 1.92 minutes.

Example 34

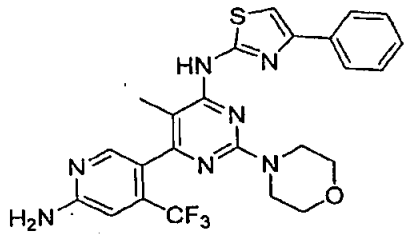
Synthesis of N-(6-(6-amino-4-(trifluoromethyl)pyridin-3-yl)-2-morpholinopyrimidin-4-yl)-4-phenylthiazol-2-amine



[0438] A solution of *N*-(6-chloro-2-morpholinopyrimidin-4-yl)-4-phenylthiazol-2-amine (15 mg, 0.040 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)pyridin-2-amine (23 mg, 0.080 mmol) and 1,1'-bis(diphenylphosphino)ferrocene palladium (II) chloride (6.6 mg, 0.0080 mmol) in 0.5 mL of 1,4-dioxane and 0.05 mL of 2 M *aq.* sodium carbonate was heated in the microwave at 120 °C for 600 seconds. The crude product was purified by reverse phase prep HPLC to give N-(6-(6-amino-4-(trifluoromethyl)pyridin-3-yl)-2-morpholinopyrimidin-4-yl)-4-phenylthiazol-2-amine. LC/MS (*m/z*): 500 (MH^+), R_t 2.46 minutes.

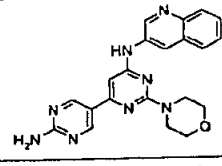
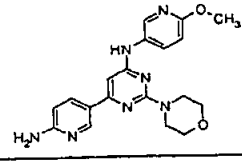
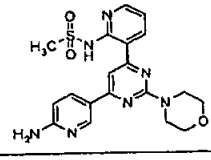
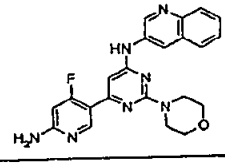
Examples 35

Preparation of N-(6-(6-amino-4-(trifluoromethyl)pyridin-3-yl)-5-methyl-2-morpholinopyrimidin-4-yl)-4-phenylthiazol-2-amine

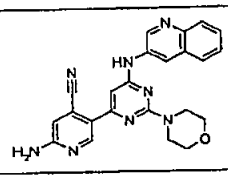
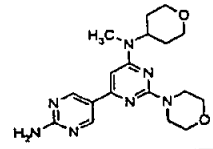
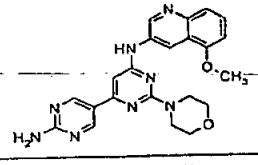
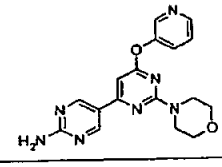
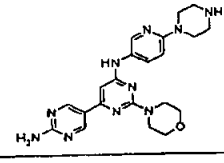
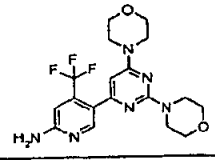
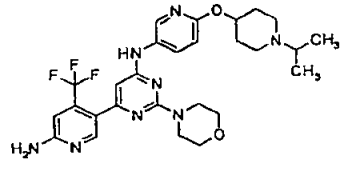
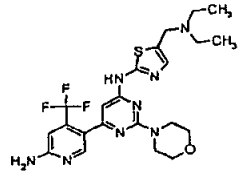


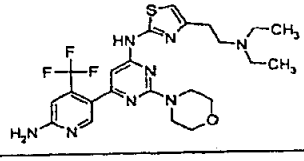
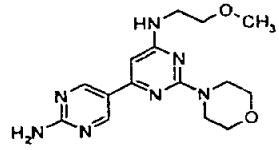
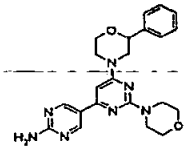
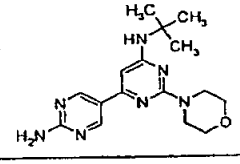
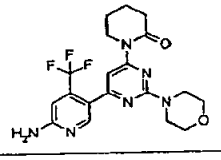
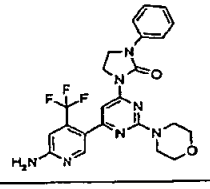
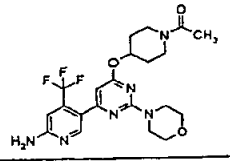
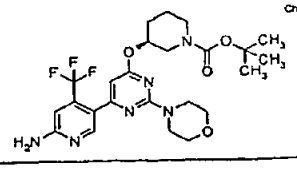
[0439] N-(6-(6-amino-4-(trifluoromethyl)pyridin-3-yl)-5-methyl-2-morpholinopyrimidin-4-yl)-4-phenylthiazol-2-amine was prepared according to Example 35. LC/MS (*m/z*): 514 (MH^+), R_t 2.62 minutes.

TABLE 1

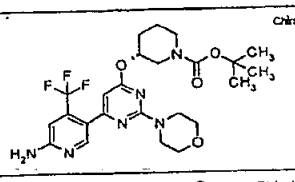
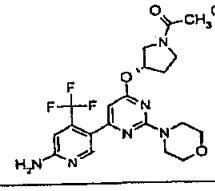
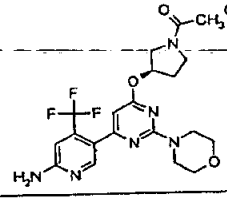
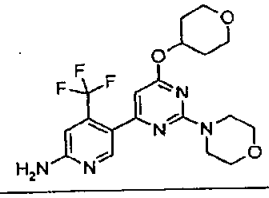
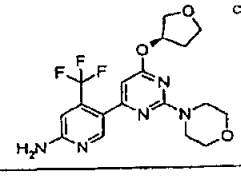
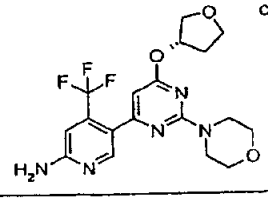
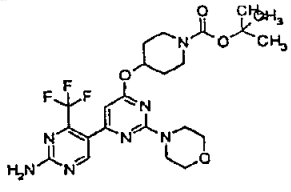
Compound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Proliferation, EC_{50}
1		401.4, 2.00		++++	++++	++++
2		380.1, 1.82	9.67 L	++++	N/D	N/D
3		428.2, 2.09	11.50 L	++++	++++	++++
4		418.0	1.99	++++	++++	++++

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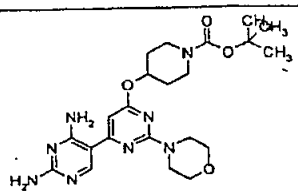
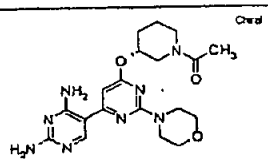
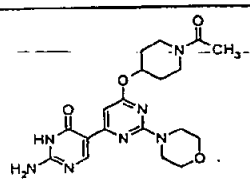
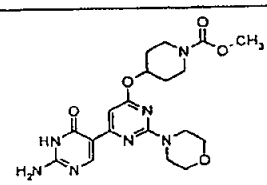
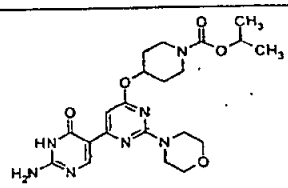
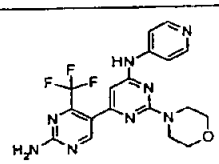
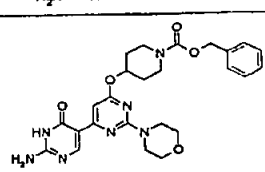
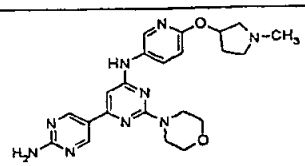
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
5		425.0	11.16 L	++++	+++	++++
6		372.2	8.74 L	++++	N/D	+++
7		431.2, 2.03	11.11 L	++++	++++	++++
8		352.1, 1.83	7.96 L	++++	++++	++++
9		435.2, 1.52	6.45 L	++++	++++	++++
10		411.3, 1.88		++++	++++	++++
11		559.2, 1.92		++++	++++	++++
12		509.0, 1.72	1.98	++++	++++	+++

Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
13		523.1, 2.02	2.11	++++	++++	+++
14		332.2	7.50 L	++++	N/D	+++
15		420.1	13.14 L	++++	++++	++++
16		330.2	10.83 L	++++	N/D	+++
17		423.1	2.57	++++	N/D	+++
18		486	3.23	++++	N/D	+++
19		467.1, 2.36		++++	N/D	+++
20		525.0, 3.42		++++	N/D	+++

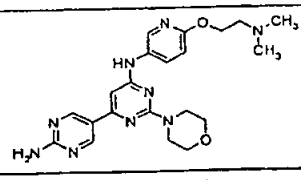
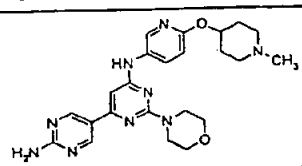
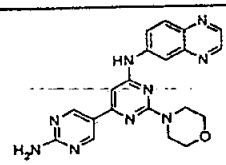
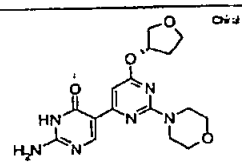
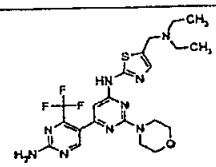
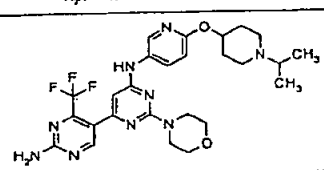
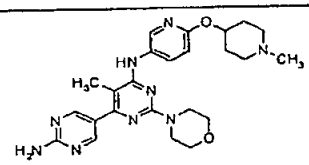
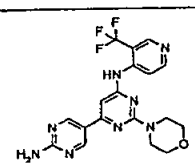
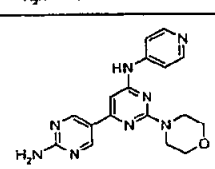
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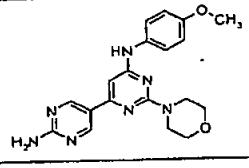
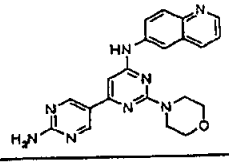
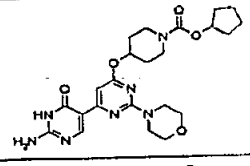
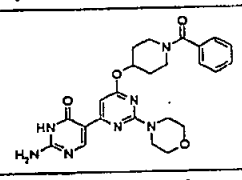
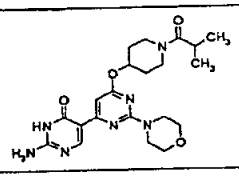
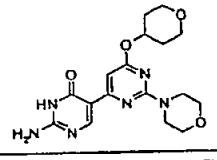
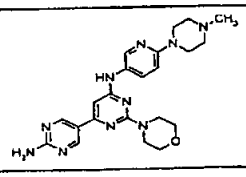
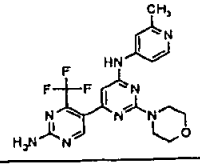
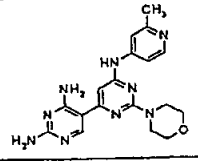
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
21		525.0, 3.42		++++	N/D	N/D
22		453.1, 2.18		++++	N/D	+++
23		453.1, 2.18		++++	N/D	N/D
24		426.1, 2.26	2.54	++++	++++	++++
25		412.1, 2.47		++++	++++	+++
26		412.1, 2.19	2.47, (12.34)	++++	N/D	+++
27		526.0, 4.30		++++	++++	++++

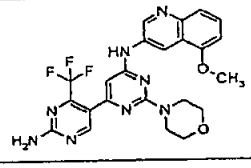
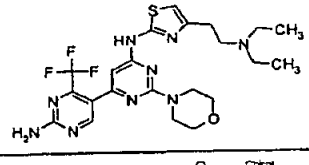
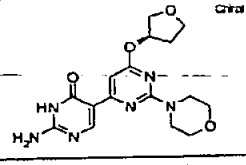
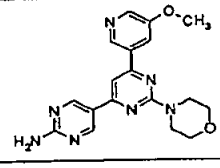
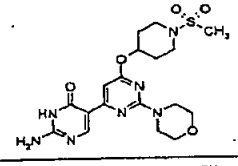
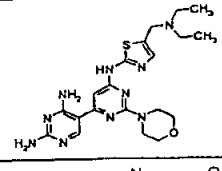
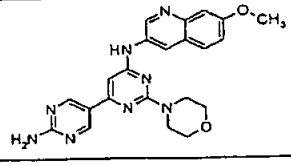
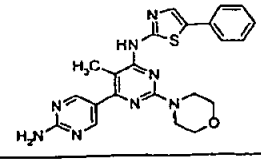
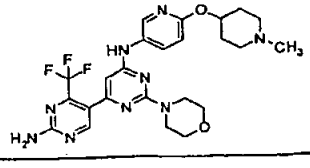
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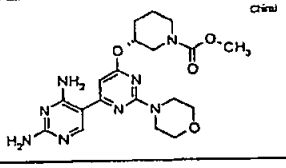
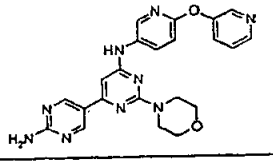
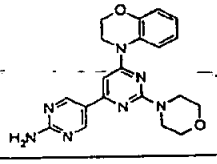
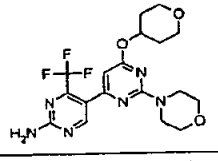
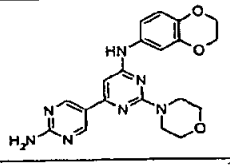
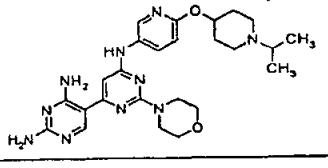
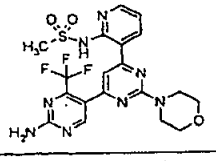
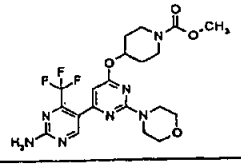
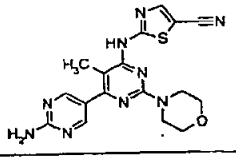
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
28		473.1, 3.02		++++	++++	++++
29		415.1, 2.06		++++	++++	+++
30		416.0, 1.67		++++	++++	++++
31		432.0, 2.05		++++	++++	++++
32		460.1, 2.51		++++	++++	++++
33		419.0, 2.17		++++	++++	++++
34		508.0, 2.17	2.96, (14.82)	++++	++++	++++
35		450.2, 1.61		++++	++++	++++

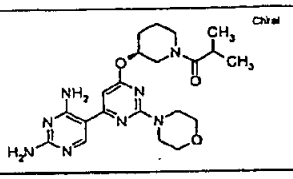
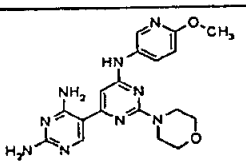
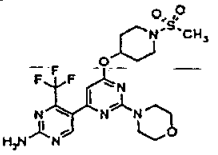
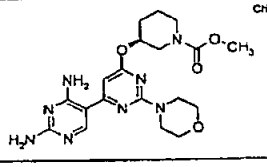
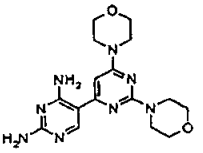
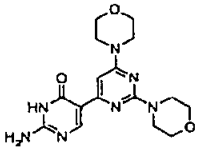
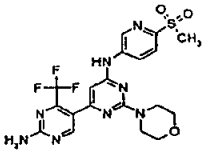
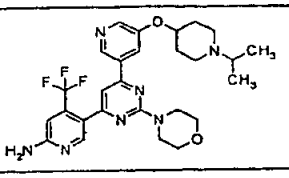
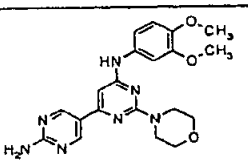
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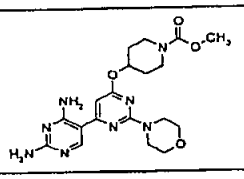
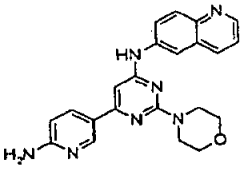
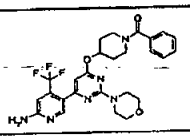
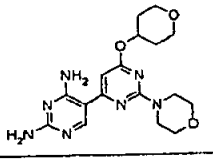
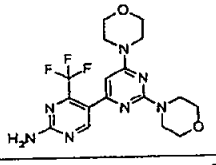
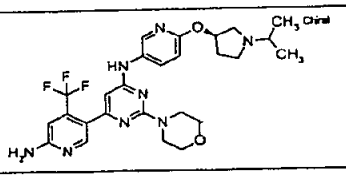
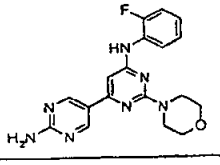
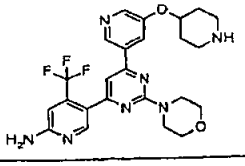
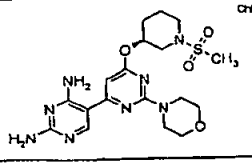
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
36		438.1, 1.61		++++	++++	++++
37		464.4, 1.53		++++	++++	++++
38		402.2, 1.88 min		++++	++++	++++
39		361.0, 1.44	1.73, (8.13)	++++	++++	++++
40		510.1, 1.98	2.18	++++	++++	++++
41		560.2, 1.93	1.98	++++	++++	++++
42		478.4, 1.59		++++	++++	++++
43		419.1	9.23 L	++++	++++	++++
44		351.1	8.23 L	++++	++++	++++

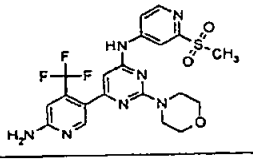
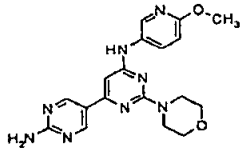
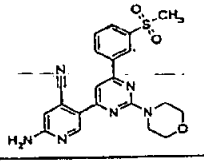
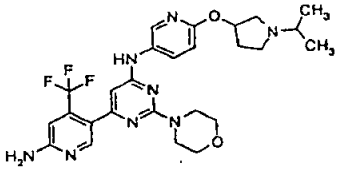
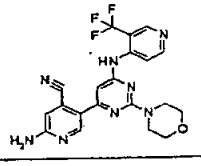
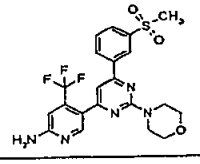
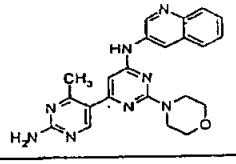
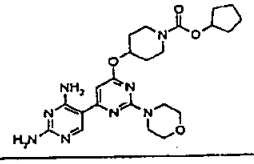
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
45		375.0, 2.11	2.41	++++	++++	+++
46		401.1, 1.70	1.70	++++	++++	++++
47		486.1, 2.11	2.76, (14.49)	++++	++++	++++
48		478.0, 1.79	2.23, (11.48)	++++	++++	++++
49		444.1, 1.70	2.06, (10.23)	++++	++++	++++
50		375.1, 1.80	1.82, (8.95)	++++	++++	++++
51		449.1, 1.51	6.56 L	++++	++++	++++
52		433.0, 2.30		++++	++++	++++
53		380.1, 1.65		++++	++++	++++

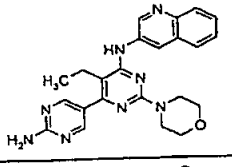
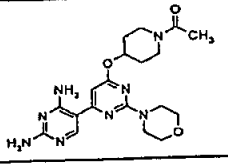
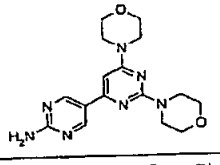
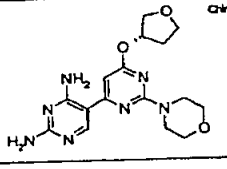
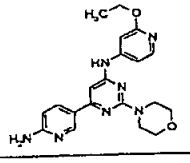
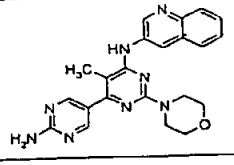
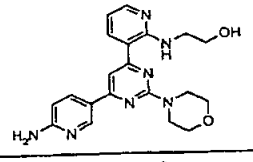
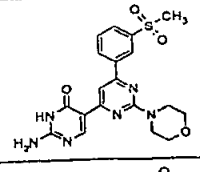
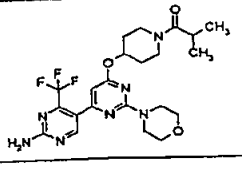
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
54		498.9, 2.55		++++	++++	++++
55		524.1, 2.10	2.37	++++	++++	++++
56		361.0, 1.45	1.64, (8.18)	++++	++++	++++
57		366.1, 1.85	1.95	++++	++++	++++
58		452.0, 1.65		++++	++++	++++
59		457.2 ,1.72	1.71	++++	++++	++++
60		431.2, 1.95	10.48 L	++++	++++	++++
61		447.4, 2.85		++++	++++	++++
62		532.0, 1.85		++++	++++	++++

Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
63		431.2, 2.43		++++	++++	++++
64		444.4, 1.66		++++	++++	++++
65		392.3, 2.55		++++	++++	++++
66		427.1, 3.21		++++	++++	+++
67		408.1, 1.98	2.16	++++	++++	++++
68		507.2, 1.79	1.78	++++	++++	++++
69		496.9, 2.40	3.39, (16.57)	++++	++++	++++
70		484.0, 3.36		++++	++++	++++
71		396.3, 2.32		++++	++++	++++

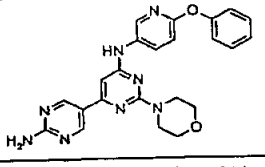
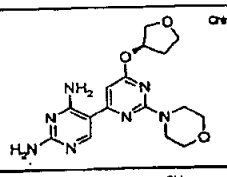
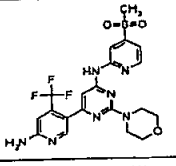
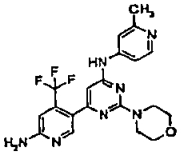
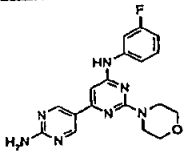
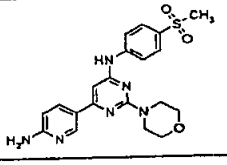
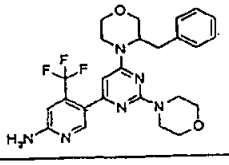
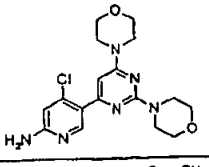
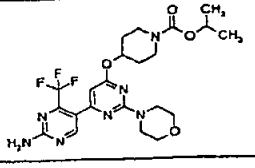
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Proliferation, EC_{50}
72		443.2, 2.45		++++	++++	+++
73		396.1, 1.58	1.89, (9.53)	++++	++++	+++
74		504.0, 3.19		++++	++++	++++
75		431.2, 2.38		++++	++++	+++
76		359.1, 1.42		++++	++++	+++
77		360.0, 1.47	1.79, (8.61)	++++	++++	++++
78		496.9, 2.42		++++	++++	++++
79		544.2, 1.97	2.04	++++	++++	+++
80		410.1, 1.91	10.36 L	++++	++++	++++

Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
81		431.0, 2.45		++++	++++	++++
82		400.0, 1.74	1.76	++++	++++	++++
83		529.2, 2.98		++++	++++	+++
84		374.1, 2.13		++++	++++	++++
85		412.0, 2.03		++++	++++	++++
86		545.6, 1.78		++++	++++	++++
87		368.1, 2.05	2.26	++++	++++	+++
88		502.1, 1.89	1.95	++++	++++	+++
89		451.1, 2.30		++++	++++	++++

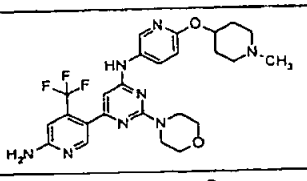
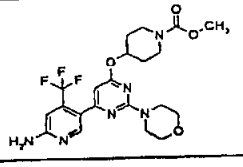
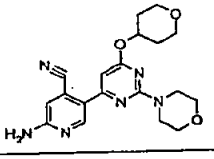
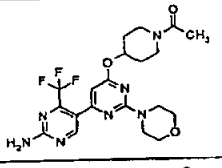
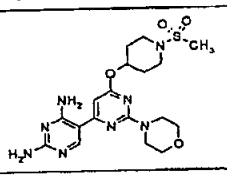
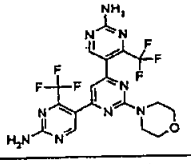
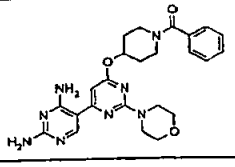
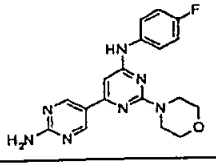
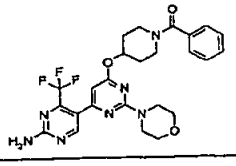
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
90		496	2.29	++++	++++	++++
91		381.4, 1.95		++++	++++	++++
92		437.1, 2.33	2.8	++++	++++	+++
93		545.6, 1.78		++++	++++	+++
94		443.1	2.07	++++	++++	++++
95		480.4, 2.13	2.85, (14.41)	++++	++++	+++
96		415.3, 1.90		++++	++++	++++
97		485.1, 3.04		++++	++++	+++

Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
98		429.2	8.99 L	++++	++++	++++
99		415.1, 1.97		++++	++++	+++
100		344.1	7.58 L	++++	++++	++++
101		360.1, 2.05		++++	++++	+++
102		394.2, 1.85	1.92	++++	++++	++++
103		415.3, 1.68		++++	++++	++++
104		394.4, 1.62		++++	++++	+++
105		428.9, 1.72	2.25, (10.78)	++++	++++	++++
106		496.0, 3.28		++++	++++	++++

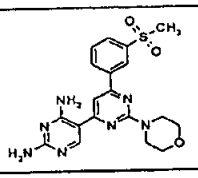
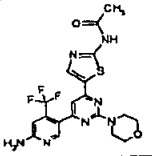
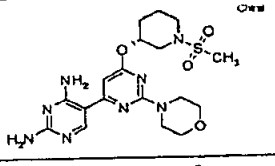
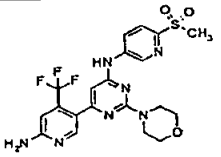
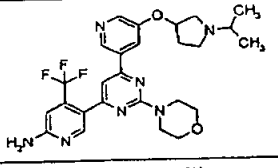
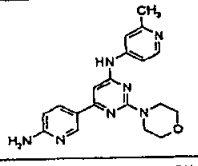
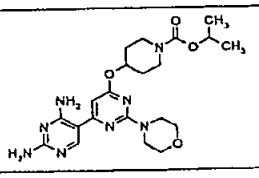
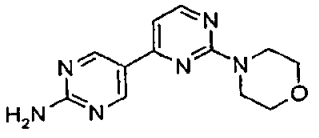
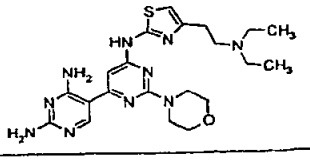
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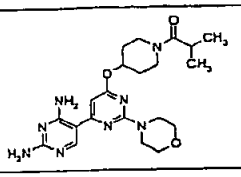
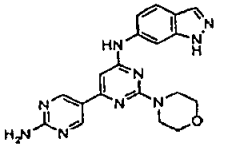
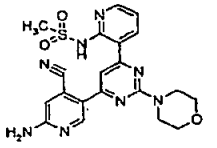
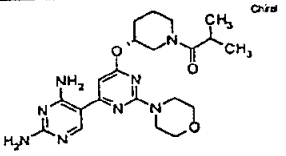
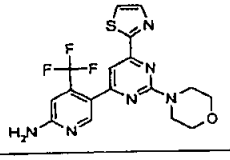
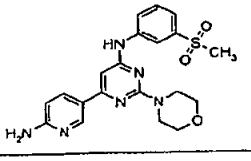
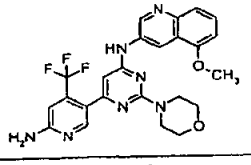
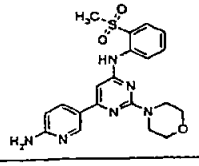
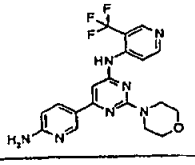
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
107		443.4, 2.70		++++	++++	+++
108		360.1, 2.05		++++	++++	++++
109		496.0, 2.07	2.39	++++	++++	+++
110		432.1	1.97	++++	++++	++++
111		368.0; 2.15	2.48	++++	++++	+++
112		427.1	2.08	++++	++++	+++
113		501.1, 2.34	14.12 L	++++	++++	+++
114		377.0, 1.54		++++	++++	+++
115		512.0, 3.96		++++	++++	+++

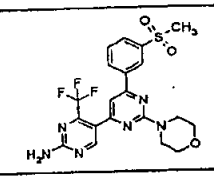
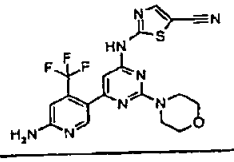
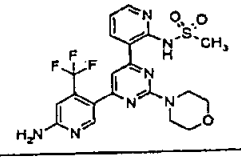
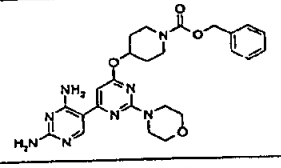
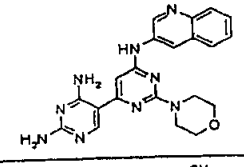
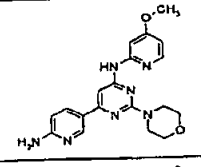
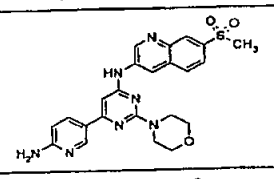
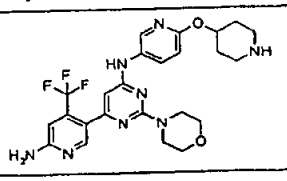
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Compound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Proliferation, EC_{50}
116		531.5, 1.77		++++	++++	+++
117		483.1, 2.37	2.82, (14.09)	++++	++++	+++
118		383.0, 2.76	2.53	++++	++++	++++
119		468.0, 2.70		++++	++++	++++
120		451.0, 2.28		++++	++++	+++
121		487.9	3.45	++++	++++	++++
122		477.1, 2.60		++++	++++	++++
123		368.1, 2.09	2.34	++++	++++	+++
124		530.0, 3.53		++++	++++	++++

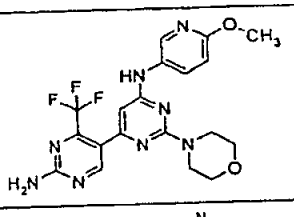
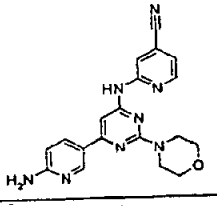
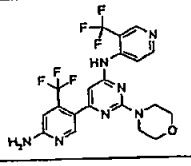
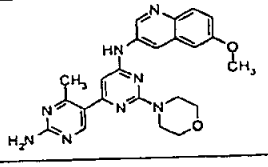
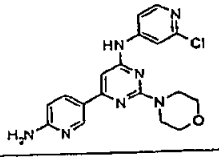
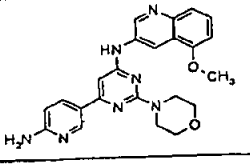
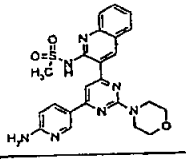
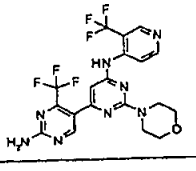
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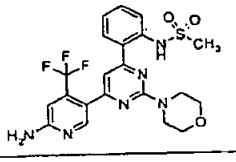
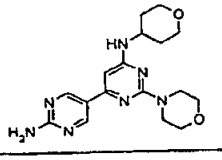
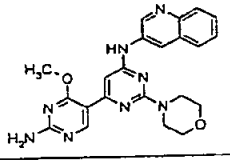
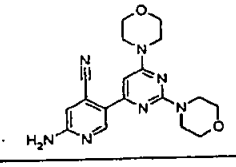
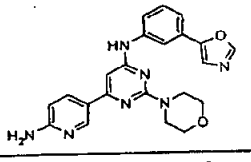
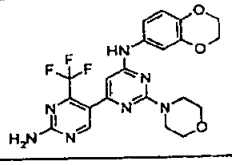
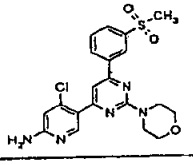
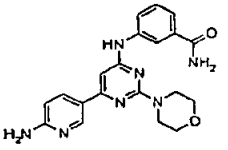
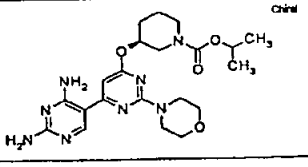
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
125		428.0, 2.38		++++	++++	++++
126		466.1, 2.25	2.62	++++	++++	+++
127		451.1, 2.25		++++	++++	+++
128		496.1	2.26	++++	++++	+++
129		530.1, 1.93	1.99	++++	++++	+++
130		364.1, 1.69	1.76	++++	++++	++++
131		459.1, 2.82		++++	++++	++++
132		259.2, 1.27	1.34, (6.23)	++++	++++	+++
133		471.2, 1.79	1.88	++++	++++	++++

Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
134		443.2, 2.37		++++	++++	++++
135		390.1, 1.85	9.52 L	++++	++++	++++
136		453.0, 2.29	2.76	++++	++++	++++
137		443.2, 2.38		++++	++++	+++
138		409.0, 2.95		++++	++++	+++
139		427.1	2.03	++++	++++	+++
140		498.5, 2.36		++++	++++	+++
141		427	2.38	++++	++++	+++
142		418.1, 1.78	8.81 L	++++	++++	++++

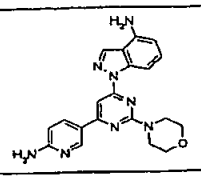
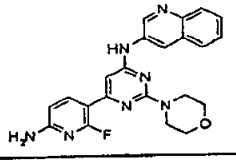
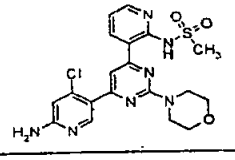
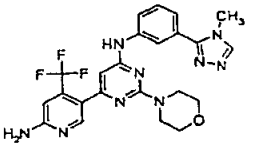
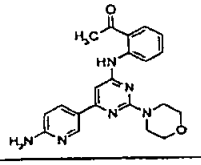
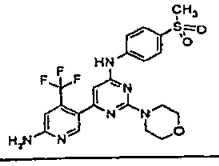
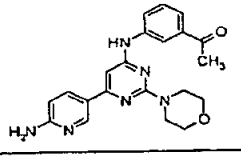
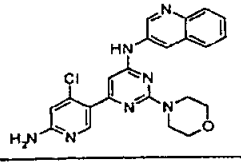
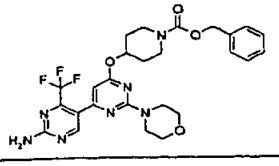
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Proliferation, EC_{50}
143		480.9, 2.46	3.50, (17.16)	++++	++++	++++
144		448.9, 2.76		++++	++++	+++
145		496.0, 2.35	2.75	++++	++++	+++
146		507.2, 3.12		++++	++++	++++
147		416.0, 1.98		++++	++++	++++
148		380.1	1.78	++++	++++	++
149		478.9, 1.75		++++	++++	+++
150		517.5, 1.78		++++	++++	++++

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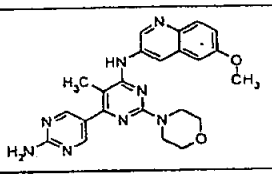
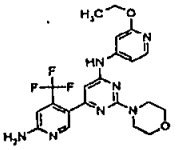
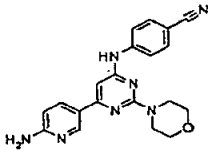
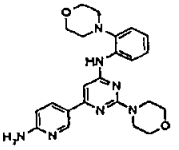
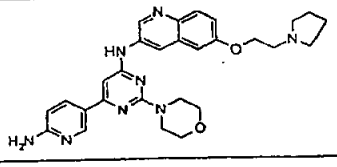
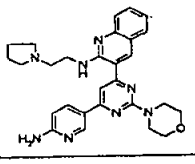
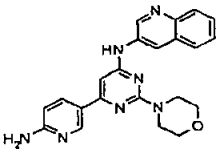
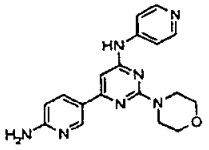
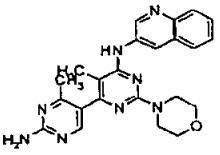
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
151		449.0, 2.42		++++	++++	+++
152		375.0	2.22	++++	++++	+++
153		486.4, 2.12		++++	++++	++++
154		445.3, 2.02		++++	++++	++++
155		384.0, 2.04	2.28	++++	++++	+++
156		430.2, 2.05	11.18 L	++++	++++	++++
157		478.1, 2.40	14.67 L	++++	++++	++
158		486.9, 2.48		++++	++++	++++

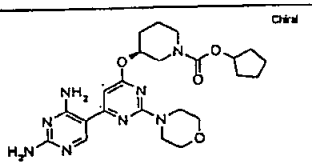
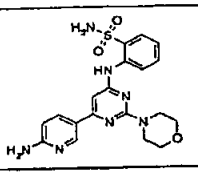
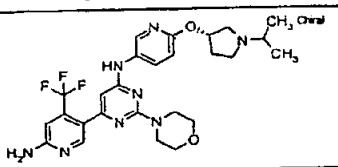
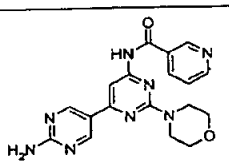
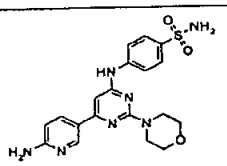
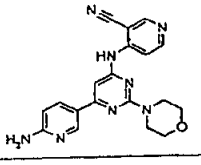
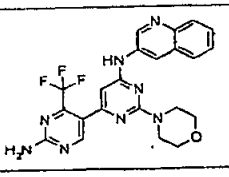
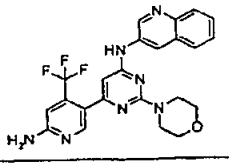
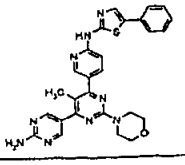
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
159		495.0, 2.57	3.13	++++	++++	+++
160		358.1	8.00 L	++++	++++	+++
161		431.4, 1.96		++++	++++	++++
162		368.2	1.84	++++	++++	++++
163		416.1	2.23	++++	++++	+++
164		475.9, 2.69		++++	++++	++++
165		445.9, 1.95	2.57, (12.84)	++++	++++	++++
166		392.1	1.62	++++	++++	+++
167		459.2, 2.71		++++	++++	+++

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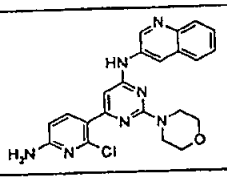
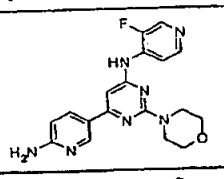
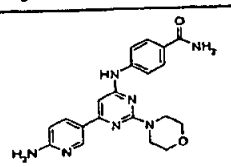
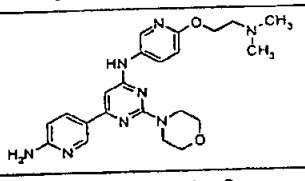
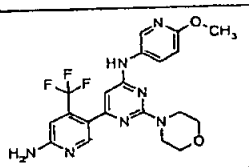
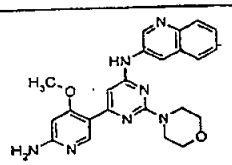
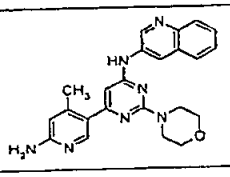
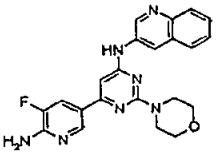
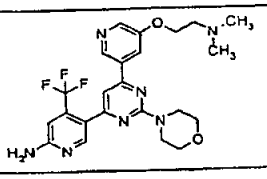
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Proliferation, EC_{50}
168		389.1	2.38	++++	++++	++++
169		418.3, 1.70	2.16, (10.66)	++++	++++	++++
170		462.9, 2.41		++++	++++	++++
171		498.1	1.92	++++	++++	++++
172		391.2	2.62	++++	++++	+++
173		495.0	2.32	++++	++++	+++
174		391.1	2.14	++++	++++	+++
175		434.3, 1.95		++++	++++	++++
176		560.0, 4.28		++++	++++	+++

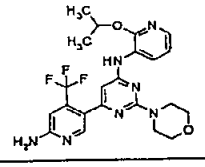
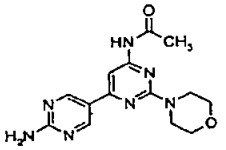
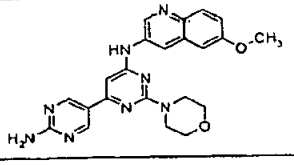
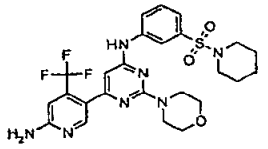
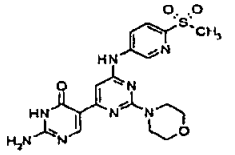
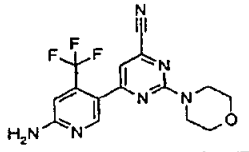
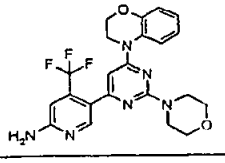
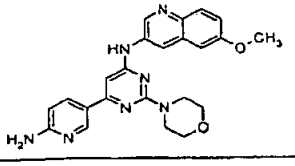
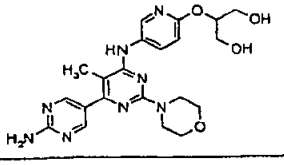
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Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
177		445.3, 1.79		++++	++++	++++
178		462.0, 1.98	2.19	++++	++++	+++
179		374.0, 2.16	2.48	++++	++++	+++
180		434.1	2.4	++++	++++	+++
181		513.1, 1.76	1.72	++++	++++	++++
182		497.2, 1.90	9.89 L	++++	++++	++++
183		400.4, 2.03		++++	++++	++++
184		350.1	7.65 L	++++	++++	++++
185		429.4, 1.67		++++	++++	++++

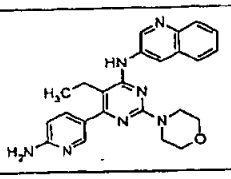
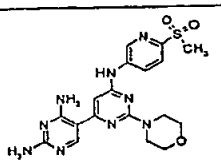
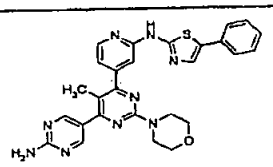
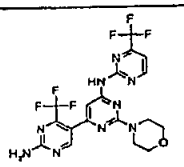
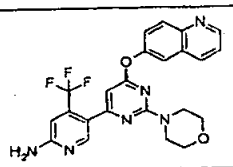
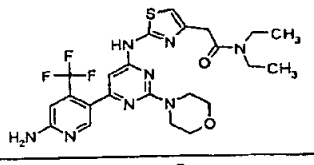
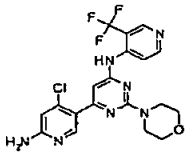
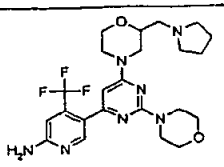
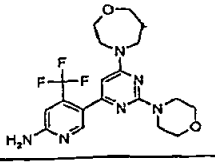
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
186		485.1, 2.91		++++	++++	+++
187		428.1	2.17	++++	++++	+++
188		545.2, 1.84	1.89	++++	++++	+++
189		379.4, 1.42		++++	++++	+++
190		428.1	1.85	++++	++++	+++
191		375.1, 1.75	1.74	++++	++++	+++
192		469.4, 2.44		++++	++++	++++
193		468.4, 2.26		++++	++++	++++
194		524.5, 2.44	3.44	++++	++++	+++

200

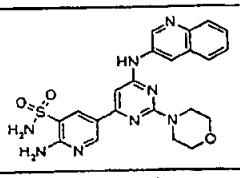
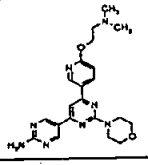
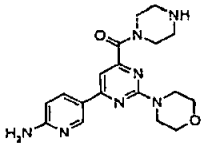
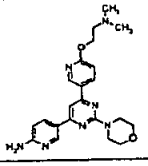
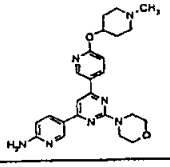
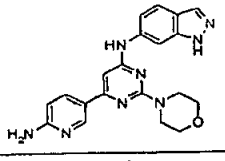
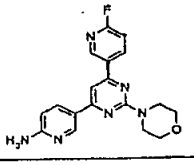
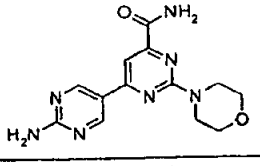
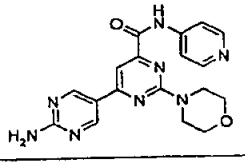
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
195		434.3, 2.06		++++	++++	++++
196		368.1, 1.69	1.63	++++	++++	++++
197		392.1	1.68	++++	++++	+++
198		437.2, 1.60	1.45	++++	++++	N/D
199		448.4, 2.24		++++	++++	+++
200		430.1, 1.84	9.55 L	++++	++++	++++
201		414.1, 1.85	9.53 L	++++	++++	++++
202		418.3	2.16	++++	++++	++++
203		490.1, 1.85	1.83	++++	++++	+++

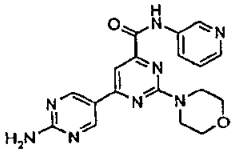
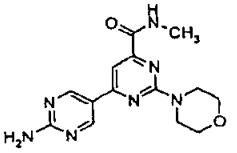
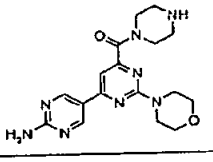
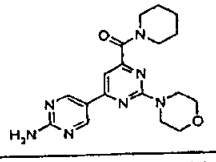
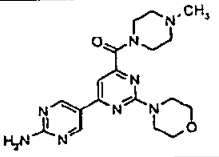
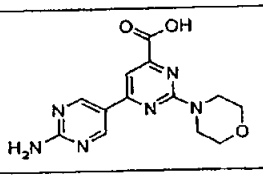
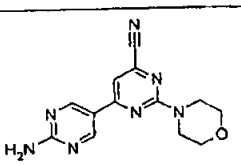
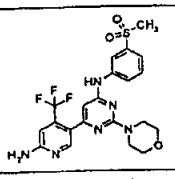
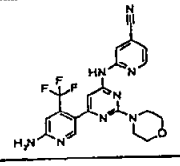
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
204		476.1, 2.42	2.86	++++	++++	++
205		316.2, 1.45		++++	++++	+++
206		431.0, 1.91	2.16	++++	++++	++++
207		564.1	3.08	++++	+++	++++
208		445.0, 1.50	1.78, (8.91)	++++	+++	++
209		351.0, 2.12	2.88, (14.36)	++++	+++	+++
210		459.4, 2.80		++++	+++	+++
211		430.2, 2.02	2.14	++++	+++	++++
212		455.5, 1.53		++++	+++	++

202

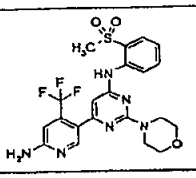
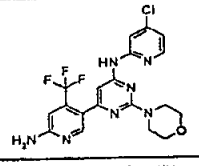
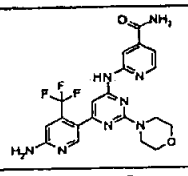
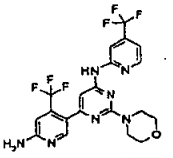
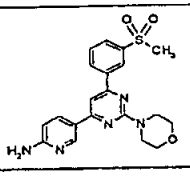
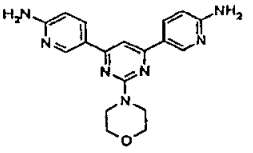
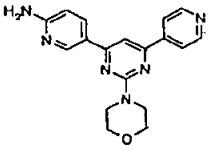
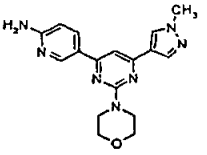
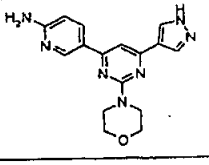
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
213		428.2, 1.74	8.55 L	++++	+++	++++
214		444.0, 2.06		++++	+++	++
215		524.5, 2.44	3.36	++++	+++	+++
216		487.9, 3.60		++++	N/D	+++
217		469.1, 2.01	2.13	++++	N/D	+++
218		537.1, 2.27	2.53	++++	N/D	+++
219		452.0, 1.85	1.89	++++	N/D	+++
220		494.1, 1.67	1.59	+++	N/D	++
221		425.0, 1.66	1.98	++++	N/D	+++

203

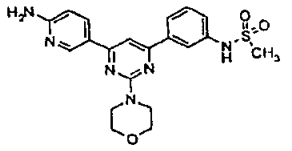
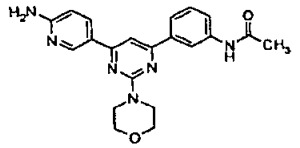
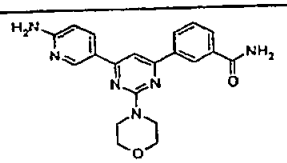
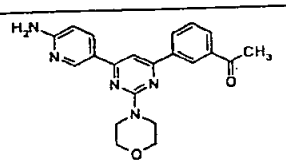
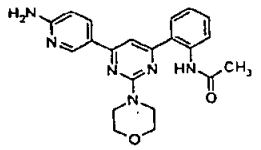
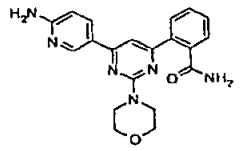
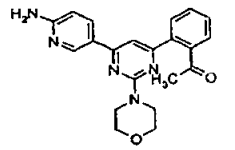
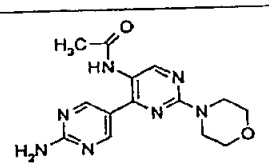
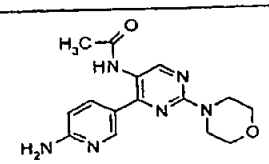
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
222		479.1, 1.98	2.20	+++	N/D	N/D
223		423.2, 1.83	1.99	++++	N/D	+++
224		370.3, 1.25	1.39	+++	N/D	N/D
225		422.2, 1.84	1.86	++++	N/D	N/D
226		448.3, 1.93	1.94	++++	N/D	N/D
227		389.2, 1.93	1.93	++++	N/D	+++
228		353.1, 2.25	2.55	++++	N/D	N/D
229		302.1, 1.68	1.74	++++	N/D	N/D
230		379.1, 1.73	1.74	++++	N/D	+++

Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
231		379.1, 1.75	1.78	++++	N/D	+++
232		316.1, 1.84	2.24	++++	N/D	++
233		371.2, 1.49	1.39	++++	N/D	+++
234		370.0, 2.12	2.37	++++	N/D	++
235		385.2, 1.50	1.40	++++	N/D	+++
236		303.1, 1.65	1.70	++++	N/D	N/D
237		284.1, 2.12	2.56	++++	N/D	+++
238		495.0	2.3	++++	N/D	+++
239		443.1	2.63	++++	N/D	+++

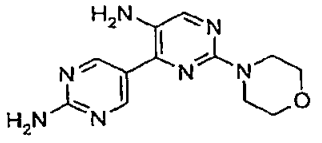
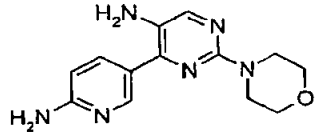
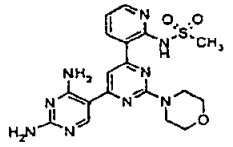
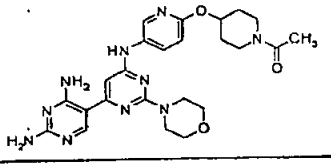
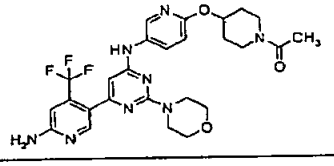
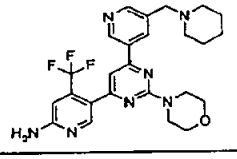
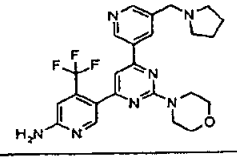
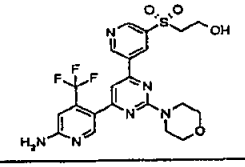
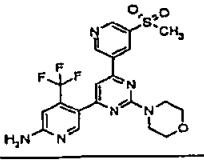
205

Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
240		495, 2.20	3.29	++++	N/D	N/D
241		452.0	2.57	++++	N/D	+++
242		461.1	1.85	++++	N/D	+++
243		486, 2.01	2.26	++++	N/D	N/D
244		413, 2.13	2.41	++++	N/D	+++
245		350, 1.72	1.66	++++	N/D	+++
246		335, 1.66	1.57	++++	N/D	+++
247		338, 1.92	2.02	++++	N/D	+++
248		324, 1.79	1.82	++++	N/D	+++

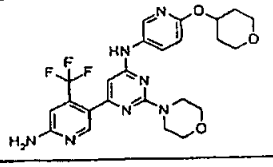
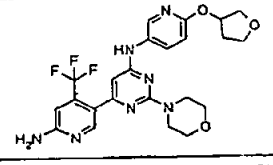
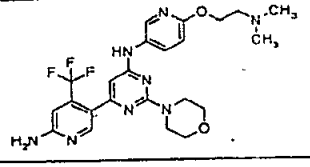
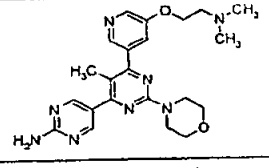
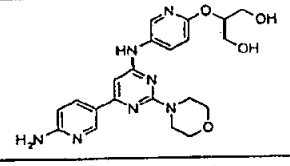
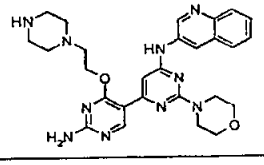
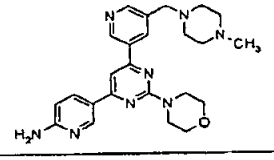
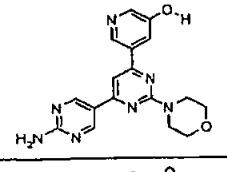
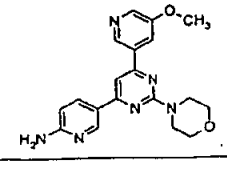
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Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
249		427, 2.15	2.40	++++	N/D	+++
250		391, 2.07	2.30	++++	N/D	+++
251		377, 1.98	2.14	++++	N/D	+++
252		376, 2.31	2.66	++++	N/D	+++
253		391, 2.13	2.56	++++	N/D	+++
254		377, 1.76	1.81	++++	N/D	++
255		376, 2.14	2.39	++++	N/D	++
256		316, 1.44	1.32	++++	N/D	N/D
257		315, 1.46	1.30	+++	N/D	N/D

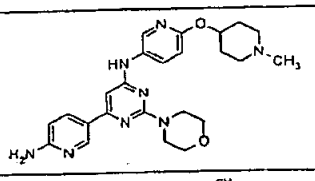
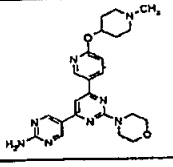
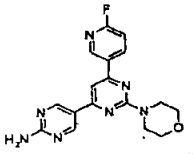
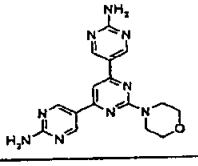
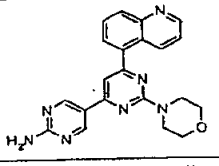
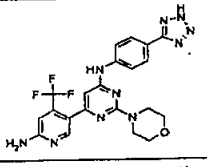
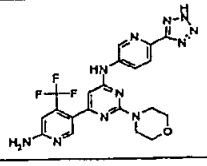
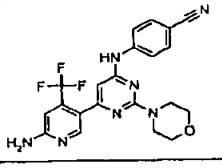
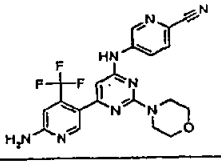
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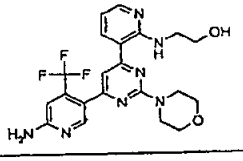
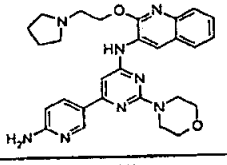
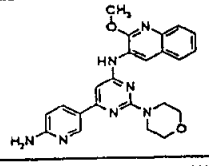
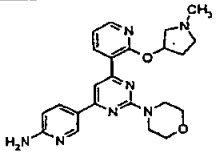
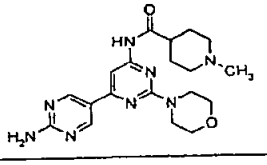
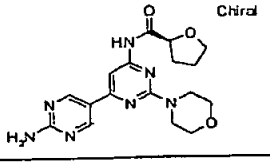
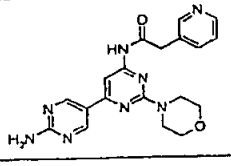
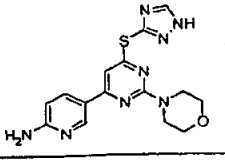
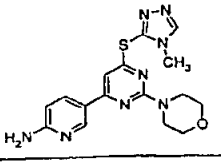
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
258		274, 1.40	1.22	++++	N/D	++
259		273, 1.40	1.23	+++	N/D	++
260		444.1, 2.02	2.24	++++	N/D	+++
261		507.2, 1.92	1.98	++++	N/D	+++
262		559.2, 2.07	2.25	++++	N/D	+++
263		500.2, 1.66	2.03	++++	N/D	+++
264		486.1, 1.61	1.94	++++	N/D	+++
265		511.1, 2.09	2.44	++++	N/D	+++
266		481.1, 2.23	2.59	++++	N/D	+++

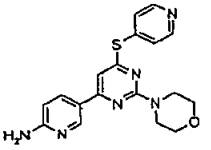
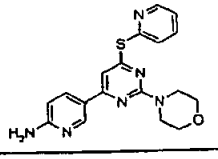
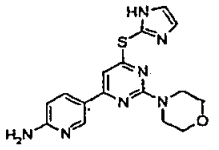
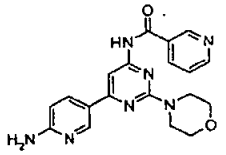
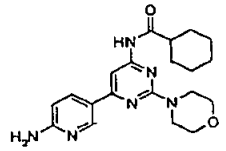
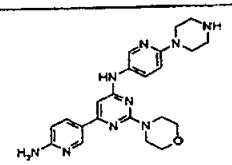
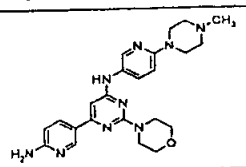
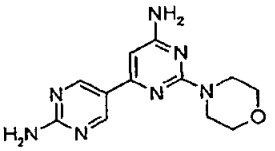
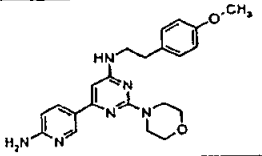
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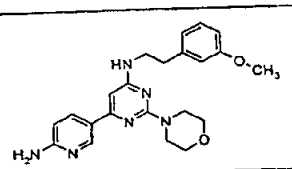
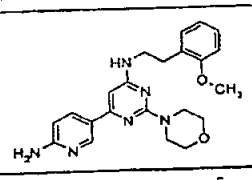
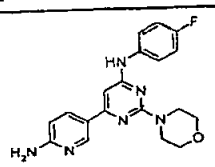
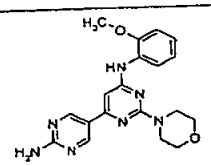
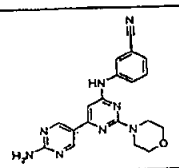
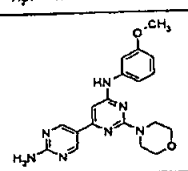
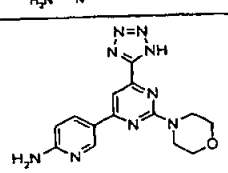
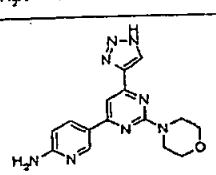
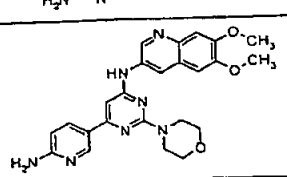
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
267		518.2, 2.18		++++	N/D	+++
268		504.1, 2.13		++++	N/D	+++
269		505.2, 1.76		++++	N/D	+++
270		437.1, 1.56	1.44	++++	N/D	++
271		440.1, 1.59	1.45	++++	N/D	++
272		529.1, 1.64	1.72	++++	N/D	N/D
273		447.2, 1.61	1.54	++++	N/D	+++
274		352.2, 1.81	1.77	++++	N/D	+++
275		365.2, 1.88	1.90	++++	N/D	+++

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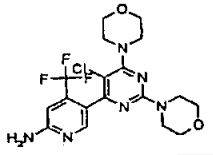
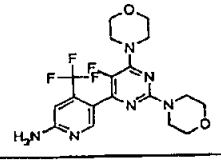
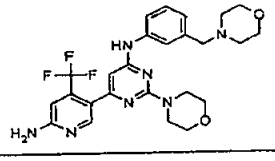
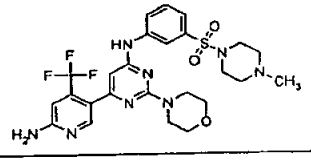
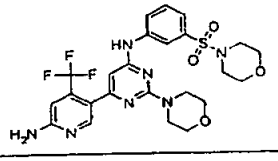
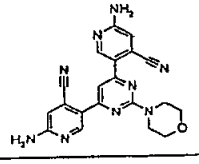
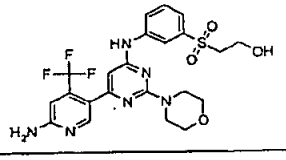
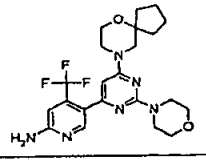
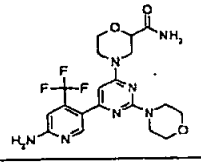
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
276		463.3, 1.72		++++	N/D	+++
277		449.2, 2.00	2.11	++++	N/D	+++
278		354.2, 2.32	2.12	++++	N/D	++++
279		352.1, 1.81	1.48	++++	N/D	++++
280		386.1, 1.83	1.91	++++	N/D	+++
281		485.1, 2.17		++++	N/D	++
282		486.0, 1.69		++++	N/D	++
283		442.0, 2.02		++++	N/D	+++
284		443.1, 2.22		++++	N/D	+++

Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
285		462.1, 1.95		++++	N/D	+++
286		513.1, 2.46		+++	N/D	N/D
287		430.1, 2.98		++++	N/D	+++
288		434.4, 1.97		+++	N/D	N/D
289		399.4, 1.50		++++	N/D	+++
290		372.3, 1.74		++++	N/D	+++
291		393.4, 1.32		++++	N/D	++
292		357.2, 1.78		+++	N/D	N/D
293		371.4, 1.68		+++	N/D	N/D

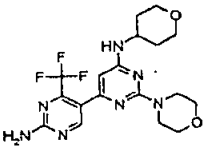
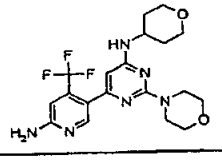
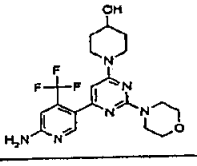
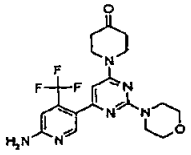
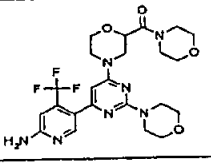
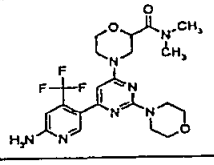
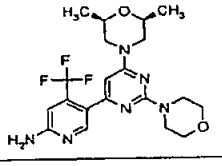
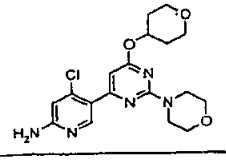
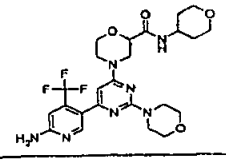
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
294		367.3, 1.65		++++	N/D	+++
295		367.2, 2.17		++++	N/D	+++
296		356.3, 1.22		+++	N/D	N/D
297		378.4, 1.72		++++	N/D	N/D
298		383.4, 2.69		++++	N/D	N/D
299		434.5, 1.41		++++	N/D	+++
300		448.4, 1.44		++++	N/D	+++
301		274.2, 0.46		++++	N/D	++
302		407.2, 2.04	3.73	+++	N/D	++

Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
303		407.2, 2.02	3.77	++++	N/D	+++
304		407.1; 2.10	2.25	++++	N/D	++
305		367.0; 2.07	2.28	++++	N/D	+++
306		380.1; 2.07	2.29	++++	N/D	+++
307		375.0; 2.09	2.39	++++	N/D	+++
308		380.1; 2.07	2.32	++++	N/D	+++
309		326.1, 1.79	2.99	++++	N/D	N/D
310		325.0, 1.51	1.88	++++	N/D	N/D
311		460.1, 1.96	2.09	++++	N/D	++++

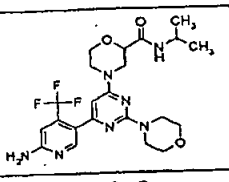
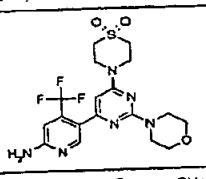
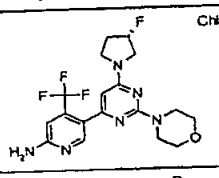
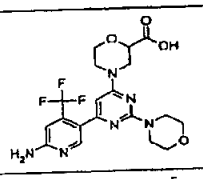
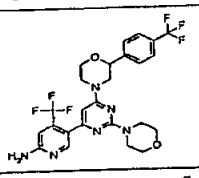
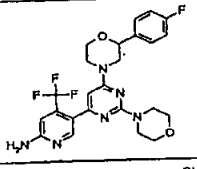
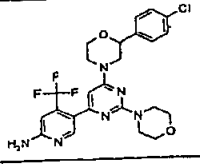
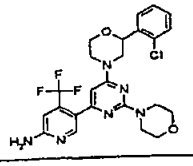
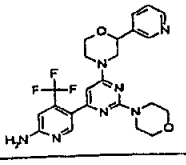
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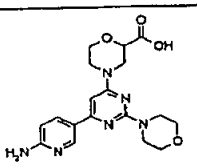
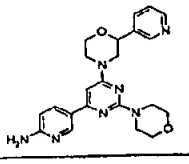
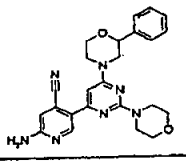
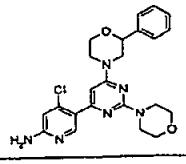
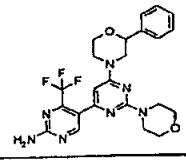
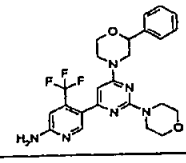
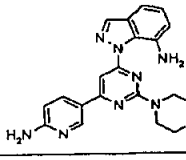
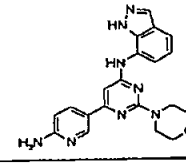
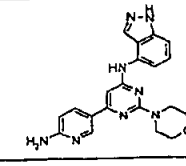
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Proliferation, EC_{50}
312		445.1, 2.30	2.7	++++	N/D	N/D
313		429.1	2.32	++++	N/D	++
314		516.1	1.78	++++	N/D	++
315		579.1	2.09	++++	N/D	+++
316		566	2.64	++++	N/D	+++
317		400.1, 2.02	2.27	++++	N/D	+++
318		525.1	2.15	++++	N/D	+++
319		465.1, 2.28	2.5	++++	N/D	N/D
320		454.1, 1.74	1.74	++++	N/D	+++

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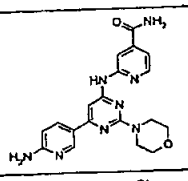
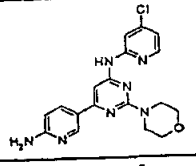
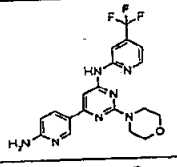
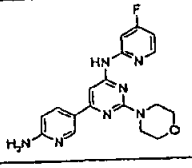
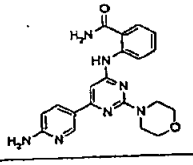
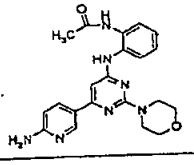
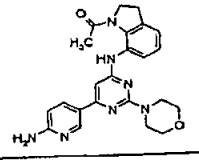
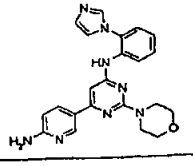
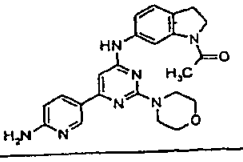
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
321		426.1	2.08	++++	N/D	+++
322		425.1, 1.92	1.97	++++	N/D	++
323		425.0, 1.78	1.83	++++	N/D	++
324		423.0, 1.82	1.79	++++	N/D	+++
325		524.1, 1.88	1.96	++++	N/D	++
326		482.1, 1.88	1.93	++++	N/D	++
327		439.2, 2.15	2.38	++++	N/D	+++
328		392.0, 2.08	2.26	++++	N/D	+++
329		538.2, 1.90	1.98	++++	N/D	++

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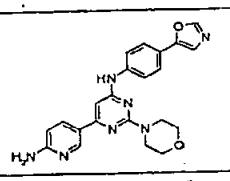
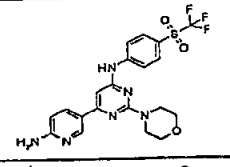
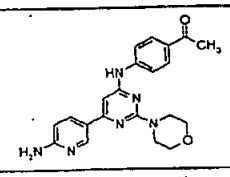
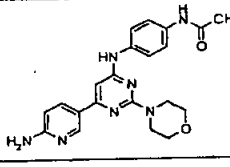
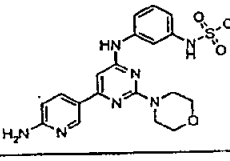
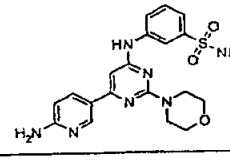
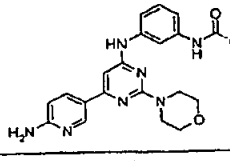
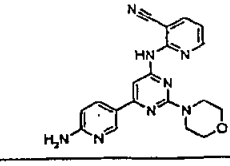
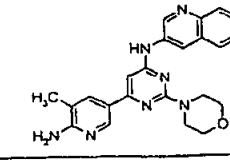
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
330		496.2, 2.04	2.2	++++	N/D	++
331		459.1, 1.83	1.89	++++	N/D	++
332	 Chiral	413.1, 2.04	2.21	++++	N/D	++++
333		455.1, 1.77	1.79	++++	N/D	++
334		555.1, 2.76	3.36	++++	N/D	+++
335		505.1	2.94	++++	N/D	+++
336		521.1, 2.66	3.18	++++	N/D	+++
337		521.1	3.1	++++	N/D	++
338		488.1, 1.73	1.67	++++	N/D	+++

Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
339		387.1, 1.55	1.44	+++	N/D	N/D
340		420.1, 1.57	1.44	++++	N/D	N/D
341		444.1	2.84	++++	N/D	+++
342		453.1	2.51	++++	N/D	+++
343		488.1	3.02	++++	N/D	++
344		487.2	2.86	++++	N/D	+++
345		389.1, 2.06	2.28	++++	N/D	+++
346		389.1, 1.92	1.94	++++	N/D	N/D
347		389.1	1.83	++++	N/D	+++

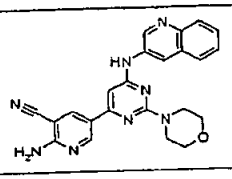
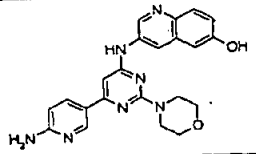
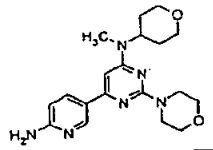
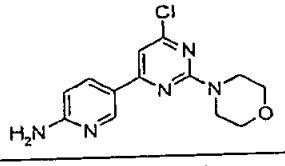
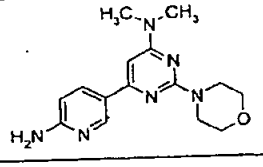
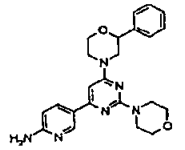
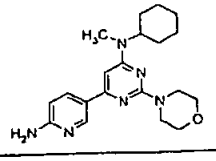
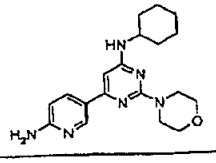
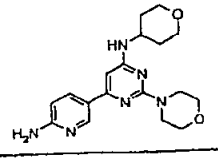
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Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
348		393.1	1.57	++++	N/D	++
349		384.1	2.13	++++	N/D	++
350		418.1	2.77	++++	N/D	++
351		368.2	1.77	++++	N/D	++
352		392.1, 1.89	1.94	++++	N/D	+++
353		406.1, 1.78	1.77	+++	N/D	N/D
354		432.2, 2.05	2.25	++++	N/D	N/D
355		415.0, 1.73	1.61	++++	N/D	N/D
356		432.0	2.0	++++	N/D	+++

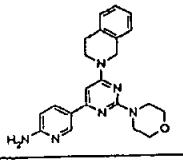
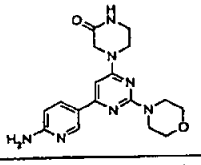
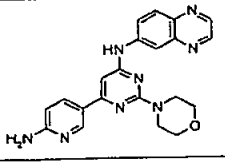
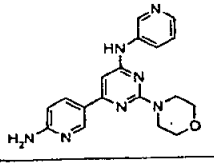
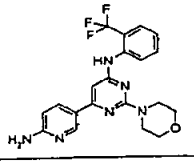
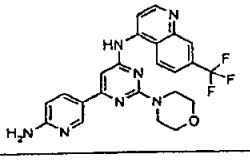
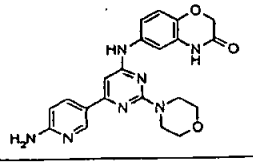
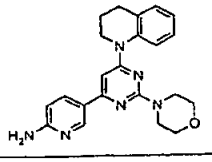
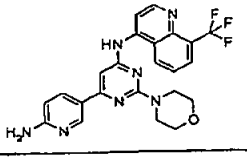
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Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Proliferation, EC_{50}
357		416.0, 2.05	2.21	++++	N/D	++
358		481.1, 2.64	3.27	++++	N/D	+++
359		391.1, 2.06	2.28	++++	N/D	++++
360		406.1, 1.71	1.71	++++	N/D	+++
361		442.1	1.89	++++	N/D	+++
362		428.1	1.77	++++	N/D	+++
363		406.1	1.77	++++	N/D	+++
364		375.1, 1.93	2.04	+++	N/D	++
365		414.1, 1.94	10.78 L	+++	N/D	N/D

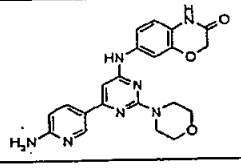
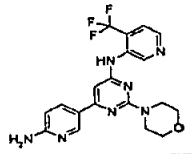
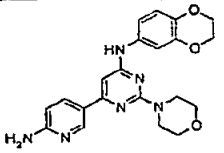
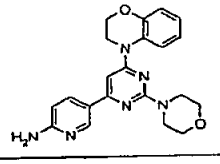
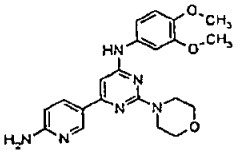
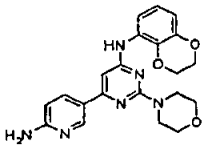
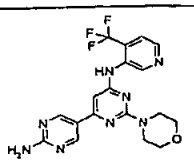
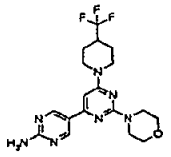
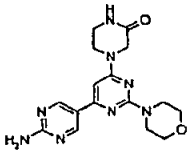
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Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
366		425.1, 2.14	12.06 L	+++	N/D	N/D
367		416.1	9.23 L	++++	N/D	+++
368		371.2, 1.69	7.86 L	++++	N/D	+++
369		292.1, 2.07	11.31 L	++++	N/D	++
370		301.2, 1.57	6.77 L	+++	N/D	N/D
371		419.2	12.26 L	++++	N/D	+++
372		369.2, 2.15	11.91 L	+++	N/D	N/D
373		355.2, 2.07	11.27 L	+++	N/D	N/D
374		357.2, 1.62	7.19 L	+++	N/D	N/D

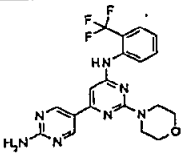
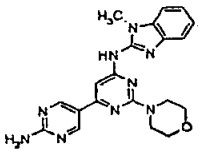
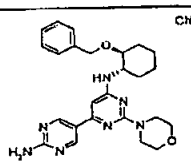
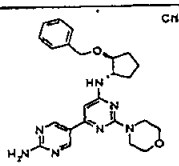
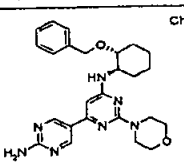
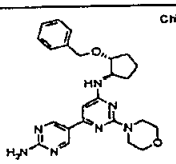
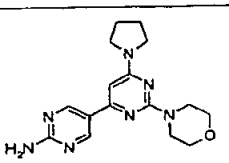
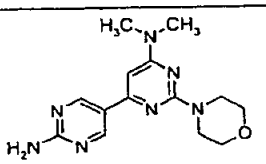
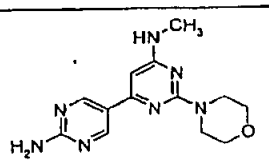
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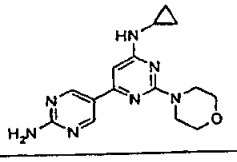
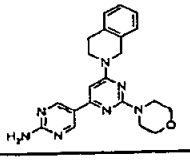
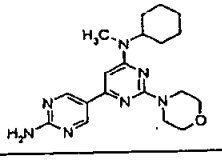
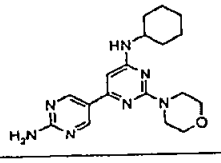
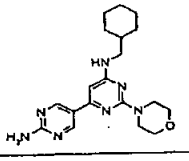
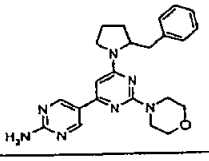
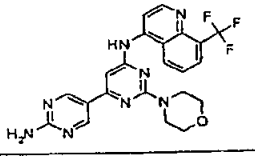
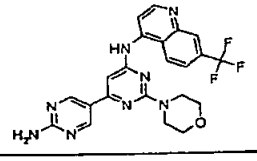
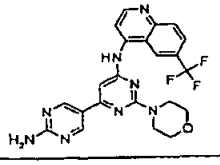
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Proliferation, EC_{50}
375		389.2, 2.13	12.07 L	++++	N/D	N/D
376		356.2, 1.40	5.75 L	+++	N/D	N/D
377		401.1	10.23 L	++++	N/D	+++
378		350.2, 1.66	7.63 L	++++	N/D	+++
379		417.1, 2.28	13.32 L	++++	N/D	N/D
380		468.1, 2.16	11.42 L	++++	N/D	+++
381		420.1, 1.81	9.41 L	++++	N/D	N/D
382		389.2, 2.28	13.47 L:	++++	N/D	N/D
383		468.2, 2.13	11.64 L	++++	N/D	+++

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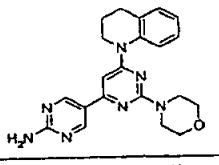
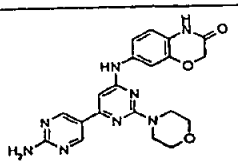
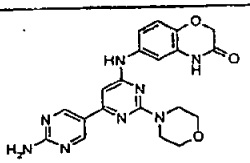
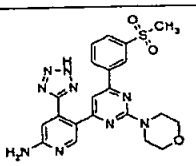
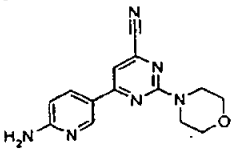
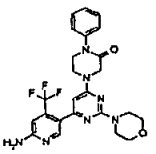
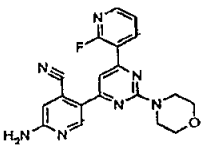
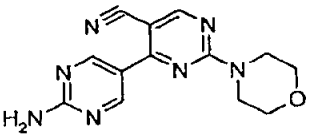
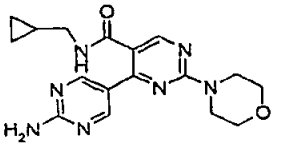
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
384		420.1, 1.68	8.71 L	++++	N/D	+++
385		418.1, 1.98	11.04 L	++++	N/D	N/D
386		407.1, 1.95	10.57 L	++++	N/D	+++
387		391.1, 2.25	13.62 L	++++	N/D	+++
388		409.1, 1.87	9.91 L	++++	N/D	N/D
389		407.1, 2.08	11.36 L	++++	N/D	N/D
390		419.1	10.41 L	++++	N/D	+++
391		410.1, 2.20	12.63 L	++++	N/D	N/D
392		357.1	5.96 L	++++	N/D	+++

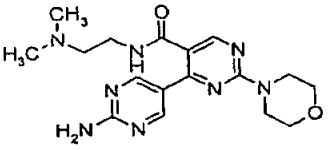
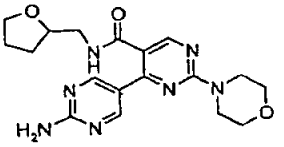
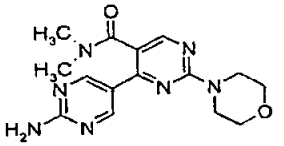
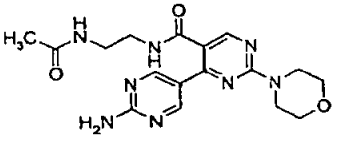
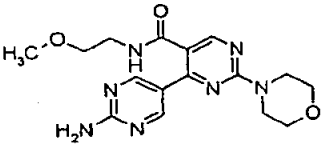
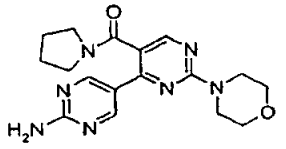
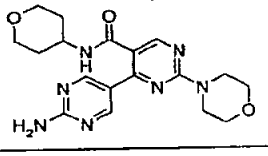
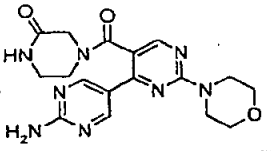
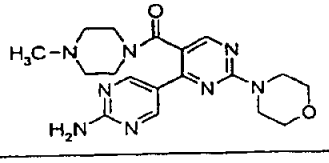
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Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
393		418.1	13.00 L	++++	N/D	+++
394		404.2	10.64 L	++++	N/D	+++
395		462.2, 2.38	14.83 L	++++	N/D	N/D
396		448.2	14.53 L	++++	N/D	+++
397		462.2, 2.40	14.82 L	++++	N/D	N/D
398		448.2, 2.38	14.52 L	++++	N/D	N/D
399		328.2	9.63 L	++++	N/D	+++
400		302.2	7.77 L	++++	N/D	+++
401		288.2	6.92 L	++++	N/D	++

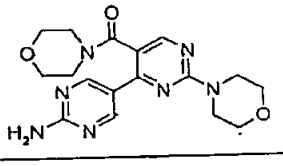
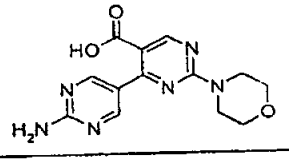
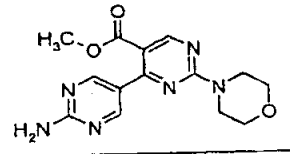
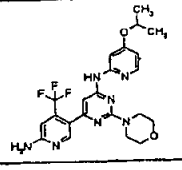
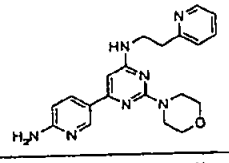
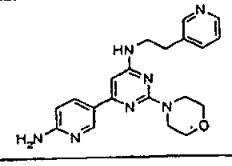
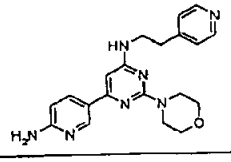
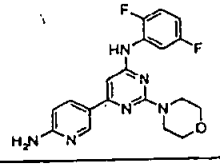
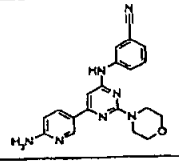
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
402		314.2	8.39 L	++++	N/D	+++
403		390.1	13.44 L	++++	N/D	+++
404		370.2	13.71 L	++++	N/D	+++
405		356.2	12.73 L	++++	N/D	+++
406		370.2	14.24 L	++++	N/D	++
407		418.2	14.81 L	++++	N/D	+++
408		469.1	12.14 L	++++	N/D	+++
409		469.1	12.17 L	++++	N/D	++++
410		469.1	12.17 L	++++	N/D	+++

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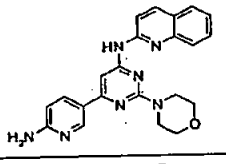
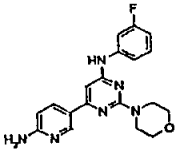
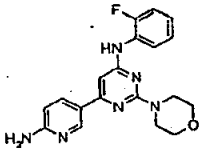
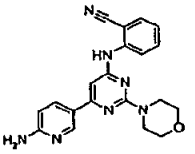
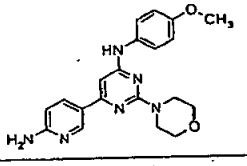
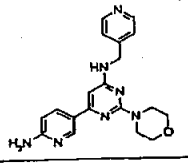
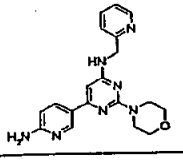
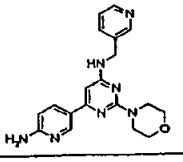
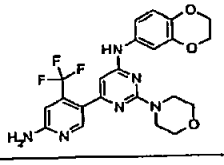
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
411		390.1	13.47 L	++++	N/D	+++
412		421.1	8.70 L	++++	N/D	++++
413		421.1	9.60 L	++++	N/D	+++
414		480.0, 1.98	2.19	++++	N/D	N/D
415		283.2, 1.95		++++	N/D	++
416		500.0, 1.83	2.36	++++	N/D	N/D
417		378.0, 3.02	2.79	++++	N/D	++
418		284.2, 1.94	2.2	++++	N/D	++
419		356.2, 1.77	1.86	+++	N/D	N/D

Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
420		373.2, 1.37	1.23	+++	N/D	N/D
421		386.2, 1.57	1.73	+++	N/D	N/D
422		330.2, 1.47	1.58	+++	N/D	N/D
423		387.2, 1.47	1.32	+++	N/D	N/D
424		360.2, 1.57	1.47	+++	N/D	N/D
425		356.2, 1.79	1.83	+++	N/D	N/D
426		386.2, 1.61	1.56	+++	N/D	N/D
427		385.2, 1.48	1.4	+++	N/D	++
428		385.2, 0.5	1.34	+++	N/D	++

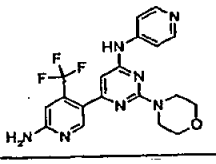
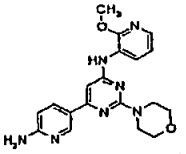
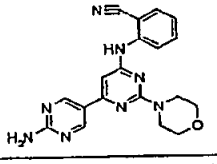
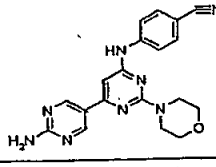
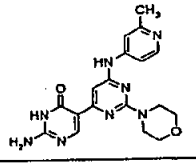
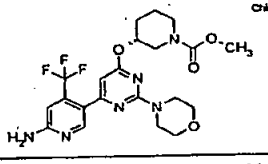
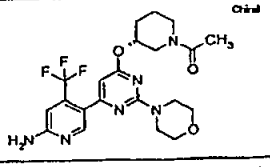
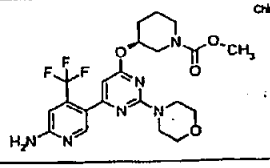
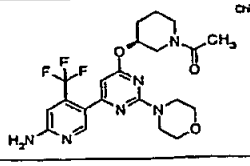
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Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
429		372.3, 1.39	1.69	+++	N/D	N/D
430		303.1, 1.66	1.66	+++	N/D	N/D
431		317.2, 1.59	2.02	++++	N/D	++
432		476.1, 2.16	2.46	++++	N/D	+++
433		378.1, 1.31	1.13	+++	N/D	N/D
434		378.2, 1.46	1.14	+++	N/D	N/D
435		378.2, 1.44	1.13	+++	N/D	N/D
436		385.1, 2.25	2.58	++++	N/D	+++
437		374.0, 2.14	2.42	++++	N/D	+++

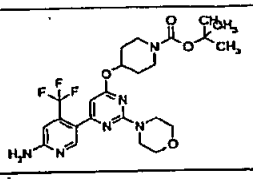
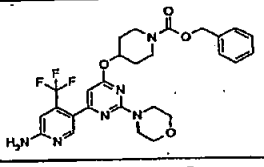
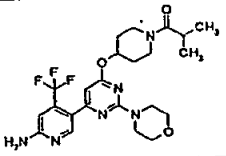
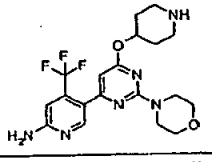
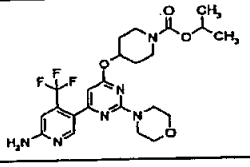
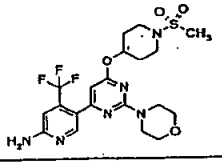
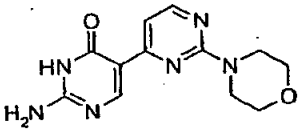
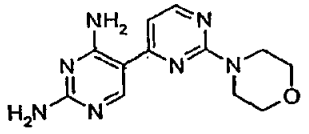
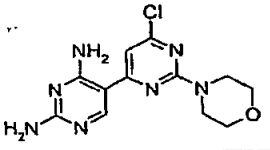
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Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Proliferation, EC_{50}
438		400.0, 1.90	2.04	++++	N/D	+++
439		367.1, 2.20	2.47	++++	N/D	+++
440		367.1, 2.07	2.29	++++	N/D	+++
441		374.1, 2.07	2.26	++++	N/D	+++
442		379.1, 1.94	2.19	++++	N/D	+++
443		364.1, 1.41	1.10	+++	N/D	N/D
444		364.1, 1.33	1.16	+++	N/D	N/D
445		364.1, 1.37	1.10	+++	N/D	N/D
446		475.4, 1.99	2.52	++++	N/D	++

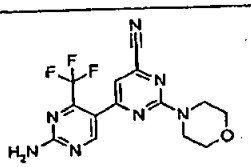
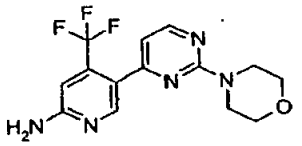
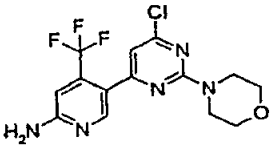
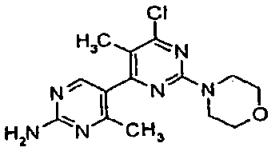
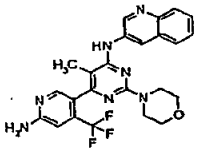
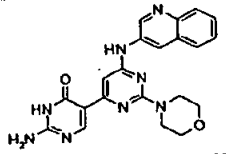
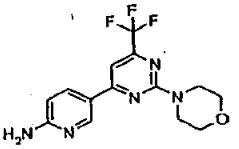
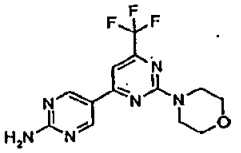
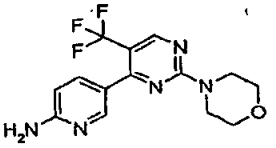
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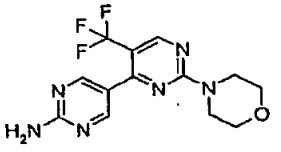
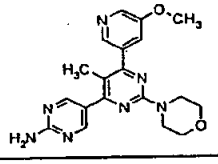
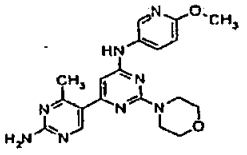
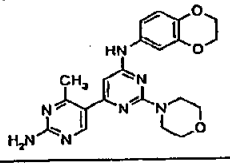
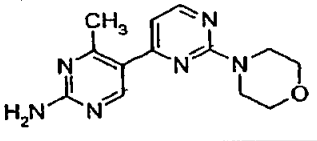
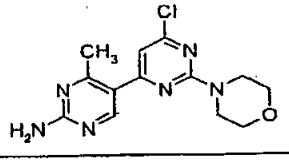
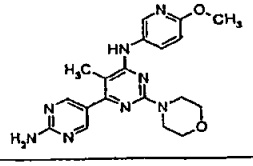
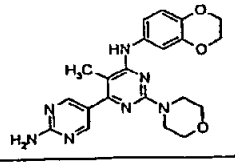
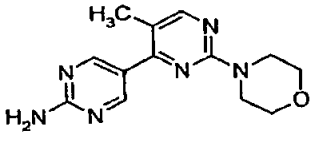
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Proliferation, EC_{50}
447		418.3, 1.54	1.93	++++	N/D	++
448		380.1, 1.98	2.06	++++	N/D	+++
449		375.0, 2.00	2.21	++++	N/D	+++
450		380.1, 2.01	2.19	++++	N/D	++
451		381.0, 1.30	1.48, (7.22)	++++	N/D	+++
452		483.0, 2.83		++++	N/D	+++
453		467.0, 2.87		++++	N/D	+++
454		483.0, 2.83		++++	N/D	+++
455		467.0, 2.87		++++	N/D	+++

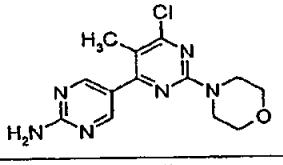
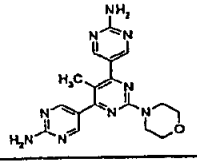
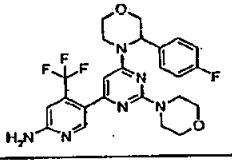
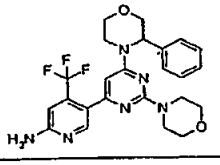
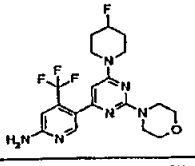
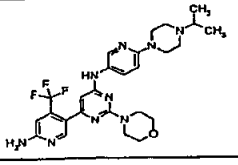
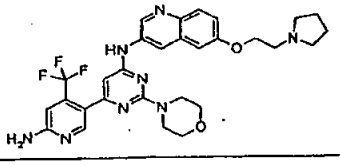
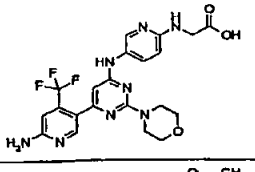
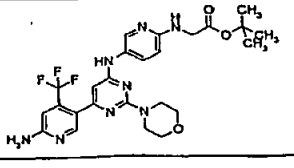
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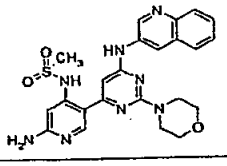
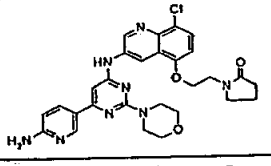
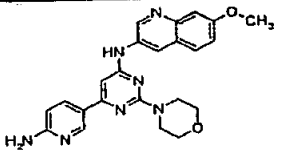
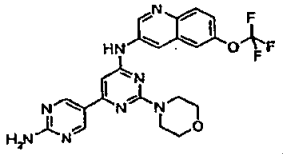
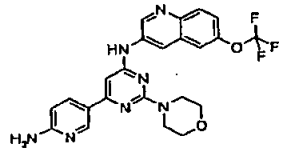
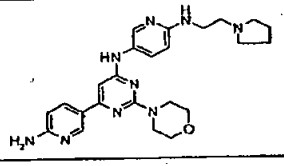
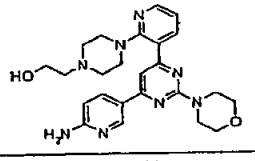
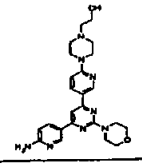
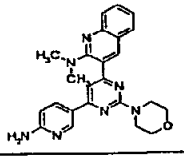
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{60}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{60}
456		525.1, 2.90		++++	N/D	+++
457		599.2, 3.60		++++	N/D	+++
458		495.1, 2.77		++++	N/D	+++
459		425.1, 1.80		++++	N/D	N/D
460		511.1, 3.28		++++	N/D	+++
461		503.1, 2.66		++++	N/D	+++
462		275.0, 1.16	1.23, (5.79)	++++	N/D	+++
463		274.0, 1.36		++++	N/D	++
464		307.9, 2.09		++++	N/D	++

230

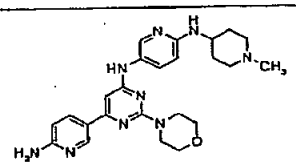
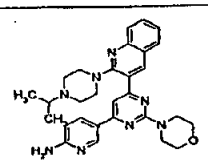
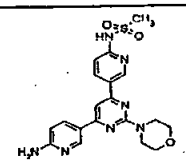
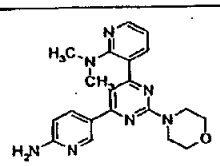
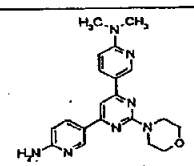
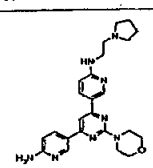
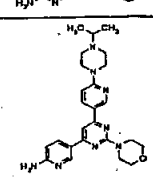
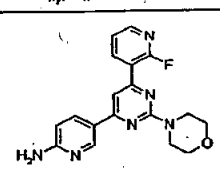
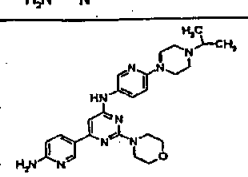
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
465		352.0, 2.46	3.57, (17.04)	++++	N/D	+++
466		326.2, 1.66	2.04, (10.20)	++++	N/D	++
467		360.2, 2.18	2.92, (14.71)	++++	N/D	++
468		321.2, 1.84	2.35, 11.87	++++	N/D	++
469		482.4, 1.70	2.08, (10.76)	++++	N/D	N/D
470		417.3, 1.58	1.83, (9.39)	++++	N/D	+++
471		326.3, 1.98	2.53, (13.21)	++++	N/D	N/D
472		327.2, 2.21	3.13, (15.01)	++++	N/D	+++
473		326.3, 1.76	2.24, (11.11)	+++	N/D	N/D

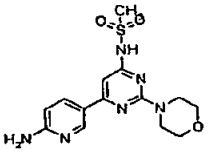
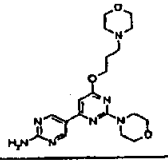
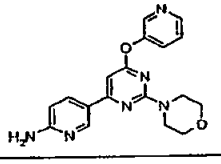
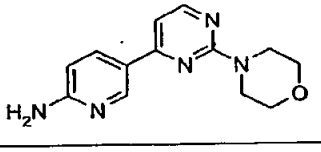
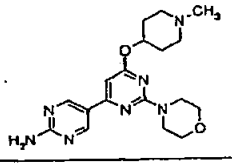
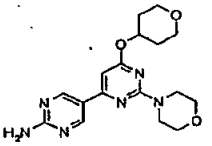
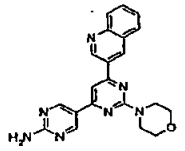
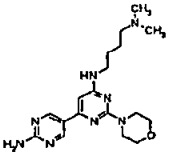
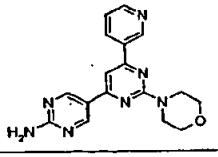
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Proliferation, EC_{50}
474		327.3, 1.97	2.69, (12.81)	++++	N/D	++
475		380.3, 1.49	1.76, (8.70)	++++	N/D	+++
476		395.3, 1.89		++++	N/D	+++
477		422.3, 2.15		++++	N/D	+++
478		273.2, 1.55	1.44, (6.80)	++++	N/D	++
479		307.1, 2.05	2.33, (11.43)	++++	N/D	N/D
480		395.3, 1.79		++++	N/D	+++
481		422.3, 2.10		++++	N/D	++++
482		273.2, 1.29	1.43, (6.78)	++++	N/D	+++

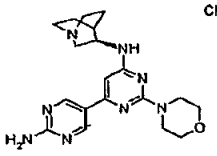
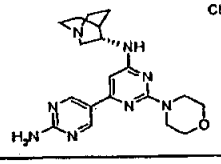
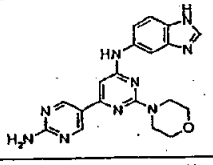
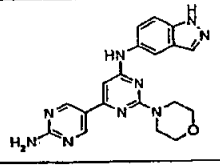
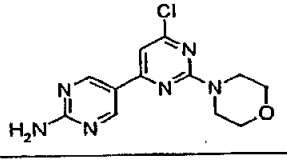
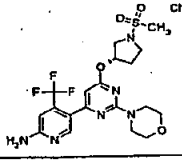
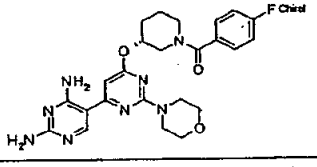
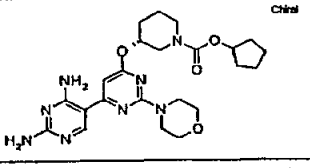
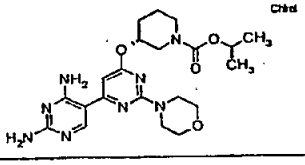
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Proliferation, EC_{50}
483		307.2, 1.96	2.58, (12.75)	++++	N/D	++
484		366.3, 1.39	1.63, (7.75)	++++	N/D	+++
485		505.1, 2.35	14.35 L	++++	N/D	N/D
486		487.2, 2.31	13.84 L	++++	N/D	N/D
487		427.1, 2.12	11.84 L	++++	N/D	N/D
488		544.2, 1.76	1.67	++++	N/D	+++
489		581.2, 1.82	1.90	++++	N/D	+++
490		491.1, 1.70	1.59	++++	N/D	N/D
491		547.1, 2.09	11.59 L	++++	N/D	++

Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
492		492.9, 1.78	2.24	+++	N/D	N/D
493		561.1, 2.20	2.46	++++	N/D	N/D
494		430.2, 1.97	10.65 L	++++	N/D	+++
495		485.0, 2.47	15.16 L	++++	N/D	++
496		484.1, 2.47	15.14 L	+++	N/D	N/D
497		462.4, 1.29	7.09 L	++++	N/D	+++
498		463.2, 1.77	8.92 L	+++	N/D	N/D
499		463.2, 1.72	8.24 L	++++	N/D	+++
500		428.4; 1.63	10.17	++++	N/D	+++

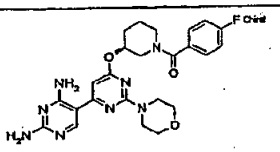
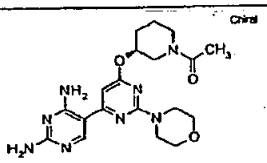
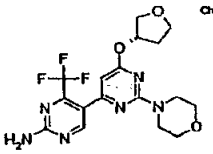
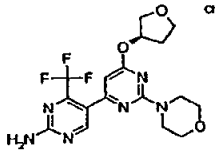
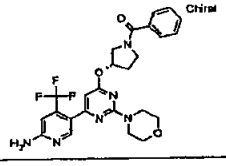
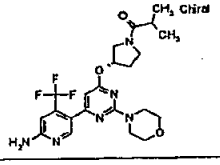
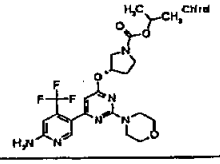
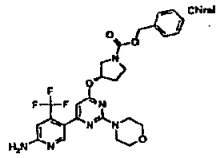
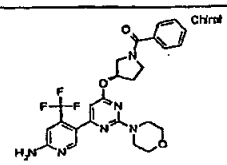
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Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Proliferation, EC_{50}
501		462.4, 1.28	1.51	++++	N/D	+++
502		511.3, 2.08	11.82 L	+++	N/D	N/D
503		428.2, 1.93	10.1 L	++++	N/D	+++
504		378.2, 1.66	7.72 L	+++	N/D	N/D
505		378.2, 1.76	8.73 L	++++	N/D	+++
506		447.3, 1.78	8.02	++++	N/D	N/D
507		461.2, 1.8	8.93 L	++++	N/D	N/D
508		353.1, 2.16	2.34	++++	N/D	+++
509		476.3, 1.65	7.27 L	++++	N/D	+++

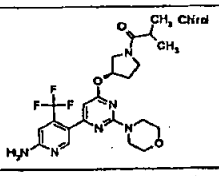
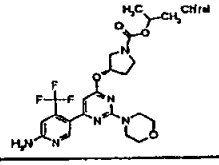
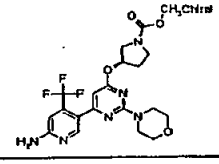
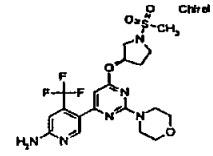
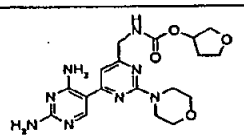
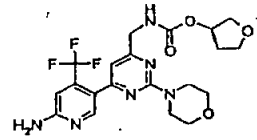
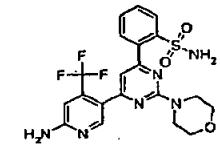
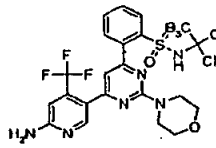
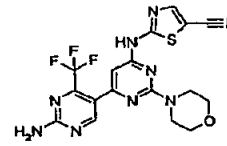
Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
510		351.1, 1.74	1.70	+++	N/D	N/D
511		402.2, 1.65	7.51 L	++++	N/D	+++
512		351.2, 1.66	7.85 L	++++	N/D	+++
513		258.2, 1.48	6.33 L	++++	N/D	N/D
514		372.2, 1.65	7.49	++++	N/D	+++
515		359.2, 2.05	11.16 L	++++	N/D	++++
516		387.2, 1.54	6.71 L	++++	N/D	+++
517		373.2, 0.71	5.93	+++	N/D	N/D
518		336.2, 1.61	8.11 L	++++	N/D	++++

Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Proliferation, EC_{50}
519		383.2, 1.44	2.04	++++	N/D	N/D
520		383.2, 1.53	2.09	++++	N/D	+++
521		390.1, 1.59	7.15 L	++++	N/D	+++
522		390.1, 1.75	8.62 L	++++	N/D	+++
523		293.1, 1.93	2.20	++++	N/D	+++
524		489.1, 2.47		++++	N/D	+++
525		495.2, 2.49		++++	N/D	N/D
526		485.1, 2.90		++++	N/D	+++
527		459.2, 2.75		++++	N/D	+++

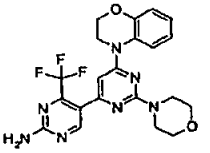
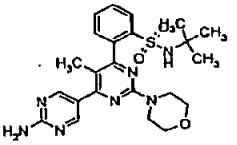
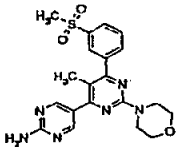
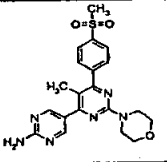
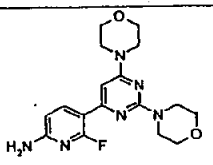
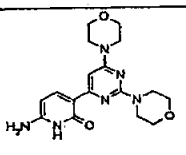
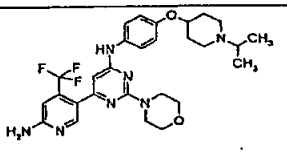
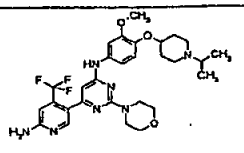
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Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
528		495.2, 2.47		++++	N/D	+++
529		415.1, 2.06		++++	N/D	+++
530		413.1, 3.09		++++	N/D	+++
531		413.1, 3.07		++++	N/D	+++
532		515.1, 2.74		++++	N/D	+++
533		481.1, 2.54		+++	N/D	N/D
534		497.1, 3.01		++++	N/D	+++
535		545.1, 3.37		++++	N/D	N/D
536		515.1, 2.79		++++	N/D	N/D

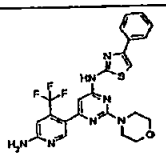
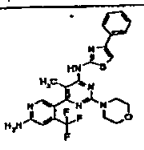
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Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
537		481.1, 2.55		++++	N/D	N/D
538		497.1, 2.54	3.00, (15.55)	++++	N/D	N/D
539		469.1, 2.56		++++	N/D	+++
540		489.1, 2.47		++++	N/D	+++
541		417.0, 1.51	1.84, (8.78)	++++	N/D	++
542		469.0, 1.76	2.27, (10.99)	++++	N/D	N/D
543		481.1, 1.93	2.57, (12.58)	++++	N/D	+++
544		536.9, 2.47	3.38, (17.30)	++++	N/D	++
545		449.9, 3.44		++++	N/D	++

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Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Prolifer ation, EC_{50}
546		460.0, 3.00		++++	N/D	+++
547		484.5, 2.28	3.12, (15.46)	+++	N/D	N/D
548		427.3, 1.83	2.49, (11.84)	++++	N/D	+++
549		427.3, 1.82	2.51, (11.79)	++++	N/D	+++
550		360.9, 1.56		N/D	N/D	+++
551		358.9, 1.63		++++	N/D	+++
552		558.3, 1.90		++++	++++	+++
553		588.3, 1.92		++++	++++	++++

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Com-pound	Structure	LC/MS (M+H, Rt min)	hplc 10min (L = 45min)	PI3 Kinase Alpha, IC_{50}	PSer473 AKT, EC_{50}	Cellular Proliferation, EC_{50}
554		500.0; 2.46		++++	N/D	+++
555		514.0; 2.62		+++	N/D	N/D

[0440] The compounds in Table 1 were synthesized according to Methods 1-30 and Examples 1-35 provided above. PI3K IC_{50} values and pSer473 Akt EC_{50} values for inhibition of Akt phosphorylation were determined according to Biological Methods 1 and 2, respectively. The cellular proliferation EC_{50} values shown in Table 1 were determined according to Biological Method 3.

[0441] Table 1 shows the IC_{50} and EC_{50} values of the compounds as determined by the Biological Methods 1, 2, 3 and 4 as described herein. In Table 1, "+" indicates that the compound had an IC_{50} or EC_{50} value of >25μM; "++" indicates that the compound had an IC_{50} or EC_{50} value of <25μM; "+++" indicates that the compound had an IC_{50} or EC_{50} value of >10μM; and "++++"indicates that the compound had an IC_{50} or EC_{50} value of >1μM. An "N/D" in Table 1indicates that the values were not determined.

[0442] Each of the Compounds in Table 1 exhibited IC_{50} values of less than 10 μM with respect to inhibition of PI3K. Many of the Compunds of Table 1 exhibited IC_{50} values of less than 1 μM and even less than 0.1 μM with respect to inhibition of PI3K. For this reason, each of the compounds is individually preferred and is preferred as a group. The PI3 kinase alpha IC_{50} values shown in Table 1 were determined according to the ATP depletion assay as disclosed herein in Biological Method 1.

[0443] Furthermore, many of the compounds of Table 1 exhibited an EC_{50} value with respect inhibition of pSer473 Akt phosphorylation of less than 10 μM. Many of

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those compounds exhibited EC_{50} values of less than 1 μM and even less than 0.1 μM with respect to pAkt inhibition. Table 1 shows the EC_{50} values for inhibition of phosphorylation of pSER473 AKT. The assays were performed according to the Biological Method 2 described herein.

[0444] In addition, many of the compounds of Table 1 were tested to determine their inhibitory activity in a cellular proliferation assay according to Biological Method 4. Many of those compounds exhibited EC_{50} values of less than 1 μM and even less than 0.1 μM, demonstrating their potent ability to inhibit cellular proliferation. Table 1 shows the EC_{50} values for inhibition of cellular proliferation of an an ovarian cance cell line, A2780/

Biological Method 1:

Phosphorylation Assays

Assay 1: Homogenous solution phase assay

[0445] Compounds to be tested are dissolved in DMSO and directly distributed into 384-well flashplates at 1.25 μL per well. To start the reaction, 20 μL of 6 nM PI3 kinase are added into each well followed by 20 μL of 400 nM ATP containing a trace of radiolabeled ATP and 900 nM 1-alpha-phosphatidylinositol (PI). The plates are briefly centrifuged to remove any air gap. The reaction is performed for 15 minutes and then stopped by the addition of 20 μL of 100 mM EDTA. The stopped reaction is incubated overnight at RT to allow the lipid substrate to bind by hydrophobic interaction to the surface of the flashplate. The liquid in the wells is then washed away, and the labeled substrate is detected with scintillation counting.

Assay 2: One step solid phase assay

[0446] This method is similar to Assay 1 except that the lipid substrate (1-alpha-phosphatidylinositol (PIP)) is first dissolved in a coating buffer and incubated on flashplate at room temperature overnight to allow the lipid substrate to bind by

hydrophobic interaction to the surface of the flashplate. Unbound substrate is then washed away. On the day of assay, 20 μL of 6 nM PI3 kinase are added into each well followed by 20 μL of 400 nM ATP containing trace of radiolabeled ATP. Compounds are added together with enzyme and ATP to the lipid-coated plates. The plates are briefly centrifuged to remove any air gap. The reaction is performed for two to three hours. The reaction is stopped by addition of 20 μL of 100 mM EDTA or by immediate plate washing. Phosphorylated lipid substrate is detected by scintillation counting.

Assay 3: ATP depletion assay

[0447] Compounds to be tested are dissolved in DMSO and directly distributed into a black 384-well plate at 1.25 μL per well. To start the reaction, 25 μL of 10 nM PI3 kinase and 5 μg/mL 1-alpha-phosphatidylinositol (PI) are added into each well followed by 25 μL of 2 μM ATP. The reaction is performed until approx 50% of the ATP is depleted, and then stopped by the addition of 25 μL of KinaseGlo solution purchased from Promega. The stopped reaction is incubated for 5 minutes and the remaining ATP is then detected via luminescence.

Biological Method 2:

pSer473 Akt Assays to Monitor PI3K Pathway

[0448] In this method, an assay for measuring the PI3K-mediated pSer473-Akt status after treatment with representative inhibitor compounds of the invention is described.

[0449] A2780 cells were cultured in DMEM supplemented with 10% FBS. L-glutamine, sodium pyruvate, and antibiotics. Cells were plated in the same medium at a density of 15,000 cells per well into 96 well tissue culture plates, with outside wells vacant, and allowed to adhere overnight.

[0450] Test compounds supplied in DMSO were diluted further into DMSO at 500 times the desired final concentrations before dilution into culture media to 2 times the final concentrations. Equal volumes of 2x compounds were added to the cells in 96 well plates and incubated at 37 °C for one hour. The media and compounds were then

removed, the plates chilled and cells lysed in a lysis buffer (150 mM NaCl, 20 mM Tris pH 7.5, 1 mM EDTA, 1 mM EGTA, 1% Triton X-100) supplemented with phosphatase and protease inhibitors. After thorough mixing, lysates were transferred to both pSer473Akt and total Akt assay plates from Meso Scale Discovery (MSD), and incubated overnight with shaking at 4 °C. The plates were washed with 1 x MSD wash buffer and the captured analytes detected with secondary antibodies. After incubation with the secondary antibody at room temperature for 1-2 hours, the plates were washed again and 1.5x concentration of Read Buffer T (MSD) was added to the wells.

[0451] The assays were read on a SECTOR Imager 6000 instrument (Meso Scale Discovery). Ratios of the signal from pSer473Akt and total Akt assays were used to correct for any variability and the percent inhibition of pSer473Akt from the total signal seen in cells treated with compound versus DMSO alone was calculated and used to determine EC_{50} values for each compound.

Biological Method 3:

Pharmacology Target Modulation and Efficacy Study

in Ovarian Cancer Xenograft Model

[0452] A2780 ovarian cancer cells obtained from George Coukos (Fox Chase Cancer Center, University of Pennsylvania, Philadelphia, PA) were maintained in DMEM (Invitrogen, Inc.) supplemented with 10% heat-inactivated fetal bovine serum with 1% glutamine. Cells were propagated as recommended by the Dr. Coukos and colleagues.. Female nu/nu mice (8-12 weeks old, 20-25 g, Charles River) were used for all *in vivo* pharmacology studies. The mice were housed and maintained in accordance with state and federal guidelines for the humane treatment and care of laboratory animals and received food and water *ad libitum*. Cancer cells were harvested from mid-log phase cultures using trypsin-EDTA (Invitrogen, Inc.). Five million cells were subcutaneously injected into the right flank of each mouse. Compound treatment was initiated when

tumor size reached to 300–400 mm^3 for PK/PD studies and 200-300 mm^3 for efficacy studies. All compound treatment was administrated orally. Tumor volumes were determined by using StudyDirector software.

[0453] For *in vivo* target modulation PK/PD time-course studies, tumor tissues were resected from individual mice at different time points ranging from 30 min to 36 hr after a single dose of compound (60 or 100 mg/kg) or vehicle was administrated orally. For PK/PD dose-dependent studies, tumor-bearing mice were given a single oral dose of compound at different concentrations (10, 30, 60 and 100 mg/kg or vehicle) and tumors were resected at 10 hr or 24 hr after dosing. Blood samples were taken by cardiac puncture using a syringe primed with heparin sulfate. Resected tumors were snap frozen on dry ice and pulverized using a liquid nitrogen-cooled cryomortar and pestle, and lysed in cold cell extraction buffer (Biosource) containing protease inhibitor tablet (Complete; EDTA-free, Amersham). Supernatants were taken after centrifugation of tumor lysates at 300xg for 10 min at 4 °C and the protein concentration in each supernatant was determined by BCA (BioRad). An equal amount of protein from each tumor lysate was loaded onto 10% Tris-glycine gels (Invitrogen), for sodiumdoceylsulfate-polyacrylamide gel electrophoresis (SDS-PAGE) after which proteins were transferred from the gel onto PVDF membrane. Membranes were probed with antibodies that recognize phosphoAkt^{Ser473} or phosphoAkt^{Thr308} (Cell Signaling) followed by secondary goat anti-rabbit IgG conjugated to HRP(Amersham). Positive bands were visualized by enhanced chemiluminescence with X-ray film. Similar procedures were used to determine total AKT in the same tumor lysates to serve as normalization for total protein in each determination. The density of the positive band on the X-ray film was scanned and the target modulation for each compound was expressed as percentage inhibition by each compound compared to vehicle treatment. A rank order (<50%, 50-75%, >75%, as compared to vehicle treatment) of target inhibition is used to present compound target modulation activity.

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[0454] For efficacy studies, A2780 cancer cells (5×10^6 in 100 µl of DMEM culture medium) were injected subcutaneously into the right flank of each nu/nu mouse. When average tumor sizes reached about 200 mm^3, mice were dosed orally daily (q.d.) or twice a day (b.i.d.) at three different compound concentrations (typically at 10, 30 and 100 mg/kg) in 100 µl incipient. Tumor growth and animal body weight was measured twice weekly with daily clinical observation to monitor potential toxicities related to the treatment. Typically, studies were terminated when tumors in vehicle-treated group reached 2500 mm^3 or adverse clinical effects were observed. Activation of the PI3K signaling pathway results in the phosphorylation of the downstream signaling molecule Akt at Ser^{473} and/or Thr^{308}. Compound modulation of Akt^{Ser473} phosphorylation was examined in A2780 xenograft tumors at time points ranging from 30 min to 36 hr after a single compound dose at 60 or 100 mg/kg. Table 2 summarizes modulation of AKT^{Ser473} phosphorylation by representative compounds at 8 hr or 10 hr time points. Percentage inhibition was ranked as <50%, 50-75%, and >75%, as compared to vehicle treatment.

[0455] Table 2. Modulation of Akt^{Ser473} phosphorylation by representative pyrimidine compounds of the invention.

Compound	60 mg/kg	100 mg/kg
91 at 8 hr		>50%
183 at 8 hr		50-75%
103 at 8 hr		<50%
10 at 10 hr	>75%	>75%
84 at 10 hr	50-75%	
76 at 10 hr	>75%	>75%
66 at 10 hr	<50%	

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[0456] Efficacy of Compound 91 was tested in the A2780 tumor xenograft model. Mice bearing A2780 tumors received oral administration of Compound 91 twice daily at 10 and 60 mg/kg. Tumor growth inhibition (50%) was observed at 60 mg/kg treatment, while at 10 mg/kg no inhibitory activity was observed (FIGURE 1).

[0457] The modest tumor growth inhibition by Compound 91 at 60 mg/kg q.d. was due to its short-lived target modulation (50% inhibition lasted for 8 hr). Therefore, antitumor efficacy of three other compounds (Compound 10, Compound 76, and Compound 66), that demonstrated longer inhibition of Akt^{Ser473} (>50% inhibition > 10 hr) in A2780 tumors were evaluated in A2780 model. Compounds were orally administrated daily when tumor sizes reached to about 200 mm^3. Compound 10 demonstrated a dose-dependent tumor growth inhibition: 40% at 30 mg/kg, 70% at 60 mg/kg and tumor growth stasis at 100 mg/kg (FIGURE 2). A similar dose-dependent tumor growth inhibition was observed with Compound 76 treatment at 30 and 60 mg/kg in the A2780 tumor model (FIGURE 3) while Compound 84 was found to possess weaker antitumor activity (<50% TGI at 60 mg/kg) (FIGURE 4).

[0458] Antitumor activity of Compound 10 was also evaluated at more frequent dosing regimen (b.i.d). As shown in FIGURE 5, Compound 10 demonstrated a significant antitumor activity at 30 mg/kg when orally dosed b.i.d. Notably, tumor growth inhibition at 30 mg/kg b.i.d. was more potent than when dosed on a schedule at an equivalent daily dose (60 mg/kg, FIGURE 2). The compounds were well tolerated in this study. This result indicated that a sustained but less profound target inhibition (covering the whole dosing period, but with <75% target inhibition) in A2780 tumors by Compound 10 was able to induce significant antitumor efficacy.

[0459] While the preferred embodiment of the invention has been illustrated and described, it will be appreciated that various changes can be made therein without departing from the spirit and scope of the invention.

Biological Method 4:

Celllar Proliferation Studies in A2780 cell.

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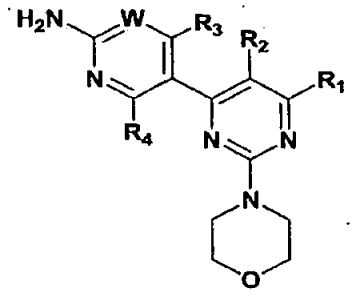
[0460] The ability of the compounds of the invention to inhibit cellular proliferation were determined by using Cell Titer Glo, a commercially available assay from Promega Corporation. A2780 ovarian cancer cells were seeded in TC treated 96-well plates at a density of 1,000 per well in DMEM, 10%FBS, 1% Sodium Pyruvate, and 1% Penicillin Streptomycin for a minimum of 2hrs prior to addition of compound. For each concentration of test compound, 2µl (500x) aliquots of compound or 100% DMSO diluted in 500µl of culture medium for 2x concentration then diluted 1x on the Cells. Cells were incubated for 72hrs at 37°C, 5% CO_2. After the 72 hour incubation, Cell Titer Glo reagent is added to determine number of viable cells remaining after exposure to the compound, and the EC_{50} value was calculated. The assay was performed according to the manufacturer's instruction (Promega Corporation, Madison, WI. USA). Each experimental condition was performed in duplicate. The results are provided in Table 1

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CLAIMS

What is claimed is:

1. A compound having Formula I:



I

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein,

W is CR_w or N, wherein R_w is selected from the group consisting of

(1) hydrogen,

(2) cyano,

(3) halogen,

(4) methyl,

(5) trifluoromethyl,

(6) sulfonamido;

R_1 is selected from the group consisting of

(1) hydrogen,

(2) cyano,

(3) nitro,

(4) halogen,

(5) substituted and unsubstituted alkyl,

(6) substituted and unsubstituted alkenyl,

(7) substituted and unsubstituted alkynyl,

(8) substituted and unsubstituted aryl,

(9) substituted and unsubstituted heteroaryl,

(10) substituted and unsubstituted heterocyclyl,

(11) substituted and unsubstituted cycloalkyl,

(12) $-COR_{1a}$,

(13) $-CO_2R_{1a}$,

(14) $-CONR_{1a}R_{1b}$,

(15) $-NR_{1a}R_{1b}$,

(16) $-NR_{1a}COR_{1b}$,

(17) $-NR_{1a}SO_2R_{1b}$,

(18) $-OCOR_{1a}$,

(19) $-OR_{1a}$,

(20) $-SR_{1a}$,

(21) $-SOR_{1a}$,

(22) $-SO_2R_{1a}$, and

(23) $-SO_2NR_{1a}R_{1b}$,

wherein R_{1a}, and R_{1b} are independently selected from the group consisting of

(a) hydrogen,

(b) substituted or unsubstituted alkyl,

(c) substituted and unsubstituted aryl,

(d) substituted and unsubstituted heteroaryl,

(e) substituted and unsubstituted heterocyclyl, and

(f) substituted and unsubstituted cycloalkyl;

R_2 is selected from the group consisting

(1) hydrogen,

(2) cyano,

(3) nitro,

(4) halogen,

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(5) hydroxy,

(6) amino,

(7) substituted and unsubstituted alkyl,

(8) $-COR_{2a}$, and

(9) $-NR_{2a}COR_{2b}$,

wherein R_{2a}, and R_{2b} are independently selected from the group consisting of

(a) hydrogen, and

(b) substituted or unsubstituted alkyl;

R_3 is selected from the group consisting of

(1) hydrogen,

(2) cyano,

(3) nitro,

(4) halogen,

(5) substituted and unsubstituted alkyl,

(6) substituted and unsubstituted alkenyl,

(7) substituted and unsubstituted alkynyl,

(8) substituted and unsubstituted aryl,

(9) substituted and unsubstituted heteroaryl,

(10) substituted and unsubstituted heterocyclyl,

(11) substituted and unsubstituted cycloalkyl,

(12) $-COR_{3a}$,

(13) $-NR_{3a}R_{3b}$,

(14) $-NR_{3a}COR_{3b}$,

(15) $-NR_{3a}SO_2R_{3b}$,

(16) $-OR_{3a}$,

(17) $-SR_{3a}$,

(18) $-SOR_{3a}$,

(19) $-SO_2R_{3a}$, and

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(20) $-SO_2NR_{3a}R_{3b}$,

wherein R_{3a}, and R_{3b} are independently selected from the group consisting of

(a) hydrogen,

(b) substituted or unsubstituted alkyl,

(c) substituted and unsubstituted aryl,

(d) substituted and unsubstituted heteroaryl,

(e) substituted and unsubstituted heterocyclyl, and

(f) substituted and unsubstituted cycloalkyl; and

R_4 is selected from the group consisting of

(1) hydrogen, and

(2) halogen.

2. A compound of Claim 1, wherein W is N.

3. A compound of Claim 1, wherein W is CH.

4. A compound of Claim 1, wherein R_1 is selected from the group consisting of

(1) substituted and unsubstituted alkyl,

(2) substituted and unsubstituted aryl,

(3) substituted and unsubstituted heteroaryl,

(4) substituted and unsubstituted heterocyclyl,

(5) substituted and unsubstituted cycloalkyl,

(6) $-OR_{1a}$, and

(7) $-NR_{1a}R_{1b}$,

wherein R_{1a} and R_{1b} are independently selected from the group consisting of

(a) substituted and unsubstituted heteroaryl, and

(b) substituted and unsubstituted heterocyclyl.

5. A compound of Claim 4, wherein R_1 is substituted or unsubstituted heterocyclyl, or substituted or unsubstituted -O-heterocyclyl.

6. A compound of Claim 4, wherein R_1 is substituted or unsubstituted morpholinyl.

7. A compound of Claim 6, wherein R_1 is unsubstituted N-linked morpholinyl.

8. A compound of Claim 4, wherein R_1 is substituted or unsubstituted tetrahydropyran or substituted or unsubstituted tetrahydropyranyloxy.

9. A compound of Claim 8, wherein R_1 is unsubstituted 4-tetrahydropyranyloxy.

10. A compound of Claim 4, wherein R_1 is substituted or unsubstituted tetrahydrofuran or substituted or unsubstituted tetrahydrofuranyloxy.

11. A compound of Claim 10, wherein R_1 is unsubstituted 3-tetrahydrofuranyloxy.

12. A compound of Claim 1, wherein R_2 is selected from the group consisting

(1) hydrogen,

(2) cyano,

(3) hydroxy,

(4) halogen,

(5) amino,

(6) methyl, and

(7) trifluoromethyl.

13. A compound of Claim 1, wherein R_2 is hydrogen or halogen.

14. A compound of Claim 1, wherein R_2 is hydrogen.

15. A compound of Claim 1, wherein R_3 is selected from the group consisting of

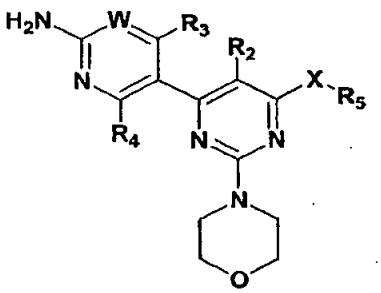
(1) cyano,
(2) nitro,
(3) halogen,
(4) hydroxy,
(5) amino, and
(6) trifluoromethyl.

16. A compound of Claim 1, wherein R_3 is trifluoromethyl.

17. A compound of Claim 1, wherein R_3 is cyano.

18. A compound of Claim 2, wherein R_3 is =O.

19. A compound having Formula II:



II

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein, W is CR_w or N, wherein R_w is selected from the group consisting of

(1) hydrogen,
(2) cyano,
(3) halogen,
(4) methyl,

(5) trifluoromethyl, and

(6) sulfonamido;

X is O, S, NH, or a direct bond;

R_2 is selected from the group consisting

(1) hydrogen,

(2) cyano,

(3) nitro,

(4) halogen,

(5) hydroxy,

(6) amino,

(7) substituted and unsubstituted alkyl,

(8) $-COR_{2a}$, and

(9) $-NR_{2a}COR_{2b}$,

wherein R_{2a}, and R_{2b} are independently selected from the group consisting of

(a) hydrogen, and

(b) substituted or unsubstituted alkyl;

R_3 is selected from the group consisting of

(1) hydrogen,

(2) cyano,

(3) nitro,

(4) halogen,

(5) substituted and unsubstituted alkyl,

(6) substituted and unsubstituted alkenyl,

(7) substituted and unsubstituted alkynyl,

(8) substituted and unsubstituted aryl,

(9) substituted and unsubstituted heteroaryl,

(10) substituted and unsubstituted heterocyclyl,

(11) substituted and unsubstituted cycloalkyl,

(12) $-COR_{3a}$,

(13) $-NR_{3a}R_{3b}$,

(14) $-NR_{3a}COR_{3b}$,

(15) $-NR_{3a}SO_2R_{3b}$,

(16) $-OR_{3a}$,

(17) $-SR_{3a}$,

(18) $-SOR_{3a}$,

(19) $-SO_2R_{3a}$, and

(20) $-SO_2NR_{3a}R_{3b}$,

wherein R_{3a}, and R_{3b} are independently selected from the group consisting of

(a) hydrogen,

(b) substituted or unsubstituted alkyl,

(c) substituted and unsubstituted aryl,

(d) substituted and unsubstituted heteroaryl,

(e) substituted and unsubstituted heterocyclyl, and

(f) substituted and unsubstituted cycloalkyl;

R_4 is selected from the group consisting of

(1) hydrogen, and

(2) halogen; and

R_5 is selected from the group consisting of

(1) substituted and unsubstituted cycloalkyl,

(2) substituted and unsubstituted heterocyclyl,

(3) substituted and unsubstituted aryl, and

(4) substituted and unsubstituted heteroaryl.

20. A compound of Claim 19, wherein R_2 is selected from the group consisting of

(1) hydrogen,

(2) cyano,

(3) hydroxy,

(4) amino,

(5) halogen, and

(6) substituted and unsubstituted C_{1-3} alkyl.

21. A compound of Claim 19, wherein R_3 is selected from the group consisting of

(1) hydrogen,

(2) cyano,

(3) thio,

(4) halogen,

(5) nitro,

(6) substituted and unsubstituted alkyl,

(7) substituted and unsubstituted alkenyl,

(8) substituted and unsubstituted alkynyl,

(9) $-OR_{3a}$,

(10) $-NR_{3a}R_{3b}$,

(11) $-COR_{3a}$, and

(12) $-NR_{3a}COR_{3b}$,

wherein R_{3a}, and R_{3b} are independently selected from the group consisting of

(a) hydrogen, and

(b) substituted or unsubstituted alkyl.

22. A compound of Claim 19, wherein R_3 is trifluoromethyl.

23. A compound of Claim 19, wherein W is CH.

24. A compound of Claim 19, wherein R_2 is H.

25. A compound of Claim 19, wherein R_5 is selected from the group consisting of

(1) substituted or unsubstituted morpholinyl,

(2) substituted or unsubstituted tetrahydropyranyl, and

(3) substituted or unsubstituted tetrahydrofuranyl.

26. A compound of Claim 19, wherein X is a direct link and R_5 is unsubstituted N-linked morpholinyl.

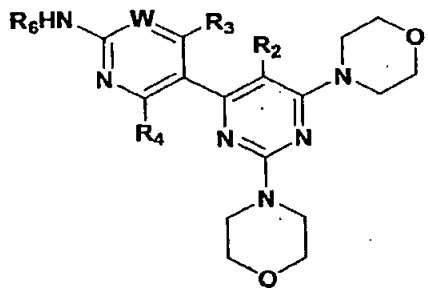
27. A compound of Claim 19, wherein X is O and R_5 is 4-tetrahydropyranyl.

28. A compound of Claim 19, wherein X is O and R_5 is 3-tetrahydrofuranyl.

29. A compound of Claim 19, wherein W is N.

30. A compound of Claim 19, wherein R_3 is =O.

31. A compound having Formula III:



III

or a stereoisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein, W is CR_w or N, wherein R_w is selected from the group consisting of

(1) hydrogen,

(2) cyano,

(3) halogen,

(4) methyl,

(5) trifluoromethyl, and

(6) sulfonamido;

R_2 is selected from the group consisting

(1) hydrogen,

(2) cyano,

(3) nitro,

(4) halogen,

(5) hydroxy,

(6) amino,

(7) substituted and unsubstituted alkyl,

(8) $-COR_{2a}$, and

(9) $-NR_{2a}COR_{2b}$,

wherein R_{2a}, and R_{2b} are independently selected from the group consisting of

(a) hydrogen, and

(b) substituted or unsubstituted alkyl;

R_3 is selected from the group consisting of

(1) hydrogen,

(2) cyano,

(3) nitro,

(4) halogen,

(5) substituted and unsubstituted alkyl,

(6) substituted and unsubstituted alkenyl,

(7) substituted and unsubstituted alkynyl,

(8) substituted and unsubstituted aryl,

(9) substituted and unsubstituted heteroaryl,

(10) substituted and unsubstituted heterocyclyl,

(11) substituted and unsubstituted cycloalkyl,

(12) $-COR_{3a}$,

(13) $-NR_{3a}R_{3b}$,

(14) $-NR_{3a}COR_{3b}$,

(15) $-NR_{3a}SO_2R_{3b}$,

(16) $-OR_{3a}$,

(17) $-SR_{3a}$,

(18) $-SOR_{3a}$,

(19) $-SO_2R_{3a}$, and

(20) $-SO_2NR_{3a}R_{3b}$,

wherein R_{3a}, and R_{3b} are independently selected from the group consisting of

(a) hydrogen,

(b) substituted or unsubstituted alkyl,

(c) substituted and unsubstituted aryl,

(d) substituted and unsubstituted heteroaryl,

(e) substituted and unsubstituted heterocyclyl, and

(f) substituted and unsubstituted cycloalkyl;

R_4 is selected from the group consisting of

(1) hydrogen, and

(2) halogen; and

R_6 is selected from the group consisting of

(1) hydrogen,

(2) substituted and unsubstituted alkyl, and

(3) substituted and unsubstituted cycloalkyl.

32. A compound of Claim 31, wherein R_2 is selected from the group consisting

(1) hydrogen,

(2) cyano,

(3) hydroxy,

(4) halogen,

(5) amino,

(6) methyl, and

(7) trifluoromethyl.

33. A compound of Claim 31, wherein R_3 is selected from the group consisting of

(1) cyano,

(2) nitro,

(3) halogen,

(4) hydroxy,

(5) amino, and

(6) trifluoromethyl.

34. A compound of Claim 31, wherein R_6 is selected from the group consisting

(1) hydrogen,

(2) methyl, and

(3) ethyl.

35. A method for inhibiting phosphorylation of Akt in a human or animal subject, comprising administering to a human or animal subject an effective amount of a compound of any one of Claims 1-34.

36. A composition, comprising a pharmaceutically acceptable carrier and an amount of a compound of any one of Claims 1-34 effective to inhibit PI3-K activity in a human or animal subject when administered thereto.

37. The composition of claim 36, effective to inhibit PI3-K alpha activity in a human or animal subject when administered thereto.

38. The composition of Claim 35 further comprising at least one additional agent for the treatment of cancer.

39. The composition of Claim 38, wherein the at least one additional agent for the treatment of cancer is vatalanib, imatinib or gefitinib.

40. A method for treating a condition by modulation of PI3-K activity comprising administering to a human or animal subject in need of such treatment an effective amount of a compound of any one of Claims 1-34.

41. The method of Claim 40, wherein the compound has an IC_{50} value of less than about 1 μM with respect to inhibition of PI3K.

42. The method of Claim 40, wherein the condition is cancer.

43. A method for inhibiting PI3-K activity in a human or animal subject, comprising administering to the human or animal subject a composition comprising an amount of a compound of any one of Claims 1-34 effective to inhibit PI3-K activity the human or animal subject.

44. A method for treating a cancer disorder in a human or animal subject, comprising administering to the human or animal subject a composition comprising an amount of a compound of any one of Claims 1-34 effective to inhibit PI3-K activity the human or animal subject.

45. The method of Claim 44 further comprising administering to the human or animal subject at least one additional agent for the treatment of cancer.

46. The method of Claim 45, wherein the at least one additional agent for the treatment of cancer is vatalanib, imatinib or gefitinib.

47. The method of Claim 44, wherein the cancer is breast cancer, bladder cancer, colon cancer, glioma, glioblastoma, lung cancer, hepatocellular cancer, gastric cancer, melanoma, thyroid cancer, endometrial cancer, renal cancer, cervical cancer, pancreatic cancer, esophageal cancer, prostate cancer, brain cancer, or ovarian cancer.

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48. A method of modulating phosphorylation of Akt comprising contacting a compound of any one of Claims 1-34 with a cell.

49. The method of Claim 48, wherein the compound has an EC_{50} value of less than about 1 μM with respect to inhibition of pAKT.

50. A compound of any one of Claims 1-34 for use in the treatment of cancer.

51. Use of a compound of any one of Claims 1-34 in the manufacture of a medicament for the treatment for cancer.

52. A kit, comprising a compound of any one of Claims 1-34 and a package insert or other labeling including directions for treating a cellular proliferative disease by administering a PI3-K inhibitory amount of the compound.

53. A method for inhibiting the activity of KSP kinesin which method comprises contacting said kinesin with an effective inhibitory amount of a compound of claim 1.

54. A method for inhibiting the activity of KSP kinesin in a cell which method comprises contacting said cell with an effective inhibitory amount of a compound of claim 1.

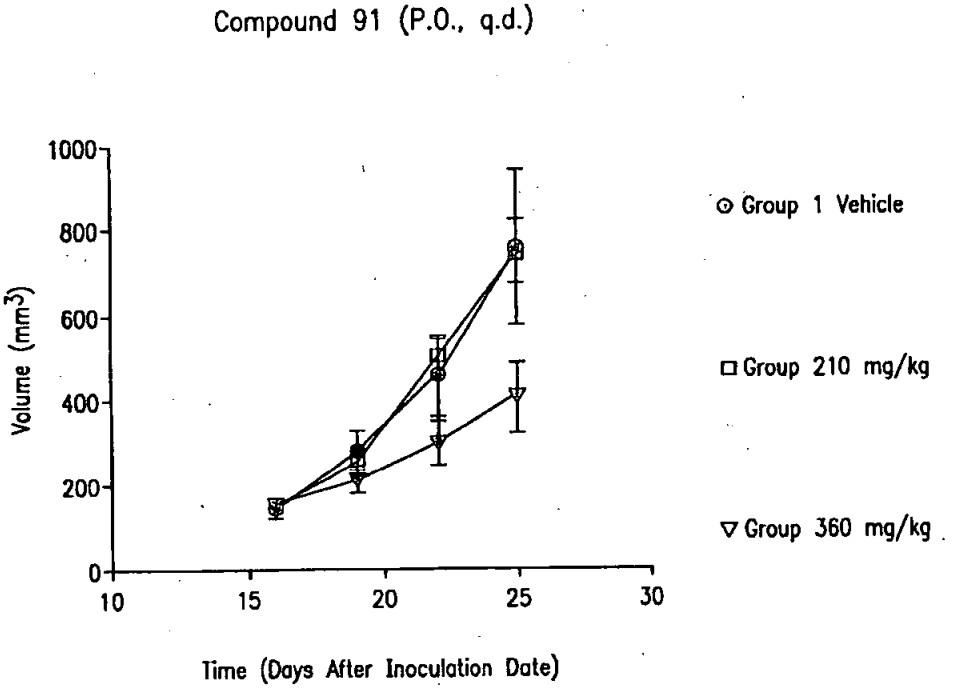

Compound 91 (P.O., q.d.)
1000
800
600
400
200
0
Volume (mm3)
10
15
20
25
30
Time (Days After Inoculation Date)
Group 1 Vehicle
Group 210 mg/kg
Group 360 mg/kg

FIG. 1

Compound 10 (P.O., q.d.)

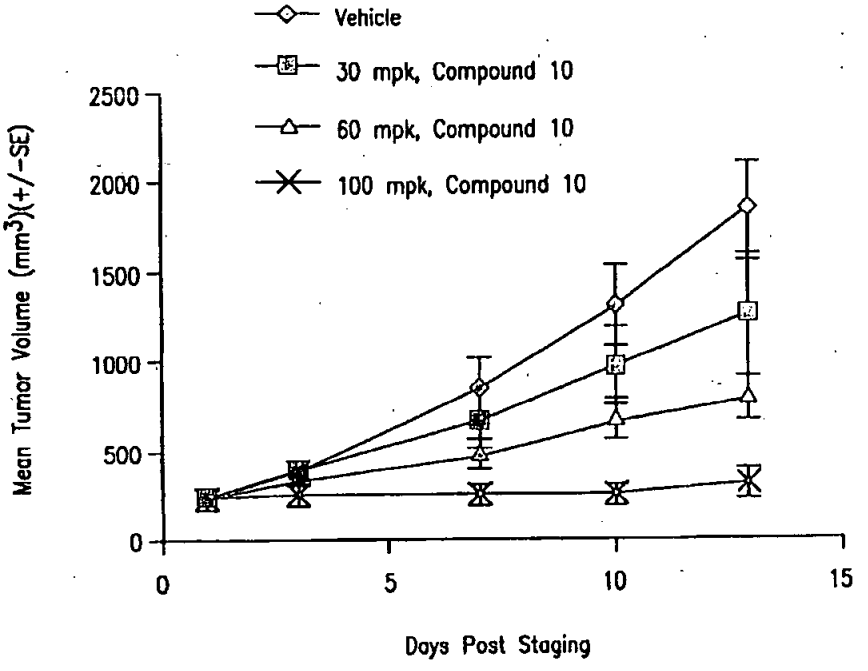


FIG. 2

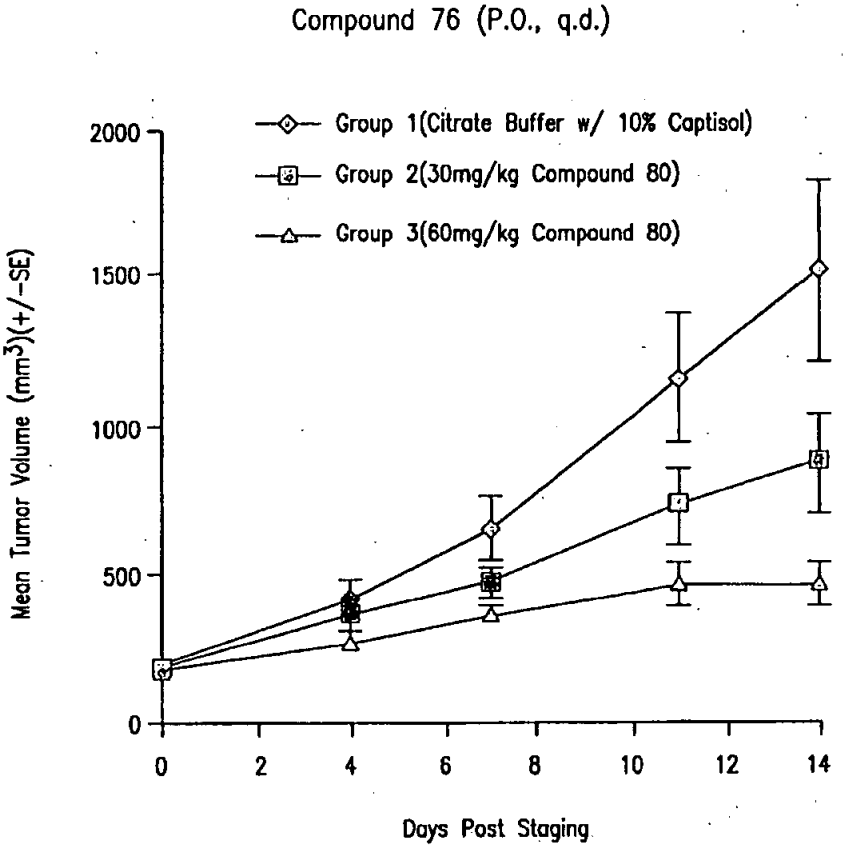

Compound 76 (P.O., q.d.)
Group 1(Citrate Buffer w/ 10% Captisol)
Group 2(30mg/kg Compound 80)
Group 3(60mg/kg Compound 80)
Mean Tumor Volume (mm3)(+/-SE)
2000
1500
1000
500
0
0
2
4
6
8
10
12
14
Days Post Staging

FIG. 3

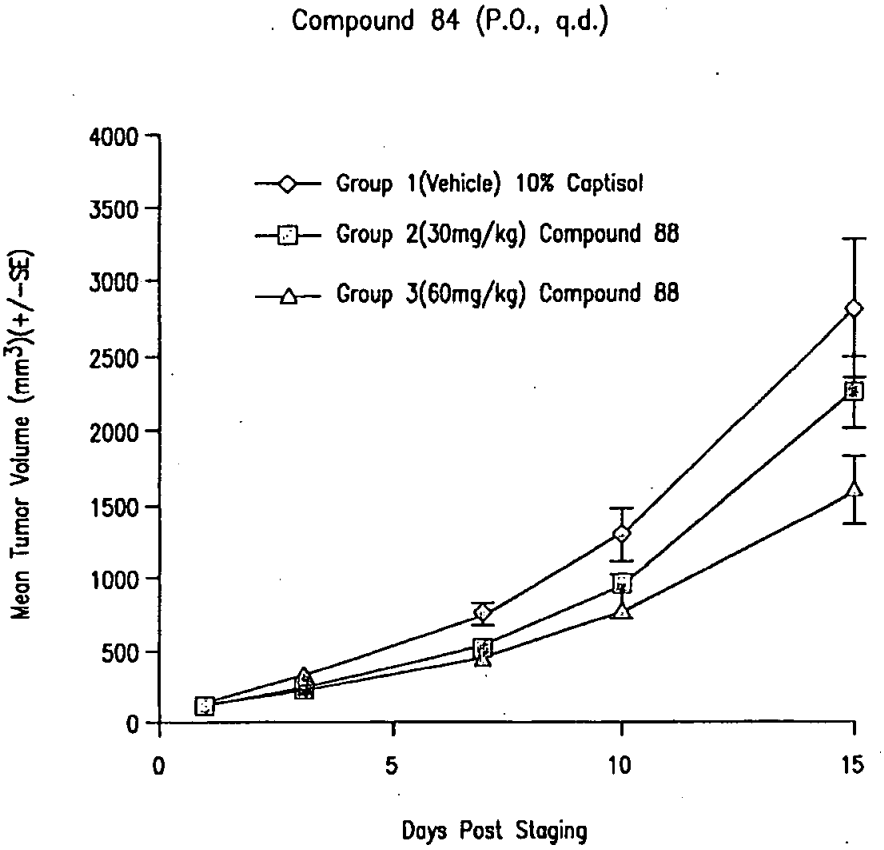

Compound 84 (P.O., q.d.)
Group 1(Vehicle) 10% Captisol
Group 2(30mg/kg) Compound 88
Group 3(60mg/kg) Compound 88
Mean Tumor Volume (mm3)(+/-SE)
4000
3500
3000
2500
2000
1500
1000
500
0
0
5
10
15
Days Post Staging

FIG. 4

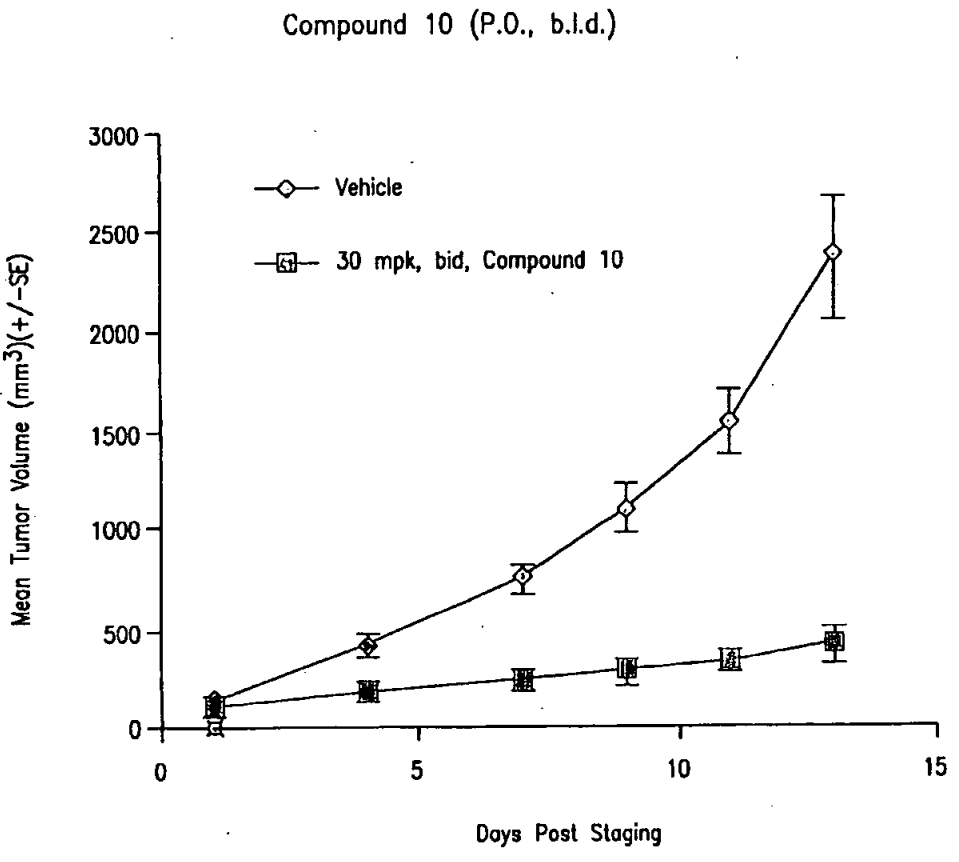

Compound 10 (P.O., b.i.d.)
Vehicle
30 mpk, bid, Compound 10
Mean Tumor Volume (mm^3)(+/-SE)
3000
2500
2000
1500
1000
500
0
0
5
10
15
Days Post Staging

FIG. 5

TRATADO DE COOPERACION EN MATERIA DE PATENTES

TCP

NOTIFICACION DEL REGISTRO DE UN CAMBIO

(Regla 92bis.1 del TCP e
Instrucciones Administrativas, Sección 422)

De la OFICINA INTERNACIONAL.

Para:
SUH, Young, J.
NOVARTIS VACCINES AND DIAGNOSTICS INC.
PROPIEDAD INTELECTUAL CORPORATIVA R338
P. O. Box 897
Emeryville, CA 94662-8097
ESTADOS UNIDOS DE AMÉRICA

Fecha de envío por correo (día/mes/año):
11 de julio de 2008 (11.07.2008)

Referencia de expediente del solicitante o agente:
PP028161.0002

NOTIFICACION IMPORTANTE

Solicitud Internacional No.
PCT/US2007/001708

Fecha de presentación internacional (día/mes/año):
22 de enero de 2007 (22.01.2007)

1. Las siguientes indicaciones aparecieron en el registro con respecto a:
(X) el solicitante.
(X) el inventor.
( ) el agente.
( ) el representante general.

Nombre y Dirección:
BARTULLIS, Sarah
HENDRYCKSON, Tom
c/o NOVARTIS VACCINES AND DIAGNOSTICS INC.
P. O. Box 8097
Emeryville, CA 94662-8097
Estados Unidos de América

País de Nacionalidad:

País de Residencia:
US

Teléfono No.

Facsímil No.

Teleimpresor No.

2. La Oficina Internacional notifica mediante la presente que se ha registrado el siguiente cambio con respecto a:
( ) la persona.
(X) el nombre.
( ) la dirección.
( ) la nacionalidad.
( ) la residencia.

Nombre y Dirección:
BARTULIS, Sarah
HENDRICKSON, Thomas
c/o NOVARTIS VACCINES AND DIAGNOSTICS INC.
P. O. Box 8097
Emeryville, CA 94662-8097
Estados Unidos de América

País de Nacionalidad:

País de Residencia:
US

Teléfono No.

Facsímil No.

Teleimpresor No.

3. Otras observaciones, si son necesarias:

4. Se ha enviado una copia de esta notificación a:
(X) la Oficina receptora.
( ) la Autoridad de Búsqueda Internacional.
( ) la Autoridad Examinadora Preliminar Internacional.
(X) las Oficinas designadas concernidas.
( ) las Oficinas elegidas concernidas.
( ) otra:

La Oficina Internacional de OMPI
34, chemin des Colombettes
1211 Ginebra 20, Suiza

Facsímil No. +41 22 338 89 65

Funcionario autorizado
Samuels Frederick

e-mail: pt02.pct@wipo.int
Teléfono No. +41 22 338 74 02

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From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

SUH, Young, J.
NOVARTIS VACCINES AND DIAGNOSTICS INC.
CORPORATE INTELLECTUAL PROPERTY R338
P.O. Box 897
Emeryville, CA 94662-8097
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*: 11 July 2008 (11.07.2008)

Applicant's or agent's file reference: PP028161.0002

IMPORTANT NOTIFICATION

International application No.: PCT/US2007/001708

International filing date *(day/month/year)*: 22 January 2007 (22.01.2007)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address:
BARTULLIS, Sarah
HENDRYCKSON, Tom
c/o NOVARTIS VACCINES AND DIAGNOSTICS INC.
P.O. Box 8097
Emeryville, CA 94662-8097
United States of America

State of Nationality:

State of Residence: US

Telephone No.:

Facsimile No.:

Teleprinter No.:

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:
BARTULIS, Sarah
HENDRICKSON, Thomas
c/o NOVARTIS VACCINES AND DIAGNOSTICS INC.
P.O. Box 8097
Emeryville, CA 94662-8097
United States of America

State of Nationality:

State of Residence: US

Telephone No.:

Facsimile No.:

Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ 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 89 65

Authorized officer
Samuels Frederick
e-mail pt02.pct@wipo.int
Telephone No. +41 22 338 74 02

(12) SOLICITUD INTERNACIONAL PUBLICADA DE ACUERDO CON EL TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES (TCP)
OMPI

(19) **Organización Mundial de la Propiedad Intelectual**
Oficina Internacional

TCP

(10) **Número de la Publicación Internacional:**
WO 2007/084786 A1

(43) **Fecha de la Publicación Internacional:**
26 de julio de 2007 (26.07.2007)

(51) **Clasificación de Patente Internacional:**
C07D 401/04 (2006.01) *C07D 405/12* (2006.01)
C07D 401/14 (2006.01) *A61K 31/506* (2006.01)
C07D 405/12 (2006.01) *A61P 35/00* (2006.01)
C07D 405/14 (2006.01)

(21) **Número de Solicitud Internacional:**
PCT/US2007/001708

(22) **Fecha de Presentación Internacional:**
22 de enero de 2007 (22.01.2007)

(25) **Idioma de Presentación:** Inglés

(26) **Idioma de Publicación:** Inglés

(30) **Información de Prioridad:**
60/760,789 20 de enero de 2006 (20.01.2006) US

(71) **Solicitante** (*para todos los Estados (Países) designados excepto US):* **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basilea (CH).

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(72) **Inventores; e**

(75) **Inventores/Solicitantes** (*para US solamente*): **BURGER, Matthew** [US/US]; C/O NOVARTIS VACCINES AND DIAGNOSTICS INC., P.O. Box 8097, Emeryville, CA 94662-8097 (US). **NI, Zhi-jie** [UG/US]; C/O NOVARTIS VACCINES AND DIAGNOSTICS INC., P.O. Box 8097, Emeryville, CA 94662-8097 (US). **PECCHI, Sabina** [--/US]; C/O NOVARTIS VACCINES AND DIAGNOSTICS INC., P.O. Box 8097, Emeryville, CA 94662-8097 (US). **ATALLAH, Gordana** [--/US]; C/O NOVARTIS VACCINES AND DIAGNOSTICS INC., P.O. Box 8097, Emeryville, CA 94662-8097 (US). **BARTULLIS, Sarah** [--/US]; C/O NOVARTIS VACCINES AND DIAGNOSTICS INC., P.O. Box 8097, Emeryville, CA 94662-8097 (US). **FRAZIER, Kelly** [US/US]; C/O NOVARTIS VACCINES AND DIAGNOSTICS INC., P.O. Box 8097, Emeryville, CA 94662-8097 (US). **SMITH, Aaron** [US/US]; C/O NOVARTIS VACCINES AND DIAGNOSTICS INC., PO Box 8097, Emeryville, CA 94662-8097 (US). **VERHAGEN, Joelle** [--/US]; C/O NOVARTIS VACCINES AND DIAGNOSTICS INC., PO Box 8097, Emeryville, CA 94662-8097 (US). **ZHANG, Yanchen** [--/US]; C/O NOVARTIS VACCINES AND DIAGNOSTICS INC., PO Box 8097, Emeryville, CA 94662-8097 (US). **WAGMAN, Allan** [US/US]; C/O NOVARTIS VACCINES AND DIAGNOSTICS INC., PO Box 8097, Emeryville, CA 94662-8097 (US). **NG, Simon** [US/US]; C/O NOVARTIS VACCINES AND DIAGNOSTICS INC., PO Box 8097, Emeryville, CA 94662-8097 (US). **PFISTER, Keith** [US/US]; C/O NOVARTIS VACCINES AND DIAGNOSTICS INC., PO Box 8097, Emeryville, CA 94662-8097 (US). **POON, Daniel** [US/US]; C/O NOVARTIS VACCINES AND DIAGNOSTICS INC., PO Box 8097, Emeryville, CA 94662-8097 (US). **LOUIE, Alicia** [--/US]; C/O NOVARTIS VACCINES AND DIAGNOSTICS INC., PO Box 8097, Emeryville, CA 94662-8097 (US).

(74) **Agentes:** **SUH, Young, J. et al.**; NOVARTIS VACCINES AND DIAGNOSTICS INC., PROPIEDAD INTELECTUAL CORPORATIVA R338, P.O. Box 897, Emeryville, CA 94662-8097 (US).

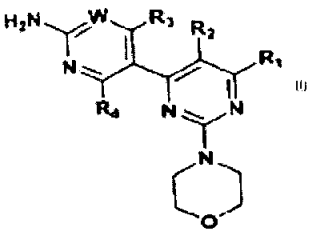
(81) **Estados (Países) Designados** (*a menos que se indique de otra manera, para cada clase de protección nacional disponible*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Estados (Países) Designados** (*a menos que se indique de otra manera, para cada clase de protección regional disponible*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, 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).

Publicada:
-- *con reporte de búsqueda internacional*

Para los códigos de dos letras y otras abreviaturas, refiérase a las "Notas de Orientación sobre Códigos y Abreviaturas" que aparecen al principio de cada publicación regular de la Gaceta del TCP.

(54) **Título:** DERIVADOS DE PIRIMIDINA UTILIZADOS COMO INHIBIDORES DE CINASA PI-3.



(I)

(57) **Resumen:** Compuestos inhibidores de cinasa de fosfatidil-inositol (PI) 3 (I), sus sales farmacéuticamente aceptables, y pro-fármacos de los mismos; composiciones de los nuevos compuestos, ya sea solos o en combinación con cuando menos un agente terapéutico adicional, con un vehículo farmacéuticamente aceptable; y usos de los nuevos compuestos, ya sea solos o en combinación con cuando menos un agente terapéutico adicional, en la profilaxis o el tratamiento de enfermedades proliferativas caracterizadas por la actividad anormal de los factores de crecimiento, cinasas de proteína serina/treonina,

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DERIVADOS DE PIRIMIDINA UTILIZADOS COMO INHIBIDORES DE CINASA PI-3

CAMPO DE LA INVENCIÓN

La presente invención se refiere a nuevos compuestos inhibidores de cinasa de fosfatidil-inositol (PI)-3, a sus sales farmacéuticamente aceptables, y a pro-fármacos de los mismos; a composiciones de los nuevos compuestos, ya sea solos o bien en combinación con cuando menos un agente terapéutico adicional, con un vehículo farmacéuticamente aceptable; y al uso de los nuevos compuestos, ya sea solos o bien en combinación con cuando menos un agente terapéutico adicional, en la profilaxis o el tratamiento de un número de enfermedades, en particular, aquéllas caracterizadas por una actividad anormal de factores del crecimiento, cinasas de tirosina receptoras, cinasas de proteína serina/treonina, receptores acoplados con proteína-G y cinasas y fosfatasas de fosfolípido.

ANTECEDENTES DE LA INVENCIÓN

Las cinasas de fosfatidil-inositol-3 (PI3Ks) comprenden una familia de cinasas de lípido y de serina/treonina que catalizan la transferencia de fosfato a la posición D-3' de los lípidos de inositol para producir fosfoinositol-3-fosfato (PIP), fosfoinositol-3,4-difosfato (PIP_2) y fosfoinositol-3,4,5-trifosfato (PIP_3) que, a su vez, actúan como segundos mensajeros en las cascadas de señalización mediante las proteínas de acoplamiento que contienen homología de pleckstrina, FYVE, Phox y otros dominios enlazadores de fosfolípido

en una variedad de complejos de señalización a menudo en la membrana de plasma ((Vanhaesebroeck y colaboradores, *Annu. Rev. Biochem* 70:535 (2001); Katso y colaboradores, *Annu. Rev. Cell Dev. Biol.* 17: 615 (2001)). De las dos PI3Ks Clase 1, las PI3Ks Clase 1A son heterodímeros compuestos de una subunidad catalítica p110 (isoformas α, ß, δ) constitutivamente asociada con una subunidad reguladora que puede ser p85α, p55α, p50α, p85ß o p55γ. La sub-clase Clase 1B tiene un miembro de la familia, un heterodímero compuesto de una subunidad catalítica p110γ asociada con una de dos subunidades reguladoras, p101 o p84 (Fruman y colaboradores, *Annu Rev. Biochem.* 67: 481 (1998); Suire y colaboradores, *Curr. Biol.* 15: 566 (2005)). Los dominios modulares de las subunidades p85/55/50 incluyen los dominios de Homología con Src (SH2) que se enlazan con los residuos de fosfotirosina en un contexto de secuencia específico sobre las cinasas de tirosina citoplásmicas y receptoras activadas, dando como resultado la activación y localización de las PI3Ks Clase 1A. La PI3K Clase 1B es directamente activada por los receptores acoplados con proteína-G que se enlazan con un diverso repertorio de ligandos peptídicos y no peptídicos (Stefens y colaboradores, *Cell* 89: 105 (1997)); Katso y colaboradores, *Annu. Rev. Cell Dev. Biol.* 17: 615-675 (2001)). En consecuencia, los productos de fosfolípido resultantes de PI3K Clase I se enlazan con los receptores corriente arriba con actividades celulares corriente abajo, incluyendo la proliferación, sobrevivencia, quimiotaxis, tráfico celular, movilidad, metabolismo, respuestas

inflamatorias y alérgicas, transcripción y traducción (Cantley y colaboradores, *Cell* 64: 281 (1991); Escobedo y Williams, *Nature* 335:85 (1988); Fantl y colaboradores, *Cell* 69: 413 (1992)).

En muchos casos, PIP2 y PIP3 reclutan la Akt, el producto del homólogo humano del oncogén viral *v-Akt*, hacia la membrana de plasma, en donde actúa como un punto nodal para muchas sendas de señalización intracelulares importantes para el crecimiento y la sobrevivencia (Fantl y colaboradores, *Cell* 69: 413-423(1992); Bader y colaboradores, *Nat Rev. Cancer* 5: 921 (2005); Vivanco y Sawyer, *Nat. Rev. Cancer* 2: 489 (2002)). La regulación aberrante de PI3K, que con frecuencia aumenta la sobrevivencia a través de la activación de Akt, es uno de los eventos más prevalecientes en el cáncer humano, y se ha demostrado que se presenta en múltiples niveles. El gen supresor de tumor *PTEN*, que desfosforila las fosfoinositidas en la posición 3' del anillo de inositol, y al hacerlo de esa manera antagoniza la actividad de PI3K, se suprime funcionalmente en una variedad de tumores. En otros tumores, se amplifican los genes para la isoforma p110α, *PIK3CA*, y para *Akt*, y se ha demostrado un aumento de la expresión de proteína de sus productos genéticos en varios cánceres humanos. Adicionalmente, se han descrito mutaciones y la translocalización de p85α que sirven para aumentar el complejo p85-p110 en unos cuantos cánceres humanos.. Finalmente, se han descrito mutaciones en mal sentido somáticas en *PIK3CA* que activan las sendas de señalización corriente abajo en frecuencias significativas en una amplia

diversidad de cánceres humanos (Kang y colaboradores, *Proc. Natl. Acad. Sci. EUA* 102: 802 (2005); Samuels y colaboradores, *Science* 304: 554 (2004); Samuels y colaboradores, *Cancer Cell* 7:561-573 (2005)). Estas observaciones muestran que la desregulación de la cinasa de fosfoinositol-3 y los componentes corriente arriba y corriente abajo de esta senda de señalización, es una de las desregulaciones más comunes asociadas con los cánceres humanos y las enfermedades proliferativas (Parsons y colaboradores, *Nature* 436: 792 (2005); Hennessey y colaboradores, *Nature Rev. Drug Dis.* 4: 988-1004 (2005)).

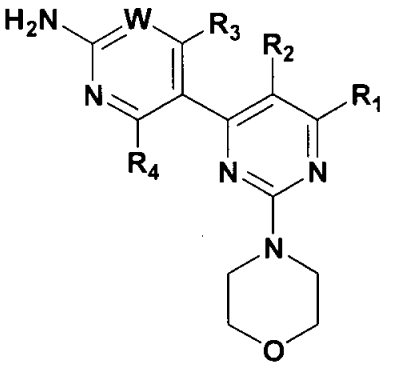
BREVE DESCRIPCIÓN DE LA INVENCIÓN

La presente invención proporciona nuevos compuestos inhibidores de cinasa de fostatildil-inositol-3 (PI3K), formulaciones farmacéuticas que incluyen los compuestos, métodos para inhibir la cinasa de fosfatidil-inositol-3 (PI3K), y métodos para el tratamiento de enfermedades proliferativas.

En un aspecto de la presente invención, se proporcionan nuevos compuestos inhibidores de cinasa de fosfatidil-inositol-3 (PI3K) que son compuestos basados en pirimidina, sus sales farmacéuticamente aceptables, y pro-fármacos de los mismos. Los compuestos de pirimidina, las sales farmacéuticamente aceptables, y los pro-fármacos son inhibidores de PI3K y son útiles en el tratamiento de enfermedades de proliferación celular.

Una modalidad de la invención proporciona un compuesto que tiene la fórmula I:

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I

o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable del mismo, en donde,

W es CR_w o N, en donde R_w se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) halógeno,

(4) metilo,

(5) trifluoro-metilo,

(6) sulfonamido;

R_1 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) nitro,

(4) halógeno,

(5) alquilo sustituido e insustituido,

(6) alquenilo sustituido e insustituido,

(7) alquinilo sustituido e insustituido,

(8) arilo sustituido e insustituido,

(9) heteroarilo sustituido e insustituido,

(10) heterociclilo sustituido e insustituido,

(11) cicloalquilo sustituido e insustituido,

(12) $-COR_{1a}$,

(13) $-CO_2R_{1a}$,

(14) $-CONR_{1a}R_{1b}$,

(15) $-NR_{1a}R_{1b}$,

(16) $-NR_{1a}COR_{1b}$,

(17) $-NR_{1a}SO_2R_{1b}$,

(18) $-OCOR_{1a}$,

(19) $-OR_{1a}$,

(20) $-SR_{1a}$,

(21) $-SOR_{1a}$,

(22) $-SO_2R_{1a}$, y

(23) $-SO_2NR_{1a}R_{1b}$,

en donde R_{1a} y R_{1b} se seleccionan independientemente a partir del grupo que consiste en:

(a) hidrógeno,

(b) alquilo sustituido o insustituido,

(c) arilo sustituido e insustituido,

(d) heteroarilo sustituido e insustituido,

(e) heterociclilo sustituido e insustituido, y

(f) cicloalquilo sustituido e insustituido;

R_2 se selecciona a partir del grupo que consiste en:

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(1) hidrógeno,

(2) ciano,

(3) nitro,

(4) halógeno,

(5) hidroxilo,

(6) amino,

(7) alquilo sustituido e insustituido,

(8) $-COR_{2a}$, y

(9) $-NR_{2a}COR_{2b}$,

en donde R_{2a} y R_{2b} se seleccionan independientemente a partir del grupo que consiste en:

(a) hidrógeno, y

(b) alquilo sustituido o insustituido;

R_3 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) nitro,

(4) halógeno,

(5) alquilo sustituido e insustituido,

(6) alquenilo sustituido e insustituido,

(7) alquinilo sustituido e insustituido,

(8) arilo sustituido e insustituido,

(9) heteroarilo sustituido e insustituido,

(10) heterociclilo sustituido e insustituido,

(11) cicloalquilo sustituido e insustituido,

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(12) $-COR_{3a}$,

(13) $-NR_{3a}R_{3b}$,

(14) $-NR_{3a}COR_{3b}$,

(15) $-NR_{3a}SO_2R_{3b}$,

(16) $-OR_{3a}$,

(17) $-SR_{3a}$,

(18) $-SOR_{3a}$,

(19) $-SO_2R_{3a}$, y

(20) $-SO_2NR_{3a}R_{3b}$,

en donde R_{3a} y R_{3b} se seleccionan independientemente a partir del grupo que consiste en:

(a) hidrógeno,

(b) alquilo sustituido o insustituido,

(c) arilo sustituido e insustituido,

(d) heteroarilo sustituido e insustituido,

(e) heterociclilo sustituido e insustituido, y

(f) cicloalquilo sustituido e insustituido; y

R_4 se selecciona a partir del grupo que consiste en:

(1) hidrógeno, y

(2) halógeno.

En otra modalidad de la presente, R_1 comprende aril-alquilo sustituido o insustituido, hetero-aril-alquilo sustituido o insustituido, cicloalquil-alquilo sustituido o insustituido, o heterociclil-alquilo sustituido o insustituido.

En una modalidad más particular, W es CH.

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En otra modalidad, W es N. En una modalidad más particular de la presente, R_3 es =O.

En otra modalidad, R_1 se selecciona a partir del grupo que consiste en:

(1) alquilo sustituido e insustituido,

(2) arilo sustituido e insustituido,

(3) heteroarilo sustituido e insustituido,

(4) heterociclilo sustituido e insustituido,

(5) cicloalquilo sustituido e insustituido,

(6) $-OR_{1a}$, y

(7) $-NR_{1a}R_{1b}$,

en donde R_{1a} y R_{1b} se seleccionan independientemente a partir del grupo que consiste en:

(a) heteroarilo sustituido e insustituido, y

(b) heterociclilo sustituido e insustituido.

En otra modalidad R_1 es heterociclilo sustituido o insustituido, u -O-heterociclilo sustituido o insustituido. En otra modalidad, R_1 es morfolinilo sustituido o insustituido; todavía más particularmente, R_1 es morfolinilo N-enlazado insustituido.

En otra modalidad de la misma, R_1 comprende heterociclil-alquilo sustituido o insustituido, o hetero-aril-alquilo sustituido o insustituido. En otra modalidad, R_1 comprende morfolinilo sustituido o insustituido; todavía más particularmente, el morfolinilo comprende morfolinilo N-enlazado.

En otra modalidad, R_1 es tetrahidro-pirano sustituido o

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insustituido o tetrahidro-piraniloxilo sustituido o insustituido. Todavía más particularmente, R_1 es 4-tetrahidro-piraniloxilo insustituido.

En otra modalidad de la misma, R_1 comprende tetrahidro-pirano sustituido o insustituido. En una modalidad más particular, el tetrahidro-pirano comprende 4-tetrahidro-piraniloxilo.

En otra modalidad, R_1 es tetrahidrofurano sustituido o insustituido o tetrahidro-furaniloxilo sustituido o insustituido. Todavía más particularmente, R_1 es 3-tetrahidro-furaniloxilo insustituido.

En otra modalidad, R_1 comprende tetrahidrofurano sustituido o insustituido. En otra modalidad de la presente, tetrahidrofurano comprende 3-tetrahidro-furaniloxilo.

En otra modalidad, R_2 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) hidroxilo,

(4) halógeno,

(5) amino,

(6) metilo, y

(7) trifluoro-metilo.

En otra modalidad, R_2 es hidrógeno o halógeno. En a una modalidad más particular, R_2 es hidrógeno.

En otra modalidad, R_3 se selecciona a partir del grupo que consiste en;

(1) ciano,

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(2) nitro,

(3) halógeno,

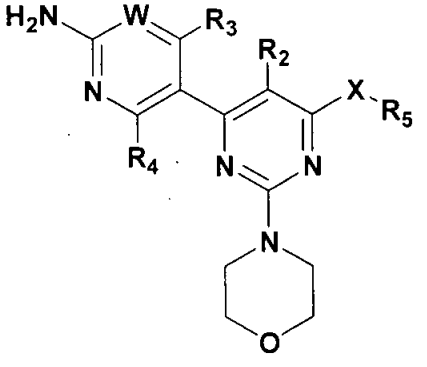
(4) hidroxilo,

(5) amino, y

(6) trifluoro-metilo.

En otra modalidad, R_3 es trifluoro-metilo. En otra modalidad, R_3 es ciano.

Otra modalidad de la invención proporciona un compuesto que tiene la fórmula II:



II

o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable del mismo, en donde:

W es CR_w o N, en donde R_w se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

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(3) halógeno,

(4) metilo,

(5) trifluoro-metilo, y

(6) sulfonamido;

X es O, S, NH, o un enlace directo;

R_2 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) nitro,

(4) halógeno,

(5) hidroxilo,

(6) amino,

(7) alquilo sustituido e insustituido,

(8) $-COR_{2a}$, y

(9) $-NR_{2a}COR_{2b}$,

en donde R_{2a} y R_{2b} se seleccionan independientemente a partir del grupo que consiste en:

(a) hidrógeno, y

(b) alquilo sustituido o insustituido;

R_3 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) nitro,

(4) halógeno,

(5) alquilo sustituido e insustituido,

(6) alquenilo sustituido e insustituido,

(7) alquinilo sustituido e insustituido,

(8) arilo sustituido e insustituido,

(9) heteroarilo sustituido e insustituido,

(10) heterociclilo sustituido e insustituido,

(11) cicloalquilo sustituido e insustituido,

(12) $-COR_{3a}$,

(13) $-NR_{3a}R_{3b}$,

(14) $-NR_{3a}COR_{3b}$,

(15) $-NR_{3a}SO_2R_{3b}$,

(16) $-OR_{3a}$,

(17) $-SR_{3a}$,

(18) $-SOR_{3a}$,

(19) $-SO_2R_{3a}$, y

(20) $-SO_2NR_{3a}R_{3b}$,

en donde R_{3a} y R_{3b} se seleccionan independientemente a partir del grupo que consiste en:

(a) hidrógeno,

(b) alquilo sustituido o insustituido,

(c) arilo sustituido e insustituido,

(d) heteroarilo sustituido e insustituido,

(e) heterociclilo sustituido e insustituido, y

(f) cicloalquilo sustituido e insustituido;

R_4 se selecciona a partir del grupo que consiste en:

(1) hidrógeno, y

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(2) halógeno; y

R_5 se selecciona a partir del grupo que consiste en:

(1) cicloalquilo sustituido e insustituido,

(2) heterociclilo sustituido e insustituido,

(3) arilo sustituido e insustituido, y

(4) heteroarilo sustituido e insustituido.

En otra modalidad de la fórmula II, R_2 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) hidroxilo,

(4) amino,

(5) halógeno, y

(6) alquilo de 1 a 3 átomos de carbono sustituido e insustituido.

En otra modalidad de la fórmula II, R_3 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) tio,

(4) halógeno,

(5) nitro,

(6) alquilo sustituido e insustituido,

(7) alquenilo sustituido e insustituido,

(8) alquinilo sustituido e insustituido,

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(9) $-OR_{3a}$,

(10) $-NR_{3a}R_{3b}$,

(11) $-COR_{3a}$, y

(12) $-NR_{3a}COR_{3b}$,

en donde R_{3a} y R_{3b} se seleccionan independientemente a partir del grupo que consiste en:

(a) hidrógeno, y

(b) alquilo sustituido o insustituido.

En otra modalidad de la fórmula II, R_3 es trifluoro-metilo. En otra modalidad, W es CH. En otra modalidad, R_2 es H.

En otra modalidad de la fórmula II, R_5 se selecciona a partir del grupo que consiste en:

(1) morfolinilo sustituido o insustituido,

(2) tetrahidro-piranilo sustituido o insustituido, y

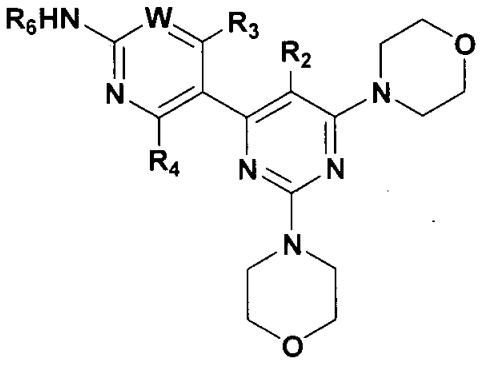
(3) tetrahidro-furanilo sustituido o insustituido.

En una modalidad más particular de la presente, R_5 es morfolinilo N-enlazado; todavía más particularmente, X es un enlace directo. En otra modalidad más particular, R_5 es 4-tetrahidro-piranilo; todavía más particularmente, X es O. En otra modalidad, R_5 es 3-tetrahidro-furanilo; todavía más particularmente, X es O.

En otra modalidad, W es N. En una modalidad más particular de la presente, R_3 es =O.

Otra modalidad de la invención proporciona un compuesto que tiene la fórmula III:

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III

o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable del mismo, en donde:

W es CR_w o N, en donde R_w se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) halógeno,

(4) metilo,

(5) trifluoro-metilo, y

(6) sulfonamido;

R_2 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) nitro,

(4) halógeno,

(5) hidroxilo,

(6) amino,

(7) alquilo sustituido e insustituido,

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(8) $-COR_{2a}$, y

(9) $-NR_{2a}COR_{2b}$,

en donde R_{2a} y R_{2b} se seleccionan independientemente a partir del grupo que consiste en:

(a) hidrógeno, y

(b) alquilo sustituido o insustituido;

R_3 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) nitro,

(4) halógeno,

(5) alquilo sustituido e insustituido,

(6) alquenilo sustituido e insustituido,

(7) alquinilo sustituido e insustituido,

(8) arilo sustituido e insustituido,

(9) heteroarilo sustituido e insustituido,

(10) heterociclilo sustituido e insustituido,

(11) cicloalquilo sustituido e insustituido,

(12) $-COR_{3a}$,

(13) $-NR_{3a}R_{3b}$,

(14) $-NR_{3a}COR_{3b}$,

(15) $-NR_{3a}SO_2R_{3b}$,

(16) $-OR_{3a}$,

(17) $-SR_{3a}$,

(18) $-SOR_{3a}$,

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(19) $-SO_2R_{3a}$, y

(20) $-SO_2NR_{3a}R_{3b}$,

en donde R_{3a} y R_{3b} se seleccionan independientemente a partir del grupo que consiste en:

(a) hidrógeno,

(b) alquilo sustituido o insustituido,

(c) arilo sustituido e insustituido,

(d) heteroarilo sustituido e insustituido,

(e) heterociclilo sustituido e insustituido, y

(f) cicloalquilo sustituido e insustituido;

R_4 se selecciona a partir del grupo que consiste en:

(1) hidrógeno, y

(2) halógeno; y

R_6 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) alquilo sustituido e insustituido, y

(3) cicloalquilo sustituido e insustituido.

En otra modalidad de la fórmula III, R_2 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) hidroxilo,

(4) halógeno,

(5) amino,

(6) metilo, y

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(7) trifluoro-metilo.

En otra modalidad de la fórmula III, R_3 se selecciona a partir del grupo que consiste en:

(1) ciano,

(2) nitro,

(3) halógeno,

(4) hidroxilo,

(5) amino, y

(6) trifluoro-metilo.

En otra modalidad de la fórmula III, R_6 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) metilo, y

(3) etilo.

Otra modalidad proporciona un método para inhibir la fosforilación de Akt en un sujeto humano o animal, el cual comprende administrar a un sujeto humano o animal una cantidad efectiva de un compuesto de cualquiera de las modalidades proporcionadas en la presente.

Otra modalidad proporciona una composición, que comprende un vehículo farmacéuticamente aceptable, y una cantidad de un compuesto de cualquiera de las modalidades proporcionadas en la presente, efectiva para inhibir la actividad del PI3-K en un sujeto humano o animal cuando se administra al mismo. En una modalidad más particular de la presente, la composición es efectiva para inhibir

la actividad de PI3-K alfa en un sujeto humano o animal cuando se administra al mismo.

Otra modalidad proporciona una composición, que comprende un vehículo farmacéuticamente aceptable, una cantidad de un compuesto de cualquiera de las modalidades proporcionadas en la presente efectiva para inhibir la actividad del PI3-K en un sujeto humano o animal cuando se administra al mismo, y cuando menos un agente adicional para el tratamiento de cáncer. En una modalidad más particular de la presente, cuando menos un agente adicional para el tratamiento de cáncer es vatalanib (PTK-787), imatinib ó gefitinib. De una manera alternativa, cuando menos un agente adicional para el tratamiento de cáncer se selecciona a partir de inhibidores de cinasa, anti-estrógenos, anti-andrógenos, otros inhibidores, fármacos quimioterapéuticos de cáncer, agentes alquilantes, agentes quelantes, modificadores de la respuesta biológica, vacunas de cáncer, o terapias anti-sentido (grupos A-J) enlistadas más adelante. Además, cuando menos un agente adicional para el tratamiento de cáncer se selecciona a partir de radiación, análogos de nucleósidos, o agentes anti-mitóticos.

Otra modalidad proporciona un método para el tratamiento de una condición mediante la modulación de la actividad de PI3-K, el cual comprende administrar a un sujeto humano o animal que necesite dicho tratamiento una cantidad efectiva de un compuesto de cualquiera de las modalidades proporcionadas en la presente. En una modalidad más particular, el compuesto tiene un valor IC_{50} de

menos de aproximadamente 1 μM con respecto a la inhibición de PI3K. En otra una modalidad más particular, la condición es cáncer.

Otra modalidad proporciona un método para inhibir la actividad de PI3-K en un sujeto humano o animal, el cual comprende administrar al sujeto humano o animal una composición que comprende una cantidad de un compuesto de cualquiera de las modalidades proporcionadas en la presente, efectiva para inhibir la actividad del PI3-K en un sujeto humano o animal.

Otra modalidad proporciona un método para el tratamiento de un trastorno de cáncer en un sujeto humano o animal, el cual comprende administrar al sujeto humano o animal una composición que comprende una cantidad de un compuesto de cualquiera de las modalidades proporcionadas en la presente, efectiva para inhibir la actividad del PI3-K en un sujeto humano o animal. Una modalidad más particular además comprende administrar al sujeto humano o animal cuando menos un agente adicional para el tratamiento de cáncer. En otra modalidad, cuando menos un agente adicional para el tratamiento de cáncer es vatalanib, imatinib ó gefitinib. De una manera alternativa, cuando menos un agente adicional para el tratamiento de cáncer se selecciona a partir de inhibidores de cinasa, anti-estrógenos, anti-andrógenos, otros inhibidores, fármacos quimioterapéuticos de cáncer, agentes alquilantes, agentes quelantes, modificadores de la respuesta biológica, vacunas de cáncer, o terapias anti-sentido (grupos A-J) enlistadas más adelante.

En otra modalidad de cualquiera de las mencionadas

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mencionadas, el cáncer es cáncer de mama, cáncer de vejiga, cáncer de colon, glioma, glioblastoma, cáncer de pulmón, cáncer de células hepáticas, cáncer gástrico, melanoma, cáncer de tiroides, cáncer endometrial, cáncer renal, cáncer cervical, cáncer pancreático, cáncer esofágico, cáncer de próstata, cáncer de cerebro, o cáncer de ovario.

Otra modalidad proporciona un método para modular la fosforilación de Akt, el cual comprende poner un compuesto de cualquiera de las modalidades descritas en la presente en contacto con una célula. Otra modalidad proporciona un método para modular la fosforilación de Akt, el cual comprende poner una célula en contacto con un compuesto de cualquiera de las modalidades descritas en la presente. En una modalidad más particular de la presente, dicha modulación es inhibición. En a una modalidad más particular, el compuesto tiene un valor EC_{50} de menos de aproximadamente 1 μM con respecto a la inhibición de pAKT. En a una modalidad todavía más particular, el compuesto tiene un valor EC_{50} de menos de aproximadamente 0.5 μM con respecto a la inhibición de pAKT. En todavía una modalidad más particular, el compuesto tiene un valor EC_{50} de menos de aproximadamente 0.1 μM con respecto a la inhibición de pAKT.

Otra modalidad proporciona un compuesto de cualquiera de las modalidades descritas en la presente para utilizarse en el tratamiento de cáncer.

Otra modalidad proporciona el uso de un compuesto de

cualquiera de las modalidades descritas en la presente en la fabricación de un medicamento para el tratamiento de cáncer.

Otra modalidad proporciona un método para modular la fosforilación de Akt, el cual comprende poner un compuesto de la presente invención en contacto con una célula. En una modalidad más particular de la presente, el compuesto tiene un valor EC_{50} de menos de aproximadamente 1 μM con respecto a la inhibición de pAKT.

Otra modalidad proporciona un compuesto de cualquiera de las modalidades descritas en la presente, y un inserto del paquete u otra etiqueta, incluyendo instrucciones para el tratamiento de una enfermedad de proliferación celular mediante la administración de una cantidad inhibidora de PI3-K del compuesto.

La invención proporciona además composiciones, kits, métodos de uso, y métodos de fabricación como se describen en la Descripción Detallada de la Invención.

BREVE DESCRIPCIÓN DE LOS DIBUJOS

Los aspectos anteriores y muchas de las ventajas aunadas de esta invención llegarán a ser más fácilmente apreciadas a medida que las mismas lleguen a ser mejor entendidas haciendo referencia a la siguiente descripción detallada, al tomarse en conjunto con los dibujos acompañantes, en donde:

La Figura 1 es una gráfica que ilustra la inhibición del crecimiento tumoral para un compuesto representativo de la invención en dos dosificaciones comparándose con un vehículo de

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control;

La Figura 2 es una gráfica que ilustra la inhibición del crecimiento tumoral para un compuesto representativo de la invención en tres dosificaciones comparándose con un vehículo de control;

La Figura 3 es una gráfica que ilustra la inhibición del crecimiento tumoral para un compuesto representativo de la invención en dos dosificaciones comparándose con un vehículo de control;

La Figura 4 es una gráfica que ilustra la inhibición del crecimiento tumoral para un compuesto representativo de la invención en dos dosificaciones comparándose con un vehículo de control; y

La Figura 5 es una gráfica que ilustra la inhibición del crecimiento tumoral para un compuesto representativo de la invención comparándose con un vehículo de control.

DESCRIPCIÓN DETALLADA DE LA MODALIDAD PREFERIDA

La cinasa de fosfatidil-inositol-3 (PI3K) media la señal a partir de diferentes factores de crecimiento para regular la proliferación y sobrevivencia celular. Una cinasa de proteína serina/treonina (Ser/Thr, o S/T), denominada como Akt, se identifica como un objetivo corriente abajo de la cinasa-PI3. Esta cinasa de proteína se recluta en la membrana celular mediante la interacción de su dominio de homología de pleckstrina con los productos de PI3K, fosfatidil-inositol-3,4,5-trifosfato (PIP_3), y fosfatidil-inositol-3,4-bifosfato

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(PIP_2), en donde se activa mediante la fosforilación de su dominio catalítico por medio de la cinasa dependiente de 3-fosfoinositida-1 (PDK-1). Akt se activa además mediante la fosforilación de una serina en su motivo hidrofóbico C-terminal mediante otra cinasa candidata (PDK-2). La activación de Akt actúa corriente abajo para regular cinasas adicionales, muchas de las cuales están implicadas en los procesos celulares que controlan la sobrevivencia, proliferación, metabolismo, y traducción del crecimiento. La PI3K también puede impulsar los procesos celulares que impactan la transformación, la proliferación celular, la reconfiguración y sobrevivencia citoesquelética a través de una senda paralela que no involucra a la Akt (Hennessy y colaboradores, *Nat. Rev. Drug Disc.* 4: 988-1004 (2005)). Dos de estas sendas son la activación de las proteínas de enlace de GTP pequeñas Cdc42 y Rac1, y la activación de la cinasa de suero e inducible por glucocorticoide (SGK). Cdc42 y Rac1, las cuales regulan el movimiento citoesquelético y la movilidad celular, y pueden funcionar como oncogenes cuando se sobre-expresan, y también se enlazan con la senda de RAS. Por consiguiente, la actividad de PI3K genera lípidos de 3'-fosfatidil-inositol que actúan como un punto nodal para estimular una diversidad de sendas de señalización corriente abajo.

El hecho de que estas sendas impacten las propiedades de proliferación, sobrevivencia, movilidad, y morfología celular, que con frecuencia son alteradas en el cáncer, en las enfermedades proliferativas, en las enfermedades trombóticas, y en la inflamación,

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entre otras, sugiere que los compuestos que inhiben PI3K (y las isoformas de los mismos) tengan utilidad, ya sea como un solo agente o bien en combinación, en el tratamiento de estas enfermedades. En el cáncer, la desregulación de la senda de PI3K/Akt está extensamente documentada, incluyendo la sobre-expresión del gen *PIK3CA*, la activación de mutaciones del gen *PIK3CA*, la sobre-expresión de Akt, las mutaciones de *PDK-1*, y las supresiones/la inactivación de *PTEN* (Parsons y colaboradores, *Nature* 436: 792 (2005); Hennessy y colaboradores, *Nat. Rev. Drug Disc.* 4: 988 (2005); Stefens y colaboradores, *Curr. Opin. Pharmacol.* 5: 1 (2005); Bonneau y Longy, *Human Mutation* 16: 109 (2000) y Ali y colaboradores, *J. Natl. Can. Inst.* 91:1922 (1999)). Los descubrimientos recientes indican que *PIK3CA* se muta con frecuencia (>30 por ciento) en diferentes tumores sólidos en los seres humanos (Samuels y Ericson, *Curr. Opin. Oncology* 18: 77 (2005)) y las más frecuentes de estas mutaciones promueven el crecimiento celular y la invasión (Samuels y colaboradores, *Cancer Cell* 7: 561 (2005), y son transformantes (Kang y colaboradores, *Proc. Natl. Acad. Sci. EUA* 102: 802 (2005), Zhao y colaboradores, *Proc. Natl. Acad. Sci. EUA* 102: 18443 (2005)). Por consiguiente, los inhibidores de PI3K, en particular de la isoforma p110α codificada por *PIK3CA* y sus mutaciones, serán útiles en el tratamiento de cánceres impulsados por estas mutaciones y desregulaciones.

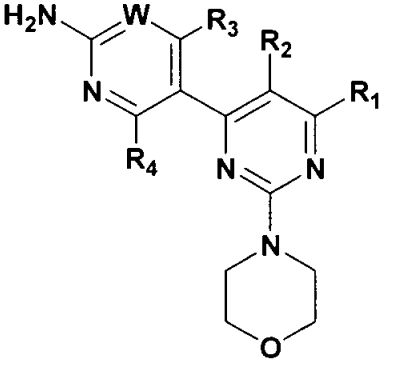
La presente invención proporciona compuestos novedosos que actúan como inhibidores de las cinasas de serina-treonina, de las

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cinasas de lípido, y, más particularmente, como inhibidores de la función de la cinasa de fosfatidil-inositol-3 (PI3K). Los compuestos proporcionados en la presente se pueden formular en formulaciones farmacéuticas que son útiles en el tratamiento de pacientes con necesidad de un inhibidor de PI3K, en especial, en las modalidades particulares, para proporcionar composiciones y métodos para reducir la proliferación celular y aumentar la muerte celular en el tratamiento de cáncer.

En un aspecto de la presente invención, se proporcionan nuevos compuestos inhibidores de cinasa de fosfatidil-inositol-3 (PI3K), sus sales farmacéuticamente aceptables, y pro-fármacos de los mismos. Los compuestos inhibidores de PI3-K son compuestos basados en pirimidina. Los compuestos de pirimidina, las sales farmacéuticamente aceptables, y pro-fármacos de los mismos, son inhibidores de PI3-K, y son útiles en el tratamiento de enfermedades de proliferación celular.

En una modalidad, los compuestos inhibidores de cinasa de fosfatidil-inositol-3 (PI3-K) de la invención tienen la fórmula (I):



I

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o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, en donde,

W es CR_w o N, en donde R_w se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) halógeno,

(4) metilo,

(5) trifluoro-metilo, y

(6) sulfonamido;

R_1 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) nitro,

(4) halógeno,

(5) alquilo sustituido e insustituido,

(6) alquenilo sustituido e insustituido,

(7) alquinilo sustituido e insustituido,

(8) arilo sustituido e insustituido,

(9) heteroarilo sustituido e insustituido,

(10) heterociclilo sustituido e insustituido,

(11) cicloalquilo sustituido e insustituido,

(12) $-COR_{1a}$,

(13) $-CO_2R_{1a}$,

(14) $-CONR_{1a}R_{1b}$,

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(15) $-NR_{1a}R_{1b}$,

(16) $-NR_{1a}COR_{1b}$,

(17) $-NR_{1a}SO_2R_{1b}$,

(18) $-OCOR_{1a}$,

(19) $-OR_{1a}$,

(20) $-SR_{1a}$,

(21) $-SOR_{1a}$,

(22) $-SO_2R_{1a}$, y

(23) $-SO_2NR_{1a}R_{1b}$,

en donde R_{1a} y R_{1b} se seleccionan independientemente a partir del grupo que consiste en:

(a) hidrógeno,

(b) alquilo sustituido o insustituido,

(c) arilo sustituido e insustituido,

(d) heteroarilo sustituido e insustituido,

(e) heterociclilo sustituido e insustituido, y

(f) cicloalquilo sustituido e insustituido;

R_2 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) nitro,

(4) halógeno,

(5) hidroxilo,

(6) amino,

(7) alquilo sustituido e insustituido,

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(8) $-COR_{2a}$, y

(9) $-NR_{2a}COR_{2b}$,

en donde R_{2a} y R_{2b} se seleccionan independientemente a partir del grupo que consiste en:

(a) hidrógeno, y

(b) alquilo sustituido o insustituido;

R_3 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) nitro,

(4) halógeno,

(5) alquilo sustituido e insustituido,

(6) alquenilo sustituido e insustituido,

(7) alquinilo sustituido e insustituido,

(8) arilo sustituido e insustituido,

(9) heteroarilo sustituido e insustituido,

(10) heterociclilo sustituido e insustituido,

(11) cicloalquilo sustituido e insustituido,

(12) $-COR_{3a}$,

(13) $-NR_{3a}R_{3b}$,

(14) $-NR_{3a}COR_{3b}$,

(15) $-NR_{3a}SO_2R_{3b}$,

(16) $-OR_{3a}$,

(17) $-SR_{3a}$,

(18) $-SOR_{3a}$,

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(19) $-SO_2R_{3a}$, y

(20) $-SO_2NR_{3a}R_{3b}$,

en donde R_{3a} y R_{3b} se seleccionan independientemente a partir del grupo que consiste en:

(a) hidrógeno,

(b) alquilo sustituido o insustituido,

(c) arilo sustituido e insustituido,

(d) heteroarilo sustituido e insustituido,

(e) heterociclilo sustituido e insustituido, y

(f) cicloalquilo sustituido e insustituido; y

R_4 se selecciona a partir del grupo que consiste en:

(1) hidrógeno, y

(2) halógeno.

R_1 sustituido comprende aril-alquilo sustituido o insustituido, hetero-aril-alquilo sustituido o insustituido, cicloalquil-alquilo sustituido o insustituido, o heterociclil-alquilo sustituido o insustituido.

En una modalidad, W es CH.

En otra modalidad, W es N. En una modalidad más particular de la presente, R_3 es =O.

En una modalidad, R_1 se selecciona a partir del grupo que consiste en:

(1) alquilo sustituido e insustituido,

(2) arilo sustituido e insustituido,

(3) heteroarilo sustituido e insustituido,

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(4) heterociclilo sustituido e insustituido,

(5) cicloalquilo sustituido e insustituido,

(6) $-OR_{1a}$, y

(7) $-NR_{1a}R_{1b}$,

en donde R_{1a} y R_{1b} se seleccionan independientemente a partir del grupo que consiste en:

(a) heteroarilo sustituido e insustituido, y

(b) heterociclilo sustituido e insustituido.

En otra modalidad R_1 es heterociclilo sustituido o insustituido, u -O-heterociclilo sustituido o insustituido. En otra modalidad, R_1 es morfolinilo sustituido o insustituido; todavía más particularmente, R_1 es morfolinilo N-enlazado insustituido.

En otra modalidad, R_1 es tetrahidro-pirano sustituido o insustituido ó tetrahidro-piraniloxilo sustituido o insustituido. Todavía más particularmente, R_1 es 4-tetrahidro-piraniloxilo insustituido.

En otra modalidad, R_1 es tetrahidrofurano sustituido o insustituido o tetrahidro-furaniloxilo sustituido o insustituido. Todavía más particularmente, R_1 es 3-tetrahidro-furaniloxilo insustituido.

En una modalidad, R_1 comprende heterociclil-alquilo sustituido o insustituido, o hetero-aril-alquilo sustituido o insustituido. En una modalidad, R_1 comprende morfolinilo sustituido o insustituido. En una modalidad, morfolinilo comprende morfolinilo N-enlazado. En una modalidad, R_1 comprende tetrahidro-pirano sustituido o insustituido. En una modalidad, tetrahidro-pirano comprende 4-tetrahidro-piraniloxilo. En una modalidad, tetrahidro-pirano comprende 3-

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tetrahidro-piraniloxilo. En una modalidad, R_1 comprende tetrahidrofurano sustituido o insustituido. En una modalidad, tetrahidrofurano comprende 3-tetrahidro-furaniloxilo. En una modalidad, R_1 comprende piperidina sustituida o insustituida. En una modalidad, piperidina comprende 4-piperidiniloxilo. En otra modalidad, piperidina comprende 3-piperidiniloxilo. En una modalidad, R_1 comprende pirrolidina sustituida o insustituida. En una modalidad, pirrolidina comprende 3-pirrolidiniloxilo.

En una modalidad, R_2 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) hidroxilo,

(4) halógeno,

(5) amino,

(6) metilo, y

(7) trifluoro-metilo.

En una modalidad, R_3 se selecciona a partir del grupo que consiste en:

(1) ciano,

(2) nitro,

(3) halógeno,

(4) hidroxilo,

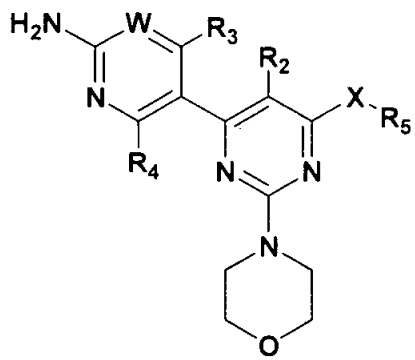
(5) amino, y

(6) trifluoro-metilo.

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En una modalidad, R_3 es trifluoro-metilo. En una modalidad, R_3 es ciano.

En una modalidad, los compuestos inhibidores de cinasa de fosfatidil-inositol-3 (PI3-K) de la invención tienen la fórmula (II):



II

o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable de los mismos, en donde,

W es CR_w o N, en donde R_w se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) halógeno,

(4) metilo,

(5) trifluoro-metilo, y

(6) sulfonamido;

X es O, S, NH, o un enlace directo;

R_2 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

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(3) nitro,

(4) halógeno,

(5) hidroxilo,

(6) amino,

(7) alquilo sustituido e insustituido,

(8) $-COR_{2a}$, y

(9) $-NR_{2a}COR_{2b}$,

en donde R_{2a} y R_{2b} se seleccionan independientemente a partir del grupo que consiste en:

(a) hidrógeno, y

(b) alquilo sustituido o insustituido;

R_3 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) nitro,

(4) halógeno,

(5) alquilo sustituido e insustituido,

(6) alquenilo sustituido e insustituido,

(7) alquinilo sustituido e insustituido,

(8) arilo sustituido e insustituido,

(9) heteroarilo sustituido e insustituido,

(10) heterociclilo sustituido e insustituido,

(11) cicloalquilo sustituido e insustituido,

(12) $-COR_{3a}$,

(13) $-NR_{3a}R_{3b}$,

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(14) $-NR_{3a}COR_{3b}$,

(15) $-NR_{3a}SO_2R_{3b}$,

(16) $-OR_{3a}$,

(17) $-SR_{3a}$,

(18) $-SOR_{3a}$,

(19) $-SO_2R_{3a}$, y

(20) $-SO_2NR_{3a}R_{3b}$,

en donde R_{3a} y R_{3b} se seleccionan independientemente a partir del grupo que consiste en:

(a) hidrógeno,

(b) alquilo sustituido o insustituido,

(c) arilo sustituido e insustituido,

(d) heteroarilo sustituido e insustituido,

(e) heterociclilo sustituido e insustituido, y

(f) cicloalquilo sustituido e insustituido;

R_4 se selecciona a partir del grupo que consiste en

(1) hidrógeno, y

(2) halógeno; y

R_5 se selecciona a partir del grupo que consiste en:

(1) cicloalquilo sustituido e insustituido,

(2) heterociclilo sustituido e insustituido,

(3) arilo sustituido e insustituido, y

(4) heteroarilo sustituido e insustituido.

En una modalidad, W es CH.

En una modalidad, W es N. En una modalidad más particular de

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la presente, R_3 es =O.

En una modalidad, R_2 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) hidroxilo,

(4) amino,

(5) halógeno, y

(6) alquilo de 1 a 3 átomos de carbono sustituido e insustituido.

En una modalidad, R_3 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) $-SR_{3a}$

(4) halógeno,

(5) nitro,

(6) alquilo sustituido e insustituido,

(7) alquenilo sustituido e insustituido,

(8) alquinilo sustituido e insustituido,

(9) $-OR_{3a}$,

(10) $-NR_{3a}R_{3b}$,

(11) $-COR_{3a}$, y

(12) $-NR_{3a}COR_{3b}$,

en donde R_{3a} y R_{3b} se seleccionan independientemente a partir

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del grupo que consiste en:

(a) hidrógeno, y

(b) alquilo sustituido o insustituido.

En una modalidad, R_3 es trifluoro-metilo.

En una modalidad, R_5 se selecciona a partir del grupo que consiste en:

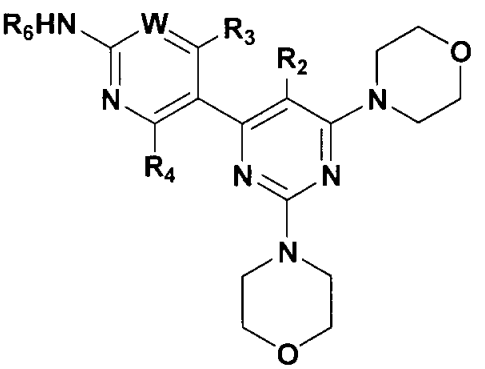
(1) morfolinilo sustituido o insustituido,

(2) tetrahidro-piranilo sustituido o insustituido, y

(3) tetrahidro-furanilo sustituido o insustituido.

En una modalidad más particular de la presente, R_5 es morfolinilo N-enlazado; todavía más particularmente, X es un enlace directo. En otra modalidad más particular, R_5 es 4-tetrahidro-piranilo; todavía más particularmente, X es O. En otra modalidad, R_5 es 3-tetrahidro-furanilo; todavía más particularmente, X es O.

En una modalidad, los compuestos inhibidores de cinasa de fosfatidil-inositol-3 (PI3-K) de la invención tienen la fórmula (III):



III

o un estereoisómero, tautómero, o una sal farmacéuticamente

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aceptable de los mismos, en donde:

W es CR_w o N, en donde R_w se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) halógeno,

(4) metilo,

(5) trifluoro-metilo, y

(6) sulfonamido;

R_2 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) nitro,

(4) halógeno,

(5) hidroxilo,

(6) amino,

(7) alquilo sustituido e insustituido,

(8) $-COR_{2a}$, y

(9) $-NR_{2a}COR_{2b}$,

en donde R_{2a} y R_{2b} se seleccionan independientemente a partir del grupo que consiste en:

(a) hidrógeno, y

(b) alquilo sustituido o insustituido;

R_3 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

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(2) ciano,

(3) nitro,

(4) halógeno,

(5) alquilo sustituido e insustituido,

(6) alquenilo sustituido e insustituido,

(7) alquinilo sustituido e insustituido,

(8) arilo sustituido e insustituido,

(9) heteroarilo sustituido e insustituido,

(10) heterociclilo sustituido e insustituido,

(11) cicloalquilo sustituido e insustituido,

(12) $-COR_{3a}$,

(13) $-NR_{3a}R_{3b}$,

(14) $-NR_{3a}COR_{3b}$,

(15) $-NR_{3a}SO_2R_{3b}$,

(16) $-OR_{3a}$,

(17) $-SR_{3a}$,

(18) $-SOR_{3a}$,

(19) $-SO_2R_{3a}$, y

(20) $-SO_2NR_{3a}R_{3b}$,

en donde R_{3a} y R_{3b} se seleccionan independientemente a partir del grupo que consiste en:

(a) hidrógeno,

(b) alquilo sustituido o insustituido,

(c) arilo sustituido e insustituido,

(d) heteroarilo sustituido e insustituido,

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(e) heterociclilo sustituido e insustituido, y

(f) cicloalquilo sustituido e insustituido;

R_4 se selecciona a partir del grupo que consiste en:

(1) hidrógeno, y

(2) halógeno; y

R_6 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) alquilo sustituido e insustituido, y

(3) cicloalquilo sustituido e insustituido.

En una modalidad, R_2 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) hidroxilo,

(4) halógeno,

(5) amino,

(6) metilo, y

(7) trifluoro-metilo.

En una modalidad, R_3 se selecciona a partir del grupo que consiste en:

(1) ciano,

(2) nitro,

(3) halógeno,

(4) hidroxilo,

(5) amino, y

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(6) trifluoro-metilo.

En una modalidad, R_5 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) metilo, y

(3) etilo.

Se debe entender que los compuestos inhibidores de acuerdo con la invención pueden exhibir el fenómeno de tautomerismo. Debido a que las estructuras químicas dentro de esta memoria descriptiva solamente pueden representar una de las posibles formas tautoméricas, se debe entender que la invención abarca cualquier forma tautomérica de la estructura trazada.

Para los compuestos de las fórmulas (I) a (III), los grupos alquilo sustituido representativos incluyen los grupos aril-alquilo, hetero-aril-alquilo, heterociclil-alquilo, amino-alquilo, alquil-amino-alquilo, dialquil-amino-alquilo, y sulfonamido-alquilo. Los grupos arilo sustituido representativos incluyen los grupos sulfonamido-arilo. Los grupos hetero-arilo sustituido representativos incluyen los grupos alquil-hetero-arilo.

Las síntesis de los compuestos inhibidores de PI3K representativos de la invención se describen en los métodos presentados en la Sección de Ejemplos más adelante, y la preparación de los compuestos representativos se describen en los Ejemplos 1 a 31.

Los compuestos inhibidores de PI3K representativos de la invención se muestran en la Tabla 1.

En otros aspectos, la presente invención proporciona métodos para la fabricación de los compuestos inhibidores de PI3K. Además se contempla que, en adición a los compuestos de las fórmulas (I) a (III), los intermediarios, y sus métodos de síntesis correspondientes, se incluyen dentro del alcance de la invención.

Otra modalidad proporciona un método para inhibir la fosforilación de Akt, el cual comprende administrar un compuesto de la fórmula I, II, o III a un ser humano que lo necesite. Otra modalidad proporciona un método para el tratamiento de cáncer que responda a la inhibición de la fosforilación de Akt, el cual comprende administrar un compuesto de la fórmula I, II, o III. Otra modalidad proporciona un método para inhibir la fosforilación de Akt el cual comprende poner una célula en contacto con un compuesto de la fórmula I, II, o III.

Otra modalidad proporciona un método para inhibir la fosforilación de Akt, el cual comprende administrar oralmente un compuesto de la fórmula I, II, o III a un ser humano que lo necesite. En una modalidad más particular, el ser humano está sufriendo de cáncer. En a una modalidad más particular, el cáncer responde al tratamiento con un compuesto que inhibe la fosforilación de Akt. En otra modalidad, el compuesto es oralmente biodisponible.

Otra modalidad proporciona un método para el tratamiento de cáncer, el cual comprende administrar oralmente un compuesto de la fórmula I, II, o III, en donde el compuesto mencionado es capaz de

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inhibir la actividad de pAkt.

En algunas modalidades del método para inhibir PI3K utilizando un compuesto inhibidor de PI3K de la invención, el valor IC_{50} del compuesto es menor o igual a 1 mM con respecto a PI3K. En otra de estas modalidades, el valor IC_{50} es menor o igual a 100 µM, es menor o igual a 25 µM, es menor o igual a 10 µM, es menor o igual a 1 µM, es menor o igual a 0.1 µM, es menor o igual a 0.050 µM, o es menor o igual a 0.010 µM.

Los compuestos de la presente invención son también útiles en ensayos para evaluar la actividad relativa de inhibición de cinasa PI3. En estos ensayos, se puede utilizar un compuesto de la presente invención para determinar la actividad inhibidora relativa de un compuesto en comparación con un segundo compuesto. Cuando se emplea de esta manera, el compuesto de la presente invención se emplea en una cantidad suficiente para permitir que el experto detecte la inhibición de la cinasa PI3. Esta cantidad algunas veces es referida en la presente como una "cantidad inhibidora efectiva". En una modalidad preferida la cantidad inhibidora es una cantidad que reducirá la actividad de cinasa PI3 por aproximadamente el 50 por ciento comparándose con la actividad en ausencia de un compuesto. Entonces se pueden evaluar otros compuestos por proporcionar una inhibición mayor o menor a la misma concentración, como para proporcionar una clasificación de actividad relativa. Esta información es útil para determinar los cambios estructurales y otras modificaciones al compuesto de prueba con el fin de mejorar su

actividad. De conformidad con lo anterior, la presente invención proporciona un método para inhibir la actividad de la cinasa PI3, cuyo método comprende poner en contacto esta cinasa PI3 con una cantidad inhibidora efectiva de un compuesto de la presente invención como se da a conocer en la presente. También se proporciona un método para inhibir la actividad de cinasa PI3 en una célula, cuyo método comprende poner en contacto esta célula con una cantidad inhibidora efectiva de un compuesto como se reivindica en la presente.

Algunas modalidades proporcionan métodos para inhibir la fosforilación de Akt utilizando un compuesto de la invención que tiene un valor EC_{50} de menos de aproximadamente 10 µM con respecto a la inhibición de pAKT. En otra modalidad más particular, el compuesto tiene un valor EC_{50} de menos de aproximadamente 1 µM con respecto a la inhibición de pAKT. En a una modalidad todavía más particular, el compuesto tiene un valor EC_{50} de menos de aproximadamente 0.5 µM con respecto a la inhibición de pAKT. En una modalidad aún más particular, el compuesto tiene un valor EC_{50} de menos de aproximadamente 0.1 µM con respecto a la inhibición de pAKT.

En ciertas modalidades, los componentes de la presente invención son capaces de inhibir la fosforilación de Akt. En ciertas modalidades, los componentes de la invención son capaces de inhibir la fosforilación de Akt en un sujeto humano o animal (es decir, *in vivo*).

En una modalidad, se proporciona un método para reducir la actividad de pAkt en un sujeto humano o animal. En el método, se administra un compuesto de la invención en una cantidad efectiva para reducir la actividad de pAkt.

En algunas modalidades del método para inhibir PI3K utilizando un compuesto inhibidor de PI3K de la invención, el valor EC_{50} del compuesto es de entre 1 nM y 10 nM. En otra de estas modalidades, el valor EC_{50} es de entre 10 nM y 50 nM, de entre 50 nM y 100 nM, de entre 100 nM y 1 µM, de entre 1 µM y 25 µM, o es de entre 25 µM y 100 µM.

Los compuestos de la presente invención son también útiles en ensayos para evaluar la actividad relativa de inhibición de la fosforilación de AKT. En estos ensayos, se puede utilizar un compuesto de la presente invención para determinar la actividad inhibidora relativa de un compuesto en comparación con un segundo compuesto. Cuando se emplea de esta manera, el compuesto de la presente invención se emplea en una cantidad suficiente para permitir que el experto detecte la inhibición de la fosforilación de AKT. Esta cantidad algunas veces es referida en la presente como una "cantidad inhibidora efectiva". En una modalidad preferida, la cantidad inhibidora es una cantidad que reducirá la actividad de fosforilación de AKT por aproximadamente el 50 por ciento comparándose con la actividad en ausencia de un compuesto. Entonces se pueden evaluar otros compuestos por proporcionar una inhibición mayor o menor a la misma concentración, como para

proporcionar una clasificación de actividad relativa. Esta información es útil para determinar los cambios estructurales y otras modificaciones al compuesto de prueba con el fin de mejorar su actividad. De conformidad con lo anterior, la presente invención proporciona un método para inhibir la fosforilación de AKT, cuyo método comprende poner en contacto una célula con una cantidad inhibidora efectiva de un compuesto de la presente invención, como se describe en la presente. También se proporciona un método para inhibir la actividad de cinasa PI3 en una célula, cuyo método comprende poner en contacto esta célula con una cantidad inhibidora efectiva de un compuesto como se reivindica en la presente.

En otra modalidad, la invención proporciona métodos para el tratamiento de un trastorno mediado por PI3K. En un método, se administra una cantidad efectiva de un compuesto inhibidor de PI3K a un paciente (por ejemplo, un sujeto humano o animal) que lo necesite, para mediar (o modular) la actividad de PI3K.

Los compuestos de la presente invención son útiles en composiciones farmacéuticas para uso humano o veterinario, en donde se indique la inhibición de PI3K, por ejemplo, en el tratamiento de enfermedades proliferativas celulares, tales como el crecimiento celular tumoral y/o canceroso mediado por PI3K. En particular, los compuestos son útiles en el tratamiento de cánceres humanos o animales (por ejemplo, de murino), incluyendo, por ejemplo, pulmón y bronquios; próstata; mama; páncreas; colon, y recto; tiroides; hígado y conducto biliar intrahepático, hepatocelular;

gástrico; glioma/glioblastoma; endometrial; melanoma; riñón y pelvis renal; vejiga urinaria; cuerpo uterino; cérvix uterino; ovario; mieloma múltiple; esófago; leucemia mielógena aguda; leucemia mielógena crónica; leucemia linfocítica; leucemia mieloide; cerebro; cavidad oral y faringe; laringe; intestino delgado; linfoma no de Hodgkin; melanoma; y adenoma de colon velloso.

Los agentes de la invención, en particular aquéllos que tienen selectividad para la inhibición de la cinasa PI3 gamma, son particularmente útiles en el tratamiento de enfermedades inflamatorias u obstructivas de las vías respiratorias, que dan como resultado, por ejemplo, la reducción del daño del tejido, de la inflamación de las vías respiratorias, de la híper-reactividad bronquial, de la remodelación, o del progreso de la enfermedad. Las enfermedades inflamatorias u obstructivas de las vías respiratorias a las que es aplicable la presente invención incluyen asma de cualquier tipo o génesis, incluyendo tanto asma intrínseco (no alérgico) como asma extrínseco (alérgico), asma leve, asma moderado, asma severo, asma bronquítico, asma inducido por ejercicio, asma ocupacional, y asma inducido en seguida de infección bacteriana. También se debe entender que el tratamiento de asma abarca el tratamiento de sujetos, por ejemplo, de menos de 4 ó 5 años de edad, que exhiban síntomas de jadeo y sean diagnosticados o diagnosticables como "bebés jadeantes", una categoría de paciente establecida de importante preocupación médica y ahora identificada con frecuencia como asmáticos incipientes o en fase temprana

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("síndrome de bebé jadeante").

Los compuestos de la invención que son selectivos para una isoforma de la cinasa PI3 (α, β, γ, δ) sobre una isoforma diferente, son los compuestos que inhiben preferencialmente una isoforma. Por ejemplo, un compuesto puede inhibir preferencialmente la isoforma alfa sobre la isoforma gamma. D una manera alternativa, un compuesto puede inhibir preferencialmente la isoforma gamma sobre la isoforma alfa. Con el objeto de determinar la selectividad de un compuesto, se determina la actividad del compuesto de acuerdo con los Métodos Biológicos descritos en la presente. Por ejemplo, se determina el valor IC_{50}, o el valor EC_{50}, de un compuesto, para dos o más isoformas de cinasa PI3, por ejemplo, alfa y gamma, de acuerdo con los Métodos Biológicos 1 y 2, respectivamente. Entonces se comparan los valores obtenidos para determinar la selectividad del compuesto probado. De preferencia, los compuestos de la invención son selectivos para una isoforma sobre una segunda isoforma por cuando menos dos veces, cinco veces, o diez veces. Todavía más preferiblemente, los compuestos de la invención son selectivos para una isoforma sobre una segunda isoforma por cuando menos cincuenta veces o 100 veces. Aún más preferiblemente, los compuestos de la invención son selectivos para una isoforma sobre una segunda isoforma por cuando menos 1,000 veces.

Otras enfermedades y condiciones inflamatorias u obstructivas de las vías respiratorias para las que es aplicable la presente invención incluyen lesión pulmonar aguda (ALI), síndrome de

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insuficiencia respiratoria de adultos (ARDS), enfermedad obstructiva crónica pulmonar, de las vías respiratorias, o del pulmón (COPD, COAD o COLD), incluyendo fibrosis pulmonar, bronquitis crónica o disnea asociada con la misma, enfisema, así como exacerbación de hiper-reactividad de las vías respiratorias a consecuencia de otra terapia con fármacos, en particular otra terapia con fármacos inhalados. La invención también es aplicable al tratamiento de bronquitis de cualquier tipo o génesis, incluyendo, por ejemplo, bronquitis aguda, araquídica, catarral, cruposa, crónica, o ftinoide. Otras enfermedades inflamatorias u obstructivas de las vías respiratorias a las que es aplicable la presente invención incluyen neumoconiosis (una enfermedad inflamatoria, comúnmente ocupacional, de los pulmones, con frecuencia acompañada por obstrucción de las vías respiratorias, ya sea crónica o aguda, y ocasionada por la inhalación repetida de polvos) de cualquier tipo o génesis, incluyendo, por ejemplo, aluminosis, antracosis, asbestosis, calicosis, ptilosis, siderosis, silicosis, tabacosis y bisinosis.

Teniendo consideración de su actividad anti-inflamatoria, en particular en relación con la inhibición de la activación de los eosinófilos, los agentes de la invención son también útiles en el tratamiento de trastornos relacionados con los eosinófilos, por ejemplo, eosinofilia, en particular trastornos relacionados con los eosinófilos de las vías respiratorias (por ejemplo, que involucren infiltración eosinofílica patológica de los tejidos pulmonares), incluyendo hiper-eosinofilia como afecta a las vías respiratorias y/o a

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los pulmones, así como, por ejemplo, trastornos relacionados con los eosinófilos de las vías respiratorias a consecuencia de, o concomitantes con, síndrome de Löffler, neumonía eosinofílica, infestación parasitaria (en particular de metazoarios) (incluyendo eosinofilia tropical), aspergilosis broncopulmonar, poliarteritis nodosa (incluyendo síndrome de Churg-Strauss), granuloma eosinofílico, y trastornos relacionados con los eosinófilos que afecten a las vías respiratorias, ocasionados por reacción a fármacos.

Los agentes de la invención son también útiles en el tratamiento de condiciones inflamatorias o alérgicas de la piel, por ejemplo soriasis, dermatitis por contacto, dermatitis atópica, alopecia areata, eritema multiforme, dermatitis herpetiforme, esclerodermia, vitiligo, angiitis por hipersensibilidad, urticaria, penfigoide bulloso, lupus eritematoso, pénfigo, epidermólisis bullosa adquirida, y otras condiciones inflamatorias o alérgicas de la piel.

Los agentes de la invención también se pueden utilizar para el tratamiento de otras enfermedades o condiciones, en particular enfermedades o condiciones que tengan un componente inflamatorio, por ejemplo, el tratamiento de enfermedades y condiciones de los ojos, tales como conjuntivitis, queratoconjuntivitis sicca, y conjuntivitis vernal, enfermedades que afecten a la nariz, incluyendo rinitis alérgica, y enfermedad inflamatoria en donde estén implicadas reacciones autoinmunes o que tenga un componente o etiología autoinmune, incluyendo trastornos hematológicos autoinmunes (por

ejemplo, anemia hemolítica, anemia aplásica, anemia de glóbulos rojos puros, y trombocitopenia idiopática), lupus eritematoso sistémico, policondritis, esclerodermia, granulomatosis de Wegener, dermatomiositis, hepatitis activa crónica, miastenia gravis, síndrome de Steven-Johnson, prurito idiopático, enfermedad inflamatoria autoinmune del intestino (por ejemplo, colitis ulcerativa y enfermedad de Crohn), oftalmopatía endocrina, enfermedad de Graves, sarcoidosis, alveolitis, neumonitis de hipersensibilidad crónica, esclerosis múltiple, cirrosis biliar primaria, uveítis (anterior y posterior), fibrosis pulmonar intersticial, artritis soriática, y glomerulonefritis (con y sin síndrome nefrótico, por ejemplo, incluyendo síndrome nefrótico idiopático o nefropatía de cambio mínimo).

En otra modalidad de la invención, se proporciona un método para inhibir los leucocitos, en particular los neutrófilos y los linfocitos B y T. Las condiciones médicas de ejemplo que se pueden tratar incluyen aquéllas caracterizadas por una función indeseable de los neutrófilos seleccionada a partir del grupo que consiste en liberación de superóxido estimulada, exocitosis estimulada, y migración quimiotáctica, de preferencia sin inhibir la actividad fagocítica o la aniquilación bacteriana por parte de los neutrófilos.

En otra modalidad, la invención es un método para alterar la función de los osteoclastos y para mejorar un trastorno de resorción ósea, tal como osteoporosis.

En otra modalidad, las enfermedades o condiciones que se

pueden tratar con los agentes de la invención incluyen choque séptico, rechazo de aloinjerto en seguida de trasplante, trastornos óseos, tales como, pero no limitándose a, artritis reumatoide, espondilitis anquilosante, osteoartritis, obesidad, restenosis, diabetes, por ejemplo, diabetes mellitus tipo I (diabetes juvenil) y diabetes mellitus tipo II, y enfermedades diarreicas.

En otras modalidades, la condición o el trastorno mediado por PI3K se selecciona a partir del grupo que consiste en: enfermedades cardiovasculares, ateroesclerosis, hipertensión, trombosis venosa profunda, embolia, infarto de miocardio, angina inestable, tromboembolia, embolia pulmonar, enfermedades trombolíticas, isquemia arterial aguda, oclusiones trombóticas periféricas, y enfermedad de arterias coronarias, lesiones por reperfusión, retinopatía, tal como retinopatía diabética o retinopatía inducida por oxígeno hiperbárico, y condiciones caracterizadas por una presión intraocular elevada o por secreción del humor acuoso ocular, tales como glaucoma.

Como se describe anteriormente, debido a que PI3K sirve como un nodo de segundo mensajero que integra las sendas de señalización paralelas, está surgiendo una evidencia de que la combinación de un inhibidor de PI3K con inhibidores de otras sendas, será útil en el tratamiento de cáncer y enfermedades proliferativas en seres humanos.

Aproximadamente del 20 al 30 por ciento de los cánceres de mama humanos sobre-expresan Her-2/neu-ErbB2, el objetivo para el

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fármaco trastuzumab. Aunque el trastuzumab ha demostrado respuestas durables en algunos pacientes que expresan Her2/neu-ErbB2, solamente responde un subconjunto de estos pacientes. El trabajo reciente ha indicado que este índice de respuesta limitado puede ser sustancialmente mejorado mediante la combinación de trastuzumab con inhibidores de PI3K o de la senda de PI3K/AKT (Chan y colaboradores, *Breast Can. Res. Treat.* 91: 187 (2005), Woods Ignatoski y colaboradores, Brit. *J. Cancer* 82: 666 (2000), Nagata y colaboradores, *Cancer Cell* 6: 117 (2004)).

Una variedad de malignidades humanas expresan mutaciones activadoras o niveles incrementados de Her1/EGFR, y se ha desarrollado un número de anticuerpos e inhibidores de moléculas pequeñas contra esta cinasa de tirosina receptora, incluyendo tarceva, gefitinib y erbitux. Sin embargo, aunque los inhibidores de EGFR demuestran actividad anti-tumoral en ciertos tumores humanos (por ejemplo, NSCLC), fracasan para aumentar la sobrevivencia global del paciente, en todos los pacientes con tumores que expresan EGFR. Esto se puede racionalizar por el hecho de que muchos objetivos corriente abajo de Her1/EGFR son mutados o desregulados a altas frecuencias en una variedad de malignidades, incluyendo la senda de PI3K/Akt. Por ejemplo, el gefitinib inhibe el crecimiento de una línea celular de adenocarcinoma en los ensayos *in vitro*. No obstante, se pueden seleccionar sub-clones de estas líneas celulares, que sean resistentes al gefitinib, que demuestran una mayor activación de la senda de PI3/Akt. La disminución o

inhibición de esta senda hace que los sub-clones resistentes sean sensibles al gefitinib (Kokubo y colaboradores, Brit. J. Cancer 92: 1711 (2005)). Adicionalmente, en un modelo de cáncer de mama *in vitro* con una línea celular que aloja la mutación PTEN que sobre-expresa la inhibición de EGFR tanto de la senda de PI3K/Akt como del EGFR, se produjo un efecto sinérgico (She y colaboradores, Cancer Cell 8: 287-297(2005)). Estos resultados indican que la combinación de gefitinib e inhibidores de la senda de PI3K/Akt sería una estrategia terapéutica atractiva en el cáncer.

La combinación de AEE778 (un inhibidor de Her-2/neu/ErbB2, VEGFR y EGFR) y RAD001 (un inhibidor de mTOR, un objetivo corriente abajo de Akt) produjo una mayor eficacia combinada que cualquier agente solo en un modelo de xenoinjerto de glioblastoma (Goudar y colaboradores, *Mol. Cancer. Ther.* 4: 101-112 (2005)).

Los anti-estrógenos, tales como tamoxifeno, inhiben el crecimiento de cáncer de mama a través de la inducción del paro del ciclo celular que requiere de la acción del inhibidor del ciclo celular p27Kip. Recientemente, se ha demostrado que la activación de la senda de cinasa Ras-Raf-MAP altera e estado de fosforilación de p27Kip, de tal manera que se atenúa su actividad inhibidora para detener el ciclo celular, contribuyendo de esta manera a la resistencia al anti-estrógeno (Donovan, y colaboradores, *J. Biol. Chem.* 276: 40888, 2001). Como es reportado por Donovan y colaboradores, la inhibición de la señalización de MAPK a través del tratamiento con el inhibidor de MEK revirtió el estado de fosforilación

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aberrante del p27 en el cáncer refractario a hormonas de las líneas celulares de mama, y al hacerlo de esta manera, restableció la sensibilidad a hormonas. De una manera similar, la fosforilación de p27Kip mediante Akt también abroga su papel para detener el ciclo celular (Viglietto y colaboradores, *Nat Med.* 8: 1145 (2002)). De conformidad con lo anterior, en un aspecto, los compuestos de la fórmula (I) se pueden utilizar en el tratamiento de cánceres dependientes de hormonas, tales como cánceres de mama y de próstata, para revertir la resistencia a hormonas que se ve comúnmente en estos cánceres con los agentes contra el cáncer convencionales.

En los cánceres hematológicos, tales como leucemia mielógena crónica (CML), la translocalización cromosómica es responsable de la cinasa de tirosina BCR-Abl constitutivamente activada. Los pacientes afligidos responden al imatinib, un inhibidor de cinasa de tirosina de moléculas pequeñas, como un resultado de la inhibición de la actividad de cinasa Abl. Sin embargo, muchos pacientes con la enfermedad en etapa avanzada responden al imatinib inicialmente, pero luego recurren posteriormente debido a las mutaciones que confieren resistencia en el dominio de cinasa Abl. Los estudios *in vitro* han demostrado que BCR-Abl emplea la senda de cinasa Ras-Raf para provocar sus efectos. En adición, la inhibición de más de una cinasa en la misma senda proporciona una protección adicional contra las mutaciones que confieren resistencia. De conformidad con lo anterior, en otro aspecto de la invención, los compuestos de la

fórmula (I) se utilizan en combinación con cuando menos un agente adicional, tal como Gleevec®, en el tratamiento de cánceres hematológicos, tales como leucemia mielógena crónica (CML), para revertir o prevenir la resistencia a cuando menos un agente adicional.

Debido a que la activación de la senda de PI3K/Akt impulsa la sobrevivencia celular, la inhibición de la senda en combinación con terapias que impulsan la apoptosis en las células de cáncer, incluyendo radioterapia y quimioterapia, dará como resultado mejores respuestas (Ghobrial y colaboradores, CA *Cancer J. Clin* 55: 178-194 (2005)). Como un ejemplo, la combinación del inhibidor de cinasa PI3 con carboplatina demostró efectos sinérgicos en los ensayos *in vitro* tanto de proliferación como de apoptosis, así como una eficacia tumoral *in vivo* en un modelo de xenoinjerto de cáncer de ovario (Westfall y Skinner, *Mol. Cancer Ther.* 4: 1764-1771 (2005)).

En adición al cáncer y a las enfermedades proliferativas, existe una evidencia acumulativa de que los inhibidores de las cinasas PI3 Clases 1A y 1B serían terapéuticamente útiles en otras áreas de enfermedad. Se ha demostrado que la inhibición de p110ß, el producto de isoforma PI3K del gen PIK3CB, está involucrada en la activación de las plaquetas inducida por desgarre (Jackson y colaboradores, *Nature Medicine* 11: 507-514 (2005)). Por consiguiente, un inhibidor de PI3K que inhiba p110ß sería útil como un solo agente o en combinación en la terapia anti-trombótica. La

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isoforma p110ß, el producto del gen PIK3CD, es importante en la función y diferenciación de las células-B (Clayton y colaboradores, *J. Exp. Med.* 196: 753-763 (2002)), en las respuestas de antígeno dependientes e independientes de células-T (Jou y colaboradores, *Mol. Cell. Biol.* 22: 8580-8590 (2002)), y en la diferenciación de los mastocitos (Ali y colaboradores, *Nature* 431: 1007-1011 (2004)). Por consiguiente, se espera que los inhibidores de p110ß sean útiles en el tratamiento de las enfermedades autoinmunes impulsadas por las células-B y en asma. Finalmente, la inhibición de p110ß, el producto de isoforma del gen PI3KCG, da como resultado una respuesta de células-T reducida, pero no de células-B (Reif y colaboradores, *J. Immunol.* 173: 2236-2240 (2004)), y su inhibición demuestra eficacia en modelos de enfermedades autoinmunes en animales (Camps y colaboradores, *Nature Medicine* 11: 936-943 (2005), Barber y colaboradores, *Nature Medicine* 11: 933-935 (2005)).

La presente invención proporciona composiciones farmacéuticas que comprenden cuando menos un compuesto inhibidor de PI3K (por ejemplo, un compuesto de las fórmulas (I) a (III), junto con un vehículo farmacéuticamente aceptable adecuado para su administración a un sujeto humano o animal, ya sea solo o junto con otros agentes contra el cáncer.

En una modalidad, la presente invención proporciona métodos para el tratamiento de sujetos humanos o animales que sufran de una enfermedad proliferativa celular, tal como cáncer. La presente invención proporciona métodos para el tratamiento de un sujeto

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humano o animal que necesite dicho tratamiento, los cuales comprenden administrar al sujeto una cantidad terapéuticamente efectiva de un compuesto inhibidor de PI3K (por ejemplo, un compuesto de las fórmulas (I) a (III)), ya sea solo o bien en combinación con otros agentes contra el cáncer.

En particular, las composiciones se formularán juntas como una combinación terapéutica, o bien se administrarán por separado. Los agentes contra el cáncer para utilizarse con la invención incluyen, pero no se limitan a, uno o más de los siguientes:

A. Inhibidores de Cinasa

Los inhibidores de cinasa para utilizarse como agentes contra el cáncer en conjunto con las composiciones de la presente invención incluyen los inhibidores de las cinasas receptoras del factor de crecimiento epidérmico (EGFR), tales como las quinazolinas de moléculas pequeñas, por ejemplo gefitinib (US 5457105, US 5616582, y US 5770599), ZD-6474 (WO 01/32651), erlotinib (Tarceva®, US 5,747,498 y WO 96/30347), y lapatinib (US 6,727,256 y WO 02/02552); los inhibidores de cinasa receptora del factor de crecimiento endotelial vascular (VEGFR), incluyendo SU-11248 (WO 01/60814), SU 5416 (US 5,883,113 y WO 99/61422), SU 6668 (US 5,883,113 y WO 99/61422), CHIR-258 (US 6,605,617 y US 6,774,237), vatalanib o PTK-787 (US 6,258,812), VEGF-Trap (WO 02/57423), B43-Genisteína (WO-09606116), fenretinida (p-hidroxi-fenil-amina del ácido retinoico) (US 4,323,581), IM-862 (WO 02/62826), bevacizumab o Avastin® (WO 94/10202), KRN-951, 3-[5-

(metil-sulfonil-piperidin-metil)-indolil]-quinolona, AG-13736 y AG-13925, pirrolo-[2,1-f][1,2,4]-triazinas, ZK-304709, Veglin®, VMDA-3601, EG-004, CEP-701 (US 5,621,100), Cand5 (WO 04/09769); inhibidores de cinasa de tirosina Erb2, tales como pertuzumab (WO 01/00245), trastuzumab, y rituximab; inhibidores de cinasa de proteína Akt, tales como RX-0201; inhibidores de cinasa C de proteína (PKC), tales como LY-317615 (WO 95/17182), y perifosina (US 2003171303); inhibidores de cinasa Raf/Map/MEK/Ras, incluyendo sorafenib (BAY 43-9006), ARQ-350RP, LErafAON, BMS-354825 AMG-548, y otros que se dan a conocer en la Publicación Internacional Número WO 03/82272; inhibidores de cinasa receptora del factor de crecimiento de fibroblastos (FGFR); inhibidores de cinasa dependiente de las células (CDK), incluyendo CYC-202 o roscovitina (WO 97/20842 y WO 99/02162); inhibidores de cinasa receptora del factor de crecimiento derivado de plaquetas (PGFR), tales como CHIR-258, mAb 3G3, AG-13736, SU-11248 y SU6668; e inhibidores de cinasa Bcr-Abl, y proteínas de fusión, tales como STI-571 o Gleevec® (imatinib).

B. Anti-Estrógenos

Los agentes con dirección a estrógeno para utilizarse en la terapia contra el cáncer en conjunto con las composiciones de la presente invención incluyen los moduladores selectivos de receptores de estrógeno (SERMs) incluyendo tamoxifeno, toremifeno, raloxifeno; los inhibidores de aromatasa incluyendo Arimidex® o anastrozol; los reductores de receptores de estrógeno (ERDs)

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incluyendo Faslodex® o fulvestrant.

C. Anti-Andrógenos

Los agentes con dirección a andrógeno para utilizarse en la terapia contra el cáncer en conjunto con las composiciones de la presente invención incluyen flutamida, bicalutamida, finasterida, amino-glutetamida, quetoconazol, y corticosteroides.

D. Otros Inhibidores

Otros inhibidores para utilizarse como agentes contra el cáncer en conjunto con las composiciones de la presente invención incluyen inhibidores de farnesil-transferasa de proteína, incluyendo tipifarnib o R-115777 (US 2003134846 y WO 97/21701), BMS-214662, AZD-3409, y FTI-277; inhibidores de topoisomerasa, incluyendo merbarona y diflomotecano (BN-80915); inhibidores de proteína de huso de cinesina mitótica (KSP), incluyendo SB-743921 y MKI-833; moduladores de proteasa, tales como bortezomib o Velcade® (US 5,780,454), XL-784; e inhibidores de ciclo-oxigenasa 2 (COX-2), incluyendo fármacos anti-inflamatorios no esteroideos I (NSAIDs).

E. Fármacos Quimioterapéuticos de Cáncer

Los agentes quimioterapéuticos de cáncer particulares para utilizarse como agentes contra el cáncer en conjunto con las composiciones de la presente invención incluyen anastrozol (Arimidex®), bicalutamida (Casodex®), sulfato de bleomicina (Blenoxane®), busulfano (Myleran®), inyección de busulfano (Busulfex®), capecitabina (Xeloda®), N4-pentoxi-carbonil-5-desoxi-5-fluorocitidina, carboplatina (Paraplatin®), carmustina (BiCNU®),

clorambucil (Leukeran®), cisplatina (Platinol®), cladribina (Leustatin®), ciclofosfamida (Cytoxan® o Neosar®), citarabina, citosina-arabinosida (Cytosar-U®), inyección de liposoma de citarabina (DepoCyt®), dacarbazina (DTIC-Dome®), dactinomicina (Actinomicina D, Cosmegan), clorhidrato de daunorrubicina (Cerubidine®), inyección de liposoma de citrato de daunorrubicina (Daunoxome®), dexametasona, docetaxel (Taxotere®, US 2004073044), clorhidrato doxorrubicina (Adriamycin®, Rubex®), etoposida (Vepesid®), fosfato de fludarabina (Fludara®), 5-fluoro-uracilo (Adrucil®, Efudex®), flutamida (Eulexin®), tezacitibina, Gemcitabina (difluoro-desoxicitidina), hidroxi-urea (Hidrea®), Idarrubicina (Idamycin®), ifosfamida (IFEX®), irinotecano (Camptosar®), L-asparaginasa (ELSPAR®), leucovorina-calcio, melfalano (Alkeran®), 6-mercapto-purina (Purinethol®), metotrexato (Folex®), mitoxantrona (Novantrone®), milotarg, paclitaxel (Taxol®), Phoenix (Itrio 90/MX-DTPA), pentostatina, polifeprosano 20 con implante de carmustina (Gliadel®), citrato de tamoxifeno (Nolvadex®), teniposida (Vumon®), 6-tioguanina, tiotepa, tirapazamina (Tirazone®), clorhidrato de topotecano para inyección (Hycamptin®), vinblastina (Velban®), vincristina (Oncovin®), y vinorelbina (Navelbine®).

F. Agentes Alquilantes

Los agentes alquilantes para utilizarse en conjunto con las composiciones de la presente invención para las terapias contra el cáncer incluyen VNP-40101M o cloretizina, oxaliplatina (US

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4,169,846, WO 03/24978 y WO 03/04505), glufosfamida, mafosfamida, etopofos (US 5,041,424), prednimustina; treosulfano; busulfano; irofluveno (acilfulveno); penclomedina; pirazoloacridina (PD-115934); O6-bencilguanina; decitabina (5-aza-2-deoxicitidina); brostalicina; mitomicina C (MitoExtra); TLK-286 (Telcyta®); temozolomida; trabectedina (US 5,478,932); AP-5280 (formulación de platinato de cisplatina); porfiromicina; y clearazida (mecloretamina).

G. Agentes Quelantes

Los agentes quelantes para utilizarse en conjunto con las composiciones de la presente invención para las terapias contra el cáncer incluyen tetratiomolibdato (WO 01/60814); RP-697; T84.66 Quimérico (cT84.66); gadofosveset (Vasovist®); desferoxamina; y bleomicina, opcionalmente en combinación con electroporación (EPT).

H. Modificadores de la Respuesta Biológica

Los modificadores de la respuesta biológica, tales como los inmuno-moduladores, para utilizarse en conjunto con las composiciones de la presente invención para las terapias contra el cáncer, incluyen estaurosporina y análogos macrocíclicos de la misma, incluyendo UCN-01, CEP-701 y midostaurina (véase WO 02/30941, WO 97/07081, WO 89/07105, US 5,621,100, WO 93/07153, WO 01/04125, WO 02/30941, WO 93/08809, WO 94/06799, WO 00/27422, WO 96/13506 y WO 88/07045); escualamina (WO 01/79255); DA-9601 (WO 98/04541 y US 6,025,387); alemtuzumab; interferones (por ejemplo, IFN-a, IFN-b etc.); interleucinas,

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específicamente IL-2 o aldesleucina, así como IL-1, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, y las variantes biológicas de las mismas que tengan secuencias de aminoácidos mayores del 70 por ciento de la secuencia humana nativa; altretamina (Hexalen®); SU 101 o leflunomida (WO 04/06834 y US 6,331,555); imidazoquinolinas, tales como resiquimod e imiquimod (US 4,689,338, 5,389,640, 5,268,376, 4,929,624, 5,266,575, 5,352,784, 5,494,916, 5,482,936, 5,346,905, 5,395,937, 5,238,944, y 5,525,612); y SMIPs, incluyendo benzazoles, antraquinonas, tiosemicarbazonas, y triptantrinas (WO 04/87153, WO 04/64759, y WO 04/60308).

I. Vacunas de Cáncer:

Las vacunas contra el cáncer para utilizarse en conjunto con las composiciones de la presente invención incluyen Avicine® (*Tetrahedron Letters* 26. 1974, 2269-70); oregovomab (OvaRex®); Theratope® (STn-KLH); Vacunas de Melanoma; la serie GI-4000 (GI-4014, GI-4015, y GI-4016), que se dirigen a cinco mutaciones en la proteína Ras; GlioVax-1; MelaVax; Advexin® o INGN-201 (WO 95/12660); Sig/E7/LAMP-1, que codifica HPV-16 E7; Vacuna MAGE-3 o M3TK (WO 94/05304); HER-2VAX; ACTIVE, que estimula las células-T específicas para tumores; vacuna de cáncer GM-CSF; y vacunas basadas en monocitogenes de Listeria.

J. Terapia Anti-Sentido:

Los agentes contra el cáncer para utilizarse en conjunto con las composiciones de la presente invención también incluyen composiciones anti-sentido, tales como AEG-35156 (GEM-640); AP-

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12009 y AP-11014 (oligonucleótidos anti-sentido específicos de TGF-beta2); AVI-4126; AVI-4557; AVI-4472; oblimersen (Genasense®); JFS2; aprinocarsen (WO 97/29780); GTI-2040 (oligonucleótido anti-sentido de ARNm de reductasa de ribonucleótido R2) (WO 98/05769); GTI-2501 (WO 98/05769); oligodesoxinucleótidos anti-sentido de c-Raf encapsulados en liposomas (LErafAON) (WO 98/43095); y Sirna-027 (ARNm de VEGFR-1 de dirección terapéutica basado en el ARNi).

Los compuestos de la invención también se pueden combinar en una composición farmacéutica con sustancias de fármaco broncodilatadoras y antihistamínicas. Estos fármacos broncodilatadores incluyen a los agentes anticolinérgicos o antimuscarínicos, en particular bromuro de ipratropio, bromuro de oxitropio, y bromuro de tiotropio, y agonistas del adreno-receptor ß-2, tales como salbutamol, terbutalina, salmeterol y, en especial, formoterol. Las sustancias de fármaco antihistamínicas co-terapéuticas incluyen clorhidrato de cetirizina, fumarato de clemastina, prometazina, loratadina, desloratadina, difenhidramina, y clorhidrato de fexofenadina.

La efectividad de un agente de la invención en la inhibición de las condiciones inflamatorias, por ejemplo en las enfermedades inflamatorias de las vías respiratorias, se pueden demostrar en un modelo animal, por ejemplo, un modelo de ratón o de rata, de inflamación de las vías respiratorias u otras condiciones inflamatorias, por ejemplo como es descrito por Szarka y

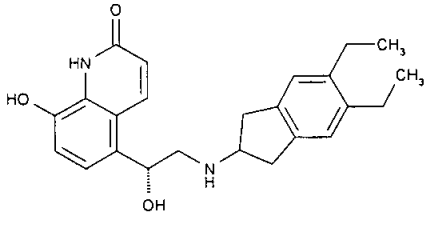
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colaboradores, J. Immunol. Methods (1997) 202: 49-57; Renzi y colaboradores, Am. Rev. Respir. Dis. (1993) 148: 932-939; Tsuyuki y colaboradores, J. Clin. Invest. (1995) 96: 2924-2931; y Cernadas y colaboradores (1999) Am. J. Respir. Cell Mol. Biol. 20: 1-8.

Los agentes de la invención también son útiles como agentes co-terapéuticos para utilizarse en combinación con otras sustancias de fármaco, tales como sustancias de fármaco anti-inflamatorias, broncodilatadoras, o antihistamínicas, en particular en el tratamiento de enfermedades obstructivas o inflamatorias de las vías respiratorias, tales como aquéllas mencionadas anteriormente en la presente, por ejemplo como potenciadores de la actividad terapéutica de tales fármacos, o como un medio para reducir la dosificación requerida o los efectos secundarios potenciales de estos fármacos. Un agente de la invención se puede mezclar con la otra sustancia de fármaco en una composición farmacéutica, o se puede administrar por separado, antes, de una manera simultánea con, o después de la otra sustancia de fármaco. De conformidad con lo anterior, la invención incluye una combinación de un agente de la invención como se describe anteriormente en la presente, con una sustancia de fármaco anti-inflamatoria, broncodilatadora, o antihistamínica, estando este agente de la invención y la sustancia de fármaco mencionada en la misma o diferente composición farmacéutica. Estos fármacos anti-inflamatorios incluyen esteroides, en particular glucocorticosteroides, tales como budesonida, beclametasona, fluticasona, ciclesonida o mometasona, antagonistas de LTB4, tales

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como aquéllos descritos en la Patente de los Estados Unidos de Norteamérica Número US5451700, antagonistas de LTD4, tales como montelukast y zafirlukast, agonistas del receptor de dopamina, tales como cabergolina, bromocriptina, ropinirol, y 4-hidroxi-7-[2-[[2-[[3-(2-fenil-etoxi)-propil]-sulfonil]-etil]-amino]-etil]-2(3H)-benzotiazolona y las sales farmacéuticamente aceptables del mismo (siendo el clorhidrato, Viozan® - AstraZeneca), e inhibidores de PDE4, tales como Ariflo® (GlaxoSmith Kline), Roflumilast (Byk Gulden), V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), Arofilina (Almirall Prodesfarma) y PD189659 (Parke-Davis). Los fármacos broncodilatadores incluyen a los agentes anticolinérgicos o antimuscarínicos, en particular bromuro de ipratropio, bromuro de oxitropio, y bromuro de tiotropio, y los agonistas del adreno-receptor beta-2, tales como salbutamol, terbutalina, salmeterol y, en especial, formoterol, y las sales farmacéuticamente aceptables de los mismos, y los compuestos (en forma libre o de sal o de solvato) de la fórmula I de la Publicación de Patente Internacional del TCP Número WO 00/75114, cuyo documento se incorpora a la presente como referencia, de preferencia los compuestos de los Ejemplos del mismo, en especial un compuesto de la fórmula:



y las sales farmacéuticamente aceptables del mismo. Las

sustancias de fármaco antihistamínicas co-terapéuticas incluyen clorhidrato de cetirizina, acetaminofeno, fumarato de clemastina, prometazina, loratidina, desloratidina, difenhidramina, y clorhidrato de fexofenadina. Se pueden utilizar combinaciones de los agentes de la invención y esteroides, agonistas beta-2, inhibidores de PDE4, o antagonistas de LTD4, por ejemplo, en el tratamiento de COPD o, en particular, asma. Se pueden utilizar combinaciones de los agentes de la invención y agentes anticolinérgicos o antimuscarínicos, inhibidores de PDE4, agonistas del receptor de dopamina, o antagonistas de LTB4, por ejemplo, en el tratamiento de asma o, en particular, COPD.

Otras combinaciones útiles de agentes de la invención con fármacos anti-inflamatorios son aquéllas con antagonistas de los receptores de quimiocina, por ejemplo, CCR-1, CCR-2, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CCR-9 y CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, en particular los antagonistas de CCR-5, tales como los antagonistas Schering-Plough SC-351125, SCH-55700 y SCH-D, los antagonistas Takeda, tales como cloruro de N-[[4-[[[6,7-dihidro-2-(4-metil-fenil)-5H-benzo-ciclohepten-8-il]-carbonil]-amino]-fenil]-metil]-tetrahidro-N,N-dimetil-2H-piran-4-aminio (TAK-770), y los antagonistas de CCR-5 descritos en la Patente de los Estados Unidos de Norteamérica Número US 6166037 (en particular en las reivindicaciones 18 y 19), en la Publicación Internacional Número WO 00/66558 (en particular en la reivindicación 8), y en la Publicación Internacional Número WO 00/66559 (en particular en la

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reivindicación 9).

Los compuestos de la invención también se pueden combinar en una composición farmacéutica con compuestos que sean útiles para el tratamiento de una enfermedad trombolítica, una enfermedad cardíaca, embolia, etc. (por ejemplo, aspirina, estreptocinasa, activador de plasminógeno del tejido, urocinasa, anticoagulantes, fármacos anti-plaquetas (por ejemplo, PLAVIX; bisulfato de clopidogrel), una estatina (por ejemplo, LIPITOR o Atorvastatina-calcio), ZOCOR (Simvastatina), CRESTOR (Rosuvastatina), etc.), un bloqueador Beta (por ejemplo, Atenolol), NORVASC (besilato de amlodipina), y un inhibidor de ACE (por ejemplo, lisinopril).

Los compuestos de la invención también se pueden combinar en una composición farmacéutica con compuestos que sean útiles para el tratamiento con agentes contra la hipertensión, tales como inhibidores de ACE, agentes reductores de lípidos, tales como estatinas, LIPITOR (Atorvastatina-calcio), bloqueadores del canal de calcio, tales como NORVASC (besilato de amlodipina). Los compuestos de la presente invención también se pueden utilizar en combinación con fibratos, bloqueadores-beta, inhibidores de NEPI, antagonistas del receptor de angiotensina-2, e inhibidores de la acumulación de plaquetas.

Para el tratamiento de enfermedades inflamatorias, incluyendo artritis reumatoide, los compuestos de la invención se pueden combinar con agentes tales como inhibidores de TNF-α, tales como anticuerpos monoclonales anti-TNF-α (tales como REMICADE, CDP-

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870) y D2E7 (HUMIRA) y moléculas de fusión de inmunoglobulina con el receptor de TNF (tales como ENBREL), inhibidores de IL-1, antagonistas de receptores o IL-1Rα solubles (por ejemplo, KINERET o inhibidores de ICE), agentes anti-inflamatorios no esteroideos (NSAIDs), piroxicam, diclofenaco, naproxeno, flurbiprofeno, fenoprofeno, quetoprofeno, ibuprofeno, fenamatos, ácido mefenámico, indometacina, sulindaco, apazona, pirazolonas, fenil-butazona, aspirina, inhibidores de COX-2 (tales como CELEBREX (celecoxib), PREXIGE (lumiracoxib)), inhibidores de metaloproteasa (de preferencia inhibidores selectivos de MMP-13), inhibidores de p2x7, inhibidores de α2α, NEUROTINA, pregabalina, metotrexato de dosis baja, leflunomida, hidroxicloroquina, d-penicilamina, auranofina, u oro parenteral u oral.

Los compuestos de la invención también se pueden utilizar en combinación con los agentes terapéuticos existentes para el tratamiento de osteoartritis. Los agentes adecuados para utilizarse en combinación incluyen agentes anti-inflamatorios no esteroideos convencionales (posteriormente en la presente NSAIDs), tales como piroxicam, diclofenaco, ácidos propiónicos, tales como naproxeno, flurbiprofeno, fenoprofeno, quetoprofeno e ibuprofeno, fenamatos tales como ácido mefenámico, indometacina, sulindaco, apazona, pirazolonas, tales como fenil-butazona, salicilatos tales como aspirina, inhibidores de COX-2 tales como celecoxib, valdecoxib, lumiracoxib y etoricoxib, analgésicos y terapias intra-articulares tales como corticosteroides y ácidos hialurónicos, tales como hialgano y

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synvisc.

Los compuestos de la invención también se pueden utilizar en combinación con agentes antivirales tales como Viracept, AZT, aciclovir y famciclovir, y compuestos antisepsis tales como Valant.

Los compuestos de la invención también se pueden utilizar en combinación con agentes para el sistema nervioso central, tales como antidepresivos (sertralina), fármacos anti-Parkinsonianos (tales como deprenilo, L-dopa, Requip, Mirapex, inhibidores de MAOB tales como selegina y rasagilina, inhibidores de comP, tales como Tasmar, inhibidores de A-2, inhibidores de la reabsorción de dopamina, antagonistas de NMDA, agonistas de Nicotina, agonistas de Dopamina, e inhibidores de sintasa de óxido nítrico neuronal), y fármacos contra Alzheimer tales como donepezil, tacrina, inhibidores de α2δ, NEUROTINA, pregabalina, inhibidores de COX-2, propentofilina, o metrifonato.

Los compuestos de la presente invención también se pueden utilizar en combinación con agentes para la osteoporosis tales como EVISTA (clorhidrato de raloxifeno), droloxifeno, lasofoxifeno, o fosomax, y agentes inmunosupresores tales como FK-506 y rapamicina.

En otro aspecto de la invención, se proporcionan kits que incluyen uno o más compuestos de la invención. Los kits representativos incluyen un compuesto inhibidor de PI3K de la invención (por ejemplo, un compuesto de las fórmulas (I) a (III)) y un inserto del paquete u otra etiqueta, incluyendo instrucciones para el

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tratamiento de una enfermedad proliferativa celular mediante la administración de una cantidad inhibidora de PI3K del compuesto.

Las siguientes definiciones se proporcionan para entender mejor la invención.

"Alquilo" se refiere a los grupos alquilo que no contienen heteroátomos. Por consiguiente, la frase incluye los grupos alquilo de cadena recta, tales como metilo, etilo, propilo, butilo, pentilo, hexilo, heptilo, octilo, nonilo, decilo, undecilo, dodecilo y similares. La frase también incluye los isómeros de cadena ramificada de los grupos alquilo de cadena recta, incluyendo, pero no limitándose a, los siguientes, los cuales se proporcionan a manera de ejemplo: $-CH(CH_3)_2$, $-CH(CH_3)-(CH_2CH_3)$, $-CH(CH_2CH_3)_2$, $-C(CH_3)_3$, $-C(CH_2CH_3)_3$, $-CH_2CH(CH_3)_2$, $-CH_2CH(CH_3)-(CH_2CH_3)$, $-CH_2CH(CH_2CH_3)_2$, $-CH_2C(CH_3)_3$, $-CH_2C(CH_2CH_3)_3$, $-CH(CH_3)-CH(CH_3)-(CH_2CH_3)$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH(CH_3)-(CH_2CH_3)$, $-CH_2CH_2CH(CH_2CH_3)_2$, $-CH_2CH_2C(CH_3)_3$, $-CH_2CH_2C(CH_2CH_3)_3$, $-CH(CH_3)CH_2-CH(CH_3)_2$, $-CH(CH_3)CH(CH_3)CH(CH_3)_2$, $-CH(CH_2CH_3)CH(CH_3)CH(CH_3)-(CH_2CH_3)$, y otros. Por consiguiente, la frase " grupos alquilo" incluye los grupos alquilo primarios, los grupos alquilo secundarios, y los grupos alquilo terciarios. Los grupos alquilo preferidos incluyen los grupos alquilo de cadena recta y ramificada que tienen de 1 a 12 átomos de carbono o de 1 a 6 átomos de carbono.

"Alquileno" se refiere a los mismos residuos que se observan anteriormente para "alquilo", pero que tienen dos puntos de unión. Los grupos alquileno de ejemplo incluyen etileno ($-CH_2CH_2-$),

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propileno ($-CH_2CH_2CH_2-$), dimetil-propileno ($-CH_2C(CH_3)_2CH_2-$), y ciclohexil-propileno ($-CH_2CH_2CH(C_6H_{13})-$).

"Alquenilo" se refiere a grupos de cadena recta, ramificada, o cíclica, de 2 a aproximadamente 20 átomos de carbono, tales como los descritos con respecto a los grupos alquilo como se definen anteriormente, excepto que tienen uno o más dobles enlaces de carbono-carbono. Los ejemplos incluyen, pero no se limitan a, vinilo, $-CH=C(H)-(CH_3)$, $-CH=C(CH_3)_2$, $-C(CH_3)=C(H)_2$, $-C(CH_3)=C(H)-(CH_3)$, $-C(CH_2CH_3)=CH_2$, ciclohexenilo, ciclopentenilo, ciclohexadienilo, butadienilo, pentadienilo, y hexadienilo, entre otros. Los grupos alquenilo preferidos incluyen los grupos alquenilo de cadena recta y ramificada, y los grupos alquenilo cíclicos que tienen de 2 a 12 átomos de carbono o de 2 a 6 átomos de carbono.

"Alquinilo" se refiere a grupos de cadena recta, ramificada, o cíclica de 2 a aproximadamente 20 átomos de carbono, tales como los descritos con respecto a los grupos alquilo como se definen anteriormente, excepto que tienen uno o más triples enlaces de carbono-carbono. Los ejemplos incluyen, pero no se limitan a, $-C\equiv C(H)$, $-C\equiv C(CH_3)$, $-C\equiv C(CH_2CH_3)$, $-C(H_2)C\equiv C(H)$, $-C(H)_2C\equiv C(CH_3)$, y $-C(H)_2C\equiv C(CH_2CH_3)$, entre otros. Los grupos alquinilo preferidos incluyen los grupos alquinilo de cadena recta y ramificada que tienen de 2 a 12 átomos de carbono o de 2 a 6 átomos de carbono.

Los grupos alquilo, alquenilo, y alquinilo pueden estar sustituidos. "Alquilo sustituido" se refiere a un grupo alquilo como se

define anteriormente, en donde uno o más enlaces con los átomos de carbono o de hidrógeno son reemplazados por un enlace con átomos que no son de hidrógeno y que no son de carbono, tales como, pero no limitándose a, un átomo de halógeno, tal como F, Cl, Br, e I; un átomo de oxígeno en grupos tales como grupos hidroxilo, grupos alcoxilo, grupos ariloxilo, y grupos éster; un átomo de azufre en grupos tales como grupos tiol, grupos de sulfuro de alquilo y arilo, grupos sulfona, grupos sulfonilo, y grupos sulfóxido; un átomo de nitrógeno en grupos tales como aminas, amidas, alquil-aminas, dialquil-aminas, aril-aminas, alquil-aril-aminas, diaril-aminas, N-óxidos, imidas, y enaminas; un átomo de silicio en grupos tales como grupos trialquil-sililo, grupos dialquil-aril-sililo, grupos alquil-diaril-sililo, y grupos triaril-sililo; y otros heteroátomos en otros diferentes grupos. Los grupos alquilo sustituido también incluyen los grupos en donde uno o más enlaces con un átomo de carbono o de hidrógeno son reemplazados por un enlace de orden más alto (por ejemplo, un doble o triple enlace) a un heteroátomo tal como oxígeno en grupos oxo, carbonilo, carboxilo, y éster; nitrógeno en grupos tales como iminas, oximas, hidrazonas, y nitrilos. Los grupos alquilo sustituido incluyen además grupos alquilo en donde uno o más enlaces con un átomo de carbono o de hidrógeno, son reemplazados por un enlace con un grupo arilo, hetero-arilo, heterociclilo, o cicloalquilo. Los grupos alquilo sustituido preferidos incluyen, entre otros, grupos alquilo en donde uno o más enlaces con un átomo de carbono o de hidrógeno es/son reemplazados por uno o más enlaces con un grupo

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flúor, cloro, o bromo. Otro grupo alquilo sustituido preferido es el grupo trifluoro-metilo y otros grupos alquilo que contienen el grupo trifluoro-metilo. Otros grupos alquilo sustituido preferidos incluyen aquéllos en donde uno o más enlaces con un átomo de carbono o de hidrógeno es reemplazado por un enlace con un átomo de oxígeno, de tal manera que el grupo alquilo sustituido contiene un grupo hidroxilo, alcoxilo, o ariloxilo. Otros grupos alquilo sustituido preferidos incluyen grupos alquilo que tienen una amina, o un grupo alquil-amina, dialquil-amina, aril-amina, (alquil)-(aril)-amina, diaril-amina, heterociclil-amina, diheterociclil-amina, (alquil)-(heterociclil)-amina, o (aril)-(heterociclil)-amina sustituido o insustituido. Todavía otros grupos alquilo sustituido preferidos incluyen aquéllos en donde uno o más enlaces con un átomo de carbono o de hidrógeno son reemplazados por un enlace con un grupo arilo, hetero-arilo, heterociclilo, o cicloalquilo. Los ejemplos de alquilo sustituido son: $-(CH_2)_3NH_2$, $-(CH_2)_3NH(CH_3)$, $-(CH_2)_3NH(CH_3)_2$, $-CH_2C(=CH_2)CH_2NH_2$, $-CH_2C(=O)CH_2NH_2$, $-CH_2S(=O)_2CH_3$, $-CH_2OCH_2NH_2$, $-CO_2H$. Los ejemplos de los sustituyentes de alquilo sustituido son: $-CH_3$, $-C_2H_5$, $-CH_2OH$, $-OH$, $-OCH_3$, $-OC_2H_5$, $-OCF_3$, $-OC(=O)CH_3$, $-OC(=O)NH_2$, $-OC(=O)N(CH_3)_2$, $-CN$, $-NO_2$, $-C(=O)CH_3$, $-CO_2H$, $-CO_2CH_3$, $-CONH_2$, $-NH_2$,$-N(CH_3)_2$, $-NHSO_2CH_3$, $-NHCOCH_3$, $-NHC(=O)OCH_3$, $-NHSO-_2CH_3$, $-SO_2CH_3$, $-SO_2NH_2$, Halógeno.

"Alquenilo sustituido" tiene el mismo significado con respecto a los grupos alquenilo, que tienen los grupos alquilo sustituido con respecto a los grupos alquilo insustituido. Un grupo alquenilo

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sustituido incluye grupos alquenilo en donde un átomo que no es de carbono y que no es de hidrógeno, se enlaza con un átomo carbono doblemente enlazado con otro átomo de carbono, y aquéllos en donde uno de los átomos que no son carbono y que no son hidrógeno, se enlaza con un átomo de carbono no involucrado en un doble enlace con otro átomo de carbono.

"Alquinilo sustituido" tiene el mismo significado con respecto a los grupos alquinilo, que tienen los grupos alquilo sustituido con respecto a los grupos alquilo insustituido. Un grupo alquinilo sustituido incluye los grupos alquinilo en donde un átomo que no es de carbono o que no es de hidrógeno, está enlazado con un átomo de carbono triplemente enlazado con otro átomo de carbono, y aquéllos en donde un átomo que no es de carbono o que no es de hidrógeno, está enlazado con un átomo de carbono no involucrado en un triple enlace con otro átomo de carbono.

"Alcoxilo" se refiere a RO-, en donde R es alquilo. Los ejemplos representativos de los grupos alcoxilo incluyen metoxilo, etoxilo, t-butoxilo, trifluoro-metoxilo, y similares.

"Halógeno" o "halo" se refiere a cloro, bromo, flúor, y yodo. El término "halo-alquilo" se refiere a un radical de alquilo sustituido con uno o más átomos de halógeno. El término "halo-alcoxilo" se refiere a un radical de alcoxilo sustituido con uno o más átomos de halógeno.

"Amino" se refiere en la presente al grupo $-NH_2$. El término "alquil-amino" se refiere en la presente al grupo –NRR' en donde R

es alquilo y R' es hidrógeno o alquilo. El término "aril-amino" se refiere en la presente al grupo –NRR' en donde R es arilo y R' es hidrógeno, alquilo, o arilo. El término "aralquil-amino" se refiere en la presente al grupo –NRR' en donde R es aralquilo y R' es hidrógeno, alquilo, arilo, o aralquilo.

"Alcoxi-alquilo" se refiere al grupo $-alk_1-O-alk_2$ en donde alk_1 es alquilo o alquenilo, y alk_2 es alquilo o alquenilo. El término "ariloxi-alquilo" se refiere al grupo -alquilo-O-arilo. El término "aralcoxi-alquilo" se refiere al grupo -alquilenilo-O-aralquilo.

"Alcoxi-alquil-amino" se refiere en la presente al grupo –NR-(alcoxi-alquilo), en donde R es típicamente hidrógeno, aralquilo, o alquilo.

"Amino-carbonilo" se refiere en la presente al grupo $-C(O)-NH_2$. "Amino-carbonilo sustituido" se refiere en la presente al grupo –C(O)-NRR' en donde R es alquilo y R' es hidrógeno o alquilo. El término "aril-amino-carbonilo" se refiere en la presente al grupo -C(O)-NRR' en donde R es arilo y R' es hidrógeno, alquilo o arilo. "Aralquil-amino-carbonilo" se refiere en la presente al grupo -C(O)-NRR' en donde R es aralquilo y R' es hidrógeno, alquilo, arilo, o aralquilo.

"Amino-sulfonilo" se refiere en la presente al grupo $-S(O)_2-NH_2$. "Amino-sulfonilo sustituido" se refiere en la presente al grupo $-S(O)_2$-NRR' en donde R es alquilo y R' es hidrógeno o alquilo. El término "aralquil-amino-sulfonil-arilo" se refiere en la presente al grupo -aril-$S(O)_2$–NH-aralquilo.

"Carbonilo" se refiere al grupo divalente –C(O)-.

"Carboniloxilo" se refiere en términos generales al grupo –C(O)-O. Estos grupos incluyen ésteres, -C(O)-O-R, en donde R es alquilo, cicloalquilo, arilo, o aralquilo. El término "carboniloxi-cicloalquilo" se refiere en términos generales en la presente tanto a "carboniloxi-carbociclo-alquilo" como a "carboniloxi-heterociclo-alquilo," es decir, en donde R es un carbocicloalquilo o hetero-cicloalquilo, respectivamente. El término "aril-carboniloxilo" se refiere en la presente al grupo -C(O)-O-arilo, en donde arilo es un carbocicloarilo o hetero-cicloarilo mono- o poli-cíclico,. El término "aralquil-carboniloxilo" se refiere en la presente al grupo –C(O)-O-aralquilo.

"Sulfonilo" se refiere en la presente al grupo $-SO_2-$. "Alquil-sulfonilo" se refiere a un sulfonilo sustituido de la estructura $-SO_2R-$ en donde R es alquilo. Los grupos alquil-sulfonilo empleados en los compuestos de la presente invención son típicamente grupos alquil-sulfonilo que tienen de 1 a 6 átomos de carbono en su estructura base. Por consiguiente, los grupos alquil-sulfonilo típicos empleados en los compuestos de la presente invención incluyen, por ejemplo, metil-sulfonilo (es decir, en donde R es metilo), etil-sulfonilo (es decir, en donde R es etilo), propil-sulfonilo (es decir, en donde R es propilo), y similares. El término "aril-sulfonilo" se refiere en la presente al grupo $-SO_2$-arilo. El término "aralquil-sulfonilo" se refiere en la presente al grupo $-SO_2$-aralquilo. El término "sulfonamido" se refiere en la presente a $-SO_2NH_2$.

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"Carbonil-amino" se refiere al grupo divalente -NH-C(O)- en donde el átomo de hidrógeno del nitrógeno de amida nitrógeno del grupo carbonil-amino puede ser reemplazado por un grupo alquilo, arilo, o aralquilo. Estos grupos incluyen fracciones tales como ésteres de carbamato (-NH-C(O)-O-R) y amidas –NH-C(O)-R, en donde R es un alquilo de cadena recta o ramificada, cicloalquilo, o arilo, o aralquilo. El término "alquil-carbonil-amino" se refiere a alquil-carbonil-amino, en donde R es alquilo que tiene de 1 a aproximadamente 6 átomos de carbono en su estructura base. El término "aril-carbonil-amino" se refiere un grupo –NH-C(O)-R en donde R es un arilo. De una manera similar, el término "aralquil-carbonil-amino" se refiere a carbonil-amino, en donde R es aralquilo.

"Guanidino" o "guanidilo" se refiere a las fracciones derivadas a partir de guanidina, H_2N-C(=NH)-NH_2. Estas fracciones incluyen aquéllas enlazadas en el átomo de nitrógeno que lleva el doble enlace formal (la posición "2" de la guanidina, por ejemplo, diamino-metilen-amino, $(H_2N)_2C$=NH-)), y aquéllas enlazadas en cualquiera de los átomos de nitrógeno que llevan un enlace individual formal (las posiciones "1" y/o "3" de la guanidina, por ejemplo, H_2N-C(=NH)-NH-)). Los átomos de hidrógeno en cualquiera de los nitrógenos, pueden ser reemplazados con un sustituyente adecuado, tal como alquilo, arilo, o aralquilo.

"Amidino" se refiere a las fracciones R-C(=N)-NR'- (estando el radical en el nitrógeno "N^1") y R(NR')C=N- (estando el radical en el nitrógeno "N^2"), en donde R y R' pueden ser hidrógeno, alquilo, arilo,

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o aralquilo.

"Cicloalquilo" se refiere a un sustituyente de alquilo heterocíclico o carbocíclico, mono- o poli-cíclico. Los grupos cicloalquilo representativos incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, y ciclo-octilo, y estos anillos sustituidos con grupos alquilo de cadena recta y ramificada, como se definen anteriormente. Los sustituyentes típicos de cicloalquilo tienen de 3 a 8 átomos de la estructura base (es decir, del anillo), en donde cada átomo de la estructura base es carbono o bien un heteroátomo. El término "hetero-cicloalquilo" se refiere en la presente a los sustituyentes de cicloalquilo que tienen de 1 a 5, y más típicamente de 1 a 4 heteroátomos en la estructura del anillo. Los heteroátomos adecuados empleados en los compuestos de la presente invención son nitrógeno, oxígeno, y azufre. Las fracciones de hetero-cicloalquilo representativas incluyen, por ejemplo, morfolino, piperazinilo, piperadinilo, y similares. Los grupos carbocicloalquilo son grupos cicloalquilo en donde todos los átomos del anillo son carbono. Cuando se utilizan en conexión con los sustituyentes de cicloalquilo, el término "policíclico" se refiere en la presente a las estructuras cíclicas de alquilo fusionadas y no fusionadas.

" Heterociclo sustituido", "grupo heterocíclico", "heterociclo", o "heterociclilo", como se utilizan en la presente, se refieren a cualquier anillo de 3 o 4 miembros que contiene un heteroátomo seleccionado a partir de nitrógeno, oxígeno, y azufre, o un anillo de

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5 o 6 miembros que contiene de uno a tres heteroátomos seleccionados a partir del grupo que consiste en nitrógeno, oxígeno, o azufre; en donde el anillo de 5 miembros tiene de 0 a 2 dobles enlaces, y el anillo de 6 miembros tiene de 0 a 3 dobles enlaces; en donde los átomos de nitrógeno y azufre pueden estar opcionalmente oxidados; en donde los heteroátomos nitrógeno y azufre pueden estar opcionalmente cuaternizados; e incluyendo cualquier grupo bicíclico, en donde cualquiera de los anillos heterocíclicos anteriores se fusiona con un anillo de benceno u otro anillo heterocíclico de 5 o 6 miembros independientemente definido en lo anterior. Los ejemplos de los grupos heterociclilo incluyen, pero no se limitan a: anillos insaturados de 3 a 8 miembros que contienen de 1 a 4 átomos de nitrógeno, tales como, pero no limitándose a, pirrolilo, dihidro-piridilo, pirimidilo, pirazinilo, tetrazolilo (por ejemplo, 1H-tetrazolilo, 2H-tetrazolilo); grupos heterocíclicos insaturados condensados que contienen de 1 a 4 átomos de nitrógeno, tales como, pero no limitándose a, isoindolilo, indolinilo, indolizinilo, quinolilo, indazolilo; anillos insaturados de 3 a 8 miembros que contienen de 1 a 2 átomos de oxígeno y de 1 a 3 átomos de nitrógeno, tales como, pero no limitándose a, oxadiazolilo (por ejemplo, 1,2,4-oxadiazolilo, 1,3,4-oxadiazolilo, 1,2,5-oxadiazolilo); anillos saturados de 3 a 8 miembros que contienen de 1 a 2 átomos de oxígeno y de 1 a 3 átomos de nitrógeno, tales como, pero no limitándose a, morfolinilo; grupos heterocíclicos condensados insaturados que contienen de 1 a 2 átomos de oxígeno y de 1 a 3 átomos de nitrógeno, por ejemplo,

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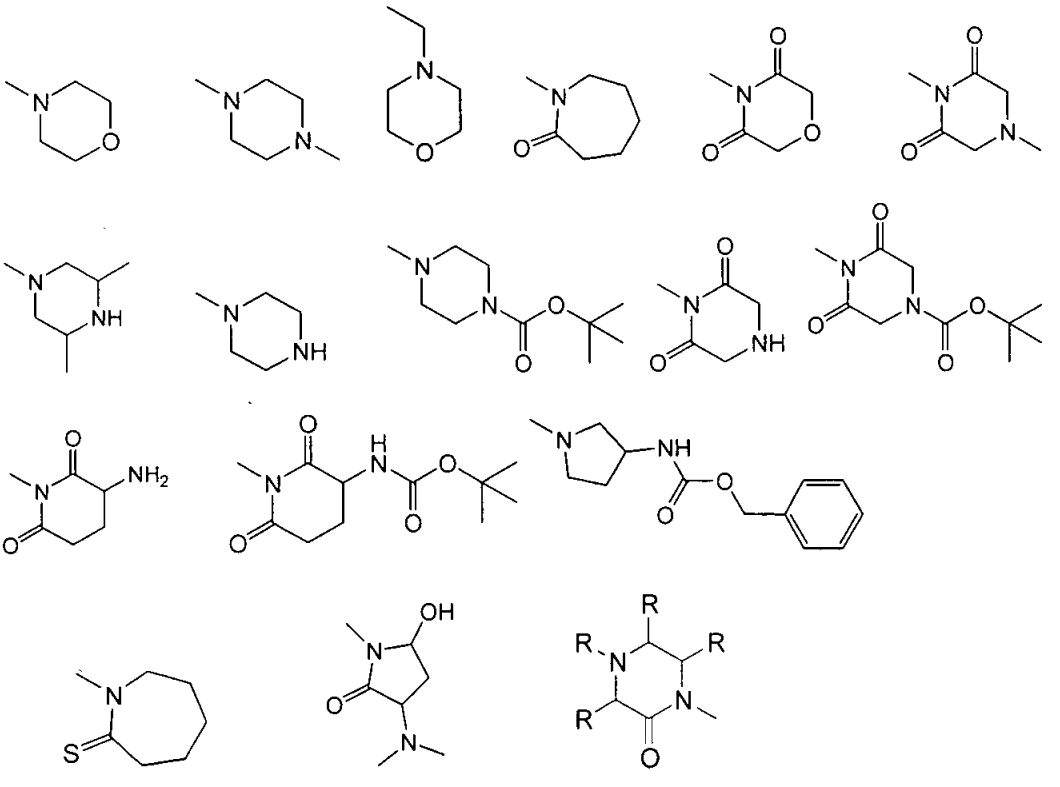
benzoxadiazolilo, benzoxazinilo (por ejemplo, 2H-1,4-benzoxazinilo); anillos insaturados de 3 a 8 miembros que contienen de 1 a 3 átomos de azufre y de 1 a 3 átomos de nitrógeno, tales como, pero no limitándose a, tiadiazolilo (por ejemplo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,3,4-tiadiazolilo, 1,2,-tiadiazolilo); anillos saturados de 3 a 8 miembros que contienen de 1 a 2 átomos de azufre y de 1 a 3 átomos de nitrógeno, tales como, pero no limitándose a, tiazolodinilo; anillos de 3 a 8 miembros saturados e insaturados que contienen de 1 a 2 átomos de azufre, , tales como, pero no limitándose a, dihidro-ditienilo, dihidro-ditionilo, tetrahidro-tiofeno, tetra-hidro-tiopirano; anillos heterocíclicos condensados insaturados que contienen de 1 a 2 átomos de azufre y de 1 a 3 átomos de nitrógeno, tales como, pero no limitándose a, benzotiadiazolilo, benzotiazinilo (por ejemplo, 2H-1,4-benzotiazinilo), dihidro-benzotiazinilo (por ejemplo, 2H-3,4-dihidro-benzotiazinilo), anillos insaturados de 3 a 8 miembros que contienen átomos de oxígeno, tales como, pero no limitándose a, furilo; anillos heterocíclicos condensados insaturados que contienen de 1 a 2 átomos de oxígeno, tales como benzodioxoílo (por ejemplo, 1,3-benzodioxoílo); anillos insaturados de 3 a 8 miembros que contienen un átomo de oxígeno y de 1 a 2 átomos de azufre, tales como, pero no limitándose a, dihidro-oxatienilo; anillos saturados de 3 a 8 miembros que contienen de 1 a 2 átomos de oxígeno y de 1 a 2 átomos de azufre, tales como 1,4-oxatiano; anillos insaturados condensados que contienen de 1 a 2 átomos de azufre, tales como benzoditienilo; y anillos heterocíclicos condensados insaturados que

contienen un átomo de oxígeno y de 1 a 2 átomos de azufre, tales como benzoxatienilo. Los heterociclos preferidos incluyen, por ejemplo: diazapinilo, pirrilo, pirrolinilo, pirrolidinilo, pirazolilo, pirazolinilo, pirazolidinilo, imidazoílo, imidazolinilo, imidazolidinilo, piridilo, piperidinilo, pirazinilo, piperazinilo, N-metil-piperazinilo, azetidinilo, N-metil-azetidinilo, pirimidinilo, piridazinilo, oxazolilo, oxazolidinilo, isoxazolilo, isoxazolidinilo, morfolinilo, tiazolilo, tiazolidinilo, isotiazolilo, isotiazolidinilo, indolilo, quinolinilo, isoquinolinilo, bencimidazolilo, benzotiazolilo, benzoxazolilo, furilo, tienilo, triazolilo, y benzotienilo. Los grupos heterociclilo también incluyen los descritos anteriormente, en donde uno o más átomos de azufre del anillo están doblemente enlazados a uno o dos átomos de oxígeno (sulfóxidos y sulfonas). Por ejemplo, los grupos heterociclilo incluyen tetrahidro-tiofeno, óxido de tetrahidro-tiofeno, y 1,1-dióxido de tetrahidro-tiofeno. Los grupos heterociclilo preferidos contienen 5 ó 6 miembros del anillo. Los grupos heterociclilo más preferidos incluyen piperazina, 1,2,3-triazol, 1,2,4-triazol, tetrazol, tiomorfolina, homopiperazina, oxazolidin-2-ona, pirrolidin-2-ona, quinuclidina, y tetrahidrofurano.

Las fracciones heterocíclicas pueden estar insustituidas o mono-sustituidas o di-sustituidas con diferentes sustituyentes seleccionados independientemente a partir de hidroxilo, halógeno, oxo (C=O), alquil-imino (RN=, en donde R es un grupo alquilo o alcoxilo), amino, alquil-amino, dialquil-amino, acil-amino-alquilo, alcoxilo, tioalcoxilo, polialcoxilo, alquilo, cicloalquilo o halo-alquilo.

"Heterociclilo insustituido" incluye anillos heterocíclicos condensados, tales como bencimidazolilo, y no incluye grupos heterociclilo que tengan otros grupos, tales como grupos alquilo o halógeno, enlazados a uno de los miembros del anillo, debido a que los compuestos tales como 2-metil-bencimidazolilo son grupos heterociclilo sustituidos.

Los grupos heterocíclicos se pueden unir en diferentes posiciones, como será evidente para aquéllos que tengan experiencia en el campo de la química orgánica y medicinal, en conjunto con la divulgación de la presente.



en donde R es H o un sustituyente heterocíclico, como se describe en la presente.

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Los heterocíclicos representativos incluyen, por ejemplo, imidazolilo, piridilo, piperazinilo, azetidinilo, tiazolilo, furanilo, triazolilo, bencimidazolilo, benzotiazolilo, benzoxazolilo, quinolinilo, isoquinolinilo, quinazolinilo, quinoxalinilo, ftalazinilo, indolilo, naftpiridinilo, indazolilo, y quinolizinilo.

"Arilo" se refiere a grupos aromáticos monocíclicos o policíclicos opcionalmente sustituidos que tienen de 3 a 14 átomos de carbono o heteroátomos de la estructura base, e incluyen tanto grupos arilo carbocíclico como grupos arilo heterocíclico. El término se refiere a, pero no se limita a, grupos tales como fenilo, bifenilo, antracenilo, naftenilo a manera de ejemplo. Los grupos arilo carbocíclico son grupos arilo en donde todos los átomos del anillo en el anillo aromático son de carbono. El término "hetero-arilo" se refiere en la presente a grupos arilo que tienen de 1 a 4 heteroátomos como los átomos del anillo en un anillo aromático, siendo el resto de los átomos del anillo, átomos de carbono.

"Arilo insustituido" incluye grupos que contienen anillos condensados, tales como naftaleno. No incluye los grupos arilo que tengan otros grupos, tales como grupos alquilo o halógeno enlazados a uno de los miembros del anillo, debido a que los grupos arilo, tales como tolilo, se consideran en la presente como grupos arilo sustituidos, como se describen más adelante. Un grupo arilo insustituido preferido es fenilo. Sin embargo, los grupos arilo insustituidos se pueden enlazar a uno o más átomos de carbono, átomos de oxígeno, átomos de nitrógeno, y/o átomos de azufre en el

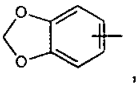
compuesto progenitor.

"Grupo arilo sustituido" tiene el mismo significado con respecto a los grupos arilo insustituidos, que tienen los grupos alquilo sustituidos con respecto a los grupos alquilo insustituidos. Sin embargo, un grupo arilo sustituido también incluye grupos arilo en donde uno de los átomos de carbono aromáticos está enlazado a uno de los átomos que no son de carbono y que no son de hidrógeno descritos anteriormente, y también incluye los grupos arilo en donde uno o más átomos de carbono aromáticos del grupo arilo están enlazados a un grupo enlazado con un grupo alquilo, alquenilo, o alquinilo sustituido y/o insustituido, como se define en la presente. Esto incluye las configuraciones de enlace en donde dos átomos de carbono de un grupo arilo están enlazados con dos átomos de un grupo alquilo, alquenilo, o alquinilo, para definir un sistema de anillos fusionados (por ejemplo, dihidro-naftilo o tetrahidro-naftilo). Por consiguiente, la frase "arilo sustituido" incluye, pero no se limita a, tolilo e hidroxi-fenilo, entre otros.

"Hetero-arilo sustituido", como se utiliza en la presente, se refiere a un grupo hetero-arilo como se define en la presente, sustituido mediante el reemplazo independiente de uno, dos, o tres de los átomos de hidrógeno del mismo, con Cl, Br, F, I, -OH, -CN, alquilo de 1 a 3 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono sustituido con arilo, halo-alquilo, tioalcoxilo, amino, alquil-amino, dialquil-amino, mercapto, nitro, carboxaldehído, carboxilo, alcoxi-carbonilo y

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carboxamida. En adición, cualquier sustituyente puede ser un grupo arilo, hetero-arilo, o hetero-cicloalquilo.

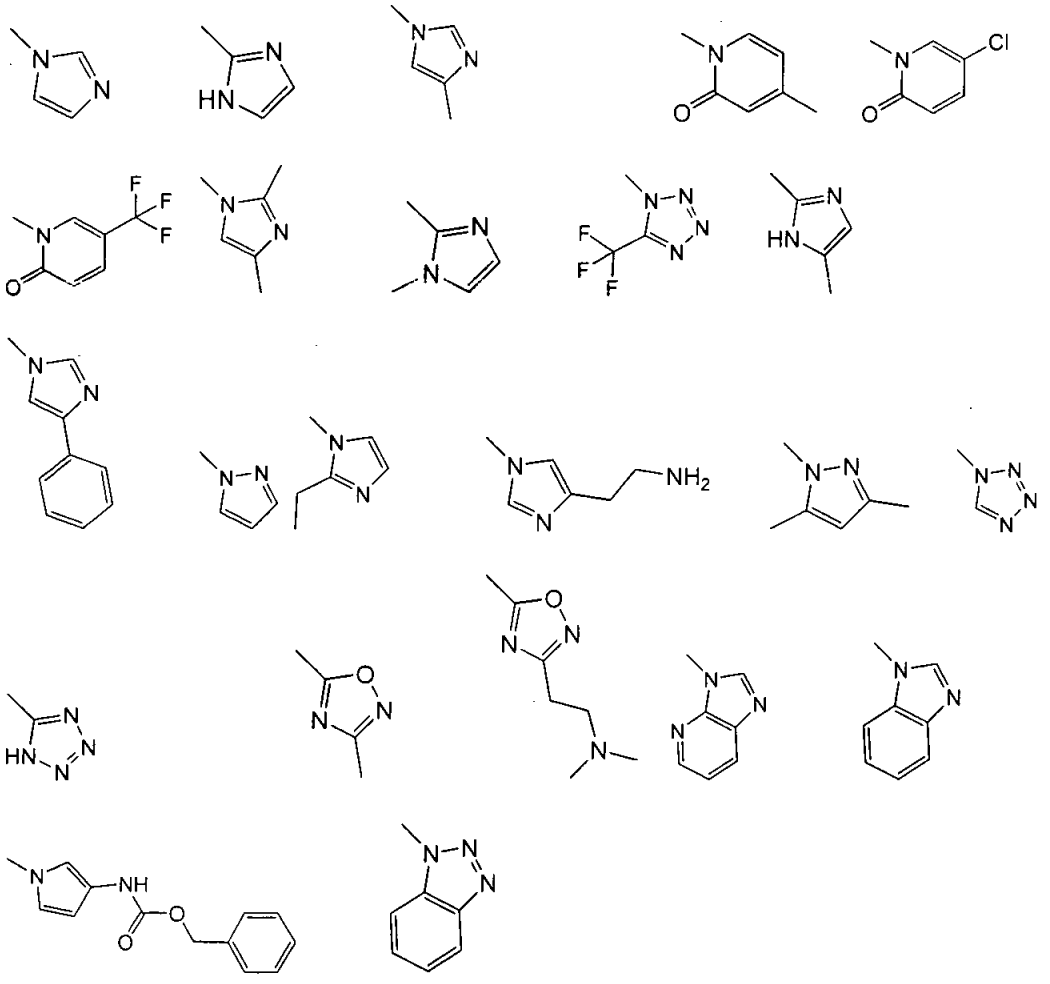
Cuando se utilizan en conexión con los sustituyentes de arilo, el término "arilo policíclico" se refiere en la presente a las estructuras cíclicas fusionadas y no fusionadas, en donde cuando menos una estructura cíclica es aromática, tal como, por ejemplo, benzodioxol (el cual tiene una estructura heterocíclica fusionada con un grupo fenilo, es decir,  ,) naftilo, y similares. Las fracciones de arilo o hetero-arilo de ejemplo empleadas como sustituyentes en los compuestos de la presente invención incluyen fenilo, piridilo, pirimidinilo, tiazolilo, indolilo, imidazolilo, oxadiazolilo, tetrazolilo, pirazinilo, triazolilo, tiofenilo, furanilo, quinolinilo, purinilo, naftilo, benzotiazolilo, benzopiridilo, y bencimidazolilo, y similares.

"Aralquilo" o "aril-alquilo" se refiere a un grupo alquilo sustituido con un grupo arilo. Típicamente, los grupos aralquilo empleados en los compuestos de la presente invención, tienen de 1 a 6 átomos de carbono incorporados dentro de la porción de alquilo del grupo aralquilo. Los grupos aralquilo adecuados empleados en los compuestos de la presente invención incluyen, por ejemplo, bencilo, picolilo, y similares.

Los grupos hetero-arilo representativos incluyen, por ejemplo, aquéllos mostrados más adelante. Estos grupos hetero-arilo pueden estar adicionalmente sustituidos, y se pueden unir en diferentes

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posiciones, como será evidente para aquéllos que tengan experiencia en el campo de la química orgánica y medicinal, en conjunto con la divulgación de la presente.



Los hetero-arilos representativos incluyen, por ejemplo, imidazolilo, piridilo, tiazolilo, triazolilo bencimidazolilo, benzotiazolilo, y benzoxazolilo.

"Biarilo" se refiere a un grupo o sustituyente con el que se enlazan dos grupos arilo, los cuales no se condensan uno con el

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otro. Los compuestos de biarilo de ejemplo incluyen, por ejemplo, fenil-benceno, difenil-diazeno, 4-tiometil-1-fenil-benceno, fenoxi-benceno, (2-fenil-etinil)-benceno, difenil-cetona, (4-fenil-buta-1,3-diinil)-benceno, fenil-bencil-amina, (fenil-metoxi)-benceno, y similares. Los grupos biarilo opcionalmente sustituidos preferidos incluyen: 2-(fenil-amino)-N-[4-(2-fenil-etinil)-fenil]-acetamida, 1,4-difenil-benceno, N-[4-(2-fenil-etinil)-fenil]-2-[bencil-amino]-acetamida, 2-amino-N-[4-(2-fenil-etinil)-fenil]-propanamida, 2-amino-N-[4-(2-fenil-etinil)-fenil]-acetamida, 2-(ciciopropil-amino)-N-[4-(2-fenil-etinil)-fenil]-acetamida, 2-(etil-amino)-N-[4-(2-fenil-etinil)-fenil]-acetamida, 2-[(2-metil-propil)-amino]-N-[4-(2-fenil-etinil)-fenil]-acetamida, 5-fenil-2H-benzo-[d]1,3-dioxolina, 2-cloro-1-metoxi-4-fenil-benceno, 2-[(imidazolil-metil)-amino]-N-[4-(2-fenil-etinil)-fenil]-acetamida, 4-fenil-1-fenoxi-benceno, N-(2-amino-etil)-[4-(2-fenil-etinil)-fenil]-carboxamida, 2-{[(4-fluoro-fenil)-metil]-amino}-N-[4-(2-fenil-etinil)-fenil]-acetamida, 2-{[(4-metil-fenil)-metil]-amino}-N-[4-(2-fenil-etinil)-fenil]-acetamida, 4-fenil-1-(trifluoro-metil)-benceno, 1-butil-4-fenil-benceno, 2-(ciclohexil-amino)-N-[4-(2-fenil-etinil)-fenil]-acetamida, 2-(etil-metil-amino)-N-[4-(2-fenil-etinil)-fenil]-acetamida, 2-(butil-amino)-N-[4-(2-fenil-etinil)-fenil]-acetamida, N-[4-(2-fenil-etinil)-fenil]-2-(4-piridil-amino)-acetamida, N-[4-(2-fenil-etinil)-fenil]-2-(quinuclidin-3-il-amino)-acetamida, N-[4-(2-fenil-etinil)-fenil]-pirrolidin-2-il-carboxamida, 2-amino-3-metil-N-[4-(2-fenil-etinil)-fenil]-butanamida, 4-(4-fenil-buta-1,3-diinil)-fenil-amina, 2-(dimetil-amino)-N-[4-(4-fenil-buta-1,3-diinil)-fenil]-acetamida, 2-(etil-amino)-N-[4-(4-

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fenil-buta-1,3-diinil)-fenil]-acetamida, 4-etil-1-fenil-benceno, 1-[4-(2-fenil-etinil)-fenil]-etan-1-ona, N-(1-carbamoil-2-hidroxi-propil)[4-(4-fenil-buta-1,3-diinil)-fenil]-carboxamida, N-[4-(2-fenil-etinil)-fenil]-propanamida, 4-metoxi-fenilo fenil-cetona, fenil-N-benzamida, (terbutoxi)-N-[(4-fenil-fenil)-metil]-carboxamida, ácido 2-(3-fenil-fenoxi)-etan-hidroxámico, propanoato de 3-fenil-fenilo, 1-(4-etoxi-fenil)-4-metoxi-benceno, y [4-(2-fenil-etinil)-fenil]-pirrol.

"Hetero-aril-arilo" se refiere a un grupo biarilo, en donde uno de los grupos arilo es un grupo hetero-arilo. Los grupos hetero-aril-arilo de ejemplo incluyen, por ejemplo, 2-fenil-piridina, fenil-pirrol, 3-(2-fenil-etinil)-piridina, fenil-pirazol, 5-(2-fenil-etinil)-1,3-dihidro-pirimidin-2,4-diona, 4-fenil-1,2,3-tiadiazol, 2-(2-fenil-etinil)-pirazina, 2-feniltiofeno, fenil-imidazol, 3-(2-piperazinil-fenil)-furano, 3-(2,4-dicloro-fenil)-4-metil-pirrol, y similares. Los grupos hetero-aril-arilo opcionalmente sustituidos preferidos incluyen: 5-(2-fenil-etinil)-pirimidin-2-il-amina, 1-metoxi-4-(2-tienil)-benceno, 1-metoxi-3-(2-tienil)-benceno, 5-metil-2-fenil-piridina, 5-metil-3-fenil-isoxazol, 2-[3-(trifluoro-metil)-fenil]-furano, 3-fluoro-5-(2-furil)-2-metoxi-1-prop-2-enil-benceno, (hidroxi-imino)-(5-fenil-(2-tienil))-metano, 5-[(4-metil-piperazinil)-metil]-2-fenil-tiofeno, 2-(4-etil-fenil)-tiofeno, 4-metil-tio-1-(2-tienil)-benceno, 2-(3-nitro-fenil)-tiofeno, (terbutoxi)-N-[(5-fenil-(3-piridil))-metil]-carboxamida, hidroxi-N-[(5-fenil-(3-piridil))-metil]-amida, 2-(fenil-tiometil)-piridina, y bencilimidazol.

"Heteroaril-heteroarilo" se refiere a un grupo biarilo en donde ambos grupos arilo son un grupo hetero-arilo. Los grupos heteroaril-

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heteroarilo de ejemplo incluyen, por ejemplo, 3-piridil-imidazol, 2-imidazolil-pirazina, y similares. Los grupos heteroaril-heteroarilo opcionalmente sustituidos preferidos incluyen: 2-(4-piperazinil-3-piridil)-furano, dietil-(3-pirazin-2-il-(4-piridil))-amina, y dimetil-{2-[2-(5-metil-pirazin-2-il)-etinil](4-piridil)}-amina.

"Opcionalmente sustituido" o "sustituido" se refiere al reemplazo de hidrógeno con uno o más radicales monovalentes o divalentes. Los grupos de sustitución adecuados incluyen, por ejemplo, hidroxilo, nitro, amino, imino, ciano, halógeno, tio, sulfonilo, tioamido, amidino, imidino, oxo, oxamidino, metoxamidino, imidino, guanidino, sulfonamido, carboxilo, formilo, alquilo, alquilo sustituido, halo-alquilo, alquil-amino, halo-alquil-amino, alcoxilo, halo-alcoxilo, alcoxi-alquilo, alquil-carbonilo, amino-carbonilo, aril-carbonilo, aralquil-carbonilo, hetero-aril-carbonilo, hetero-aralquil-carbonilo, tioalquilo, amino-alquilo, ciano-alquilo, arilo, bencilo, piridilo, pirazolilo, pirrol, tiofeno, imidazolilo, y similares.

El grupo de sustitución puede estar él mismo sustituido. El grupo sustituido sobre el grupo de sustitución puede ser carboxilo, halógeno, nitro, amino, ciano, hidroxilo, alquilo, alcoxilo, amino-carbonilo, -SR, tioamido, $-SO_3H$, $-SO_2R$, o cicloalquilo, en donde R es típicamente hidrógeno, hidroxilo o alquilo.

Cuando el sustituyente sustituido incluye un grupo de cadena recta, la sustitución puede ocurrir ya sea dentro de la cadena (por ejemplo, 2-hidroxi-propilo, 2-amino-butilo, y similares), o en el término de la cadena (por ejemplo, 2-hidroxi-etilo, 3-ciano-propilo, y

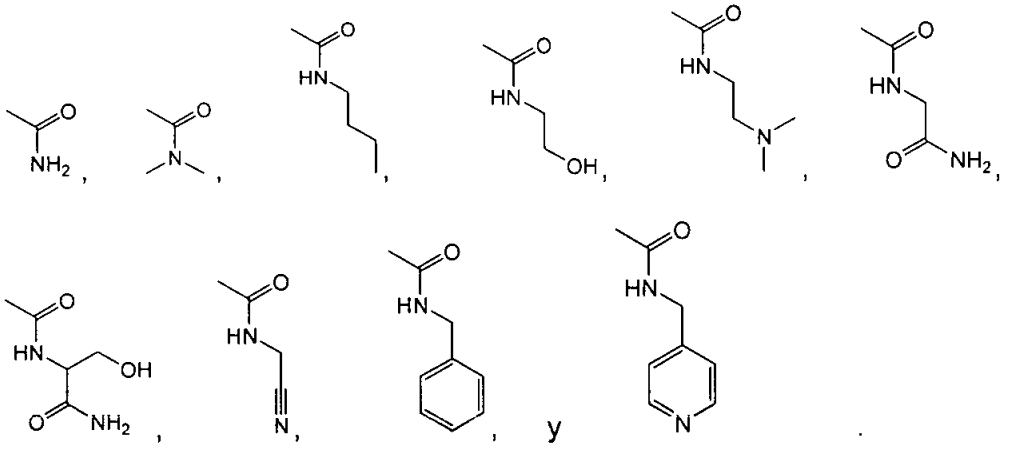
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similares). Los sustituyentes sustituidos pueden ser configuraciones de cadena recta, ramificada, o cíclica de átomos de carbono o heteroátomos covalentemente enlazados.

Los grupos amino-carbonilo sustituidos representativos incluyen, por ejemplo, aquéllos mostrados más adelante. Éstos puede estar adicionalmente sustituidos por grupos heterociclilo y hetero-arilo, como será evidente para aquéllos que tengan experiencia en el campo de la química orgánica y medicinal, en conjunto con la divulgación en la presente. Los grupos amino-carbonilo preferidos incluyen: N-(2-ciano-etil)-carboxamida, N-(3-metoxi-propil)-carboxamida, N-ciclopropil-carboxamida, N-(2-hidroxi-isopropil)-carboxamida, 2-carbonil-amino-3-hidroxi-propanoato de metilo, N-(2-hidroxi-propil)-carboxamida, N-(2-hidroxi-isopropil)-carboxamida, N-[2-hidroxi-1-(hidroxi-metil)-etil]-carboxamida, N-(2-carbonil-amino-etil)-acetamida, N-(2-(2-piridil)-etil)-carboxamida, N-(2-piridil-metil)-carboxamida, N-(oxolan-2-il-metil)-carboxamida, N-(4-hidroxi-pirrolidin-2-il)-carboxamida, N-[2-(2-hidroxi-etoxi)-etil]-carboxamida, N-(4-hidroxi-ciclohexil)-carboxamida, N-[2-(2-oxo-4-imidazolinil)-etil]-carboxamida, N-(carbonil-amino-metil)-acetamida, N-(3-pirrolidinil-propil)-carboxamida, N-[1-(carbonil-amino-metil)-pirrolidin-3-il]-acetamida, N-(2-morfolin-4-il-etil)-carboxamida, N-[3-(2-oxo-pirrolidinil)-propil]-carboxamida, 4-metil-2-oxopiperazin-carbaldehído, N-(2-hidroxi-3-pirrolidinil-propil)-carboxamida, N-(2-hidroxi-3-morfolin-4-il-propil)-carboxamida, N-{2-[(5-ciano-2-piridil)-amino]-etil}-carboxamida, 3-(dimetil-amino)-pirrolidin-carbaldehído,

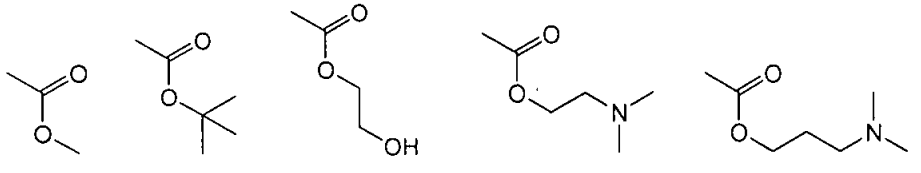
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N-[(5-metil-pirazin-2-il)-metil]-carboxamida, 2,2,2-trifluoro-N-(1-formil-pirrolidin-3-il)acetamida,

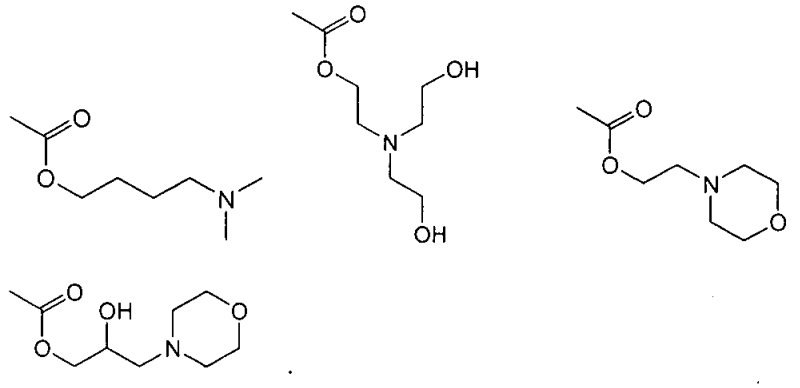


Los grupos alcoxi-carbonilo sustituidos representativos incluyen, por ejemplo, aquéllos mostrados más adelante. Estos grupos alcoxi-carbonilo pueden estar adicionalmente sustituidos como será evidente para aquéllos que tengan experiencia en el campo de la química orgánica y medicinal en conjunto con la divulgación de la presente.

Los grupos alcoxi-carbonilo sustituidos representativos incluyen, por ejemplo, aquéllos mostrados más adelante. Estos grupos alcoxi-carbonilo pueden estar adicionalmente sustituidos como será evidente para aquéllos que tengan experiencia en el campo de la química orgánica y medicinal en conjunto con la divulgación de la presente.



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El término "protegido" con respecto a los grupos hidroxilo, los grupos amina, y los grupos sulfhidrilo, se refiere a las formas de estas funcionalidades que están protegidas de la reacción indeseable, con un grupo protector conocido por los expertos en este campo, tales como aquéllos estipulados en *Protective Groups in Organic Synthesis*, Greene, T. W.; Wuts, P. G. M., John Wiley & Sons, Nueva York, NY, (3a. Edición, 1999), los cuales se pueden agregar o remover empleando los procedimientos estipulados en el mismo. Los ejemplos de los grupos hidroxilo protegidos incluyen, pero no se limitan a, silil-éteres tales como aquéllos obtenidos mediante la reacción de un grupo hidroxilo con un reactivo, tal como, pero no limitándose a, terbutil-dimetil-cloro-silano, trimetil-cloro-silano, tri-isopropil-cloro-silano, trietil-cloro-silano; metilo sustituido, y etil-éteres, tales como, pero no limitándose a, metoxi-metil-éter, metil-tiometil-éter, benciloxi-metil-éter, terbutoxi-metil-éter, 2-metoxi-etoxi-metil-éter, tetrahidro-piranil-éteres, 1-etoxi-etil-éter, alil-éter, bencil-éter; ésteres, tales como, pero no limitándose a, formato de benzoílo, formato, acetato, tricloro-acetato, y trifluoro-acetato. Los

ejemplos de los grupos amina protegidos incluyen, pero no se limitan a, amidas tales como, formamida, acetamida, trifluoro-acetamida, y benzamida; imidas, tales como ftalimida, y ditio-succinimida; y otros. Los ejemplos de los grupos sulfhidrilo protegidos incluyen, pero no se limitan a, tioéteres tales como S-bencil-tioéter, y S-4-picolil-tioéter; derivados de S-metilo sustituidos, tales como tiohemi-, ditio-, y tioamino-acetales; y otros.

"Grupo protector de carboxilo" se refiere a un grupo carbonilo, el cual se ha esterificado con uno de los grupos éster protectores de ácido carboxílico comúnmente utilizados, empleados para bloquear o proteger la función de ácido carboxílico, mientras que se llevan a cabo las reacciones que involucran otros sitios funcionales del compuesto. En adición, un grupo protector de carboxilo se puede unir a un soporte sólido en donde el compuesto permanece conectado al soporte sólido como el carboxilato, hasta que sea disociado mediante métodos hidrolíticos para liberar el ácido libre correspondiente. Los grupos protectores de carboxilo representativos incluyen, por ejemplo, alquil-ésteres, amidas secundarias, y similares.

Ciertos compuestos de la invención comprenden átomos de carbono asimétricamente sustituidos. Estos átomos de carbono asimétricamente sustituidos pueden dar como resultado los compuestos de la invención que comprenden las mezclas de estereoisómeros en un átomo de carbono asimétricamente sustituido particular, o un solo estereoisómero. Como un resultado, en la presente invención se incluyen mezclas racémicas, mezclas de

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diaestereómeros, así como los diaestereómeros individuales de los compuestos de la invención. Los términos configuración "S" y "R", como se utilizan en la presente, son como los define la IUPAC 1974 "RECOMMENDATIONS FOR SECTION E, FUNDAMENTAL STEREOCHEMISTRY," *Pure Appl. Chem. 45*: 13-30, 1976. Los términos α y ß se emplean para las posiciones del anillo de los compuestos cíclicos. El lado-α del plano de referencia es el lado sobre el cual queda el sustituyente preferido en la posición numerada más baja. A los sustituyentes que quedan sobre el lado opuesto del plano de referencia, se les asigna el descriptor ß. Se debe observar que este uso difiere de aquél para los estereoprogenitores cíclicos, en donde "α" significa "debajo del plano" y denota la configuración absoluta. Los términos configuración α y ß, como se utilizan en la presente, son como se definen en "Chemical Abstracts Index Guide", Apéndice IV, párrafo 203, 1987.

Como se utiliza en la presente, el término "sales farmacéuticamente aceptables" se refiere a las sales de ácido o de metales alcalinotérreos no tóxicas de los compuestos de pirimidina de la invención. Estas sales se pueden preparar *in situ* durante el aislamiento y la purificación final de los compuestos de pirimidina, o mediante la reacción por separado de las funciones de base o de ácido con un ácido o base orgánicos o inorgánicos adecuados, respectivamente. Las sales representativas incluyen, pero no se limitan a, las siguientes: acetato, adipato, alginato, citrato, aspartato, benzoato, bencen-sulfonato, bisulfato, butirato, canforato, canfor-

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sulfonato, digluconato, ciclopentan-propionato, dodecil-sulfato, etan-sulfonato, gluco-heptanoato, glicerofosfato, hemi-sulfato, heptanoato, hexanoato, fumarato, clorhidrato, bromhidrato, yodhidrato, 2-hidroxi-etan-sulfonato, lactato, maleato, metan-sulfonato, nicotinato, 2-naft-alquen-sulfonato, oxalato, pamoato, pectinato, persulfato, 3-fenil-propionato, picrato, pivalato, propionato, succinato, sulfato, tartrato, tiocianato, p-toluen-sulfonato, y undecanoato. También, los grupos que contienen nitrógeno básico se pueden cuaternizar con agentes tales como haluros de alquilo, tales como cloruros, bromuros, y yoduros de metilo, etilo, propilo, y butilo; sulfatos de dialquilo, como sulfatos de dimetilo, dietilo, dibutilo, y diamilo; haluros de cadena larga, tales como cloruros, bromuros, y yoduros de decilo, laurilo, miristilo, y estearilo, haluros de aralquilo, como bromuros de bencilo y fenetilo, y otros. De esta manera se obtienen productos solubles o dispersables en agua o en aceite.

Los ejemplos de los ácidos que se pueden emplear para formar las sales de adición de ácido farmacéuticamente aceptables incluyen los ácidos inorgánicos, tales como ácido clorhídrico, ácido hidrobórico, ácido nítrico, ácido sulfúrico, y ácido fosfórico, y los ácidos orgánicos, tales como ácido fórmico, ácido acético, ácido trifluoro-acético, ácido fumárico, ácido tartárico, ácido oxálico, ácido maleico, ácido metan-sulfónico, ácido succínico, ácido málico, ácido metan-sulfónico, ácido bencen-sulfónico, y ácido p-toluen-sulfónico, ácido cítrico, y aminoácidos ácidos, tales como ácido aspártico y ácido glutámico.

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Las sales de adición básicas se pueden preparar *in situ* durante el aislamiento y purificación final de los compuestos de pirimidina, o por separado mediante la reacción de las fracciones de ácido carboxílico con una base adecuada tal como el hidróxido, carbonato o bicarbonato de un catión de metal farmacéuticamente aceptable, o con amoníaco, o con una amina orgánica primaria, secundaria, o terciaria. Las sales farmacéuticamente aceptables incluyen, pero no se limitan a, los cationes basados en los metales alcalinos y alcalinotérreos, tales como sales de sodio, litio, potasio, calcio, magnesio, aluminio y similares, así como los cationes de amonio, amonio cuaternario, y amina no tóxicos, incluyendo, pero no limitándose a, amonio, tetrametil-amonio, tetraetil-amonio, metil-amina, dimetil-amina, trimetil-amina, trietil-amina, etil-amina, y similares. Otras aminas orgánicas representativas útiles para la formación de las sales de adición de base incluyen dietil-amina, etilen-diamina, etanolamina, dietanolamina, piperazina, piridina, picolina, trietanolamina y similares, y los aminoácidos básicos, tales como arginina, lisina y ornitina.

Como se utiliza en la presente, el término "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 ácidos alcanoico,

alquenoico, cicloalcanoico y alcanodioico, en donde cada fracción de alquilo o alquenilo convenientemente tiene no 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.

El término "pro-fármacos farmacéuticamente aceptables", como se utiliza en la presente, se refiere a los pro-fármacos de los compuestos de la presente invención que, dentro del alcance de un buen juicio médico, son adecuados para utilizarse en contacto con los tejidos de seres humanos y animales inferiores sin una indebida toxicidad, irritación, respuesta alérgica, y similares, de una manera conmensurada con una proporción razonable de beneficio/riesgo, y efectivos para su uso pretendido, así como las formas zwiteriónicas, donde sea posible, de los compuestos de la invención. El término "pro-fármaco" se refiere a los compuestos que se transforman rápidamente *in vivo* para proporcionar el compuesto progenitor de la fórmula anterior, por ejemplo mediante hidrólisis en la sangre. Se proporciona una discusión completa en Higuchi, T., y V. Stella, "Pro-drugs as Novel Delivery Systems," *A.C.S. Symposium Series 14*, y en "Bioreversible Vehicles in Drug Design," en Edward B. Roche (editor), *American Pharmaceutical Association*, Pergamon Press, 1987, ambos de los cuales se incorporan a la presente como referencia.

"Tratamiento" dentro del contexto de la presente invención, significa un alivio de los síntomas asociados con un trastorno o

enfermedad, o la detención del progreso adicional o del empeoramiento de estos síntomas, o la prevención o profilaxis de la enfermedad o trastorno. Por ejemplo, dentro del contexto del tratamiento de los pacientes que necesiten un inhibidor de PI3K, el tratamiento de éxito puede incluir una reducción en la proliferación de los capilares que alimentan un tumor o un tejido enfermo, un alivio de los síntomas relacionados con un crecimiento canceroso o tumor, la proliferación de los capilares, o el tejido enfermo; una detención en la proliferación de los capilares; o una detención en el progreso de una enfermedad tal como cáncer o en el crecimiento de las células cancerosas. El tratamiento también puede incluir la administración de las formulaciones farmacéuticas de la presente invención en combinación con otras terapias. Por ejemplo, los compuestos y formulaciones farmacéuticas de la presente invención se pueden administrar antes, durante, o después del procedimiento quirúrgico y/o de la terapia de radiación. Los compuestos de la invención también se pueden administrar en conjunto con otros fármacos contra el cáncer, incluyendo aquéllos utilizados en la terapia anti-sentido y genética.

Como se utiliza en la presente, "limitar", "tratar" y "tratamiento" son términos intercambiables, así como "limitando" y "tratando" y, como se utilizan en la presente, incluyen el tratamiento preventivo (por ejemplo, profiláctico) y paliativo, o el acto de proporcionar un tratamiento preventivo o paliativo.

El término "trastorno mediado por PI3K" se refiere a un

trastorno que se puede tratar benéficamente mediante la inhibición de PI3K.

El término "enfermedades de proliferación celular" se refiere a las enfermedades que incluyen, por ejemplo, cáncer, tumor, hiperplasia, restenosis, hipertrofia cardíaca, trastorno inmune, e inflamación.

El término "cáncer" se refiere a enfermedades de cáncer que se pueden tratar benéficamente mediante la inhibición de PI3K, incluyendo, por ejemplo, de tumor y bronquios; próstata; mama; páncreas; colon, y recto; tiroides; hígado y conducto biliar intrahepático, hepatocelúlar; gástrico; glioma/glioblastoma; endometrial; melanoma; riñón y pelvis renal; vejiga urinaria; cuerpo uterino; cérvix uterino; ovario; mieloma múltiple; esófago; leucemia mielógena aguda; leucemia mielógena crónica; leucemia linfocítica; leucemia mieloide; cerebro; cavidad oral y faringe; laringe; intestino delgado; linfoma no de Hodgkin; melanoma; y adenoma de colon velloso.

Los inhibidores de PI3K de esta invención, como se describen en la presente, se pueden administrar en la forma de sales de adición de ácido. Las sales se forman, de una manera conveniente, mediante la reacción de un compuesto, si es básico, con un ácido adecuado, tales como se han descrito anteriormente. Las sales se forman rápidamente en altos rendimientos a temperaturas moderadas, y con frecuencia se preparan meramente aislando el compuesto a partir de un lavado ácido adecuado como el paso final

de la síntesis. El ácido formador de sal se disuelve en un solvente orgánico apropiado, o en un solvente orgánico acuoso, tal como un alcanol, cetona, o éster. Por otra parte, si el compuesto de esta invención se desea en la forma de base libre, se aísla a partir de un paso de lavado final básico, de acuerdo con la práctica usual. Una técnica preferida para la preparación de clorhidratos es disolver la base libre en un solvente adecuado, y se seca la solución completamente, como sobre tamices moleculares, antes de burbujear gas de cloruro de hidrógeno a través de ella. También se reconocerá que es posible administrar las formas amorfas de los inhibidores de PI3K.

La invención también proporciona inhibidores de PI3K isotópicamente marcados, los cuales son estructuralmente idénticos a aquéllos que se dan a conocer anteriormente, salvo por el hecho de que uno o más átomos son reemplazados por un átomo que tiene una masa atómica o número de masa diferente de la masa atómica o número de masa que se encuentran usualmente en la naturaleza. 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 pro-fármacos de los mismos, y las sales farmacéuticamente aceptables de estos compuestos y de los pro-fármacos mencionados, que contienen los isótopos anteriormente mencionados y/u otros isótopos

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de otros átomos, están dentro del alcance de esta invención. Ciertos compuestos isotópicamente marcados de la presente invención, por ejemplo, aquéllos en los cuales se incorporan isótopos radioactivos, tales como ^{3}H y ^{14}C, son útiles en los ensayos de distribución en tejido de fármacos y/o sustratos. Se prefieren en particular los isótopos tritiados, es decir, ^{3}H, y carbono-14, es decir, ^{14}C, por su facilidad de preparación y detectabilidad. Además, la sustitución con isótopos más pesados, tales como deutero, es decir, ^{2}H, puede proporcionar ciertas ventajas terapéuticas que resultan de la mayor estabilidad metabólica, por ejemplo, mayor 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, en términos generales, se pueden preparar llevando a cabo los procedimientos conocidos o referenciados, y sustituyendo un reactivo no isotópicamente marcado por un reactivo isotópicamente marcado fácilmente disponible.

Los compuestos de la invención son útiles *in vitro* o *in vivo* en la inhibición del crecimiento de células de cáncer. Los compuestos se pueden utilizar solos o en composiciones junto con un vehículo o excipiente farmacéuticamente aceptable. Las composiciones farmacéuticas de la presente invención comprenden una cantidad terapéuticamente efectiva de un compuesto inhibidor de cinasa de fosfatidil-inositol-3 descrito en la presente, formulado junto con uno o más vehículos farmacéuticamente aceptables. Como se utiliza en la

presente, el término "vehículo farmacéuticamente aceptable" significa un relleno, diluyente, material encapsulante, o auxiliar de formulación de cualquier tipo, sólido, semi-sólido, o líquido inerte y no tóxico. Algunos ejemplos de los materiales que pueden servir como vehículos farmacéuticamente aceptables son azúcares, tales como lactosa, glucosa, y sacarosa; almidones, tales como almidón de maíz y almidón de papa; celulosa y sus derivados, tales como carboxi-metil-celulosa de sodio, etil-celulosa, y acetato de celulosa; tragacanto en polvo; malta; gelatina; talco; excipientes, tales como manteca de cacao y ceras para supositorios; aceites, tales como aceite de cacahuate, aceite de semilla de algodón; aceite de azafrán; aceite de ajonjolí; aceite de oliva; aceite de maíz; y aceite de semilla de soya; glicoles, tales como un propilenglicol; ésteres, tales como oleato de etilo y laurato de etilo; agar; agentes reguladores del pH, tales como hidróxido de magnesio e hidróxido de aluminio; ácido algínico; agua libre de pirógeno; suero isotónico; solución de Ringer; alcohol etílico, y soluciones reguladoras de fosfato, así como también pueden estar presentes en la composición otros lubricantes no tóxicos compatibles, tales como lauril-sulfato de sodio y estearato de magnesio, así como agentes colorantes, agentes de liberación, agentes de recubrimiento, edulcorantes, agentes saborizantes y perfumantes, conservadores, y antioxidantes, de acuerdo con el juicio del formulador. Otros excipientes farmacéuticamente aceptables adecuadas se describen en "Remington's Pharmaceutical Sciences," Mack Pub. Co., Nueva Jersey, 1991, incorporado a la

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presente como referencia.

Los compuestos de la presente invención se pueden administrar a seres humanos y a otros animales oralmente, parenteralmente, sublingualmente, mediante aerosolización o rocío para inhalación, rectalmente, intracisternalmente, intravaginalmente, intraperitonealmente, bucalmente, o tópicamente formulaciones unitarias de dosificación que contengan vehículos no tóxicos convencionales farmacéuticamente aceptables, adyuvantes, y vehículos, según se desee. La administración tópica también puede involucrar el uso de administración transdérmica, tal como parches transdérmicos o dispositivos de iontoforesis. El término parenteral como se utiliza en la presente, incluye inyecciones subcutáneas, intravenosas, intramusculares, intraesternales, o técnicas de infusión.

Los métodos de formulación son bien conocidos en la técnica, y se dan a conocer, por ejemplo, en Remington: *The Science and Practice of Pharmacy*, Mack Publishing Company, Easton, Pa., 19a. Edición (1995). Las composiciones farmacéuticas para utilizarse en la presente invención pueden estar en la forma de soluciones o suspensiones líquidas no pirogénicas estériles, cápsulas recubiertas, supositorios, polvos liofilizados, parches transdérmicos, u otras formas conocidas en este campo.

Las preparaciones inyectables, por ejemplo, las suspensiones acuosas u oleaginosas inyectables estériles, se pueden formular de acuerdo con la técnica conocida, utilizando agentes de dispersión o

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humectación y agentes de suspensión adecuados. La preparación inyectable estéril también puede ser una solución, suspensión o emulsión inyectable estéril en un diluyente o solvente no tóxico parenteralmente aceptable, por ejemplo, como una solución en 1,3-propanodiol o 1,3-butanodiol. Entre los vehículos y solventes aceptables que se pueden emplear están agua, solución de Ringer, solución de cloruro de sodio U.S.P. e isotónica. En adición, los aceites fijos estériles se emplean convencionalmente como un solvente o medio de suspensión. Para este propósito, se puede emplear cualquier aceite fijo blando, incluyendo mono- o di-glicéridos sintéticos. En adición, los ácidos grasos, tales como ácido oleico, encuentran uso en la preparación de inyectables. Las formulaciones inyectables se pueden esterilizar, por ejemplo, mediante filtración a través de un filtro de retención de bacterias, o mediante la incorporación de agentes esterilizantes en la forma de composiciones sólidas estériles, las cuales se pueden disolver o dispersar en agua estéril u otro medio inyectable estéril antes de usarse.

Con el objeto de prolongar el efecto de un fármaco, con frecuencia es recomendable hacer más lenta la absorción del fármaco a partir de la inyección subcutánea o intramuscular. Esto se puede llevar a cabo mediante el uso de una suspensión líquida de material cristalino o amorfo con una pobre solubilidad en agua. Entonces, la velocidad de absorción del fármaco depende de su velocidad de disolución, la cual, a su vez, puede depender del

tamaño del cristal y de la forma cristalina. De una manera alternativa, se puede llevar a cabo una absorción demorada de una forma de fármaco parenteralmente administrado, mediante la disolución o suspensión del fármaco en un vehículo oleoso. Las formas de depósito inyectables se hacen formando matrices microencapsuladas del fármaco en polímeros biodegradables, tales como polilácticido-poliglicólido. Dependiendo de la proporción del fármaco al polímero, y de la naturaleza del polímero particular empleado, se puede controlar la velocidad de liberación del fármaco. Los ejemplos de otros polímeros biodegradables incluyen poli-(orto-ésteres) y poli-(anhídridos). Las formulaciones inyectables de depósito también se pueden preparar atrapando el fármaco en liposomas o microemulsiones, que sean compatibles con los tejidos corporales.

Las composiciones para administración rectal o vaginal de preferencia son supositorios, los cuales se pueden preparar mezclando los compuestos de esta invención con excipientes o vehículos no irritantes adecuados, tales como manteca de cacao, polietilenglicol, o una cera para supositorios, que sean sólidos a la temperatura ambiente, pero líquidos a la temperatura de corporal, y por consiguiente, que se fundan en el recto o en la cavidad vaginal, y liberen el compuesto activo.

Las formas de dosificación sólida para administración oral incluyen cápsulas, tabletas, píldoras, polvos, y gránulos. En estas formas de dosificación sólida, el compuesto activo se mezcla con

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cuando menos un excipiente o vehículo farmacéuticamente aceptable inerte, tal como citrato de sodio o difosfato de calcio, y/o: a) rellenos o extensores, tales como almidones, lactosa, sacarosa, glucosa, manitol, y ácido silícico; b) aglutinantes, tales como, por ejemplo, carboxi-metil-celulosa, alginatos, gelatina, polivinil-pirrolidona, sacarosa, y acacia; c) humectantes, tales como glicerol; d) agentes desintegrantes, tales como agar-agar, carbonato de calcio, almidón de papa o de tapioca, ácido algínico, ciertos silicatos, y carbonato de sodio; e) agentes retardantes de solución, tales como parafina; f) aceleradores de absorción, tales como compuestos de amonio cuaternario; g) agentes humectantes, tales como, por ejemplo, alcohol cetílico y monoestearato de glicerol; h) absorbentes, tales como caolín y arcilla de bentonita, e i) lubricantes, tales como talco, estearato de calcio, estearato de magnesio, polietilenglicoles sólidos, lauril-sulfato de sodio, y mezclas de los mismos. En el caso de las cápsulas, tabletas, y píldoras, la forma de dosificación también puede comprender agentes reguladores del pH.

También se pueden emplear composiciones sólidas de un tipo similar como rellenos en las cápsulas de gelatina blandas y duras rellenas, utilizando excipientes tales como lactosa o azúcar de leche, así como polietilenglicoles de alto peso molecular, y similares.

Las formas de dosificación sólidas de tabletas, grageas, cápsulas, píldoras, y gránulos se pueden preparar con recubrimientos y cubiertas, tales como recubrimientos entéricos y otros recubrimientos bien conocidos en la técnica de la formulación

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farmacéutica. Opcionalmente pueden contener agentes opacificantes, y también pueden ser de una composición tal que liberen los ingredientes activos solamente, o preferencialmente, en cierta parte del tracto intestinal, opcionalmente, de una manera retardada. Los ejemplos de las composiciones de empotramiento incluyen sustancias poliméricas y ceras.

Los compuestos activos también pueden estar en una forma microencapsulada con uno o más excipientes, como se mencionan anteriormente. Las formas de dosificación sólidas de tabletas, grageas, cápsulas, píldoras, y gránulos se pueden preparar con recubrimientos y cubiertas, tales como recubrimientos entéricos, recubrimientos de control de liberación, y otros recubrimientos bien conocidos en la técnica de la formulación farmacéutica. 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 comprender, como es la práctica normal, sustancias adicionales diferentes de los diluyentes inertes, por ejemplo, lubricantes de formación de tabletas y otros auxiliares de formación de tabletas, tales como estearato de magnesio y celulosa microcristalina. En el caso de las cápsulas, tabletas y píldoras, las formas de dosificación también pueden comprender agentes reguladores del pH. Opcionalmente pueden contener agentes opacificantes, y también pueden ser de una composición tal que liberen los ingredientes activos solamente, o preferencialmente, en cierta parte del tracto

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intestinal, opcionalmente, de una manera retardada. Los ejemplos de las composiciones de empotramiento incluyen sustancias poliméricas y ceras.

Las formas de dosificación líquidas para administración oral incluyen emulsiones, microemulsiones, soluciones, suspensiones, jarabes, y elíxires farmacéuticamente aceptables. En adición a los compuestos activos, las formas de dosificación líquidas pueden contener los diluyentes inertes comúnmente utilizados en la materia, tales como, por ejemplo, agua u otros solventes, agentes solubilizantes y emulsionantes, tales como alcohol etílico, alcohol isopropílico, carbonato de etilo, EtOAc, alcohol bencílico, benzoato de bencilo, propilenglicol, 1,3-butilenglicol, dimetil-formamida, aceites (en particular, aceites de semilla de algodón, de cacahuate, de maíz, de germen, de oliva, de ricino, y de ajonjolí), glicerol, alcohol tetrahidrofurfurílico, polietilenglicoles, y ésteres de ácidos grasos de sorbitán, y mezclas de los mismos. Además de los diluyentes inertes, las composiciones orales también pueden incluir adyuvantes, tales como agentes humectantes, agentes emulsionantes y de suspensión, agentes edulcorantes, saborizantes, y perfumantes.

Las formas de dosificación para administración tópica o transdérmica de un compuesto de esta invención incluyen ungüentos, pastas, cremas, lociones, geles, polvos, soluciones, aerosoles, inhalantes, o parches. El componente activo se mezcla bajo condiciones estériles con un vehículo farmacéuticamente aceptable,

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y con cualesquiera conservadores o reguladores necesarios que se puedan requerir. También se contempla que las formulaciones oftálmicas, gotas para los oídos, y similares, están dentro del alcance de esta invención.

Los ungüentos, pastas, cremas y geles pueden contener, en adición a un compuesto activo de esta invención, excipientes, tales como grasas animales y vegetales, aceites, ceras, parafinas, almidón, tragacanto, derivados de celulosa, polietilenglicoles, siliconas, bentonitas, ácido silícico, talco, y óxido de zinc, o mezclas de los mismos.

Las composiciones de la invención también se pueden formular para suministrarse como un aerosol líquido o como un polvo seco inhalable. Las formulaciones en aerosol líquidas se pueden nebulizar predominantemente en tamaños de partículas que se puedan suministrar a los bronquiolos terminales y respiratorios.

Las formulaciones aerosolizadas de la invención se pueden suministrar utilizando un dispositivo formador de aerosol, tal como un nebulizador de chorro, de placa porosa vibratoria, o ultrasónico, de preferencia seleccionado para permitir la formación de partículas de aerosol con un diámetro promedio de masa predominantemente de entre 1 y 5 micras. Además, la formulación de preferencia tiene una fuerza iónica y una concentración de cloruro de osmolaridad equilibrada, y el volumen aerosolizable más pequeño es capaz de suministrar una dosis efectiva de los compuestos de la invención al sitio de la infección. Adicionalmente, la formulación aerosolizada de

preferencia no perjudica negativamente la funcionalidad de las vías respiratorias y no provoca efectos secundarios indeseables.

Los dispositivos de aerosolización adecuados para la administración de las formulaciones en aerosol de la invención incluyen, por ejemplo, nebulizadores de chorro, de placa porosa vibratoria, ultrasónicos, e inhaladores de polvo seco energetizados, que sean capaces de nebulizar la formulación de la invención en un tamaño de partículas de aerosol predominantemente en el intervalo de tamaños de 1 a 5 micras. Predominantemente, en esta solicitud, significa que cuando menos el 70 por ciento, pero de preferencia más del 90 por ciento de todas las partículas de aerosol generadas están dentro del intervalo de 1 a 5 micras. Un nebulizador de chorro trabajo mediante la presión del aire, para romper una solución líquida en gotitas de aerosol. Los nebulizadores de placa porosa vibratoria trabajan utilizando un vacío sónico producido mediante la vibración rápida de una placa porosa para extruir una gotita de solvente a través de una placa porosa. Un nebulizador ultrasónico trabaja mediante un cristal piezoeléctrico que desgarra un líquido en pequeñas gotitas de aerosol. Hay una variedad de dispositivos adecuados disponibles, incluyendo, por ejemplo, los nebulizadores de placa porosa vibratoria AERONEB y AERODOSE (AeroGen, Inc., Sunnyvale, California), los nebulizadores SIDESTREAM (Medic-Aid Ltd., West Sussex, Inglaterra), los nebulizadores de chorro PARI LC y PARI LC STAR (Pari Respiratory Equipment, Inc., Richmond, Virginia), y los nebulizadores ultrasónicos AEROSONIC (DeVilbiss

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Medizinische Produkte (Deutschland) GmbH, Heiden, Alemania) y ULTRAAIRE (Omron Healthcare, Inc., Vernon Hills, Illinois).

Los compuestos de la invención también se pueden formular para utilizarse como polvos y aerosoles tópicos que pueden contener, en adición a los compuestos de esta invención, excipientes tales como lactosa, talco, ácido silícico, hidróxido de aluminio, silicatos de calcio, y polvo de poliamida, o mezclas de estas sustancias. Los aerosoles pueden contener adicionalmente los propelentes acostumbrados, tales como cloro-fluoro-hidrocarbonos.

Los parches transdérmicos tienen la ventaja adicional de proporcionar el suministro controlado de un compuesto al cuerpo. Estas formas de dosificación se pueden hacer mediante la disolución o dosificación del compuesto en el medio apropiado. También se pueden utilizar mejoradores de absorción para aumentar el flujo del compuesto a través de la piel. La velocidad se puede controlar ya sea disponiendo una membrana de control de velocidad, o bien dispersando el compuesto en una matriz polimérica o gel. Los compuestos de la presente invención también se pueden administrar en la forma de liposomas. Como se conoce en la materia, los liposomas se derivan en general 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

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pueden contener, en adición a un compuesto de la presente invención, estabilizantes, conservadores, excipientes, y similares. Los lípidos preferidos son los fosfolípidos y las fosfatidil-colinas (lecitinas), tanto naturales como sintéticos. Los métodos para formar liposomas son conocidos en la materia. Véase, por ejemplo, Prescott (editor), "Methods in Cell Biology," Volumen XIV, Academic Press, Nueva York, 1976, páginas 33 y siguientes.

Las cantidades efectivas de los compuestos de la invención incluyen, en términos generales, cualquier cantidad suficiente para inhibir de una manera detectable la actividad de PI3K, mediante cualquiera de los ensayos descritos en la presente, mediante otros ensayos de la actividad de PI3K conocidos por aquéllos que tienen una experiencia ordinaria en este campo, o mediante la detección de una inhibición o alivio de los síntomas de cáncer. 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, sexo, dieta, tiempo de administración, vía de administración, índice de excreción, combinación de fármacos, y de la severidad 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.

De acuerdo con los métodos de tratamiento de la presente invención, se reduce o se previene el crecimiento tumoral en un paciente, tal como un ser humano o un mamífero inferior, mediante la administración al paciente, de una cantidad terapéuticamente efectiva de un compuesto de la invención, en las cantidades y durante el tiempo necesarios para lograr el resultado deseado. Una "cantidad terapéuticamente efectiva" de un compuesto de la invención significa una cantidad suficiente del compuesto para tratar el crecimiento tumoral, a una proporción razonable de beneficio/ riesgo aplicable a cualquier tratamiento médico. Sin embargo, se entenderá que el uso diario total de los compuestos y composiciones de la presente invención será decidido por el médico que atienda dentro del alcance de un buen juicio médico. El nivel de dosis terapéuticamente efectiva específico para cualquier paciente particular dependerá de una variedad de factores, incluyendo el trastorno que se esté tratando y la severidad del trastorno; la actividad del compuesto específico empleado; la composición específica empleada; la edad, el peso corporal, la salud general, el sexo y la dieta del paciente; el tiempo de administración, la vía de administración, y el índice de excreción del compuesto específico empleado; la duración del tratamiento; los fármacos utilizados en combinación o en coincidencia con el compuesto específico empleado; y factores similares bien conocidos en el ámbito médico.

Para los propósitos de la presente invención, una dosis terapéuticamente efectiva será en general una dosis diaria total administrada a un huésped en una sola dosis o en dosis divididas, que pueden estar en cantidades, por ejemplo, de 0.001 a 1,000 miligramos/kilogramo de peso corporal al día, y más preferiblemente de 1.0 a 30 miligramos/kilogramo de peso corporal al día. Las composiciones unitarias de dosificación pueden contener las cantidades de submúltiplos de las mismas para formar la dosis diaria. En general, los regímenes de tratamiento de acuerdo con la presente invención comprenden la administración a un paciente que necesite dicho tratamiento, de aproximadamente 10 miligramos a aproximadamente 2,000 miligramos de los compuestos de esta invención al día, en dosis individuales o múltiples.

En otro aspecto de la invención, se proporcionan kits que incluyen uno o más compuestos de la invención. Los kits representativos incluyen un compuesto inhibidor de PI3K de la invención (por ejemplo, un compuesto de las fórmulas (I) a (III)) y un inserto del paquete u otra etiqueta, incluyendo instrucciones para el tratamiento de una enfermedad proliferativa celular mediante la administración de una cantidad inhibidora de PI3K del compuesto.

El término "kit", como se utiliza en la presente, comprende un recipiente para contener las composiciones farmacéuticas, y también puede incluir recipientes divididos, tales como una botella dividida o un paquete de lámina dividido. El recipiente puede ser de cualquier configuración o forma convencional, como se conoce en la materia,

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el cual se hace de un material farmacéuticamente aceptable, por ejemplo una caja de papel o de cartón, una botella o frasco de vidrio o plástico, una bolsa resellable (por ejemplo, para contener un "repuesto" de tabletas para colocarse en un recipiente diferente), o un paquete de burbuja con dosis individuales para presionarlas fuera del paquete de acuerdo con un programa terapéutico. El recipiente empleado puede depender de la forma de dosificación exacta involucrada, por ejemplo, en general no se utilizaría una caja de cartón convencional para contener una suspensión líquida. Es factible que se pueda utilizar más de un recipiente en un solo paquete para comerciar una sola forma de dosificación. Por ejemplo, las tabletas pueden estar contenidas en una botella, la cual a su vez esté contenida dentro de una caja.

Un ejemplo de este kit es el denominado como paquete de burbuja. Los paquetes de burbuja son bien conocidos en la industria de empaque, y se están utilizando ampliamente para el empaque de las formas de dosificación unitaria farmacéutica (tabletas, cápsulas, y similares). Los paquetes de burbuja consisten en general en una hoja de material relativamente rígido cubierta con una lámina de un material de plástico preferiblemente transparente. Durante el proceso de empaque, se forman recesos en la lámina de plástico. Los recesos tienen el tamaño y la forma de las tabletas o cápsulas individuales que se vayan a empacar, o pueden tener el tamaño y la forma para acomodar múltiples tabletas y/o cápsulas que se vayan a empacar. En seguida, las tabletas o cápsulas se colocan en los

recesos de acuerdo con lo anterior, y la hoja de material relativamente rígido se sella contra la lámina de plástico en la cara de la lámina que quede opuesta a la dirección en la cual se formaron los recesos. Como resultado, las tabletas o cápsulas se sellan individualmente o se sellan colectivamente, según se desee, en los recesos entre la lámina de plástico y la hoja. De una manera preferible, la resistencia de la hoja es tal que se pueden remover las tabletas o cápsulas del paquete de burbuja aplicando presión manualmente sobre los recesos, mediante lo cual se forma una abertura en la hoja en el lugar del receso. Entonces se puede remover la tableta o cápsula por esta abertura.

Puede ser deseable proporcionar un auxiliar de memoria escrito, en donde el auxiliar de memoria escrito sea del tipo que contenga información y/o instrucciones para el médico, farmacéutico, u otro proveedor del cuidado de la salud, o sujeto, por ejemplo, en la forma de números en seguida de las tabletas o cápsulas, en donde los números correspondan a los días del régimen en que se deben ingerir las tabletas o cápsulas así especificadas, o una tarjeta que contenga el mismo tipo de información. Otro ejemplo de este auxiliar de memoria es un calendario impreso en la tarjeta, por ejemplo como sigue: "Primera Semana, Lunes, Martes", "Segunda Semana, Lunes, Martes...". Otras variaciones de los auxiliares de memoria serán fácilmente evidentes. Una "dosis diaria" puede ser una sola tableta o cápsula, o varias tabletas o cápsulas, para tomarse en un día dado. Cuando el kit contiene composiciones separadas, una dosis diaria de

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una o más composiciones del kit puede consistir en una tableta o cápsula, mientras que una dosis diaria de otra o más composiciones del kit puede consistir en varias tabletas o cápsulas

Otra modalidad específica de un kit es un dosificador diseñado para dosificar las dosis diarias, una a la vez, en el orden de su uso pretendido. De una manera preferible, el dosificador está equipado con un auxiliar de memoria, para facilitar adicionalmente el cumplimiento con el régimen. Un ejemplo de este auxiliar de memoria es un contador mecánico, el cual indica el número de dosis diarias que se haya dosificado. Otro ejemplo de este auxiliar de memoria es una memoria de micro-chip energetizado por batería acoplada con una pantalla de cristal líquido, o una señal de recordatorio audible que, por ejemplo, lee la fecha en que se tomó la última dosis diaria, y/o que recuerde a la persona cuándo debe tomar la siguiente dosis.

Los kits de la presente invención también pueden comprender, en adición a un inhibidor de PI3K, uno o más compuestos farmacéuticamente activos adicionales. De preferencia, el compuesto adicional es otro inhibidor de PI3K u otro compuesto útil para tratar cáncer, angiogénesis, o crecimiento tumoral. Los compuestos adicionales se pueden administrar en la misma forma de dosificación que el inhibidor de PI3K o en diferentes formas de dosificación. De la misma manera, los compuestos adicionales se pueden administrar al mismo tiempo que el inhibidor de PI3K o en diferentes tiempos.

La presente invención se entenderá más fácilmente haciendo referencia a los siguientes ejemplos, los cuales se proporcionan a

manera de ilustración y no pretenden ser limitantes de la presente invención.

EJEMPLOS

Haciendo referencia a los siguientes ejemplos, los compuestos de la presente invención se sintetizaron empleando los métodos descritos en la presente, u otros métodos, los cuales 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 Alltima C-18 de fase inversa, 4.6 x 50 milímetros, flujo: 2.5 mililitros/ minuto, de Alltech (Deerfield, IL). Se utilizó una elución en gradiente, 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 40 minutos. Todos los solventes contuvieron ácido trifluoro-acético al 0.1 por ciento (TFA). Los compuestos se detectaron mediante absorción de luz ultravioleta (UV) a 220 ó 254 nanómetros. Los solventes de HPLC fueron de Burdick and Jackson (Muskegan, MI), o Fisher Scientific (Pittsburgh, PA). En algunos casos, la pureza se evaluó mediante cromatografía de capa delgada (TLC), utilizando placas de gel de sílice con respaldo de 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 técnicas de

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vapor de yodo conocidas, y otras diversas técnicas de teñido.

El análisis espectrométrico de masas se llevó a cabo en uno de dos instrumentos de LCMS: un Waters System (Alliance HT HPLC y un espectrómetro de masas Micromass ZQ; Columna: Eclipse XDB-C18, 2.1 x 50 milímetros; sistema de solvente: del 5 al 95 por ciento (o del 35 al 95 por ciento, o del 65 al 95 por ciento, o del 95 al 95 por ciento) de acetonitrilo en agua con ácido trifluoro-acético al 0.05 por ciento; velocidad de flujo de 0.8 mililitros/minuto; intervalo de peso molecular de 200 a 1500; Voltaje del Cono de 20 Voltios; temperatura de la columna de 40°C), o un Hewlett Packard System (Serie 1100 HPLC; Columna: Eclipse XDB-C18, 2.1 x 50 milímetros; sistema de solvente: del 1 al 95 por ciento de acetonitrilo en agua con ácido trifluoro-acético al 0.05 por ciento; velocidad de flujo de 0.8 mililitros/minuto; intervalo de peso molecular de 150 a 850; Voltaje del Cono de 50 Voltios; temperatura de la columna de 30°C). Todas las masas se reportaron como aquéllas de los iones progenitores protonados.

El análisis de GCMS se lleva a cabo en un instrumento Hewlett Packard (cromatógrafo de gases 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).

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El análisis de resonancia magnética nuclear (RMN) se llevó a cabo en algunos de los compuestos con un Varian 300 MHz NMR (Palo Alto, CA). La referencia espectral fue TMS o el cambio químico conocido del solvente. Algunas muestras de compuestos se ejecutaron a temperaturas elevadas (por ejemplo, a 75°C) para promover una mayor solubilidad de las muestras.

La pureza de algunos de los compuestos de la invención se evalúa mediante análisis elemental (Desert Analytics, Tucson, AZ).

Los puntos de fusión se determinan 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 de fase inversa C-18, 30 X 50 milímetros, flujo: 75 mililitros/minuto. Los solventes típicos empleados para el sistema Flash 40 Biotage y para la cromatografía en columna por evaporación instantánea fueron dicloro-metano, metanol, acetato de etilo, hexano, acetona, amoníaco acuoso (o hidróxido de amonio), y trietil-amina. Los solventes típicos empleados para la HPLC en fase inversa fueron concentraciones variables de acetonitrilo y agua con ácido trifluoro-acético al 0.1 por ciento.

Se debe entender que los compuestos orgánicos de acuerdo

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con la invención pueden exhibir el fenómeno de tautomerismo. Debido a que las estructuras químicas dentro de esta memoria descriptiva solamente pueden representar una de las posibles formas tautoméricas, se debe entender que la invención abarca cualquier forma tautomérica de la estructura trazada.

Se entiende que la invención no está limitada a las modalidades estipuladas en la presente para ilustración, sino que abarca todas las formas de la misma que entren en el alcance de la divulgación anterior.

Abreviaturas

ACN	Acetonitrilo
BINAP	2,2'-bis(difenil-fosfino)-1,1'-binaftilo
DIEA	di-isopropil-etil-amina
DME	1,2-dimetoxi-etano
DMF	N,N-dimetil-formamida
DPPF	1,1'-bis(difenil-fosfino)ferroceno
EtOAc	acetato de etilo
EtOH	etanol
MCPBA	ácido *meta*-cloroperoxi-benzoico
NBS	N-bromo-succinimida
NMP	N-metil-2-pirrolidona
RT	temperatura ambiente
THF	tetrahidrofurano

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Métodos Generales para Sintetizar los Compuestos Inhibidores de PI3K

Se proporcionan métodos para la preparación de los compuestos de la fórmula I y/o II. Los métodos incluyen: hacer reaccionar una 4-halo-2-morfolino-pirimidina con un grupo piridinilo o pirimidinilo sustituido que contiene un sustituyente de éster borónico reactivo, en la presencia de un catalizador de paladio. En una modalidad, el grupo piridinilo o pirimidinilo sustituido que contiene un sustituyente de éster borónico reactivo tiene un grupo $-NH_2$ colocado en *para* en relación con el éster borónico. En otra modalidad, el grupo piridinilo o pirimidinilo sustituido que contiene un sustituyente de éster borónico reactivo tiene un grupo $-NH_2$ colocado en *para* en relación con el éster borónico y otro sustituyente no de hidrógeno colocado en *orto* en relación con el éster borónico. En ciertas modalidades, el sustituyente no de hidrógeno es $-CF_3$, -CN, $-NH_2$, halógeno, o alquilo de 1 a 3 átomos de carbono sustituido o insustituido.

En otra modalidad, el grupo 4-halo-2-morfolino-pirimidina es un grupo 4-halo-6-heterociclil-2-morfolino-pirimidina. En otra modalidad, el grupo 4-halo-2-morfolino-pirimidina es un grupo 4-halo-6-heterocicliloxi-2-morfolino-pirimidina. En otra modalidad, el grupo 4-halo-2-morfolino-pirimidina es un grupo 4-halo-6-hetero-aril-amino-2-morfolino-pirimidina. En otra modalidad, el grupo 4-halo-2-morfolino-pirimidina es 4-cloro-2,6-dimorfolino-pirimidina.

En otra modalidad, el éster piridinil-borónico es 4-(trifluoro-

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metil)-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-piridin-2-amina. En otra modalidad, el catalizador de paladio es un aducto de $Pd(dppf)Cl_2$ / dicloro-metano.

En otra modalidad, el grupo 4-halo-6-heterociclil-2-morfolino-pirimidina se prepara mediante la reacción de un grupo heterociclilo con un grupo 4,6-dihalo-2-morfolino-pirimidina. En otra modalidad, el grupo 4-cloro-2,6-dimorfolino-pirimidina se prepara mediante la reacción de 4,6-dicloro-2-morfolino-pirimidina con morfolina. En otra modalidad, el grupo 4,6-dicloro-2-morfolino-pirimidina se prepara mediante la reacción de 2-morfolino-pirimidin-4,6-diol con $POCl_3$. En otra modalidad, el 2-morfolino-pirimidin-4,6-diol se prepara mediante la reacción de morfolin-4-carboxamidina con malonato de dietilo en la presencia de una base, tal como etóxido de sodio.

En otra modalidad, el grupo piridinilo o pirimidinilo sustituido que contiene un sustituyente de éster borónico reactivo se prepara mediante la reacción de un grupo piridinilo o pirimidinilo sustituido que contiene un sustituyente de bromo con un éster diborónico, tal como 4,4,5,5-tetrametil-2-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1,3,2-dioxaborolano. En otra modalidad, el grupo piridinilo o pirimidinilo sustituido que contiene un sustituyente de bromo se prepara mediante la reacción del grupo piridinilo o pirimidinilo sustituido con N-bromo-succinimida (NBS).

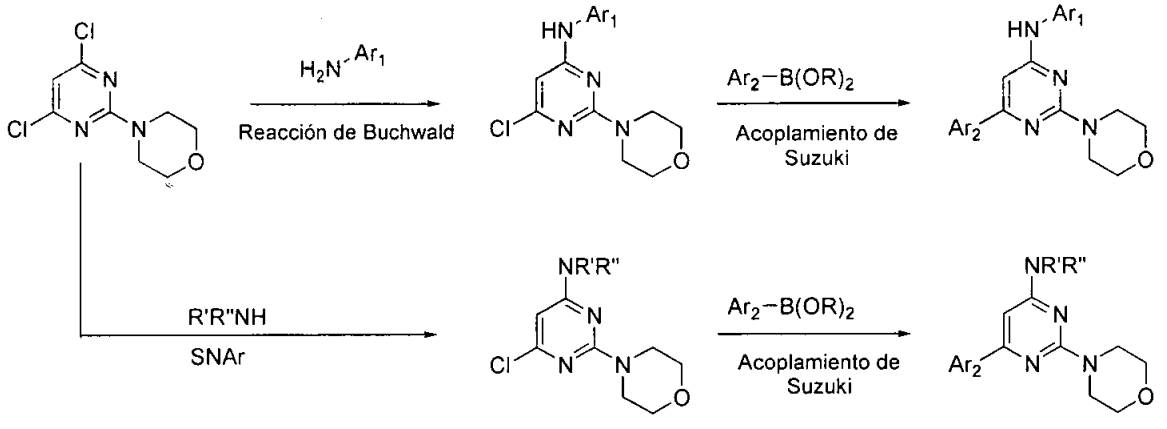
Otra modalidad de la presente invención proporciona un método para la preparación de una 4-cloro-2,6-dimorfolino-pirimidina, el cual comprende hacer reaccionar morfolina con 2,4,6-tricloro-

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pirimidina en un solvente adecuado. En a una modalidad más particular, el solvente es un solvente aprótico polar. Todavía de una manera más particular, el solvente es tetrahidrofurano. En otra modalidad más particular, la 4-cloro-2,6-dimorfolino-pirimidina se agrega durante un período de cuando menos 10 minutos, o cuando menos 20 minutos, o 30 minutos, a una solución que comprende morfolina. De una manera alternativa, la morfolina se agrega a una solución que comprende 4-cloro-2,6-dimorfolino-pirimidina. Todavía más particularmente, la solución se enfría debajo de 20°C, o debajo de 10°C, o debajo de 5°C, o debajo de 0°C. Más particularmente, durante o después de la adición de la 4-cloro-2,6-dimorfolino-pirimidina, la solución se deja calentar a más de 20°C, o más de 25°C, o más de 30°C. En otra modalidad, después de que se combinan la morfolina y la 4-cloro-2,6-dimorfolino-pirimidina, la solución se apaga mediante la adición de una solución acuosa. Más particularmente, cuando menos 10 horas, o cuando menos 20 horas, o cuando menos 30 horas, o cuando menos 40 horas, o cuando menos 50 horas, o aproximadamente 64 horas después de la combinación de la morfolina y la 4-cloro-2,6-dimorfolino-pirimidina, la solución se apaga mediante la adición de una solución acuosa. Más particularmente, después de apagar, la solución se purifica mediante cromatografía en columna. Todavía más particularmente, la columna es de gel de sílice. En otra modalidad, la 4-cloro-2,6-dimorfolino-pirimidina se hace reaccionar con una fracción de 2-amino-piridilo o 2-amino-pirimidilo para formar un compuesto de la fórmula III.

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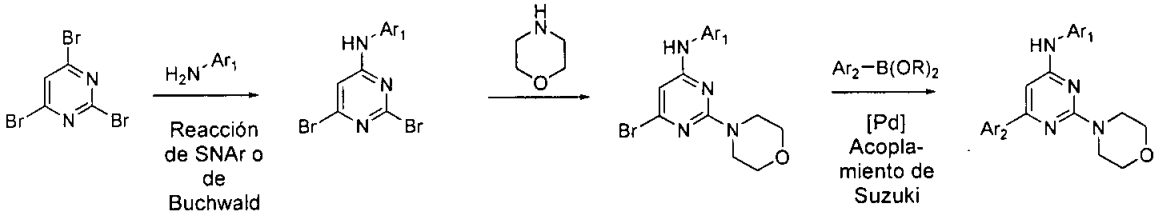
Los compuestos de la invención que contienen un núcleo de pirimidina, tales como aquéllos de la fórmula I, se pueden preparar utilizando un número de métodos familiares para un experto en este campo. En un método, las aminas adecuadamente funcionalizadas se pueden acoplar con 4,6-dicloro-2-morfolino-pirimidina mediante reacciones de sustitución aromática nucleofílica, o mediante una reacción de acoplamiento cruzado de Buchwald-Hartwig (Hartwig y colaboradores, Tetrahedron Letters 36, (1995) 3609), en donde Ar representa fracciones de arilo o hetero-arilo. Subsiguientemente, se puede efectuar el acoplamiento de Suzuki (Suzuki y colaboradores, Chem. Commun. (1979) 866) para formar el producto final se puede efectuar bajo condiciones conocidas, tales como mediante el tratamiento con ésteres borónicos funcionalizados, como en los siguientes:



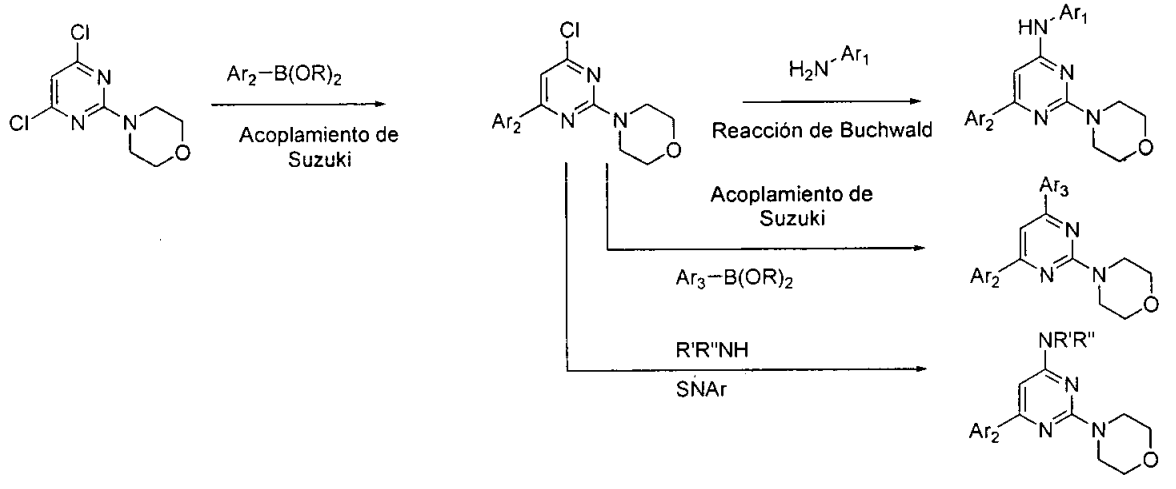
A partir de la 2,4,6-tribromo-pirimidina: La reacción de SNAr (o de Buchwald) de las aril-aminas funcionalizadas con 2,4,6-tribromo-pirimidina dio los productos preferencialmente 4-sustituidos. La

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sustitución con morfolina en la posición 2, seguida por la reacción de Suzuki, proporciona los análogos de pirimidina finales:



De una manera alternativa, se pueden emplear múltiples acoplamientos de Suzuki para proporcionar los grupos arilo o heteroarilo unidos directamente al núcleo de en las posiciones 4 y 6; o se puede llevar a cabo un acoplamiento de Suzuki inicial, seguido por una reacción de sustitución aromática nucleofílica o una reacción de acoplamiento cruzado de Buchwald-Hartwig, como se muestra en el siguiente esquema:

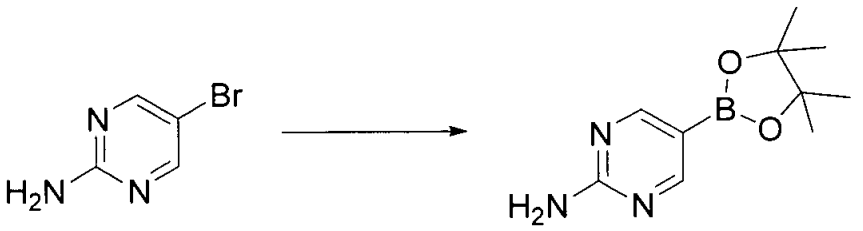


En los siguientes Métodos y Ejemplos, se proporcionan síntesis más particulares de los compuestos de la presente invención, en particular aquéllos de las fórmulas I, II, y III:

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Método 1

Síntesis de 5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-pirimidin-2-il-amina



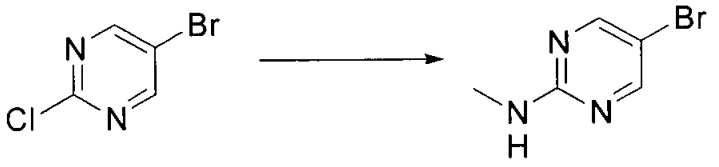
A un matraz de 500 mililitros seco se le agregó 2-amino-5-bromopirimidina (10 gramos, 57.5 milimoles), acetato de potasio (16.9 gramos, 172 milimoles), 4,4,5,5-tetrametil-2-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1,3,2-dioxaborolano (16.1 gramos, 63.0 milimoles) y dioxano (300 mililitros). Se burbujeó argón a través de la solución durante 15 minutos, en este tiempo se agregó dicloro-[1,1'-bis(difenil-fosfino)ferroceno]-paladio(II)/dicloro-metano ($Pd(dppf)Cl_2/CH_2Cl_2$) (2.34 gramos, 2.87 milimoles). La mezcla de reacción se puso a reflujo en un baño de aceite a 115°C durante 4 horas bajo argón. Después de enfriar a temperatura ambiente, se agregó EtOAc (500 mililitros) y la pasta acuosa resultante se sonicó y se filtró. Se utilizó EtOAc (500 mililitros) adicional para lavar el sólido. Los extractos orgánicos combinados se lavaron con H_2O (300 mililitros, 2 veces), $NaCl_{(sat.)}$ (300 mililitros), se secó sobre Na_2SO_4, y se filtró a través de un cojín de 5 centímetros de gel de sílice. Se utilizó EtOAc adicional para inundar el producto. Después el solvente se concentró, el crudo se trató con una mezcla de 1:3 dicloro-metano

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y hexano (40 mililitros), se filtró, y se lavó con hexano proporcionando un sólido amarillo claro (8.5 gramos, 75 por ciento). LCMS (*m/z*): 140 (MH^+ de ácido borónico, derivando a partir del producto de la hidrólisis sobre LC). ^1H RMN ($CDCl_3$): δ 8.58 (s, 2H), 5.74 (s, 2H), 1.32 (s, 12H).

Método 2

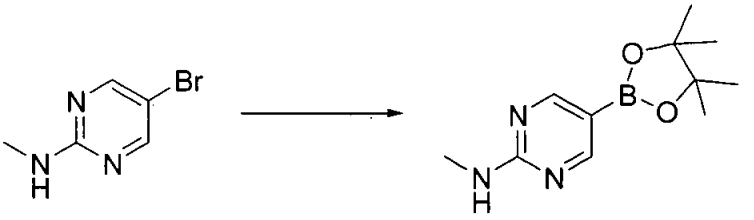
Síntesis de 2-amino-metil-5-bromopirimidina



Se agregó metil-amina (2.0 M en metanol, 40 mililitros, 80 milimoles) a 5-bromo-2-cloro-pirimidina (5.6 gramos, 29.0 milimoles) en un recipiente de reacción sellable. Después de dejar ventilar durante unos minutos, el recipiente se selló, se colocó detrás de un protector de seguridad y se calentó en un baño de aceite 115°C durante 48 horas. Después de enfriarse los volátiles se removieron *al vacío*. El material se disolvió en CH_2Cl_2 (200 mililitros) y se lavó con NaOH 1M (40 mililitros). La capa acuosa se extrajo además con CH_2Cl_2 (50 mililitros, 2 veces). Los orgánicos combinados se secaron sobre $MgSO_4$, se filtraron, y se concentró proporcionando un sólido grisáceo (5.1 gramos, 93 por ciento). LCMS (*m/z*): 188.0/190.0 (MH^+).

Síntesis de metil-[5-(4,4,5,5-tetrametil-(1,3,2-dioxaborolan-2-il))-pirimidin-2-il]-amina

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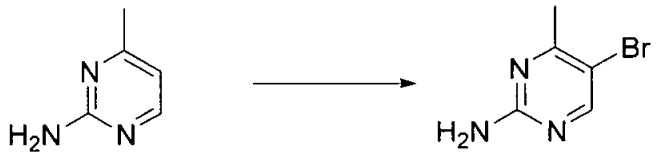


A un matraz de 500 mililitros seco se le agregó 2-metil-amino-5-bromopirimidina (9.5 gramos, 50.5 milimoles), acetato de potasio (15.1 gramos, 154.4 milimoles), 4,4,5,5,-tetrametil-2-(4,4,5,5,-tetrametil-1,3,2-dioxaborolan-2-il)-1,3,2-dioxaborolano (14.1 gramos, 55.5 milimoles) y dioxano (280 mililitros). Se burbujeó argón a través de la solución durante 15 minutos, en este tiempo se agregó aducto de cloruro de 1,1'-bis(difenil-fosfino)-ferroceno-paladio(II)/dicloro-metano (2.05 gramos, 2.51 milimoles. La reacción se puso a reflujo en un baño de aceite 115°C durante 4 horas bajo argón. Después de enfriar a temperatura ambiente, se agregó EtOAc (500 mililitros) y la pasta acuosa resultante se sonicó y se filtró. Se utilizó EtOAc (500 mililitros) adicional para lavar el sólido. Los orgánicos combinados se lavaron con H_2O (300 mililitros, 2 veces), $NaCl_{(sat.)}$, (300 mililitros), se secaron sobre Na_2SO_4, se filtraron, y los solventes se removieron *al vacío*. La purificación mediante cromatografía en SiO_2 (EtOAc 50 por ciento/hexanos) proporcionó un sólido grisáceo (7.66 gramos, 64 por ciento). LCMS (*m/z*): 154 (MH^+ de ácido borónico, derivando a partir de hidrólisis sobre LC del producto *in situ*). ^1H RMN ($CDCl_3$): δ 8.58 (s, 2H), 5.56 (s, 1H), 3.02 (d, 3H), 1.32 (s, 12H).

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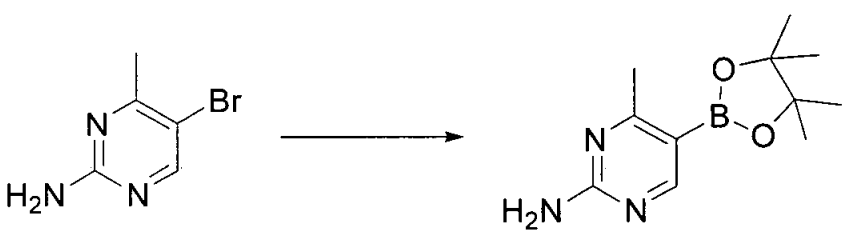
Método 3

Síntesis de 5-bromo-4-metil-pirimidin-2-il-amina



A una solución de 4-metil-pirimidin-2-il-amina (10.9 gramos, 100 milimoles) en cloroformo (400 mililitros) se le agregó N-bromo-succinimida (17.8 gramos, 100 milimoles). La solución se agitó en la oscuridad durante 15 horas, a este tiempo se agregó CH_2Cl_2 (1400 mililitros), se lavó con NaOH 1N (200 mililitros, 3 veces) y $NaCl_{(sat.)}$ (100 mililitros), se secó sobre Na_2SO_4, se filtró, y se concentró, proporcionando 5-bromo-4-metil-pirimidin-2-il-amina (18.8 gramos, 99 por ciento). LCMS (*m/z*): 188.0/190.0 (MH^+). ^1H RMN ($CDCl_3$): δ 8.22 (s, 1H), 5.02 (bs, 2H), 2.44 (s, 3H).

Síntesis de 4-metil-5-(4,4,5,5-tetrametil-(1,3,2-dioxaborolan-2-il))pirimidin-2-il-amina



A un matraz de 1 litro seco se le agregó 5-bromo-4-metil-pirimidin-2-il-amina (18.8 gramos, 100 milimoles), acetato de potasio (29.45 gramos, 300 milimoles), 4,4,5,5-tetrametil-2-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1,3,2-dioxaborolano (26.7 gramos, 105 milimoles) y dioxano (500 mililitros). Se burbujeó argón a través

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de la solución durante 15 minutos, en este tiempo se agregó aducto de cloruro de 1,1'-bis(difenil-fosfino)-ferroceno-paladio(II)/dicloro-metano (4.07 gramos, 5 milimoles). La reacción se puso a reflujo en un baño de aceite 115°C durante 18 horas bajo argón. Después de enfriar a temperatura ambiente, se agregó EtOAc (500 mililitros) y la pasta acuosa resultante se sonicó y se filtró. Se utilizó EtOAc (500 mililitros) adicional para lavar el sólido. Los extractos orgánicos combinados se lavaron con H_2O (300 mililitros, 2 veces), $NaCl_{(sat.)}$ (300 mililitros), se secaron sobre Na_2SO_4, concentraron y se purifica mediante cromatografía en SiO_2 (eluyente de EtOAc) proporcionando 18.1 gramos de un sólido grisáceo. Mediante ^1H RMN el material fue una mezcla 5:1 de éster de boronato y 4-metil-pirimidin-2-il-amina como un subproducto. El material se utilizó como es en las reacciones de Suzuki subsecuentes. LCMS (*m/z*): 154 (MH^+ de ácido borónico, derivando a partir de hidrólisis sobre LC del producto *in situ*). ^1H RMN ($CDCl_3$): δ 8.52 (s, 1H), 5.14 (bs, 2H), 2.56 (d, 3H), 1.32 (s, 12H).

Método 4

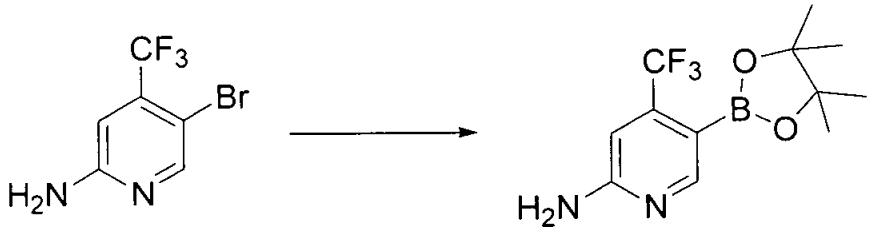
Síntesis de 5-bromo-4-(trifluoro-metil)-2-piridil-amina



A una solución de 2-amino-4-trifluoro-metil-piridina (10.0 gramos, 62.1 milimoles) en cloroformo (200 mililitros) se le agregó N-bromo-succinimida (12.0 gramos, 67.4 milimoles). La solución se

agitó en la oscuridad durante 2 horas, a este tiempo se agregó CH_2Cl_2 (200 mililitros) y NaOH 1N (200 mililitros). Después de mezclar, las capas se separaron y la capa orgánica se lavó con $NaCl_{(sat.)}$ (100 mililitros), se secó sobre Na_2SO_4, se filtró, y se concentró. El material crudo se purificó mediante cromatografía en SiO_2 (EtOAc del 0 al 5 por ciento/CH_2Cl_2) proporcionando 12.0 gramos (80 por ciento) de 5-bromo-4-(trifluoro-metil)-2-piridil-amina. LCMS (*m/z*): 241/243 (MH^+). ^1H RMN ($CDCl_3$): δ 8.28(s, 1H), 6.77(s, 1H), 4.78(bs, 2H).

Síntesis de 5-(4,4,5,5-tetrametil-(1,3,2-dioxaborolan-2-il))-4-(trifluoro-metil)-2-piridil-amina



A un matraz de 500 mililitros seco se le agregó 5-bromo-4-(trifluoro-metil)-2-piridil-amina (11.8 gramos, 49.0 milimoles), acetato de potasio (14.4 gramos, 146.9 milimoles), 4,4,5,5-tetrametil-2-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1,3,2-dioxaborolano (13.6 gramos, 53.9 milimoles) y dioxano (300 mililitros). Se burbujeó argón a través de la solución durante 15 minutos, en este tiempo se agregó aducto de cloruro de 1,1'-bis(difenil-fosfino)-ferroceno-paladio(II)/dicloro-metano (2.0 gramos, 2.45 milimoles). La reacción se puso a reflujo en un baño de aceite a 115°C durante 8 horas bajo argón. Después de enfriar a temperatura ambiente, el dioxano se

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removió *al vacío*. Se agregó EtOAc (500 mililitros), y la pasta acuosa resultante se sonicó y se filtró. Se utilizó EtOAc (500 mililitros) adicional para lavar el sólido. Los extractos orgánicos combinados se concentraron y el material crudo se purificó parcialmente mediante cromatografía en SiO_2 (EtOAc del 30 al 40 por ciento/Hexanos). Después de remover el solvente, se agregaron hexanos (75 mililitros); después de la sonicación, el sólido resultante se filtró y se secó al alto vacío durante 3 días, proporcionando 2.4 gramos de un sólido grisáceo. Mediante ^1H RMN el material fue una mezcla 5:1 de éster de boronato y el subproducto de 2-amino-4-trifluoro-metil-piridina. El material se utilizó como es en las reacciones de Suzuki subsecuentes. LCMS (*m/z*): 207 (MH^+ de ácido borónico, derivando a partir de hidrólisis sobre LC del producto *in situ*). ^1H RMN ($CDCl_3$): δ 8.50 (s, 1H), 6.72 (s, 1H), 4.80 (bs, 2H), 1.34 (s, 12H).

Método 5

Síntesis de 5-bromo-4-(trifluoro-metil)-pirimidin-2-amina

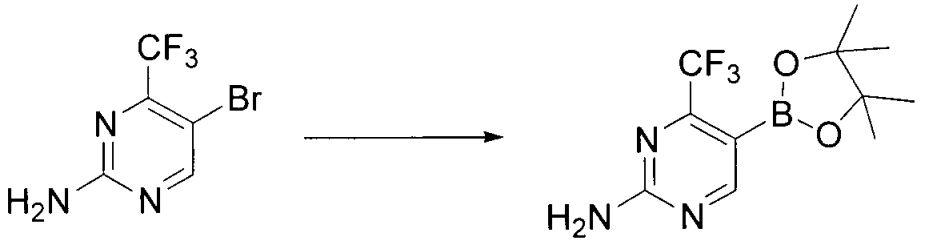


A una solución de 2-amino-4-trifluoro-metil-pirimidina (8.0 gramos, 49.1 milimoles) en cloroformo (300 mililitros) se le agregó N-bromo-succinimida (8.9 gramos, 50 milimoles). La solución se agitó en la oscuridad durante 16 horas, a este tiempo se agregó N-bromo-succinimida (4.0 gramos, 22.5 milimoles) adicional. Después de agitar durante 4 horas adicionales, se agregó CH_2Cl_2 (200 mililitros)

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y NaOH 1N (200 mililitros) a la solución. Después de mezclar, las capas se separaron y la capa orgánica se lavó con $NaCl_{(sat.)}$ (100 mililitros), se secó sobre Na_2SO_4, se filtró, y se concentró, proporcionando 10.9 gramos (82 por ciento) de 5-bromo-4-(trifluoro-metil)-2-pirimidil-amina. LCMS (*m/z*): 242/244 (MH^+). ^1H RMN ($CDCl_3$): δ 8.52 (s, 1H), 5.38 (bs, 2H).

Síntesis de 5-(4,4,5,5-tetrametil-(1,3,2-dioxaborolan-2-il))-4-(trifluoro-metil)-pirimidin-2-il-amina

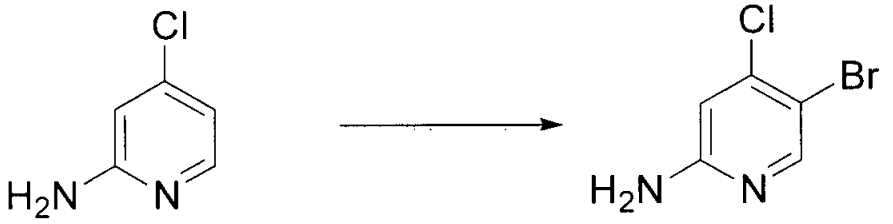


A un matraz de 500 mililitros seco se le agregó 5-bromo-4-(trifluoro-metil)-2-pirimidil-amina (10.1 gramos, 41.7 milimoles), acetato de potasio (12.3 gramos, 125.2 milimoles), 4,4,5,5-tetrametil-2-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1,3,2-dioxaborolano (11.6 gramos, 45.9 milimoles) y dioxano (150 mililitros). Se burbujeó argón a través de la solución durante 15 minutos, en este tiempo se agregó cloruro de 1,1'-bis(difenil-fosfino)-ferroceno-paladio(II) (1.7 gramos, 2.1 milimoles). La reacción se puso a reflujo en un baño de aceite a 115°C durante 6 horas bajo argón. Después de enfriar a temperatura ambiente, el dioxano se removió *al vacío*. Se agregó EtOAc (500 mililitros) y la pasta acuosa resultante se sonicó y se filtró. Se utilizó EtOAc (500 mililitros) adicional para lavar el sólido. Los extractos orgánicos combinados se concentraron y el material

crudo se purificó mediante cromatografía en SiO_2 (EtOAc del 30 al 40 por ciento/hexanos) proporcionando 4.40 gramos de un sólido grisáceo. Mediante ^1H RMN el material fue una mezcla 1:1 de éster de boronato y el subproducto de 2-amino-4-trifluoro-metil-pirimidina. El material se utilizó como es en las reacciones de Suzuki subsecuentes. LCMS (*m/z*): 208 (MH^+ de ácido borónico, derivando a partir de hidrólisis sobre LC del producto *in situ*). ^1H RMN ($CDCl_3$): δ 8.72 (s, 1H), 5.50 (bs, 2H), 1.34 (s, 12H).

Método 6

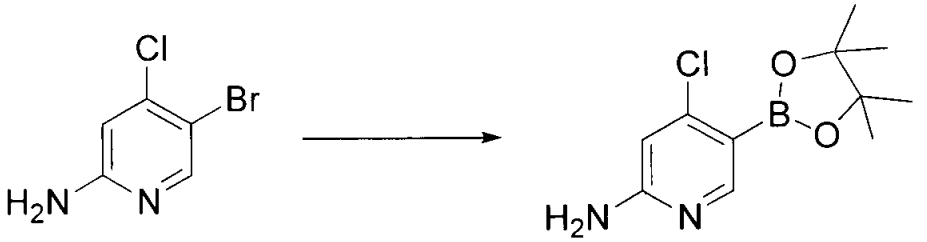
Síntesis de 5-bromo-4-cloro-2-piridil-amina



A una solución de 4-cloro-2-piridil-amina (6.0 gramos, 46.7 milimoles) en cloroformo (180 mililitros) se le agregó N-bromo-succinimida (8.3 gramos, 46.7 milimoles). La solución se agitó en la oscuridad durante 2 horas, a este tiempo se agregó CH_2Cl_2 (800 mililitros) y NaOH 1N (100 mililitros). Después de mezclar, las capas se separaron y la capa orgánica se lavó con $NaCl_{(sat.)}$ (100 mililitros), se secó sobre Na_2SO_4, se filtró, y se concentró. El material crudo se purificó mediante cromatografía en SiO_2 (EtOAc del 25 al 35 por ciento/hexanos) proporcionando 3.63 gramos (38 por ciento) de 5-bromo-4-cloro-2-piridil-amina. LCMS (*m/z*): 206.9/208.9 (MH^+). ^1H RMN ($CDCl_3$): δ 8.18 (s, 1H), 6.62 (s, 1H), 4.52 (bs, 2H).

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Síntesis de 4-cloro-5-(4,4,5,5-tetrametil-(1,3,2-dioxaborolan-2-il))-2-piridil-amina



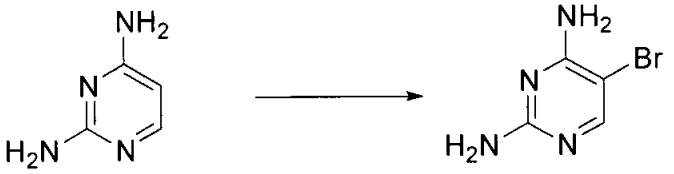
A un matraz de 500 mililitros seco se le agregó 5-bromo-4-cloro 2-piridil-amina (7.3 gramos, 35.8 milimoles), acetato de potasio (10.3 gramos, 105 milimoles), 4,4,5,5-tetrametil-2-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1,3,2-dioxaborolano (10.1 gramos, 39.8 milimoles) y dioxano (150 mililitros). Se burbujeó argón a través de la solución durante 15 minutos, en este tiempo se agregó aducto de cloruro de 1,1'-bis(difenil-fosfino)-ferroceno-paladio(II)/dicloro-metano (0.85 gramos, 1.04 milimoles). La reacción se puso a reflujo en un baño de aceite a 115°C durante 6 horas bajo argón. Después de enfriar a temperatura ambiente, el dioxano se removió *al vacío*. Entonces se agregó EtOAc (500 mililitros) y la pasta acuosa resultante se sonicó y se filtró. Se utilizó EtOAc (500 mililitros) adicional para lavar el sólido. Los extractos orgánicos combinados se concentraron y el material crudo se purificó mediante cromatografía en SiO_2 (EtOAc como eluyente). Después de remover el solvente, se agregó 3:1 hexanos/CH_2Cl_2 (100 mililitros). Después de la sonicación, el sólido resultante se filtró y se concentró al vacío proporcionando 2.8 gramos de un sólido blanco. Mediante ^1H RMN el material fue una mezcla 10:1 de éster de boronato y el subproducto de 2-amino-4-

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cloro-piridina. El material se utilizó como es en las reacciones de Suzuki subsecuentes. LCMS (*m/z*): 173 (MH^+ de ácido borónico, derivando a partir de hidrólisis sobre LC del producto *in situ*). ^1H RMN ($CDCl_3$): δ 8.36 (s, 1H), 6.46 (s, 1H), 4.70 (bs, 2H), 1.38 (s, 12H).

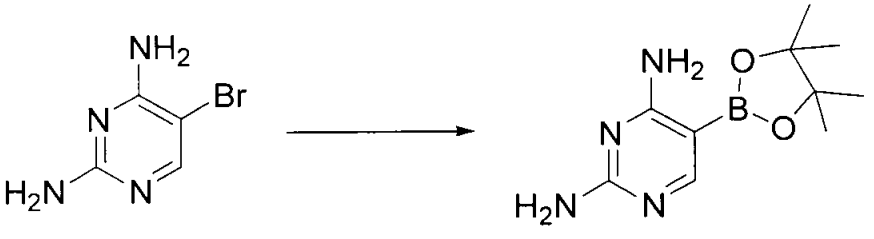
Método 7

Síntesis de 5-bromopirimidin-2,4-diamina



A una solución de 2,4-diamino-pirimidina (1.0 gramos, 9.1 milimoles) en cloroformo (30 mililitros) se le agregó N-bromo-succinimida (1.62 gramos, 9.08 milimoles). La solución se agitó en la oscuridad durante 12 horas, a este tiempo se agregó CH_2Cl_2 (150 mililitros) y NaOH 1N (50 mililitros). El sólido que se formó se filtró, se enjuagó con agua y se concentró *al vacío*, proporcionando 1.4 gramos (74 por ciento) de 5-bromopirimidin-2,4-diamina. LCMS (*m/z*): 189/191 (MH^+). ^1H RMN (DMSO-$_{d6}$): δ 7.78 (s, 1H), 6.58 (bs, 2H), 6.08 (bs, 2H).

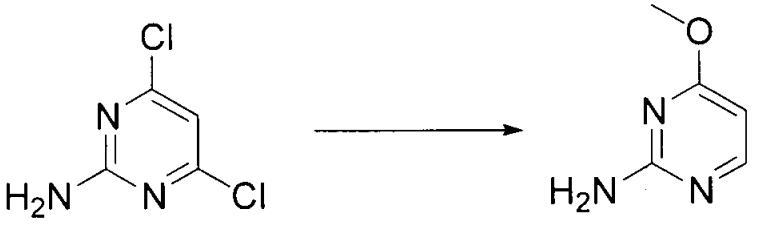
Síntesis de 5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-pirimidin-2,4-diamina



A un matraz de 1 litro seco se le agregó 5-bromopirimidin-2,4-diamina (30.0 gramos, 158.7 milimoles), acetato de potasio (45.8 gramos, 466.7 milimoles), 4,4,5,5-tetrametil-2-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1,3,2-dioxaborolano (51.2 gramos, 202.2 milimoles) y dioxano (500 mililitros). Se burbujeó argón a través de la solución durante 15 minutos, en este tiempo se agregó cloruro de 1,1'-bis(difenil-fosfino)-ferroceno-paladio(II) (2.5 gramos, 3.11 milimoles). La reacción se puso a reflujo en un baño de aceite a 115°C durante 16 horas bajo argón. Después de enfriar a temperatura ambiente, el material sólido inorgánico se filtró, se enjuagó con EtOAc (1 litro). El filtrado orgánico se concentró al vacío y al sólido resultante se le agregó dicloro-metano (1 litros). Después de la sonicación el sólido se filtró. El sólido fue 2,4-diamino-pirimidina desbromada. El filtrado que contiene el éster de boronato deseado se concentró *al vacío*. A este residuo se le agregó dietil-éter (100 mililitros). Después de la sonicación, la solución se filtró, se enjuagó con dietil-éter adicional (50 mililitros) y el sólido obtenido se secó bajo un alto vacío para proporcionar el éster 2,4-diamino-pirimidil-5-boronato deseado (10.13 gramos, 27 por ciento). Mediante ^{1}H RMN el material fue una mezcla 4:1 de éster de 2,4-diamino-pirimidil-5-boronato y el subproducto de 2,4-diamino-pirimidina. El material se utilizó como es en las reacciones de Suzuki subsecuentes. LCMS (*m/z*): 155 (MH^+ de ácido borónico, derivando a partir de hidrólisis sobre LC del producto *in situ*). ^{1}H RMN ($CDCl_3$+CD_3OD): δ 8.16 (s, 1H), 1.34 (s, 12H).

Método 8

Síntesis de 4-metoxi-pirimidin-2-il-amina



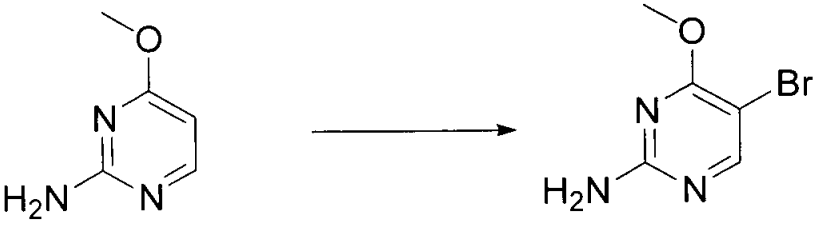
A una solución de 4,6-dicloro-2-amino pirimidina (5.0 gramos, 30.5 milimoles) en metanol (100 mililitros) se le agregó metóxido de sodio al 25 por ciento (6.59 gramos, 30.5 milimoles). La solución se puso a reflujo durante 20 horas, a este tiempo se removió el metanol *al vacío*. El residuo se disolvió en EtOAc (350 mililitros), se lavó con H_2O (100 mililitros) y con $NaCl_{(sat.)}$ (100 mililitros), se secó sobre Na_2SO_4, se filtró, y se concentró proporcionando 4.4 gramos (90 por ciento) de 4-cloro-6-metoxi-pirimidin-2-il-amina.

A una solución de 4-cloro-6-metoxi-pirimidin-2-il-amina (4.4 gramos, 27.7 milimoles) en EtOAc (200 mililitros) y etanol (150 mililitros), se le agregó di-isopropil-etil-amina (9.6 mililitros, 55.3 milimoles) y paladio al 10 por ciento sobre carbón (2.9 gramos, 2.77 milimoles). La solución heterogénea se agitó bajo una atmósfera de globo de H_2 durante 14 horas, a este tiempo la solución se filtró a través de un cojín de Celite y los volátiles se removieron *al vacío*. El residuo se disolvió en EtOAc (200 mililitros), se lavó con $Na_2CO_{3(sat.)}$ (100 mililitros) y con $NaCl_{(sat.)}$ (100 mililitros), se secó sobre Na_2SO_4, se filtró, y se concentró proporcionando 3.1 gramos (90 por ciento) de 4-metoxi-pirimidin-2-il-amina. LCMS (*m/z*): 126 (MH^+). ^1H RMN

48

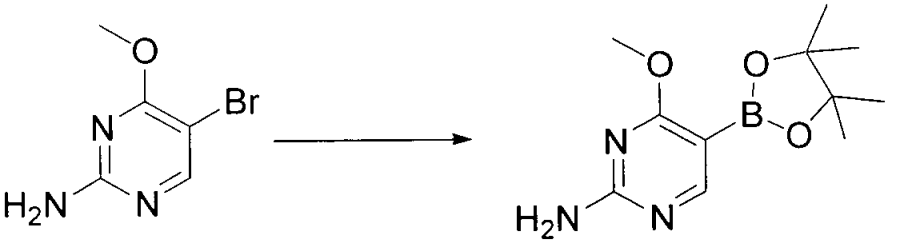
($CDCl_3$): δ 8.00 (d, *J* = 5.7 Hz, 1H), 6.08 (d, *J* = 5.7 Hz, 1H), 4.98 (bs, 2H), 3.84 (s, 3H).

Síntesis de 5-bromo-4-metoxi-pirimidin-2-il-amina



A una solución de 4-metoxi-pirimidin-2-il-amina (1.84 gramos, 14.7 milimoles) en cloroformo (600 mililitros) se le agregó N-bromo-succinimida (2.62 gramos, 14.7 milimoles). Después de agitar en la oscuridad durante 5 horas, a la solución se le agregó CH_2Cl_2 (200 mililitros) y NaOH 1N (100 mililitros). Después de mezclar, las capas se separaron y la capa orgánica se lavó con $NaCl_{(sat.)}$ (100 mililitros), se secó sobre Na_2SO_4, se filtró, y se concentró proporcionando 2.88 gramos (96 por ciento) de 5-bromo-4-metoxi-pirimidin-2-il-amina. LCMS (*m/z*): 204/206 (MH^+). ^1H RMN ($CDCl_3$): δ 8.10 (s, 1H), 4.93 (bs, 2H), 3.96 (s, 3H).

Síntesis de 4-metoxi-5-(4,4,5,5-tetrametil-(1,3,2-dioxaborolan-2-il))-pirimidin-2-il-amina

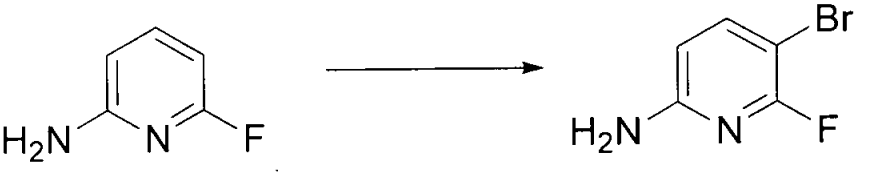


A un matraz de 200 mililitros seco se le agregó 5-bromo-4-metoxi-pirimidin-2-il-amina (2.88 gramos, 14.1 milimoles), acetato de

potasio (4.16 gramos, 42.4 milimoles), 4,4,5,5-tetrametil-2-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1,3,2-dioxaborolano (3.76 gramos, 14.8 milimoles) y dioxano (75 mililitros). Se burbujeó argón a través de la solución durante 15 minutos, en este tiempo se agregó aducto de cloruro de 1,1'-bis(difenil-fosfino)-ferroceno-paladio(II)/dicloro-metano (0.58 gramos, 0.71 milimoles). La reacción se puso a reflujo en un baño de aceite a 115°C durante 21 horas bajo argón. Después de enfriar a temperatura ambiente, el dioxano se removió *al vacío*. Se agregó EtOAc (500 mililitros) y la pasta acuosa resultante se sonicó y se filtró. Se utilizó EtOAc (500 mililitros) adicional para lavar el sólido. Los orgánicos combinados se concentraron y el material crudo se purificó mediante cromatografía en SiO_2 cromatografía (EtOAc as eluyente) proporcionando 2.4 gramos de un sólido grisáceo. Mediante ^1H RMN el material fue una mezcla 1:1 de éster de boronato y 4-metoxi-pirimidin-2-il-amina. El material se utilizó como es en las reacciones de Suzuki subsecuentes. LCMS (*m/z*): 170 (MH^+ de ácido borónico, derivando a partir de hidrólisis sobre LC del producto *in situ*). ^1H RMN ($CDCl_3$): δ 8.42 (s, 1H), 5.22 (bs, 2H), 3.90 (s, 3H), 1.34 (s, 12H).

Método 9

Síntesis de 5-bromo-6-fluoro-2-piridil-amina

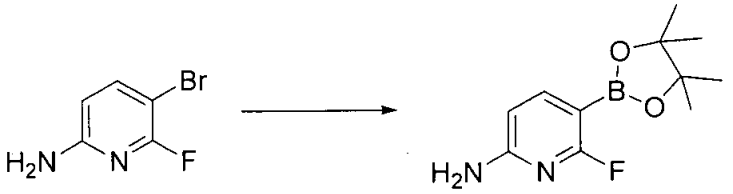


A una solución de 6-fluoro-2-piridil-amina (1.0 gramos, 8.93

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milimoles) en cloroformo (55 mililitros) se le agregó N-bromo-succinimida (1.59 gramos, 8.93 milimoles). La solución se agitó en la oscuridad durante 15 horas, a este tiempo se agregó CH_2Cl_2 (200 mililitros) y NaOH 1N (50 mililitros). Después de mezclar, las capas se separaron y la capa orgánica se lavó con $NaCl_{(sat.)}$ (50 mililitros), se secó sobre Na_2SO_4, se filtró, y se concentró. El material crudo se purificó mediante cromatografía en SiO_2 (EtOAc al 25 por ciento/ hexanos) proporcionando 5-bromo-6-fluoro-2-piridil-amina (386 miligramos, 22 por ciento). LCMS (*m/z*): 190.9/192.9 (MH^+); ^1H RMN ($CDCl_3$): δ 7.59 (t, *J* = 8.7 Hz, 1H), 6.25 (dd, *J* = 8.1, 1.2 Hz, 1H), 4.58 (bs, 1H).

Síntesis de 6-fluoro-5-(4,4,5,5-tetrametil-(1,3,2-dioxaborolan-2-il))-2-piridil-amina

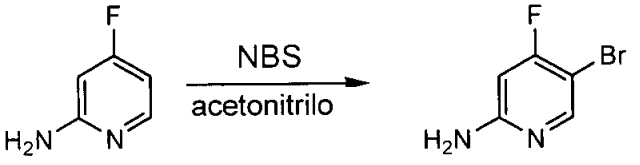


A un matraz de 50 mililitros seco se le agregó 5-bromo-6-fluoro-2-piridil-amina (370 miligramos, 1.93 milimoles), acetato de potasio (569 miligramos, 5.8 milimoles), 4,4,5,5-tetrametil-2-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1,3,2-dioxaborolano (538 miligramos, 2.12 milimoles) y dioxano (15 mililitros). Se burbujeó argón a través de la solución durante 15 minutos, en este tiempo se agregó aducto de cloruro de 1,1'-bis(difenil-fosfino)-ferroceno-paladio(II)/dicloro-metano (79 miligramos, 0.09 milimoles). La reacción se puso a reflujo en un baño de aceite a 115°C durante

4 horas bajo argón. Después de la remoción de los volátiles *al vacío*, se agregó EtOAc (150 mililitros) y la solución se lavó con H_2O (40 mililitros, 3 veces), con $NaCl_{(sat.)}$ (300 mililitros), se secó sobre Na_2SO_4, se filtró, y se concentró. La purificación mediante cromatografía en SiO_2 (EtOAc 30 por ciento/hexanos) proporcionó el éster de boronato (161 miligramos, 35 por ciento). LCMS (*m/z*): 157 (MH^+ de ácido borónico, derivando a partir de hidrólisis sobre LC del producto *in situ*) ^1H RMN ($CDCl_3$): δ 7.86 (t, *J* = 8.4 Hz, 1H), 6.29 (dd, *J* = 8.1, 2.7 Hz, 1H), 4.70 (bs, 1H), 1.32 (s, 12H).

Método 10

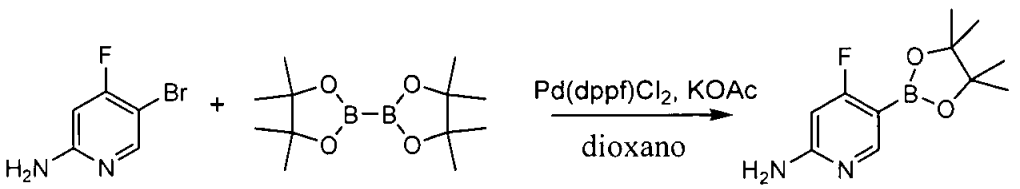
Síntesis de 5-bromo-4-fluoro-piridin-2-amina



Se agregó *N*-Bromo-succinimida (126 miligramos, 0.71 milimoles) a una solución de sal del ácido trifluoro-acético de 4-fluoro-piridin-2-amina (162 miligramos, 0.72 milimoles) en acetonitrilo (4 mililitros) en un matraz envuelto en una lámina de aluminio en una campana oscurecida. La solución de la reacción se agitó a temperatura ambiente en oscuridad durante 2 horas. Después de la evaporación del solvente, el producto crudo se purificó sobre una columna de gel de sílice eluyendo con EtOAc para dar 5-bromo-4-fluoro-piridin-2-amina as un sólido color marfil (92 miligramos, 67 por ciento). LC/MS (*m/z*): 190.9/192.9 (MH^+), R_t 1.02 minutos.

Síntesis de 4-fluoro-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-

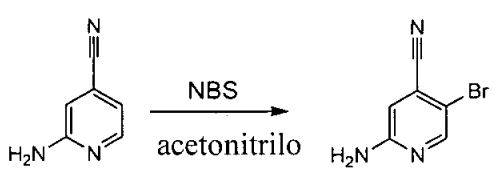
il)-piridin-2-amina



En un recipiente de presión Pyrex sellable, una mezcla de 5-bromo-4-fluoro-piridin-2-amina (25 miligramos, 0.13 milimoles), 4,4,5,5-tetrametil-2-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1,3,2-dioxaborolano (40 miligramos, 0.16 milimoles), acetato de potasio (51 miligramos, 0.52 milimoles) y aducto de dicloro[1,1'-bis(difenil-fosfino)-ferroceno]-paladio(II)/dicloro-metano (16 miligramos, 0.019 milimoles) se suspendió en dioxano (1.7 mililitros) bajo argón. El recipiente de presión se selló y la mezcla de reacción se agitó a 110°C durante 2 horas. Después de que la reacción estuvo completa, como fue juzgado mediante LCMS, la mezcla de reacción se enfrió a temperatura ambiente y la 4-fluoro-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-piridin-2-amina se usó en las siguientes reacciones sin mayor purificación, suponiendo un rendimiento cuantitativo (0.13 milimoles). LC/MS (*m/z*): 157.0 (MH^+ del ácido borónico formado mediante hidrólisis sobre LC del producto), R_t 0.34 minutos.

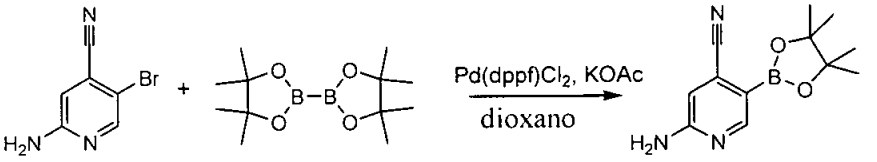
Método 11

Síntesis de 2-amino-5-bromo-isonicotinonitrilo



En un matraz cubierto con lámina de aluminio en una campana oscurecida, se disolvió sal de ácido trifluoro-acético de 2-amino-isonicotinonitrilo (125 miligramos, 0.54 milimoles) en acetonitrilo (3.5 mililitros). Se agregó *N*-bromo-succinimida sólida (89.2 miligramos, 0.501 milimoles), una solución agitada en una porción a temperatura ambiente. La solución de la reacción se agitó a temperatura ambiente en oscuridad durante 90 minutos. Después de la evaporación del solvente, el material crudo se purificó adicionalmente mediante cromatografía en gel de sílice para dar 2-amino-5-bromo-isonicotinonitrilo (53 miligramos, 49 por ciento). LC/MS (*m/z*): 197.9 (MH^+), R_t 2.92 minutos.

Síntesis del éster 2-amino-5-borónico-isonicotinonitrilo



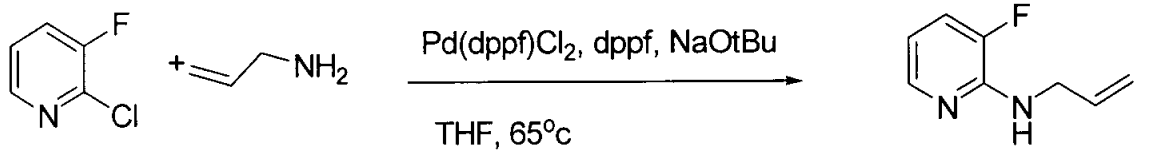
En un recipiente de presión de vidrio, una mezcla de 2-amino-5-bromo-isonicotinonitrilo (25 miligramos, 0.126 milimoles), 4,4,5,5-tetrametil-2-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1,3,2-dioxaborolano (38 miligramos, 0.151 milimoles) y acetato de potasio (49 miligramos, 0.504 milimoles) se suspendieron en dioxano (1.8 mililitros). Después de purgar la mezcla con argón durante 1 a 2 minutos, se agregó aducto de dicloro-[1,1'-bis(difenil-fosfino)-ferroceno]-paladio(II)/dicloro-metano (16 miligramos, 0.019 milimoles) en una porción. El recipiente de reacción se selló y se calentó a 120°C con agitación durante 2 horas. La solución de

reacción cruda se enfrió a temperatura ambiente y se utilizó sin mayor purificación suponiendo un rendimiento cuantitativo del éster borónico (0.126 milimoles). LC/MS (*m/z*): 164.0 (MH^+ del ácido borónico formado mediante hidrólisis sobre LC del producto), R_t 0.37 minutos.

Método 12

Síntesis de 3-fluoro-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-piridin-2-amina

Síntesis de *N*-alil-3-fluoro-piridin-2-amina

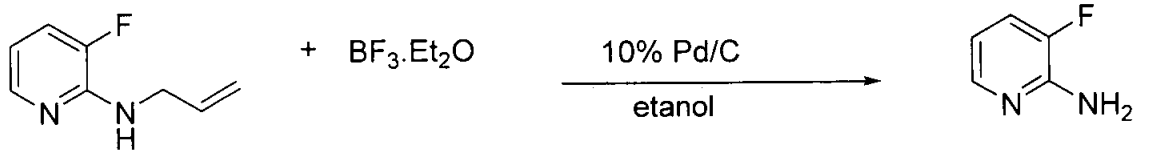


A un complejo amarillo brillante preformado de $Pd(dppf)Cl_2$ CH_2Cl_2 (41 miligramos, 0.05 milimoles), dppf (83 miligramos, 0.15 milimoles) y NaO*t*-Bu (1.4 gramos, 15 milimoles) en tetrahidrofurano (20 mililitros) se agregó 2-cloro-3-fluoro-piridina (1.32 gramos, 10 milimoles) y alil-amina (1.2 mililitros, 15 milimoles). La mezcla se salpicó con nitrógeno y el recipiente de presión se tapó y se selló. La reacción se calentó de 65 a 70°C durante 16 horas. La reacción fría se filtró a través de un tapón de Celite y el cojín se lavó con EtOAc (30 mililitros). El solvente se removió bajo presión reducida para dar a un aceite espeso color café. El producto crudo se purificó mediante cromatografía en gel de sílice eluyendo con metanol 5 por ciento en EtOAc. Las fracciones que contiene el producto se diluyeron con EtOAc (100 mililitros) y se extrajeron con HCl 1M (50 mililitros, 2

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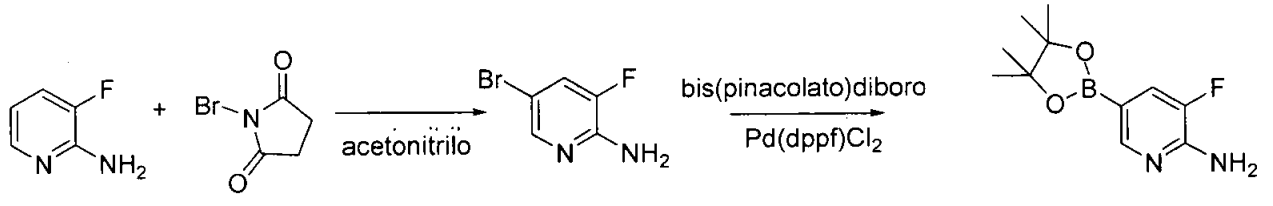
veces). El producto ácido acuoso se liofilizó hasta un sólido color café claro dando *N*-alil-3-fluoro-piridin-2-amina (1.6 gramos, 85 por ciento). LC/MS (*m/z*): 153.1 (MH^+), R_t 0.5 minutos.

Síntesis de 3-fluoro-piridin-2-amina



Se agregó en una porción Pd/C 10 por ciento (1.23 g) a una solución de *N*-alil-3-fluoro-piridin-2-amina (1.62 gramos, 7.18 milimoles) y $BF_3 \cdot Et_2O$ (900 microlitros, 7.18 milimoles) en EtOH (20 mililitros) a temperatura ambiente bajo nitrógeno. Después de agitar a 80°C durante 2 días, la mezcla de reacción se filtró a través de un tapón de Celite y el cojín se lavó con EtOH (20 mililitros). Se agregó HCl 6N al filtrado amarillo claro hasta que la solución se acidificó. La sal de HCl de 3-fluoro-piridin-2-amina es mucho menos volátil que la base libre. El filtrado se concentró bajo presión reducida. La sal residual se secó al vacío para dar la 3-fluoro-piridin-2-amina como un sólido vidriado amarillo claro (1.66 gramos, rendimiento cuantitativo). LC/MS (*m/z*): 113.0 (MH^+), R_t 0.41 minutos.

Síntesis de 5-bromo-3-fluoro-piridin-2-amina y 3-fluoro-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-piridin-2-amina



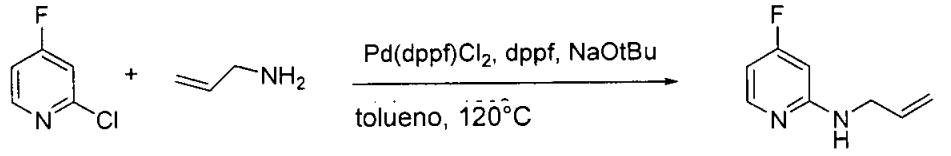
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Se agregó NBS sólido (750 miligramos, 4.2 milimoles) a una solución de sal de HCl de 3-fluoro-piridin-2-amina (1.66 gramos, 7.18 milimoles) en ACN (30 mililitros) a temperatura ambiente con agitación. La reacción se protegió a partir de luz y se agitó bajo nitrógeno. Después de 1 hora, se agregó una cantidad adicional de NBS (250 miligramos, 1.4 milimoles) a la reacción. Después de 1 hora, el solvente se removió bajo presión reducida y el residuo se purificó mediante la cromatografía por evaporación instantánea en gel de sílice eluyendo con EtOAc 70 por ciento/hexano seguida por 100 por ciento de EtOAc para proporcionar 5-bromo-3-fluoro-piridin-2-amina como un sólido café amarillento (1.26 gramos, 92 por ciento de rendimiento). LC/MS (*m*/z): 191.0/193.0 (MH^+), R_t 1.18 minutos.

El bromuro se convirtió en el éster de pinacol-borano bajo las condiciones descritas en el Método 1. LC/MS (*m*/z): 157.0 (MH^+), R_t 0.36 minutos.

Síntesis de 4-fluoro-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-piridin-2-amina

Síntesis de *N*-alil-4-fluoro-piridin-2-amina

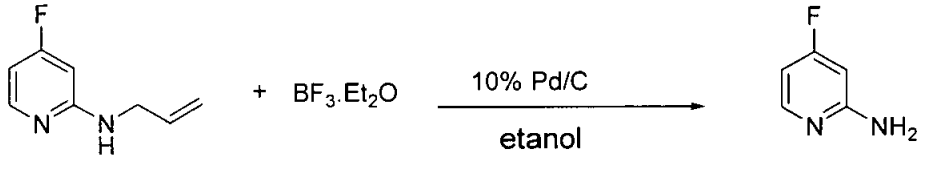


A un complejo color café rojizo preformado de $Pd(dppf)Cl_2$ (817 miligramos, 1.0 milimoles), dppf (1.66 gramos, 3.0 milimoles) y NaO*t*Bu (2.9 gramos, 30 milimoles) en tolueno (30 mililitros) se le agregó 2-cloro-4-fluoro-piridina (2.16 gramos, 20 milimoles) y alil-

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amina (1.2 mililitros, 15 milimoles). La mezcla se salpicó con nitrógeno y el recipiente de presión se tapó y se selló. La reacción se calentó de 120 a 125°C durante 18 horas. La reacción color café oscuro fría se filtró a través de un tapón de Celite y el cojín se lavó con EtOAc (60 mililitros). El solvente se removió gentilmente bajo presión reducida para dar un aceite espeso color café, el cual se puede sublimar al vacío. La mezcla cruda se acidificó con HCl 6N (10 mililitros) y se liofilizó a sequedad para dar un polvo color café como la sal de HCl. El producto crudo se dividió entre EtOAc (100 mililitros) y $NaHCO_3$ saturado (80 mililitros). Las capas se separaron y la capa acuosa se extrajo otra vez con EtOAc (100 mililitros). Las capas orgánicas combinadas se lavaron con salmuera (100 mililitros), se secaron sobre sulfato de sodio, se filtraron, y se concentraron bajo presión reducida para dar un sólido de *N*-alil-4-fluoro-piridin-2-amina color café (690 miligramos, 25 por ciento). LC/MS (*m/z*): 153.0 (MH^+), R_t 1.13 minutos.

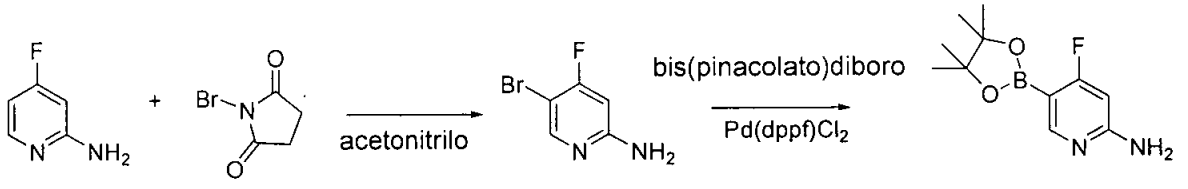
Síntesis de *N*-alil-4-fluoro-piridin-2-amina



Se agregó en una porción, Pd/C al 10 por ciento (552 miligramos) a una solución de *N*-alil-4-fluoro-piridin-2-amina (690 miligramos, 3.07 milimoles) y $BF_3 \cdot Et_2O$ (0.386 mililitros, 3.07 milimoles) en EtOH absoluto (12 mililitros) a temperatura ambiente bajo nitrógeno. Después de agitar a 80°C durante 24 horas, la

mezcla de reacción se filtró a través de un tapón de Celite y el cojín se lavó con metanol (100 mililitros). Se agregó HCl 6N (2 mililitros) al filtrado oscuro hasta que la solución se acidificó. La sal de HCl de 4-fluoro-piridin-2-amina es mucho menos volátil que la base libre. El filtrado se concentró bajo presión reducida y se secó *al vacío*. El producto crudo se purificó mediante HPLC de preparación para dar 4-fluoro-piridin-2-amina como un polvo color café de la sal de ácido trifluoro-acético (162 miligramos, 23 por ciento). LC/MS (*m/z*): 113.0 (MH^+), R_t 0.40 minutos.

Síntesis de 5-bromo-4-fluoro-piridin-2-amina y 4-fluoro-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-piridin-2-amina



Se agregó NBS sólido (78 miligramos, 0.43 milimoles) a una solución sal de HCl de 3-fluoro-piridin-2-amina (162 miligramos, 0.72 milimoles) en ACN (4 mililitros) a temperatura ambiente con agitación. La reacción se protegió a partir de luz y se agitó bajo nitrógeno. Después de 1.5 horas, se agregó una cantidad adicional de NBS (15 miligramos, 0.084 milimoles) a la reacción. Verificando la reacción otra vez después de 1.5 horas, se agregó una cantidad adicional de NBS (15 miligramos, 0.084 milimoles) a la reacción hasta que el material de partida se haya consumido mediante LCMS. Después de 1 hora, el solvente se removió bajo presión reducida y el

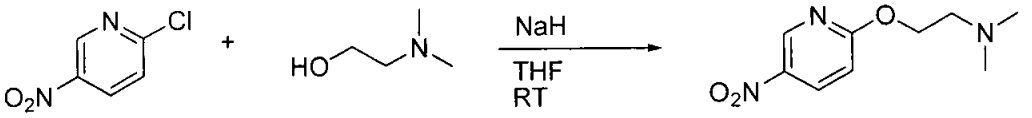
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residuo se purifica mediante cromatografía por evaporación instantánea en sílice eluyendo con acetato de etilo al 50 por ciento/hexano para proporcionar 5-bromo-4-fluoro-piridin-2-amina como un sólido color marfil (92 miligramos, 68 por ciento). LC/MS (*m/z*): 190.9/192.9 (MH^+), R_t 1.02 minutos.

El bromuro se convirtió en pinacol-borano bajo las condiciones descritas en Método 1. LC/MS (*m/z*): 157.0 (MH^+), R_t 0.34 minutos.

Método 14

Síntesis de 2-(5-nitro-piridin-2-iloxi)-N,N-dimetil-etanamina

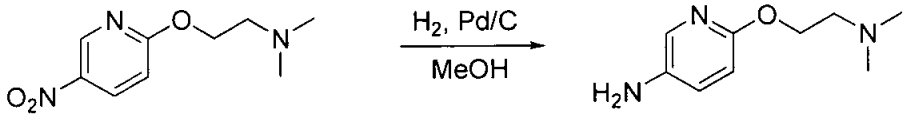


Calentamiento por microondas. A una solución de 2-(dimetil-amino)-etanol (339 miligramos, 3.80 milimoles) en N,N-dimetil-formamida (5 mililitros) se le agregó sodio bis-(trimetil-silil)amida (4.75 mililitros, 1M solución en tetrahidrofurano, 4.75 milimoles). La mezcla se agitó a temperatura ambiente durante 15 minutos. Entonces se agregó 2-cloro-5-nitro-piridina (500 miligramos, 3.16 milimoles). El recipiente se tapó y se sometió a irradiación de microondas (150°C durante 10 minutos). La mezcla se diluyó con agua (250 mililitros) y EtOAc (250 mililitros). Las dos capas se separaron, y la capa acuosa se extrajo dos veces más con EtOAc. Los extractos orgánicos se combinaron, se lavaron con agua y salmuera, se secaron sobre sulfato de sodio y se evaporaron, para dar el material crudo como un aceite color café. La purificación mediante cromatografía en columna en gel de sílice utilizando 5 por

ciento metanol/cloruro de metileno proporcionó 2-(5-nitro-piridin-2-iloxi)-N,N-dimetil-etanamina como un sólido amarillo claro (295 miligramos, 44 por ciento).

Hidruro de sodio y calentamiento en baño de aceite. A una mezcla de hidruro de sodio (189 miligramos, 4.73 milimoles) en tetrahidrofurano anhidro (2 mililitros) a 0°C se le agregó por goteo una solución de 2-cloro-5-nitro-piridina (500 miligramos, 3.16 milimoles) y 2-(dimetil-amino)-etanol (353 miligramos, 3.96 milimoles) en tetrahidrofurano anhidro (4 mililitros). La reacción se calentó a temperatura ambiente y se agitó durante 16 horas. El tetrahidrofurano se evaporó, y se agregaron agua (100 mililitros) y EtOAc (200 mililitros). La capa acuosa se extrajo con EtOAc (200 mililitros), y las capas orgánicas combinadas, se lavaron con salmuera, se secaron sobre sulfato de sodio y se concentraron para dar un aceite color café. La purificación por cromatografía en columna en gel de sílice utilizando metanol al 5 por ciento/cloruro de metileno proporcionó 2-(5-nitro-piridin-2-iloxi)-N,N-dimetil-etanamina como un sólido amarillo claro (233 = miligramos, 35 por ciento). LC/MS (*m*/z): 212.2 (MH^+), R_t 1.28 minutos.

Síntesis de 6-(2-(dimetil-amino)-etoxi)piridin-3-amina



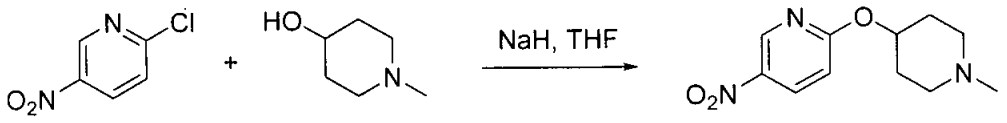
Se disolvió 2-(5-Nitro-piridin-2-iloxi)-N,N-dimetil-etanamina (295 miligramos, 1.40 milimoles) en 5 mililitros de metanol y se colocó bajo una atmósfera de nitrógeno. Se agregó una cantidad

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catalítica de de paladio al 10 por ciento sobre carbón y se conectó un globo de hidrógeno al matraz de reacción. El matraz se inundó cinco veces con hidrógeno y se agitó a temperatura ambiente bajo una atmósfera de hidrógeno durante 16 horas. El sólido se filtró y se lavó con metanol. El filtrado se evaporó bajo presión reducida proporcionando 6-[2-(dimetil-amino)-etoxi]-piridin-3-amina como un aceite color café (250 miligramos, 99 por ciento). LC/MS (*m*/z): 182.1 (MH^+), R_t 0.36 minutos.

Método 15

Síntesis de 2-(1-metil-piperidin-4-iloxi)-5-nitro-piridina

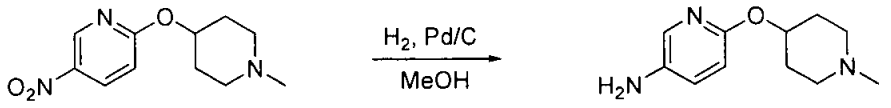


A una mezcla de hidruro de sodio (189 miligramos, 4.73 milimoles) en tetrahidrofurano anhidro (2 mililitros) a 0°C, se le agregó por goteo una solución de 2-cloro-5-nitro-piridina (500 miligramos, 3.16 milimoles) y 1-metil-piperidin-4-ol (455 miligramos, 3.96 milimoles) en tetrahidrofurano anhidro (4 mililitros). La reacción se calentó reflujo durante 16 horas. El tetrahidrofurano se evaporó y se agregaron agua (100 mililitros) y EtOAc (200 mililitros). La capa acuosa se extrajo con EtOAc (200 mililitros). Las capas orgánicas se combinaron, se lavaron con salmuera, se secaron sobre sulfato de sodio y se concentraron para dar un aceite color café. La purificación mediante cromatografía en columna de gel de sílice utilizando metanol al 3 por ciento/cloruro de metileno proporcionó 2-(1-metil-piperidin-4-iloxi)-5-nitro-piridina como un sólido amarillo, (367

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miligramos, 49 por ciento). LC/MS (*m*/z): 238.0 (MH^+), R_t 1.59 minutos.

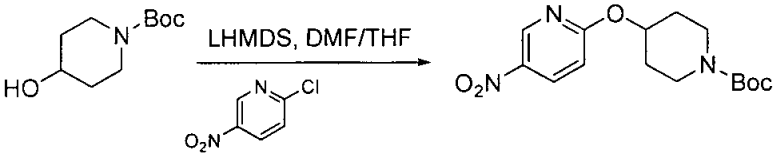
Síntesis de 6-(1-metil-piperidin-4-iloxi)piridin-3-amina



2-(1-Metil-piperidin-4-iloxi)-5-nitro-piridina (100 miligramos, 0.42 milimoles) se disolvió en 5 mililitros de metanol y se colocó bajo una atmósfera de nitrógeno. Se agregó una cantidad catalítica de de paladio al 10 por ciento sobre carbón y se conectó un globo de hidrógeno al matraz de reacción. El matraz se inundó cinco veces con hidrógeno y se agitó a temperatura ambiente bajo una atmósfera de hidrógeno. El sólido se filtró y se lavó con metanol. El filtrado se evaporó bajo presión reducida para proporcionar 6-(1-metil-piperidin-4-iloxi)piridin-3-amina como un sólido color café (85 miligramos, 98 por ciento). LC/MS (*m*/z): 208.2 (MH^+), R_t 0.34 minutos.

Método 16

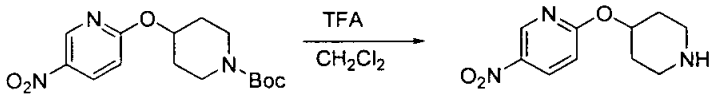
Síntesis de 4-(5-nitro-piridin-2-iloxi)-piperidin-1-carboxilato de terbutilo



A una solución de 4-hidroxipiperidin-1-carboxilato de terbutilo (1 equivalente) en N,N-dimetil-formamida se le agregó bis-trimetil-sililamida de potasio (1.5 equivalentes, 1M solución en tetrahidro-furano). La solución se agitó a temperatura ambiente durante

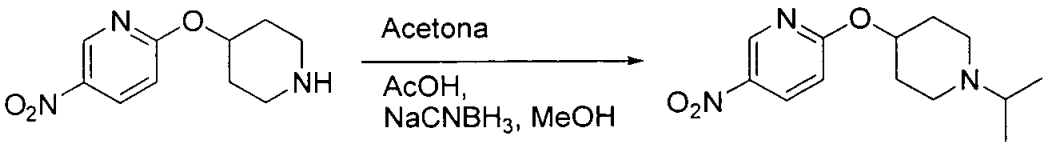
10 minutos, y se agregó 2-cloro-5-nitro-piridina (1.2 equivalentes). La mezcla de reacción se sometió a irradiación de microondas durante 600 segundos a 145°C. Se agregaron EtOAc y agua a la reacción y las capas se separaron. La capa orgánica se lavó con agua, salmuera, se secó sobre sulfato de sodio y se evaporó, para dar el material crudo color café. La purificación mediante cromatografía en columna de gel de sílice utilizando EtOAc al 10 por ciento/hexano proporcionó el producto como un sólido amarillo claro. LC/MS (*m/z*): 324.3 (MH^+), R_t 3.33 minutos

Síntesis de 5-nitro-2-(piperidin-4-iloxi)piridina



Se agregó ácido trifluoro-acético (5 equivalentes) a una solución de 4-(5-nitro-piridin-2-iloxi)-piperidin-1-carboxilato de terbutilo (1 equivalente) en dicloro-metano, agitando a temperatura ambiente durante 1 hora. Entonces el solvente se evaporó, el residuo se llevó a un pH = 10 con una solución de Na_2CO_3 saturada acuosa y se extrajo con EtOAc. La capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio y se evaporó para proporcionar el producto como un sólido cristalino amarillo claro. LC/MS (*m/z*): 224.3 (MH^+), R_t 1.64 minutos

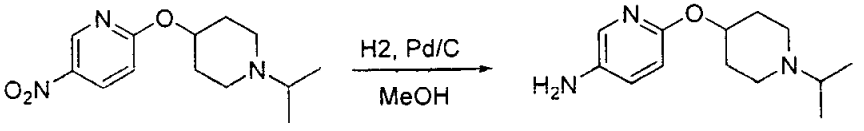
Síntesis de 2-(1-isopropil-piperidin-4-iloxi)-5-nitro-piridina



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A una solución de ácido acético al 10 por ciento en metanol se le agregó 5-nitro-2-(piperidin-4-iloxi)piridina (1 equivalente) y acetona anhidra (5 equivalentes). La solución se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se enfrió a 0°C sobre un baño de hielo y se agregó ciano-borohidruro de sodio (1.5 equivalentes). La mezcla de reacción entonces se calentó a temperatura ambiente y se agitó durante 5 horas. El solvente se evaporó, el residuo se llevó a un pH = 10 con carbonato de sodio y se extrajo con EtOAc. La capa orgánica se lavó con agua, salmuera, se secó sobre sulfato de sodio, y se evaporó, para dar el material crudo. la purificación mediante cromatografía en columna de gel de sílice utilizando metanol al 2 por ciento/dicloro-metano proporcionó el producto como un sólido amarillo. LC/MS (*m*/z): 266.3 (MH^+), R_t 1.85 minutos.

Síntesis de 6-(1-isopropil-piperidin-4-iloxi)piridin-3-amina



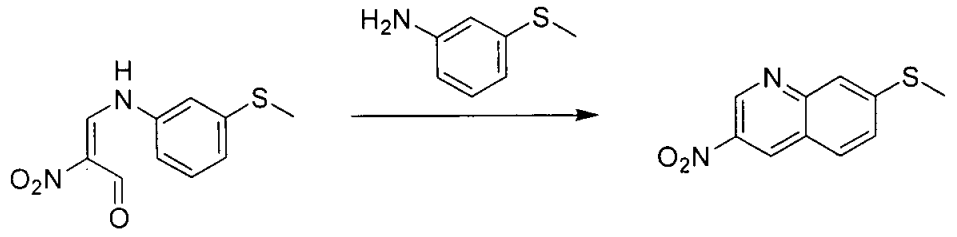
Se disolvió 2-(1-isopropil-piperidin-4-iloxi)-5-nitro-piridina (1 equivalente) en metanol y colocó bajo una atmósfera de nitrógeno. Una cantidad catalítica de de paladio al 10 por ciento sobre carbón se le agregó y se conectó un globo de hidrógeno al matraz de reacción. El matraz se inundó cinco veces con hidrógeno y se agitó a temperatura ambiente durante 4 horas bajo una atmósfera de hidrógeno. El sólido se filtró y se lavó con metanol. El filtrado se evaporó bajo presión reducida proporcionando el producto como un

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aceite color café. LC/MS (*m/z*): 236.3 (MH^+), R_t 0.38 minutos.

Método 17

Síntesis de 7-tiometil-3-nitro-quinolina



A una mezcla a reflujo de 3-[(3-metiltiofenil)-amino]-2-nitroprop-2-enal (2.3 gramos, 9.6 milimoles) y la sal de HCl de 3-metiltiofenil-amina (2.7 gramos, 19.3 milimoles) en ácido acético (25 mililitros) se le agregó tiofenol (0.2 gramos, 1.9 milimoles). Después de estar a reflujo durante 18 horas, la mezcla se enfrió a temperatura ambiente y el ácido acético se removió bajo presión reducida. Al sólido coloreado oscuro remanente se agregó EtOAc (50 mililitros) con agitación. La filtración dio un sólido amarillo/verde y un filtrado oscuro. El producto cristalizado a partir de solución de EtOAc después de reposar. La filtración y enjuague con EtOAc frío dio 330 miligramos del producto cristalino. El sólido amarillo/verde se lavó con 250 mililitros, 3 veces, con porciones de dicloro-metano. El dicloro-metano se lavó, y se concentró para dar 150 miligramos adicionales del producto (23 por ciento). LC/MS (*m/z*): 221.1 (MH^+), R_t 2.54 minutos.

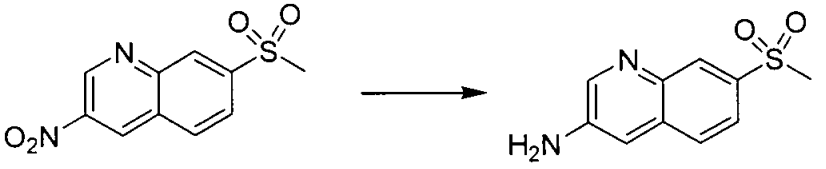
Síntesis de 7-(metil-sulfonil)-3-nitroquinolina



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A una solución helada en un baño de hielo de 7-tiometil-3-nitroquinolina (141 miligramos, 0.6 milimoles) en dicloro-metano (6 mililitros) se le agregó MCPBA (221 miligramos, 1.3 milimoles) en dicloro-metano (3 mililitros). Después de calentar a temperatura ambiente, el precipitado blanco formado se filtró y se enjuagó con 10 mililitros adicionales de dicloro-metano para proporcionar el producto crudo (85 miligramos, 53 por ciento). LC/MS (*m/z*): 252.9 (MH^+), R_t 1.82 minutos.

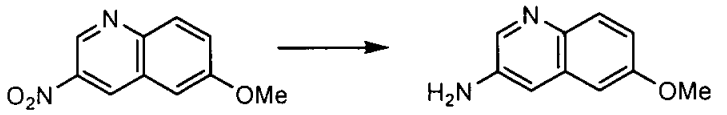
Síntesis de 7-(metil-sulfonil)-3-quinolil-amina



A una suspensión de 7-(metil-sulfonil)-3-nitroquinolina (85 miligramos, 0.4 milimoles) en EtOAc (6 mililitros,) bajo argón, se le agregó Pd/C al 10 por ciento (22 miligramos, 0.04 milimoles). Se conectó un globo de H_2 al matraz de reacción, el matraz se purgó con H_2 tres veces y la mezcla de reacción se dejó para agitar bajo una atmósfera de H_2 durante 18 horas. El material de partida sin reaccionar se pudo ver asentándose en el fondo del matraz junto con el catalizador. Los sólidos se removieron a partir de la solución de EtOAc mediante filtración. La evaporación del EtOAc bajo presión reducida proporcionó 7-(metil-sulfonil)-3-quinolil-amina (22 miligramos, 30 por ciento). LC/MS (*m/z*): 223.0 (MH^+), R_t 1.10 minutos.

Método 18

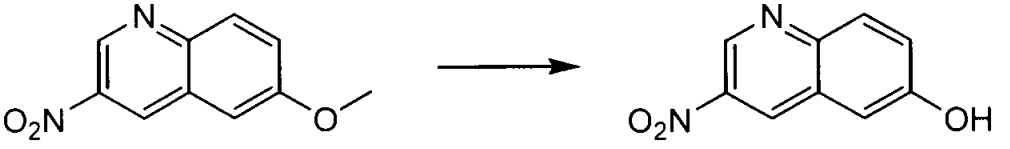
Síntesis de 6-metoxiquinolin-3-amina



Una mezcla de 6-metoxi-3-nitroquinolina (Magnus, P. y colaboradores, *J. Am. Chem. Soc. 119*, 5591, 1997; 0.17 gramos, 0.83 milimoles) y Pd/C (al 10 por ciento, 80 miligramos) en EtOAc (15 mililitros) se hidrogenó con un globo de hidrógeno para dar 6-metoxiquinolin-3-amina en un rendimiento cuantitativo. LC/MS (*m/z*): 175.1 (MH+), R_t 1.54 minutos.

Método 19

Síntesis 6-hidroxi-3-nitro-quinolina

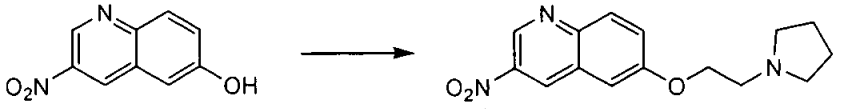


6-metoxi-3-nitroquinolina (Magnus, P. y colaboradores, *J. Am. Chem. Soc. 119*, 5591, 1997; 100 miligramos, 0.49 milimoles) se disolvió en una solución de bromuro de ácido (al 47 por ciento acuoso, 2.5 mililitros, 0.2 M), se calentó y se agitó a 120°C durante 16 horas. La mezcla de reacción se enfrió a temperatura ambiente, se neutralizó con NaOH 6N, entonces se extrajo con EtOAc (150 mililitros). La capa orgánica se secó sobre Na_2SO_4 y se purificó mediante cromatografía por evaporación instantánea (SiO_2, EtOAc del 40 al 50 por ciento/hexanos), obteniendo 73 miligramos (78 por ciento) de 6-hidroxi-3-nitro-quinolina. LC/MS (*m/z*): 190.9 (MH^+), R_t

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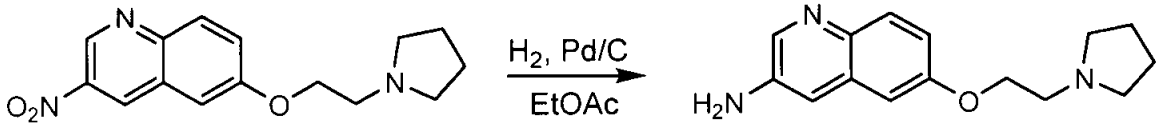
1.97 minutos.

Síntesis de 3-nitro-6-(2-(pirrolidin-1-il)-etoxi)-quinolina



Se disolvió 6-hidroxi-3-nitroquinolina (148 miligramos, 0.78 milimoles) en tetrahidrofurano (18 mililitros). Se agregaron 2-(pirrolidin-1-il)-etanol (0.091 mililitros, 0.78 milimoles) y trifenil-fosfina (306 miligramos, 1.17 milimoles). Finalmente, se agregó azodicarboxilato de dietilo (0.184 mililitros, 1.17 milimoles) y la mezcla de reacción se dejó agitar a temperatura ambiente durante 2 horas. El solvente se concentró entonces al vacío y el residuo se purificó mediante cromatografía por evaporación instantánea (SiO_2) para proporcionar 134 miligramos (60 por ciento) de 3-nitro-6-(2-(pirrolidin-1-il)-etoxi)-quinolina. LC/MS (*m/z*): 288.1 (MH^+), R_t 1.80 minutos.

Síntesis de 3-amino-6-(2-(pirrolidin-1-il)-etoxi)-quinolina



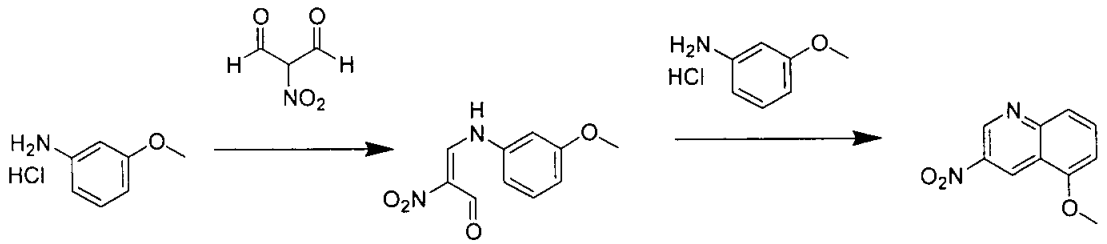
Se disolvió 3-Nitro-6-(2-(pirrolidin-1-il)-etoxi)-quinolina (134 miligramos, 0.46 milimoles) en EtOAc (10 mililitros) y la solución se salpicó con N_2 durante varios minutos. Entonces se agregó trietil-amina (0.065 mililitros, 0.46 milimoles) seguida por una cantidad catalítica de de Pd/C al 10 por ciento. El lavado con N_2 se repitió después de cada adición. Se conectó un globo de H_2 al matraz de la

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reacción y la mezcla de reacción se agitó a temperatura ambiente bajo una atmósfera de H_2 durante 48 horas. La mezcla entonces se filtró a través de un cojín de Celite y se concentró para obtener 3-amino-6-(2-(pirrolidin-1-il)-etoxi)-quinolina cruda, la cual se utilizó como es en la siguiente reacción. LC/MS (*m/z*): 258.1 (MH^+), R_t 0.33 minutos.

Método 20

Síntesis de 5-metoxi-3-nitro-quinolina



Síntesis de 3-(3-metoxi-fenil-amino)-2-nitro-propenal

A una sal de HCl de 3-metoxi-fenil-amina (4.6 gramos, 28.9 milimoles) en HCl 1N (300 mililitros) se le agregó una solución de 2-nitro-malonaldehído (2.7 gramos, 19.3 milimoles) en 150 mililitros agua. Después de 30 minutos, el precipitado se filtró y se enjuagó con HCl 0.1 N. Se secó con aire en un embudo Büchner durante 18 horas, dio 3.36 gramos (78 por ciento) de un polvo amarillo/verde claro. LC/MS (*m/z*): 245.1 (MH^+ +Na), R_t 2.21 minutos.

Síntesis de 5-metoxi-3-nitroquinolina y 7-metoxi-3-nitroquinolina

A la sal de HCl de 3-metoxi-fenil-amina (4.7 gramos, 29.7 milimoles) en 30 mililitros ácido acético se le agregó 3-(3-metoxi-fenil-amino)-2-nitro-propenal (3.3 gramos, 14.9 milimoles). La mezcla

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de reacción se calentó a reflujo, y se agregó tiofenol (0.3 mililitros, 2.98 milimoles). Después de 22 horas, la mezcla de reacción se enfrió a temperatura ambiente y el solvente se removió *al vacío*. La adición de 70 mililitros de EtOAc y la filtración dio el subproducto sólido, 7-metoxi-3-nitro-quinolina, y un filtrado, el cual contenía 5-metoxi-3-nitro-quinolina impura. El filtrado se cargó sobre una columna de sílice y se eluyó a partir de EtOAc del 5 por ciento a 25 por ciento en hexanos a 85 mililitros/minuto durante 30 minutos. Las fracciones del producto enriquecidas se concentraron y se recuperaron para el siguiente paso como una mezcla de 5- y 7-metoxilo sustituido 3-nitroquinolinas. LC/MS (*m/z*): 205.1 (MH^+), R_t 2.26 minutos.

Síntesis de 5-metoxiquinolin-3-amina



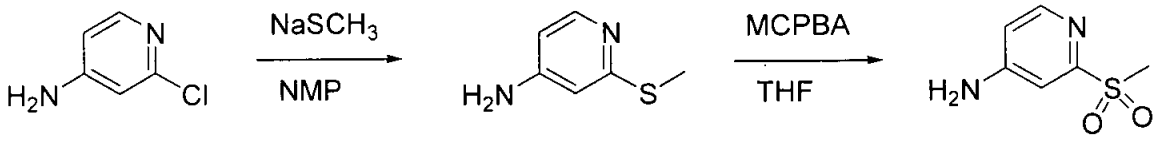
Una mezcla de 5- y 7-metoxilo sustituido 3-nitroquinolinas (780 miligramos, 3.82 milimoles) se disolvió en EtOAc (75 mililitros) y la mezcla de reacción se salpicó con N_2 durante varios minutos. Entonces, se agregó Pd/C al 10 por ciento (54 miligramos) y se conectó un globo de H_2 al matraz de reacción. La mezcla de reacción se salpicó con H_2 y se agitó a temperatura ambiente bajo una atmósfera de H_2 durante la noche. El solvente se removió al vacío y la purificación mediante cromatografía en columna en gel de sílice (EtOAc al 100 por ciento) proporcionó los dos isómeros separados 5-

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metoxiquinolin-3-amina y 7-metoxiquinolin-3-amina. El producto deseado 5-metoxiquinolin-3-amina (80 miligramos, 12 por ciento) se obtuvo como un polvo amarillo. La estructura se asignó mediante ^{1}H RMN (CD_3OD): δ 8.40 (d, 1H), 7.69 (d, 1H), 7.40 (d, 1H), 7.30 (t, 1H), 6.85 (d, 1H). LC/MS (isómero deseado) (*m/z*): 175.0 (MH^+), R_t 1.54 minutos; LC/MS (isómero indeseado) (*m/z*): 175.0 (MH^+), R_t 1.53 minutos.

Método 21

Síntesis de 2-(metil-sulfonil)-piridin-4-amina



Síntesis de 2-(tiometil)-piridin-4-amina

Se agregó tio-metóxido de sodio (140 miligramos, 1.98 milimoles) a una solución de 2-cloro-piridin-4-amina (150 miligramos, 1.17 milimoles) en NMP (0.65 mililitros) en un recipiente a presión. El recipiente se selló y se calentó en un microondas a 200°C durante 800 segundos. La purificación mediante cromatografía por evaporación instantánea en sílice eluyendo con metanol al 8 por ciento/dicloro-metano proporcionó 2-(tiometil)-piridin-4-amina (435 miligramos, 50 por ciento de rendimiento). LC/MS (*m/z*): 140.9 (MH^+), R_t 0.59 minutos.

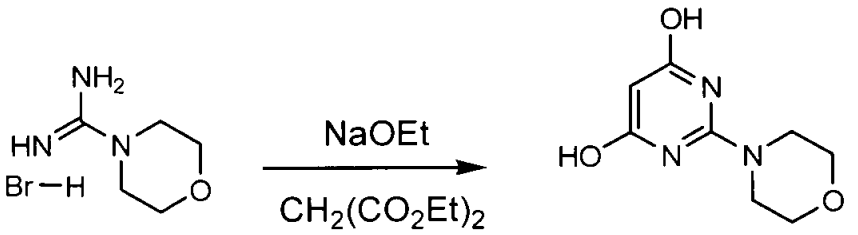
Se agregó lentamente MCPBA sólido (780 miligramos, 2-3 milimoles) en pequeñas porciones a una solución de 2-(tiometil)-piridin-4-amina (435 miligramos, 1.17 milimoles) en tetrahidrofurano

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(7 mililitros) a temperatura ambiente, con agitación. La reacción fue seguida por LCMS como el material de partida se consumió mediante titulación con MCPBA. Se agregó sílice a la mezcla de reacción, la cual se concentró entonces a sequedad bajo presión reducida. El crudo soportado por sílice se purificó mediante cromatografía por evaporación instantánea en sílice, eluyendo con MeOH al 5 por ciento/DCM, para proporcionar 2-(metil-sulfonil)-piridin-4-amina (220 miligramos, rendimiento cuantitativo). LC/MS (*m/z*): 173.0 (MH^+), R_t 0.34 minutos.

Método 22

Síntesis de 2-morfolinopirimidin-4,6-diol

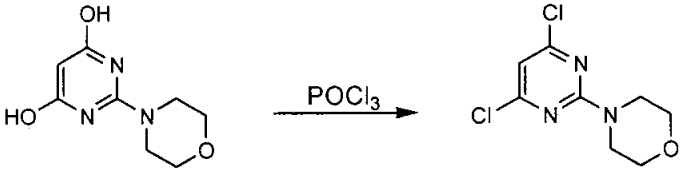


Se cortó sodio (17.25 gramos, 150 milimoles) en pequeñas piezas y se agregó lentamente al EtOH (500 mililitros) en un matraz de fondo redondo de 1 litro bajo N_2 y se enfrió con agua. Después, todo el sodio se disolvió, se agregaron bromhidrato de morfolino-formamidina (52.5 gramos, 50 milimoles) y malonato de dietilo (40 gramos, 50 milimoles). La mezcla se calentó a reflujo durante tres horas. La mezcla de reacción se enfrió a temperatura ambiente, y se removió el etanol *al vacío*. Se agregó HCl acuoso (1N, 800 mililitros) al sólido blanco, a temperatura ambiente. El sólido se disolvió inicialmente, dando una solución transparente, entonces el producto

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se trituró como un sólido blanco. Después de 1 hora a temperatura ambiente, el sólido se filtró, se lavó con agua (3 veces), se secó (aire y luego sobre P_2O_5) para dar 2-morfolino-pirimidin-4,6-diol (42.5 gramos, 86 por ciento). LC/MS (*m/z*): 198.1 (MH^+), R_t 0.51 minutos.

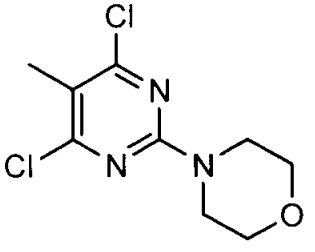
Síntesis de 4,6-dicloro-2-morfolino-pirimidina



Una mezcla de 2-morfolino-pirimidin-4,6-diol (30 gramos, 0.15 moles) y $POCl_3$ (150 mililitros, 1.61 moles) se calentó a 120°C durante 16 horas, entonces se enfrió a temperatura ambiente. El exceso de $POCl_3$ se removió para dar un semi-sólido. El sólido se transfirió gradualmente a una solución agitada de agua (700 mililitros) y EtOH (100 mililitros), ocasionalmente se enfrió con agua. Se formó un sólido blanco y subsiguientemente se filtró, se lavó con agua, EtOH al 10 por ciento en agua, y se secó sobre P_2O_5 para dar 4,6-dicloro-2-morfolino-pirimidina (17.82 gramos, 50 por ciento). LC/MS (*m/z*): 233.9 (MH^+), R_t 2.95 minutos.

Método 23

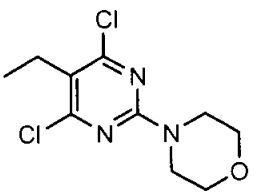
Síntesis de 4,6-dicloro-5-metil-2-morfolino-pirimidina



4,6-dicloro-5-metil-2-morfolino-pirimidina se preparó mediante un procedimiento similar a la 4,6-dicloro-2-morfolino-pirimidina (en el Método 22) utilizando 2-metil-malonato de dimetilo en lugar del malonato de dietilo. LC/MS (*m/z*): 248.1 (MH^+).

Método 24

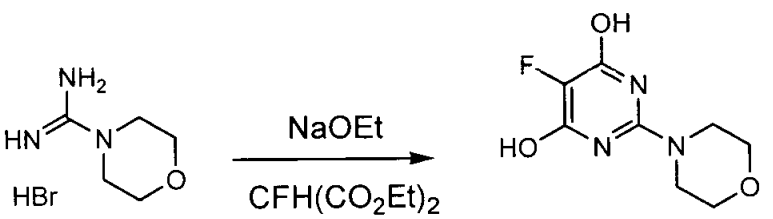
Síntesis de 4,6-dicloro-5-etil-2-morfolino-pirimidina



4,6-dicloro-5-etil-2-morfolino-pirimidina se preparó mediante un procedimiento similar a la 4,6-dicloro-2-morfolino-pirimidina (en el Método 22) utilizando 2-etil-malonato de dimetilo en lugar de malonato de dietilo. LC/MS (*m/z*): 262.1 (MH^+), R_t 3.59 minutos.

Método 25

Síntesis de 5-fluoro-2-morfolino-pirimidin-4,6-diol

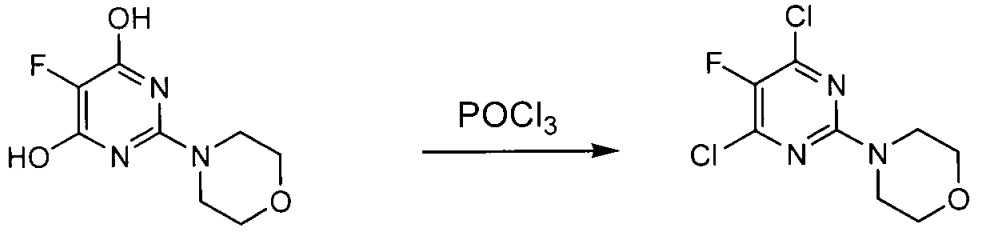


El hidruro de sodio (al 60 por ciento en aceite, 3.9 gramos, 96.5 milimoles) se lavó con hexanos en un matraz de fondo redondo bajo argón y se enfrió con un baño de agua helada. Se agregó lentamente EtOH (100 mililitros). La mezcla resultante se calentó a temperatura ambiente y se agitó durante 30 minutos. A la mezcla de la base, se le agregó 2-fluoro-malonato de dietilo (5.7 gramos, 32.2

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milimoles), seguida por bromhidrato de morfolin-formamidina (6.8 gramos, 32.2 milimoles). La mezcla se calentó de 90 a 95°C con agitación bajo argón. Después de 12 horas, la reacción se enfrió a temperatura ambiente y el EtOH se removió *al vacío*. El sólido blanco resultante se disolvió en agua (25 mililitros) y se acidificó con HCl, concentrando a un pH = 3 a 4. Se formó un precipitado blanco, el cual se recolectó en un filtro Büchner, se lavó con agua (50 mililitros, 2 veces), se secó con aire sobre el filtro, y se secó al vacío para dar 5-fluoro-2-morfolino-pirimidin-4,6-diol (0.87 gramos, 12 por ciento). LC/MS (*m/z*): 216.0 (MH^+), R_t 0.63 minutos.

Síntesis de 4-(4,6-dicloro-5-fluoro-pirimidin-2-il)-morfolina

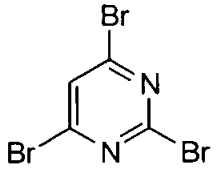


Una mezcla de 5-fluoro-2-morfolino-pirimidin-4,6-diol (0.87 gramos, 4.0 milimoles) y $POCl_3$ (10 mililitros) se calentó a 120°C durante 16 horas, entonces se enfrió a temperatura ambiente. El exceso de $POCl_3$ se removió bajo presión reducida para dar un semi-sólido, el cual se secó además *al vacío*. Después de 12 horas de secado al vacío, el sólido se diluyó en EtOAc (150 mililitros) y se lavó con $NaHCO_3$ saturado (60 mililitros). Se formó un sólido durante el lavado, y se desechó con la capa acuosa. La capa orgánica se lavó nuevamente con $NaHCO_3$ saturado (30 mililitros, 2 veces), salmuera (30 mililitros), se secó con Na_2SO_4, se filtró, y se evaporó

bajo presión reducida para dar un producto crudo. El producto se purificó mediante cromatografía por evaporación instantánea eluyendo con EtOAc al 25 por ciento/hexano para dar 4-(4,6-dicloro-5-fluoro-pirimidin-2-il)-morfolina (418 miligramos, 42 por ciento). LC/MS (*m/z*): 251.9 (MH^+), R_t 3.22 minutos.

Método 26

Síntesis de 2,4,6-tribromo-pirimidina

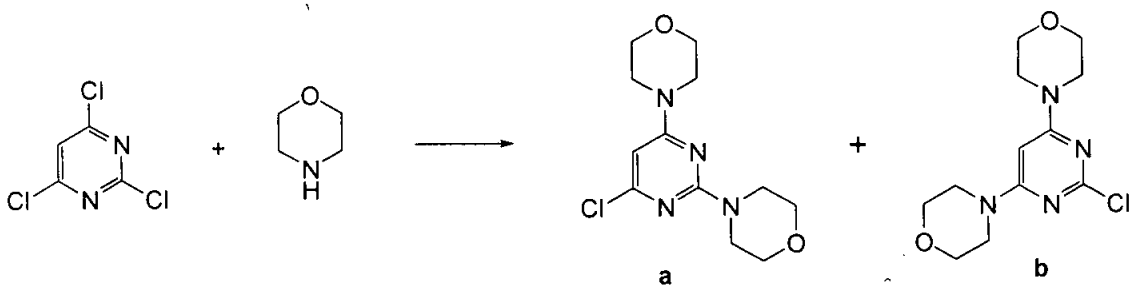


A una mezcla de pirimidin-2,4,6-(1*H*,3*H*,5*H*)-triona (2.66 gramos, 20.87 milimoles) y $POBr_3$ (25 gramos, 87.2 milimoles) en tolueno (35 mililitros) en un matraz 200 mililitros, se le agregó *N,N*-dimetilanilina (4.52 mililitros, 35.7 milimoles). La pasta acuosa color rojo ladrillo se calentó a reflujo durante 3 horas. Durante el proceso se formó una solución bifásica con una goma roja en el fondo del matraz y un líquido amarillo transparente arriba. La mezcla de reacción se enfrió a temperatura ambiente y la capa orgánica amarilla se decantó. La goma roja se enjuagó una vez con EtOAc. Los extractos orgánicos combinados se lavaron con $NaHCO_3$ saturado (3 veces, o hasta que la evolución de CO_2 termine), H_2O (3 veces), salmuera (2 veces) y se secó sobre Na_2SO_4. La solución se concentró entonces y se secó bajo un alto vacío para proporcionar 2,4,6-tribromo-pirimidina (5.40 gramos, 82 por ciento), el cual se utilizó sin mayor purificación. LC/MS (*m/z*): 316.8/318.7 (MH^+), R_t

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2.78 minutos.

Método 27



Una solución de morfolina (100 gramos; 1.15 moles; 5.3 equivalentes) en tetrahidrofurano (450 mililitros) se enfrió con un baño de hielo. Se agregó una solución de 2,4,6-tricloro-pirimidina (39.9 gramos; 217 milimoles; 1.0 equivalentes) en tetrahidrofurano (100 mililitros) durante un período de 30 minutos. Se formó un precipitado blanco copioso sobre la adición de 2,4,6-tricloro-pirimidina y la mezcla de reacción engrosó rápidamente. La mezcla se dejó calentar a temperatura ambiente y se agitó mecánicamente durante 64 horas (calentando la mezcla de reacción a reflujo siguiendo con la adición de 2,4,6-tricloro-pirimidina conduce a completar la reacción en 60 minutos. El intervalo de **a** a **b** no se cambió). La mezcla entonces se filtró y la torta del filtro se lavó con tetrahidrofurano adicional (100 mililitros, 2 veces). El filtrado se concentró sobre un evaporador giratorio. Se agregó agua (600 mililitros) y la pasta acuosa resultante se agitó durante 30 minutos. Los sólidos se aislaron mediante filtración, se lavaron con agua adicional (100 mililitros, 2 veces) y se secó durante la noche al vacío. Proporcionando **a** + **b**: 61.3 gramos (99 por ciento). El

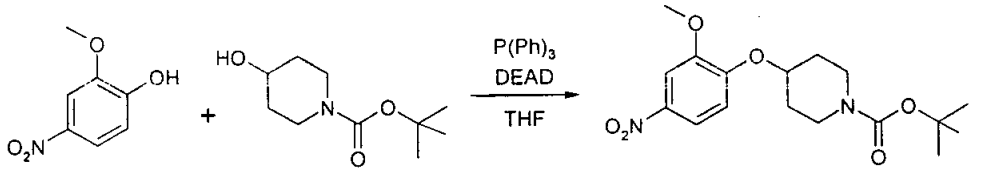
producto fue el 87 por ciento de acuerdo con el porcentaje de área de la HPLC; el resto es el b.

Se disolvieron 31 gramos del sólido crudo en 200 mililitros de CH_2Cl_2 y se aplicaron a 600 gramos de sílice seco en un embudo de vidrio fritado. Se eluyó el sílice con 1:1 de hexano:EtOAc y se recolectaron fracciones de 300 mililitros. El análisis de TLC muestra que **a** está presente en las fracciones 1 a 7 y 4,6-dimorfolino-2-cloro-pirimidina en las fracciones 6 a 10. Las fracciones 1 a 5 se reunieron y se concentraron para proporcionar un sólido blanco. Rendimiento: 28.2 gramos (el producto fue el 98 por ciento de acuerdo con el porcentaje de área de HPLC).

Método 28

Síntesis de 4-(1-isopropil-piperidin-4-iloxi)-anilina

Síntesis de *terbutilo* 4-(2-metoxi-4-nitro-fenoxi)-piperidin-1-carboxilato

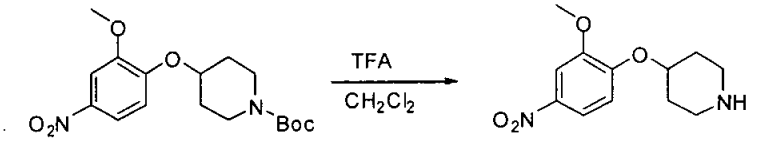


A una mezcla de trifenil-fosfina (3.10 gramos, 11.8 milimoles) y dietil-azodi-carboxilato (2.06 gramos, 11.8 milimoles) bajo N_2 en tetrahidrofurano (40 mililitros) se le agregó terbutilo de 4-hidroxi-piperidin-1-carboxilato (2.00 gramos, 9.94 milimoles). Después de agitar 10 minutos, se agregó 2-metoxi-4-nitro-fenol (1.00 gramos, 5.91 milimoles). La reacción se agitó durante 16 horas y el solvente se evaporó bajo presión reducida para dar un aceite color naranja. El

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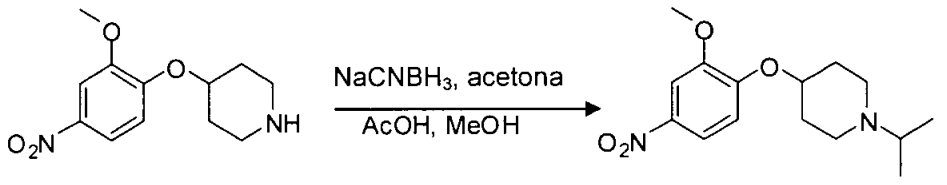
producto crudo se purificó mediante cromatografía en columna en gel de sílice utilizando EtOAc al 25 por ciento /hexano proporcionando terbutilo de 4-(2-metoxi-4-nitro-fenoxi)-piperidin-1-carboxilato como un sólido color beige (1.70 gramos, 82 por ciento). LC/MS (*m*/z): 353.2 (MH^+), R_t 3.23 minutos

Síntesis de 4-(2-metoxi-4-nitro-fenoxi)-piperidina



Se agregó ácido trifluoro-acético (5 equivalentes) a una solución de 4-(2-metoxi-4-nitro-fenoxi)-piperidin-1-carboxilato de terbutilo (200 miligramos, 0.57 milimoles, 1 equivalentes) en dicloro-metano, agitando a temperatura ambiente durante 1 hora. El solvente entonces se evaporó, el residuo se llevó a un pH 10 con una solución acuosa saturada de Na_2CO_3 y se extrajo con EtOAc. La capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio y se evaporó para proporcionar el producto 4-(2-metoxi-4-nitro-fenoxi)-piperidina como un sólido amarillo claro (137.3 miligramos, 96 por ciento). LC/MS (m/z): 253.2(MH+), Rt 1.81 minutos.

Síntesis de 1-isopropil-4-(2-metoxi-4-nitro-fenoxi)-piperidina

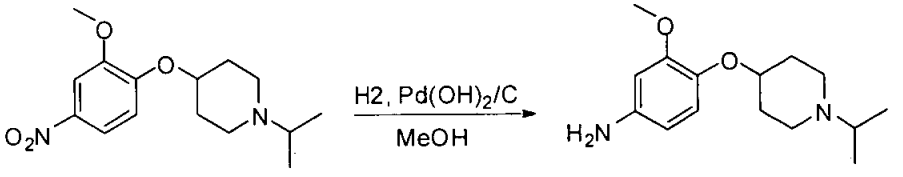


A una solución de ácido acético al 10 por ciento en metanol se

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le agregó 4-(2-metoxi-4-nitro-fenoxi)-piperidina (148 miligramos, 0.59 milimoles, 1 equivalentes), acetona anhidra (5 equivalentes), y ciano-borohidruro de sodio (1.5 equivalentes). La solución se agitó a temperatura ambiente durante 24 horas. Se agregaron acetona anhidra adicional (5 equivalentes) y ciano-borohidruro de sodio (1.5 equivalentes) y la reacción se agitó durante 24 horas. El solvente se evaporó, el residuo se llevó a un pH 10 con carbonato de sodio acuoso y se extrajo con EtOAc. La capa orgánica se lavó con agua, salmuera, se secó con sulfato de magnesio y se evaporó para proporcionar 1-isopropil-4-(2-metoxi-4-nitro-fenoxi)-piperidina como un aceite amarillo (163 miligramos, 97 por ciento). LC/MS (*m*/z): 295.2 (MH^+), R_t 1.96 minutos.

Síntesis de 4-(1-isopropil-piperidin-4-iloxi)-3-metoxianilina



Se disolvió 1-isopropil-4-(2-metoxi-4-nitro-fenoxi)-piperidina (167 miligramos, 0.57 milimoles) en metanol (20 mililitros) y se puso bajo una atmósfera de nitrógeno. Se agregó una cantidad catalítica de hidróxido de paladio al 20 por ciento sobre carbono y se conectó un globo de hidrógeno al matraz de reacción. El matraz se inundó cinco veces con hidrógeno y se agitó a temperatura ambiente bajo una atmósfera de hidrógeno durante 16 horas. La mezcla de reacción se filtró y se lavó con metanol. El filtrado se evaporó bajo presión

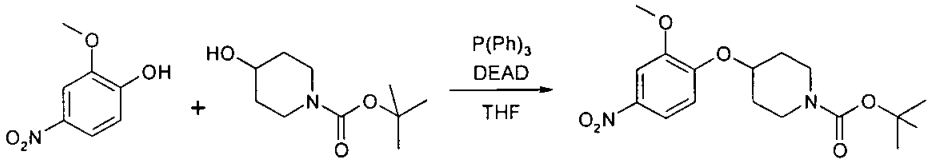
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reducida. Se agregó acetonitrilo (10 mililitros) al residuo, se puso en remolino durante 10 minutos, y se decantó afuera a partir de una película blanca. La capa de acetonitrilo se evaporó bajo presión reducida proporcionando 4-(1-isopropil-piperidin-4-iloxi)-anilina como un aceite color café (131 miligramos, 87 por ciento). LC/MS (*m*/z): 265.2 (MH^+), R_t 0.33 minutos.

Método 29

Síntesis de 4-(1-isopropil-piperidin-4-iloxi)-3-metoxi-anilina;

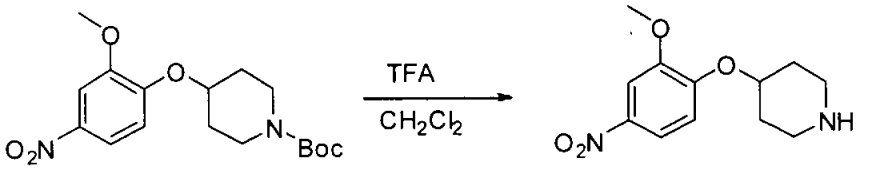
Síntesis de 4-(2-metoxi-4-nitro-fenoxi)-piperidin-1-carboxilato de terbutilo



A una mezcla de trifenil-fosfina bajo N_2 (3.10 gramos, 11.825 milimoles) y azodicarboxilato de dietilo (2.06 gramos, 11.825 milimoles) en tetrahidrofurano (40 mililitros) se le agregó 4-hidroxi-piperidin-1-carboxilato de terbutilo (2.00 gramos, 9.937 milimoles). Después de agitar 10 minutos, se agregó 2-metoxi-4-nitro-fenol (1.00 gramos, 5.912 milimoles). La reacción se agitó 16 horas y se evaporó bajo presión reducida para dar un aceite color naranja. El producto crudo se purificó mediante cromatografía en columna en gel de sílice utilizando EtOAc al 25 por ciento /hexano proporcionando el 4-(2-metoxi-4-nitro-fenoxi)-piperidin-1-carboxilato de terbutilo como un sólido color beige (1.70 gramos, 82 por ciento). LC/MS (*m*/z): 353.2 (MH^+), R_t 3.23 minutos

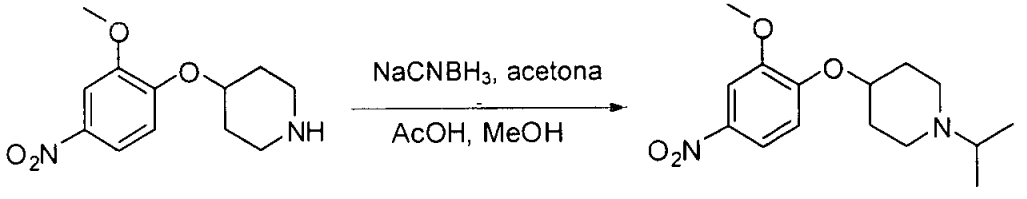
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Síntesis de 4-(2-metoxi-4-nitro-fenoxi)-piperidina



Se agregó ácido trifluoro-acético (5 equivalentes) a una solución de 4-(2-metoxi-4-nitro-fenoxi)-piperidin-1-carboxilato de terbutilo (200 miligramos, 0.5676 milimoles, 1 equivalentes) en dicloro-metano, agitando a temperatura ambiente durante 1 hora. El solvente, entonces, se evaporó, el residuo se llevó a un pH = 10 con solución acuosa saturada de Na_2CO_3 y se extrajo con EtOAc. La capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio y se evaporó para proporcionar el producto 4-(2-metoxi-4-nitro-fenoxi)-piperidina como un sólido amarillo claro (137.3 miligramos, 96 por ciento). LC/MS (*m/z*): 253.2(MH^+), R_t 1.81 minutos.

Síntesis de 1-isopropil-4-(2-metoxi-4-nitro-fenoxi)-piperidina

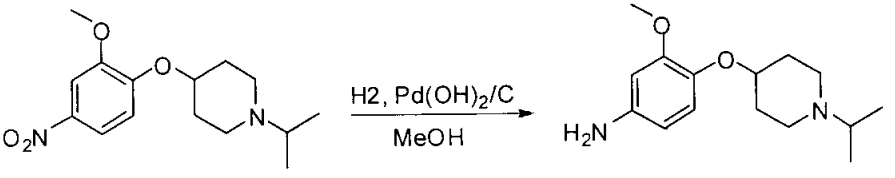


A una solución de ácido acético al 10 por ciento en metanol se le agregó 4-(2-metoxi-4-nitro-fenoxi)-piperidina (148 miligramos, 0.59 milimoles, 1 equivalentes), acetona anhidra (5 equivalentes), y cianoborohidruro de sodio (1.5 equivalentes). La solución se agitó a temperatura ambiente durante 24 horas. Reacción se completó al 85 por ciento. Se cargó acetona anhidra adicional (5 equivalentes) y

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ciano-borohidruro de sodio (1.5 equivalentes) y se agitó durante 24 horas. El solvente se evaporó, el residuo se llevó a un pH = 10 con carbonato de sodio y se extrajo con EtOAc. La capa orgánica se lavó con agua, salmuera, se secó con sulfato de magnesio y se evaporó para proporcionar la 1-isopropil-4-(2-metoxi-4-nitro-fenoxi)-piperidina como un aceite amarillo (163 miligramos, 97 por ciento). LC/MS (*m*/z): 295.2 (MH^+), R_t 1.96 minutos.

Síntesis de 4-(1-isopropil-piperidin-4-iloxi)-3-metoxianilina

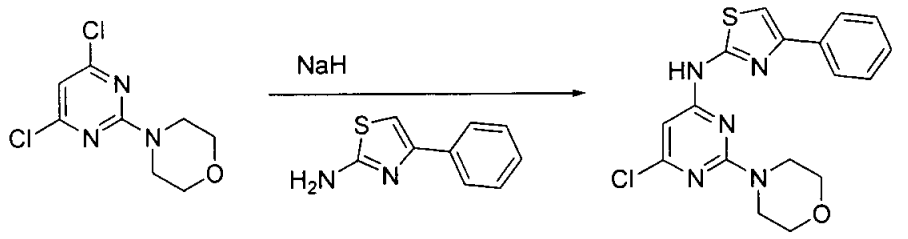


Se disolvió 1-isopropil-4-(2-metoxi-4-nitro-fenoxi)-piperidina (167 miligramos, 0.57 milimoles) en 20 mililitros de metanol y se colocó bajo una atmósfera de nitrógeno. Se agregó una cantidad catalítica de paladio hidróxido al 20 por ciento sobre carbono y se conectó un globo de hidrógeno al matraz de reacción. El matraz se inundó cinco veces con hidrógeno y se agitó a temperatura ambiente bajo una atmósfera de hidrógeno durante 16 horas. La mezcla de reacción se filtró y se lavó con metanol. El filtrado se evaporó bajo presión reducida. Se agregó acetonitrilo (10 mililitros) al residuo, se puso en remolino durante 10 minutos, y se decantó hacia afuera a partir de una película blanca. La capa de acetonitrilo se evaporó bajo presión reducida proporcionando 4-(1-isopropil-piperidin-4-iloxi)-anilina como un aceite color café (131 miligramos, 87 por ciento). LC/MS (*m*/z): 265.2 (MH^+), R_t 0.33 minutos.

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Método 30

Síntesis de N-(6-cloro-2-morfolino-pirimidin-4-il)-4-fenil-tiazol-2-amina

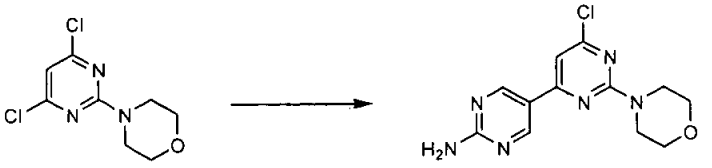


A una solución de 4-fenil-tiazol-2-amina (374 miligramos, 2.1 milimoles) en 10 mililitros de N,N-dimetil-acetamida se le agregó hidruro de sodio (50 miligramos, 2.1 milimoles) a temperatura ambiente. Después de que la mezcla se agitó a esa temperatura durante 10 minutos, se agregó dicloruro (470 miligramos, 2.0 milimoles) a la mezcla de reacción. Después de agitarse a temperatura ambiente durante 1 hora, se agregó hidruro de sodio adicional (50 miligramos, 2.1 milimoles) a la mezcla de reacción. La mezcla se agitó durante 1 hora y se apagó con 5 mililitros de cloruro de amonio acuoso. La mezcla resultante se extrajo con acetato de etilo (10 mililitros, 2 veces). Las capas orgánicas combinadas se lavaron con agua (10 mililitros), salmuera (10 mililitros), entonces se secaron sobre MgSO4, se filtraron, y se evaporaron bajo presión reducida para dar el producto crudo, el cual se purificó mediante columna en gel de sílice eluyendo con acetato de etilo y hexano para dar la N-(6-cloro-2-morfolinopirimidin-4-il)-4-fenil-tiazol-2-amina. LC/MS (m/z): 374 y 376 (MH+), Rt 3.40 minutos.

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Ejemplo 1

Preparación de N-(6-(2-amino-pirimidin-5-il)-2-morfolino-pirimidin-4-il)-quinolin-3-amina

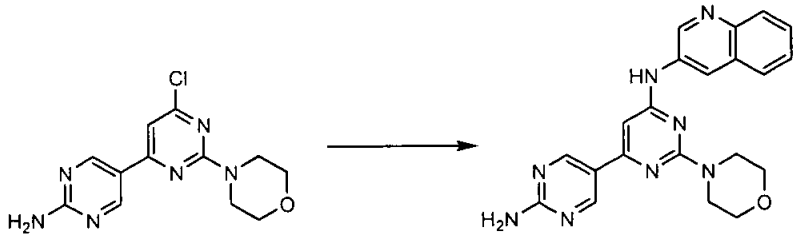


La 4,6-dicloro-2-morfolinopirimidina (preparado como en el Método 22; 3.0 gramos, 12.9 milimoles) y 5-(4,4,5,5-tetrametil-1,3,2-dioxa-borolan-2-il)-pirimidin-2-amina (3.43 gramos, 15.5 milimoles) se disolvieron en DME (130 mililitros). Entonces, se agregó Na_2CO_3 acuoso (2 M, 32 mililitros, 64 milimoles) y la mezcla de reacción se salpicó con N_2 durante varios minutos. Entonces, se agregaron $Pd(OAc)_2$ (145 miligramos, 0.65 milimoles) y PPh_3 (339 miligramos, 1.29 milimoles) y la mezcla de reacción se calentó a 95°C durante 1 hora. La mezcla de reacción se dejó enfriar a temperatura ambiente, la solución se decantó hacia afuera a partir del residuo sólido y se concentró. El sólido así formado se separó a partir de la fase de agua. El agua se extrajo con EtOAc y esta capa orgánica se combino con el precipitado. La remoción del solvente al vacío dio un residuo sólido, el cual se trituró con aproximadamente 20 mililitros de EtOAc, se filtró, y se evaporó bajo presión reducida para dar el producto deseado. Se obtuvo producto adicional concentrando el licor madre y purificando el sólido triturando mediante la trituración con EtOAc. Las dos cosechas se combinaron obteniendo 1.98 gramos (52 por ciento) del producto deseado. LC/MS (*m/z*): 293.1 (MH^+), R_t 1.92

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minutos

N-(6-(2-amino-pirimidin-5-il)-2-morfolino-pirimidin-4-il)-quinolin-3-amina

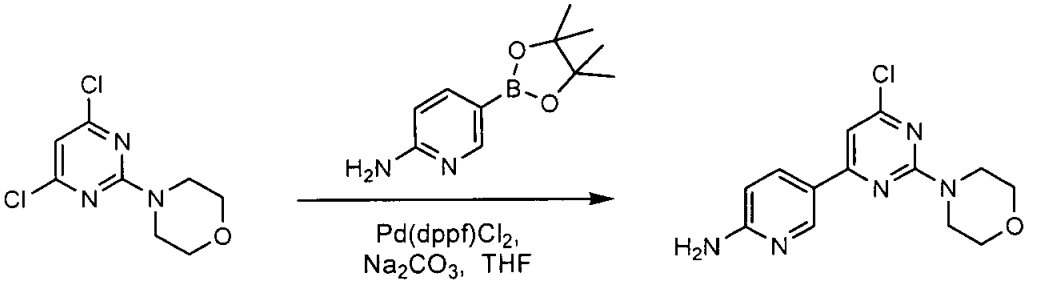


Se mezclaron $Pd(OAc)_2$, BINAP, carbonata cesio, tetrahidrofurano (0.8 mililitros) con 5-(6-cloro-2-morfolino-pirimidin-4-il)-pirimidin-2-amina (1 equivalente) y quinolin-3-amina (2 equivalentes). La mezcla se calentó bajo irradiación con microondas durante 10 minutos a 110°C. La solución se filtró y se concentró bajo presión reducida. LC/MS (*m*/z): 401.4 (MH^+).

Ejemplo 2

Preparación de N-(6-(6-amino-piridin-3-il)-2-morfolino-pirimidin-4-il)-quinolin-3-amina

5-(6-cloro-2-morfolin-4-il-pirimidin-4-il)-piridin-2-il-amina

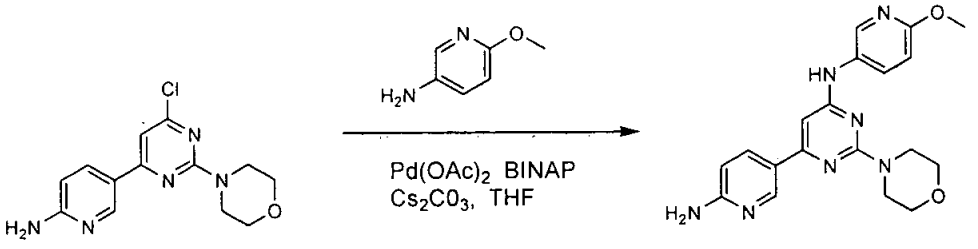


Se agregaron THF (130 mililitros) y Na_2CO_3 acuoso (2M, 40 mililitros, 80 milimoles) a un recipiente de presión de vidrio que contenía 4,6-dicloro-2-morfolino-pirimidina (preparado como en el

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Método 22; 4.5 gramos, 19.2 milimoles) y 5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-piridin-2-amina (4.7 gramos, 21.2 milimoles). La mezcla resultante se agitó y se salpicó con argón durante 1 a 2 minutos. Entonces, se agregó en una porción el catalizador, aducto de dicloro-[1,1'-bis(difenil-fosfino)-ferroceno]-paladio(II)/dicloro-metano (1.26 gramos, 1.54 milimoles). Después de sellar el recipiente de reacción, la reacción se calentó a 85°C durante 1 hora con agitación. Después de enfriarse a temperatura ambiente, el tetrahidrofurano se removió bajo presión reducida para dejar un residuo vicioso. Se agregaron EtOAc (450 mililitros) y agua (50 mililitros). Después de agitar vigorosamente durante 1 a 2 minutos, los sólidos se filtraron y se lavaron con EtOAc (100 mililitros). La capa orgánica se separó y la capa acuosa se extrajo con EtOAc (100 mililitros). Las capas orgánicas combinadas se lavaron con solución de NaCl saturada (50 mililitros, 1 ves), se secaron con Na_2SO_4, se filtran, y se evaporaron bajo presión reducida. El material crudo se purificó adicionalmente mediante cromatografía en gel de sílice para dar la 5-(6-cloro-2-morfolin-4-il-pirimidin-4-il)-piridin-2-il-amina (2.48 gramos, 44 por ciento). LC/MS (*m/z*): 292.1 (MH^+), R_t 2.06 minutos.

[6-(6-amino-piridin-3-il)-2-morfolin-4-il-pirimidin-4-il]-(6-metoxi-piridin-3-il)-amina



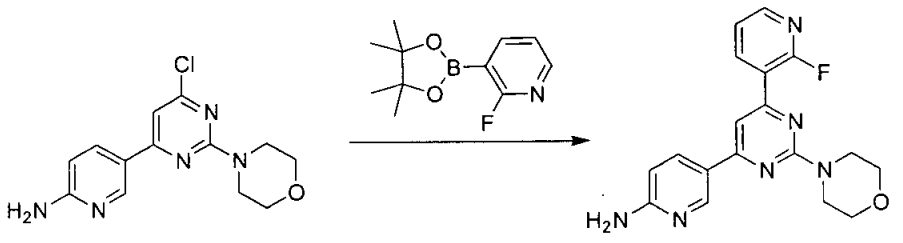
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En un recipiente de presión de vidrio, se mezclaron $Pd(OAc)_2$ (2.0 miligramos, 0.0082 milimoles), BINAP (6.4 miligramos, 0.0102 milimoles), carbonato de cesio (20.0 miligramos, 0.0615 milimoles) y tetrahidrofurano (0.8 mililitros), y se agitaron a temperatura ambiente durante 1 a 3 minutos. A la mezcla resultante se le agregó 5-(6-cloro-2-morfolin-4-il-pirimidin-4-il)-piridin-2-il-amina (12.0 miligramos, 0.041 milimoles) seguida por 6-metoxi-piridin-3-il-amina (10.2 miligramos, 0.082 milimoles). El recipiente de presión de vidrio se selló y se agitó a 95°C durante 90 minutos. La mezcla de reacción se filtró y se concentró bajo presión reducida. El producto se purificó mediante fase inversa de HPLC de para dar la [6-(6-amino-piridin-3-il)-2-morfolin-4-il-pirimidin-4-il]-(6-metoxi-piridin-3-il)-amina (5.0 miligramos, 32 por ciento). LC/MS (*m/z*): 380.1 (MH^+), R_t 1.82 minutos.

Ejemplo 3

Preparación de 5-(6-[2-(metil-sulfonamida)-piridin]-3-il)-2-morfolino-pirimidin-4-il)-piridin-2-amina

5-[6-(2-fluoro-piridin-3-il)-2-morfolin-4-il-pirimidin-4-il]-piridin-2-il-amina

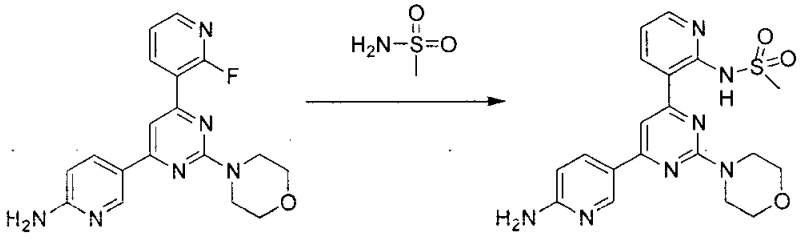


A una solución de 5-(6-cloro-2-morfolin-4-il-pirimidin-4-il)-piridin-2-il-amina, preparada como en el Ejemplo 2, (252 miligramos,

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0.87 milimoles) y 2-fluoro-3-(4,4,5,5-tetrametil-[1,3,2]-dioxaborolan-2-il)-piridina (183 miligramos, 1.30 milimoles) en DME (4 mililitros) se le agregó una solución de Na_2CO_3 acuosa (2 M, 1 mililitro), seguida por dicloro[1,1'-bis-(difenil-fosfino)-ferroceno]-paladio(II)/dicloro-metano (71 miligramos, 0.087 milimoles). La mezcla se calentó en un microondas durante 20 minutos a 120°C. La fase acuosa se separó a partir de DME, y se extrajo con EtOAc. Las fases orgánicas combinadas se lavaron con salmuera, se secaron, se filtraron, y se concentraron para dar el producto crudo deseado, el cual se trituró en el siguiente paso sin mayor purificación. LC/MS (*m/z*): 353.3 (MH^+), 1.84 minutos.

N-{3-[6-(6-amino-piridin-3-il)-2-morfolin-4-il-pirimidin-4-il]-piridin-2-il}-metan-sulfonamida



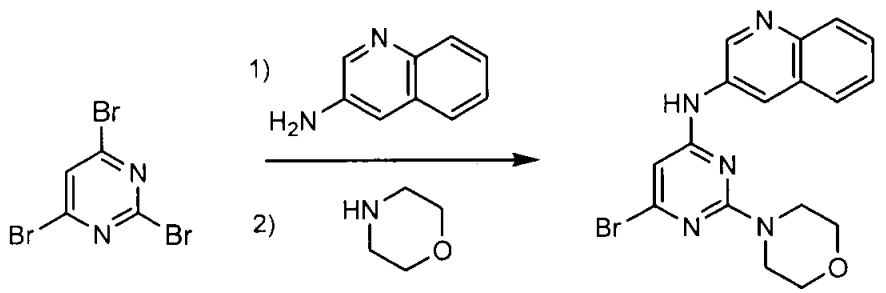
A una solución de 5-[6-(2-fluoro-piridin-3-il)-2-morfolin-4-il-pirimidin-4-il]-piridin-2-il-amina (200 miligramos, 0.57 milimoles) y metan-sulfonamida (216 miligramos, 2.3 milimoles) en NMP (8 mililitros) se agregó Cs_2CO_3 (372 miligramos, 1.1 milimoles). La solución se calentó a 125°C durante 4 horas. La mezcla de reacción se enfrió a temperatura ambiente, se filtró, y se purificó mediante fase inversa de HPLC de preparación para dar el compuesto del título. LC/MS (*m/z*): 428.3 (MH^+), R_t 1.80 minutos.

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Ejemplo 4

Preparación de N-(6-(6-amino-4-fluoro-piridin-3-il)-2-morfolino-pirimidin-4-il)-quinolin-3-amina

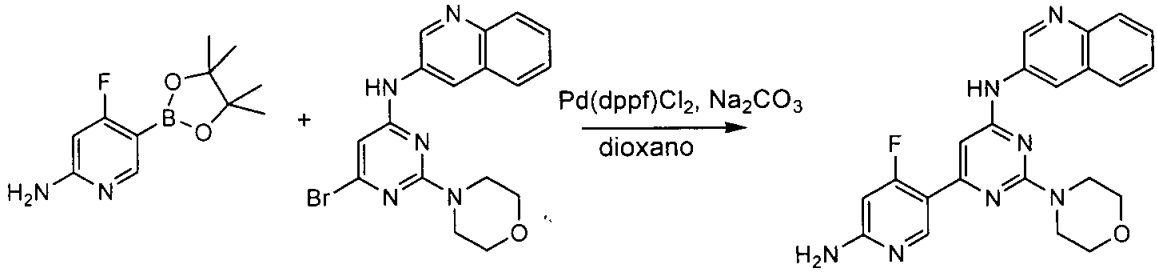
N-(6-bromo-2-morfolinopirimidin-4-il)-quinolin-3-amina



A una solución de 2,4,6-tribromopirimidina (5.40 gramos, 17.2 milimoles) en acetonitrilo (60 mililitros) se agregó quinolin-3-amina, seguida por DIEA (8.99 mililitros, 51.6 milimoles). La mezcla de reacción se calentó a 45°C durante la noche. Entonces, se agregó morfolina (1.50 mililitros, 17.2 milimoles), y la mezcla de reacción se continuó calentando durante 4 horas. La mezcla de reacción entonces se enfrió a temperatura ambiente, se concentró y se disolvió en EtOAc (aproximadamente 500 mililitros), la solución orgánica se lavó con $NaHCO_3$ saturado (3 veces), H_2O (2 veces), salmuera (1 vez) y se secó sobre Na_2SO_4. La solución, entonces, se evaporó en la presencia de gel de sílice y se purificó mediante cromatografía en columna (SiO_2, EtOAc del 15 al 25 por ciento/Hexanos) para proporcionar *N*-(6-bromo-2-morfolino-pirimidin-4-il)-quinolin-3-amina. LC/MS (*m/z*): 386.1 (MH^+).

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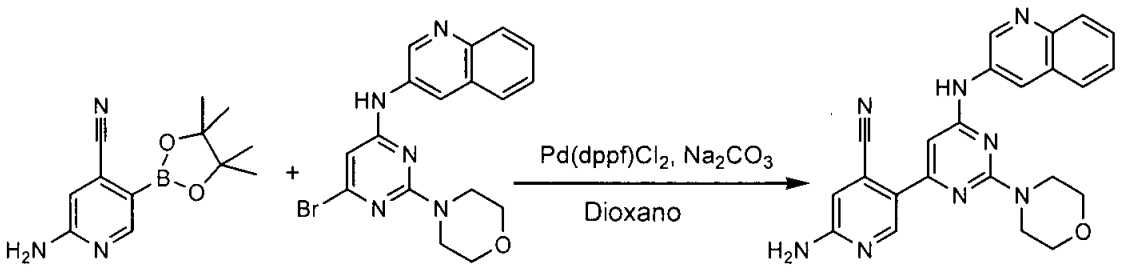
N-(6-(6-amino-4-fluoro-piridin-3-il)-2-morfolinopirimidin-4-il)-quinolin-3-amina



A una solución de 4-fluoro-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-piridin-2-amina (preparado como se muestra en el Método 10) en dioxano (1.7 mililitros, 0.13 milimoles), *N*-(6-bromo-2-morfolino-pirimidin-4-il)-quinolin-3-amina (20 miligramos, 0.052 milimoles), aducto de dicloro[1,1'-bis(difenil-fosfino)-ferroceno]-paladio(II)/dicloro-metano (11 miligramos, 0.013 milimoles) y solución de carbonato de sodio acuosa 2M (0.6 mililitros, 1.2 milimoles) se agregaron bajo argón. El recipiente de presión se selló y la mezcla de reacción se calentó en un reactor de microondas a 120°C durante 15 minutos. El producto crudo se dividió entre EtOAc (30 mililitros) y bicarbonato de sodio saturado (10 mililitros). La capa orgánica se separaron, se secaron sobre sulfato de sodio, se filtraron, y se concentraron bajo presión reducida. El producto se purificó mediante fase inversa de HPLC de preparación para dar *N*-(6-(6-amino-4-fluoro-piridin-3-il)-2-morfolino-pirimidin-4-il)-quinolin-3-amina como un polvo amarillo (14 miligramos, 26 por ciento). LC/MS (*m/z*): 418.0 (MH^+), R_t 2.31 minutos.

Ejemplo 5

Preparación de 2-amino-5-[2-morfolin-4-il-6-(quinolin-3-il-amino)-pirimidin-4-il]-isonicotinonitrilo

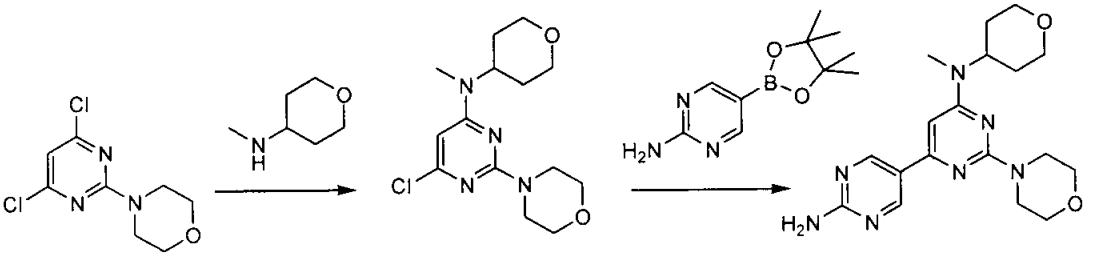


A una solución del 2-amino-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-piridin-4-carbonitrilo crudo (preparado como en el Método 11) (25 miligramos, 0.13 milimoles) en dioxano (1.8 mililitros) en un recipiente de presión, se le agregaron (6-bromo-2-morfolin-4-il-pirimidin-4-il)-quinolin-3-il-amina (19.4 miligramos, 0.05 milimoles) y Na_2CO_3 acuoso (2 M, 0.6 mililitros, 1.2 milimoles). Después de purgar la mezcla de reacción con argón, se le agregó el aducto de dicloro-[1,1'-bis(difenil-fosfino)-ferroceno]-paladio(II)/dicloro-metano (10.3 miligramos, 0.01 milimoles) en una porción. El recipiente de presión se selló y la mezcla se calentó en un reactor de microondas a 120°C durante 900 segundos. La mezcla cruda se filtró y se concentró bajo presión reducida. El producto crudo se purificó mediante HPLC de preparación en fase inversa para dar el 2-amino-5-[2-morfolin-4-il-6-(quinolin-3-il-amino)-pirimidin-4-il]-isonicotino-nitrilo (4.4 miligramos, 20 por ciento). LC/MS (*m/z*): 425.0 (MH^+), R_t 2.03 minutos.

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Ejemplo 6

Preparación de N^6-metil-2-morfolino-N^6-(tetrahidro-2H-piran-4-il)-4,5'-bipirimidin-2',6-diamina



N-Metil-tetrahidro-2*H*-piran-4-amina

La tetrahidro-2*H*-piran-4-amina (90 miligramos, 0.9 milimoles) se agregó a una solución de formaldehído (solución al 37 por ciento en agua, 0.091 mililitros, 1.13 milimoles) y ácido acético (0.162 mililitros) en ACN (0.8 mililitros). Después de agitar durante 5 minutos, se agregó $Na(CN)BH_3$ (60 miligramos, 1.13 milimoles) en una porción a temperatura ambiente. Después de 1 hora, se agregó un exceso de Cs_2CO_3 a la reacción hasta que se hizo alcalina. Después de agitar durante 15 minutos, la reacción se filtró para remover los sólidos, y el solvente se evaporó bajo presión reducida. El producto crudo, *N*-metil-tetrahidro-2*H*-piran-4-amina, se utilizó para el siguiente desplazamiento sin mayor purificación. LC/MS (*m/z*): 116.1 (MH^+), R_t 0.34 minutos.

6-cloro-*N*-metil-2-morfolino-*N*-(tetrahidro-2*H*-piran-4-il)-pirimidin-4-amina

La *N*-metil-tetrahidro-2*H*-piran-4-amina cruda (104 miligramos,

0.9 milimoles) se disolvió en NMP (0.8 mililitros). A la solución se le agregaron Cs_2CO_3 (366 miligramos, 1.13 milimoles) y 4-(4,6-dicloro-pirimidin-2-il)-morfolina (preparada como en el Método 22) (80 miligramos, 0.34 milimoles) a temperatura ambiente. La mezcla de reacción se calentó a 95°C. Después de 90 minutos, la mezcla de reacción se enfrió a temperatura ambiente, se filtró, y se purificó mediante HPLC de preparación en fase inversa proporcionando 24 miligramos (23 por ciento) de la 6-cloro-*N*-metil-2-morfolino-*N*-(tetrahidro-2*H*-piran-4-il)-pirimidin-4-amina pura. LC/MS (*m*/z): 313.2 (MH^+), R_t 2.61 minutos.

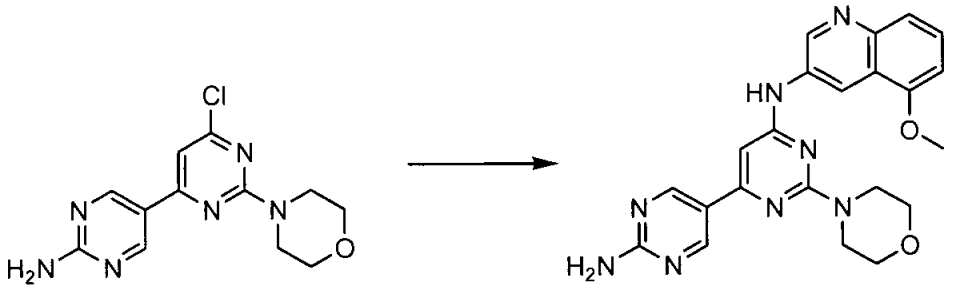
N^6-metil-2-morfolino-N^6-(tetrahidro-2H-piran-4-il)-4,5'-bipirimidin-2',6-diamina

A una mezcla inundada con argón de 5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-pirimidin-2-amina (42 miligramos, 0.19 milimoles), 6-cloro-*N*-metil-2-morfolino-*N*-(tetrahidro-2*H*-piran-4-il)-pirimidin-4-amina (12 miligramos, 0.038 milimoles) en tetrahidrofurano (0.8 mililitros), y Na_2CO_3 acuoso (2M, 0.27 mililitros) en un recipiente de presión, se le agregó el aducto de dicloro-[1,1'-bis(difenil-fosfino)-ferroceno]-paladio(II)/dicloro-metano (8 miligramos, 0.0095 milimoles) en una porción. El recipiente de presión se selló y la mezcla se calentó en un reactor de microondas a 120°C durante 600 segundos. La mezcla cruda se filtró, se concentró bajo presión reducida, y se purificó mediante HPLC de preparación en fase inversa para dar la N^6-metil-2-morfolino-N^6-(tetrahidro-2H-piran-4-il)-4,5'-bipirimidin-2',6-diamina (4.6 miligramos, 32 por ciento).

LC/MS (*m/z*): 372.2 (MH^+), R_t 1.76 minutos.

Ejemplo 7

Preparación de N-(6-(2-amino-pirimidin-5-il)-2-morfolino-pirimidin-4-il)-5-metoxiquinolin-3-amina

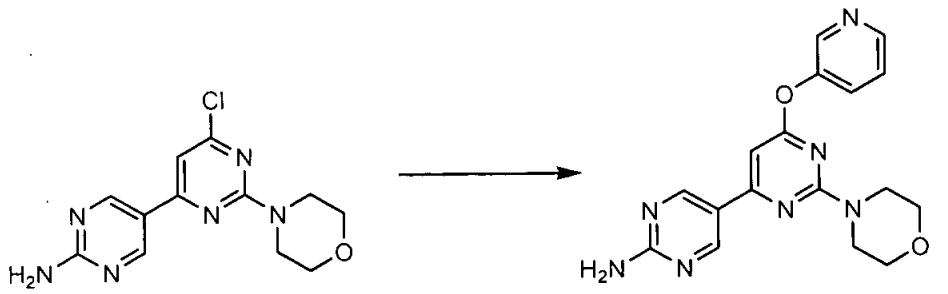


El compuesto deseado se preparó como se describe en el Ejemplo 2: Se mezclaron $Pd(OAc)_2$, BINAP, carbonato de cesio, y tetrahidrofurano (0.8 mililitros), con 5-(6-cloro-2-morfolino-pirimidin-4-il)-pirimidin-2-amina (1 equivalente) y 5-metoxiquinolin-3-amina (2 equivalentes), que se preparó como se muestra en el Método 20. La mezcla se calentó bajo irradiación con microondas durante 10 minutos a 110°C. La solución se filtró y se concentró bajo presión reducida. El producto crudo se purificó mediante HPLC de preparación en fase inversa. LC/MS (*m/z*): 431.2 (MH^+), R_t 2.03 minutos.

Ejemplo 8

Preparación de 5-(2-morfolino-6-(piridin-3-iloxi)-pirimidin-4-il)-pirimidin-2-amina

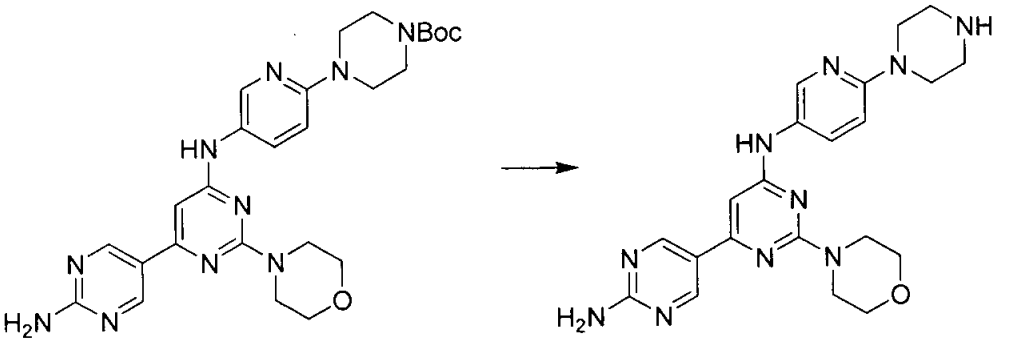
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La 5-(6-cloro-2-morfolino-pirimidin-4-il)-pirimidin-2-amina (10 miligramos, 0.034 milimoles, preparada como en el Ejemplo 1), terbutóxido de potasio (6 miligramos, 0.051 milimoles), piridin-3-ol (5 miligramos, 0.051 milimoles), y sulfóxido de dimetilo (0.5 mililitros), se combinaron todos entre sí y se calentaron a 110°C durante 2 días. El producto crudo se purificó directamente mediante HPLC de preparación en fase inversa para dar la 5-(2-morfolino-6-(piridin-3-iloxi)-pirimidin-4-il)-pirimidin-2-amina (5.1 miligramos, 32 por ciento). LC/MS (*m/z*): 352.1 (MH^+), R_t 1.83 minutos.

Ejemplo 9

Preparación de 6-(2-amino-pirimidin-5-il)-2-morfolino-N-(6-(piperazin-1-il)-piridin-3-il)-pirimidin-4-amina

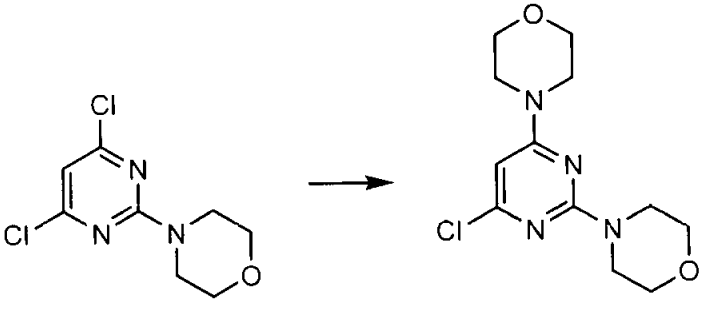


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Al 4-(5-(6-(2-amino-pirimidin-5-il)-2-morfolino-pirimidin-4-il-amino)-piridin-2-il)-piperazin-1-carboxilato de terbutilo (preparado como se describe en el Ejemplo 1 a partir de la de 5-(6-cloro-2-morfolino-pirimidin-4-il)-pirimidin-2-amina y el 4-(5-amino-piridin-2-il)-piperazin-1-carboxilato de terbutilo comercialmente disponible, 30 miligramos, 0.06 milimoles) se le agregaron 5 mililitros de HCl 4N en dioxano. Después de agitar durante una hora, la solución se concentró al vacío. El residuo se disolvió en 3:1 de acetonitrilo y agua, y se liofilizó para proporcionar el producto deseado LC/MS (*m/z*): 435.2 (MH^+), R_t 1.52 minutos.

Ejemplo 10

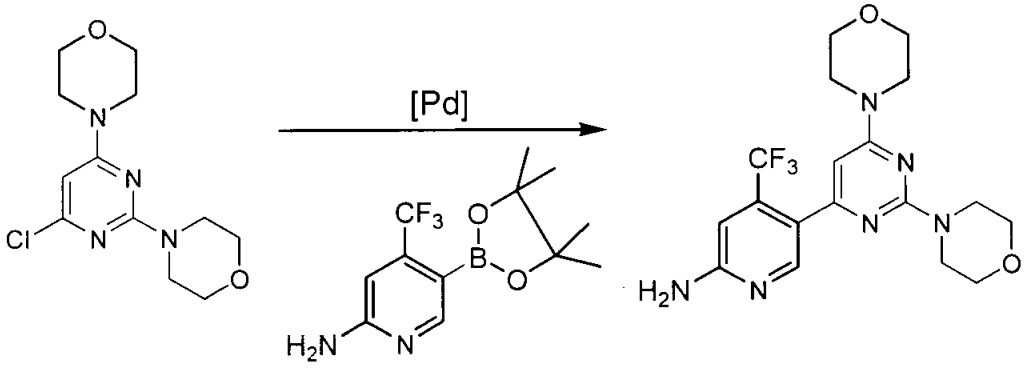
Preparación de 4-(trifluoro-metil)-5-(2,6-dimorfolino-pirimidin-4-il)-piridin-2-amina



A una pasta acuosa de 2-morfolino-4,6-dicloro-pirimidina (preparada como en el Método 22, 2.0 gramos, 8.54 milimoles) en NMP (14 mililitros), se le agregó trietil-amina (1.43 mililitros, 10.25 milimoles). La mezcla heterogénea se agitó durante 15 minutos, y entonces se trató con morfolina (0.75 mililitros, 8.54 milimoles). Después del reflujo a 85°C bajo argón durante 2 horas, la solución

se enfrió, y luego se agregó a EtOAc (160 mililitros). La solución orgánica se lavó con 25 mililitros de $NaHCO_{3(sat.)}$ (2 veces), agua (2 veces), y salmuera, se secó sobre Na_2SO_4, se filtró, y se concentró. El material crudo se disolvió en 200 mililitros de EtOAc y se filtró a través de un cojín de SiO_2, eluyendo adicionalmente con EtOAc, proporcionando 2.2 gramos (93 por ciento) de la 2,4-dimorfolino-6-cloro-pirimidina como un sólido grisáceo. LCMS (*m/z*): 285.0 (MH^+), ^1H RMN ($CDCl_3$): δ 5.86 (s, 1H), 3.71-3.76(m, 12H), 3.52-3.56(m, 4H).

4-(trifluoro-metil)-5-(2,6-dimorfolino-pirimidin-4-il)-piridin-2-amina



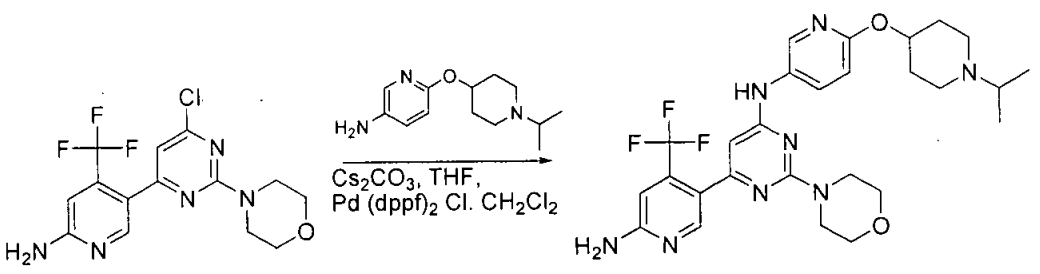
Se burbujeó argón a través de una mezcla heterogénea de 2,4-dimorfolino-6-cloro-pirimidina (4.1 gramos, 14.3 milimoles) y 4-(trifluoro-metil)-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-piridin-2-amina (16.5 gramos, 57.3 milimoles) en 1,2-dimetoxi-etano y Na_2CO_3 2M (3:1) durante 20 minutos. Se agregó cloruro de 1,1'-Bis(difenil-fosfino)ferroceno-paladio(II) (292 miligramos, 0.36 milimoles), y el recipiente de vidrio de alta presión que contenía la

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mezcla se selló. La mezcla de reacción se calentó entonces a 90°C durante 15 horas, se enfrió y se diluyó con EtOAc (300 mililitros). La solución orgánica se lavó con 300 mililitros de una mezcla de agua : $Na_2CO_{3(sat.)}$: $NH_4OH_{(conc.)}$ = 5:4:1, luego $NH_4Cl_{(sat.)}$, y salmuera (2 veces), se secó sobre Na_2SO_4, se filtró, y se concentró. El material crudo se purificó mediante cromatografía sobre SiO_2 (del 50 al 90 por ciento de EtOAc/hexanos con trietil-amina al 0.1 por ciento), dando como resultado 5.62 gramos (95 por ciento) de la 4-(trifluoro-metil)-5-(2,6-dimorfolino-pirimidin-4-il)-piridin-2-amina como un sólido grisáceo. LCMS (*m/z*): 411.3 (MH^+); ^1H RMN ($CDCl_3$): δ 8.27 (s, 1H), 6.78 (s, 1H), 5.97 (s, 1H), 4.77 (bs, 2H), 3.59-3.80(m, 12H), 3.58-3.61(m, 4H).

Ejemplo 11

Preparación de N-(6-(1-isopropil-piperidin-4-iloxi)-piridin-3-il)-6-(6-amino-4-(trifluoro-metil)-piridin-3-il)-2-morfolino-pirimidin-4-amina



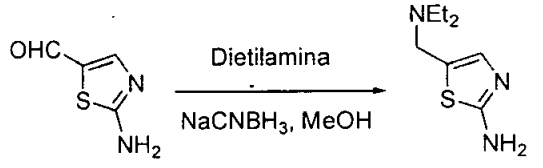
La N-(6-(1-isopropil-piperidin-4-iloxi)-piridin-3-il)-6-(6-amino-4-(trifluoro-metil)-piridin-3-il)-2-morfolino-pirimidin-4-amina se sintetizó de acuerdo con el procedimiento general para la reacción de

Buchwald del Ejemplo 2, mediante la reacción de la 6-(1-isopropil-piperidin-4-iloxi)-piridin-3-amina (preparada como en el Método 16) con la 5-(6-cloro-2-morfolino-pirimidin-4-il)-4-(trifluoro-metil)-piridin-2-amina. LC/MS (*m/z*): 559.2 (MH^+), R_t 1.92 minutos. ^1H RMN (DMSO): δ 10.27 (1H, bs, NH); 8.41 (1H, bs); 8.17 (1H, s); 7.98 y 7.94 (1H, 2 b dobletes, *J*= 9.0 Hz, 2 conformadores); 6.97 (1H, s); 6.90 y 6.84 (1H, 2 dobletes, *J*= 9.0 Hz, 2 conformadores); 6.23 (1H, bs); 5.25 y 5.15 (1H, 2 multipletes, 2 conformadores); 3.66 (8H, bs); 3.44 (1H, m); 3.35 (2H, m); 3.10 (2H, m); 2.22 (2H, m); 2.03 (2H, m); 1.27 (6H, dobletes traslapados debido a los conformadores, triplete aplicado, *J*= 5.7 Hz).

Ejemplo 12

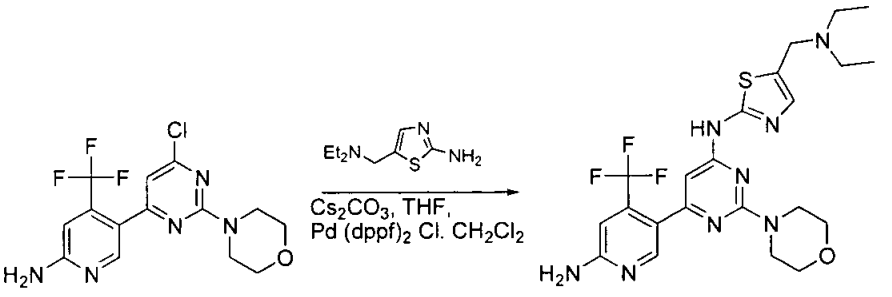
Preparación de N-(5-((dietil-amino)-metil)-tiazol-2-il)-6-(6-amino-4-(trifluoro-metil)-piridin-3-il)-2-morfolino-pirimidin-4-amina

5-((dietil-amino)-metil)-tiazol-2-amina



El 2-amino-tiazol-5-carbaldehído (1 equivalente) se agregó a una solución en agitación de dietil-amina (4 equivalentes) en metanol anhidro a 0°C. Entonces se agregó en porciones ciano-borohidruro de sodio (1.5 equivalentes) a 0°C. La mezcla de reacción se agitó a 70°C durante 10 horas. Después de este tiempo, la solución se apagó con H_2O y se extrajo con EtOAc. Los extractos orgánicos combinados se secaron sobre Na_2SO_4 y se concentraron para

proporcionar un aceite viscoso color café. LC/MS (*m/z*): 186.2 (MH^+), R_t 0.33 minutos.

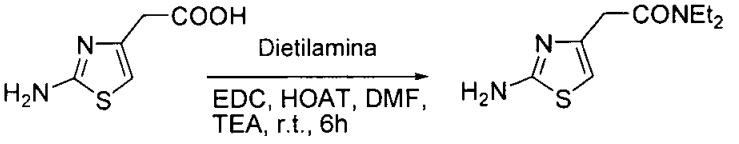


El compuesto del título se sintetizó de acuerdo con el procedimiento general mostrado en el Ejemplo 2. LC/MS (*m/z*): 509.2 (MH^+), R_t 1.98 minutos. ^1H RMN (DMSO): δ 11.0, (2H, bs, NH2), 8.17 (1H, s); 7.63 (1H, s); 7.08 (1H, bs), 6.40 (1H, s); 4.48 (2H, bd, *J*= 4.2 Hz); 3.80 (4H, m); 3.68 (4H, m); 3.03 (4H, bq, *J*= 6.9 Hz); 1.30 (6H, t, *J*= 6.9 Hz).

Ejemplo 13

Síntesis de 6-(6-amino-4-(trifluoro-metil)-piridin-3-il)-N-(4-(2-(dietil-amino)-etil)-tiazol-2-il)-2-morfolino-pirimidin-4-amina

2-(2-amino-tiazol-4-il)-N,N-dietil-acetamida

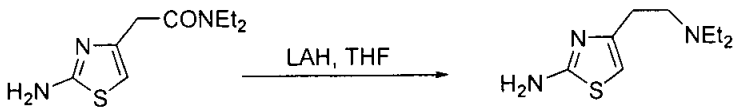


Una mezcla del ácido 2-(2-amino-tiazol-4-il)acético (1 equivalente), HOAT (1 equivalente), EDC (1.1 equivalentes), trietil-amina (1 equivalente), y $HNEt_2$ (1 equivalente) en DMA, se agitó a

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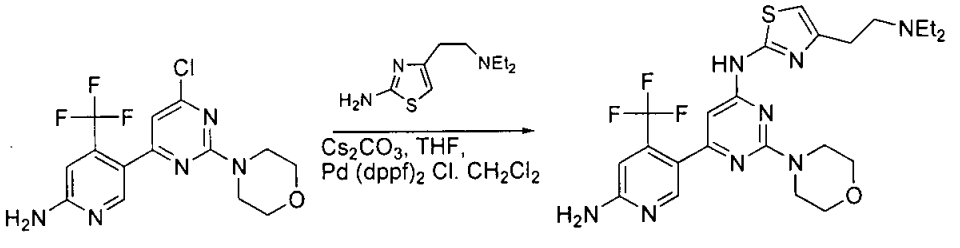
temperatura ambiente durante 6 horas. La mezcla de reacción entonces se apagó con H_2O y se concentró. El residuo se disolvió en una mezcla agitada de 4:1 de EtOAc y $NaHCO_{3(sat.)}$. Las dos fases se separaron, y la solución orgánica se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró a sequedad. El sólido resultante se lavó dos veces con Et_2O y se secó para proporcionar el producto deseado como un sólido blanco. LC/MS (*m/z*): 214.0 (MH^+), R_t 1.13 minutos.

4-(2-(dietil-amino)-etil)-tiazol-2-amina



Una suspensión de 2-(2-amino-tiazol-4-il)-N,N-dietil-acetamida (1 equivalente) en tetrahidrofurano se agregó por goteo a una suspensión vigorosamente agitada de LAH (1 equivalente) en tetrahidrofurano a 0°C. La mezcla se agitó a temperatura ambiente durante 2 horas. En este tiempo, la mezcla resultante se enfrió a 0°C y se agregaron por goteo 1 parte de H_2O, seguida por 1 parte de NaOH al 10 por ciento, y finalmente 3 partes de H_2O,. La mezcla se agitó durante 10 minutos, se filtró, y el residuo sólido se lavó con tetrahidrofurano. El filtrado se recolectó y se concentró a sequedad. El material crudo resultante se lavó con Et_2O dos veces y se secó para proporcionar un aceite viscoso color café. LC/MS (*m/z*): 200.1, (MH^+), R_t 0.34 minutos.

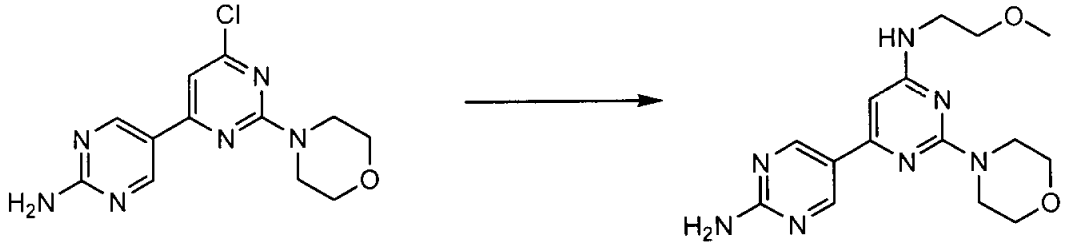
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El compuesto del título se sintetizó de acuerdo con el procedimiento general mostrado en el Ejemplo 2. LC/MS (*m/z*): 523.1 (MH^+), R_t 2.11 minutos. ^{1}H-RMN (DMSO): δ 8.15 (1H, s); 7.08 (1H, s); 6.96 (1H, s); 6.38 (1H, s); 3.78 (4H, m); 3.65 (4H, m); 3.31 (2H, m); 3.13 (4H, q, *J* = 7.2 Hz); 3.02 (2H, m); 1.20 (6H, t, *J* = 7.2 Hz).

Ejemplo 14

Preparación de N^6-(2-metoxi-etil)-2-morfolino-4,5'-bipirimidin-2',6-diamina



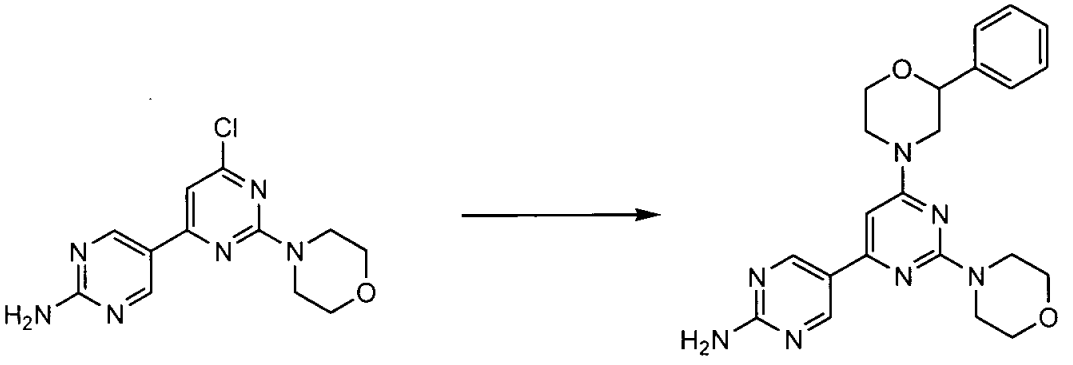
Una mezcla salpicada con argón, de 6-cloro-2-morfolino-4,5'-bipirimidin-2'-amina (10 miligramos, 0.03 milimoles) y 2-metoxi-etanamina (0.018 mililitros, 0.20 milimoles) en NMP (0.8 mililitros) contenida en un recipiente de presión sellado, se calentó en un reactor de microondas a 155°C durante 1000 segundos. La mezcla

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de reacción se filtró y se purificó mediante HPLC de preparación en fase inversa para dar la N^6-(2-metoxi-etil)-2-morfolino-4,5'-bipirimidin-2',6-diamina como la sal de ácido trifluoro-acético (4.0 miligramos, 30 por ciento). LC/MS (*m*/*z*): 332.2 (MH^+), R_t 1.44 minutos.

Ejemplo 15

Preparación de 2-morfolino-6-(2-fenil-morfolino)-4,5'-bipirimidin-2'-amina

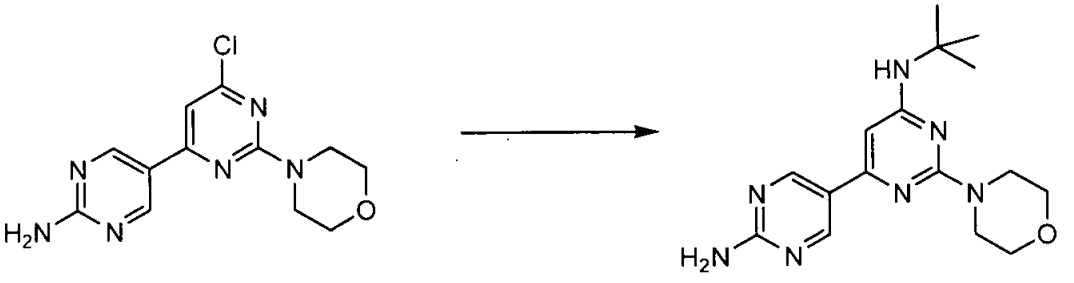


Una mezcla salpicada con argón, de 6-cloro-2-morfolino-4,5'-bipirimidin-2'-amina (10 miligramos, 0.03 milimoles), Cs_2CO_3 (27 miligramos, 0.09 milimoles) y 2-fenil-morfolina (11 miligramos, 0.068 milimoles) en NMP (0.5 mililitros) contenida en un recipiente de presión sellado, se calentó en un reactor de microondas a 170°C durante 600 segundos. La mezcla de reacción se filtró y se purificó mediante HPLC de preparación en fase inversa, para dar la 2-morfolino-6-(2-fenil-morfolino)-4,5'-bipirimidin-2'-amina como la sal de ácido trifluoro-acético (7.2 miligramos, 45 por ciento). LC/MS (*m*/*z*): 420.1 (MH^+), R_t 2.20 minutos.

Ejemplo 16

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Preparación de N^6-terbutil-2-morfolino-4,5'-bipirimidin-2',6-diamina

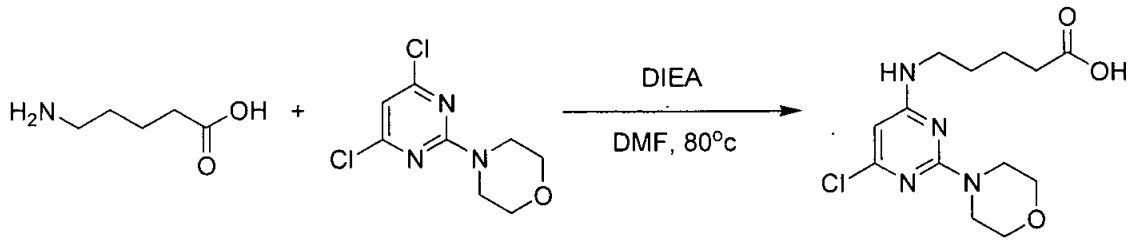


Una mezcla salpicada con argón, de 6-cloro-2-morfolino-4,5'-bipirimidin-2'-amina (10 miligramos, 0.03 milimoles) y terbutil-amina (12.5 miligramos, 0.17 milimoles) en NMP (0.5 mililitros) contenida en un recipiente de presión sellado, se calentó en un reactor de microondas a 175°C durante 800 segundos. Se agregó una cantidad adicional de terbutil-amina (50 miligramos, 0.68 milimoles) a la reacción. La reacción se calentó nuevamente en un reactor de microondas a 175°C durante 800 segundos, y nuevamente a 175°C durante 800 segundos, hasta la desaparición del material de partida. La mezcla cruda se filtró. El producto crudo se purificó mediante HPLC de preparación en fase inversa para dar la N^6-terbutil-2-morfolino-4,5'-bipirimidin-2',6-diamina como la sal de ácido trifluoro-acético (0.9 miligramos, 7 por ciento). LC/MS (*m*/z): 330.2 (MH^+), R_t 1.96 minutos.

Ejemplo 17

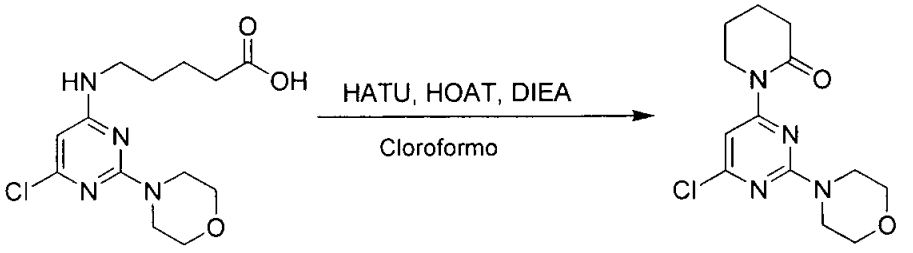
Preparación de 1-(2-(6-amino-4-(trifluoro-metil)-piridin-3-il)-6-morfolino-pirimidin-4-il)-piperidin-2-ona

Ácido 5-(2-cloro-6-morfolino-pirimidin-4-il-amino)-pentanoico



El ácido 5-amino-pentanoico (140 miligramos, 1.19 milimoles), 4-(2,6-dicloro-pirimidin-4-il)-morfolina (preparada como en el Método 22; 234 miligramos, 1.0 milimoles), y DIEA (0.530 mililitros, 3.0 milimoles) se disolvieron en N,N-dimetil-formamida (6 mililitros). La solución de la reacción se agitó a 40°C durante 40 horas. La reacción se diluyó con EtOAc (100 mililitros) y se lavó con HCl 0.5 M (40 mililitros), agua (40 mililitros), salmuera (40 mililitros), se secó con Na_2SO_4, se filtró, y se evaporó, para dar un sólido. El producto crudo se pasó por cromatografía sobre una columna de gel de sílice eluyendo con EtOAc al 80 por ciento en hexano, para dar el ácido 5-(2-cloro-6-morfolino-pirimidin-4-il-amino)-pentanoico como un sólido blanco (190 miligramos, 60 por ciento). LC/MS (*m/z*): 315.0 (MH^+), R_f 1.79 minutos.

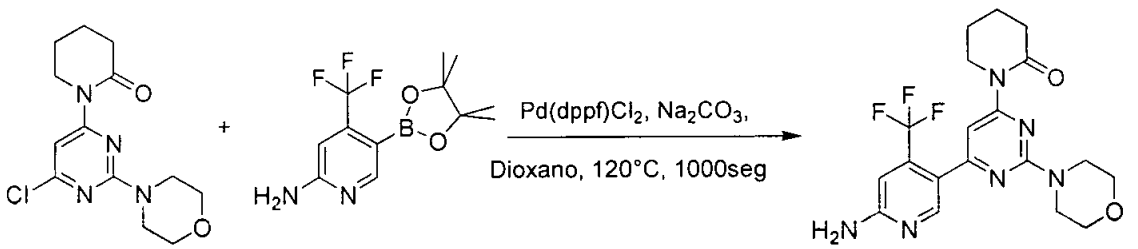
1-(2-cloro-6-morfolino-pirimidin-4-il)-piperidin-2-ona



A una solución de HATU (304 miligramos, 0.8 milimoles), HOAT (82 miligramos, 0.6 milimoles), y DIEA (0.209 mililitros, 1.2

milimoles) en cloroformo (20 mililitros) bajo argón, se le agregó lentamente una solución del ácido 5-(2-cloro-6-morfolino-pirimidin-4-il-amino)-pentanoico (190 miligramos, 0.6 milimoles) en cloroformo (10 mililitros). La solución de la reacción se agitó a temperatura ambiente durante 5 horas. Después de que la reacción estuvo completa, la solución se evaporó a sequedad para dar un sólido blanco, el cual se pasó por cromatografía sobre una columna de gel de sílice eluyendo con EtOAc al 40 por ciento/hexano, para dar la 1-(2-cloro-6-morfolino-pirimidin-4-il)-piperidin-2-ona como un sólido blanco (62 miligramos, 35 por ciento). LC/MS (*m*/z): 297.0 (MH^+), R_t 2.74 minutos.

1-(2-(6-amino-4-(trifluoro-metil)-piridin-3-il)-6-morfolino-pirimidin-4-il)-piperidin-2-ona



A una suspensión de 1-(2-cloro-6-morfolino-pirimidin-4-il)-piperidin-2-ona (16 miligramos, 0.05 milimoles), 5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-4-(trifluoro-metil)-piridin-2-amina (preparada como en el Método 4; 23 miligramos, 0.08 milimoles), y aducto de dicloro-[1,1'-bis(difenil-fosfino)-ferroceno]-paladio(II)/dicloro-metano (8 miligramos, 0.009 milimoles) en dioxano (1.1 mililitros), se le agregó una solución acuosa de carbonato de sodio 2M (0.4 mililitros, 0.8 milimoles), bajo argón. La mezcla de reacción se calentó en un

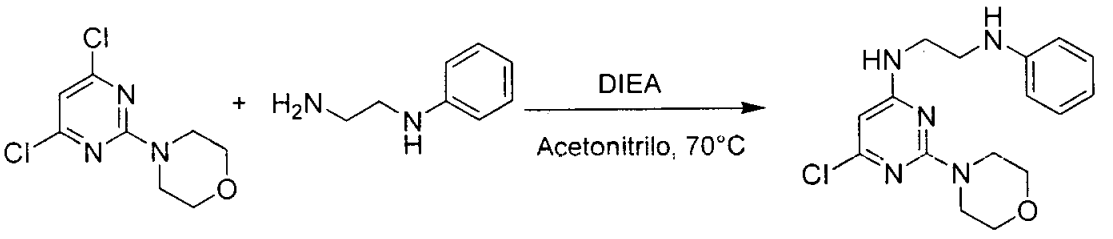
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reactor de microondas a 120°C durante 1000 segundos. El producto crudo se dividió entre EtOAc (30 mililitros) y bicarbonato de sodio saturado (10 mililitros). La capa orgánica se separó, se secó sobre sulfato de sodio, se filtró, y se concentró bajo presión reducida. El producto crudo se purificó mediante HPLC de preparación en fase inversa, para dar la 1-(2-(6-amino-4-(trifluoro-metil)-piridin-3-il)-6-morfolino-pirimidin-4-il)-piperidin-2-ona como un polvo amarillo (8.8 miligramos, 42 por ciento). LC/MS (*m/z*): 423.0 (MH^+), R_t 2.25 minutos.

Ejemplo 18

Preparación de 1-(6-(6-amino-4-(trifluoro-metil)-piridin-3-il)-2-morfolino-pirimidin-4-il)-3-fenil-imidazolidin-2-ona

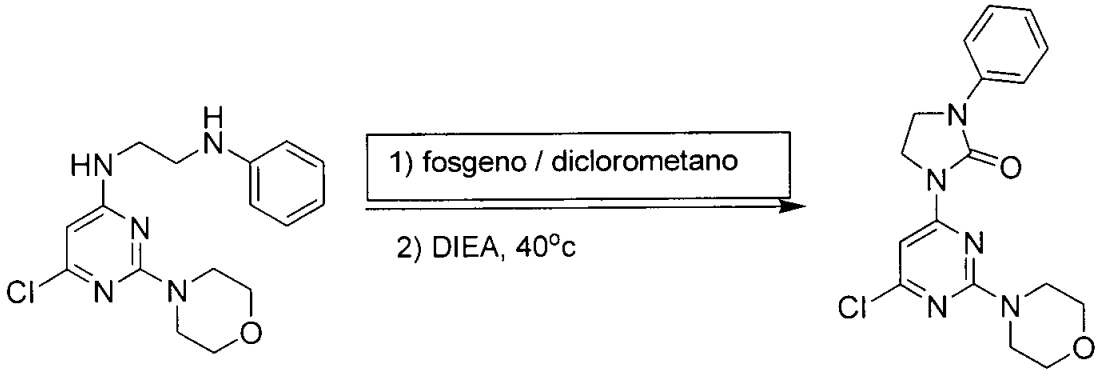
N^1-(6-cloro-2-morfolino-pirimidin-4-il)-N^2-fenil-etan-1,2-diamina



A una solución de la 4-(4,6-dicloro-pirimidin-2-il)-morfolina (preparada como se describe en Método 22; 932 miligramos, 4.0 milimoles) y DIEA (0.7 mililitros, 4.0 milimoles) en ACN (40 mililitros), se le agregó lentamente N^1-fenil-etan-1,2-diamina limpia (0.523 mililitros, 4.0 milimoles). La mezcla de reacción se agitó a 70-80°C bajo nitrógeno. Después de 20 horas, la mezcla de reacción se

enfrió, y el solvente se removió bajo presión reducida. El producto crudo se dividió entre EtOAc (120 mililitros) y $NaHCO_3$ 0.1 M (50 mililitros). La capa orgánica se lavó con $NaHCO_3$ 0.1 M adicional (50 mililitros, 2 veces), salmuera (50 mililitros), se secó, se filtró, y se concentró, para dar la N^1-(6-cloro-2-morfolino-pirimidin-4-il)-N^2-fenil-etan-1,2-diamina, como un sólido grisáceo (1.29 gramos, 96 por ciento). LC/MS (*m/z*): 334.0 (MH^+), R_t 1.94 minutos.

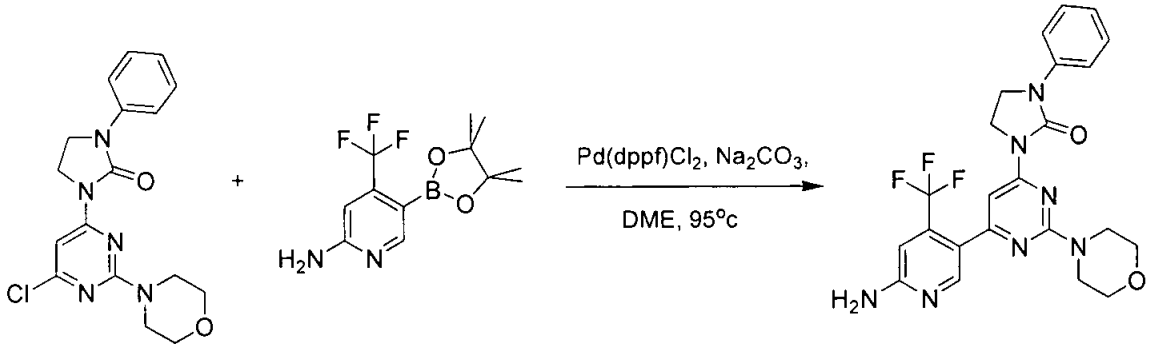
1-(6-cloro-2-morfolino-pirimidin-4-il)-3-fenil-imidazolidin-2-ona



A una solución de N^1-(6-cloro-2-morfolino-pirimidin-4-il)-N^2-fenil-etan-1,2-diamina (100 miligramos, 0.3 milimoles) en diclorometano (15 mililitros) a 0°C bajo nitrógeno, se le agregó lentamente una solución de fosgeno en tolueno (1.89 M, 0.32 mililitros, 0.6 milimoles). Después de 20 minutos, la reacción se dejó calentar a temperatura ambiente. Después de 18 horas,) se agregó DIEA (0.42 mililitros, 2.4 milimoles), y la solución de la reacción se calentó a 40-50°C durante 40 horas. La mezcla de reacción se evaporó bajo presión reducida, y el producto crudo se purificó mediante cromatografía en gel de sílice, eluyendo con EtOAc al 70 por ciento/hexano, para dar la 1-(6-cloro-2-morfolino-pirimidin-4-il)-3-

fenil-imidazolidin-2-ona como un sólido blanco (94 miligramos, 87 por ciento). LC/MS (*m/z*): 360.1 (MH^+), R_t 3.41 minutos.

1-(6-(6-amino-4-(trifluoro-metil)-piridin-3-il)-2-morfolino-pirimidin-4-il)-3-fenil-imidazolidin-2-ona



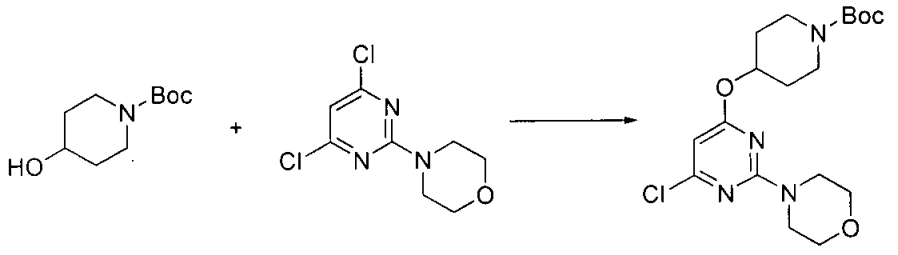
A una suspensión de 1-(6-cloro-2-morfolino-pirimidin-4-il)-3-fenil-imidazolidin-2-ona (18 miligramos, 0.05 milimoles), 5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-4-(trifluoro-metil)-piridin-2-amina (preparada como se describe en Método 4; 18 miligramos, 0.06 milimoles), y aducto de dicloro-[1,1'-bis(difenil-fosfino)-ferroceno]-paladio(II)/dicloro-metano (3.2 miligramos, 0.004 milimoles) en DME (1.2 mililitros), se le agregó una solución acuosa de carbonato de sodio 2M (0.4 mililitros, 0.8 milimoles), bajo argón. La mezcla de reacción se agitó a 95°C durante 5 horas. El producto crudo se dividió entre EtOAc (30 mililitros) y bicarbonato de sodio saturado (10 mililitros). La capa orgánica se separó, se secó sobre sulfato de sodio, se filtró, y se concentró bajo presión reducida. El producto crudo se purificó mediante HPLC de preparación para dar la 1-(6-(6-amino-4-(trifluoro-metil)-piridin-3-il)-2-morfolino-pirimidin-4-il)-3-fenil-imidazolidin-2-ona como un polvo color amarillo pálido (8.4

miligramos, rendimiento global del 35 por ciento). LC/MS (*m/z*): 448.1 (MH^+), R_t 3.29 minutos.

Ejemplo 19

Preparación de 1-(4-(6-(6-amino-4-(trifluoro-metil)-piridin-3-il)-2-morfolino-pirimidin-4-iloxi)-piperidin-1-il)-etanona

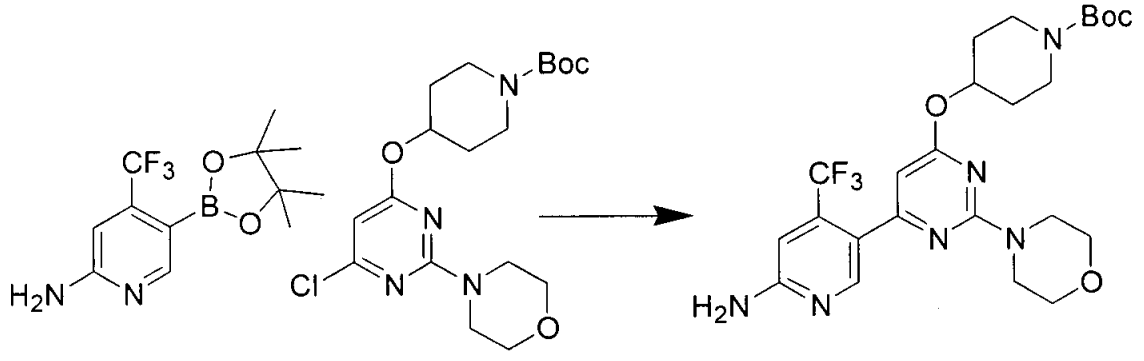
Paso 1: Alcoxilación de 2-morfolino- 4,6-dicloro-pirimidina



A una solución de N-Boc-4-hidroxi-piperidina (2.58 gramos, 12.81 milimoles) en tetrahidrofurano a 0°C bajo argón, se le agregó hidruro de sodio (60 por ciento, 512 miligramos, 12.81 milimoles). Después de agitar durante 20 minutos, se agregó una solución de 2-morfolino-4,6-dicloro-pirimidina (2.0 gramos, 8.54 milimoles) en tetrahidrofurano (20 mililitros) a través de una jeringa. La solución se agitó durante 14 horas a medida que el baño de hielo se calentaba a temperatura ambiente. En este tiempo, la mezcla de reacción se apagó con agua (2 mililitros), y se dividió entre EtOAc (350 mililitros) y Na_2CO_3(sat.) (75 mililitros). La capa orgánica se separó, se lavó con salmuera (50 mililitros), se secó sobre Na_2SO_4, se filtró, se concentró, y el residuo se purificó mediante cromatografía con SiO_2 (15-20 por ciento de EtOAc en hexanos) para proporcionar el 4-(6-cloro-2-morfolino-pirimidin-4-iloxi)-piperidin-1-carboxilato de terbutilo como un sólido blanco (2.64 gramos, 77 por ciento). LCMS (*m/z*):

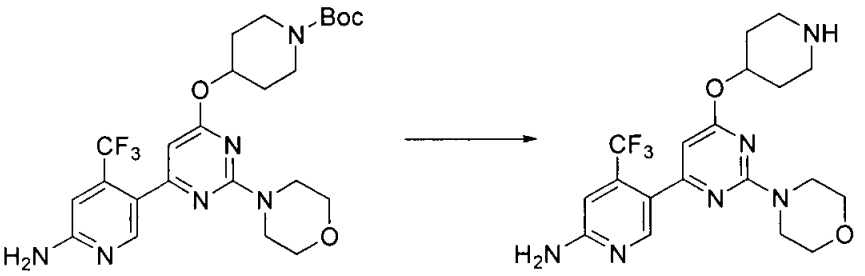
399.1 (MH^+). ^1H RMN ($CDCl_3$): δ 6.00 (s, 1H), 5.18 (m, 1H), 3.74 (s, 8H), 3.64-3.74 (m, 2H), 3.28-3.38 (m, 2H), 1.86-1.96 (m, 2H), 1.68-1.78 (m, 2H), 1.44 (s, 9H).

Paso 2: Reacción de Suzuki de la 6-cloro-pirimidina 2-morfolino-4-alcoxi-sustituida



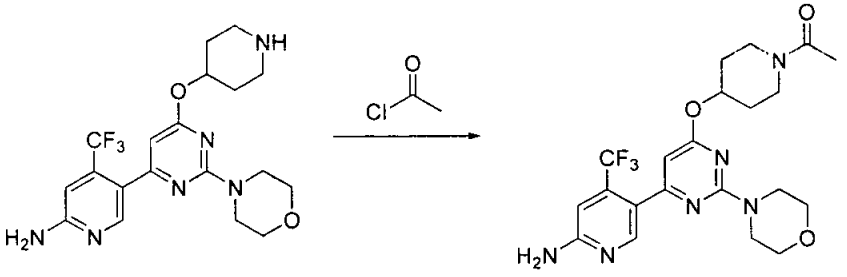
Una mezcla del 4-(6-cloro-2-morfolino-pirimidin-4-iloxi)-piperidin-1-carboxilato de terbutilo (250 miligramos, 0.63 milimoles), 5-(4,4,5,5-tetrametil-1,3,2-dioxoborolan-2-il)-4-(trifluoro-metil)-piridin-2-amina (preparada como en el Método 4, 325 miligramos, 1.13 milimoles), y $Pd(dppf)Cl_2$-CH_2Cl_2 (25.6 miligramos, 0.031 milimoles) en dimetoxi-etano/Na_2CO_3 2 M (3:1, 8 mililitros) se calentó bajo irradiación con microondas durante 15 minutos a 120°C. La mezcla de reacción se dividió entre EtOAc (200 mililitros) y $Na_2CO_{3(sat.)}$ (50 mililitros), la capa orgánica se separó, se lavó con salmuera (50 mililitros), se secó sobre Na_2SO_4, se filtró, se concentró y se purificó mediante cromatografía con SiO_2 (50-75 por ciento de EtOAc/hexanos), para proporcionar el producto como un sólido blanco (207 miligramos, 63 por ciento). LCMS (*m/z*): 525.2 (MH^+).

Paso 3: Hidrólisis del grupo protector de N-Boc



Una mezcla de 4-(6-(6-amino-4-(trifluoro-metil)-piridin-3-il)-2-morfolino-pirimidin-4-iloxi)-piperidin-1-carboxilato de terbutilo (649 miligramos, 1.24 milimoles) y HCl 4 M/dioxano (15 mililitros, 60 milimoles) se dejó reposar a temperatura ambiente durante 14 horas. Después de remover los volátiles al vacío, se agregó dietil-éter (50 mililitros), el material se sonicó y se concentró, proporcionando la sal de bis-HCl del producto deseado como un sólido grisáceo. LCMS (*m/z*): 425.1 (MH^+).

Paso 4: Acilación



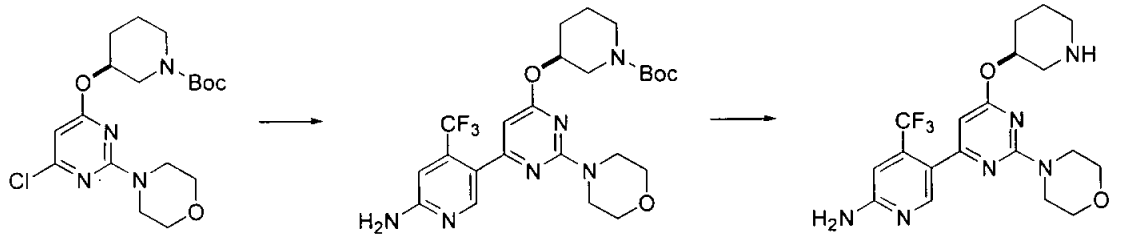
A una solución de 4-(trifluoro-metil)-5-(2-morfolino-6-(piperidin-4-iloxi)-pirimidin-4-il)-piridin-2-amina en NMP, se le agregaron di-isopropil-etil-amina (5 equivalentes) y cloruro de acetilo (1.5 equivalentes). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas, y entonces se purificó directamente

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mediante HPLC de fase inversa, y se liofilizó, proporcionando la sal de ácido trifluoro-acético del producto. De una manera alternativa, después de la HPLC en fase inversa, se pudo aislar la base libre del producto después de la extracción en EtOAc sobre la basificación, seguida por secado sobre Na_2SO_4 y la remoción de los volátiles al vacío. LCMS (m/z): 467.1 (MH^+).

Ejemplo 20

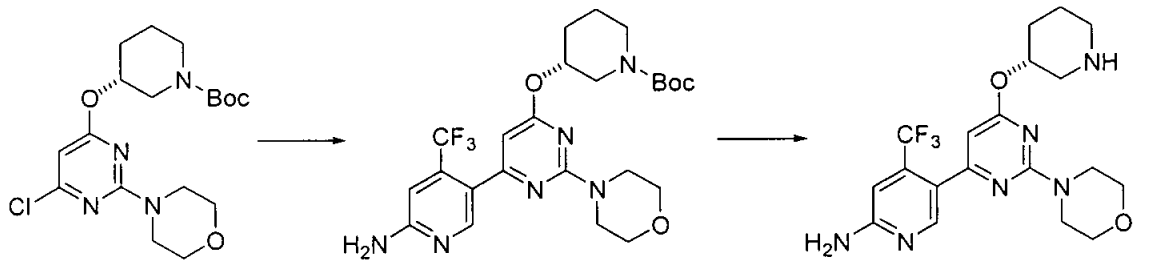
Preparación de 5-(6-((S)-piperidin-3-iloxi)-2-morfolino-pirimidin-4-il)-4-(trifluoro-metil)-piridin-2-amina



El 3-(6-cloro-2-morfolino-pirimidin-4-iloxi)-piperidin-1-carboxilato de (*S*)-terbutilo se preparó como en el Ejemplo 19, Paso 1, para la alcoxilación de la 2-morfolino-4,6-dicloro-pirimidina (87 por ciento). LCMS (*m/z*): 399.1(MH^+). El intermediario protegido por Boc se preparó mediante reacción de Suzuki, como se muestra en el paso 2 del Ejemplo 19, y se purificó mediante cromatografía con SiO_2 (30-60 por ciento EtOAc/hexanos; 78 por ciento). LCMS (*m/z*): 526.0 (MH^+). El compuesto del título se preparó mediante la disociación del grupo protector de N-Boc, como se muestra en el paso 3 del Ejemplo 19. LCMS (*m/z*): 425.1 (MH^+).

Ejemplo 21

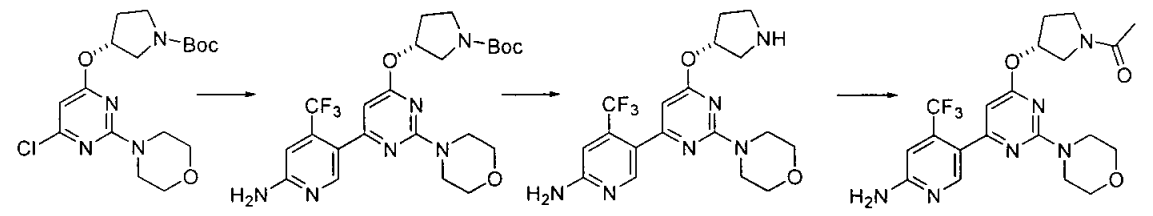
Preparación de 5-(6-((R)-piperidin-3-iloxi)-2-morfolino-pirimidin-4-il)-4-(trifluoro-metil)-piridin-2-amina



El 3-(6-cloro-2-morfolino-pirimidin-4-iloxi)-piperidin-1-carboxilato de (*R*)-terbutilo se preparó como en el Ejemplo 19, Paso 1, para la alcoxilación de la 2-morfolino-4,6-dicloro-pirimidina (82 por ciento). LCMS (*m/z*): 399.1 (MH^+). El intermediario protegido por Boc se preparó mediante reacción de Suzuki como se muestra en el paso 2 del Ejemplo 19, y se purificó mediante cromatografía en gel de sílice (30-60 por ciento de EtOAc/hexanos, 54 por ciento). LCMS (*m/z*): 526.0 (MH^+). El compuesto del título se preparó mediante la disociación del grupo protector de N-Boc como se muestra en el paso 3 del Ejemplo 19. LCMS (*m/z*): 425.1 (MH^+).

Ejemplo 22

Preparación de 1-((R)-3-(6-(6-amino-4-(trifluoro-metil)-piridin-3-il)-2-morfolino-pirimidin-4-iloxi)-pirrolidin-1-il)-etanona



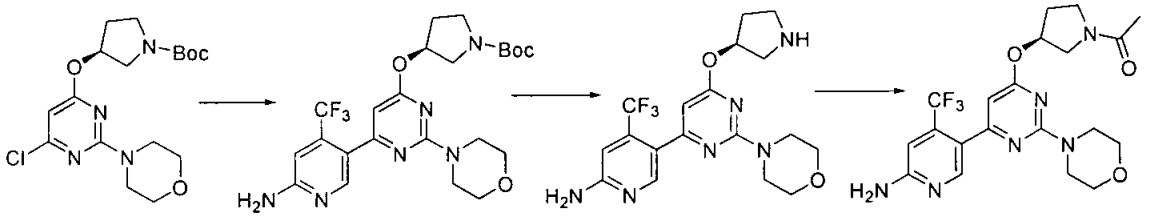
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El 3-(6-cloro-2-morfolino-pirimidin-4-iloxi)-pirrolidin-1-carboxilato de (*R*)-terbutilo se preparó como en el Ejemplo 19, Paso 1, para la alcoxilación de la 2-morfolino-4,6-dicloro-pirimidina (41 por ciento). LCMS (*m/z*): 385.0 (MH^+).

El intermediario protegido por Boc se preparó mediante reacción de Suzuki como se muestra en el paso 2 del Ejemplo 19, y se purificó mediante HPLC en fase inversa, y se aisló como la base libre después de la extracción en EtOAc sobre la basificación (71 por ciento). LCMS (*m/z*): 511.0 (MH^+). La disociación del grupo protector de N-Boc se llevó a cabo como se muestra en el paso 3 del Ejemplo 19. LCMS (*m/z*): 411.0 (MH^+). El compuesto del título se preparó como en el paso 4 del Ejemplo 19. LCMS (*m/z*): 453.1 (MH^+), R_t 2.18.

Ejemplo 23

Preparación de 1-((S)-3-(6-(6-amino-4-(trifluoro-metil)-piridin-3-il)-2-morfolino-pirimidin-4-iloxi)-pirrolidin-1-il)-etanona

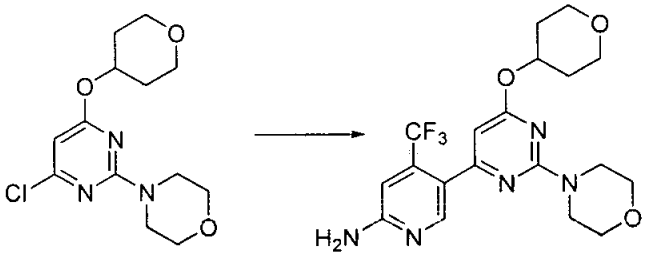


El 3-(6-cloro-2-morfolino-pirimidin-4-iloxi)-pirrolidin-1-carboxilato de (*S*)-terbutilo se preparó de acuerdo con Ejemplo 19, Paso 1, para la alcoxilación de la 2-morfolino-4,6-dicloro-pirimidina

(99 por ciento). LCMS (*m/z*): 385.0 (MH^+). El intermediario protegido por Boc se preparó mediante reacción de Suzuki como se muestra en el paso 2 del Ejemplo 19, s purificó mediante HPLC en fase inversa, y se aisló como la base libre después de la extracción en EtOAc sobre la basificación (72 por ciento). LCMS (*m/z*): 511.0 (MH^+). El grupo protector de N-Boc se disoció como se muestra en el paso 3 del Ejemplo 19. LCMS (*m/z*): 411.0 (MH^+). El compuesto del título se preparó como en el paso 4 del Ejemplo 19. LCMS (*m/z*): 453.1 (MH^+), R_t 2.18.

Ejemplo 24

Preparación de 4-(trifluoro-metil)-5-(2-morfolino-6-(tetrahidro-2H-piran-4-iloxi)-pirimidin-4-il)-piridin-2-amina

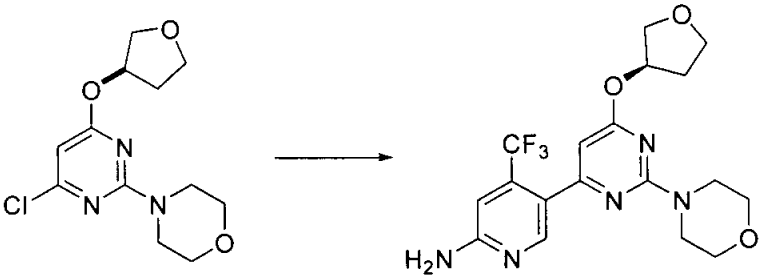


La 4-(4-cloro-6-(tetrahidro-2H-piran-4-iloxi)-pirimidin-2-il)-morfolina se preparó de acuerdo con Ejemplo 19, Paso 1, para la alcoxilación de la 2-morfolino-4,6-dicloro-pirimidina con 4-hidroxi-tetrahidro-pirano (80 por ciento). LCMS (*m/z*): 300.1 (MH^+). El compuesto del título se preparó mediante reacción de Suzuki como se muestra en el paso 2 del Ejemplo 19. LC/MS (*m/z*): 426.1 (MH+), R_t 2.26 minutos.

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Ejemplo 25

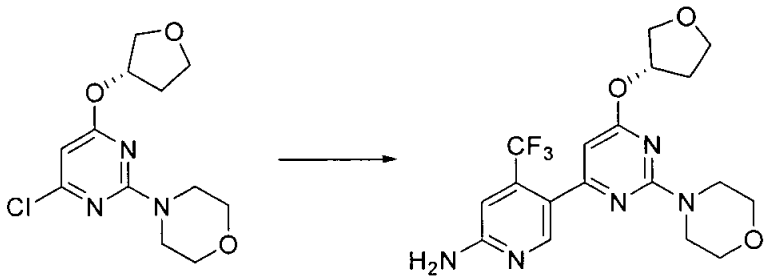
Preparación de 5-(6-((R)-tetrahidro-furan-3-iloxi)-2-morfolino-pirimidin-4-il)-4-(trifluoro-metil)-piridin-2-amina



La (R)-4-(4-cloro-6-(tetrahidro-furan-3-iloxi)-pirimidin-2-il)-morfolina se preparó de acuerdo con Ejemplo 19, Paso 1, para la alcoxilación de la 2-morfolino-4,6-dicloro-pirimidina con (R)-3-hidroxi-tetrahidrofurano (81 por ciento). LCMS (*m/z*): 286.1 (MH^+). El compuesto del título se preparó mediante reacción de Suzuki como se muestra en el paso 2 del Ejemplo 19. LC/MS (*m/z*): 412.1 (MH^+).

Ejemplo 26

Preparación de 5-(6-((S)-tetrahidro-furan-3-iloxi)-2-morfolino-pirimidin-4-il)-4-(trifluoro-metil)-piridin-2-amina

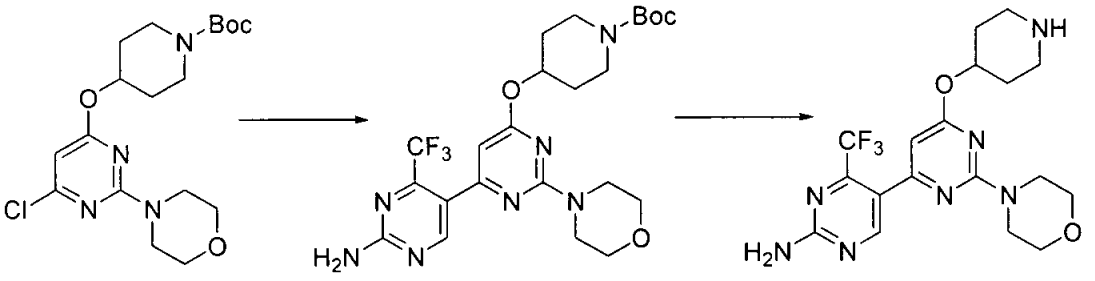


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La (S)-4-(4-cloro-6-(tetrahidro-furan-3-iloxi)-pirimidin-2-il)-morfolina se preparó de acuerdo con Ejemplo 19, Paso 1, para la alcoxilación de la 2-morfolino-4,6-dicloro-pirimidina con (S)-3-hidroxi-tetrahidrofurano (85 por ciento). LCMS (*m/z*): 286.1 (MH^+). El compuesto del título se preparó mediante reacción de Suzuki como se muestra en el paso 2 del Ejemplo 19. LC/MS (*m/z*): 412.1 (MH^+).

Ejemplo 27

Preparación de 4-(trifluoro-metil)-5-(2-morfolino-6-(piperidin-4-iloxi)-pirimidin-4-il)-pirimidin-2-amina



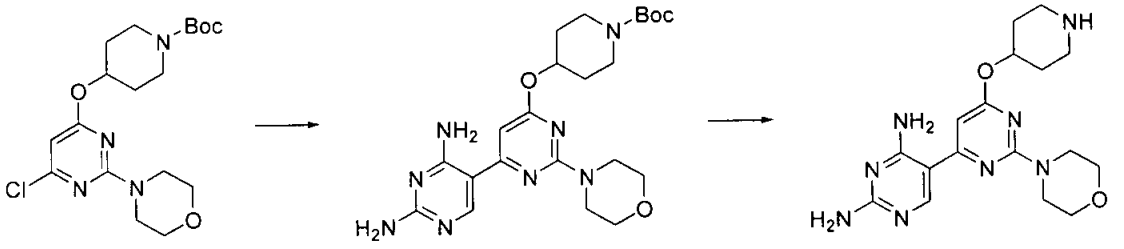
El 4-(6-(2-amino-4-(trifluoro-metil)-pirimidin-5-il)-2-morfolino-pirimidin-4-iloxi)-piperidin-1-carboxilato de terbutilo se preparó mediante la reacción de Suzuki del 4-(6-cloro-2-morfolino-pirimidin-4-iloxi)-piperidin-1-carboxilato de terbutilo, como se muestra en el paso 2 del Ejemplo 19, con 5-(4,4,5,5-tetrametil-(1,3,2-dioxaborolan-2-il))-4-(trifluoro-metil)-pirimidin-2-il-amina (preparada como en el Método 5). El producto crudo se purificó mediante cromatografía en gel de sílice (30-50 por ciento EtOAc/hexanos) (63 por ciento). LCMS (*m/z*): 526.0 (MH^+). El compuesto del título se preparó mediante la

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disociación del grupo protector de N-Boc como se muestra en el paso 3 del Ejemplo 19. LCMS (*m/z*): 426.0 (MH^+).

Ejemplo 28

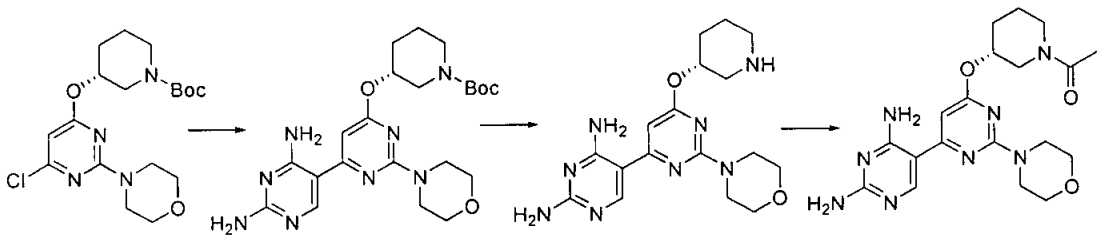
Preparación de 5-(2-morfolino-6-(piperidin-4-iloxi)-pirimidin-4-il)-pirimidin-2,4-diamina



El 4-(6-(2,4-diamino-pirimidin-5-il)-2-morfolino-pirimidin-4-iloxi)-piperidin-1-carboxilato de terbutilo se preparó mediante la reacción de Suzuki del 4-(6-cloro-2-morfolino-pirimidin-4-iloxi)-piperidin-1-carboxilato de terbutilo, como se muestra en el paso 2 del Ejemplo 19, con la 5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-pirimidin-2,4-diamina (preparada como en el Método 7). El producto crudo se purificó mediante HPLC en fase inversa, y s aisló como la base libre después de la extracción en EtOAc, sobre la basificación (70 por ciento). LCMS (*m/z*): 473.1 (MH^+). El compuesto del título se preparó mediante la disociación del grupo protector de N-Boc como se muestra en el paso 3 del Ejemplo 19. LCMS (*m/z*): 373.0 (MH^+).

Ejemplo 29

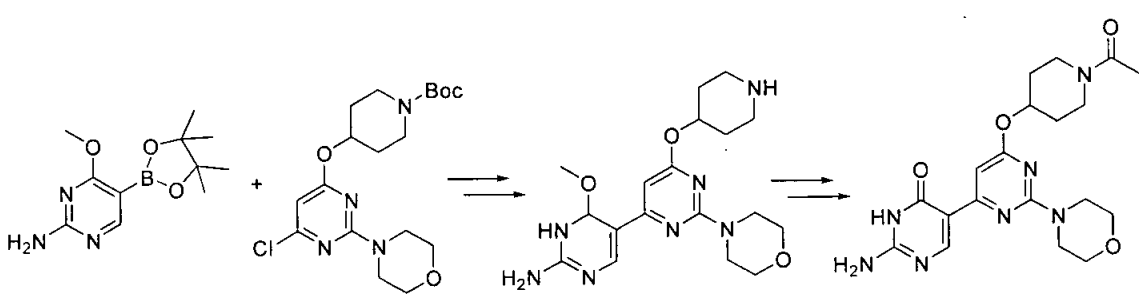
Preparación de 1-((R)-3-(6-(2,4-diamino-pirimidin-5-il)-2-morfolino-pirimidin-4-iloxi)-piperidin-1-il)-etanona



El 3-(6-(2,4-diamino-pirimidin-5-il)-2-morfolino-pirimidin-4-iloxi)-piperidin-1-carboxilato de (R)-terbutilo se preparó mediante la reacción de Suzuki del 4-(6-cloro-2-morfolino-pirimidin-4-iloxi)-piperidin-1-carboxilato, como se muestra en el paso 2 del Ejemplo 19, con la 5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-pirimidin-2,4-diamina. El producto crudo se purificó mediante HPLC en fase inversa y s aisló como la base libre después de la extracción en EtOAc, sobre la basificación (77 por ciento). LCMS (*m/z*): 473.1 (MH^+). El grupo protector de N-Boc se disoció como se muestra en el paso 3 del Ejemplo 19. LCMS (*m/z*): 373.0 (MH^+). El compuesto del título se sintetizó como se muestra en el paso 4 del Ejemplo 19. LCMS (*m/z*): 460.1 (MH^+), R_t 2.51.

Ejemplo 30

Preparación de 2-amino-5-(2-morfolino-6-(N-acil-piperidin-4-iloxi)-pirimidin-4-il)-pirimidin-4(3H)-ona



Una mezcla de 4-(6-cloro-2-morfolino-pirimidin-4-iloxi)-

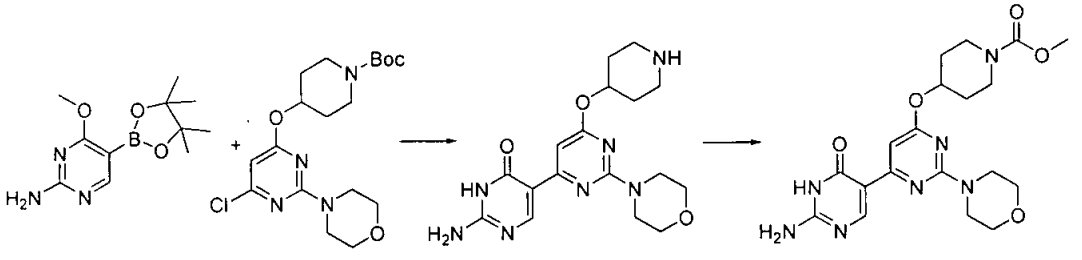
piperidin-1-carboxilato de terbutilo (500 miligramos, 1.26 milimoles), 4-metoxi-2-amino-pirimidil-éster de boronato (preparado como en el Método 8, 630 miligramos, 2.51 milimoles), y $Pd(dppf)Cl_2$-CH_2Cl_2 (51 miligramos, 0.063 milimoles) en dimetoxi-etano y Na_2CO_3 2 M (3:1, 12 mililitros) se calentó bajo irradiación con microondas durante 15 minutos a 120°C. La mezcla de reacción se dividió entre EtOAc (200 mililitros) y $Na_2CO_{3(sat.)}$ (50 mililitros), la capa orgánica se separó y se lavó con salmuera (50 mililitros). Las capas acuosas combinadas se extrajeron además con EtOAc (100 mililitros, 2 veces), y las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron, y se concentraron. A este material se le agregó HCl 4M/dioxano (20 mililitros) para remover el grupo Boc. Después de reposar durante 12 horas, los volátiles se removieron al vacío, y el residuo se dividió entre CH_2Cl_2 (200 mililitros) y NaOH 1N (50 mililitros). Después de la separación, la capa acuosa se extrajo adicionalmente con CH_2Cl_2 (200 mililitros), y luego con $CHCl_3$ (150 mililitros, 2 veces). Las capas orgánicas combinadas se concentraron, proporcionando la 1,6-dihidro-6-metoxi-5-(2-morfolino-6-(piperidin-4-iloxi)-pirimidin-4-il)-pirimidin-2-amina (464 miligramos). El compuesto crudo y morfolina (0.9 mililitros, 10.45 milimoles) en NMP (10 mililitros) se calentaron bajo irradiación con microondas durante 15 minutos a 200°C para convertir la metoxi-pirimidina hasta la pirimidona. Se agregó morfolina adicional (0.9 mililitros, 10.45 milimoles), y la solución se calentó bajo irradiación con microondas durante 15 minutos, y luego 10 minutos a 200°C. Después de

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enfriarse, el material se purificó directamente mediante HPLC en fase inversa. Después de la liofilización, se aisló la sal de ácido bis-trifluoro-acético de la 2-amino-5-(2-morfolino-6-(piperidin-4-iloxi)-pirimidin-4-il)-pirimidin-4(3H)-ona como un sólido grisáceo (325 miligramos, 45 por ciento). LCMS (*m/z*): 374.1 (MH^+). El compuesto del título se preparó mediante la acilación del grupo amino secundario, como se muestra en el Ejemplo 19, paso 4. LCMS (*m/z*): 416.0 (MH^+), R_t 1.67.

Ejemplo 31

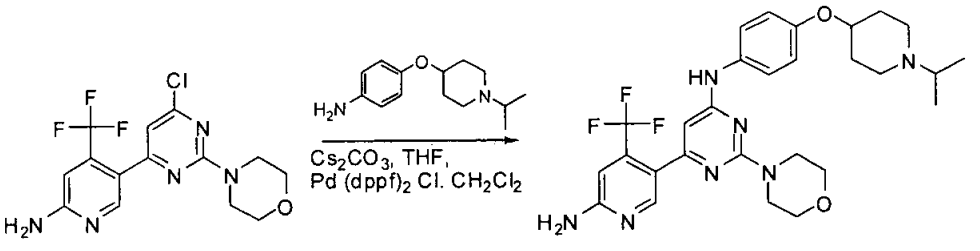
Preparación de 2-amino-5-(2-morfolino-6-(N-metoxi-carbonil-piperidin-4-iloxi)-pirimidin-4-il)-pirimidin-4(3H)-ona



El compuesto del título se preparó como en el Ejemplo 30, excepto que se utilizó cloroformato de metilo en lugar de cloruro de acetilo en el último paso. LCMS (*m/z*): 432.0 (MH^+), R_t 2.05.

Ejemplo 32

Preparación de 6-[6-amino-4-(trifluoro-metil)-piridin-3-il]-N-[4-(1-isopropil-piperidin-4-iloxi)-fenil]-2-morfolino-pirimidin-4-amina

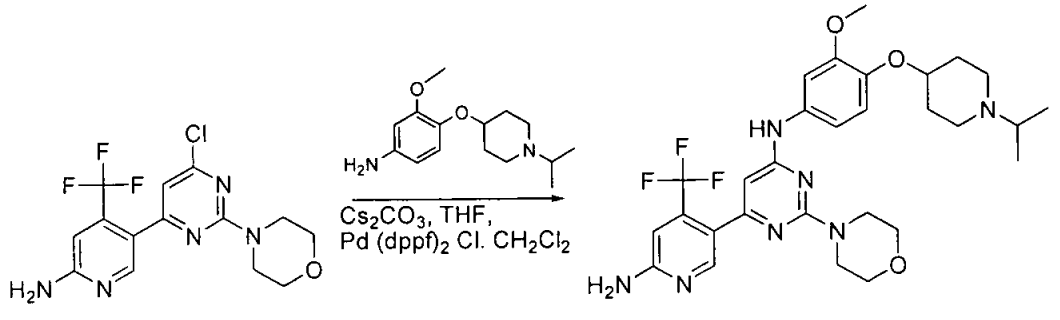


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En un recipiente de presión de vidrio, se mezclaron $Pd(OAc)_2$ (5.0 miligramos, 0.022 milimoles), BINAP (17.0 miligramos, 0.028 milimoles), carbonato de cesio (72.0 miligramos, 0.22 milimoles), y tetrahidrofurano (2.0 mililitros), y se agitaron a temperatura ambiente durante 1 a 3 minutos. A la mezcla resultante se le agregó 5-(6-cloro-2-morfolin-4-il-pirimidin-4-il)-piridin-2-il-amina (40.0 miligramos, 0.11 milimoles), seguida por 4-(1-isopropil-piperidin-4-iloxi)-anilina (37.0 miligramos, 0.16 milimoles). El recipiente de presión de vidrio se selló, se agitó, y se calentó en el reactor de microondas bajo irradiación a 110°C durante 10 minutos. La mezcla de reacción se filtró y se concentró bajo presión reducida. El producto se purificó mediante HPLC de preparación en fase inversa para dar la 6-[6-amino-4-(trifluoro-metil)-piridin-3-il]-N-[4-(1-isopropil-piperidin-4-iloxi)-fenil]-2-morfolino-pirimidin-4-amina (3.0 miligramos, 5 por ciento). LC/MS (*m/z*): 558.3(MH^+), R_t 1.90 minutos.

Ejemplo 33

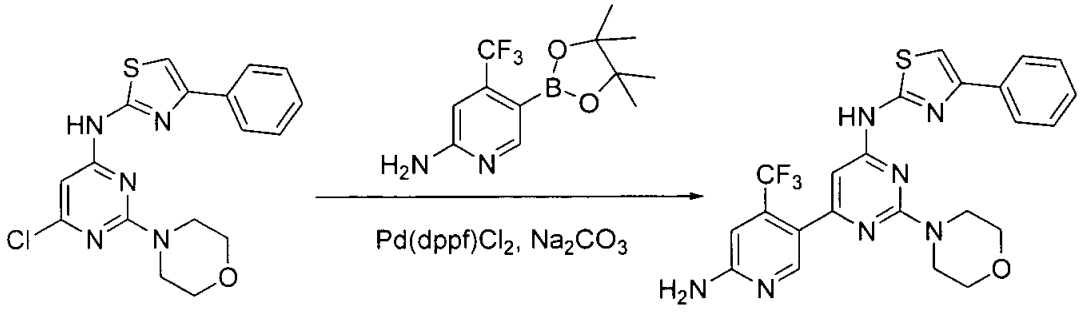
Preparación de 6-(6-amino-4-(trifluoro-metil)-piridin-3-il)-N-(4-(1-isopropil-piperidin-4-iloxi)-3-metoxi-fenil)-2-morfolino-pirimidin-4-amina



En un recipiente de presión de vidrio, se mezclaron $Pd(OAc)_2$ (5.0 miligramos, 0.02 milimoles), BINAP (17.0 miligramos, 0.028 milimoles), carbonato de cesio (72.0 miligramos, 0.22 milimoles), y tetrahidrofurano (2.0 mililitros), y se agitaron a temperatura ambiente durante 1 a 3 minutos. A la mezcla resultante se le agregó 5-(6-cloro-2-morfolin-4-il-pirimidin-4-il)-piridin-2-il-amina (40.0 miligramos, 0.11 milimoles), seguida por 4-(1-isopropil-piperidin-4-iloxi)-3-metoxi-anilina (46.6 miligramos, 0.16 milimoles). El recipiente de presión de vidrio se selló, se agitó, y se calentó en un reactor de microondas bajo irradiación a 120°C durante 10 minutos. La mezcla de reacción se filtró y se concentró bajo presión reducida. El residuo se purificó mediante HPLC de preparación en fase inversa para dar la 6-(6-amino-4-(trifluoro-metil)-piridin-3-il)-N-(4-(1-isopropil-piperidin-4-iloxi)-3-metoxi-fenil)-2-morfolino-pirimidin-4-amina (6.6 miligramos, 10 por ciento). LC/MS (*m/z*): 588.3(MH^+), R_t 1.92 minutos.

Ejemplo 34

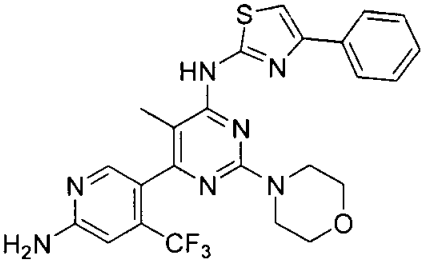
Síntesis de la N-(6-(6-amino-4-(trifluoro-metil)-piridin-3-il)-2-morfolino-pirimidin-4-il)-4-fenil-tiazol-2-amina



Una solución de *N*-(6-cloro-2-morfolino-pirimidin-4-il)-4-fenil-tiazol-2-amina (15 miligramos, 0.040 milimoles), 5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-4-(trifluoro-metil)-piridin-2-amina (23 miligramos, 0.080 milimoles) y cloruro de 1,1'-bis-(difenil-fosfino)-ferroceno-paladio(II) (6.6 miligramos, 0.0080 milimoles) en 0.5 mililitros de 1,4-dioxano y 0.05 mililitros de carbonato de sodio acuoso 2 M, se calentó en el reactor de microondas a 120°C durante 600 segundos. El producto crudo se purificó mediante HPLC de preparación en fase inversa, para dar la N-(6-(6-amino-4-(trifluoro-metil)-piridin-3-il)-2-morfolino-pirimidin-4-il)-4-fenil-tiazol-2-amina. LC/MS (*m/z*): 500 (MH^+), R_t 2.46 minutos.

Ejemplo 35

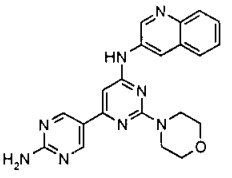
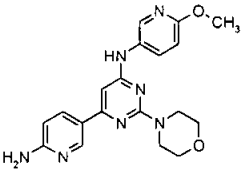
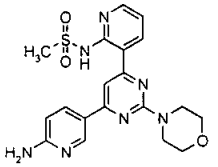
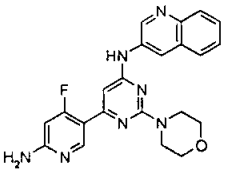
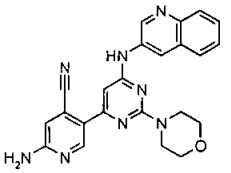
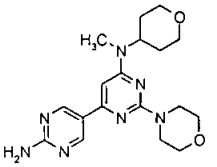
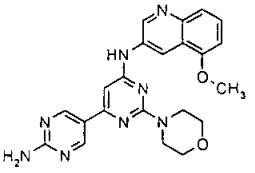
Preparación de N-(6-(6-amino-4-(trifluoro-metil)-piridin-3-il)-5-metil-2-morfolino-pirimidin-4-il)-4-fenil-tiazol-2-amina



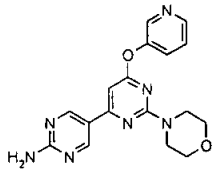
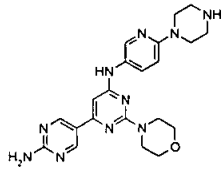
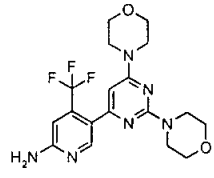
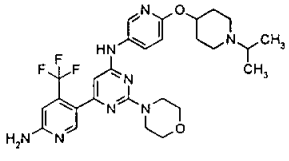
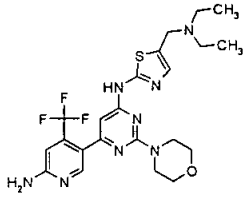
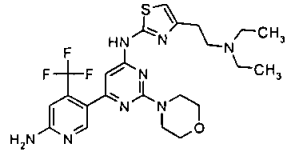
La N-(6-(6-amino-4-(trifluoro-metil)-piridin-3-il)-5-metil-2-morfolino-pirimidin-4-il)-4-fenil-tiazol-2-amina se preparó de acuerdo con Ejemplo 35. LC/MS (*m/z*): 514 (MH^+), R_t 2.62 minutos.

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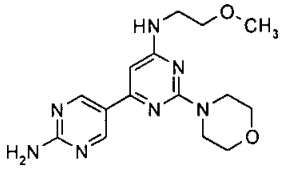
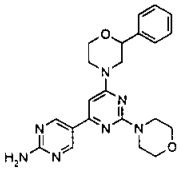
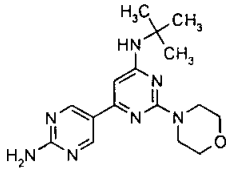
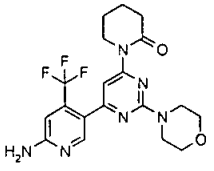
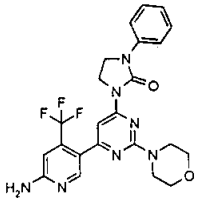
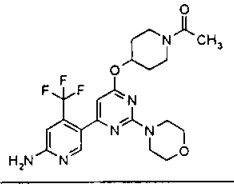
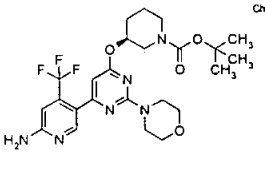
TABLA 1

Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
1		401.4, 2.00		++++	++++	++++
2		380.1, 1.82	9.67 L	++++	N/D	N/D
3		428.2, 2.09	11.50 L	++++	++++	++++
4		418.0	1.99	++++	++++	++++
5		425.0	11.16 L	++++	+++	++++
6		372.2	8.74 L	++++	N/D	+++
7		431.2, 2.03	11.11 L	++++	++++	++++

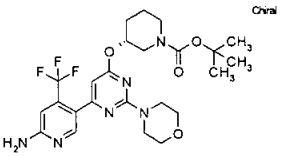
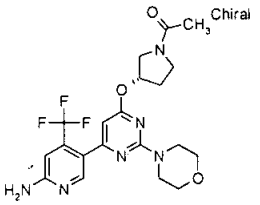
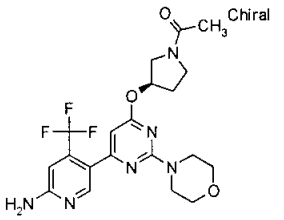
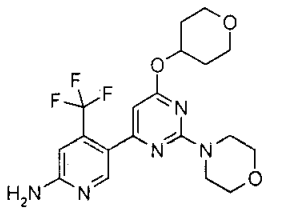
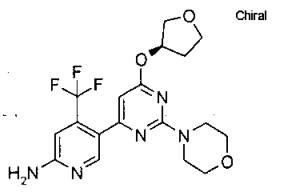
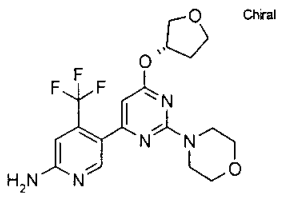
492

Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
8		352.1, 1.83	7.96 L	++++	++++	++++
9		435.2, 1.52	6.45 L	++++	++++	++++
10		411.3, 1.88		++++	++++	++++
11		559.2, 1.92		++++	++++	++++
12		509.0, 1.72	1.98	++++	++++	+++
13		523.1, 2.02	2.11	++++	++++	+++

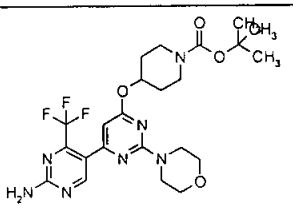
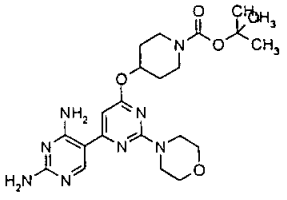
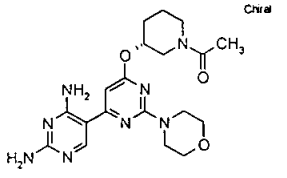
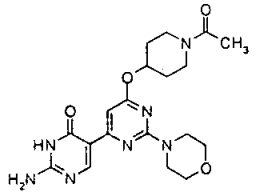
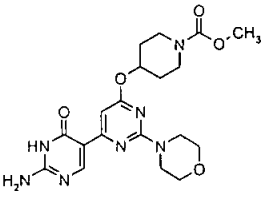
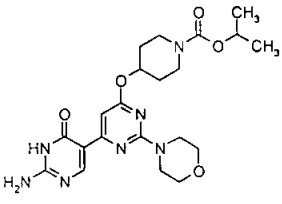
403

Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
14		332.2	7.50 L	++++	N/D	+++
15		420.1	13.14 L	++++	++++	++++
16		330.2	10.83 L	++++	N/D	+++
17		423.1	2.57	++++	N/D	+++
18		486	3.23	++++	N/D	+++
19		467.1, 2.36		++++	N/D	+++
20		525.0, 3.42		++++	N/D	+++

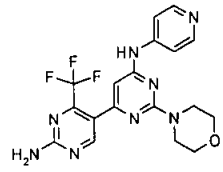
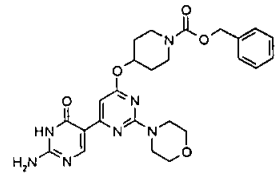
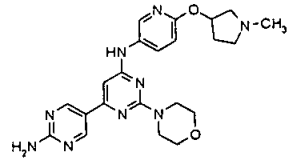
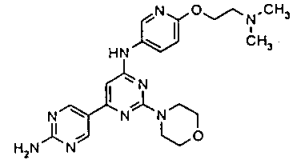
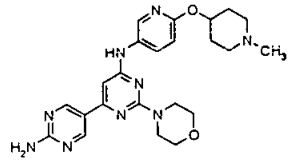
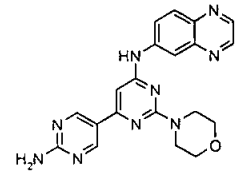
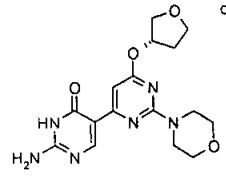
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
21		525.0, 3.42		++++	N/D	N/D
22		453.1, 2.18		++++	N/D	+++
23		453.1, 2.18		++++	N/D	N/D
24		426.1, 2.26	2.54	++++	++++	++++
25		412.1, 2.47		++++	++++	+++
26		412.1, 2.19	2.47, (12.34)	++++	N/D	+++

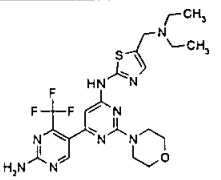
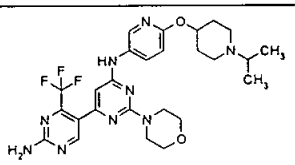
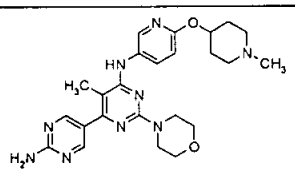
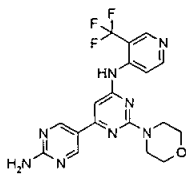
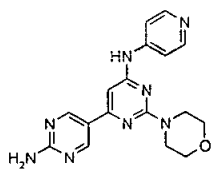
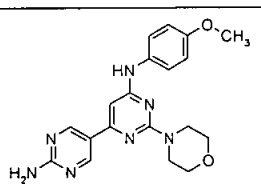
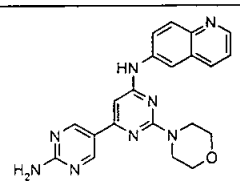
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
27		526.0, 4.30		++++	++++	++++
28		473.1, 3.02		++++	++++	++++
29		415.1, 2.06		++++	++++	+++
30		416.0, 1.67		++++	++++	++++
31		432.0, 2.05		++++	++++	++++.
32		460.1, 2.51		++++	++++	++++

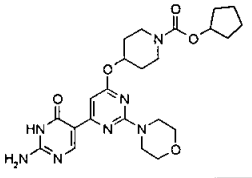
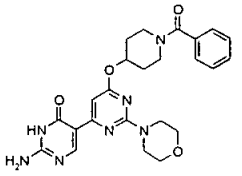
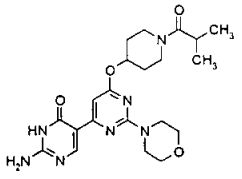
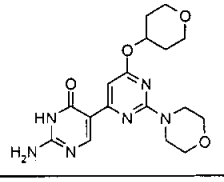
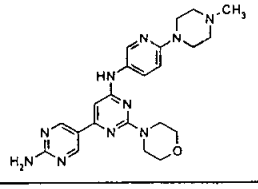
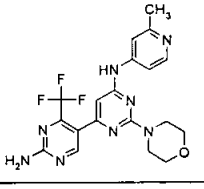
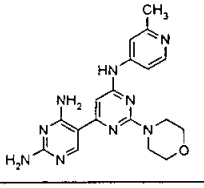
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
33		419.0, 2.17		++++	++++	++++
34		508.0, 2.17	2.96, (14.82)	++++	++++	++++
35		450.2, 1.61		++++	++++	++++
36		438.1, 1.61		++++	++++	++++
37		464.4, 1.53		++++	++++	++++
38		402.2, 1.88 min		++++	++++	++++
39		361.0, 1.44	1.73, (8.13)	++++	++++	++++

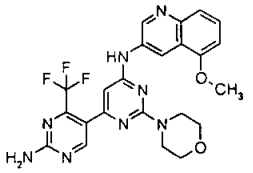
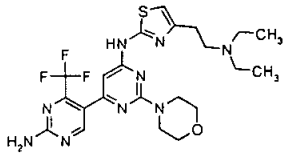
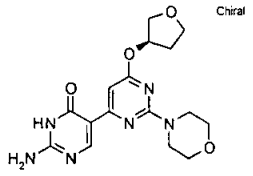
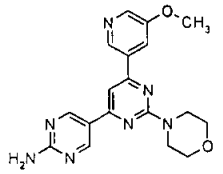
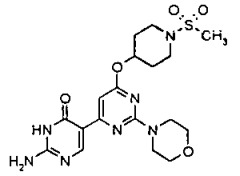
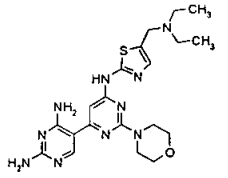
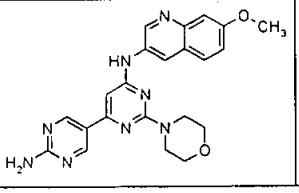
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
40		510.1, 1.98	2.18	++++	++++	++++
41		560.2, 1.93	1.98	++++	++++	++++
42		478.4, 1.59		++++	++++	++++
43		419.1	9.23 L	++++	++++	++++
44		351.1	8.23 L	++++	++++	++++
45		375.0, 2.11	2.41	++++	++++	+++
46		401.1, 1.70	1.70	++++	++++	++++

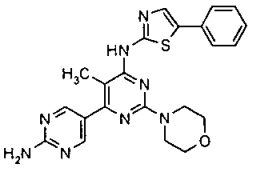
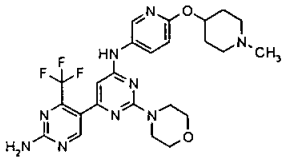
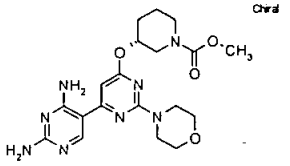
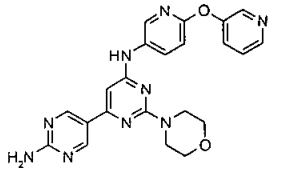
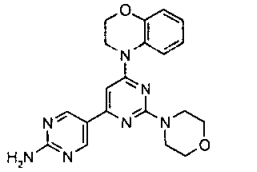
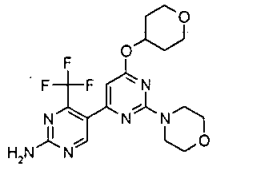
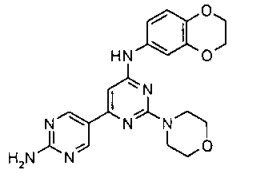
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
47		486.1, 2.11	2.76, (14.49)	++++	++++	++++
48		478.0, 1.79	2.23, (11.48)	++++	++++	++++
49		444.1, 1.70	2.06, (10.23)	++++	++++	++++
50		375.1, 1.80	1.82, (8.95)	++++	++++	++++
51		449.1, 1.51	6.56 L	++++	++++	++++
52		433.0, 2.30		++++	++++	++++
53		380.1, 1.65		++++	++++	++++

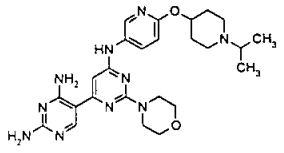
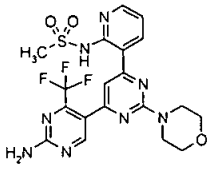
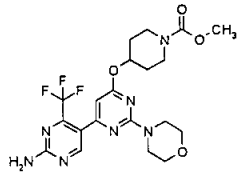
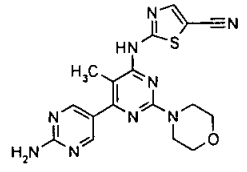
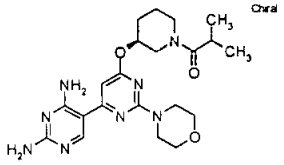
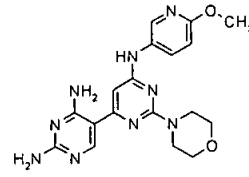
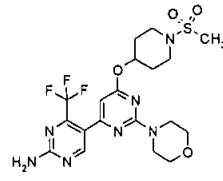
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
54		498.9, 2.55		++++	++++	++++
55		524.1, 2.10	2.37	++++	++++	++++
56		361.0, 1.45	1.64, (8.18)	++++	++++	++++
57		366.1, 1.85	1.95	++++	++++	++++
58		452.0, 1.65		++++	++++	++++
59		457.2,1.72	1.71	++++	++++	++++
60		431.2, 1.95	10.48 L	++++	++++	++++

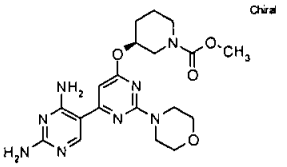
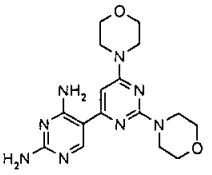
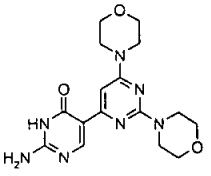
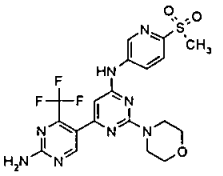
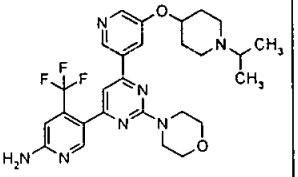
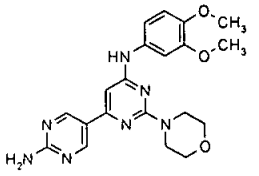
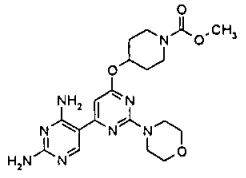
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
61		447.4, 2.85		++++	++++	++++
62		532.0, 1.85		++++	++++	++++
63		431.2, 2.43		++++	++++	++++
64		444.4, 1.66		++++	++++	++++
65		392.3, 2.55		++++	++++	++++
66		427.1, 3.21		++++	++++	+++
67		408.1, 1.98	2.16	++++	++++	++++

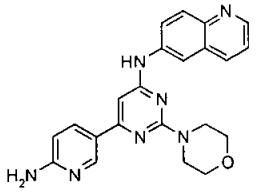
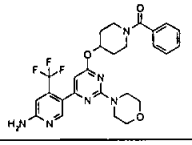
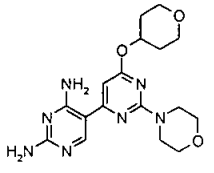
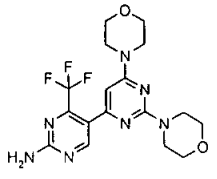
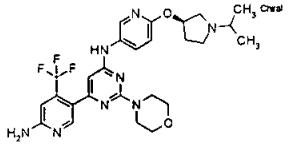
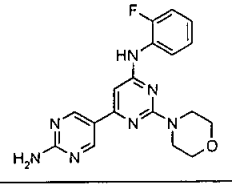
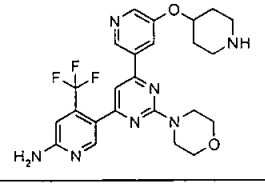
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
68		507.2, 1.79	1.78	++++	++++	++++
69		496.9, 2.40	3.39, (16.57)	++++	++++	++++
70		484.0, 3.36		++++	++++	++++
71		396.3, 2.32		++++	++++	++++
72		443.2, 2.45		++++	++++	+++
73		396.1, 1.58	1.89, (9.53)	++++	++++	+++
74		504.0, 3.19		++++	++++	++++

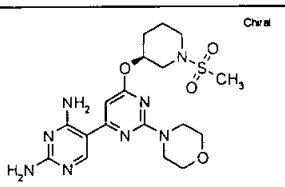
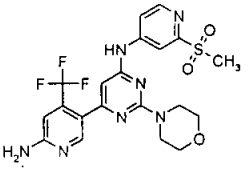
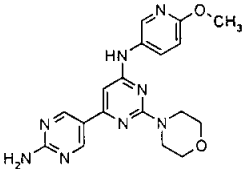
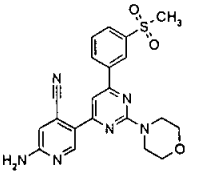
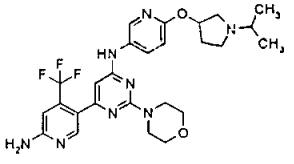
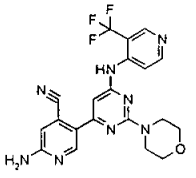
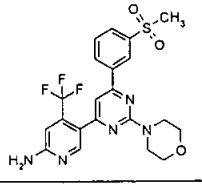
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
75		431.2, 2.38		++++	++++	+++
76		359.1, 1.42		++++	++++	+++
77		360.0, 1.47	1.79, (8.61)	++++	++++	++++
78		496.9, 2.42		++++	++++	++++
79		544.2, 1.97	2.04	++++	++++	+++
80		410.1, 1.91	10.36 L	++++	++++	++++
81		431.0, 2.45		++++	++++	++++

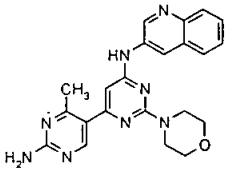
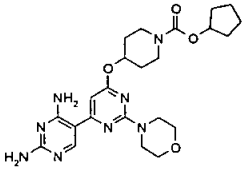
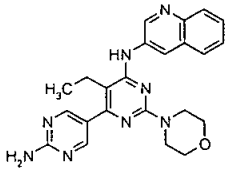
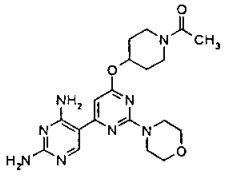
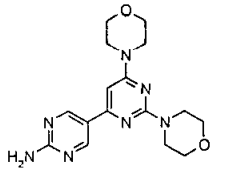
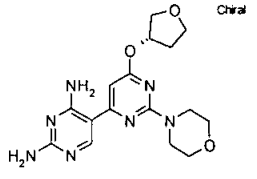
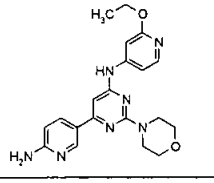
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
82		400.0, 1.74	1.76	++++	++++	++++
83		529.2, 2.98		++++	++++	+++
84		374.1, 2.13		++++	++++	++++
85		412.0, 2.03		++++	++++	++++
86		545.6, 1.78		++++	++++	++++
87		368.1, 2.05	2.26	++++	++++	+++
88		502.1, 1.89	1.95	++++	++++	+++

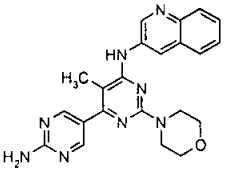
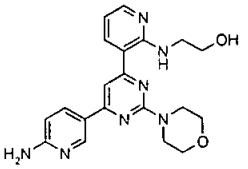
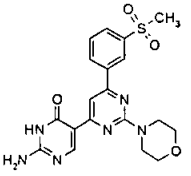
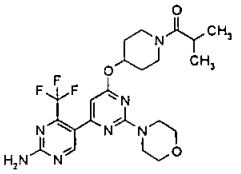
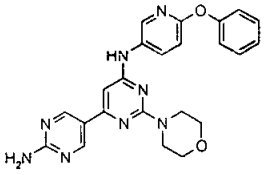
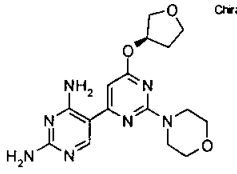
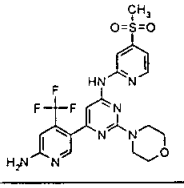
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
89		451.1, 2.30		++++	++++	++++
90		496	2.29	++++	++++	++++
91		381.4, 1.95		++++	++++	++++
92		437.1, 2.33	2.8	++++	++++	+++
93		545.6, 1.78		++++	++++	+++
94		443.1	2.07	++++	++++	++++
95		480.4, 2.13	2.85, (14.41)	++++	++++	+++

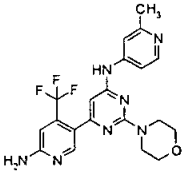
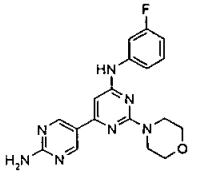
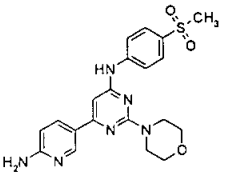
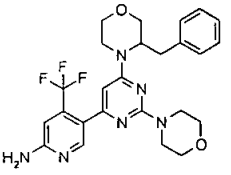
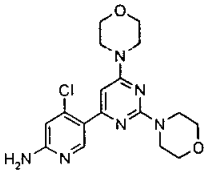
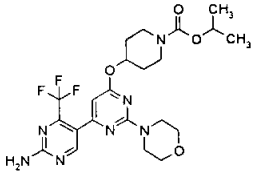
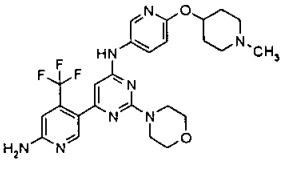
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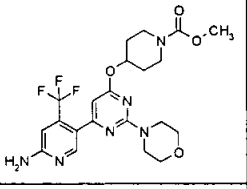
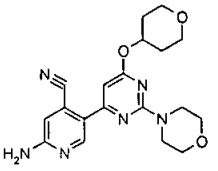
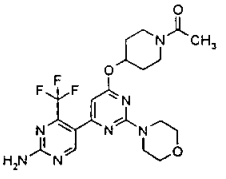
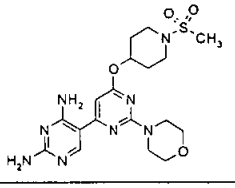
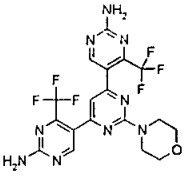
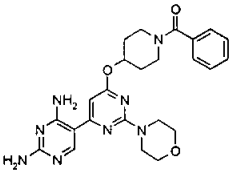
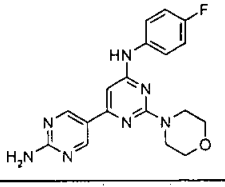
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
96		415.3, 1.90		++++	++++	++++
97		485.1, 3.04		++++	++++	+++
98		429.2	8.99 L	++++	++++	++++
99		415.1, 1.97		++++	++++	+++
100		344.1	7.58 L	++++	++++	++++
101		360.1, 2.05		++++	++++	+++
102		394.2, 1.85	1.92	++++	++++	++++

506

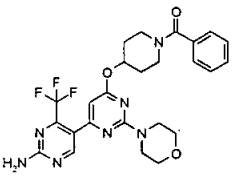
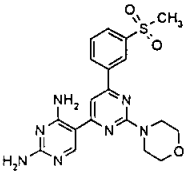
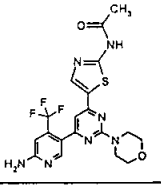
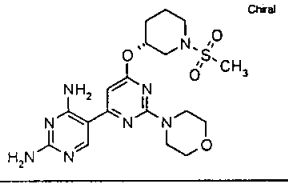
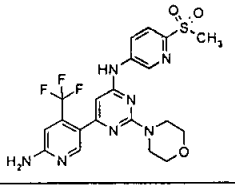
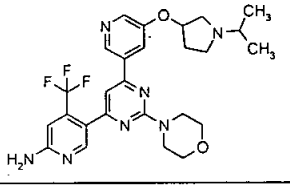
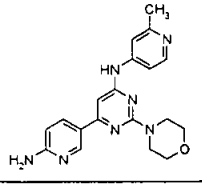
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
103		415.3, 1.68		++++	++++	++++
104		394.4, 1.62		++++	++++	+++
105		428.9, 1.72	2.25, (10.78)	++++	++++	++++
106		496.0, 3.28		++++	++++	++++
107		443.4, 2.70		++++	++++	+++
108		360.1, 2.05		++++	++++	++++
109		496.0, 2.07	2.39	++++	++++	+++

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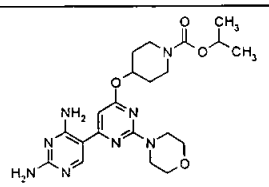
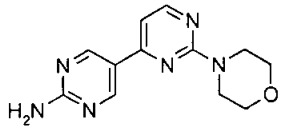
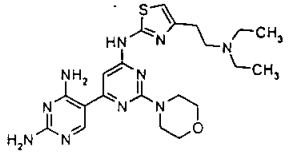
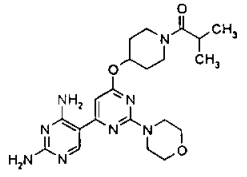
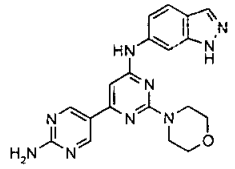
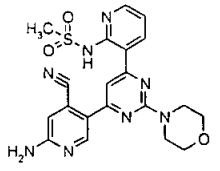
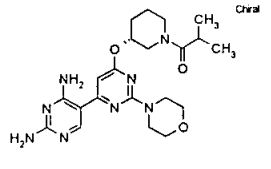
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
110		432.1	1.97	++++	++++	++++
111		368.0; 2.15	2.48	++++	++++	+++
112		427.1	2.08	++++	++++	+++
113		501.1, 2.34	14.12 L	++++	++++	+++
114		377.0, 1.54		++++	++++	+++
115		512.0, 3.96		++++	++++	+++
116		531.5, 1.77		++++	++++	+++

Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
117		483.1, 2.37	2.82, (14.09)	++++	++++	+++
118		383.0, 2.76	2.53	++++	++++	++++
119		468.0, 2.70		++++	++++	++++
120		451.0, 2.28		++++	++++	+++
121		487.9	3.45	++++	++++	++++
122		477.1, 2.60		++++	++++	++++
123		368.1, 2.09	2.34	++++	++++	+++

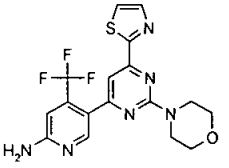
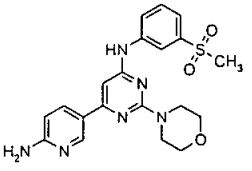
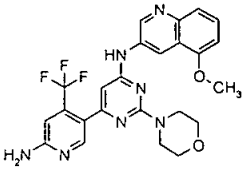
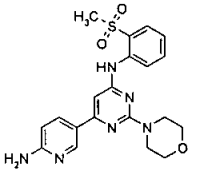
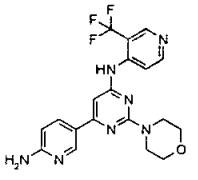
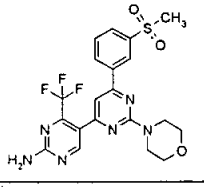
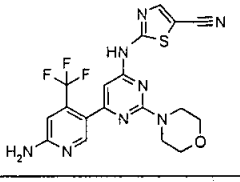
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
124		530.0, 3.53		++++	++++	++++
125		428.0, 2.38		++++	++++	++++
126		466.1, 2.25	2.62	++++	++++	+++
127		451.1, 2.25		++++	++++	+++
128		496.1	2.26	++++	++++	+++
129		530.1, 1.93	1.99	++++	++++	+++
130		364.1, 1.69	1.76	++++	++++	++++

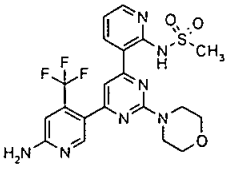
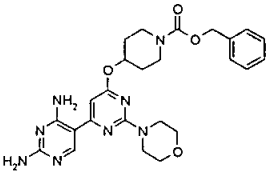
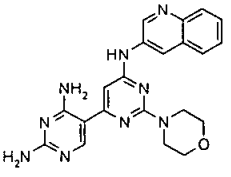
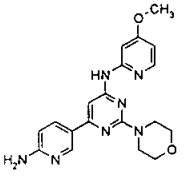
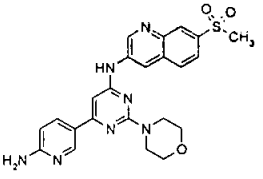
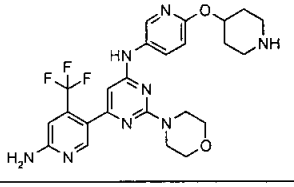
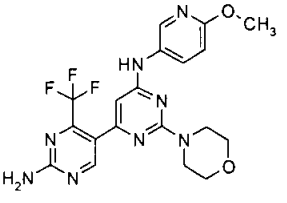
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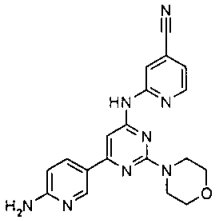
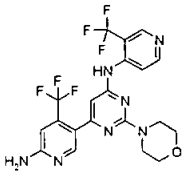
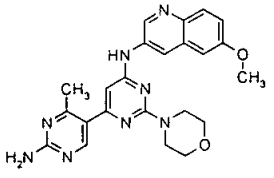
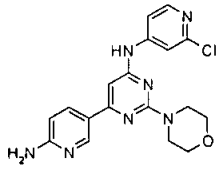
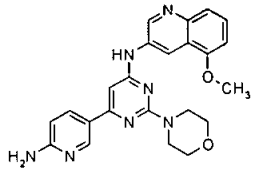
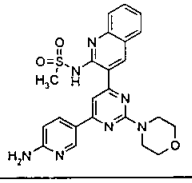
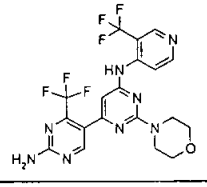
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
131		459.1, 2.82		++++	++++	++++
132		259.2, 1.27	1.34, (6.23)	++++	++++	+++
133		471.2, 1.79	1.88	++++	++++	++++
134		443.2, 2.37		++++	++++	++++
135		390.1, 1.85	9.52 L	++++	++++	++++
136		453.0, 2.29	2.76	++++	++++	++++
137		443.2, 2.38		++++	++++	+++

511

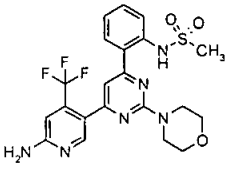
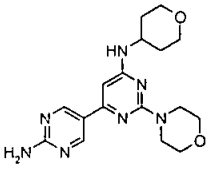
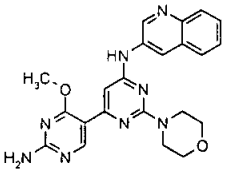
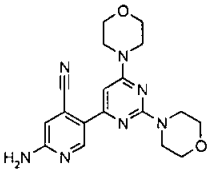
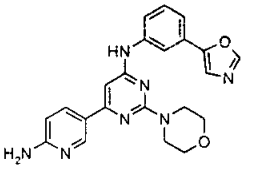
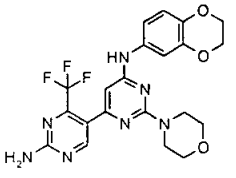
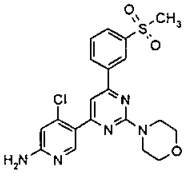
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
138		409.0, 2.95		++++	++++	+++
139		427.1	2.03	++++	++++	+++
140		498.5, 2.36		++++	++++	+++
141		427	2.38	++++	++++	+++
142		418.1, 1.78	8.81 L	++++	++++	++++
143		480.9, 2.46	3.50, (17.16)	++++	++++	++++
144		448.9, 2.76		++++	++++	+++

512

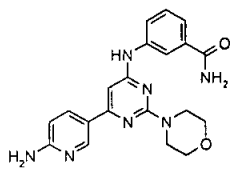
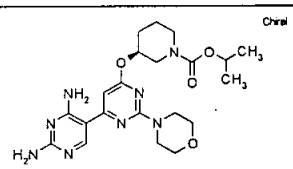
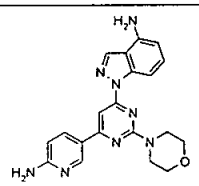
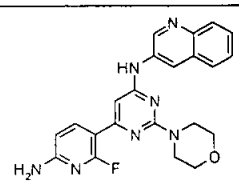
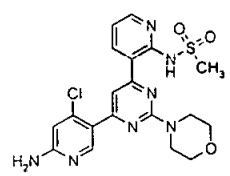
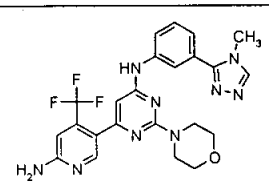
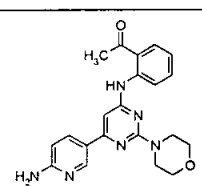
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
145		496.0, 2.35	2.75	++++	++++	+++
146		507.2, 3.12		++++	++++	++++
147		416.0, 1.98		++++	++++	++++
148		380.1	1.78	++++	++++	++
149		478.9, 1.75		++++	++++	+++
150		517.5, 1.78		++++	++++	++++
151		449.0, 2.42		++++	++++	+++

Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
152		375.0	2.22	++++	++++	+++
153		486.4, 2.12		++++	++++	++++
154		445.3, 2.02		++++	++++	++++
155		384.0, 2.04	2.28	++++	++++	+++
156		430.2, 2.05	11.18 L	++++	++++	++++
157		478.1, 2.40	14.67 L	++++	++++	++
158		486.9, 2.48		++++	++++	++++

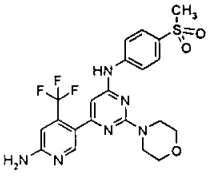
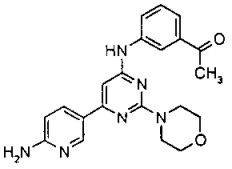
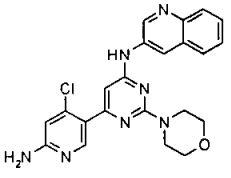
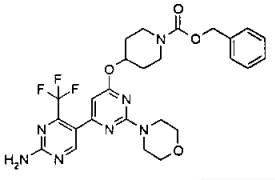
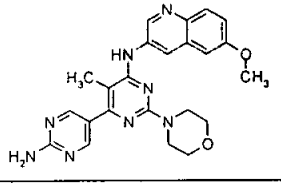
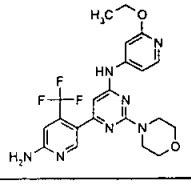
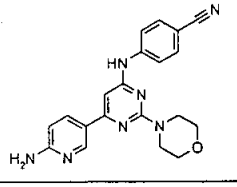
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
159		495.0, 2.57	3.13	++++	++++	+++
160		358.1	8.00 L	++++	++++	+++
161		431.4, 1.96		++++	++++	++++
162		368.2	1.84	++++	++++	++++
163		416.1	2.23	++++	++++	+++
164		475.9, 2.69		++++	++++	++++
165		445.9, 1.95	2.57, (12.84)	++++	++++	++++

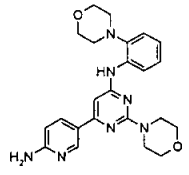
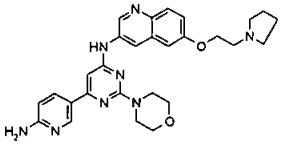
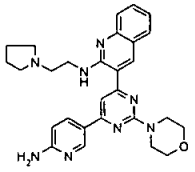
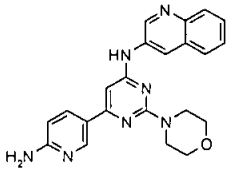
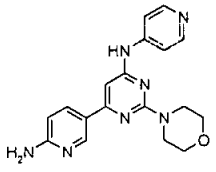
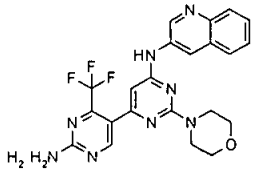
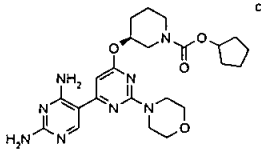
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
166		392.1	1.62	++++	++++	+++
167		459.2, 2.71		++++	++++	+++
168		389.1	2.38	++++	++++	++++
169		418.3, 1.70	2.16, (10.66)	++++	++++	++++
170		462.9, 2.41		++++	++++	++++
171		498.1	1.92	++++	++++	++++
172		391.2	2.62	++++	++++	+++

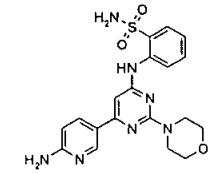
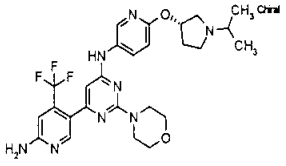
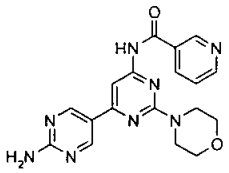
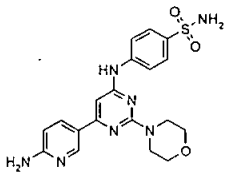
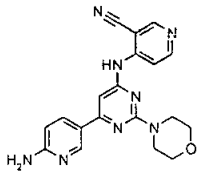
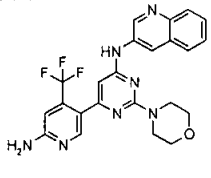
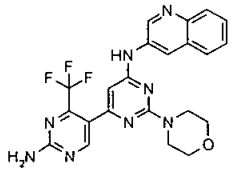
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
173		495.0	2.32	++++	++++	+++
174		391.1	2.14	++++	++++	+++
175		434.3, 1.95		++++	++++	++++
176		560.0, 4.28		++++	++++	+++
177		445.3, 1.79		++++	++++	++++
178		462.0, 1.98	2.19	++++	++++	+++
179		374.0, 2.16	2.48	++++	++++	+++

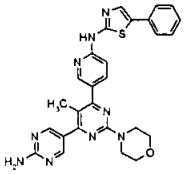
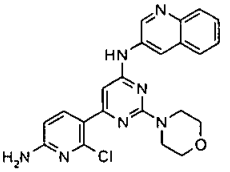
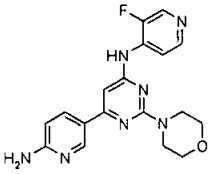
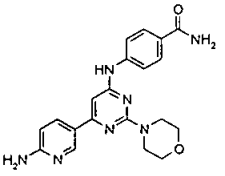
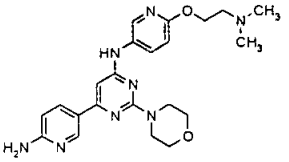
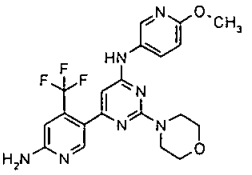
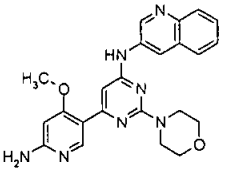
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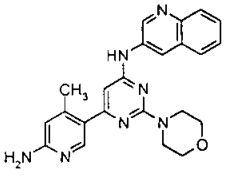
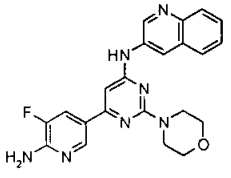
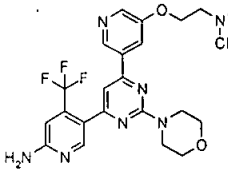
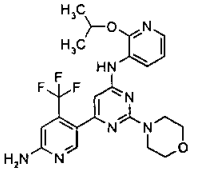
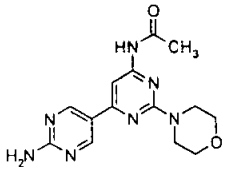
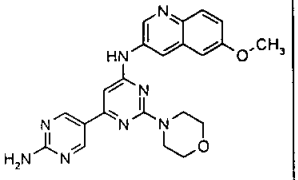
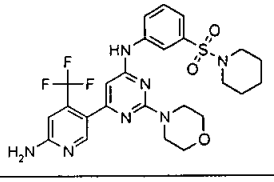
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
180		434.1	2.4	++++	++++	+++
181		513.1, 1.76	1.72	++++	++++	++++
182		497.2, 1.90	9.89 L	++++	++++	++++
183		400.4, 2.03		++++	++++	++++
184		350.1	7.65 L	++++	++++	++++
185		429.4, 1.67		++++	++++	++++
186		485.1, 2.91		++++	++++	+++

518

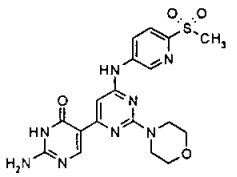
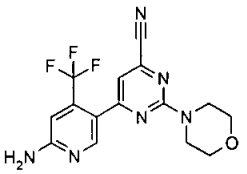
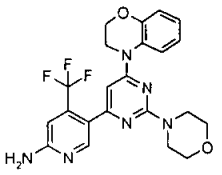
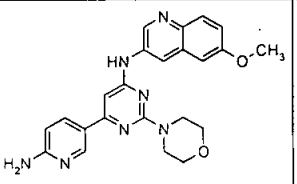
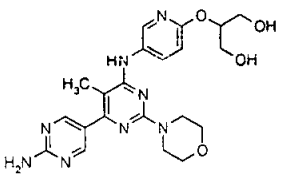
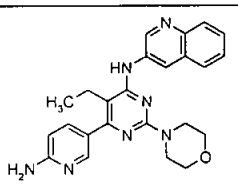
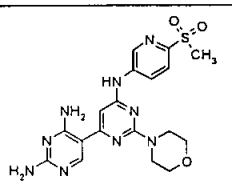
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
187		428.1	2.17	++++	++++	+++
188		545.2, 1.84	1.89	++++	++++	+++
189		379.4, 1.42		++++	++++	+++
190		428.1	1.85	++++	++++	+++
191		375.1, 1.75	1.74	++++	++++	+++
192		469.4, 2.44		++++	++++	++++
193		468.4, 2.26		++++	++++	++++

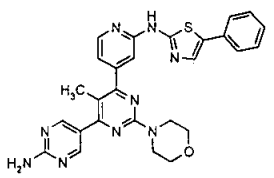
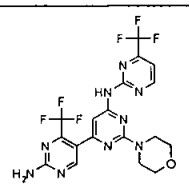
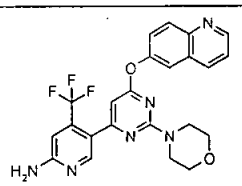
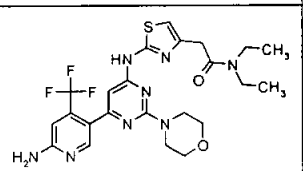
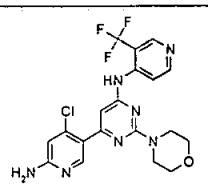
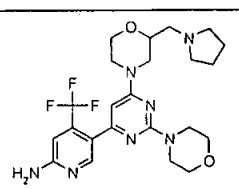
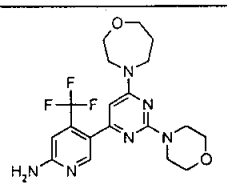
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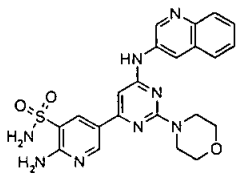
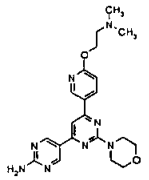
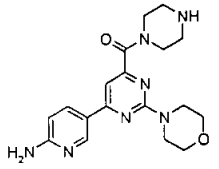
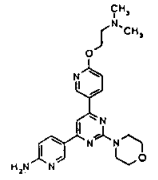
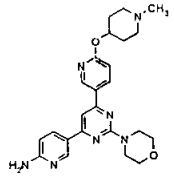
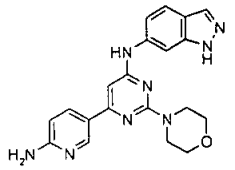
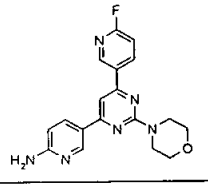
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
194		524.5, 2.44	3.44	++++	++++	+++
195		434.3, 2.06		++++	++++	++++
196		368.1, 1.69	1.63	++++	++++	++++
197		392.1	1.68	++++	++++	+++
198		437.2, 1.60	1.45	++++	++++	N/D
199		448.4, 2.24		++++	++++	+++
200		430.1, 1.84	9.55 L	++++	++++	++++

Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
201		414.1, 1.85	9.53 L	++++	++++	++++
202		418.3	2.16	++++	++++	++++
203		490.1, 1.85	1.83	++++	++++	+++
204		476.1, 2.42	2.86	++++	++++	++
205		316.2, 1.45		++++	++++	+++
206		431.0, 1.91	2.16	++++	++++	++++
207		564.1	3.08	++++	+++	++++

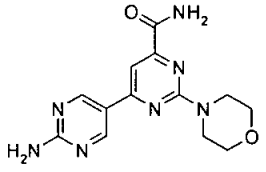
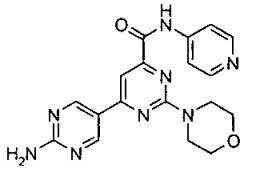
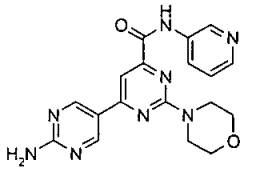
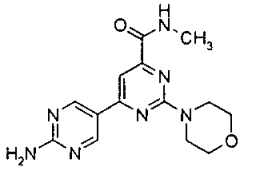
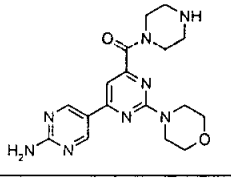
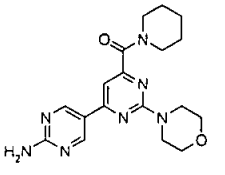
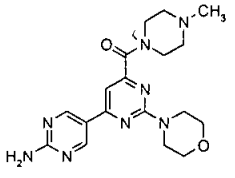
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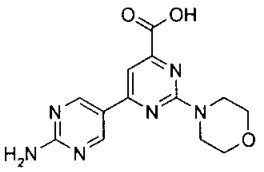
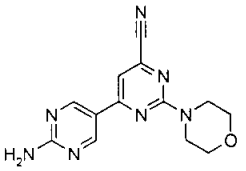
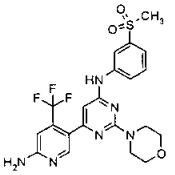
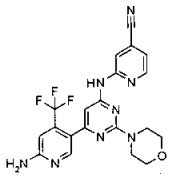
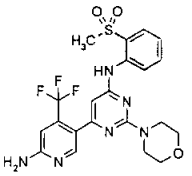
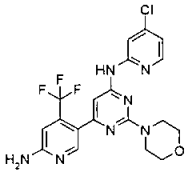
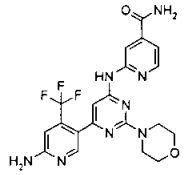
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
208		445.0, 1.50	1.78, (8.91)	++++	+++	++
209		351.0, 2.12	2.88, (14.36)	++++	+++	+++
210		459.4, 2.80		++++	+++	+++
211		430.2, 2.02	2.14	++++	+++	++++
212		455.5, 1.53		++++	+++	++
213		428.2, 1.74	8.55 L	++++	+++	++++
214		444.0, 2.06		++++	+++	++

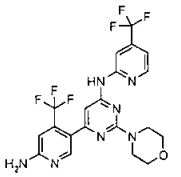
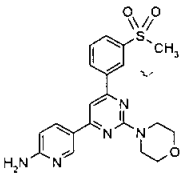
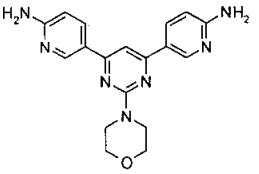
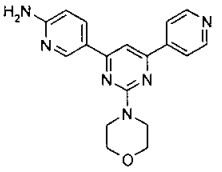
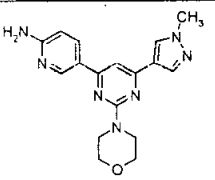
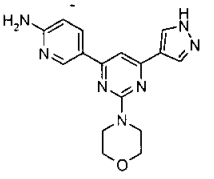
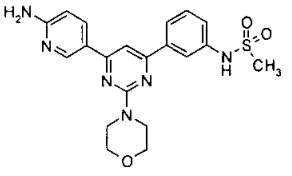
Com-puesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Prolife-ración celular, EC_{50}
215		524.5, 2.44	3.36	++++	+++	+++
216		487.9, 3.60		++++	N/D	+++
217		469.1, 2.01	2.13	++++	N/D	+++
218		537.1, 2.27	2.53	++++	N/D	+++
219		452.0, 1.85	1.89	++++	N/D	+++
220		494.1, 1.67	1.59	+++	N/D	++
221		425.0, 1.66	1.98	++++	N/D	+++

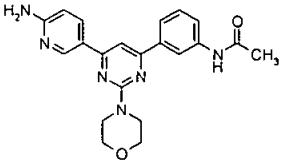
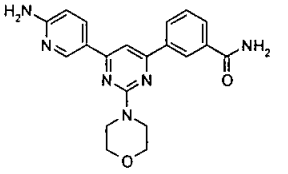
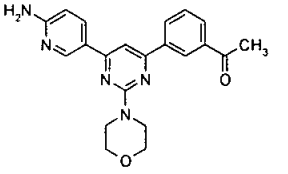
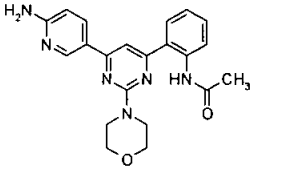
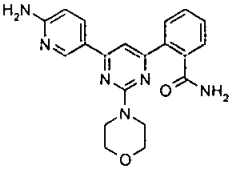
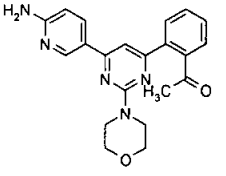
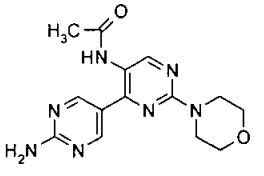
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
222		479.1, 1.98	2.20	+++	N/D	N/D
223		423.2, 1.83	1.99	++++	N/D	+++
224		370.3, 1.25	1.39	+++	N/D	N/D
225		422.2, 1.84	1.86	++++	N/D	N/D
226		448.3, 1.93	1.94	++++	N/D	N/D
227		389.2, 1.93	1.93	++++	N/D	+++
228		353.1, 2.25	2.55	++++	N/D	N/D

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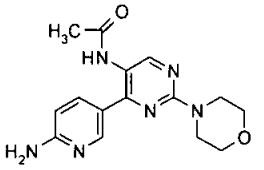
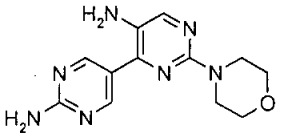
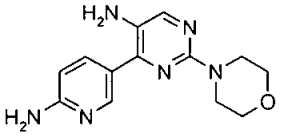
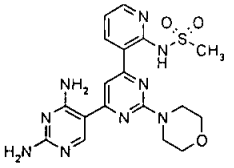
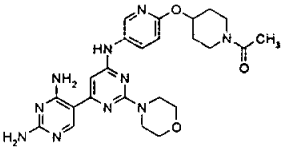
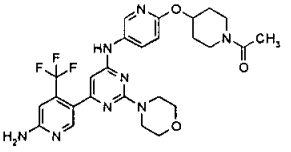
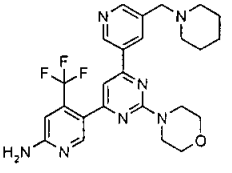
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
229		302.1, 1.68	1.74	++++	N/D	N/D
230		379.1, 1.73	1.74	++++	N/D	+++
231		379.1, 1.75	1.78	++++	N/D	+++
232		316.1, 1.84	2.24	++++	N/D	++
233		371.2, 1.49	1.39	++++	N/D	+++
234		370.0, 2.12	2.37	++++	N/D	++
235		385.2, 1.50	1.40	++++	N/D	+++

Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
236		303.1, 1.65	1.70	++++	N/D	N/D
237		284.1, 2.12	2.56	++++	N/D	+++
238		495.0	2.3	++++	N/D	+++
239		443.1	2.63	++++	N/D	+++
240		495, 2.20	3.29	++++	N/D	N/D
241		452.0	2.57	++++	N/D	+++
242		461.1	1.85	++++	N/D	+++

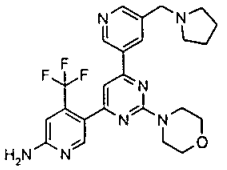
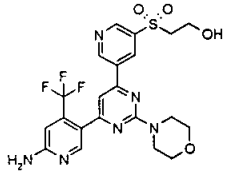
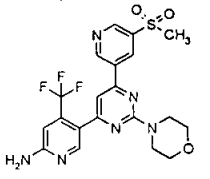
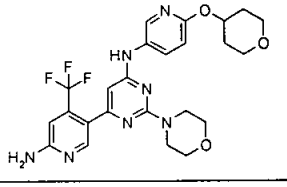
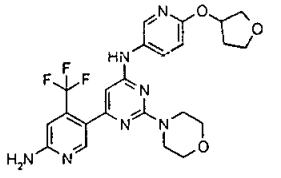
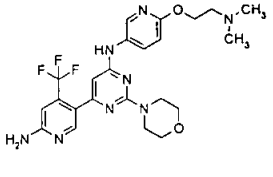
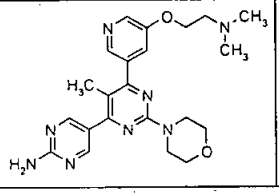
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
243		486, 2.01	2.26	++++	N/D	N/D
244		413, 2.13	2.41	++++	N/D	+++
245		350, 1.72	1.66	++++	N/D	+++
246		335, 1.66	1.57	++++	N/D	+++
247		338, 1.92	2.02	++++	N/D	+++
248		324, 1.79	1.82	++++	N/D	+++
249		427, 2.15	2.40	++++	N/D	+++

Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
250		391, 2.07	2.30	++++	N/D	+++
251		377, 1.98	2.14	++++	N/D	+++
252		376, 2.31	2.66	++++	N/D	+++
253		391, 2.13	2.56	++++	N/D	+++
254		377, 1.76	1.81	++++	N/D	++
255		376, 2.14	2.39	++++	N/D	++
256		316, 1.44	1.32	++++	N/D	N/D

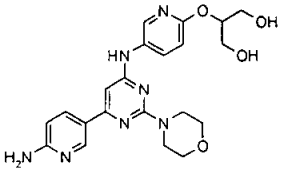
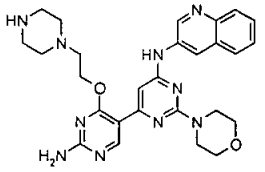
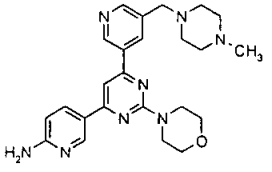
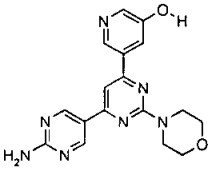
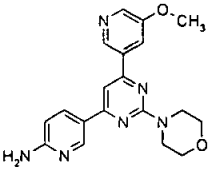
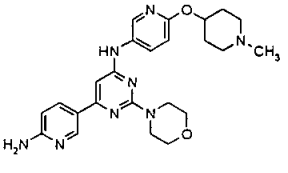
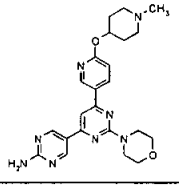
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
257		315, 1.46	1.30	+++	N/D	N/D
258		274, 1.40	1.22	++++	N/D	++
259		273, 1.40	1.23	+++	N/D	++
260		444.1, 2.02	2.24	++++	N/D	+++
261		507.2, 1.92	1.98	++++	N/D	+++
262		559.2, 2.07	2.25	++++	N/D	+++
263		500.2, 1.66	2.03	++++	N/D	+++

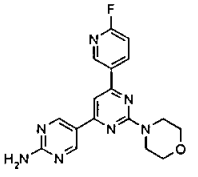
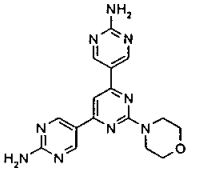
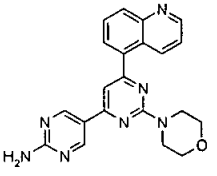
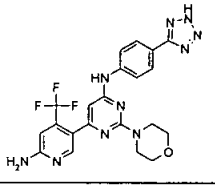
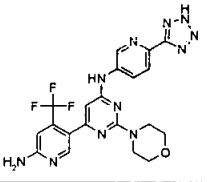
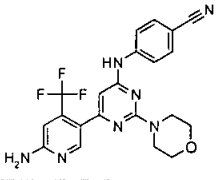
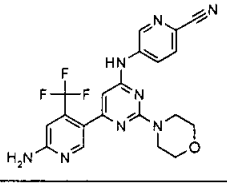
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
264		486.1, 1.61	1.94	++++	N/D	+++
265		511.1, 2.09	2.44	++++	N/D	+++
266		481.1, 2.23	2.59	++++	N/D	+++
267		518.2, 2.18		++++	N/D	+++
268		504.1, 2.13		++++	N/D	+++
269		505.2, 1.76		++++	N/D	+++
270		437.1, 1.56	1.44	++++	N/D	++

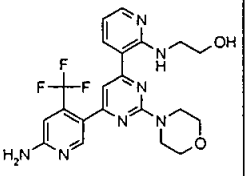
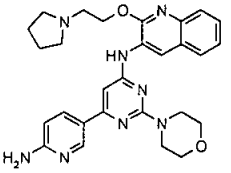
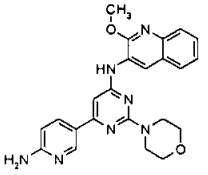
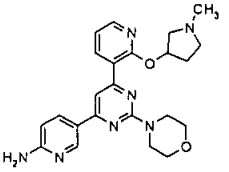
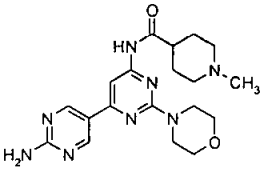
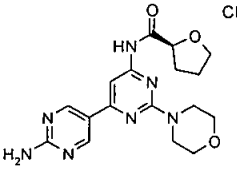
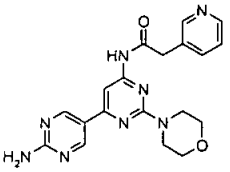
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
271		440.1, 1.59	1.45	++++	N/D	++
272		529.1, 1.64	1.72	++++	N/D	N/D
273		447.2, 1.61	1.54	++++	N/D	+++
274		352.2, 1.81	1.77	++++	N/D	+++
275		365.2, 1.88	1.90	++++	N/D	+++
276		463.3, 1.72		++++	N/D	+++
277		449.2, 2.00	2.11	++++	N/D	+++

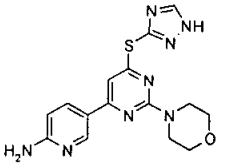
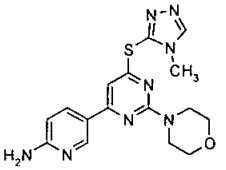
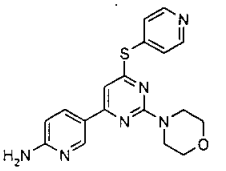
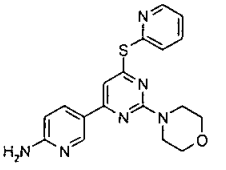
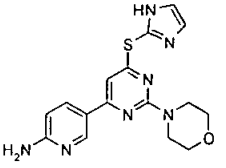
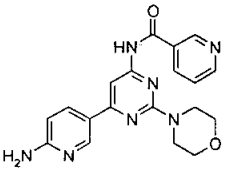
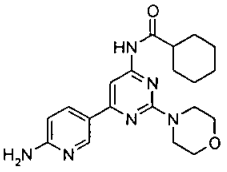
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
278		354.2, 2.32	2.12	++++	N/D	++++
279		352.1, 1.81	1.48	++++	N/D	++++
280		386.1, 1.83	1.91	++++	N/D	+++
281		485.1, 2.17		++++	N/D	++
282		486.0, 1.69		++++	N/D	++
283		442.0, 2.02		++++	N/D	+++
284		443.1, 2.22		++++	N/D	+++

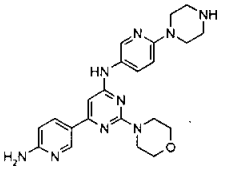
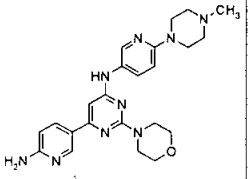
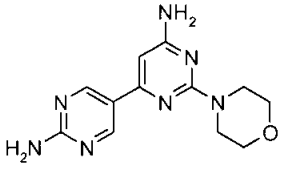
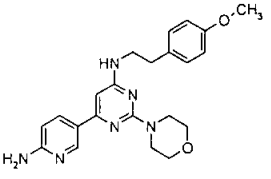
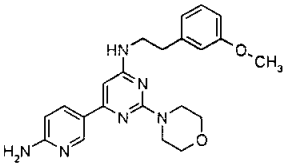
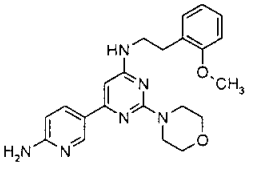
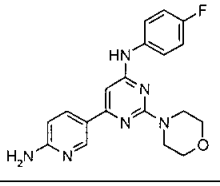
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
285		462.1, 1.95		++++	N/D	+++
286		513.1, 2.46		+++	N/D	N/D
287		430.1, 2.98		++++	N/D	+++
288		434.4, 1.97		+++	N/D	N/D
289		399.4, 1.50		++++	N/D	+++
290	 Chiral	372.3, 1.74		++++	N/D	+++
291		393.4, 1.32		++++	N/D	++

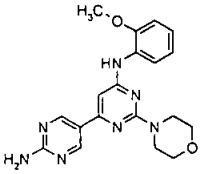
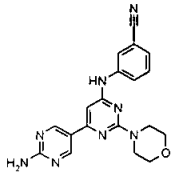
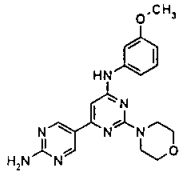
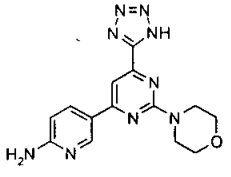
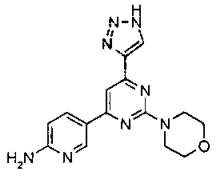
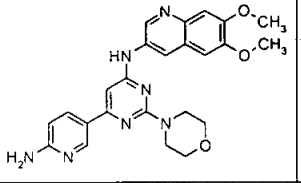
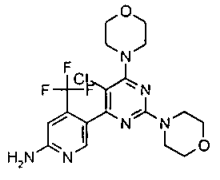
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
292		357.2, 1.78		+++	N/D	N/D
293		371.4, 1.68		+++	N/D	N/D
294		367.3, 1.65		++++	N/D	+++
295		367.2, 2.17		++++	N/D	+++
296		356.3, 1.22		+++	N/D	N/D
297		378.4, 1.72		++++	N/D	N/D
298		383.4, 2.69		++++	N/D	N/D

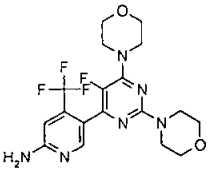
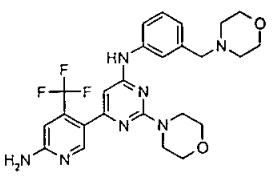
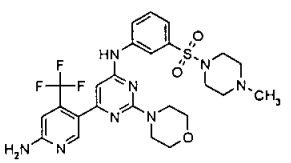
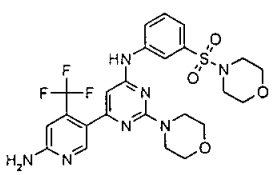
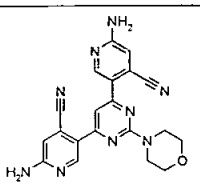
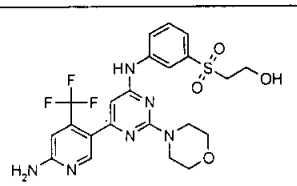
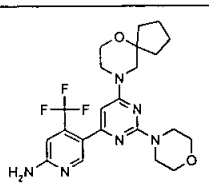
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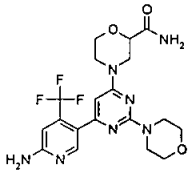
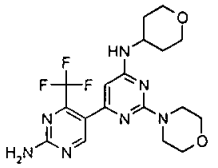
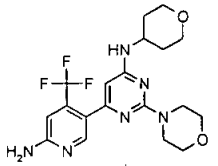
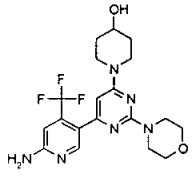
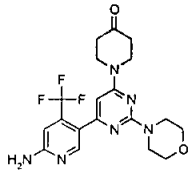
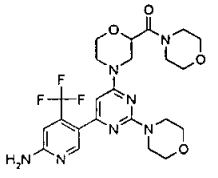
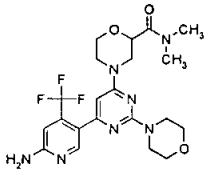
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
299		434.5, 1.41		++++	N/D	+++
300		448.4, 1.44		++++	N/D	+++
301		274.2, 0.46		++++	N/D	++
302		407.2, 2.04	3.73	+++	N/D	++
303		407.2, 2.02	3.77	++++	N/D	+++
304		407.1; 2.10	2.25	++++	N/D	++
305		367.0; 2.07	2.28	++++	N/D	+++

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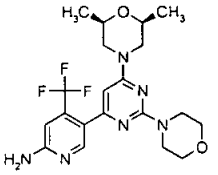
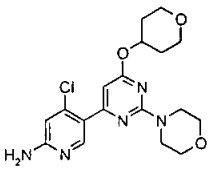
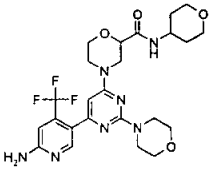
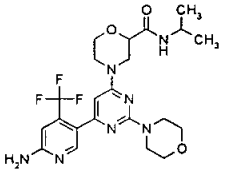
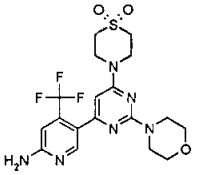
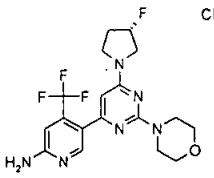
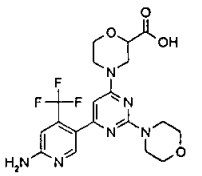
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
306		380.1; 2.07	2.29	++++	N/D	+++
307		375.0; 2.09	2.39	++++	N/D	+++
308		380.1; 2.07	2.32	++++	N/D	+++
309		326.1, 1.79	2.99	++++	N/D	N/D
310		325.0, 1.51	1.88	++++	N/D	N/D
311		460.1, 1.96	2.09	++++	N/D	++++
312		445.1, 2.30	2.7	++++	N/D	N/D

536

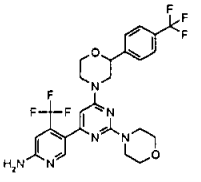
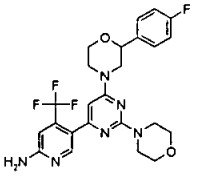
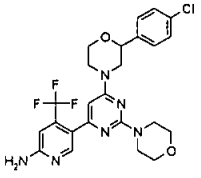
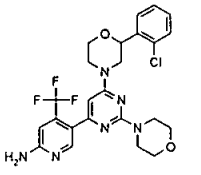
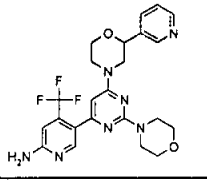
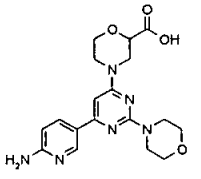
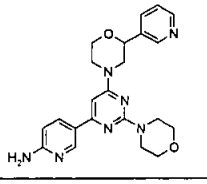
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
313		429.1	2.32	++++	N/D	++
314		516.1	1.78	++++	N/D	++
315		579.1	2.09	++++	N/D	+++
316		566	2.64	++++	N/D	+++
317		400.1, 2.02	2.27	++++	N/D	+++
318		525.1	2.15	++++	N/D	+++
319		465.1, 2.28	2.5	++++	N/D	N/D

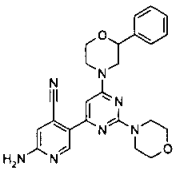
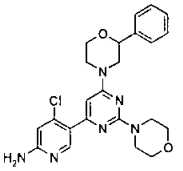
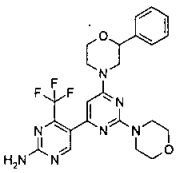
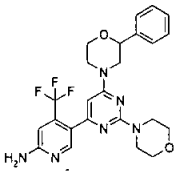
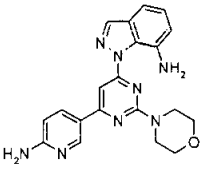
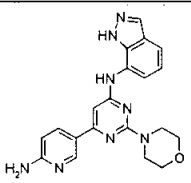
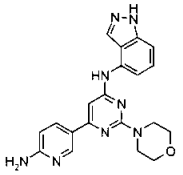
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
320		454.1, 1.74	1.74	++++	N/D	+++
321		426.1	2.08	++++	N/D	+++
322		425.1, 1.92	1.97	++++	N/D	++
323		425.0, 1.78	1.83	++++	N/D	++
324		423.0, 1.82	1.79	++++	N/D	+++
325		524.1, 1.88	1.96	++++	N/D	++
326		482.1, 1.88	1.93	++++	N/D	++

538

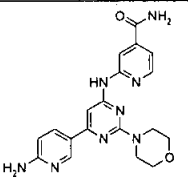
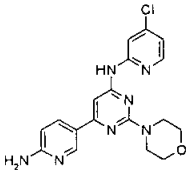
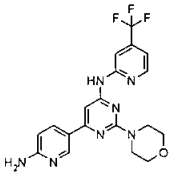
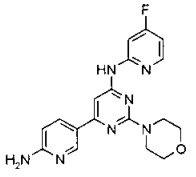
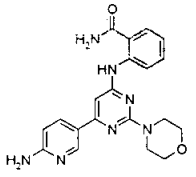
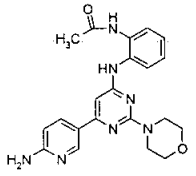
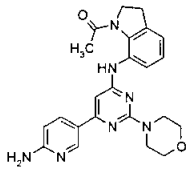
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
327		439.2, 2.15	2.38	++++	N/D	+++
328		392.0, 2.08	2.26	++++	N/D	+++
329		538.2, 1.90	1.98	++++	N/D	++
330		496.2, 2.04	2.2	++++	N/D	++
331		459.1, 1.83	1.89	++++	N/D	++
332	 Chiral	413.1, 2.04	2.21	++++	N/D	++++
333		455.1, 1.77	1.79	++++	N/D	++

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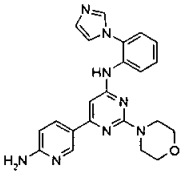
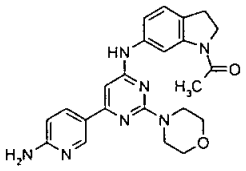
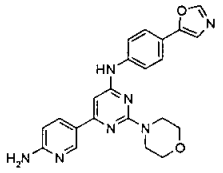
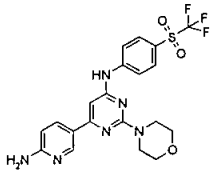
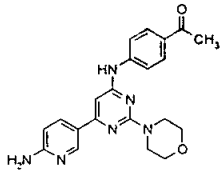
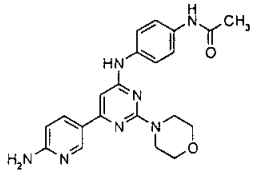
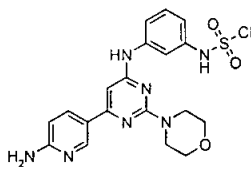
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
334		555.1, 2.76	3.36	++++	N/D	+++
335		505.1	2.94	++++	N/D	+++
336		521.1, 2.66	3.18	++++	N/D	+++
337		521.1	3.1	++++	N/D	++
338		488.1, 1.73	1.67	++++	N/D	+++
339		387.1, 1.55	1.44	+++	N/D	N/D
340		420.1, 1.57	1.44	++++	N/D	N/D

Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
341		444.1	2.84	++++	N/D	+++
342		453.1	2.51	++++	N/D	+++
343		488.1	3.02	++++	N/D	++
344		487.2	2.86	++++	N/D	+++
345		389.1, 2.06	2.28	++++	N/D	+++
346		389.1, 1.92	1.94	++++	N/D	N/D
347		389.1	1.83	++++	N/D	+++

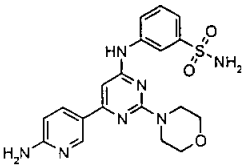
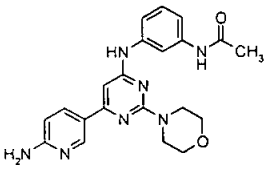
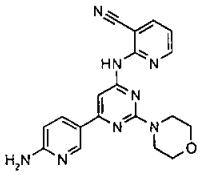
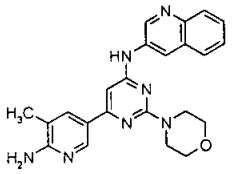
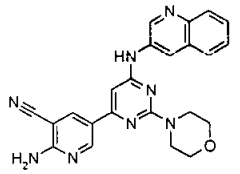
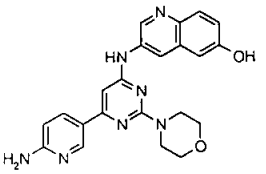
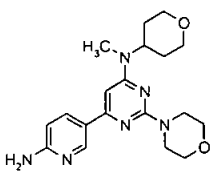
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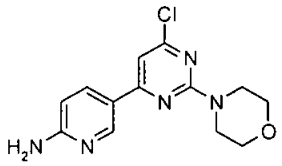
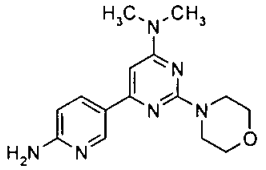
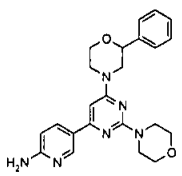
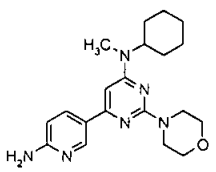
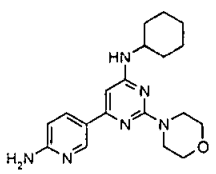
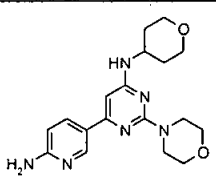
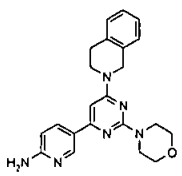
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
348		393.1	1.57	++++	N/D	++
349		384.1	2.13	++++	N/D	++
350		418.1	2.77	++++	N/D	++
351		368.2	1.77	++++	N/D	++
352		392.1, 1.89	1.94	++++	N/D	+++
353		406.1, 1.78	1.77	+++	N/D	N/D
354		432.2, 2.05	2.25	++++	N/D	N/D

542

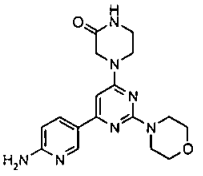
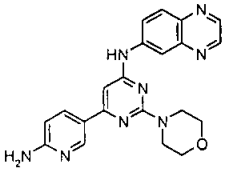
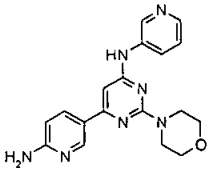
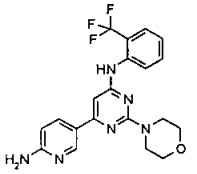
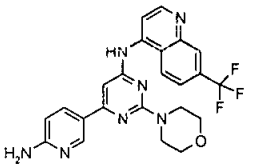
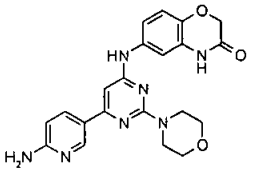
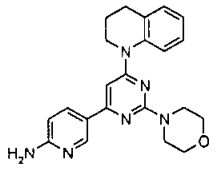
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
355		415.0, 1.73	1.61	++++	N/D	N/D
356		432.0	2.0	++++	N/D	+++
357		416.0, 2.05	2.21	++++	N/D	++
358		481.1, 2.64	3.27	++++	N/D	+++
359		391.1, 2.06	2.28	++++	N/D	++++
360		406.1, 1.71	1.71	++++	N/D	+++
361		442.1	1.89	++++	N/D	+++

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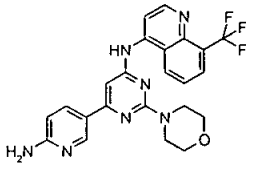
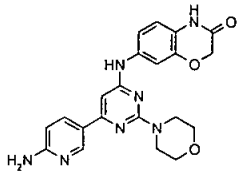
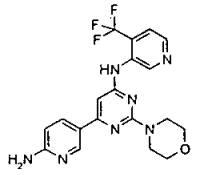
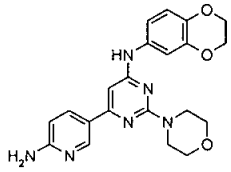
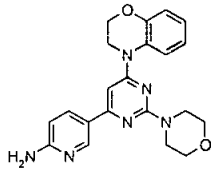
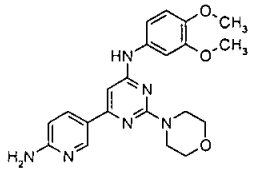
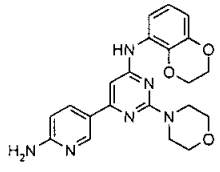
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
362		428.1	1.77	++++	N/D	+++
363		406.1	1.77	++++	N/D	+++
364		375.1, 1.93	2.04	+++	N/D	++
365		414.1, 1.94	10.78 L	+++	N/D	N/D
366		425.1, 2.14	12.06 L	+++	N/D	N/D
367		416.1	9.23 L	++++	N/D	+++
368		371.2, 1.69	7.86 L	++++	N/D	+++

Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
369		292.1, 2.07	11.31 L	++++	N/D	++
370		301.2, 1.57	6.77 L	+++	N/D	N/D
371		419.2	12.26 L	++++	N/D	+++
372		369.2, 2.15	11.91 L	+++	N/D	N/D
373		355.2, 2.07	11.27 L	+++	N/D	N/D
374		357.2, 1.62	7.19 L	+++	N/D	N/D
375		389.2, 2.13	12.07 L	++++	N/D	N/D

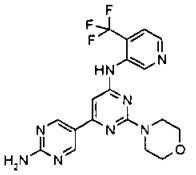
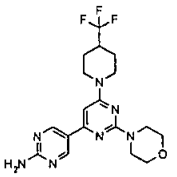
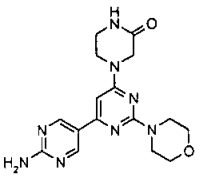
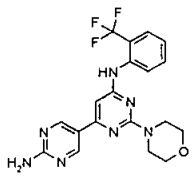
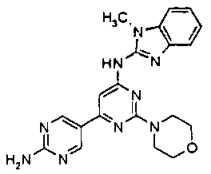
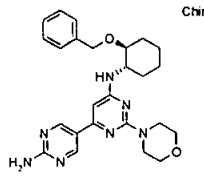
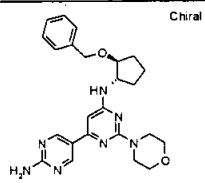
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
376		356.2, 1.40	5.75 L	+++	N/D	N/D
377		401.1	10.23 L	++++	N/D	+++
378		350.2, 1.66	7.63 L	++++	N/D	+++
379		417.1, 2.28	13.32 L	++++	N/D	N/D
380		468.1, 2.16	11.42 L	++++	N/D	+++
381		420.1, 1.81	9.41 L	++++	N/D	N/D
382		389.2, 2.28	13.47 L:	++++	N/D	N/D

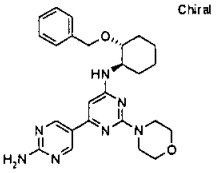
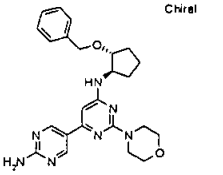
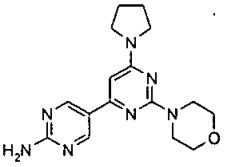
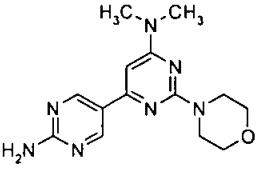
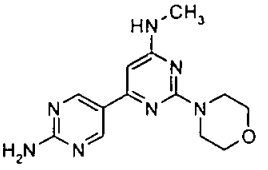
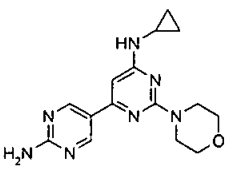
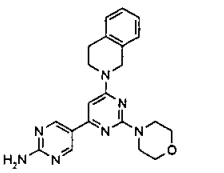
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
383		468.2, 2.13	11.64 L	++++	N/D	+++
384		420.1, 1.68	8.71 L	++++	N/D	+++
385		418.1, 1.98	11.04 L	++++	N/D	N/D
386		407.1, 1.95	10.57 L	++++	N/D	+++
387		391.1, 2.25	13.62 L	++++	N/D	+++
388		409.1, 1.87	9.91 L	++++	N/D	N/D
389		407.1, 2.08	11.36 L	++++	N/D	N/D

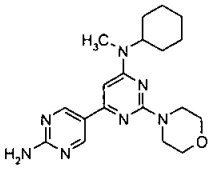
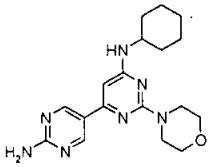
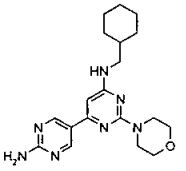
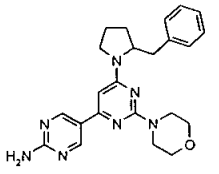
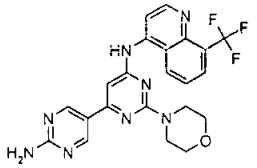
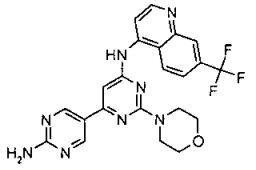
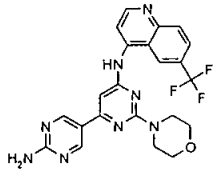
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
390		419.1	10.41 L	++++	N/D	+++
391		410.1, 2.20	12.63 L	++++	N/D	N/D
392		357.1	5.96 L	++++	N/D	+++
393		418.1	13.00 L	++++	N/D	+++
394		404.2	10.64 L	++++	N/D	+++
395	 Chiral	462.2, 2.38	14.83 L	++++	N/D	N/D
396	 Chiral	448.2	14.53 L	++++	N/D	+++

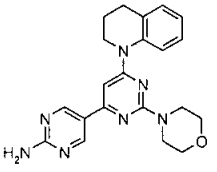
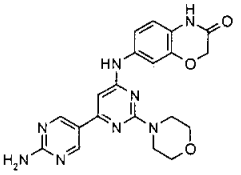
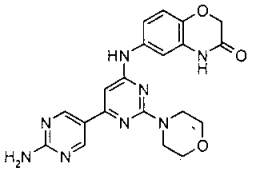
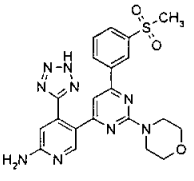
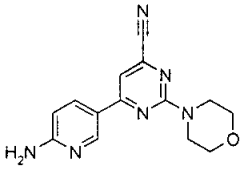
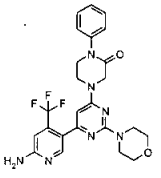
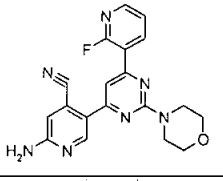
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
397		462.2, 2.40	14.82 L	++++	N/D	N/D
398		448.2, 2.38	14.52 L	++++	N/D	N/D
399		328.2	9.63 L	++++	N/D	+++
400		302.2	7.77 L	++++	N/D	+++
401		288.2	6.92 L	++++	N/D	++
402		314.2	8.39 L	++++	N/D	+++
403		390.1	13.44 L	++++	N/D	+++

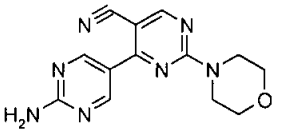
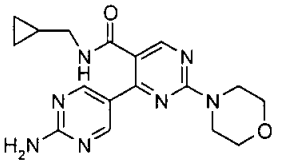
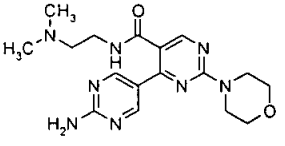
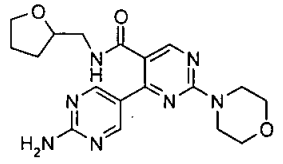
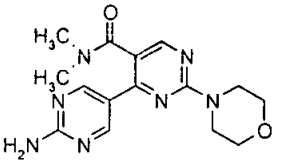
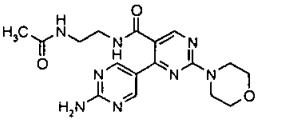
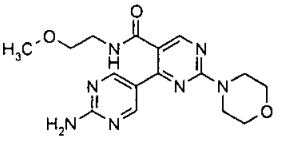
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
404		370.2	13.71 L	++++	N/D	+++
405		356.2	12.73 L	++++	N/D	+++
406		370.2	14.24 L	++++	N/D	++
407		418.2	14.81 L	++++	N/D	+++
408		469.1	12.14 L	++++	N/D	+++
409		469.1	12.17 L	++++	N/D	++++
410		469.1	12.17 L	++++	N/D	+++

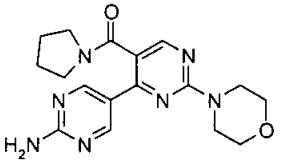
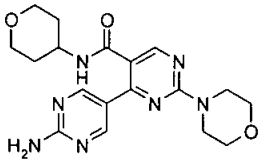
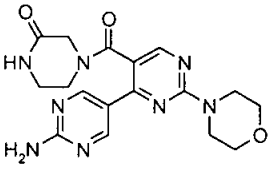
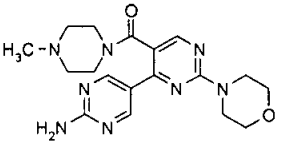
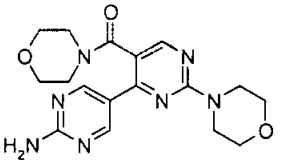
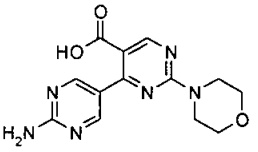
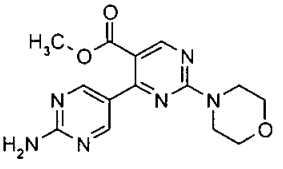
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
411		390.1	13.47 L	++++	N/D	+++
412		421.1	8.70 L	++++	N/D	++++
413		421.1	9.60 L	++++	N/D	+++
414		480.0, 1.98	2.19	++++	N/D	N/D
415		283.2, 1.95		++++	N/D	++
416		500.0, 1.83	2.36	++++	N/D	N/D
417		378.0, 3.02	2.79	++++	N/D	++

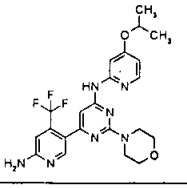
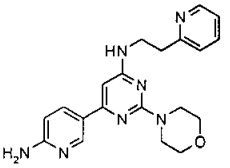
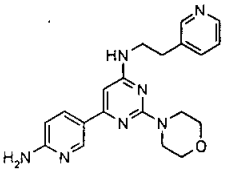
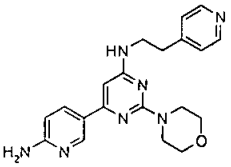
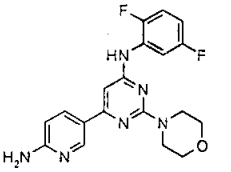
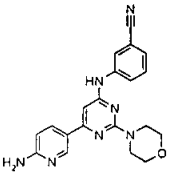
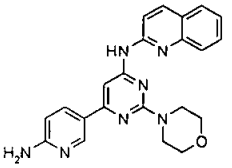
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
418		284.2, 1.94	2.2	++++	N/D	++
419		356.2, 1.77	1.86	+++	N/D	N/D
420		373.2, 1.37	1.23	+++	N/D	N/D
421		386.2, 1.57	1.73	+++	N/D	N/D
422		330.2, 1.47	1.58	+++	N/D	N/D
423		387.2, 1.47	1.32	+++	N/D	N/D
424		360.2, 1.57	1.47	+++	N/D	N/D

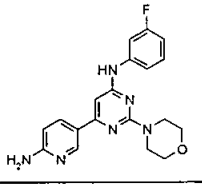
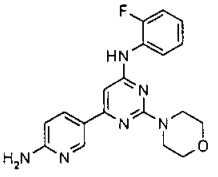
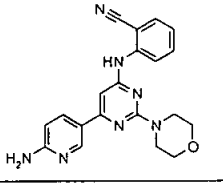
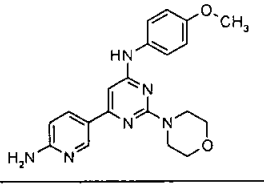
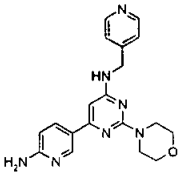
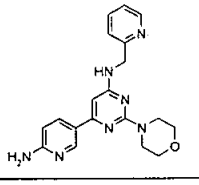
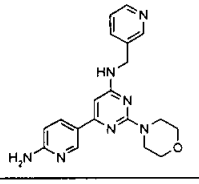
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
425		356.2, 1.79	1.83	+++	N/D	N/D
426		386.2, 1.61	1.56	+++	N/D	N/D
427		385.2, 1.48	1.4	+++	N/D	++
428		385.2, 0.5	1.34	+++	N/D	++
429		372.3, 1.39	1.69	+++	N/D	N/D
430		303.1, 1.66	1.66	+++	N/D	N/D
431		317.2, 1.59	2.02	++++	N/D	++

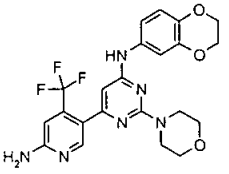
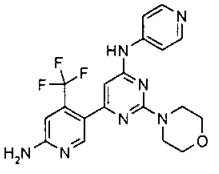
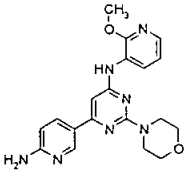
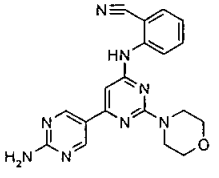
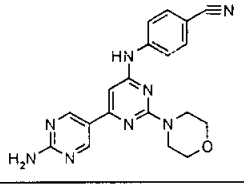
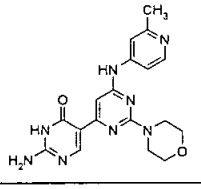
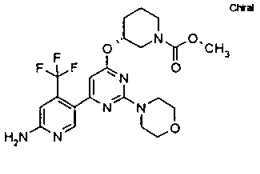
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
432		476.1, 2.16	2.46	++++	N/D	+++
433		378.1, 1.31	1.13	+++	N/D	N/D
434		378.2, 1.46	1.14	+++	N/D	N/D
435		378.2, 1.44	1.13	+++	N/D	N/D
436		385.1, 2.25	2.58	++++	N/D	+++
437		374.0, 2.14	2.42	++++	N/D	+++
438		400.0, 1.90	2.04	++++	N/D	+++

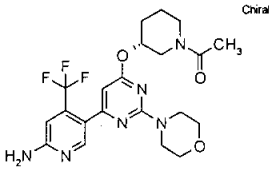
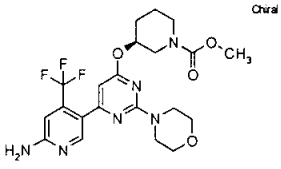
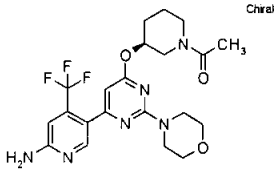
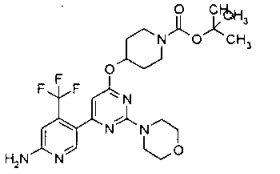
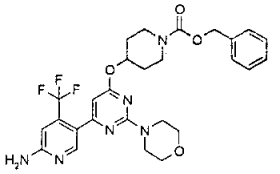
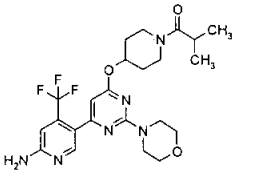
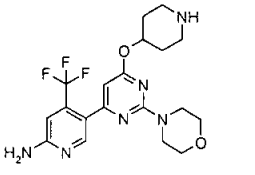
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
439		367.1, 2.20	2.47	++++	N/D	+++
440		367.1, 2.07	2.29	++++	N/D	+++
441		374.1, 2.07	2.26	++++	N/D	+++
442		379.1, 1.94	2.19	++++	N/D	+++
443		364.1, 1.41	1.10	+++	N/D	N/D
444		364.1, 1.33	1.16	+++	N/D	N/D
445		364.1, 1.37	1.10	+++	N/D	N/D

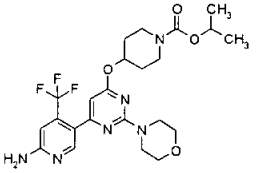
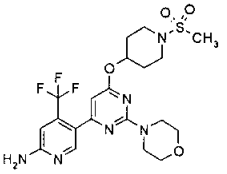
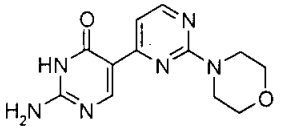
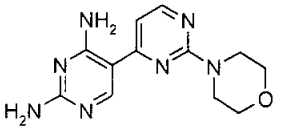
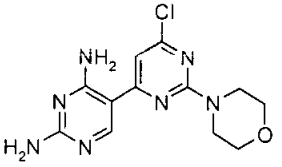
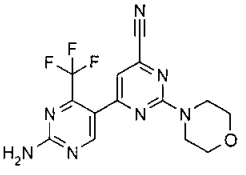
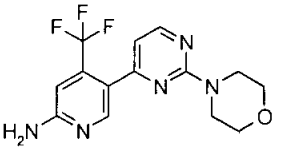
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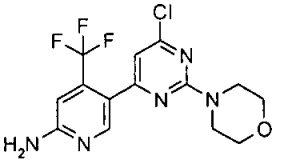
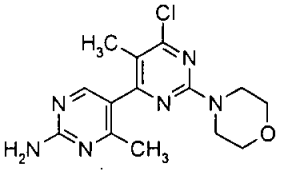
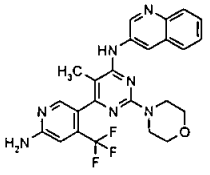
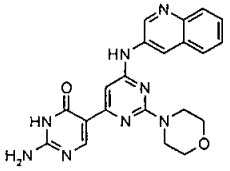
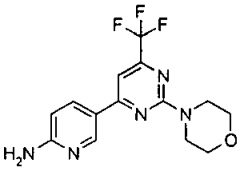
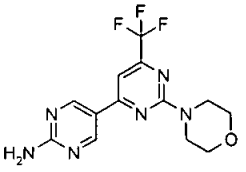
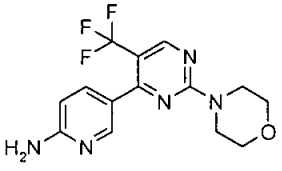
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
446		475.4, 1.99	2.52	++++	N/D	++
447		418.3, 1.54	1.93	++++	N/D	++
448		380.1, 1.98	2.06	++++	N/D	+++
449		375.0, 2.00	2.21	++++	N/D	+++
450		380.1, 2.01	2.19	++++	N/D	++
451		381.0, 1.30	1.48, (7.22)	++++	N/D	+++
452		483.0, 2.83		++++	N/D	+++

556

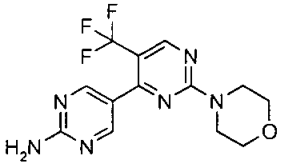
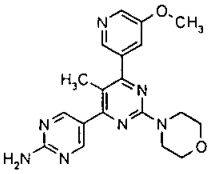
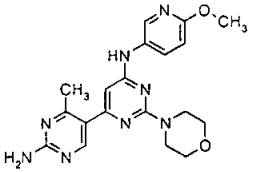
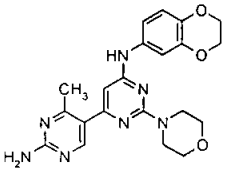
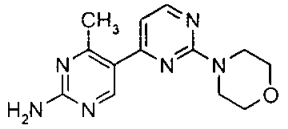
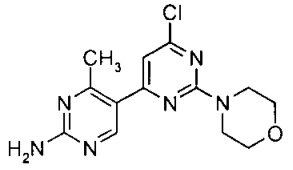
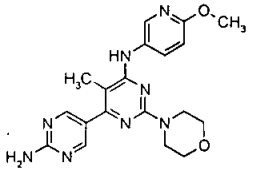
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
453		467.0, 2.87		++++	N/D	+++
454		483.0, 2.83		++++	N/D	+++
455		467.0, 2.87		++++	N/D	+++
456		525.1, 2.90		++++	N/D	+++
457		599.2, 3.60		++++	N/D	+++
458		495.1, 2.77		++++	N/D	+++
459		425.1, 1.80		++++	N/D	N/D

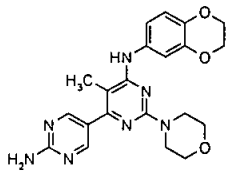
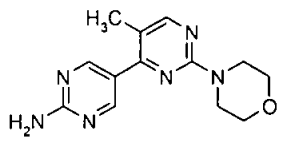
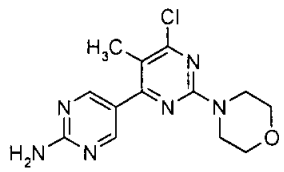
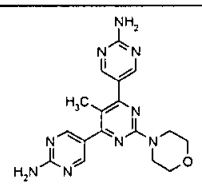
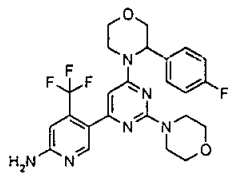
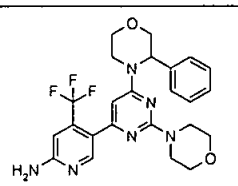
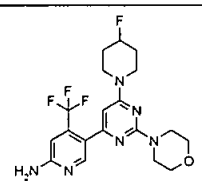
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
460		511.1, 3.28		++++	N/D	+++
461		503.1, 2.66		++++	N/D	+++
462		275.0, 1.16	1.23, (5.79)	++++	N/D	+++
463		274.0, 1.36		++++	N/D	++
464		307.9, 2.09		++++	N/D	++
465		352.0, 2.46	3.57, (17.04)	++++	N/D	+++
466		326.2, 1.66	2.04, (10.20)	++++	N/D	++

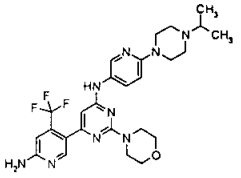
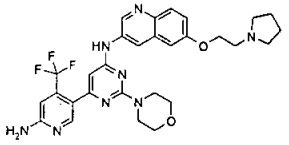
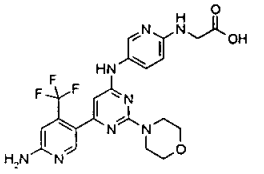
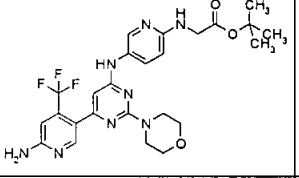
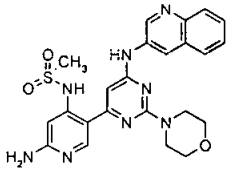
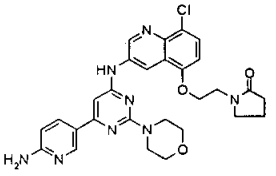
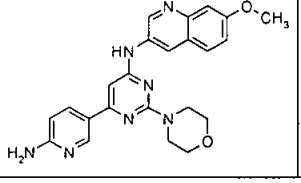
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
467		360.2, 2.18	2.92, (14.71)	++++	N/D	++
468		321.2, 1.84	2.35, 11.87	++++	N/D	++
469		482.4, 1.70	2.08, (10.76)	++++	N/D	N/D
470		417.3, 1.58	1.83, (9.39)	++++	N/D	+++
471		326.3, 1.98	2.53, (13.21)	++++	N/D	N/D
472		327.2, 2.21	3.13, (15.01)	++++	N/D	+++
473		326.3, 1.76	2.24, (11.11)	+++	N/D	N/D

559

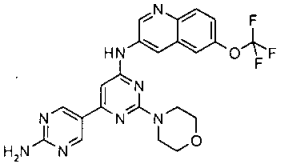
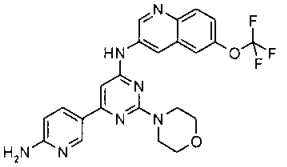
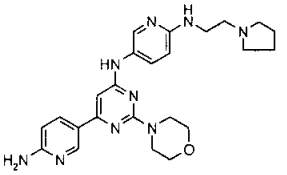
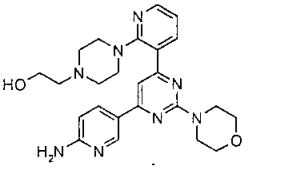
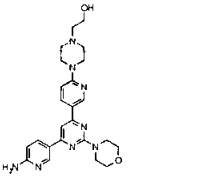
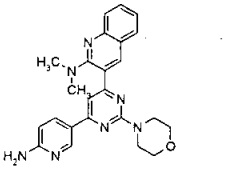
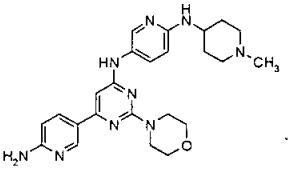
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
474		327.3, 1.97	2.69, (12.81)	++++	N/D	++
475		380.3, 1.49	1.76, (8.70)	++++	N/D	+++
476		395.3, 1.89		++++	N/D	+++
477		422.3, 2.15		++++	N/D	+++
478		273.2, 1.55	1.44, (6.80)	++++	N/D	++
479		307.1, 2.05	2.33, (11.43)	++++	N/D	N/D
480		395.3, 1.79		++++	N/D	+++

Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
481		422.3, 2.10		++++	N/D	++++
482		273.2, 1.29	1.43, (6.78)	++++	N/D	+++
483		307.2, 1.96	2.58, (12.75)	++++	N/D	++
484		366.3, 1.39	1.63, (7.75)	++++	N/D	+++
485		505.1, 2.35	14.35 L	++++	N/D	N/D
486		487.2, 2.31	13.84 L	++++	N/D	N/D
487		427.1, 2.12	11.84 L	++++	N/D	N/D

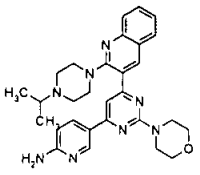
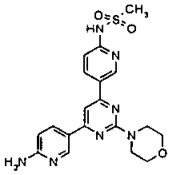
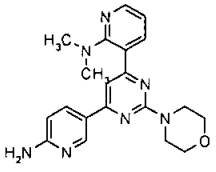
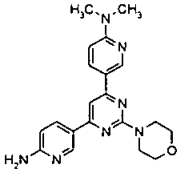
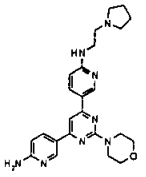
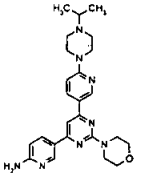
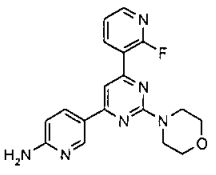
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
488		544.2, 1.76	1.67	++++	N/D	+++
489		581.2, 1.82	1.90	++++	N/D	+++
490		491.1, 1.70	1.59	++++	N/D	N/D
491		547.1, 2.09	11.59 L	++++	N/D	++
492		492.9, 1.78	2.24	+++	N/D	N/D
493		561.1, 2.20	2.46	++++	N/D	N/D
494		430.2, 1.97	10.65 L	++++	N/D	+++

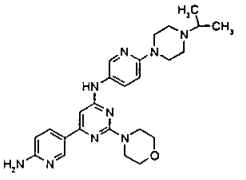
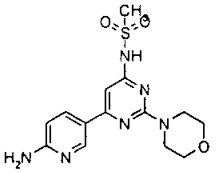
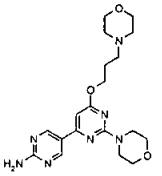
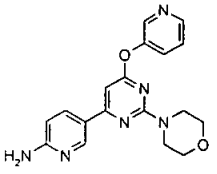
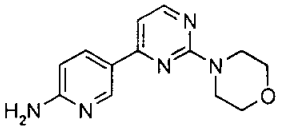
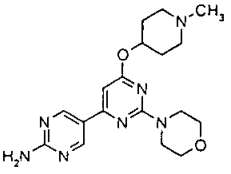
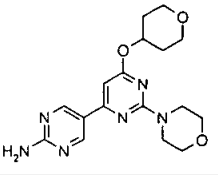
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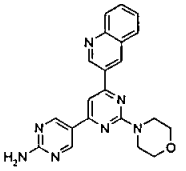
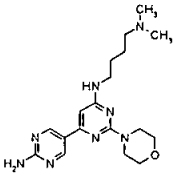
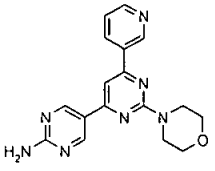
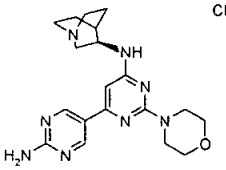
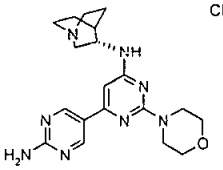
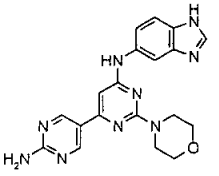
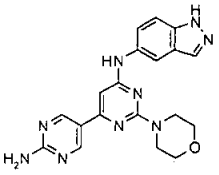
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
495		485.0, 2.47	15.16 L	++++	N/D	++
496		484.1, 2.47	15.14 L	+++	N/D	N/D
497		462.4, 1.29	7.09 L	++++	N/D	+++
498		463.2, 1.77	8.92 L	+++	N/D	N/D
499		463.2, 1.72	8.24 L	++++	N/D	+++
500		428.4, 1.63	10.17	++++	N/D	+++
501		462.4, 1.28	1.51	++++	N/D	+++

563

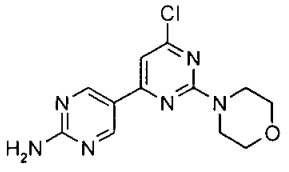
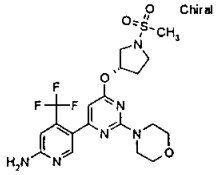
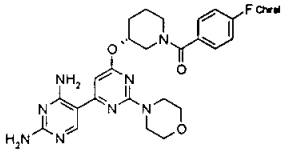
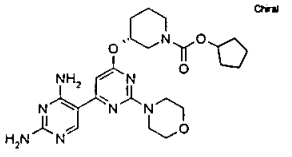
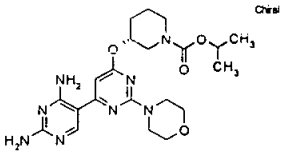
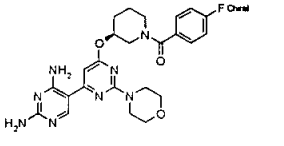
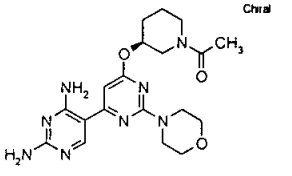
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
502		511.3, 2.08	11.82 L	+++	N/D	N/D
503		428.2, 1.93	10.1 L	++++	N/D	+++
504		378.2, 1.66	7.72 L	+++	N/D	N/D
505		378.2, 1.76	8.73 L	++++	N/D	+++
506		447.3, 1.78	8.02	++++	N/D	N/D
507		461.2, 1.8	8.93 L	++++	N/D	N/D
508		353.1, 2.16	2.34	++++	N/D	+++

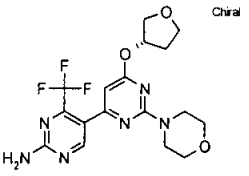
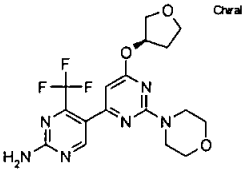
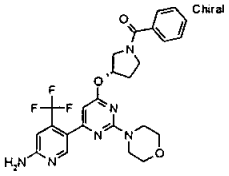
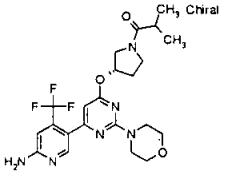
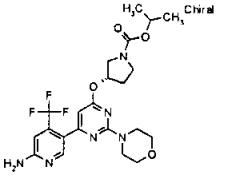
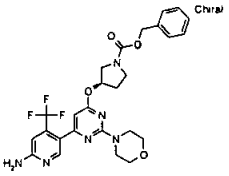
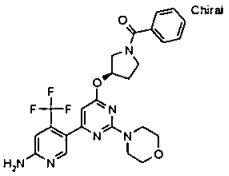
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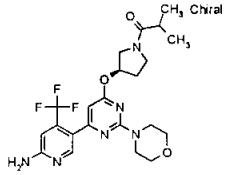
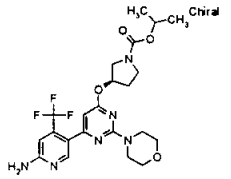
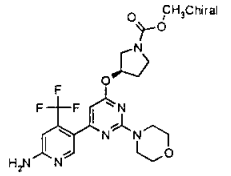
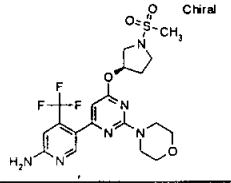
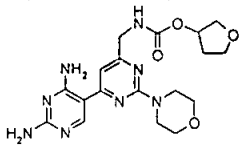
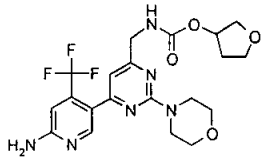
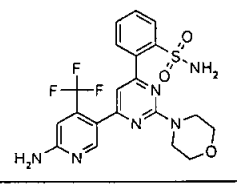
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
509		476.3, 1.65	7.27 L	++++	N/D	+++
510		351.1, 1.74	1.70	+++	N/D	N/D
511		402.2, 1.65	7.51 L	++++	N/D	+++
512		351.2, 1.66	7.85 L	++++	N/D	+++
513		258.2, 1.48	6.33 L	++++	N/D	N/D
514		372.2, 1.65	7.49	++++	N/D	+++
515		359.2, 2.05	11.16 L	++++	N/D	++++

Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
516		387.2, 1.54	6.71 L	++++	N/D	+++
517		373.2, 0.71	5.93	+++	N/D	N/D
518		336.2, 1.61	8.11 L	++++	N/D	++++
519	Chiral 	383.2, 1.44	2.04	++++	N/D	N/D
520	Chiral 	383.2, 1.53	2.09	++++	N/D	+++
521		390.1, 1.59	7.15 L	++++	N/D	+++
522		390.1, 1.75	8.62 L	++++	N/D	+++

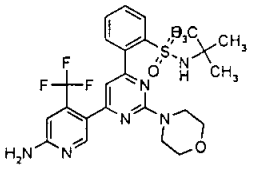
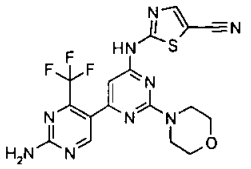
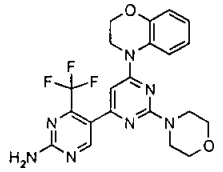
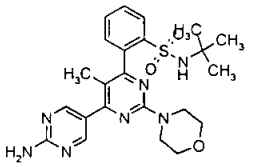
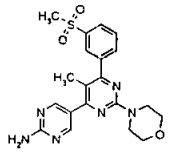
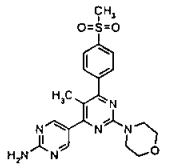
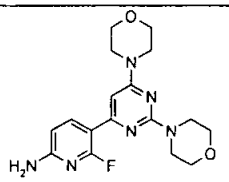
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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
523		293.1, 1.93	2.20	++++	N/D	+++
524		489.1, 2.47		++++	N/D	+++
525		495.2, 2.49		++++	N/D	N/D
526		485.1, 2.90		++++	N/D	+++
527		459.2, 2.75		++++	N/D	+++
528		495.2, 2.47		++++	N/D	+++
529		415.1, 2.06		++++	N/D	+++

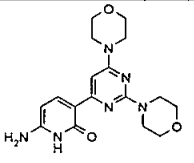
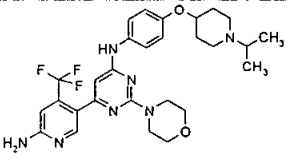
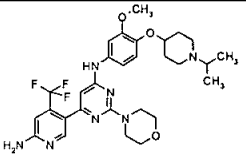
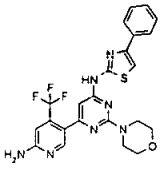
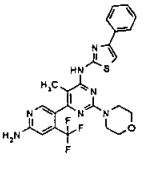
Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
530		413.1, 3.09		++++	N/D	+++
531		413.1, 3.07		++++	N/D	+++
532		515.1, 2.74		++++	N/D	+++
533		481.1, 2.54		+++	N/D	N/D
534		497.1, 3.01		++++	N/D	+++
535		545.1, 3.37		++++	N/D	N/D
536		515.1, 2.79		++++	N/D	N/D

Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
537		481.1, 2.55		++++	N/D	N/D
538		497.1, 2.54	3.00, (15.55)	++++	N/D	N/D
539		469.1, 2.56		++++	N/D	+++
540		489.1, 2.47		++++	N/D	+++
541		417.0, 1.51	1.84, (8.78)	++++	N/D	++
542		469.0, 1.76	2.27, (10.99)	++++	N/D	N/D
543		481.1, 1.93	2.57, (12.58)	++++	N/D	+++

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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
544		536.9, 2.47	3.38, (17.30)	++++	N/D	++
545		449.9, 3.44		++++	N/D	++
546		460.0, 3.00		++++	N/D	+++
547		484.5, 2.28	3.12, (15.46)	+++	N/D	N/D
548		427.3, 1.83	2.49, (11.84)	++++	N/D	+++
549		427.3, 1.82	2.51, (11.79)	++++	N/D	+++
550		360.9, 1.56		N/D	N/D	+++

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Compuesto	Estructura	LC/MS (M+H, Rt minutos)	HPLC de 10 minutos (L = 45 min)	PI3 Cinasa Alfa, IC_{50}	PSer473 AKT, EC_{50}	Proliferación celular, EC_{50}
551		358.9, 1.63		++++	N/D	+++
552		558.3, 1.90		++++	++++	+++
553		588.3, 1.92		++++	++++	++++
554		500.0; 2.46		++++	N/D	+++
555		514.0; 2.62		+++	N/D	N/D

Los compuestos de la Tabla 1 se sintetizaron de acuerdo con los Métodos 1 a 30 y los Ejemplos 1 a 35 proporcionados anteriormente. Los valores IC50 de PI3K y los valores EC_{50} de pSer473 Akt para la inhibición de la fosforilación de Akt se determinaron de acuerdo con los Métodos Biológicos 1 y 2, respectivamente. Los valores EC_{50} de proliferación celular mostrados en la Tabla 1 se determinaron de acuerdo con el Método Biológico 3.

La Tabla 1 muestra los valores IC_{50} y EC_{50} de los compuestos, como se determinaron mediante los Métodos Biológicos 1, 2, 3 y 4, como se describe en la presente. En la Tabla 1, "+" indica que el compuesto tuvo un valor IC_{50} o EC_{50} de >25μM; "++" indica que el compuesto tuvo un valor IC_{50} o EC_{50} de <25μM; "+++" indica que el compuesto tuvo un valor IC_{50} o EC_{50} de >10μM; y "++++"indica que el compuesto tuvo un valor IC_{50} o EC_{50} de >1μM. Un "N/D" en la Tabla 1 indica que no se determinaron los valores.

Cada uno de los compuestos en la Tabla 1 exhibió valores IC_{50} de menos de 10 μM con respecto a la inhibición de PI3K. Muchos de los compuestos de la Tabla 1 exhibieron valores IC_{50} de menos de 1 μM e inclusive menos de 0.1 μM con respecto a la inhibición de PI3K. Por esta razón, cada uno de los compuestos es individualmente preferido, y se prefiere como un grupo. Los valores IC_{50} de la cinasa PI3 alfa mostrados en la Tabla 1 se determinaron de acuerdo con el ensayo de consumo de ATP como se da a conocer en la presente en el Método Biológico 1.

Adicionalmente, muchos de los compuestos de la Tabla 1

exhibieron un valor EC_{50} con respecto a la inhibición de las fosforilación de pSer473 Akt de menos de 10 μM. Muchos de estos compuestos exhibieron valores EC_{50} de menos de 1 μM e inclusive de menos de 0.l μM con respecto a la inhibición de pAkt. La Tabla 1 muestra los valores EC_{50} para la inhibición de la fosforilación de pSER473 AKT. Los ensayos se llevaron a cabo de acuerdo con el Método Biológico 2 descrito en la presente.

En adición, muchos de los compuestos de la Tabla 1 se probaron para determinar su actividad inhibidora en un ensayo de proliferación celular de acuerdo con el Método Biológico 4. Muchos de estos compuestos exhibieron valores EC_{50} de menos de 1 μM, e inclusive de menos de 0.l μM, demostrando su potente capacidad para inhibir la proliferación celular. La Tabla 1 muestra los valores EC_{50} para la inhibición de la proliferación celular de una línea celular de cáncer de ovario, A2780/.

Método Biológico 1:

Ensayos de Fosforilación

Ensayo 1: Ensayo en fase de solución homogénea

Los compuestos que se van a probar se disuelven en sulfóxido de dimetilo, y se distribuyen directamente en placas de evaporación instantánea de 384 pozos a 1.25 microlitros por pozo. Para iniciar la reacción, se agregan 20 microlitros de cinasa PI3 6 nM a cada pozo, seguidos por 20 microlitros de ATP 400 nM que contiene una traza de ATP radiomarcado y 1-alfa-fosfatidil-inositol (PI) 900 nM. Las placas se centrifugan brevemente para remover cualquier hueco de

aire. La reacción se lleva a cabo durante 15 minutos, y entonces se detiene mediante la adición de 20 microlitros de EDTA 100 mM. La reacción detenida se incuba durante la noche a temperatura ambiente para permitir que el sustrato de lípido se enlace mediante la interacción hidrofóbica a la superficie de la placa de evaporación instantánea. Entonces se lava el líquido en los pozos, y el sustrato marcado se detecta mediante conteo de cintilación.

Ensayo 2: Ensayo en fase sólida de un solo paso

Este método es similar al Ensayo 1, excepto que primero se disuelve el sustrato de lípido (1-alfa-fosfatidil-inositol (PIP)) en un regulador de recubrimiento, y se incuba en una placa de evaporación instantánea a temperatura ambiente durante la noche, para permitir que el sustrato de lípido se enlace mediante la interacción hidrofóbica al sustrato de lípido para permitir que el sustrato de lípido se enlace, mediante la interacción hidrofóbica, a la superficie de la placa de evaporación. Entonces se lava el sustrato no enlazado. En el día del ensayo, se agregan 20 microlitros de cinasa PI3 6nM a cada pozo, seguidos por 20 microlitros de ATP 400 nM que contiene trazas de ATP radiomarcado. Los compuestos se agregan junto con la enzima y el ATP a las placas recubiertas con lípido. Las placas se centrifugan brevemente para remover cualquier hueco de aire. La reacción se lleva a cabo durante dos a tres horas. La reacción se detiene mediante la adición de 20 microlitros de EDTA 100 mM, o mediante lavado inmediato de la placa. El sustrato de lípido fosforilado se detecta mediante conteo de cintilación.

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Ensayo 3: Ensayo de consumo de ATP

Los compuestos que se ven a probar se disuelven en sulfóxido de dimetilo, y se distribuyen directamente en una placa negra de 384 pozos a 1.25 microlitros por pozo. Para iniciar la reacción, se agregan 25 microlitros de cinasa PI3 10 nM y 5 microgramos/mililitro de 1-alfa-fosfatidil-inositol (PI) a cada pozo, seguidos por 25 microlitros de ATP 2 µM. La reacción se lleva a cabo hasta que se consume aproximadamente el 50 por ciento del ATP, y entonces se detiene mediante la adición de 25 microlitros de solución de KinaseGlo adquirida en Promega. La reacción detenida se incuba durante 5 minutos, y entonces se detecta el ATP restante mediante luminiscencia.

Método Biológico 2:

Ensayos de $pSer^{473}$ Akt para monitorear la senda de PI3K

En este método, se describe un ensayo para medir el estado de $pSer^{473}$-Akt mediado por PI3K después del tratamiento con los compuestos inhibidores representativos de la invención.

Se cultivaron células A2780 en DMEM complementado con suero bovino fetal al 10 por ciento, L-glutamina, piruvato de sodio, y antibióticos. Las células se aplicaron en el mismo medio a una densidad de 15,000 células por pozo en las placas de cultivo de tejido de 96 pozos, con los pozos externos vacíos, y se les permite adherirse durante la noche.

Los compuestos de prueba suministrados en sulfóxido de dimetilo se diluyeron adicionalmente en sulfóxido de dimetilo a

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500 veces las concentraciones finales deseadas, antes de la dilución en el medio de cultivo hasta 2 veces las concentraciones finales. Se agregaron volúmenes iguales de los compuestos 2x a las células en placas de 96 pozos, y se incubaron a 37°C durante una hora. Entonces se removieron el medio y los compuestos, las placas se helaron, y las células se lisaron en un regulador de lisis (NaCl 150 mM, Tris 20 mM, pH de 7.5, EDTA 1 mM, EGTA 1 mM, Triton X-100 al 1 por ciento) complementado con inhibidores de fosfatasa y proteasa. Después de una mezcla completa, los lisados se transfirieron a ambas placas de ensayo de pSer473Akt Akt total de Meso Scale Discovery (MSD), y se incubaron durante la noche con agitación a 4°C. Las placas se lavaron con regulador de lavado MSD 1 x, y los analitos capturados se detectaron con anticuerpos secundarios. Después de la incubación con el anticuerpo secundario a temperatura ambiente durante 1 a 2 horas, las placas se lavaron nuevamente, y se agregó una concentración 1.5x de Regulador de Lectura T (MSD) a los pozos.

Los ensayos se leyeron en un instrumento SECTOR Imager 6000 (Meso Scale Discovery). Las proporciones de la señal a partir de los ensayos de pSer473Akt Akt total se utilizaron para corregir cualquier variabilidad y se calculó el porcentaje de inhibición de pSer473Akt a partir de la señal total que se ve en las células tratadas con el compuesto contra sulfóxido de dimetilo solo, y se utilizó para determinar los valores EC_{50} para cada compuesto.

Método Biológico 3:

Estudio Farmacológico de Modulación Objetivo y Eficacia en un Modelo de Xenoinjerto de Cáncer de Ovario

Las células de cáncer de ovario A2780 obtenidas de George Coukos (Fox Chase Cancer Center, Universidad de Pensilvania, Filadelfia, PA) se mantuvieron en DMEM (Invitrogen, Inc.) complementado con suero bovino fetal inactivado por calor al 10 por ciento con glutamina al 1 por ciento. Las células se propagaron como fue recomendado por el Dr. Coukos y colaboradores. Se utilizaron ratones nu/nu hembras (de 8 a 12 semanas de edad, de 20 a 25 gramos Charles River) para todos los estudios de farmacología *in vivo*. Los ratones se alojaron y se mantuvieron de acuerdo con los lineamientos estatales y federales para el tratamiento y cuidado humanitario de animales de laboratorio, y recibieron alimento y agua al gusto. Las células de cáncer se cosecharon a partir de los cultivos en fase media-log utilizando tripsina-EDTA (Invitrogen, Inc.). Se inyectaron subcutáneamente cinco millones de células en el flanco derecho de cada ratón. El tratamiento con el compuesto se inició cuando el tamaño del tumor alcanzó de 300 a 400 mm^3 para los estudios farmacocinéticos/farmacodinámicos, y de 200 a 300 mm^3 para los estudios de eficacia. Todo el tratamiento con el compuesto se administró oralmente. Los volúmenes tumorales se determinaron utilizando el software StudyDirector.

Para los estudios del curso del tiempo farmacocinéticos/ farmacodinámicos de modulación objetivo *in vivo*, los tejidos

tumorales se reseccionaron de los ratones individuales en diferentes puntos del tiempo, desde 30 minutos hasta 36 horas después de que se administró oralmente una sola dosis del compuesto (60 o 100 miligramos/kilogramo) o del vehículo. Para los estudios farmacocinéticos/farmacodinámicos dependientes de la dosis, a los ratones que tenían tumor e les dio una sola dosis oral del compuesto en diferentes concentraciones (10, 30, 60 y 100 miligramos/kilogramo o vehículo), y los tumores se reseccionaron a las 10 horas o a las 24 horas después de la dosificación. Se tomaron muestras de sangre mediante punción cardíaca utilizando una jeringa preparada con sulfato de heparina. Los tumores reseccionados se congelaron instantáneamente con hielo seco, y se pulverizaron utilizando un criomortero y pistilo enfriados con nitrógeno líquido, y se lisaron en un regulador de extracción celular frío (Biosource) que contenía una tableta de inhibidor de proteasa (Complete; sin EDTA, Amersham). Los sobrenadantes se tomaron después de la centrifugación de los lisados tumorales a 300 xg durante 10 minutos a 4°C, y se determinó la concentración de proteína en cada sobrenadante mediante BCA (BioRad). Se cargó una cantidad igual de proteína de cada lisado tumoral sobre geles de tris-glicina al 10 por ciento (Invitrogen), para la electroforesis en dodecil-sulfato de sodio/poliacrilamida (SDS-PAGE), después de lo cual, las proteínas se transfirieron desde el gel hasta la membrana de PVDF. Las membranas se sondearon con anticuerpos que reconocen la fosfoAkt^{Ser473} o fosfoAkt^{Thr308} (Cell Signaling), seguidos por la IgG de cabra anti-conejo secundaria

conjugada con HRP (Amersham). Las bandas positivas se visualizaron mediante quimiluminiscencia mejorada con película de rayos-X. Se emplearon procedimientos similares para determinar la AKT total en los mismos lisados tumorales, para servir como la normalización para la proteína total en cada determinación. La densidad de la banda positiva en la película de rayos-X se escaneó, y la modulación objetivo para cada compuesto se expresó como el porcentaje de inhibición por cada compuesto, comparándose con el tratamiento con vehículo. Se utiliza un orden de clasificación (<50 por ciento, 50 a 75 por ciento, >75 por ciento, comparándose con el tratamiento con vehículo) de la inhibición objetivo para la actividad de modulación objetivo del presente compuesto.

Para los estudios de eficacia, las células de cáncer A2780 (5 x 10^6 en 100 microlitros de medio de cultivo DMEM) se inyectaron subcutáneamente en el flanco derecho de cada ratón nu/nu. Cuando los tamaños de los tumores alcanzaron aproximadamente 200 mm^3, los ratones se dosificaron oralmente cada día (q.d.) o dos veces al día (b.i.d.) en tres concentraciones diferentes del compuesto (típicamente a 10, 30 y 100 miligramos/kilogramo) en 100 microlitros de incipiente. El crecimiento del tumor y el peso corporal de los animales se midieron dos veces por semana, con una observación clínica diaria para monitorear las toxicidades potenciales relacionadas con el tratamiento. Típicamente, los estudios se terminaron cuando los tumores en el grupo tratado con vehículo alcanzaron 2500 mm^3 o cuando se observaron efectos clínicos

adversos. La activación de la senda de señalización de PI3K da como resultado la fosforilación de la molécula de señalización corriente abajo Akt en Ser^{473} y/o Thr^{308}. La modulación con el compuesto de la fosforilación de Akt^{Ser473} se examinó en tumores de xenoinjerto A2780 en puntos del tiempo en el intervalo desde 30 minutos hasta 36 horas después de una sola dosis del compuesto a 60 o 100 miligramos/kilogramo. La Tabla 2 resume la modulación de la fosforilación de AKT^{Ser473} mediante los compuestos representativos en los puntos del tiempo de 8 horas o 10 horas. El porcentaje de inhibición se clasificó como <50 por ciento, 50 a 75 por ciento, y >75 por ciento, comparándose con el tratamiento con vehículo.

Tabla 2

Modulación de la fosforilación de Akt^{Ser473} mediante los compuestos de pirimidina representativos de la invención

Compuesto	60 mg/kg	100 mg/kg
91 a las 8 hr		>50 %
183 a las 8 hr		50-75 %
103 a las 8 hr		<50 %
10 a las 10 hr	>75 %	>75 %
84 a las 10 hr	50-75 %	

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Compuesto	60 mg/kg	100 mg/kg
76 a las 10 hr	>75 %	>75 %
66 a las 10 hr	<50 %	

Se probó la eficacia del Compuesto 91 en el modelo de xenoinjerto de tumor A2780. Los ratones que tenían tumores A2780 recibieron la administración oral del Compuesto 91 dos veces al día a 10 y 60 miligramos/kilogramo. La inhibición del crecimiento tumoral (50 por ciento) se observó con el tratamiento de 60 miligramos/ kilogramo, mientras que con 10 miligramos/kilogramo no se observó ninguna actividad inhibidora (Figura 1).

La modesta inhibición del crecimiento tumoral por parte del Compuesto 91 a 60 miligramos/kilogramo cada día se debió a su modulación objetivo de corta vida (la inhibición del 50 por ciento duró 8 horas). Por consiguiente, se evaluó la eficacia anti-tumoral de otros tres compuestos (Compuesto 10, Compuesto 76, y Compuesto 66), que demostraron una inhibición más larga de Akt^{Ser473} (inhibición de >50 por ciento > 10 horas) en tumores A2780 en el modelo A2780. Los compuestos se administraron oralmente cada día cuando los tamaños de los tumores alcanzaron aproximadamente 200 mm^3. El Compuesto 10 demostró una inhibición del crecimiento tumoral dependiente de la dosis: 40 por ciento a 30 miligramos/kilogramo, 70 por ciento a 60 miligramos/kilogramo, y una estasis del crecimiento

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tumoral a 100 miligramos/kilogramo (Figura 2). Se observó una inhibición del crecimiento tumoral dependiente de la dosis similar con el tratamiento con el Compuesto 76 a 30 y 60 miligramos/kilogramo en el modelo de tumor A2780 (Figura 3), mientras que se encontró que el Compuesto 84 posee una actividad anti-tumoral más débil (<50 por ciento TGI a 60 miligramos/kilogramo) (Figura 4).

También se evaluó la actividad anti-tumoral en un régimen de dosificación más frecuente (dos veces al día). Como se muestra en la Figura 5, el Compuesto 10 demostró una actividad anti-tumoral significativa a 30 miligramos/kilogramo cuando se dosificó oralmente dos veces al día. Notoriamente, la inhibición del crecimiento tumoral a 30 miligramos/kilogramo dos veces al día fue más potente que cuando se dosificó en un programa con una dosis diaria equivalente (60 miligramos/kilogramo, Figura 2). Los compuestos fueron bien tolerados en este estudio. Este resultado indicó que la inhibición objetivo sostenida pero menos profunda (cubriendo todo el período de dosificación, pero con una inhibición objetivo de <75 por ciento) en los tumores A2780 mediante el Compuesto 10, fue capaz de inducir una eficacia anti-tumoral significativa.

Aunque se ha ilustrado y descrito la modalidad preferida de la invención, se apreciará que se pueden hacer diferentes cambios en la misma sin apartarse del espíritu y alcance de la invención.

Método Biológico 4:

Estudios de Proliferación Celular en Células A2780

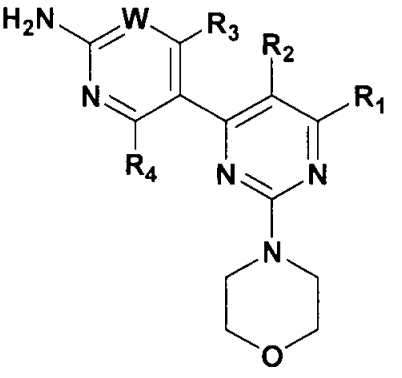
Se determinó la capacidad de los compuestos de la

invención para inhibir la proliferación celular utilizando Cell Titer Glo, un ensayo comercialmente disponible de Promega Corporation. Se sembraron células de cáncer de ovario A2780 en placas e 96 pozos tratadas con TC, a una densidad de 1,000 por pozo en DMEM, suero bovino fetal al 10 por ciento, piruvato de sodio al 1 por ciento, y penicilina/estreptomicina al 1 por ciento, durante un mínimo de 2 horas antes de la adición del compuesto. Para cada concentración del compuesto de prueba, se diluyeron alícuotas de 2 microlitros (500x) del compuesto, o sulfóxido de dimetilo al 100 por ciento, en 500 microlitros del medio de cultivo para la concentración 2x, y luego se diluyeron a 1x sobre las células. Las células se incubaron durante 72 horas a 37°C, con CO_2 al 5 por ciento. Después de la incubación de 72 horas, se agregó el reactivo Cell Titer Glo para determinar el número de células viables restantes después de la exposición al compuesto, y se calculó el valor EC_{50}. El ensayo se llevó a cabo de acuerdo con las instrucciones del fabricante (Promega Corporation, Madison, WI. EUA). Cada condición experimental se llevó a cabo por duplicado. Los resultados se proporcionan en la Tabla 1.

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REIVINDICACIONES

1. Un compuesto que tiene la fórmula I:



I

o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable del mismo, en donde:

W es CR_w o N, en donde R_w se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) halógeno,

(4) metilo,

(5) trifluoro-metilo,

(6) sulfonamido;

R_1 se selecciona a partir del grupo que consiste en

(1) hidrógeno,

(2) ciano,

(3) nitro,

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(4) halógeno,

(5) alquilo sustituido e insustituido,

(6) alquenilo sustituido e insustituido,

(7) alquinilo sustituido e insustituido,

(8) arilo sustituido e insustituido,

(9) heteroarilo sustituido e insustituido,

(10) heterociclilo sustituido e insustituido,

(11) cicloalquilo sustituido e insustituido,

(12) $-COR_{1a}$,

(13) $-CO_2R_{1a}$,

(14) $-CONR_{1a}R_{1b}$,

(15) $-NR_{1a}R_{1b}$,

(16) $-NR_{1a}COR_{1b}$,

(17) $-NR_{1a}SO_2R_{1b}$,

(18) $-OCOR_{1a}$,

(19) $-OR_{1a}$,

(20) $-SR_{1a}$,

(21) $-SOR_{1a}$,

(22) $-SO_2R_{1a}$, y

(23) $-SO_2NR_{1a}R_{1b}$,

en donde R_{1a} y R_{1b} se seleccionan independientemente a partir del grupo que consiste en

(a) hidrógeno,

(b) alquilo sustituido o insustituido,

(c) arilo sustituido e insustituido,

(d) heteroarilo sustituido e insustituido,

(e) heterociclilo sustituido e insustituido, y

(f) cicloalquilo sustituido e insustituido;

R_2 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) nitro,

(4) halógeno,

(5) hidroxilo,

(6) amino,

(7) alquilo sustituido e insustituido,

(8) $-COR_{2a}$, y

(9) $-NR_{2a}COR_{2b}$,

en donde R_{2a} y R_{2b} se seleccionan independientemente a partir del grupo que consiste en:

(a) hidrógeno, y

(b) alquilo sustituido o insustituido;

R_3 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) nitro,

(4) halógeno,

(5) alquilo sustituido e insustituido,

(6) alquenilo sustituido e insustituido,

(7) alquinilo sustituido e insustituido,

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(8) arilo sustituido e insustituido,

(9) heteroarilo sustituido e insustituido,

(10) heterociclilo sustituido e insustituido,

(11) cicloalquilo sustituido e insustituido,

(12) $-COR_{3a}$,

(13) $-NR_{3a}R_{3b}$,

(14) $-NR_{3a}COR_{3b}$,

(15) $-NR_{3a}SO_2R_{3b}$,

(16) $-OR_{3a}$,

(17) $-SR_{3a}$,

(18) $-SOR_{3a}$,

(19) $-SO_2R_{3a}$, y

(20) $-SO_2NR_{3a}R_{3b}$,

en donde R_{3a} y R_{3b} se seleccionan independientemente a partir del grupo que consiste en:

(a) hidrógeno,

(b) alquilo sustituido o insustituido,

(c) arilo sustituido e insustituido,

(d) heteroarilo sustituido e insustituido,

(e) heterociclilo sustituido e insustituido, y

(f) cicloalquilo sustituido e insustituido; y

R_4 se selecciona a partir del grupo que consiste en:

(1) hidrógeno, y

(2) halógeno.

2. Un compuesto de la reivindicación 1, en donde W es N.

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3. Un compuesto de la reivindicación 1, en donde W es CH.

4. Un compuesto de la reivindicación 1, en donde R_1 se selecciona a partir del grupo que consiste en:

(1) alquilo sustituido e insustituido,

(2) arilo sustituido e insustituido,

(3) heteroarilo sustituido e insustituido,

(4) heterociclilo sustituido e insustituido,

(5) cicloalquilo sustituido e insustituido,

(6) $-OR_{1a}$, y

(7) $-NR_{1a}R_{1b}$,

en donde R_{1a} y R_{1b} se seleccionan independientemente a partir del grupo que consiste en:

(a) heteroarilo sustituido e insustituido, y

(b) heterociclilo sustituido e insustituido.

5. Un compuesto de la reivindicación 4, en donde R_1 está heterociclilo sustituido o insustituido, o -O-heterociclilo sustituido o insustituido.

6. Un compuesto de la reivindicación 4, en donde R_1 está morfolinilo sustituido o insustituido.

7. Un compuesto de la reivindicación 6, en donde R_1 es morfolinilo N-enlazado insustituido.

8. Un compuesto de la reivindicación 4, en donde R_1 está tetrahidro-pirano sustituido o insustituido o tetrahidro-piraniloxilo sustituido o insustituido .

9. Un compuesto de la reivindicación 8, en donde R_1 es 4-

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tetrahidro-piraniloxilo insustituido.

10. Un compuesto de la reivindicación 4, en donde R_1 es tetrahidrofurano sustituido o insustituido o tetrahidro-furaniloxilo sustituido o insustituido.

11. Un compuesto de la reivindicación 10, en donde R_1 es 3-tetrahidro-furaniloxilo insustituido.

12. Un compuesto de la reivindicación 1, en donde R_2 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) hidroxilo,

(4) halógeno,

(5) amino,

(6) metilo, y

(7) trifluoro-metilo.

13. Un compuesto de la reivindicación 1, en donde R_2 es hidrógeno o halógeno.

14. Un compuesto de la reivindicación 1, en donde R_2 es hidrógeno.

15. Un compuesto de la reivindicación 1, en donde R_3 se selecciona a partir del grupo que consiste en:

(1) ciano,

(2) nitro,

(3) halógeno,

(4) hidroxilo,

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(5) amino, y

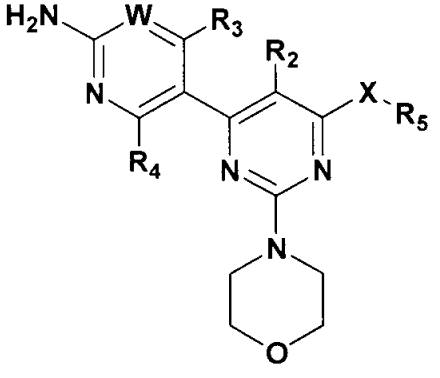
(6) trifluoro-metilo.

16. Un compuesto de la reivindicación 1, en donde R_3 es trifluoro-metilo.

17. Un compuesto de la reivindicación 1, en donde R_3 es ciano.

18. Un compuesto de la reivindicación 2, en donde R_3 es =O.

19. Un compuesto que tiene la fórmula II:



II

o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable del mismo, en donde:

W es CR_w o N, en donde R_w se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) halógeno,

(4) metilo,

(5) trifluoro-metilo, y

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(6) sulfonamido;

X es O, S, NH, o un enlace directo;

R_2 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) nitro,

(4) halógeno,

(5) hidroxilo,

(6) amino,

(7) alquilo sustituido e insustituido,

(8) $-COR_{2a}$, y

(9) $-NR_{2a}COR_{2b}$,

en donde R_{2a} y R_{2b} se seleccionan independientemente a partir del grupo que consiste en:

(a) hidrógeno, y

(b) alquilo sustituido o insustituido;

R_3 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) nitro,

(4) halógeno,

(5) alquilo sustituido e insustituido,

(6) alquenilo sustituido e insustituido,

(7) alquinilo sustituido e insustituido,

(8) arilo sustituido e insustituido,

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(9) heteroarilo sustituido e insustituido,

(10) heterociclilo sustituido e insustituido,

(11) cicloalquilo sustituido e insustituido,

(12) $-COR_{3a}$,

(13) $-NR_{3a}R_{3b}$,

(14) $-NR_{3a}COR_{3b}$,

(15) $-NR_{3a}SO_2R_{3b}$,

(16) $-OR_{3a}$,

(17) $-SR_{3a}$,

(18) $-SOR_{3a}$,

(19) $-SO_2R_{3a}$, y

(20) $-SO_2NR_{3a}R_{3b}$,

en donde R_{3a} y R_{3b} se seleccionan independientemente a partir del grupo que consiste en:

(a) hidrógeno,

(b) alquilo sustituido o insustituido,

(c) arilo sustituido e insustituido,

(d) heteroarilo sustituido e insustituido,

(e) heterociclilo sustituido e insustituido, y

(f) cicloalquilo sustituido e insustituido;

R_4 se selecciona a partir del grupo que consiste en:

(1) hidrógeno, y

(2) halógeno; y

R_5 se selecciona a partir del grupo que consiste en:

(1) cicloalquilo sustituido e insustituido,

(2) heterociclilo sustituido e insustituido,

(3) arilo sustituido e insustituido, y

(4) heteroarilo sustituido e insustituido.

20. Un compuesto de la reivindicación 19, en donde R_2 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) hidroxilo,

(4) amino,

(5) halógeno, y

(6) alquilo de 1 a 3 átomos de carbono sustituido e insustituido.

21. Un compuesto de la reivindicación 19, en donde R_3 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) tio,

(4) halógeno,

(5) nitro,

(6) alquilo sustituido e insustituido,

(7) alquenilo sustituido e insustituido,

(8) alquinilo sustituido e insustituido,

(9) $-OR_{3a}$,

(10) $-NR_{3a}R_{3b}$,

(11) $-COR_{3a}$, y

(12) $-NR_{3a}COR_{3b}$,

en donde R_{3a} y R_{3b} se seleccionan independientemente a partir del grupo que consiste en:

(a) hidrógeno, y

(b) alquilo sustituido o insustituido.

22. Un compuesto de la reivindicación 19, en donde R_3 es trifluoro-metilo.

23. Un compuesto de la reivindicación 19, en donde W es CH.

24. Un compuesto de la reivindicación 19, en donde R_2 es H.

25. Un compuesto de la reivindicación 19, en donde R_5 se selecciona a partir del grupo que consiste en:

(1) morfolinilo sustituido o insustituido,

(2) tetrahidro-piranilo sustituido o insustituido, y

(3) tetrahidro-furanilo sustituido o insustituido.

26. Un compuesto de la reivindicación 19, en donde X es un enlace directo, y R_5 es morfolinilo N-enlazado insustituido.

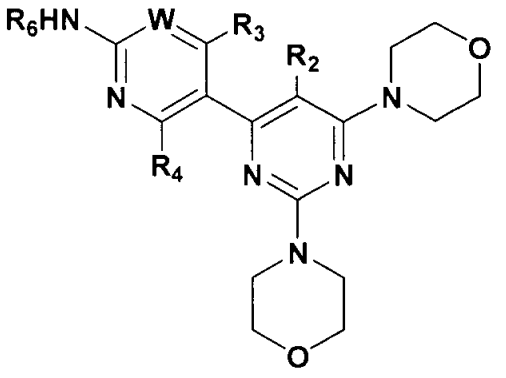
27. Un compuesto de la reivindicación 19, en donde X es O, y R_5 es 4-tetrahidro-piranilo.

28. Un compuesto de la reivindicación 19, en donde X es O, y R_5 es 3-tetrahidro-furanilo.

29. Un compuesto de la reivindicación 19, en donde W es N.

30. Un compuesto de la reivindicación 19, en donde R_3 es =O.

31. Un compuesto que tiene la fórmula III:



III

o un estereoisómero, tautómero, o una sal farmacéuticamente aceptable del mismo, en donde:

W es CR_w o N, en donde R_w se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) halógeno,

(4) metilo,

(5) trifluoro-metilo, y

(6) sulfonamido;

R_2 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) nitro,

(4) halógeno,

(5) hidroxilo,

(6) amino,

(7) alquilo sustituido e insustituido,

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(8) $-COR_{2a}$, y

(9) $-NR_{2a}COR_{2b}$,

en donde R_{2a} y R_{2b} se seleccionan independientemente a partir del grupo que consiste en:

(a) hidrógeno, y

(b) alquilo sustituido o insustituido;

R_3 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) nitro,

(4) halógeno,

(5) alquilo sustituido e insustituido,

(6) alquenilo sustituido e insustituido,

(7) alquinilo sustituido e insustituido,

(8) arilo sustituido e insustituido,

(9) heteroarilo sustituido e insustituido,

(10) heterociclilo sustituido e insustituido,

(11) cicloalquilo sustituido e insustituido,

(12) $-COR_{3a}$,

(13) $-NR_{3a}R_{3b}$,

(14) $-NR_{3a}COR_{3b}$,

(15) $-NR_{3a}SO_2R_{3b}$,

(16) $-OR_{3a}$,

(17) $-SR_{3a}$,

(18) $-SOR_{3a}$,

(19) $-SO_2R_{3a}$, y

(20) $-SO_2NR_{3a}R_{3b}$,

en donde R_{3a} y R_{3b} se seleccionan independientemente a partir del grupo que consiste en:

(a) hidrógeno,

(b) alquilo sustituido o insustituido,

(c) arilo sustituido e insustituido,

(d) heteroarilo sustituido e insustituido,

(e) heterociclilo sustituido e insustituido, y

(f) cicloalquilo sustituido e insustituido;

R_4 se selecciona a partir del grupo que consiste en:

(1) hidrógeno, y

(2) halógeno; y

R_6 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) alquilo sustituido e insustituido, y

(3) cicloalquilo sustituido e insustituido.

32. Un compuesto de la reivindicación 31, en donde R_2 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) ciano,

(3) hidroxilo,

(4) halógeno,

(5) amino,

(6) metilo, y

(7) trifluoro-metilo.

33. Un compuesto de la reivindicación 31, en donde R_3 se selecciona a partir del grupo que consiste en:

(1) ciano,

(2) nitro,

(3) halógeno,

(4) hidroxilo,

(5) amino, y

(6) trifluoro-metilo.

34. Un compuesto de la reivindicación 31, en donde R_6 se selecciona a partir del grupo que consiste en:

(1) hidrógeno,

(2) metilo, y

(3) etilo.

35. Un método para inhibir la fosforilación de Akt en un sujeto humano o animal, el cual comprende administrar a un sujeto humano o animal una cantidad efectiva de un compuesto de cualquiera de las reivindicaciones 1 a 34.

36. Una composición que comprende un vehículo farmacéuticamente aceptable, y una cantidad de un compuesto de cualquiera de las reivindicaciones 1 a 34 efectiva para inhibir la actividad del PI3-K en un sujeto humano o animal cuando se administra al mismo.

37. La composición de la reivindicación 36, efectiva para inhibir la actividad de PI3-K alfa en un sujeto humano o animal

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cuando se administra al mismo.

38. La composición de la reivindicación 35, la cual comprende además cuando menos un agente adicional para el tratamiento de cáncer.

39. La composición de la reivindicación 38, en donde el cuando menos un agente adicional para el tratamiento de cáncer es vatalanib, imatinib o gefitinib.

40. Un método para el tratamiento de una condición mediante la modulación de la actividad de PI3-K, el cual comprende administrar a un sujeto humano o animal que necesite dicho tratamiento, una cantidad efectiva de un compuesto de cualquiera de las reivindicaciones 1 a 34.

41. El método de la reivindicación 40, en donde el compuesto tiene un valor IC_{50} de menos de aproximadamente 1 μM con respecto a la inhibición de PI3K.

42. El método de la reivindicación 40, en donde la condición es cáncer.

43. Un método para inhibir la actividad de PI3-K en un sujeto humano o animal, el cual comprende administrar al sujeto humano o animal una composición que comprende una cantidad de un compuesto de cualquiera de las reivindicaciones 1 a 34, efectiva para inhibir la actividad del PI3-K en un sujeto humano o animal.

44. Un método para el tratamiento de un trastorno de cáncer en un sujeto humano o animal, el cual comprende administrar al sujeto humano o animal una composición que comprende una

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cantidad de un compuesto de cualquiera de las reivindicaciones 1 a 34, efectiva para inhibir la actividad del PI3-K en un sujeto humano o animal.

45. El método de la reivindicación 44, el cual comprende además administrar al sujeto humano o animal cuando menos un agente adicional para el tratamiento de cáncer.

46. El método de la reivindicación 45, en donde el cuando menos un agente adicional para el tratamiento de cáncer es vatalanib, imatinib o gefitinib.

47. El método de la reivindicación 44, en donde el cáncer es cáncer de mama, cáncer de vejiga, cáncer de colon, glioma, glioblastoma, cáncer de pulmón, cáncer de células hepáticas, cáncer gástrico, melanoma, cáncer de tiroides, cáncer endometrial, cáncer renal, cáncer cervical, cáncer pancreático, cáncer esofágico, cáncer de próstata, cáncer de cerebro, o cáncer de ovario.

48. Un método para modular la fosforilación de Akt, el cual comprende poner un compuesto de cualquiera de las reivindicaciones 1 a 34 en contacto con una célula.

49. El método de la reivindicación 48, en donde el compuesto tiene un valor EC_{50} de menos de aproximadamente 1 μM con respecto a la inhibición de pAKT.

50. Un compuesto de cualquiera de las reivindicaciones 1 a 34, para utilizarse en el tratamiento de cáncer.

51. El uso de un compuesto de cualquiera de las reivindicaciones 1 a 34, en la fabricación de un medicamento para el

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tratamiento de cáncer.

52. Un kit, el cual comprende un compuesto de cualquiera de las reivindicaciones 1 a 34, y un inserto del paquete u otra etiqueta, incluyendo instrucciones para el tratamiento de una enfermedad de proliferación celular mediante la administración de una cantidad inhibidora de PI3-K, del compuesto.

53. Un método para inhibir la actividad de cinesina KSP, cuyo método comprende poner en contacto esta cinesina con una cantidad inhibidora efectiva de un compuesto de la reivindicación 1.

54. Un método para inhibir la actividad de cinesina KSP en una célula, cuyo método comprende poner en contacto esta célula con una cantidad inhibidora efectiva de un compuesto de la reivindicación 1.

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RESUMEN

Compuestos inhibidores de cinasa de fosfatidil-inositol (PI)-3 (I), sus sales farmacéuticamente aceptables, y pro-fármacos de los mismos; composiciones de los nuevos compuestos, ya sea solos o en combinación con cuando menos un agente terapéutico adicional, con un vehículo farmacéuticamente aceptable; y usos de los nuevos compuestos, ya sea solos o en combinación con cuando menos un agente terapéutico adicional, en la profilaxis o el tratamiento de enfermedades proliferativas caracterizadas por la actividad anormal de los factores de crecimiento, cinasas de proteína serina/treonina, y cinasas de fosfolípido.

* * * * *

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Compuesto 91 (Oralmente, cada día)

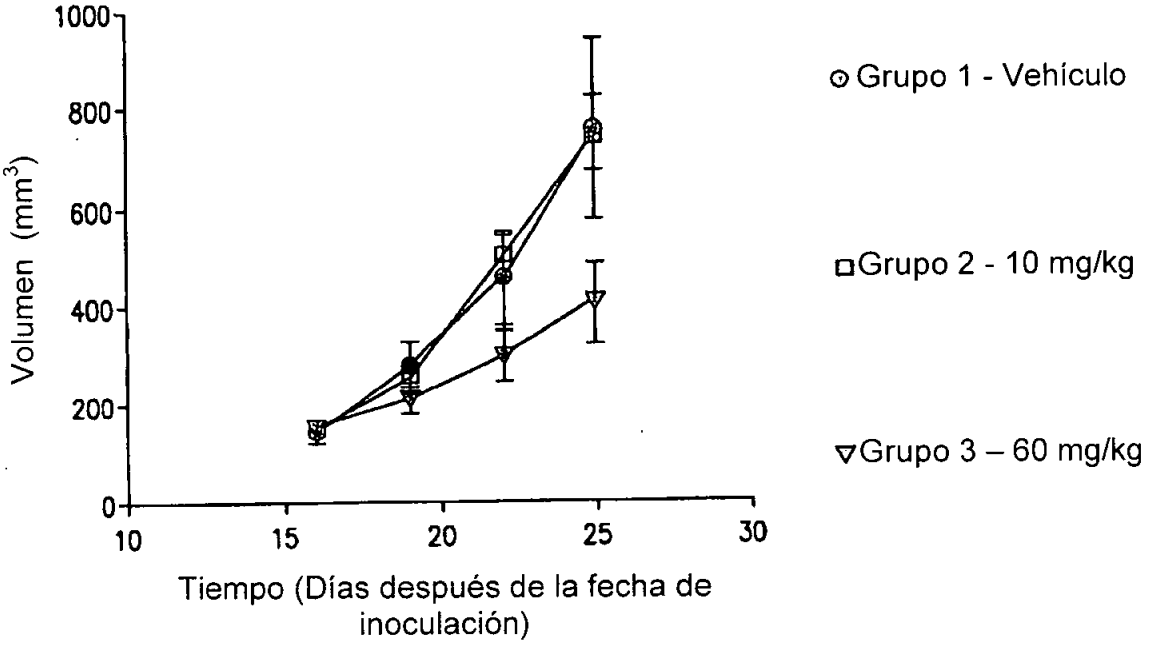


FIG. 1

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Compuesto 10 (Oralmente, cada día)

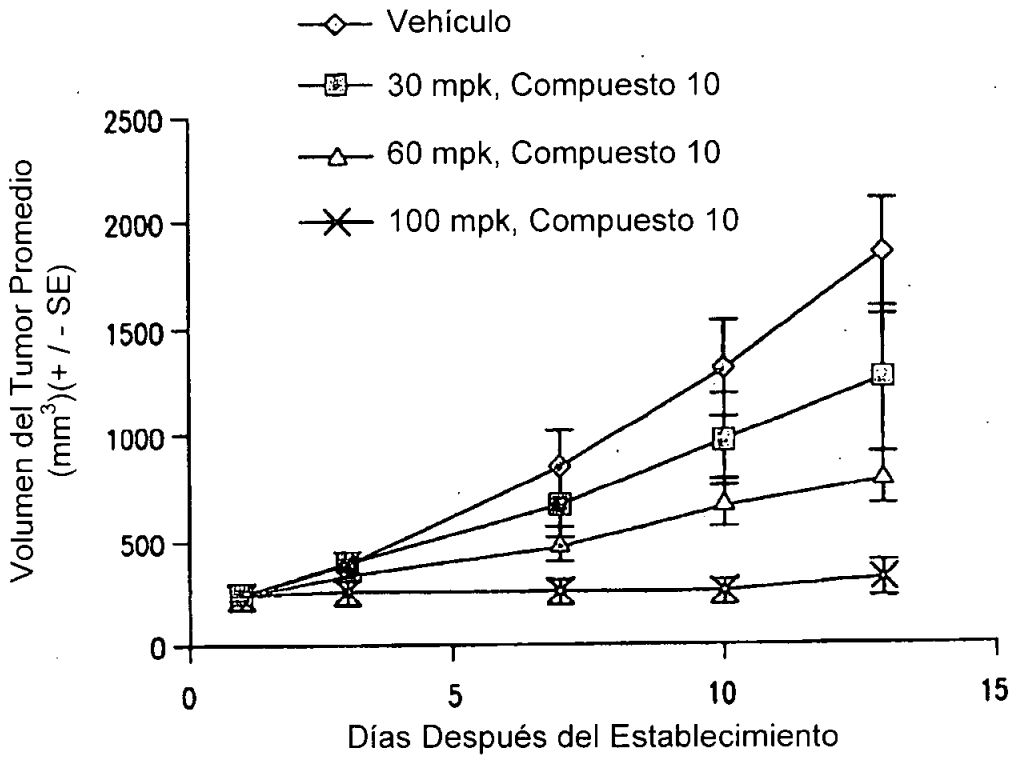


FIG. 2

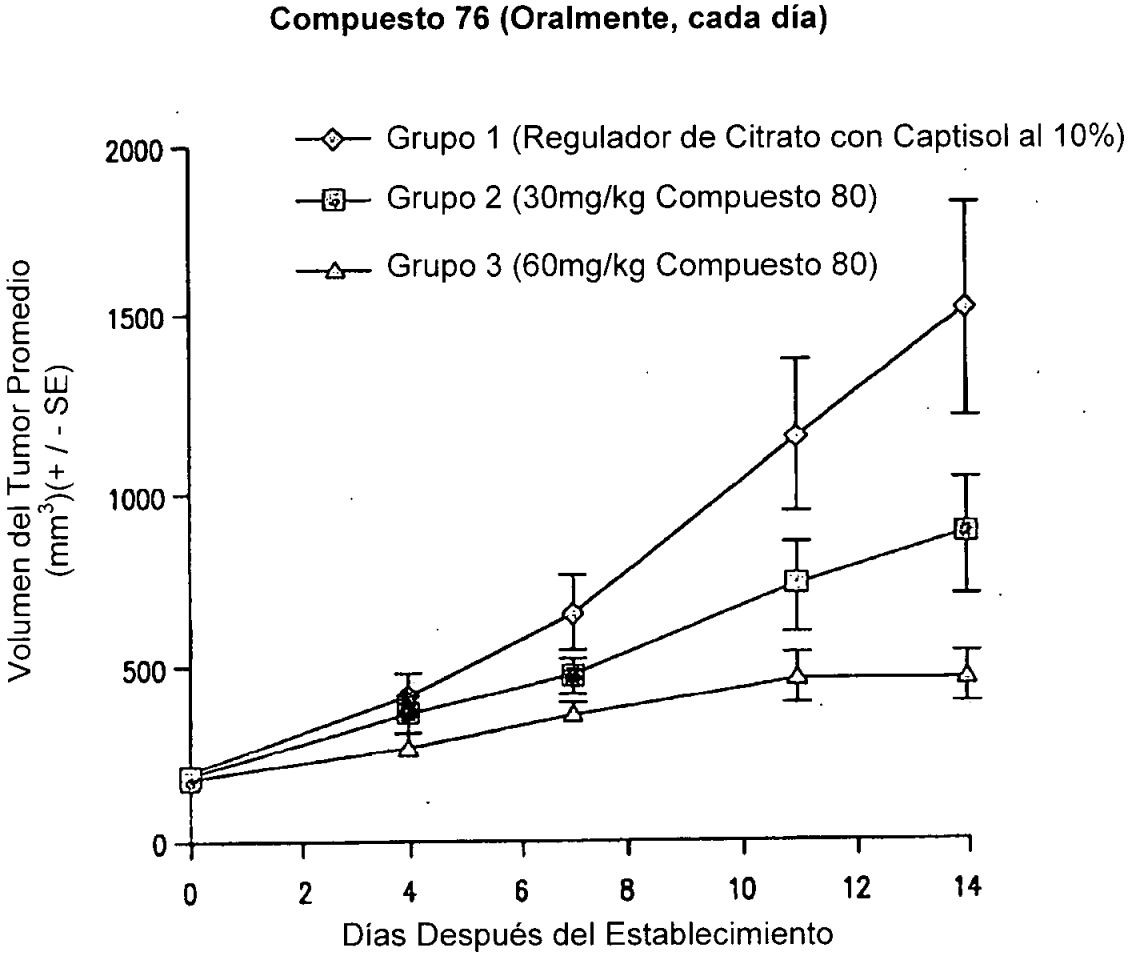

Compuesto 76 (Oralmente, cada día)
Grupo 1 (Regulador de Citrato con Captisol al 10%)
Grupo 2 (30mg/kg Compuesto 80)
Grupo 3 (60mg/kg Compuesto 80)
Volumen del Tumor Promedio
(mm3)(+ / - SE)
2000
1500
1000
500
0
0
2
4
6
8
10
12
14
Días Después del Establecimiento

FIG. 3

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Compuesto 84 (Oralmente, cada día)

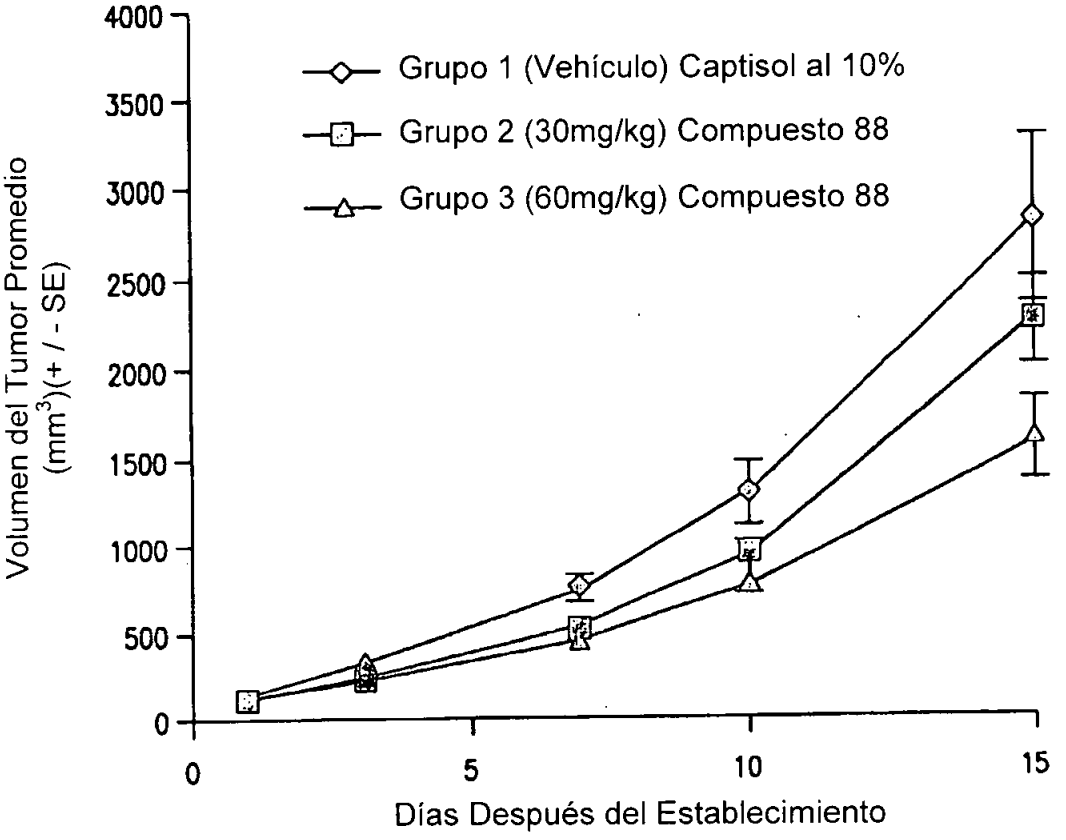


FIG. 4

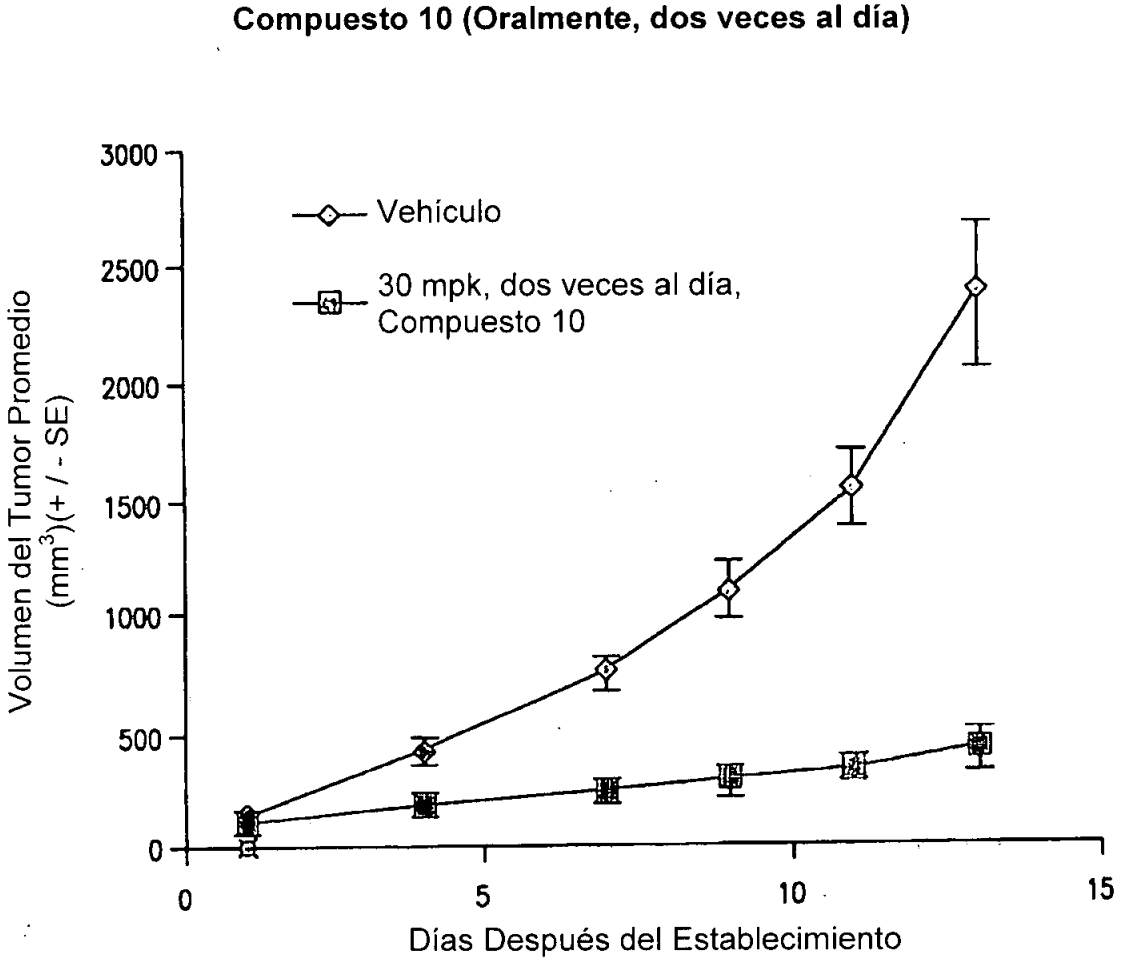

Compuesto 10 (Oralmente, dos veces al día)
Vehículo
30 mpk, dos veces al día, Compuesto 10
Volumen del Tumor Promedio (mm3)(+ / - SE)
3000
2500
2000
1500
1000
500
0
0
5
10
15
Días Después del Establecimiento

FIG. 5

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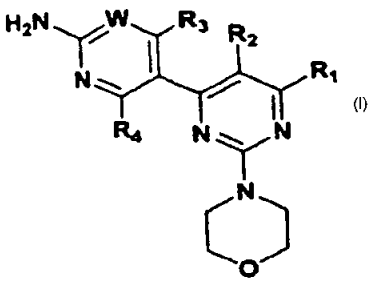
(72) Inventors; and

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(74) Agents: SUH, Young, J. et al.; NOVARTIS VACCINES AND DIAGNOSTICS INC., CORPORATE INTELLECTUAL PROPERTY R338, P.O. Box 897, Emeryville, CA 94662-8097 (US).

[Continued on next page]

(54) Title: PYRIMIDINE DERIVATIVES USED AS PI-3 KINASE INHIBITORS



(I)

(57) Abstract: Phosphatidylinositol (PI) 3-kinase inhibitor compounds (I), their pharmaceutically acceptable salts, and prodrugs thereof; compositions of the new compounds, either alone or in combination with at least one additional therapeutic agent, with a pharmaceutically acceptable carrier; and uses of the new compounds, either alone or in combination with at least one additional therapeutic agent, in the prophylaxis or treatment of proliferative diseases characterized by the abnormal activity of growth factors, protein serine/threonine kinases, and phospholipid kinases.

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, 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, 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).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/001708

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04 C07D401/14 C07D405/12 C07D405/14 C07D417/12
A61K31/506 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

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, BEILSTEIN 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 2004/048365 A (CHIRON CORP [US]; NUSS JOHN M [US]; PECCHI SABINA [US]; RENHOWE PAUL A) 10 June 2004 (2004-06-10) page 31, line 22 - line 33; claims 9,26	1-54
A	WO 2006/005914 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; BAILEY JOHN PETER [GB];) 19 January 2006 (2006-01-19) page 5, line 29 - page 6, line 4; claim 1	1-54
A	WO 2005/028444 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; FINK CYNTHIA ANNE [US]; P) 31 March 2005 (2005-03-31) claim 1; example 15	1-54

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"E" earlier document but published on or after the international filing date

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"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

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"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

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Date of the actual completion of the international search	Date of mailing of the international search report
30 April 2007	10/05/2007

Name and mailing address of the ISA/	Authorized officer
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	Gettins, Marc

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/001708

Box 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 40-54 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 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 all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers 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.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/001708

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004048365 A	10-06-2004	AU 2003295776 A1	18-06-2004
		CA 2507100 A1	10-06-2004
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-074670- -00000-0000

Fecha: 2008-07-18 17:48:39 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 611

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION [ ] MODELO DE UTILIDAD [ ]

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

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- Comprobante de pago de las tasas establecidas [ ]

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- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
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- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Edwin Navarro

Firma Responsable

Fecha 18-07-08

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