# Industria y Comercio
## SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

SOLICITUD

# PATENTE DE INVENCIÓN

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-055349- -00000-0000
Fecha: 2012-04-02 16:43:30 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 388

21. **EXPEDIENTE No.** _____

54. **TÍTULO** COMPUESTOS COMO MODULADORES DE TIROSINA CINASA

51. **CLASIFICACIÓN INTERNACIONAL** _____

71. **SOLICITANTE** ALLERGAN, INC

**DOMICILIO** 2525 Dupont Drive, Irvine, California 92612, Estados Unidos de America

74. **APODERADO** JERÓNIMO CASTILLO BONILLA

22. **BOGOTÁ, D. C.,** _____

(FORMA P-10)

115198-Imprenta Nacional de Colombia-2011

PETITORI

Industria y Comercio
SUPERINTENDENCIA

Espa

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 12-055349- -00000-0000
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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
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# FORMULARIO ÚNICO DE SOLICITUD DE PATENTES
# PCT
# ENTRADA FASE NACIONAL

**SOLICITUD DE REGISTRO DE:**

☒ Patente de Invención ☐ Patente Modelo de Utilidad

☒ Capitulo I ☐ Capitulo II

| | | |
|---|---|---|
| **SOLICITANTES** | Nombre: **ALLERGAN, INC**<br>Dirección: 2525 Dupont Drive<br>Domicilio: Irvine, California 92612,<br>Estados Unidos de América<br>Lugar de Constitución: Delaware<br>Teléfono: Fax:<br>E - mail: | **IDENTIFICACIÓN**<br>☐ C.C. ☐ NIT<br>☐ C.E. ☐ Otro<br>Cual: _____<br>Número: _____ |
| **REPRESENTANTE O APODERADO** | Nombre: **JERÓNIMO CASTILLO BONILLA**<br>Dirección: Calle 93A Nº 14-17, Ofc 311<br>Teléfono: 2363493 Fax: 2182351<br>E-mail: info@pcastillopineda.com | **IDENTIFICACIÓN**<br>☒ C.C. ☐ NIT<br>☐ C.E. ☐ Otro<br>Número: 79462057 TP: 104167 |
| **INVENTORES** | Nombre: Xialing GUO<br>Dirección: 2912 Canto De Los Ciervo, San Clemente, California 92673,<br>Estados Unidos de América.<br>Nacionalidad o Domicilio: Estadounidense | |

Solicitud Internacional No.: PCT/US2010/047800 Fecha: Septiembre 3, 2010
Publicación Internacional No.: WO 2011/028995 Fecha: Marzo 10, 2011

**Titulo**:
COMPUESTOS COMO MODULADORES DE TIROSINA CINASA

**Clasificación Internacional**:

**Prioridad**
☒ SI ☐ NO

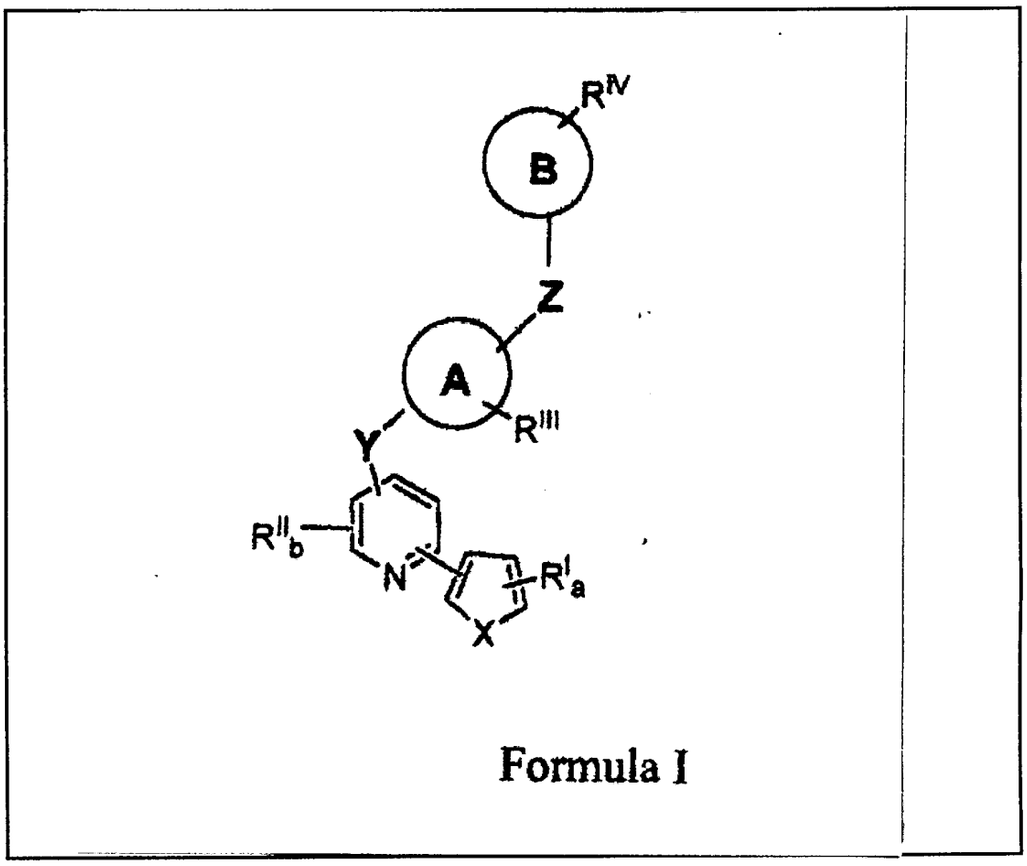
| País de Origen | Fecha | Número de Solicitud |
|---|---|---|
| US | Septiembre 3, 2009 | 61/239.603 |
| US | Febrero 22, 2010 | 61/306.616 |
| US | Junio 21, 2010 | 61/356.699 |
| US | Julio 1, 2010 | 61/360.531 |

**Comprobante de pago No:** **Fecha:**

Anexos

- ☒ Comprobante de pago de la tasa de presentación de la solicitud.
- ☒ Documento que acredita la existencia y representación legal de la persona jurídica peticionaria, en cuanto no estén inscritas en alguna Cámara de Comercio Colombiana.
- ☒ Poderes, si fuere el caso.
- Documento de cesión del inventor al solicitante o a su causante.
- ☒ 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)
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- ☐ 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 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☐ Otros.

**11. FIGURA CARACTERÍSTICA:**




Formula I

**12. Solicito la concesión de la patente**

**NOMBRE: JERÓNIMO CASTILLO B.**

**FIRMA:**

**C.C. 79.462.057 T.P. 104167**

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

(Continuación Inventores)

Nombre : Zhen ZHU
Dirección : 12 Banyan, Foothill Ranch, California 92612, Estados Unidos de América
Nacionalidad : china

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FOR PATENTS AND TRADE MARKS IN
COLOMBIA

| | **Poder General** | **General Power of Attorney** |
|---|---|---|
| 1 Applicant's name | (1) | ALLERGAN, INC. |
| 2 Applicant's address | domiciliado en (2) | domiciled in (2) 2525 Dupont Drive Irvine, CA 92612 USA |

-1

nombra al Dr. JERONIMO CASTILLO BONILLA y/o Dra. XIMENA BONILLA PEREIRA, y/o Dr. ALVARO CASTILLO GRAU, Calle 93A N° 14-17 Oficina 311 en Bogotá, Colombia, como sus representantes con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades Colombianas, administrativas, judiciales o de policía, en primera o segunda instancia, la obtención de Patentes de Invención, Registro de Marcas, de Modelos y de Dibujos Industriales, de Nombres Comerciales y Enseñas, Lemas Comerciales y Denominaciones de Origen, lo mismo que traspasos, extensiones, renovaciones, cambios de nombre, registro de licencias de explotación y registro de licencias de uso referentes a tales actuaciones, cancelación de Registros de marca, a cuyo efecto les faculta para dar ante dichas autoridades todos los pasos necesarios al objeto indicado, elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, apelaciones y reclamos, solicitar la aplicación de medidas cautelares; solicitar la nulidad de Patentes de Invención, modelos de utilidad, diseños industriales, así como la de registros de marcas ante la autoridad nacional competente; aceptar en nuestro nombre y representación la Cesión de derechos de invención y de patente de invención que se nos haga por cualquier persona, abonar todos los impuestos, cuotas y pagos determinados por la ley, recibir todos los documentos y valores dando el descargo respectivo, llenar cualesquiera otros requisitos, desistir y tomar en fin todas las medidas que creyeren conducentes al resguardo de nuestros intereses y en caso de presentarse oposiciones y/o observaciones para que intervengan como demandantes o como demandados, con todas las demás facultades necesarias, así como iniciar y tramitar procesos jurisdiccionales relativos a competencia desleal. Este poder comprende además las facultades de recibir, desistir, transigir, comprometer, sustituir, revocar sustituciones, conciliar, recibir notificaciones y nombrar apoderados judiciales o extrajudiciales.

hereby appoint, JERONMO CASTILLO BONILLA and/or XIMENA BONILLA PEREIRA, and/or ALVARO CASTILLO GRAU, Calle 93A N° 14-17 Office 311 en Bogotá, Colombia, as our representatives with special, ample and sufficient power to obtain from the offices and Colombian authorities, administrative, judicial and police, in first or in second instance, Privileged Patents of invention, Registration of Trade Marks, of Models and Industrial Drawings, of Commercial Names and ensigns, Commercial slogans and Origin Denominations as well as assignments, extensions, renewals, changes of name, registration of license of exploitation and of license of use referred to said actions, Cancellation Actions against trademark Registrations, who are empowered to take before said authorities all of the necessary steps for the purposes indicated, to file applications, to formulate descriptions, corrections, protests, declarations, appeals, and claims, apply for precautionary measures; apply for the nullity of Patent Inventions, Utility Models, Industrial Designs, as well as for Trademark Registrations before the competent national authority; to accept on our behalf and representation the assignment of rights of inventions and titles of invention that may be done to us by any person, to pay all taxes, quotas and payments prescribed by law, to receive all the documents and proceeds giving the respective acquittance or receipt, to fulfill any other requisites to desist and take in fact any other measures that may be deemed conducive to the safeguard of our interests, and in case that oppositions and/or observations are presented to intervene as complainant and defendant, with all necessary legal faculties, as well as to file jurisdictional processes related to disloyal competition. This power of attorney includes the faculties to receive, desist, compromise, transact substitute it in all or in part, to revoke substitutions, to conciliate, to receive notifications and to appoint extra-judicial or judicial attorneys.

3 Date
4 Applicant's signature

Dado y firmado en (3).....
.....
.....

Given and signed in (3).....
Irvine, California
April 12, 2005

4)Signature (s)

Martin A. Voet
Assistant Secretary

# State of California

## SECRETARY OF STATE

# *APOSTILLE*

*(Convention de La Haye du 5 octobre 1961)*

1. *Country: United States of America*
   *This public document*
2. *has been signed by TAMARA J. HALLEN*
3. *acting in the capacity of Notary Public, State of California*
4. *bears the seal/stamp of TAMARA J. HALLEN, Notary Public, State of California*

## *CERTIFIED*

5. *At Sacramento, California*
6. *the 21st day of April 2005*
7. *by Deputy Secretary of State, State of California*
8. *No. 236021*
9. *Seal/Stamp:*

10. *Signature*

BRUCE McPHERSON
Secretary of State

BY

NP-24 A (REV. 2-05)

OSP 05 88438

## CALIFORNIA ALL-PURPOSE ACKNOWLEDGMENT

State of California
County of Orange } ss.

On April 12, 2005 (Date) before me, Tamara J. Hallen, Notary Public (Name and Title of Officer (e.g., "Jane Doe, Notary Public"))

personally appeared Martin A. Voet (Name(s) of Signer(s))

☑ personally known to me
☐ proved to me on the basis of satisfactory evidence

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

TAMARA J. HALLEN
Commission # 1414872
Notary Public - California
Orange County
My Comm. Expires May 29, 2007

WITNESS my hand and official seal.

Tamara J. Hallen
Signature of Notary Public

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Document Date: April 12, 2005 Number of Pages: 1

Signer(s) Other Than Named Above: none

### Capacity(ies) Claimed by Signer

Signer's Name: Martin A. Voet

☐ Individual
☐ Corporate Officer — Title(s): Assistant Secretary
☐ Partner — ☐ Limited ☐ General
☐ Attorney-in-Fact
☐ Trustee
☐ Guardian or Conservator
☐ Other: _____

Signer Is Representing: Allergan, Inc.

RIGHT THUMBPRINT OF SIGNER
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**Pedro Castillo Pineda Y Asociados**

# AFFIDAVIT

I, (name), hereby solemnly and truly declare that I am (post of) for ALLERGAN, INC, domiciled at 2525 Dupont Drive, Irvine, California 92612, United States of America, Corporation organized in accordance with the laws of the State of ~~California~~ Delaware and that I am empowered to grant this declaration.

Signed this 19th day of July, 2006.

ALLERGAN, INC

By: (Signature)
Name

Martin A. Voet, Assistant Secretary

Note: Notarized and Legalized up by Apostille

# State of California

## SECRETARY OF STATE

# *APOSTILLE*

*(Convention de La Haye du 5 octobre 1961)*

1. *Country: United States of America*
   *This public document*
2. *has been signed by Angel Cardenas*
3. *acting in the capacity of Deputy Clerk-Recorder, County of Orange, State of California*
4. *bears the seal/stamp of the County of Orange, State of California*

***CERTIFIED***

5. *At Sacramento, California*
6. *the 3rd day of August 2006*
7. *by Deputy Secretary of State, State of California*
8. *No. 297443*
9. *Seal/Stamp:*



10. *Signature*




Bruce McPherson

Secretary of State

BY Jaime Winkel

NP-24 A (REV. 4-05)

OSP 05 90772

STATE OF CALIFORNIA

County of Orange

I, **TOM DALY**, County Clerk-Recorder in and for said County, having by law a seal do hereby certify that **MARY LOU MC NOWN** whose name is subscribed to the attached certificate of acknowledgement, proof of affidavit, was at the time of taking such acknowledgment, proof or affidavit, a Notary Public IN AND FOR ORANGE COUNTY, duly commissioned and sworn and residing in said County, and was, as such, an officer of said State, duly authorized by the laws thereof to take and certify the same, as well as to take and certify the proof and acknowledgment of deeds and other instruments in writing to be recorded in said State, and that full faith and credit are and ought to be given to his official acts; that the impression of his official seal is not required by law to be filed in the office of the County Clerk-Recorder. I further certify that I am well acquainted with his hand writing and verily believe that the signature to the attached certificate is his genuine signature, and further that the annexed instrument is executed and acknowledged according to the laws of the State of California.

IN WITNESS WHEREOF, I have hereunto set my hand and affixed the seal of said County Clerk-Recorder.

**This 25th day of JULY 2006**

**TOM DALY**
County Clerk-Recorder in and for
the County of Orange

By _____ Deputy
**ANGEL CARDENAS**

## CALIFORNIA ALL-PURPOSE ACKNOWLEDGMENT

State of California

County of ORANGE } ss.

On JULY 19 2006 Date before me, MARY LOU MCNOWN, NOTARY PUBLIC Name and Title of Officer (e.g., "Jane Doe, Notary Public")

personally appeared MARTIN A. VOET Name(s) of Signer(s)

MARY LOU MC NOWN
Commission # 1431736
Notary Public - California
Orange County
My Comm. Expires Aug 16, 2007

☒ personally known to me
☐ proved to me on the basis of satisfactory evidence

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

WITNESS my hand and official seal.

Mary Lou McNown
Signature of Notary Public

MARY LOU MC NOWN
Commission # 1431736
Notary Public - California
Orange County
My Comm. Expires Aug 16, 2007

MARY LOU MC NOWN
Commission # 1431736
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Commission # 1431736
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Orange County
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**Capacity(ies) Claimed by Signer**

Signer's Name: _____

☐ Individual
☐ Corporate Officer — Title(s): _____
☐ Partner — ☐ Limited ☐ General
☐ Attorney-in-Fact
☐ Trustee
☐ Guardian or Conservator
☐ Other: _____

Signer Is Representing: _____

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# COMPUESTOS COMO MODULADORES DE TIROSINA CINASA

INVENTORES: Xialing Guo y Zhen Zhu

## REFERENCIA CRUZADA A SOLICITUDES RELACIONADAS

La presente invención reivindica prioridad conforme al 35 U.S.C. 119(e) de las solicitudes provisionales estadounidenses Nº 61/239,603, presentada el 03 de setiembre de 2009, 61/306,616, presentada el 22 de febrero de 2010, 61/356,699, presentada el 21 de julio de 2010 y 61/360,531, presentada el 01 de julio de 2010, las cuales se incorporan expresamente a la presente en su totalidad mediante esta referencia.

## CAMPO DE LA INVENCIÓN

La presente invención se refiere a compuestos novedosos con múltiples componentes aromáticos capaces de modular, regular y/o inhibir la transducción de señales de la tirosina cinasa. La presente invención se refiere también a métodos para la prevención y/o tratamiento de trastornos relacionados con la transducción de señales de la tirosina cinasa no regulada, incluidos de modo no taxativo, trastornos de crecimiento celular, trastornos metabólicos, trastornos proliferativos de vasos sanguíneos, trastornos inflamatorios, enfermedades neurodegenerativas y trastornos inmunes.

## ANTECEDENTES DE LA INVENCIÓN

Las proteínas tirosina cinasas (PTK) cumplen una función importante en el control del crecimiento y la diferenciación celular. Las PTK comprenden una clase extensa y diversa de proteínas que tienen actividad enzimática. Las PTK pueden ser del tipo receptor (tienen dominios extracelulares, transmembrana e intracelulares) o del tipo no receptor (son totalmente intracelulares). Por ejemplo, la transducción de señales mediada por el receptor de tirosina cinasas (RTK) se inicia mediante la interacción extracelular con un factor de crecimiento específico (esto es, un ligando), seguido de la dimerización del receptor, la estimulación transitoria de la fosforilación y actividad de la proteína tirosina cinasa intrínseca. Los sitios de unión entonces se crean para moléculas de transducción intracelular de señales y conducen a la formación de complejos con un espectro de moléculas de señalización citoplásmica que facilitan la apropiada respuesta celular (por ej., división celular, homeostasis metabólica y respuestas al microambiente extracelular).

Con respecto al RTK, se ha demostrado también que los sitios de fosforilación de tirosina funcionan como sitios de unión de alta afinidad para dominios SH2 (homología src) de moléculas de señalización. Diversas proteínas de sustrato intracelular que se asocian a los RTK se identificaron y se dividieron en dos grupos principales: (1) sustratos que tienen dominio catalítico; y (2) sustratos que carecen de un dominio catalítico pero que sirven como adaptadores y se asocian a las moléculas catalíticamente activas. La especificad de las interacciones entre receptores y proteínas y dominios SH2 de sus sustratos se determina por los residuos de aminoácidos inmediatamente en torno al residuo de tirosina fosforilado. Diferencias en las afinidades de unión entre los dominios SH2 y las secuencias de aminoácidos en torno a los residuos de fosfotirosina en receptores particulares son consecuentes con las diferencias observadas en sus perfiles de fosforilación del sustrato. Estas

observaciones sugieren que la función de cada RTK está determinada no solo por su patrón de expresión y disponibilidad de ligando sino también por la gama de vías de transducción de señales corriente abajo que se activan mediante un receptor particular. Por lo tanto, la fosforilación proporciona un paso regulador importante que determina la selectividad de las vías de señalización adquiridas por receptores del factor de crecimiento específicos así como receptores del factor de diferenciación.

Los RTK comprenden una gran familia de receptores de transmembrana con diversas actividades biológicas. La función intrínseca de los RTK se activa tras la unión de ligandos que da como resultado la fosforilación del receptor y múltiples sustratos celulares y posteriormente una variedad de respuestas celulares. Hoy en día, se han identificado al menos diecinueve subfamilias RTK distintas. Una subfamilia de RTK, denominada subfamilia HER, se cree que está compuesta por EGFR, HER2, HER3 y HER4. Los ligandos de la subfamilia HER de receptores incluyen el factor de crecimiento epitelial (EGF), TGF-$\alpha$, anfiregulina, HB-EGF, betacelulina y heregulina. La segunda subfamilia de los RTK, denominada subfamilia de insulina, está compuesta por las subfamilias INS-R, IGF-1R e IR-R. La tercera subfamilia de RTK, la familia "PDGF", incluye receptores $\alpha$ y $\beta$ de PDGF, CSFIR, c-kit y FLK-II. Otra subfamilia de los RTK, identificada como la familia FLK, se cree que está compuesta por el receptor con dominio inserto-cinasa cinasa de hígado fetal 1 (KDR/FLK-1), la cinasa de hígado fetal 4 (FLK-4) y la tirosina cinasa tipo fms (flt-1). Inicialmente, se creía que cada uno de estos receptores era un receptor de factores de crecimiento hematopoyético. Otras dos subfamilias de los RTK se han denominado familia receptora FGF (FGFR1, FGFR2, FGFR3 y FGFR4) y la subfamilia Met (c-met y Ron). Dadas las similitudes entre las subfamilias PDGF y FLK, las dos subfamilias se consideran comúnmente juntas. Las subfamilias conocidas de RTK se identifican en Plowman et ál, 1994, DN&P 7(6): 334-339, la cual se incorpora a la presente en su totalidad mediante esta referencia.

Las tirosina cinasas no receptoras representan un grupo de enzimas celulares que carecen de secuencias extracelulares y de transmembrana. Hoy en día, se han identificado más de veinticuatro tirosina cinasas no receptoras individuales que comprenden once subfamilias (Src, Frk, Btk, Csk, Abl, Zap70, Fes/Fps, Fak, Jak, Ack y LIMK). Hoy en día, la subfamilia Src de tirosina cinasa está compuesta por la mayor cantidad de PTK e incluye Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr e Yrk. La subfamilia Src de enzimas se ligó a la oncogénesis. Una discusión más detallada de las tirosina cinasas no receptoras se proporciona en Bolen, 1993, Oncogen 8: 2025-2031, la cual se incorpora a la presente en su totalidad mediante esta referencia.

Muchas de las proteínas tirosina cinasas (PTK), ya sea un RTK o una tirosina cinasa no receptora, se han visto implicadas en vías de señalización celular que llevan a cascadas de señales celulares y afecciones patogénicas tales como, cáncer, psoriasis e hiper respuestas inmunitarias. Considerando la importancia de las PTK en el control, la regulación y modulación de la proliferación celular y las enfermedades y trastornos asociados a la proliferación de células anormales, se han intentado identificar "inhibidores" de la tirosina cinasa receptora o no receptora usando una variedad de enfoques, incluidos el uso de ligandos mutantes (patente estadounidense Nº 4,966,849), receptores solubles y anticuerpos (Kendall & Thomas, 1994, Proc. Nat'l Acad. Sci 90: 10705-09; Kim, et ál, 1993, Nature 362: 841-844), ligandos de ARN (Jellinek, et ál, Biochemistry 33: 10450-56); Takano, et ál, 1993, Mol. Bio. Cell 4:358A; Kinsella, et ál, 1992, Exp. Cell Res. 199: 56-62; Wright, et ál, 1992, J. Cellular Phys. 152: 448-57) e inhibidores de tirosina cinasa (patente estadounidense Nº 5,330,992; Mariani, et ál, 1994, Proc. Am. Assoc. Cancer Res. 35: 2268).

Más recientemente, se han tratado de identificar pequeñas moléculas que actúan como inhibidores de la tirosina cinasa. Por ejemplo, se han descrito en general compuestos bis monocíclicos, bicíclicos o heterocíclicos arilo (solicitud PCT Nº WO 92/20642), derivados de vinilen-azaindol (solicitud PCT Nº WO 94/14808) y 1-ciclopropil-4-piridil-quinolonas (patente estadounidense Nº 5,330,992) como inhibidores de la tirosina cinasa. Se describieron compuestos de estirilo (patente estadounidense Nº 5,217,999), compuestos de piridilo sustituidos por estirilo (patentes estadounidense Nº 5,302,606), determinados derivados de quinazolina (solicitud EP Nº 0 566 266 A1), seleoindoles y selenidas (solicitud PCT Nº WO 94/03427), compuestos polihidroxílicos tricíclicos (solicitud PCT Nº WO 92/21660) y compuestos de ácido bencilfosfónico (solicitud PCT Nº WO 91/15495) como compuestos para su uso como inhibidores de tirosina cinasa para su uso en el tratamiento de cáncer.

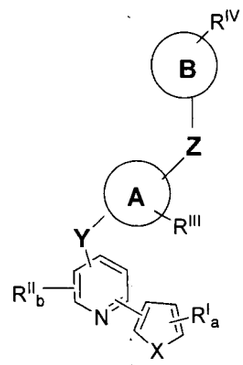
Además, otras moléculas pequeñas se estudiaron como inhibidores de tirosina cinasa, tales como los compuestos descritos en las patentes estadounidenses Nº 6,765,012; 6,541,504; 6,747,025; 5,792,783; 5,834,504; 5,883,113; 5,883,116 y 5,886,020, todas las cuales se incorporan a la presente en su totalidad mediante esta referencia.

La identificación y el uso de compuestos que inhiben específicamente la transducción de señales modulando la actividad de la tirosina receptora y no receptora es un aspecto de la presente invención.

## BREVE DESCRIPCIÓN DE LA INVENCIÓN

La presente invención se refiere a compuestos representados por la Fórmula I capaces de modular, regular y/o inhibir la transducción de señales de tirosina cinasa y a los usos de los compuestos para el tratamiento y la prevención de enfermedades.

Los compuestos de la presente invención se pueden encontrar en la Fórmula general I:




Fórmula I

donde

X se selecciona del grupo que consiste en $NR^1$, O, $S(O)_n$;

n es 0 o un entero de 1 a 2;

$R^1$ se selecciona independientemente del grupo que consiste en hidrógeno, alquenilo, alcoxialquilo, $CF_3$, alquilo, alquilcarbonilo, alcoxicarbonilo, arilo, heterocicloalquilo, hidroxialquilo y $(NR^2R^3)$alquilo, donde $R^2$ y $R^3$ se seleccionan

independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa, $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

$R^I$ se selecciona del grupo que consiste en hidrógeno, halógeno, alquilo $C_1$ a $C_8$, $S(O)_fR^4$, $(CR^5R^6)_dC(O)OR^4$, $S(O)_f(CR^5R^6)_dC(O)OR^4$, $(CR^5R^6)_dAr$, $NR^4(CR^5R^6)_dAr$, $O(CR^5R^6)_dAr$, $S(O)_f(CR^5R^6)_dAr$, $(CR^5R^6)_dS(O)_fR^4$, $NR^4(CR^5R^6)_dS(O)_fR^4$, $O(CR^5R^6)_d$ $S(O)_fR^4$, $S(O)_f(CR^5R^6)_eS(O)_fR^4$, $(CR^5R^6)_dC(O)N(R^4)_2$, $NR^4(CR^5R^6)_dC(O)N(R^4)_2$, $O(CR^5R^6)_dC(O)N(R^4)_2$, $S(O)_f(CR^5R^6)_eC(O)N(R^4)_2$, $(CR^5R^6)_dOR^4$, $S(O)_f(CR^5R^6)_dOR^4$, $(CR^5$ $R^6)_dOSO_2R^4$, $S(O)_f(CR^5R^6)_eOSO_2R^4$, $(CR^5R^6)_dP(O)(OR^4)_2$, $S(O)_f(CR^5$ $R^6)_eP(O)(OR^4)_2$, $OC(O)(CR^5R^6)_dN(R^4)_2$, $C(O)(CR^5R^6)_dN(R^4)_2$, $C(O)N{=}S(O)R^5R^6$, $NR^2C(O)(CR^5R^6)_dN(R^4)_2$, $(CR^5R^6)_dR^5$, $S(O)_f(CR^5R^6)_dR^5$, $HNC(O)R^4$, $HN\text{-}C(O)OR^4$, $(CR^5R^6)_dN(R^4)_2$, $S(O)_f(CR^5R^6)_dN(R^4)_2$, $OC(O)OR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dOR^4$, y $(CR^5R^6)_dC(O)(CR^5R^6)_dN(R^4)_2$, donde cada $R^4$ se selecciona independientemente del grupo que consiste en hidrógeno, hidroxilo, alquilo $C_1$-$C_8$, arilo, hidroxialquilo $C_1$-$C_8$, alcoxialquilo $C_1$-$C_8$, $(CR^5R^6)_d$ y $N(R^4)_2$ puede formar un anillo heterocíclico de 3-7 miembros que comprende aziridina, azetidina, pirrolidina, 5-fluoropirrolidina, piperidina, 6-fluoropiperidina, N-metilpiperazina, morfolina, 2,6-dimetilmorfolina, tiomorfolina y donde dicho anillo heterocíclico se puede sustituir opcionalmente con hasta tres de $R^5$; donde $R^5$ y $R^6$ se seleccionan independientemente del grupo que consiste en hidrógeno, halo, hidroxilo, alquilo $C_1$-$C_8$, hidroxialquilo $C_1$-$C_8$, alcoxialquilo $C_1$-$C_8$, alcoxicarbonilalquilo, alcoxicarbonilo, hidroxicarbonilo, hidroxicarbonilalquilo, amida, alquilamida, amidoalquilo, sulfonato y $CR^5R^6$ puede representar un anillo carbocíclico o heterocíclico de entre 5 y 6 carbonos o, de manera alternativa, $(CR^5R^6)_d$ y $(CR^5R^6)_e$ pueden formar un anillo carbocíclico o heterocíclico de 3-7 miembros, donde el anillo se puede sustituir opcionalmente con hasta tres de hidroxilo, halo, alquilo $C_1$-$C_8$, hidroxialquilo $C_1$-$C_8$, alcoxialquilo $C_1$-$C_8$, alcoxicarbonilalquilo, alcoxicarbonilo, hidroxicarbonilo, hidroxicarbonilalquilo, amida, alquilamida, amidoalquilo y sulfonato;

a es 0 o un entero de 1 a 3;

d es 0 o un entero de 1 a 5;

e es un entero de 1 a 4,

f es 0 o un entero de 1 a 2;

$R^{II}$ se selecciona independientemente del grupo que consiste en hidrógeno, alcoxi, alcoxialcoxi, alcoxialquilo, alquilo; ariloxi, ariloxialquilo, halo, haloalcoxi, haloalquilo, hidroxi, hidroxialcoxi, hidroxialquilo, $(NR^2R^3)$alcoxi, $(NR^2R^3)$alquenilo, $(NR^2R^3)$alquilo, $(NR^2R^3)$carbonilalquenilo y $(NR^2R^3)$carbonilalquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

b es 0 o un entero de 1 a 2;

Y se selecciona del grupo que consiste en:

(1') —$(CH_2)g$—O—$(CH_2)h$—;

(2') —$(CH_2)g$—$NR^1$—$(CH_2)h$—;

(3') —$(CH_2)g$—$S(O)_n$—$(CH_2)h$—;

(4') —$(CH_2)g$—$SO_2N$ $R^2$—$(CH_2)h$—;

(5') —$(CH_2)g$—$NR^2SO_2$—$(CH_2)h$—;

(6') —$(CH_2)g$— CO—$(CH_2)h$—;

(7') —$(CH_2)g$— $C(O)NR^2$—$(CH_2)h$—;

(8') —$(CH_2)g$— $NR^2C(O)$—$(CH_2)h$—;

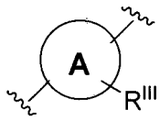
(9') —$(CH_2)g$—C≡C—$(CH_2)h$—;

(10') —$(CH_2)g$— $NR^2C(O)NR^3$—$(CH_2)h$—;
(11') —$(CH_2)g$—$(CH_2)h$—;
(12') —$(CH_2)g$—$CF_2$—$(CH_2)h$—;
(13') —$(CH_2)g$—$CCl_2$—$(CH_2)h$—;
(14') —$(CH_2)g$—CHF—$(CH_2)h$—;
(15') —$(CH_2)g$—CH(OH)—$(CH_2)h$—;
(16') —$(CH_2)g$—$CR^2R^3$—$(CH_2)h$—;
(17') —$(CH_2)g$—C=C—$(CH_2)h$—;
y (18') una unión simple;
donde
g es 0 o un entero de 1 a 3;
h es 0 o un entero de 1 a 3;

$R^1$ se selecciona independientemente del grupo que consiste en hidrógeno, alquenilo, alcoxialquilo, $CF_3$, alquilo, alquilcarbonilo, alcoxicarbonilo, arilo, heterocicloalquilo, hidroxialquilo y $(NR^2R^3)$alquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

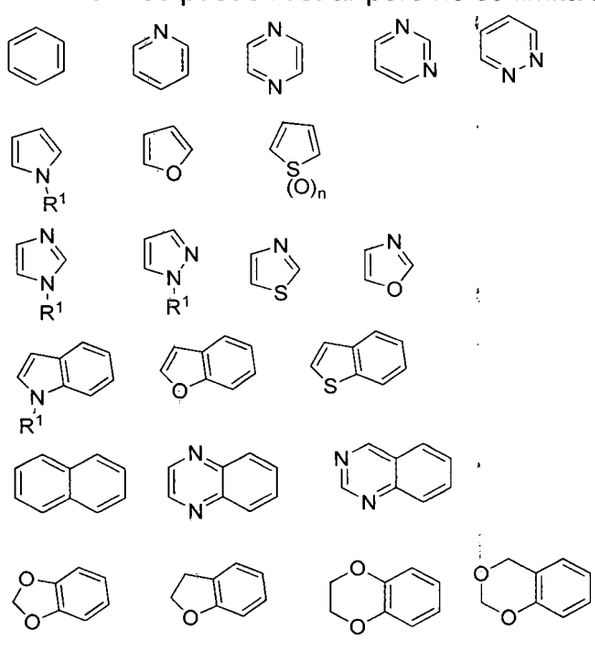
$R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo, de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo cíclico de 5-7 miembros;

El Anillo A se selecciona del grupo que consiste en:




(i) fenilo;
(ii) naftilo;
(iii) Un grupo heteroarilo monocíclico de 5 o 6 miembros que tiene 1-5 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;
y (iv) un grupo heteroarilo bicíclico de 8 a 10 miembros que tiene 1-6 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

el Anillo A se puede ilustrar pero no se limita a los siguientes:



donde

$R^1$ se selecciona independientemente del grupo que consiste en hidrógeno, alquenilo, alcoxialquilo, $CF_3$, alquilo, alquilcarbonilo, alcoxicarbonilo, arilo, heterocicloalquilo, hidroxialquilo y $(NR^2R^3)$alquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

$R^{III}$ representa opcionalmente 1-3 sustituyentes que se seleccionan independientemente del grupo que consiste en alquilo $C_1$-$C_5$ lineal o ramificado, haloalquilo $C_1$-$C_5$ lineal o ramificado, alcoxi $C_1$-$C_5$, hidroxi, amino, alquilamino $C_1$-$C_5$, dialquilamino $C_1$-$C_6$, halógeno, ciano y nitro;

Z se selecciona del grupo que consiste en:

(1') $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$;

(2') $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$;

(3') $(CH_2)_iN(R^7)C(O)$;

(4') $C(O)N(R^8)(CH_2)_j$;

(5') $(CH_2)_iN(R^7)C(O)$;

y (6') $S(O)_2N(R^8)(CH_2)_j$;

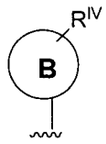
donde

i es 0 o 1;

j es 0 o 1;

$R^7$ y $R^8$ se seleccionan independientemente del grupo que consiste en hidrógeno y alquilo.

El Anillo B se selecciona del grupo que consiste en:



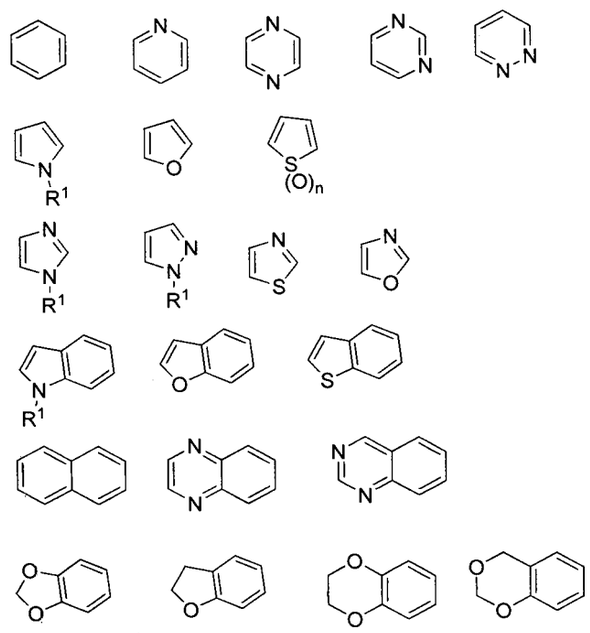

(i') fenilo;

(ii') naftilo;

(iii') Un grupo heteroarilo monocíclico de 5 o 6 miembros que tiene 1-3 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

y (iv') un grupo heteroarilo bicíclico de 8 a 10 miembros que tiene 1-3 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

el Anillo B se puede ilustrar pero no se limita a los siguientes:



donde $R^1$ se selecciona independientemente del grupo que consiste en hidrógeno, alquenilo, alcoxialquilo, $CF_3$, alquilo, alquilcarbonilo, alcoxicarbonilo, arilo, heterocicloalquilo, hidroxialquilo y $(NR^2R^3)$alquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

$R^{IV}$ representa opcionalmente 1-3 sustituyentes, se seleccionan independientemente del grupo que consiste en alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, ariloxi, arilalquilo, carboxi, ciano, halo, haloalcoxi, haloalquilo, hidroxi, hidroxialquilo, nitro y $—NR^9R^{10}$; donde $R^9$ y $R^{10}$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, arilo, arilalquilo, cicloalquilo, cicloalquilalquilo, heterociclilo y heterociclilalquilo.

Algunas modalidades de la presente invención están incluidas en los siguientes párrafos:

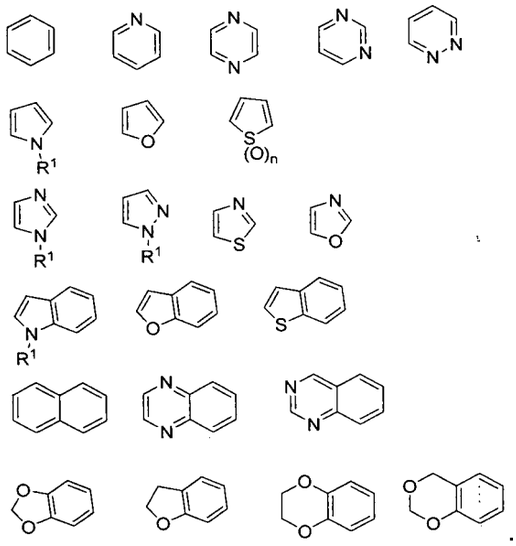
(1) Un compuesto de acuerdo con la Fórmula I, que incluye cualquier tautómero, estereoisómero, forma diastereoisomérica, forma polimórfica, forma cristalina, un solvato, un hidrato, un metabolito, una sal o profármaco farmacéuticamente aceptable, una mezcla de diferentes estereoisómeros y cualquier mezcla de diferentes formas cristalinas.

(2) Un compuesto de Fórmula I en la forma de un profármaco.

(3) El compuesto de acuerdo con el párrafo 1, donde Z se selecciona del grupo que consiste en $(CH_2)_iN(R^7)C(O)$, $C(O)N(R^8)(CH_2)_j$, $(CH_2)_iN(R^7)S(O)_2$ y $S(O)_2N(R^8)(CH_2)_j$.

(4) Los compuestos de acuerdo con los párrafos 1-3 donde Y se selecciona del grupo que consiste en $—(CH_2)g—O—(CH_2)h—$; $—(CH_2)g—NR^1—(CH_2)h—$;
$—(CH_2)g—S(O)_n—(CH_2)h—$; $—(CH_2)g—SO_2N\ R^2—(CH_2)h—$;
$—(CH_2)g—NR^2SO_2—(CH_2)h—$; $—(CH_2)g—\ CO—(CH_2)h—$;
$—(CH_2)g—\ C(O)NR^2—(CH_2)h—$; $—(CH_2)g—\ NR^2C(O\ )—(CH_2)h—$;
$—(CH_2)g—C\equiv C—(CH_2)h—$; $—(CH_2)g—\ NR^2C(O)NR^3—(CH_2)h$ y una unión simple.

(5) El compuesto de acuerdo con los párrafos 1-4 donde el Anillo A y el Anillo B se seleccionan independientemente del grupo que consiste en



(6) El compuesto de acuerdo con los párrafos 1-5 donde Y se selecciona del grupo que consiste en —$(CH_2)g$—$(CH_2)h$—; —$(CH_2)g$—$CF_2$—$(CH_2)h$—; —$(CH_2)g$—$CCl_2$—$(CH_2)h$—; —$(CH_2)g$—CHF—$(CH_2)h$—; —$(CH_2)g$—CH(OH)—$(CH_2)h$—; —$(CH_2)g$—$CR^2R^3$—$(CH_2)h$—; y —$(CH_2)g$—C=C—$(CH_2)h$—.

(7) El compuesto de acuerdo con los párrafos 1-6, donde X es NH.

(8) Un compuesto seleccionado del grupo que consiste en

(1') ácido [({5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-il}carbonil)amino]acético;

(2') [({5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-il}carbonil)amino]acetato de metilo

(3') ácido ({[5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-il]carbonil}amino)acético;

(4') ({[5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-il]carbonil}amino)acetato de metilo;

(5') ácido 5-[4-({3-[(3-metil-2-furoil)amino]fenil}amino)piridin-2-il]-1H-pirrol-3-carboxílico;

(6') 5-[4-({3-[(3-metil-2-furoil)amino]fenil}amino)piridin-2-il]-1H-pirrol-3-carboxilato de metilo;

(7') 5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-N-hidroxi-1H-pirrol-3-carboxamida;

(8') 4-fluoro-N-(2-fluoro-5-metilfenil)-3-[(2-{4-[(3-hidroxipiperidin-1-il)carbonil]-1H-pirrol-2-il}piridin-4-il)oxi]benzamida;

(9) N-(2,3-dihidroxipropil)-5-[4-(3-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxamida;

(10) N-(2-fluoro-5-metilfenil)-3-[(2-{4-[(3-hidroxipirrolidin-1-il)carbonil]-1H-pirrol-2-il}piridin-4-il)oxi]benzamida;

(11') 5-[4-(3-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-N-hidroxi-1H-pirrol-3-carboxamida;

(12') 5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de metilo;

(13') ácido 5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxílico;

(14') N-etil-5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxamida;

(15') N-(2,3-dihidroxipropil)-5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxamida;

(16') 5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxamida;

(17') N-hidroxi-5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxamida;

(18') N-(3-{[2-(4-{[(3R)-3-hidroxipirrolidin-1-il]carbonil}-1H-pirrol-2-il)piridin-4-il]oxi}fenil)-3-metil-2-furamida;

(19') ácido 5-[4-(3-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxílico;

(20') 5-[4-(3-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de metilo;

(21') 5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxilato de 2,3-dihidroxipropilo;

(22') ácido 5-[4-(3-{[(3-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxílico;

(23') 5-[4-(3-{[(3-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de metilo;

(24') 5-[4-(3-{[(3-metil-2-tienil)carbonil]amino}fenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de 2-hidroxietilo;

(25') 5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxilato de 2-hidroxietilo;

(26') ácido 5-[4-(3-{[(3-metil-2-tienil)carbonil]amino}fenoxi)piridin-2-il]-1H-pirrol-3-carboxílico;

(27') 5-[4-(3-{[(3-metil-2-tienil)carbonil]amino}fenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de metilo;

(28') ácido 5-(4-{4-fluoro-3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxílico;

(29') 5-(4-{4-fluoro-3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxilato de metilo;

(30') N-[dimetil(óxido)-lambda~4~-sulfanilideno]-5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxamida;

(31') N-(3-{[2-(4-{[(3S)-3-hidroxipirrolidin-1-il]carbonil}-1H-pirrol-2-il)piridin-4-il]oxi}fenil)-3-metil-2-furamida;

(32') ácido 5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxílico;

(33') 5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxilato de metilo;

(34') 3-metil-N-(3-{[2-(1H-pirrol-2-il)piridin-4-il]oxi}fenil)-2-furamida;

(35') 4-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-2-carboxilato de metilo;

(36') 2-fluoro-5-metil-N-(4-{[2-(1H-pirrol-2-il)piridin-4-il]oxi}fenil)benzamida;

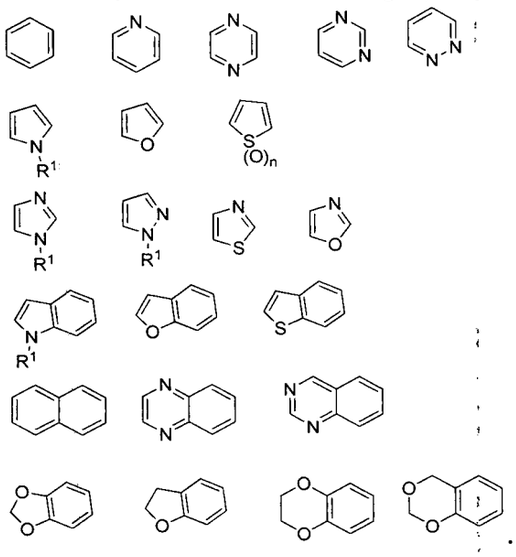
y (37') 3-metil-N-(4-{[2-(1H-pirrol-2-il)piridin-4-il]oxi}fenil)-2-furamida.

(9) El compuesto de acuerdo con el párrafo 1, donde Z es $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$ o $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$, siempre que cuando el Anillo B es pirazol, $R^{IV}$ no es fenilo ni fenilo sustituido.

(10) Los compuestos de acuerdo con el párrafo 9, donde Y se selecciona del grupo que consiste en —$(CH_2)$g—O—$(CH_2)$h—; —$(CH_2)$g—$NR^1$—$(CH_2)$h—; —$(CH_2)$g—$S(O)_n$—$(CH_2)$h—; —$(CH_2)$g—$SO_2N$ $R^2$—$(CH_2)$h—; —$(CH_2)$g—$NR^2SO_2$—$(CH_2)$h—; —$(CH_2)$g—CO—$(CH_2)$h—; —$(CH_2)$g— $C(O)NR^2$—$(CH_2)$h—; —$(CH_2)$g— $NR^2C(O)$—$(CH_2)$h—; —$(CH_2)$g—C≡C—$(CH_2)$h—; —$(CH_2)$g— $NR^2C(O)NR^3$—$(CH_2)$h, y una unión simple.

(11) El compuesto de acuerdo con el párrafo 9, donde Y se selecciona del grupo que consiste en —$(CH_2)g$—$(CH_2)h$—; —$(CH_2)g$—$CF_2$—$(CH_2)h$—; —$(CH_2)g$—$CCl_2$—$(CH_2)h$—; —$(CH_2)g$—CHF—$(CH_2)h$—; —$(CH_2)g$—CH(OH)—$(CH_2)h$—; —$(CH_2)g$—$CR^2R^3$—$(CH_2)h$—; y —$(CH_2)g$—C=C—$(CH_2)h$—.

(12) El compuesto de acuerdo con los párrafos 9-11, donde el Anillo A y el Anillo B se seleccionan independientemente del grupo que consiste en

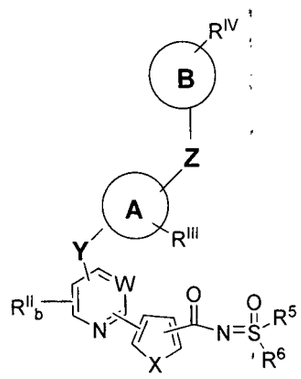


(13) El compuesto de acuerdo con los párrafos 9-12, donde X es NH.

(14) El compuesto de acuerdo con los párrafos 9-12, donde X es S.

(15) El compuesto de acuerdo con los párrafos 9-14, donde $R^1$ se selecciona del grupo que consiste en hidrógeno, halógeno, alquilo $C_1$ a $C_8$, $(CR^5R^6)_dC(O)OR^4$, $(CR^5R^6)_dAr$, $NR^4(CR^5R^6)_dAr$, $(CR^5R^6)_dC(O)N(R^4)_2$, $NR^4(CR^5R^6)_dC(O)N(R^4)_2$, $O(CR^5R^6)_dC(O)N(R^4)_2$, $(CR^5R^6)_dOR^4$, $OC(O)(CR^5R^6)_dN(R^4)_2$, $C(O)(CR^5R^6)_dN(R^4)_2$, $C(O)N{=}S(O)R^5$ $R^6$, $NR^2C(O)(CR^5R^6)_dN(R^4)_2$, $(CR^5R^6)_dR^5$, $HNC(O)R^4$, $HN\text{-}C(O)OR^4$, $(CR^5R^6)_dN(R^4)_2$, $S(O)_f(CR^5R^6)_dN(R^4)_2$, $OC(O)OR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dOR^4$, y $(CR^5R^6)_dC(O)(CR^5R^6)_dN(R^4)_2$, donde cada $R^4$ se selecciona independientemente del grupo que consiste en hidrógeno, hidroxilo, alquilo $C_1$-$C_8$, arilo, hidroxialquilo $C_1$-$C_8$, alcoxialquilo $C_1$-$C_8$, $(CR^5R^6)_d$ y $N(R^4)_2$ puede formar un anillo heterocíclico de 3-7 miembros que comprende aziridina, azetidina, pirrolidina, 5-fluoropirrolidina, piperidina, 6-fluoropiperidina, N-metilpiperazina, morfolina, 2,6-dimetilmorfolina, tiomorfolina y donde dicho anillo heterocíclico se puede sustituir opcionalmente con hasta tres de $R^5$; donde $R^5$ y $R^6$ se seleccionan independientemente del grupo que consiste en hidrógeno, halo, hidroxilo, alquilo $C_1$-$C_8$, hidroxialquilo $C_1$-$C_8$, alcoxialquilo $C_1$-$C_8$, alcoxicarbonilalquilo, alcoxicarbonilo, hidroxicarbonilo, hidroxicarbonilalquilo, amida, alquilamida, amidoalquilo, sulfonato y $CR^5R^6$ puede representar un anillo carbocíclico o heterocíclico de entre 5 y 6 carbonos o, de manera alternativa, $(CR^5R^6)_d$ y $(CR^5R^6)_e$ pueden formar un anillo carbocíclico o heterocíclico de 3-7 miembros, donde el anillo se puede sustituir opcionalmente con hasta tres de hidroxilo, halo, alquilo $C_1$-$C_8$, hidroxialquilo $C_1$-$C_8$, alcoxialquilo $C_1$-$C_8$, alcoxicarbonilalquilo, alcoxicarbonilo, hidroxicarbonilo, hidroxicarbonilalquilo, amida, alquilamida, amidoalquilo y sulfonato.

(16) Un compuesto de fórmula II:



Fórmula II

donde

W es C o N;

X se selecciona del grupo que consiste en $NR^1$, O y $S(O)_n$;

n es 0 o un entero de 1 a 2;

$R^1$ se selecciona independientemente del grupo que consiste en hidrógeno, alquenilo, alcoxialquilo, $CF_3$, alquilo, alquilcarbonilo, alcoxicarbonilo, arilo, heterocicloalquilo, hidroxialquilo y $(NR^2R^3)$alquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

$R^5$ y $R^6$ se seleccionan independientemente del grupo que consiste en hidrógeno, halo, hidroxilo, alquilo $C_1$-$C_8$, hidroxialquilo $C_1$-$C_8$, alcoxialquilo $C_1$-$C_8$, alcoxicarbonilalquilo, alcoxicarbonilo, hidroxicarbonilo, hidroxicarbonilalquilo, amida, alquilamida, amidoalquilo, sulfonato;

$R^{II}$ se selecciona independientemente del grupo que consiste en hidrógeno, alcoxi, alcoxialcoxi, alcoxialquilo, alquilo, ariloxi, ariloxialquilo, halo, haloalcoxi, haloalquilo, hidroxi, hidroxialcoxi, hidroxialquilo, $(NR^2R^3)$alcoxi, $(NR^2R^3)$alquenilo, $(NR^2R^3)$alquilo, $(NR^2R^3)$carbonilalquenilo y $(NR^2R^3)$carbonilalquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

b es 0 o un entero de 1 a 2;

Y se selecciona del grupo que consiste en:

(1') —$(CH_2)$g—O—$(CH_2)$h—;

(2') —$(CH_2)$g—$NR^1$—$(CH_2)$h—;

(3') —$(CH_2)$g—$S(O)_n$—$(CH_2)$h—;

(4') —$(CH_2)$g—$SO_2N$ $R^2$—$(CH_2)$h—;

(5') —$(CH_2)$g—$NR^2SO_2$—$(CH_2)$h—;

(6') —$(CH_2)$g— CO—$(CH_2)$h—;

(7') —$(CH_2)$g— $C(O)NR^2$—$(CH_2)$h—;

(8') —$(CH_2)$g— $NR^2C(O)$—$(CH_2)$h—;

(9') —$(CH_2)$g—C≡C—$(CH_2)$h—;

(10') —$(CH_2)$g— $NR^2C(O)NR^3$—$(CH_2)$h—;

(11') —$(CH_2)$g—$(CH_2)$h—;

(12') —$(CH_2)$g—$CF_2$—$(CH_2)$h—;

(13') —$(CH_2)$g—$CCl_2$—$(CH_2)$h—;

(14') —$(CH_2)$g—CHF—$(CH_2)$h—;

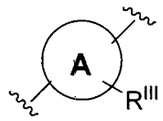
(15') —$(CH_2)$g—CH(OH)—$(CH_2)$h—;

(16') —$(CH_2)g—CR^2R^3—(CH_2)h—$;
(17') —$(CH_2)g—C{=}C—(CH_2)h—$;
y (18') una unión simple;
donde
g es 0 o un entero de 1 a 3;
h es 0 o un entero de 1 a 3;

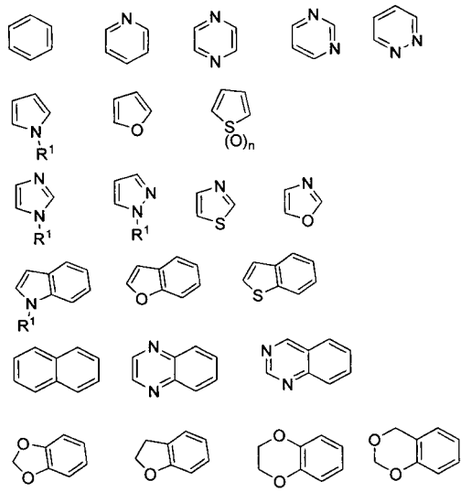
$R^1$ se selecciona independientemente del grupo que consiste en hidrógeno, alquenilo, alcoxialquilo, $CF_3$, alquilo, alquilcarbonilo, alcoxicarbonilo, arilo, heterocicloalquilo, hidroxialquilo y $(NR^2R^3)$alquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

$R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo, de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo cíclico de 5-7 miembros;

El Anillo A se selecciona del grupo que consiste en:




(i) fenilo;
(ii) naftilo;
(iii) Un grupo heteroarilo monocíclico de 5 o 6 miembros que tiene 1-5 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;
y (iv) un grupo heteroarilo bicíclico de 8 a 10 miembros que tiene 1-6 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;
el Anillo A se puede ilustrar pero no se limita a los siguientes:



donde

$R^1$ se selecciona independientemente del grupo que consiste en hidrógeno, alquenilo, alcoxialquilo, $CF_3$, alquilo, alquilcarbonilo, alcoxicarbonilo, arilo, heterocicloalquilo, hidroxialquilo y $(NR^2R^3)$alquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

$R^{III}$ representa opcionalmente 1-3 sustituyentes que se seleccionan independientemente del grupo que consiste en alquilo $C_1$-$C_5$ lineal o ramificado, haloalquilo $C_1$-$C_5$ lineal o ramificado, alcoxi $C_1$-$C_5$, hidroxi, amino, alquilamino $C_1$-$C_5$, dialquilamino $C_1$-$C_6$, halógeno, ciano y nitro;

Z se selecciona del grupo que consiste en:

(1') $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$;

(2') $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$;

(3') $(CH_2)_iN(R^7)C(O)$;

(4') $C(O)N(R^8)(CH_2)_j$;

(5') $(CH_2)_iN(R^7)C(O)$;

y (6') $S(O)_2N(R^8)(CH_2)_j$;

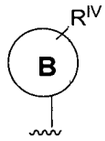
donde

i es 0 o 1;

j es 0 o 1;

$R^7$ y $R^8$ se seleccionan independientemente del grupo que consiste en hidrógeno y alquilo.

El Anillo B se selecciona del grupo que consiste en:



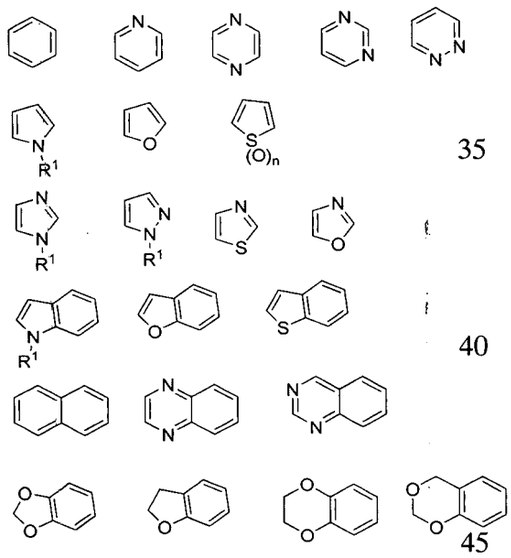

(i') fenilo;

(ii') naftilo;

(iii') Un grupo heteroarilo monocíclico de 5 o 6 miembros que tiene 1-3 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

y (iv') un grupo heteroarilo bicíclico de 8 a 10 miembros que tiene 1-3 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

el Anillo B se puede ilustrar pero no se limita a los siguientes:



donde

$R^1$ se selecciona independientemente del grupo que consiste en hidrógeno, alquenilo, alcoxialquilo, $CF_3$, alquilo, alquilcarbonilo, alcoxicarbonilo, arilo, heterocicloalquilo, hidroxialquilo y $(NR^2R^3)$alquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

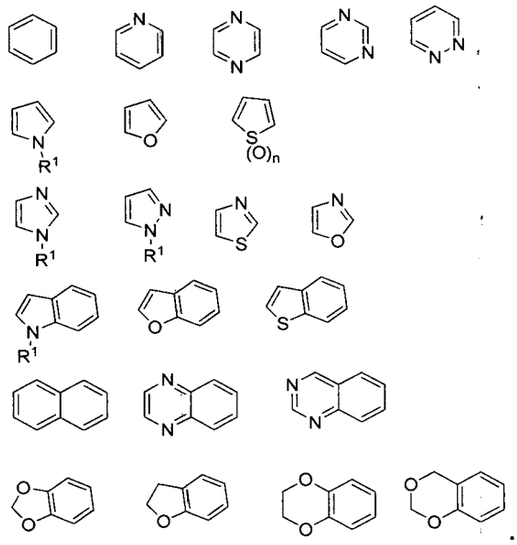
$R^{IV}$ representa opcionalmente 1-3 sustituyentes, se seleccionan independientemente del grupo que consiste en alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, ariloxi, arilalquilo, carboxi, ciano, halo, haloalcoxi, haloalquilo, hidroxi, hidroxialquilo, nitro y —$NR^9R^{10}$; donde $R^9$ y $R^{10}$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, arilo, arilalquilo, cicloalquilo, cicloalquilalquilo, heterociclilo y heterociclilalquilo;

y cualquier sal o profármaco farmacéuticamente aceptable.

(17) El compuesto de acuerdo con el párrafo 16, donde Z se selecciona del grupo que consiste en $(CH_2)_iN(R^7)C(O)$, $C(O)N(R^8)(CH_2)_j$, $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$ y $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$.

(18) El compuesto de acuerdo con los párrafos 16-17, donde Y se selecciona del grupo que consiste en —(CH2)g—O—(CH2)h—; —(CH2)g—NR1—(CH2)h—; —$(CH_2)$g—$S(O)_n$—$(CH_2)$h—; —$(CH_2)$g—$SO_2N$ $R^2$—$(CH_2)$h—; —$(CH_2)$g—$NR^2SO_2$—$(CH_2)$h—; —$(CH_2)$g— CO—$(CH_2)$h—; —$(CH_2)$g— C(O)$NR^2$—$(CH_2)$h—; —$(CH_2)$g— $NR^2C(O)$—$(CH_2)$h—; —$(CH_2)$g—C≡C—$(CH_2)$h—; —$(CH_2)$g— $NR^2C(O)NR^3$—$(CH_2)$h y una unión simple.

(19) El compuesto de acuerdo con los párrafos 16-18, donde el Anillo A y el Anillo B se seleccionan independientemente del grupo que consiste en



(20) El compuesto de acuerdo con el párrafo 16-19, donde W es C.

(21) Un método de uso de los compuestos de los párrafos 1-20, donde los compuestos se usan como moduladores de tirosina cinasa.

(22) El uso de los compuestos de los párrafos 1-20 en la preparación de un medicamento para el tratamiento o prevención de enfermedades o afecciones relacionadas con actividades de tirosina cinasa no reguladas que comprenden administrar una cantidad terapéuticamente eficaz del compuesto de los párrafos 1-20 junto con un portador farmacéuticamente aceptable.

(23) El uso del párrafo 22, donde las enfermedades o afecciones se seleccionan del grupo que consiste en trastornos metabólicos y de crecimiento celular, trastornos proliferativos de los vasos sanguíneos, trastornos inflamatorios, enfermedades neurodegenerativas y trastornos inmunes.

(24) El uso de los párrafos 22-23, donde las enfermedades o afecciones se seleccionan del grupo que consiste en cáncer colorrectal, cáncer de pulmón, cáncer hematológico, cáncer renal, cáncer de hígado, cáncer de mama, retinopatía diabética, degeneración macular, degeneración macular relacionada con la edad, retinopatía del prematuro, angiogénesis ocular, edema de retina, isquemia de retina, edema macular diabético, edema macular cistoide, oclusión venosa de la retina, oclusión de rama venosa, neovascularización preretinal, neovascularización coroidal inducida por láser, neovascularización asociada a queratoplastia, glaucoma y tumores oculares, artritis, restenosis, cirrosis hepática, ateroesclerosis, psoriasis, diabetes mellitus, cicatrización, inflamación, enfermedades neurodegenerativas y trastornos inmunes.

(25) El uso de los párrafos 22-23, donde las afecciones y enfermedades son cicatrización o para aliviar el rechazo a transplante. [sic]

(26) Una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de un compuesto de acuerdo con los párrafos 1-20 junto con un portador farmacéuticamente aceptable que es adecuado para la administración sistémica, parenteral, local o tópica.

(27) La composición farmacéutica del párrafo 26, que se encuentra en la forma seleccionada del grupo que comprende comprimidos, cápsulas, inyecciones intravenosas, inyecciones intramusculares, inyecciones locales, geles, ungüentos y cremas tópicas, gotas para los ojos, soluciones oftálmicas, suspensiones oftálmicas, emulsiones oftálmicas, inyecciones intravítrea, inyecciones sub-tenon, implantes bioerosionables oftálmicos e insertos o medicamentos de liberación mantenida no bioerosionables.

(28) El uso de los compuestos de los párrafos 1-20 en la preparación de un medicamento para el tratamiento de enfermedades y afecciones, donde el medicamento contiene una composición farmacéutica aceptable de acuerdo con los párrafos 26 y 27.

## BREVE DESCRIPCIÓN DE LOS DIBUJOS

La Fig. 1 muestra una difracción de rayos X en polvo (XRPD) del Ejemplo 78;

La Fig. 2 muestra una difracción de rayos X en polvo (XRPD) del Ejemplo 69;

La Fig 3 muestra una angiografía con fluoresceína (falla en la barrera hematorretinal) del Ejemplo 121, Ejemplo 84 sodio, Ejemplo 83, Ejemplo 78, Ejemplo 75 sodio, Ejemplo 69, y Ejemplo 66; y

La Fig 4 muestra una fotografía del fundus (vasodilatación de la retina y tortuosidad de vasos) del Ejemplo 121, Ejemplo 84 sodio, Ejemplo 83, Ejemplo 78, Ejemplo 75 sodio, Ejemplo 69, y Ejemplo 66.

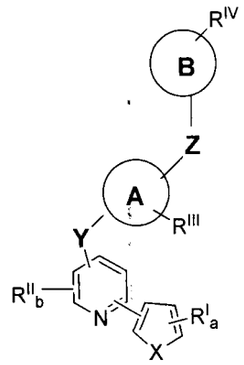
## DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

La presente invención se refiere a una serie de compuestos con múltiples componentes aromáticos útiles como inhibidores de la proteína tirosina cinasa. Los compuestos de la presente invención son útiles para tratar enfermedades relacionadas con la transducción de señales de tirosina cinasa no regulada, por ejemplo, cáncer, trastornos proliferativos de los vasos sanguíneos, trastornos fibróticos y enfermedades neurodegenerativas. En particular, los compuestos de la presente invención son útiles para el tratamiento de cáncer colorrectal, cáncer de pulmón, cáncer hematológico, cáncer renal, cáncer de hígado, cáncer de mama, retinopatía diabética, degeneración

macular, degeneración macular relacionada con la edad, retinopatía del prematuro, angiogénesis ocular, edema de retina, isquemia de retina, edema macular diabético, edema macular cistoide, oclusión venosa de la retina, oclusión de rama venosa, neovascularización preretinal, neovascularización coroidal inducida por láser, neovascularización asociada a queratoplastia, glaucoma y tumores oculares, artritis, restenosis, cirrosis hepática, ateroesclerosis, psoriasis, diabetes mellitus, cicatrización, rechazo a injertos, inflamación, enfermedades neurodegenerativas y trastornos inmunes.

1. **Compuestos de la invención**

En un aspecto de la invención, los compuestos de la presente invención se pueden representar mediante la fórmula general I:




Fórmula I

donde

X se selecciona del grupo que consiste en $NR^1$, O y $S(O)_n$;

n es 0 o un entero de 1 a 2;

$R^1$ se selecciona independientemente del grupo que consiste en hidrógeno, alquenilo, alcoxialquilo, $CF_3$, alquilo, alquilcarbonilo, alcoxicarbonilo, arilo, heterocicloalquilo, hidroxialquilo y $(NR^2R^3)$alquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

$R^I$ se selecciona del grupo que consiste en hidrógeno, halógeno, alquilo $C_1$ a $C_8$, $S(O)_fR^4$, $(CR^5R^6)_dC(O)OR^4$, $S(O)_f(CR^5R^6)_dC(O)OR^4$, $(CR^5R^6)_dAr$, $NR^4(CR^5R^6)_dAr$, $O(CR^5R^6)_dAr$, $S(O)_f(CR^5R^6)_dAr$, $(CR^5R^6)_dS(O)_fR^4$, $NR^4(CR^5R^6)_dS(O)_fR^4$, $O(CR^5R^6)_dS(O)_fR^4$, $S(O)_f(CR^5R^6)_eS(O)_fR^4$, $(CR^5R^6)_dC(O)N(R^4)_2$, $NR^4(CR^5R^6)_dC(O)N(R^4)_2$, $O(CR^5R^6)_dC(O)N(R^4)_2$, $S(O)_f(CR^5R^6)_eC(O)N(R^4)_2$, $(CR^5R^6)_dOR^4$, $S(O)_f(CR^5R^6)_dOR^4$, $(CR^5R^6)_dOSO_2R^4$, $S(O)_f(CR^5R^6)_eOSO_2R^4$, $(CR^5R^6)_dP(O)(OR^4)_2$, $S(O)_f(CR^5R^6)_eP(O)(OR^4)_2$, $OC(O)(CR^5R^6)_dN(R^4)_2$, $C(O)(CR^5R^6)_dN(R^4)_2$, $C(O)N{=}S(O)R^5$ $R^6$, $NR^2C(O)(CR^5R^6)_dN(R^4)_2$, $(CR^5R^6)_dR^5$, $S(O)_f(CR^5R^6)_dR^5$, $HNC(O)R^4$, $HN\text{-}C(O)OR^4$, $(CR^5R^6)_dN(R^4)_2$, $S(O)_f(CR^5R^6)_dN(R^4)_2$, $OC(O)OR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dOR^4$, y $(CR^5R^6)_dC(O)(CR^5R^6)_dN(R^4)_2$, donde cada $R^4$ se selecciona independientemente del grupo que consiste en hidrógeno, hidroxilo, alquilo $C_1$-$C_8$, arilo, hidroxialquilo $C_1$-$C_8$, alcoxialquilo $C_1$-$C_8$, $(CR^5R^6)_d$ y $N(R^4)_2$ puede formar un anillo heterocíclico de 3-7 miembros que comprende aziridina, azetidina, pirrolidina, 5-fluoropirrolidina, piperidina, 6-fluoropiperidina, N-metilpiperazina, morfolina, 2,6-dimetilmorfolina, tiomorfolina y donde dicho anillo heterocíclico se puede sustituir opcionalmente con hasta tres de $R^5$; donde $R^5$ y $R^6$ se seleccionan independientemente del grupo que consiste en hidrógeno, halo, hidroxilo, alquilo $C_1$-$C_8$, hidroxialquilo $C_1$-$C_8$, alcoxialquilo $C_1$-$C_8$, alcoxicarbonilalquilo, alcoxicarbonilo, hidroxicarbonilo, hidroxicarbonilalquilo, amida, alquilamida, amidoalquilo, sulfonato y $CR^5R^6$ puede

representar un anillo carbocíclico o heterocíclico de entre 5 y 6 carbonos o de manera alternativa, $(CR^5R^6)_d$ y $(CR^5R^6)_e$ pueden formar un anillo carbocíclico o heterocíclico de 3-7 miembros, donde el anillo se puede sustituir opcionalmente con hasta tres de hidroxilo, halo, alquilo $C_1$-$C_8$, hidroxialquilo $C_1$-$C_8$, alcoxialquilo $C_1$-$C_8$, alcoxicarbonilalquilo, alcoxicarbonilo, hidroxicarbonilo, hidroxicarbonilalquilo, amida, alquilamida, amidoalquilo y sulfonato;

a es 0 o un entero de 1 a 3;

d es 0 o un entero de 1 a 5;

e es un entero de 1 a 4,

f es 0 o un entero de 1 a 2;

$R^{II}$ se selecciona independientemente del grupo que consiste en hidrógeno, alcoxi, alcoxialcoxi, alcoxialquilo, alquilo, ariloxi, ariloxialquilo, halo, haloalcoxi, haloalquilo, hidroxi, hidroxialcoxi, hidroxialquilo, $(NR^2R^3)$alcoxi, $(NR^2R^3)$alquenilo, $(NR^2R^3)$alquilo, $(NR^2R^3)$carbonilalquenilo y $(NR^2R^3)$carbonilalquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa, $R^2$ y $R^3$ y se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

b es 0 o un entero de 1 a 2;

Y se selecciona del grupo que consiste en:

(1') $—(CH_2)g—O—(CH_2)h—$;

(2') $—(CH_2)g—NR^1—(CH_2)h—$;

(3') $—(CH_2)g—S(O)_n—(CH_2)h—$;

(4') $—(CH_2)g—SO_2N\ R^2—(CH_2)h—$;

(5') $—(CH_2)g—NR^2SO_2—(CH_2)h—$;

(6') $—(CH_2)g—\ CO—(CH_2)h—$;

(7') $—(CH_2)g—\ C(O)NR^2—(CH_2)h—$;

(8') $—(CH_2)g—\ NR^2C(O\ )—(CH_2)h—$;

(9') $—(CH_2)g—C\equiv C—(CH_2)h—$;

(10') $—(CH_2)g—\ NR^2C(O)NR^3—(CH_2)h—$;

(11') $—(CH_2)g—(CH_2)h—$;

(12') $—(CH_2)g—CF_2—(CH_2)h—$;

(13') $—(CH_2)g—CCl_2—(CH_2)h—$;

(14') $—(CH_2)g—CHF—(CH_2)h—$;

(15') $—(CH_2)g—CH(OH)—(CH_2)h—$;

(16') $—(CH_2)g—CR^2R^3—(CH_2)h—$;

(17') $—(CH_2)g—C=C—(CH_2)h—$;

y (18') una unión simple;

donde

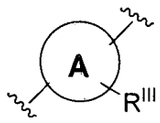
g es 0 o un entero de 1 a 3;

h es 0 o un entero de 1 a 3;

$R^1$ se selecciona independientemente del grupo que consiste en hidrógeno, alquenilo, alcoxialquilo, $CF_3$, alquilo, alquilcarbonilo, alcoxicarbonilo, arilo, heterocicloalquilo, hidroxialquilo y $(NR^2R^3)$alquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

$R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo, de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo cíclico de 5-7 miembros;

El Anillo A se selecciona del grupo que consiste en:



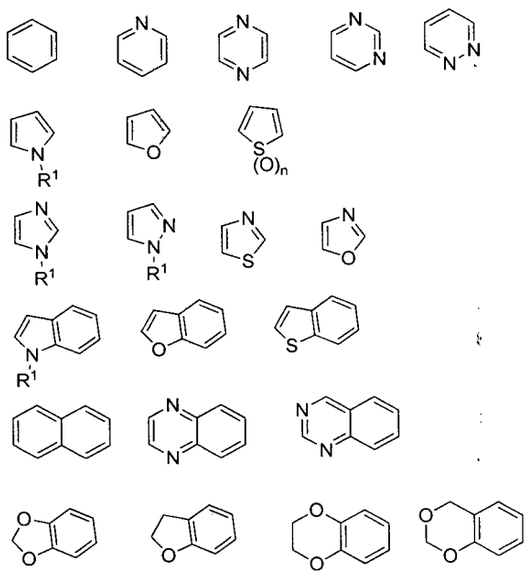

(i) fenilo;

(ii) naftilo;

(iii) Un grupo heteroarilo monocíclico de 5 o 6 miembros que tiene 1-5 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

y (iv) un grupo heteroarilo bicíclico de 8 a 10 miembros que tiene 1-6 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

el Anillo A se puede ilustrar pero no se limita a los siguientes:



donde

$R^1$ se selecciona independientemente del grupo que consiste en hidrógeno, alquenilo, alcoxialquilo, $CF_3$, alquilo, alquilcarbonilo, alcoxicarbonilo, arilo, heterocicloalquilo, hidroxialquilo y $(NR^2R^3)$alquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

$R^{III}$ representa opcionalmente 1-3 sustituyentes que se seleccionan independientemente del grupo que consiste en alquilo $C_1$-$C_5$ lineal o ramificado, haloalquilo $C_1$-$C_5$ lineal o ramificado, alcoxi $C_1$-$C_5$, hidroxi, amino, alquilamino $C_1$-$C_5$, dialquilamino $C_1$-$C_6$, halógeno, ciano y nitro;

Z se selecciona del grupo que consiste en:

(1') $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$;

(2') $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$;

(3') $(CH_2)_iN(R^7)C(O)$;

(4') $C(O)N(R^8)(CH_2)_j$;

(5') $(CH_2)_iN(R^7)C(O)$;

y (6') $S(O)_2N(R^8)(CH_2)_j$;

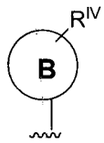
donde

i es 0 o 1;

j es 0 o 1;

$R^7$ y $R^8$ se seleccionan independientemente del grupo que consiste en hidrógeno y alquilo;

El Anillo B se selecciona del grupo que consiste en:



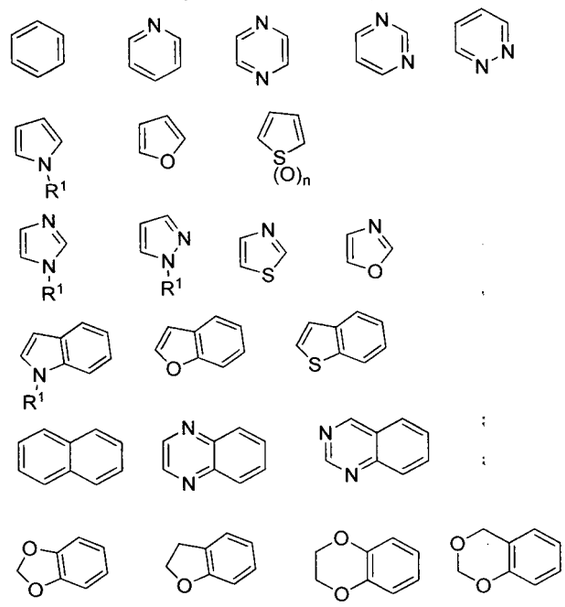

(i') fenilo;

(ii') naftilo;

(iii') Un grupo heteroarilo monocíclico de 5 o 6 miembros que tiene 1-3 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

y (iv') un grupo heteroarilo bicíclico de 8 a 10 miembros que tiene 1-3 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

el Anillo B se puede ilustrar pero no se limita a los siguientes:

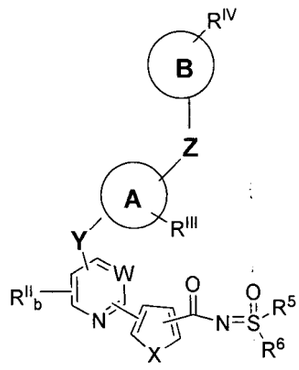


donde

$R^1$ se selecciona independientemente del grupo que consiste en hidrógeno, alquenilo, alcoxialquilo, $CF_3$, alquilo, alquilcarbonilo, alcoxicarbonilo, arilo, heterocicloalquilo, hidroxialquilo y $(NR^2R^3)$alquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

$R^{IV}$ representa opcionalmente 1-3 sustituyentes, se seleccionan independientemente del grupo que consiste en hidrógeno, alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, ariloxi, arilalquilo, carboxi, ciano, halo, haloalcoxi, haloalquilo, hidroxi, hidroxialquilo, nitro y $—NR^9R^{10}$; donde $R^9$ y $R^{10}$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, arilo, arilalquilo, cicloalquilo, cicloalquilalquilo, heterociclilo y heterociclilalquilo.

En otro aspecto de la invención, los compuestos de la presente invención se pueden representar mediante la fórmula general II:



Fórmula II

donde

W es C o N;

X se selecciona del grupo que consiste en $NR^1$, O y $S(O)_n$;

n es 0 o un entero de 1 a 2;

$R^1$ se selecciona independientemente del grupo que consiste en hidrógeno, alquenilo, alcoxialquilo, $CF_3$, alquilo, alquilcarbonilo, alcoxicarbonilo, arilo, heterocicloalquilo, hidroxialquilo y $(NR^2R^3)$alquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

$R^5$ y $R^6$ se seleccionan independientemente del grupo que consiste en hidrógeno, halo, hidroxilo, alquilo $C_1$-$C_8$, hidroxialquilo $C_1$-$C_8$, alcoxialquilo $C_1$-$C_8$, alcoxicarbonilalquilo, alcoxicarbonilo, hidroxicarbonilo, hidroxicarbonilalquilo, amida, alquilamida, amidoalquilo, sulfonato;

$R^{II}$ se selecciona independientemente del grupo que consiste en hidrógeno, alcoxi, alcoxialcoxi, alcoxialquilo, alquilo, ariloxi, ariloxialquilo, halo, haloalcoxi, haloalquilo, hidroxi, hidroxialcoxi, hidroxialquilo, $(NR^2R^3)$alcoxi, $(NR^2R^3)$alquenilo, $(NR^2R^3)$alquilo, $(NR^2R^3)$carbonilalquenilo y $(NR^2R^3)$carbonilalquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa, $R^2$ y $R^3$ y se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

b es 0 o un entero de 1 a 2;

Y se selecciona del grupo que consiste en:

(1') —$(CH_2)$g—O—$(CH_2)$h—;

(2') —$(CH_2)$g—$NR^1$—$(CH_2)$h—;

(3') —$(CH_2)$g—$S(O)_n$—$(CH_2)$h—;

(4') —$(CH_2)$g—$SO_2N$ $R^2$—$(CH_2)$h—;

(5') —$(CH_2)$g—$NR^2SO_2$—$(CH_2)$h—;

(6') —$(CH_2)$g— CO—$(CH_2)$h—;

(7') —$(CH_2)$g— $C(O)NR^2$—$(CH_2)$h—;

(8') —$(CH_2)$g— $NR^2C(O)$—$(CH_2)$h—;

(9') —$(CH_2)$g—C≡C—$(CH_2)$h—;

(10') —$(CH_2)$g— $NR^2C(O)NR^3$—$(CH_2)$h—;

(11') —$(CH_2)$g—$(CH_2)$h—;

(12') —$(CH_2)$g—$CF_2$—$(CH_2)$h—;

(13') —$(CH_2)$g—$CCl_2$—$(CH_2)$h—;

(14') —$(CH_2)$g—CHF—$(CH_2)$h—;

(15') —$(CH_2)$g—CH(OH)—$(CH_2)$h—;

(16') —$(CH_2)$g—$CR^2R^3$—$(CH_2)$h—;

(17') —$(CH_2)g$—C=C—$(CH_2)h$—;

y (18') una unión simple;

donde

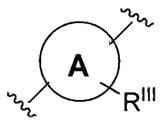
g es 0 o un entero de 1 a 3;

h es 0 o un entero de 1 a 3;

$R^1$ se selecciona independientemente del grupo que consiste en hidrógeno, alquenilo, alcoxialquilo, $CF_3$, alquilo, alquilcarbonilo, alcoxicarbonilo, arilo, heterocicloalquilo, hidroxialquilo y $(NR^2R^3)$alquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

$R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo, de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo cíclico de 5-7 miembros;

El Anillo A se selecciona del grupo que consiste en:



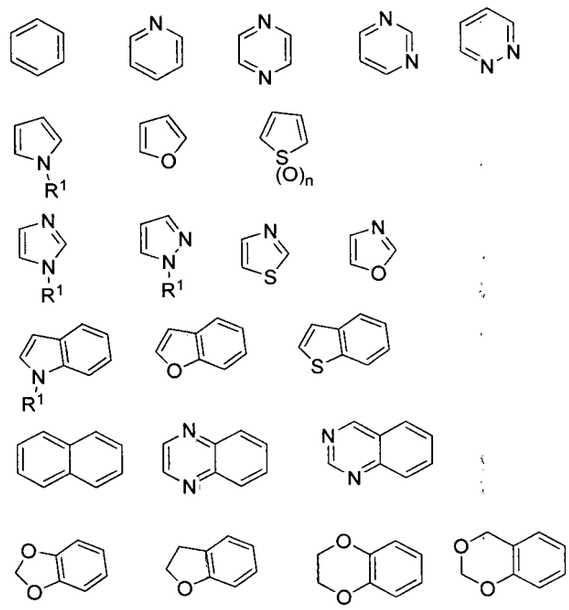

(i) fenilo;

(ii) naftilo;

(iii) Un grupo heteroarilo monocíclico de 5 o 6 miembros que tiene 1-5 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

y (iv) un grupo heteroarilo bicíclico de 8 a 10 miembros que tiene 1-6 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

el Anillo A se puede ilustrar pero no se limita a los siguientes:



donde

$R^1$ se selecciona independientemente del grupo que consiste en hidrógeno, alquenilo, alcoxialquilo, $CF_3$, alquilo, alquilcarbonilo, alcoxicarbonilo, arilo, heterocicloalquilo, hidroxialquilo y $(NR^2R^3)$alquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

$R^{III}$ representa opcionalmente 1-3 sustituyentes que se seleccionan independientemente del grupo que consiste en alquilo $C_1$-$C_5$ lineal o ramificado, haloalquilo $C_1$-$C_5$ lineal o ramificado, alcoxi $C_1$-$C_5$, hidroxi, amino, alquilamino $C_1$-$C_5$, dialquilamino $C_1$-$C_6$, halógeno, ciano y nitro;

Z se selecciona del grupo que consiste en:

(1') $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$;

(2') $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$;

(3') $(CH_2)_iN(R^7)C(O)$;

(4') $C(O)N(R^8)(CH_2)_j$;

(5') $(CH_2)_iN(R^7)C(O)$;

y (6') $S(O)_2N(R^8)(CH_2)_j$;

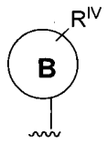
donde

i es 0 o 1;

j es 0 o 1;

$R^7$ y $R^8$ se seleccionan independientemente del grupo que consiste en hidrógeno y alquilo:

El Anillo B se selecciona del grupo que consiste en:



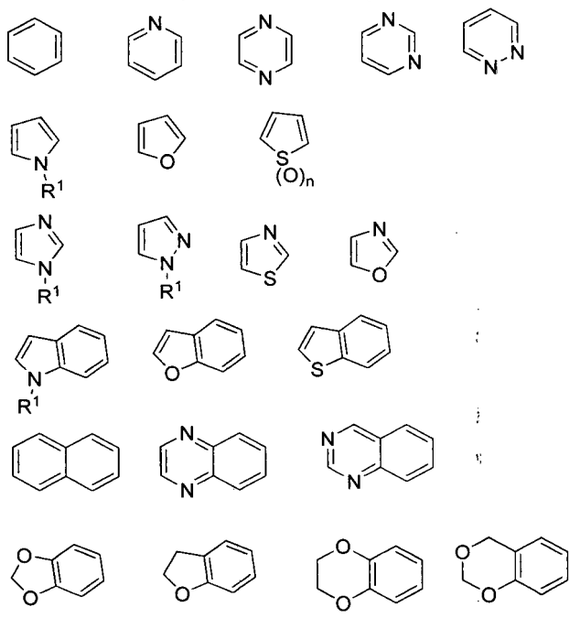

(i') fenilo;

(ii') naftilo;

(iii') Un grupo heteroarilo monocíclico de 5 o 6 miembros que tiene 1-3 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

y (iv') un grupo heteroarilo bicíclico de 8 a 10 miembros que tiene 1-3 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

el Anillo B se puede ilustrar pero no se limita a los siguientes:



donde

$R^1$ se selecciona independientemente del grupo que consiste en hidrógeno, alquenilo, alcoxialquilo, $CF_3$, alquilo, alquilcarbonilo, alcoxicarbonilo, arilo, heterocicloalquilo, hidroxialquilo y $(NR^2R^3)$alquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de

manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

$R^{IV}$ representa opcionalmente 1-3 sustituyentes, se seleccionan independientemente del grupo que consiste en alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, ariloxi, arilalquilo, carboxi, ciano, halo, haloalcoxi, haloalquilo, hidroxi, hidroxialquilo, nitro y —$NR^9R^{10}$; donde $R^9$ y $R^{10}$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, arilo, arilalquilo, cicloalquilo, cicloalquilalquilo, heterociclilo y heterociclilalquilo;

e incluye cualquier sal o profármaco farmacéuticamente aceptable.

Salvo que se indique lo contrario, la referencia a un compuesto se deberá interpretar ampliamente como que incluye compuestos, sales farmacéuticamente aceptables, profármacos, tautómeros, estereoisómeros, diaestereoisómeros, formas sólidas alternativas, formas cristalinas, formas polimórficas, hidratos, solvatos, metabolitos, mezclas de estereoisómeros, mezclas de formas cristalinas, complejos no covalentes y combinaciones de los mismos de una entidad química de una estructura o nombre químico descritos. Cada vez que exista un conflicto entre el nombre químico y el dibujo de su estructura, el dibujo de su estructura se deberá usar para interpretar el compuesto de la presente invención.

Una sal farmacéuticamente aceptable es cualquier sal del compuesto original que es adecuado para la administración a un animal o humano. Una sal farmacéuticamente aceptable también se refiere a cualquier sal que se puede formar in vivo como resultado de la administración de un ácido, otra sal o un profármaco que se convierte en ácido o sal. Una sal comprende una o más formas iónicas del compuesto, tales como un ácido o base conjugados, asociados a uno o más contraiones correspondientes. Las sales se pueden formar de o pueden incorporar uno o más grupos ácidos desprotonados (por ej., ácidos carboxílicos), uno o más grupos básicos protonados (por ej., aminas) o ambos (por ej., zwitteriones).

Un "profármaco" es un compuesto que al administrarse al cuerpo de un sujeto (tal como un mamífero) se descompone en la senda metabólica del sujeto para proporcionar un compuesto activo de Fórmula I. Más específicamente, un profármaco es un compuesto activo o inactivo "enmascarado" que se modifica químicamente a través de una acción fisiológica in vivo, tal como, hidrólisis, metabolismo y similares, en un compuesto de la presente invención luego de la administración del profármaco al sujeto o paciente. Una forma común de un profármaco es un grupo de ácido carboxílico enmascarado. Los ejemplos de un anión carboxilato enmascarado incluyen una variedad de ésteres, tales como alquilo (por ejemplo, metilo, etilo), cicloalquilo (por ejemplo, ciclohexilo), aralquilo (por ejemplo, bencilo, p-metoxibencilo) y alquilcarboniloxialquilo (por ejemplo, pivaloiloximetilo). Las aminas se enmascararon como derivados sustituidos por arilcarboniloximetilo que se escinden mediante esterasas in vivo que liberan el fármaco libre y formaldehído (Bundgaard J. Med. Chem. 2503 (1989)). También, los fármacos que contienen un grupo de NH ácido, tal como imidazol, imida, indol y similares, se enmascararon con grupos de N-aciloximetilo (Bundgaard Design of Prodrugs, Elsevier (1985)). Los grupos hidroxi se enmascararon como ésteres y éteres. EP 039,051 (Sloan and Little, 11 de abril de 1981) describe profármacos de ácido hidroxámico con base en Mannich, su preparación y uso. Por ejemplo, la conversión puede ocurrir por hidrólisis de un grupo éster o algún otro grupo biológicamente lábil. La preparación del profármaco se conoce en la técnica. Por ejemplo, “Prodrugs and Drug Delivery Systems,” que es un capítulo de Richard B.

Silverman, *Organic Chemistry of Drug Design and Drug Action*, 2d Ed., Elsevier Academic Press: Amsterdam, 2004, pp. 496-557, proporciona más detalles del sujeto.

Los tautómeros son isómeros que se encuentran en equilibrio rápido entre ellos. Por ejemplo, los tautómeros se pueden relacionar mediante la transferencia de un protón, átomo de hidrógeno o ion híbrido. Salvo que se describa de forma inequívoca o explícita la estereoquímica, se pretende que una estructura incluye cada estereoisómero posible, ambos puros o en cualquier mezcla posible.

Las formas sólidas alternativas son formas sólidas diferentes de aquellas que pueden ocasionarse de la práctica de los procedimientos descritos en la presente. Por ejemplo, las formas sólidas alternativas pueden ser formas amorfas, formas cristalinas, polimorfos y mezclas de los mismos.

Los complejos no covalentes son complejos que se pueden formar entre el compuesto y una o más especies que no implican una interacción de unión covalente entre el compuesto y las especies químicas adicionales. Pueden o no tener una proporción específica entre el compuesto y las especies químicas adicionales. Los ejemplos pueden incluir solvatos, hidratos, complejos de transferencia de cargo y similares.

**2. Usos, formulación y administración**

La presente invención también se refiere al uso de los compuestos como moduladores e inhibidores de la proteína tirosina cinasa. Estos compuestos se pueden usar para tratar enfermedades relacionadas con la transducción de señales de tirosina cinasa no regulada, por ejemplo, diversos cánceres, trastornos proliferativos de los vasos sanguíneos, trastornos fibróticos y enfermedades neurodegenerativas. En particular, los compuestos de la presente invención son útiles para el tratamiento y/o prevención de cáncer colorrectal, cáncer de pulmón, cáncer hematológico, cáncer renal, cáncer de hígado, cáncer de mama, retinopatía diabética, degeneración macular, degeneración macular relacionada con la edad, retinopatía del prematuro, angiogénesis ocular, edema de retina, isquemia de retina, edema macular diabético, edema macular cistoide, oclusión venosa de la retina, oclusión de rama venosa, neovascularización preretinal, neovascularización coroidal inducida por láser, neovascularización asociada a queratoplastia, glaucoma y tumores oculares, artritis, restenosis, cirrosis hepática, ateroesclerosis, psoriasis, diabetes mellitus, cicatrización, rechazo al implante, inflamación, enfermedades neurodegenerativas y trastornos inmunes en el ser humano.

Para los fines de la presente descripción, "tratar", "que trata" o "tratamiento" se refiere al diagnóstico, cura, alivio, tratamiento o prevención de la enfermedad u otra afección no deseada.

La presente invención también se refiere a la preparación de un medicamento para el tratamiento y prevención de enfermedades y afecciones relacionadas con actividades anormales de receptores de tirosina cinasa. El medicamento contiene una composición farmacéuticamente aceptable que comprende una cantidad terapéuticamente eficaz de los compuestos de la presente invención junto con el portador farmacéutico aceptable.

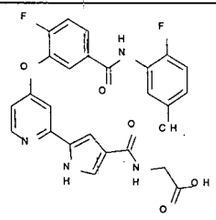
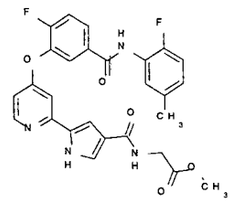
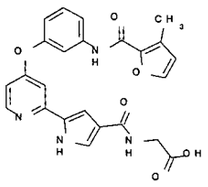
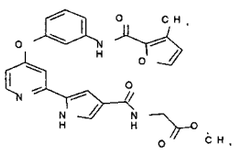
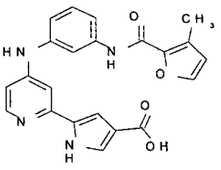
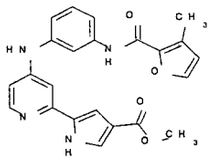
Las composiciones farmacéuticas aceptables contienen una cantidad terapéuticamente eficaz de los compuestos de la presente invención. Estas

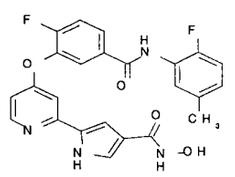
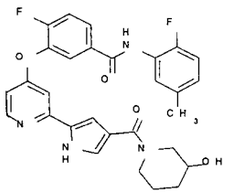
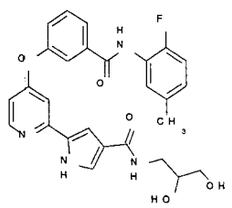
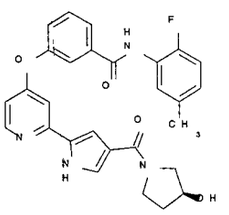
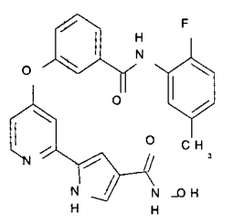
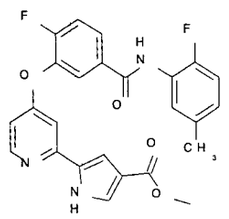
composiciones se pueden usar como un medicamento y se pueden administrar a un mamífero, tal como una persona que lo necesita. Los diferentes tipos de formas de dosificación adecuadas y medicamentos son conocidos en la técnica y se pueden adaptar fácilmente para la administración de compuestos de la presente invención, tales como de modo no taxativo, administración sistemática, parenteral, local y tópica. Las formas de dosificación pueden ser comprimidos, cápsulas, inyecciones intravenosas, inyecciones intramusculares, inyecciones locales, geles, ungüentos y cremas tópicas, gotas para los ojos, soluciones oftálmicas, suspensiones oftálmicas, emulsiones oftálmicas, inyecciones intravítrea, inyecciones sub-tenon, implantes bioerosionables oftálmicos e insertos o medicamentos de liberación mantenida no bioerosionables, aerosoles y ungüentos nasales, diversas preparaciones rectales o vaginales.

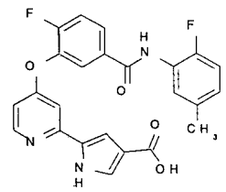
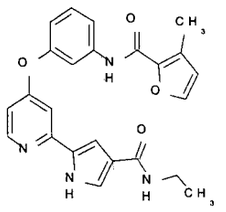
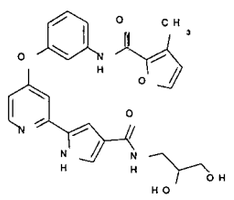
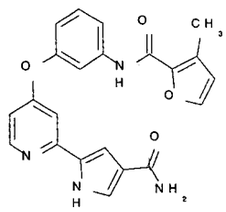
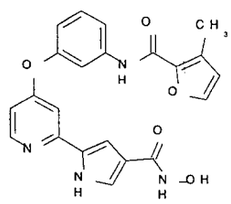
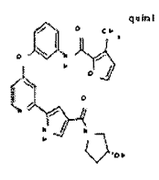
**3. Ejemplos**

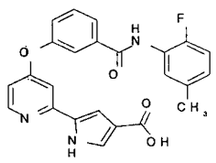
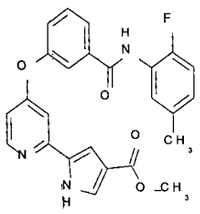
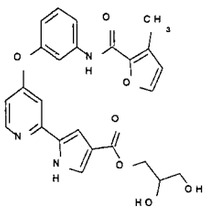
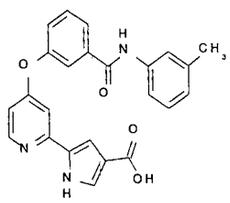
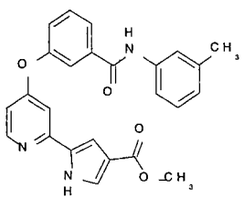
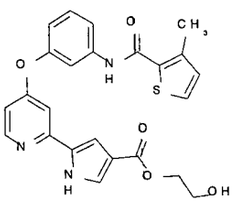
Algunos de los compuestos de la presente invención se enumeran en la Tabla I.

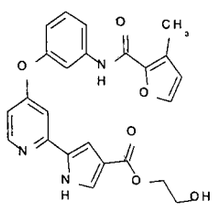
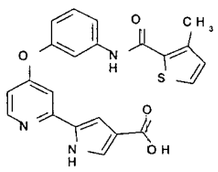
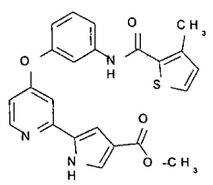
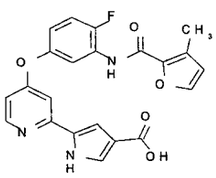
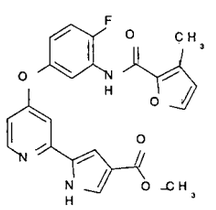
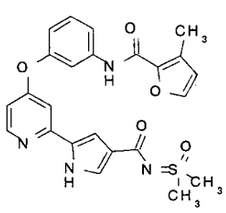
**Tabla 1: Ejemplos de compuestos de la presente invención**

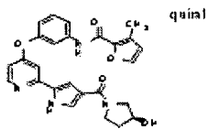
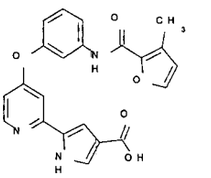
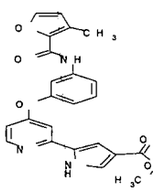
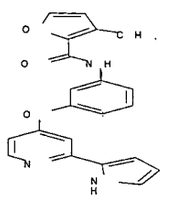
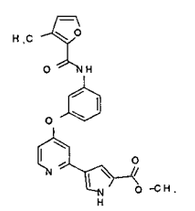
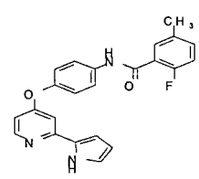
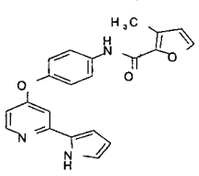
| Ejemplo Nº | Estructura química | MW | Nombre químico |
|---|---|---|---|
| 1 |  | 506 | Ácido [({5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil} fenoxi)piridin-2-il]-1H-pirrol-3-il}carbonil)amino]acético |
| 2 |  | 520 | [({5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-il}carbonil)amino]acetato de metilo |
| 3 |  | 460 | Ácido ({[5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-il]carbonil}amino)acético |
| 4 |  | 474 | ({[5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-il]carbonil}amino)acetato de metilo |
| 5 |  | 402 | Ácido 5-[4-({3-[(3-metil-2-furoil)amino]fenil}amino)piridin-2-il]-1H-pirrol-3-carboxílico |
| 6 |  | 416 | 5-[4-({3-[(3-metil-2-furoil)amino]fenil}amino)piridin-2-il]-1H-pirrol-3-carboxilato de metilo |

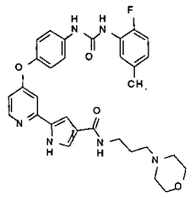
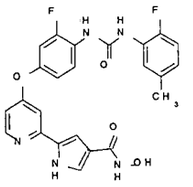
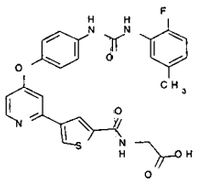
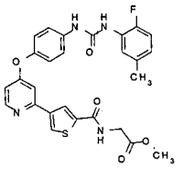
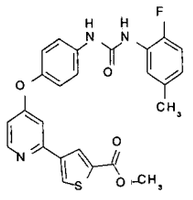
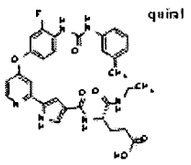
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|---|---|---|---|
| 7 |  | 464 | 5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-N-hidroxi-1H-pirrol-3-carboxamida |
| 8 |  | 533 | 4-fluoro-N-(2-fluoro-5-metilfenil)-3-[(2-{4-[(3-hidroxipiperidin-1-il)carbonil]-1H-pirrol-2-il}piridin-4-il)oxi]benzamida |
| 9 |  | 505 | N-(2,3-dihidroxipropil)-5-[4-(3-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxamida |
| 10 |  | 501 | N-(2-fluoro-5-metilfenil)-3-[(2-{4-[(3-hidroxipirrolidin-1-il)carbonil]-1H-pirrol-2-il}piridin-4-il)oxi]benzamida |
| 11 |  | 446 | 5-[4-(3-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-N-hidroxi-1H-pirrol-3-carboxamida |
| 12 |  | 463 | 5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de metilo |

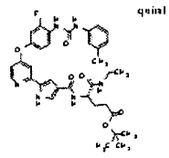
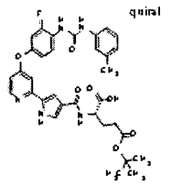
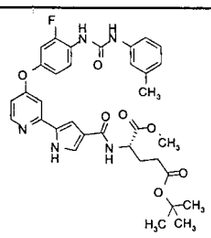
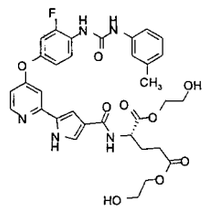
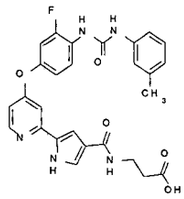
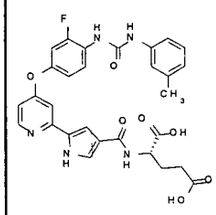
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| 13 |  | 449 | Ácido 5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxílico |
| 14 |  | 430 | N-etil-5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxamida |
| 15 |  | 476 | N-(2,3-dihidroxipropil)-5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxamida |
| 16 |  | 402 | 5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxamida |
| 17 |  | 418 | N-hidroxi-5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxamida |
| 18 |  | 472 | N-(3-{[2-(4-{[(3R)-3-hidroxipirrolidin-1-il]carbonil}-1H-pirrol-2-il)piridin-4-il]oxi}fenil)-3-metil-2-furamida |

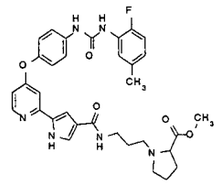
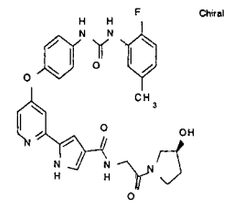
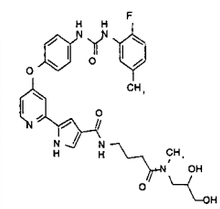
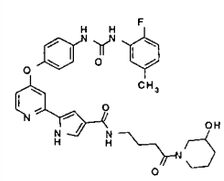
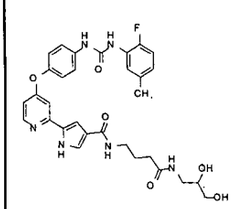
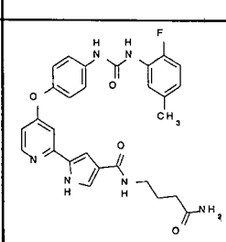
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|---|---|---|---|
| 19 |  | 431 | Ácido 5-{4-[3-(2-Fluoro-5-metil-fenilcarbamoil)-fenoxi]-piridin-2-il}-1H-pirrol-3-carboxílico |
| 20 |  | 445 | 5-[4-(3-{[(2-Fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de metilo |
| 21 |  | 477 | 5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxilato de 2,3-dihidroxipropilo |
| 22 |  | 413 | Ácido 5-[4-(3-{[(3-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de metilo |
| 23 |  | 427 | 5-[4-(3-{[(3-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxílico |
| 24 |  | 464 | 5-[4-(3-{[(3-metil-2-tienil)carbonil]amino}fenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de 2-hidroxietilo |

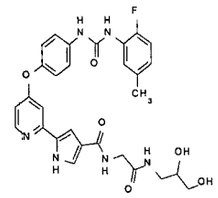
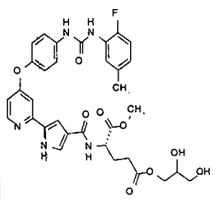
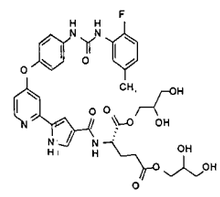
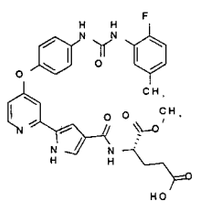
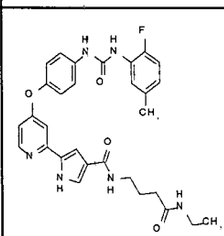
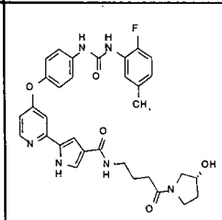
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|---|---|---|---|
| 25 |  | 447 | 5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxilato de 2-hidroxietilo |
| 26 |  | 419 | Ácido 5-[4-(3-{[(3-metil-2-tienil)carbonil]amino}fenoxi)piridin-2-il]-1H-pirrol-3-carboxílico |
| 27 |  | 433 | 5-[4-(3-{[(3-metil-2-tienil)carbonil]amino}fenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de metilo |
| 28 |  | 421 | Ácido 5-(4-{4-fluoro-3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxílico |
| 29 |  | 435 | 5-(4-{4-fluoro-3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxilato de metilo |
| 30 |  | 479 | N-[dimetil(óxido)-lambda~4~-sulfanilideno]-5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxamida |

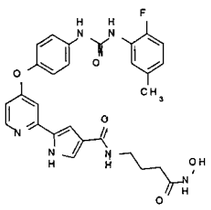
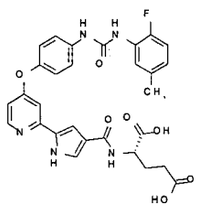
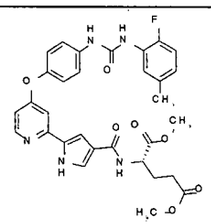
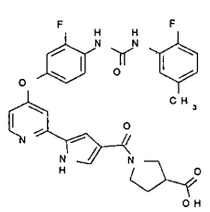
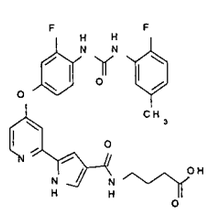
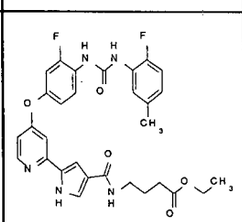
| | | | |
|---|---|---|---|
| 31 |  | 472 | N-(3-{[2-(4-{[(3S)-3-hidroxipirrolidin-1-il]carbonil}-1H-pirrol-2-il)piridin-4-il]oxi}fenil)-3-metil-2-furamida |
| 32 |  | 403 | Ácido 5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxílico |
| 33 |  | 417 | 5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxilato de metilo |
| 34 |  | 359 | 3-metil-N-(3-{[2-(1H-pirrol-2-il)piridin-4-il]oxi}fenil)-2-furamida |
| 35 |  | 417 | 4-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-2-carboxilato de metilo |
| 36 |  | 387 | 2-fluoro-5-metil-N-(4-{[2-(1H-pirrol-2-il)piridin-4-il]oxi}fenil)benzamida |
| 37 |  | 359 | 3-metil-N-(4-{[2-(1H-pirrol-2-il)piridin-4-il]oxi}fenil)-2-furamida |

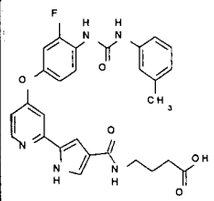
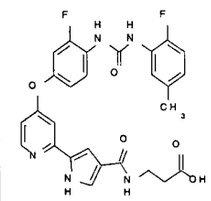
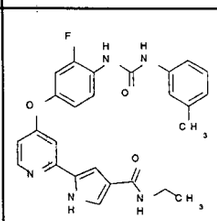
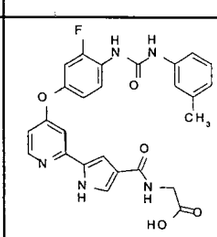
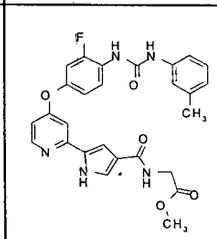
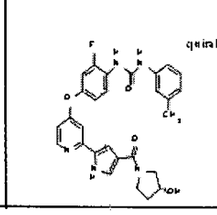
| Ejemplo Nº | Estructura química | MW | Nombre químico |
|---|---|---|---|
| 38 |  | 573 | 5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-(3-morfolin-4-ilpropil)-1H-pirrol-3-carboxamida |
| 39 |  | 479 | 5-{4-[3-fluoro-4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-hidroxi-1H-pirrol-3-carboxamida |
| 40 |  | 521 | Ácido {[(4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-2-tienil)carbonil]amino}acético |
| 41 |  | 535 | {[(4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-2-tienil)carbonil]amino}acetato de metilo |
| 42 |  | 478 | 4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}tiofeno-2-carboxilato de metilo |
| 43 |  | 603 | Ácido (4S)-5-(etilamino)-4-{[(5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}-5-oxopentanoico |

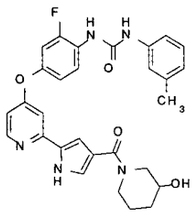
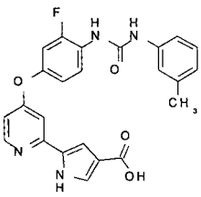
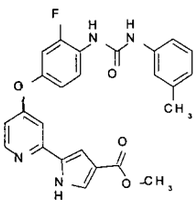
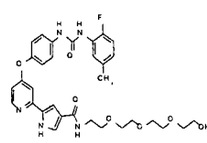
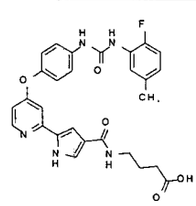
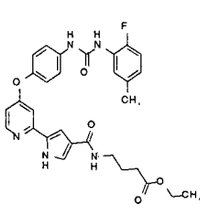
| | | | |
|---|---|---|---|
| 44 |  | 659 | (4S)-5-(etilamino)-4-{[(5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}-5-oxopentanoato de terc-butilo |
| 45 |  | 632 | Ácido (2S)-5-terc-butoxi-2-{[(5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}-5-oxopentanoico |
| 46 |  | 646 | 2-{[(5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}pentanodioato de 5-terc-butil 1-metilo |
| 47 |  | 664 | 2-{[(5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}pentanodioato de bis(2-hidroxietilo) |
| 48 |  | 518 | Ácido 3-{[(5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}propanoico |
| 49 |  | 576 | Ácido 2-{[(5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}pentanodioico |

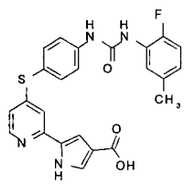
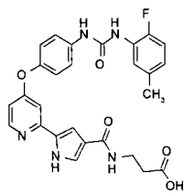
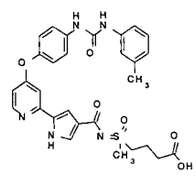
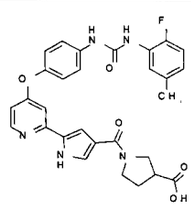
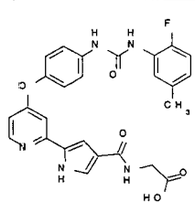
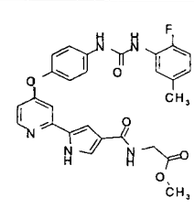
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| 50 |  | 615 | 1-(3-{[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}propil)pirrolidina-2-carboxilato de metilo |
| 51 |  | 573 | 5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-{2-[(3S)-3-hidroxipirrolidin-1-il]-2-oxoetil}-1H-pirrol-3-carboxamida |
| 52 |  | 619 | N-{4-[(2,3-dihidroxipropil)(metil)amino]-4-oxobutil}-5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida |
| 53 |  | 615 | 5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-[4-(3-hidroxipiperidin-1-il)-4-oxobutil]-1H-pirrol-3-carboxamida |
| 54 |  | 605 | N-{4-[(2,3-dihidroxipropil)amino]-4-oxobutil}-5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida |
| 55 |  | 531 | N-(4-amino-4-oxobutil)-5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida |

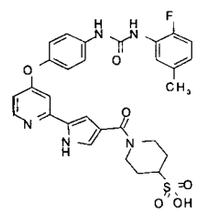
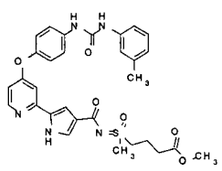
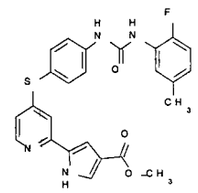
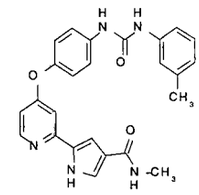
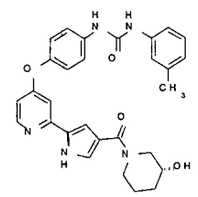
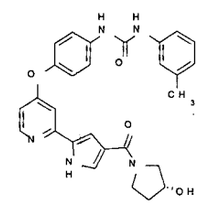
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| 56 |  | 577 | N-{2-[(2,3-dihidroxipropil)amino]-2-oxoetil}-5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida |
| 57 |  | 664 | 2-{[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}pentanodioato de 5-(2,3-dihidroxipropil) 1-metilo |
| 58 |  | 724 | 2-{[(5-{4-[4-({[(2-fluoro-5-metilfeni)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}pentanodioato de bis(2,3-dihidroxipropilo) |
| 59 |  | 590 | Ácido 4-{[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}-5-metoxi-5-oxopentanoico |
| 60 |  | 559 | N-[4-(etlamino)-4-oxobutil]-5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida |
| 61 |  | 601 | 5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-[4-(3-hidroxipirrolidin-1-il)-4-oxobutil]-1H-pirrol-3-carboxamida |

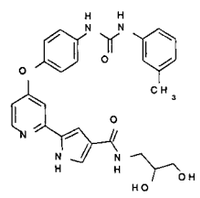
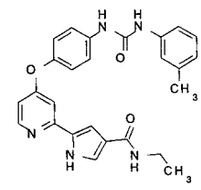
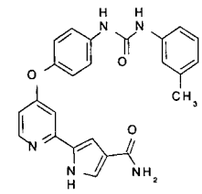
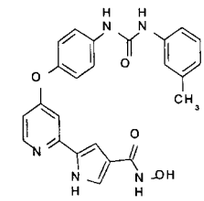
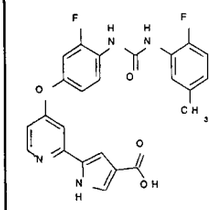
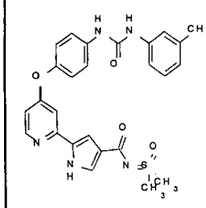
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| 62 |  | 547 | 5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-[4-hidroxiamino)-4-oxobutil]-1H-pirrol-3-carboxamida |
| 63 |  | 576 | Ácido 2-{[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}pentanodioico |
| 64 |  | 604 | 2-{[(5-{4-[4-({[(2-fluoro-5-metilfeni)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}pentanodioato de dimetilo |
| 65 |  | 562 | Ácido 1-[(5-{4-[3-fluoro-4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]pirrolidin-3-carboxílico |
| 66 |  | 550 | Áácido 4-{[(5-{4-[3-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}butanoico |
| 67 |  | 578 | 4-{[(5-{4-[3-fluoro-4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}butanoato de etilo |

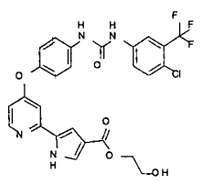
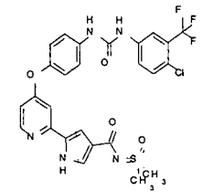
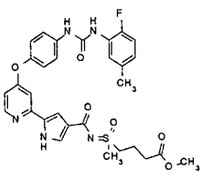
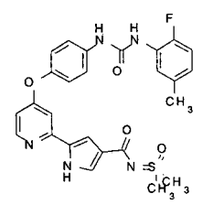
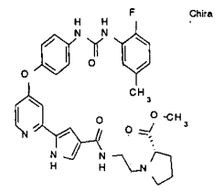
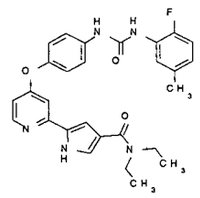
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| 68 |  | 532 | Ácido 4-{[(5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}butanoico |
| 69 |  | 536 | Ácido 3-{[(5-{4-[3-fluoro-4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}propanoico |
| 70 |  | 474 | N-etil-5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida |
| 71 |  | 503 | Ácido {[(5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}acético |
| 72 |  | 518 | {[(5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}acetato de metilo |
| 73 |  | 516 | 1-(2-fluoro-4-{[2-(4-{[(3R)-3-hidroxipirrolidin-1-il]carbonil}-1H-pirrol-2-il)piridin-4-il]oxi}fenil)-3-(3-metilfenil)urea |

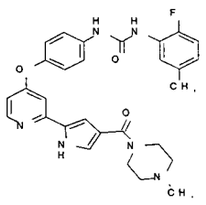
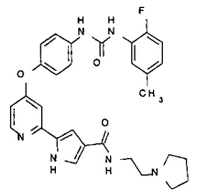
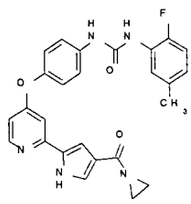
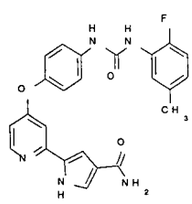
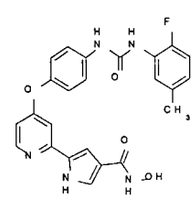
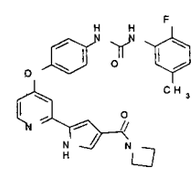
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| 74 |  | 530 | 1-(2-fluoro-4-{[2-(4-[(3-hidroxipiperidin-1-il)carbonil]-1H-pirrol-2-il)piridin-4-il]oxi}fenil}-3-(3-metilfenil)urea |
| 75 |  | 446 | Ácido 5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxílico |
| 76 |  | 460 | 5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxilato de metilo |
| 77 |  | 622 | 5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-(2-{2-[2-(2-hidroxietoxi)etoxi]etoxi}etil)-1H-pirrol-3-carboxamida |
| 78 |  | 532 | Ácido 4-{[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}butanoico |
| 79 |  | 560 | 4-{[(5-{4-[4-({[(2-fluoro-5-metilfeni)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}butanoato de etilo |

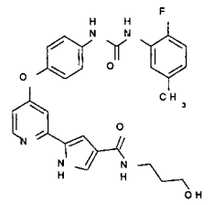
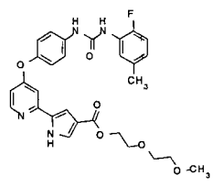
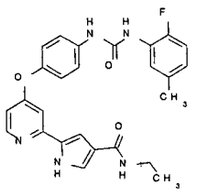
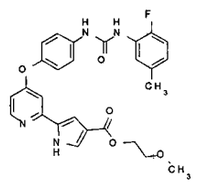
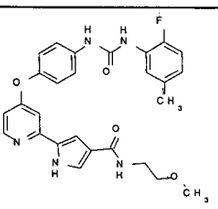
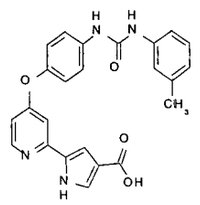
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|---|---|---|---|
| 80 |  | 463 | Ácido 5-(4-{[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenil]tio}piridin-2-il)-1H-pirrol-3-carboxílico |
| 81 |  | 518 | Ácido 3-{[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}propanoico |
| 82 |  | 576 | Ácido 4-{S-metil-N-[(5-{4-[4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]sulfonimidoil}butanoico |
| 83 |  | 544 | Ácido 1-[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]pirrolidin-3-carboxílico |
| 84 |  | 503 | Ácido {[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}acético |
| 85 |  | 518 | {[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}acetato de metilo |

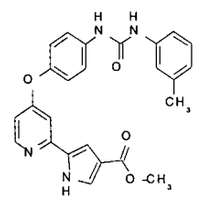
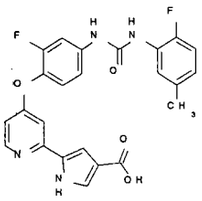
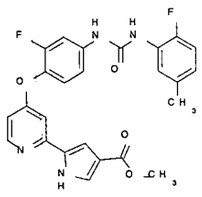
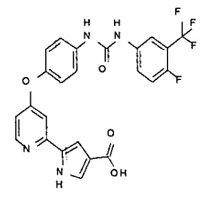
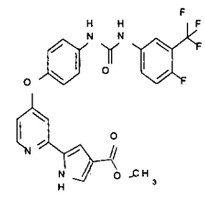
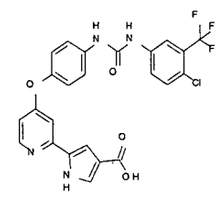
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| 86 |  | 594 | Ácido 1-[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]piperidin-4-sulfónico |
| 87 |  | 590 | 4-{S-metil-N-[(5-{4-[4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]sulfonimidoil}butanoato de metilo |
| 88 |  | 477 | 5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenil]tio}piridin-2-il)-1H-pirrol-3-carboxilato de metilo |
| 89 |  | 441 | N-metil-5-{4-[4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida |
| 90 |  | 512 | 1-(4-[2-{4-[3-hidroxipiperidin-1-il)carbonil]-1H-pirrol-2-il)piridin-4-il]oxi}fenil}-3-(3-metilfenil)urea |
| 91 |  | 498 | 1-(4-[2-{4-[3-hidroxipirrolidin-1-il)carbonil]-1H-pirrol-2-il)piridin-4-il]oxi}fenil}-3-(3-metilfenil)urea |

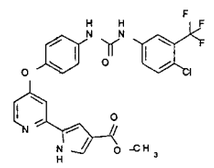
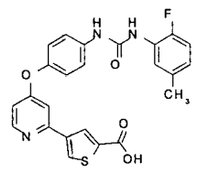
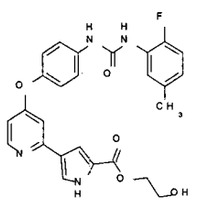
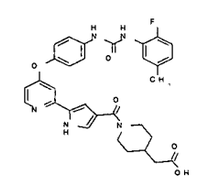
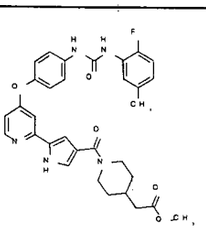
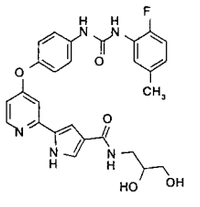
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| 92 |  | 502 | N-(2,3-dihidroxipropil)-5-{4-[4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida |
| 93 |  | 456 | N-etil-5-{4-[4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida |
| 94 |  | 427 | 5-{4-[4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida |
| 95 |  | 443 | N-hidroxi-5-{4-[4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida |
| 96 |  | 464 | Ácido 5-{4-[3-fluoro-4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxílico |
| 97 |  | 504 | N-[dimetil(óxido)-lambda~4~-sulfanilideno]-5-(4-{4-[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida |

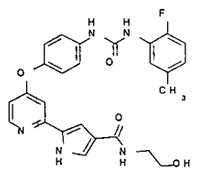
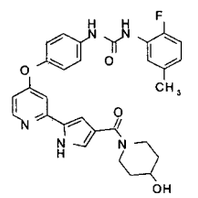
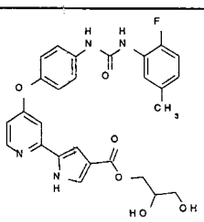
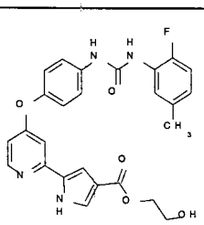
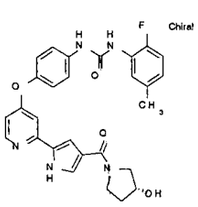
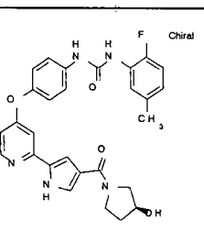
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|---|---|---|---|
| 98 |  | 561 | 5-{4-[4-({[(4-cloro-3-(trifluorometil)fenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxilato de 2-hidroxietilo |
| 99 |  | 592 | 5-(4-{4-[(4-cloro-3-(trifluorometil)fenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-[dimetil(óxido)-lambda-4~-sulfanilideno]-1H-pirrol-3-carboxamida |
| 100 |  | 608 | 4-(N-5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]-S-metilsulfonimidoil}butanoato de metilo |
| 101 |  | 522 | N-[dimetil(óxido)-lambda~4~-sulfanilideno]-5-(4-{4-[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida |
| 102 |  | 601 | (2S)-1-(2-{[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}etil)pirrolidina-2-carboxilato de metilo |
| 103 |  | 502 | N,N-dietil-5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida |

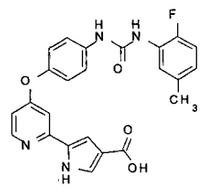
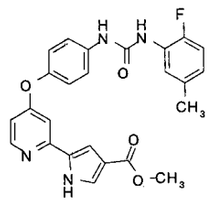
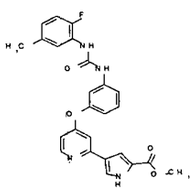
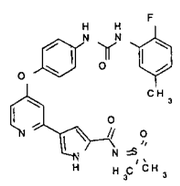
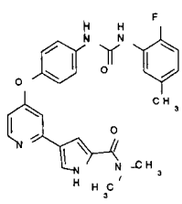
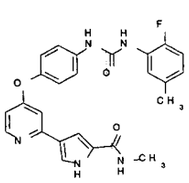
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| 104 |  | 529 | 1-(2-fluoro-5-metilfenil)-3-{4-[(2-{4-[(4-metilpiperazin-1-il)carbonil]-1H-pirrol-2-il}piridin-4-il)oxi]fenil}urea |
| 105 |  | 543 | 5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-(2-pirrolidin-1-iletil)-1H-pirrol-3-carboxamida |
| 106 |  | 471 | 1-[4-({2-[4-(aziridin-1-ilcarbonil)-1H-pirrol-2-il]piridin-4-il}oxi)fenil]-3-(2-fluoro-5-metilfenil)urea |
| 107 |  | 445 | 5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida |
| 108 |  | 461 | 5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-hidroxi-1H-pirrol-3-carboxamida |
| 109 |  | 486 | 1-[4-({2-[4-(azetidin-1-ilcarbonil)-1H-pirrol-2-il]piridin-4-il}oxi)fenil]-3-(2-fluoro-5-metilfenil)urea |

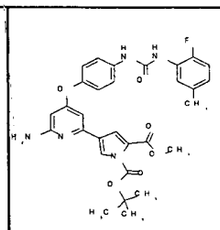
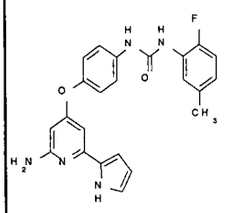
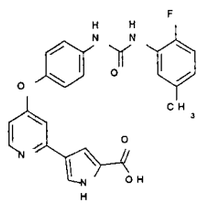
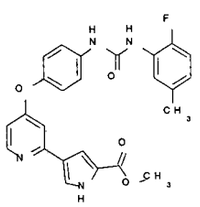
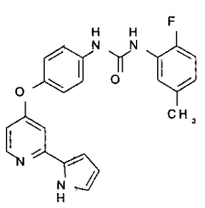
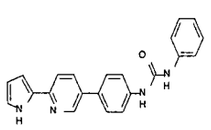
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|---|---|---|---|
| 110 |  | 504 | 5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-(3-hidroxipropil)-1H-pirrol-3-carboxamida |
| 111 |  | 549 | 5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxilato de 2-(2-metoxietoxi)etilo |
| 112 |  | 474 | N-etil-5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida |
| 113 |  | 505 | 5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxilato de 2-metoxietilo |
| 114 |  | 504 | 5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-(2-metoxietil)-1H-pirrol-3-carboxamida |
| 115 |  | 428 | Ácido 5-{4-[4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxílico |

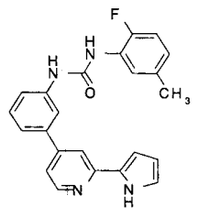
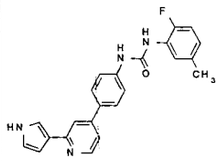
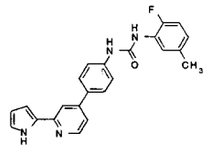
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| 116 |  | 442 | 5-{4-[4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxilato de metilo |
| 117 |  | 464 | Ácido 5-{4-[2-fluoro-4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxílico |
| 118 |  | 478 | 5-{4-[2-fluoro-4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxilato de metilo |
| 119 |  | 500 | Ácido 5-(4-{4-[({[4-fluoro-3-(trifluorometil)fenil]amino}carbonil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxílico |
| 120 |  | 514 | 5-(4-{4-[({[4-fluoro-3-(trifluorometil)fenil]amino}carbonil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxilato de metilo |
| 121 |  | 517 | Ácido 5-(4-{4-[({[4-cloro-3-(trifluorometil)fenil]amino}carbonil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxílico |

| | | | |
|---|---|---|---|
| 122 |  | 531 | 5-(4-{4-[({[4-cloro-3-(trifluorometil)fenil]amino}carbonil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxilato de metilo |
| 123 |  | 463 | Ácido 4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}tiofen-2-carboxílico |
| 124 |  | 490 | 4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-2-carboxilato de 2-hidroxietilo |
| 125 |  | 572 | Ácido 1-[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]piperidin-4-il}acético |
| 126 |  | 586 | {1-[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]piperidin-4-il}acetato de metilo |
| 127 |  | 520 | N-(2,3-dihidroxipropil)-5-{4-[4-({[(2-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida |

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|---|---|---|---|
| 128 |  | 490 | 5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-(2-hidroxietil)-1H-pirrol-3-carboxamida |
| 129 |  | 530 | 1-(2-fluoro-5-metilfenil)-3-{4-[(2-{4-[(4-hidroxipiperidin-1-il)carbonil]-1H-pirrol-2-il}piridin-4-il)oxi]fenil}urea |
| 130 |  | 521 | 5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxilato de 2,3-dihidroxipropilo |
| 131 |  | 490 | 5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxilato de 2-hidroxietilo |
| 132 |  | 516 | 1-(2-fluoro-5-metilfenil)-3-{4-[(2-{4-[(-(3R)-3-hidroxipirrolidin-1-il]carbonil}-1H-pirrol-2-il)piridin-4-il)oxi]fenil}urea |
| 133 |  | 516 | 1-(2-fluoro-5-metilfenil)-3-{4-[(2-{4-{[(3S)-3-hidroxipirrolidin-1-il]carbonil}-1H-pirrol-2-il)piridin-4-il)oxi]fenil}urea |

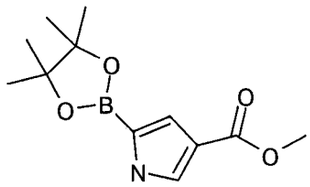
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| 134 |  | 446 | Ácido 5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxílico |
| 135 |  | 460 | 5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxilato de metilo |
| 136 |  | 460 | 4-{4-[3-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-2-carboxilato de metilo |
| 137 |  | 522 | N-[dimetil(óxido)-lambda~4~-sulfanilideno]-4-(4-{4-[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-2-carboxamida |
| 138 |  | 474 | 4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N,N-dimetil-1H-pirrol-2-carboxamida |
| 139 |  | 459 | 4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-metil-1H-pirrol-2-carboxamida |

| | | | |
|---|---|---|---|
| 140 |  | 576 | 4-{6-amino-4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-1,2-dicarboxilato de 1-terc-butil 2-metilo |
| 141 |  | 417 | 1-(4-{[2-amino-6-(1H-pirrol-2-il)piridin-4-il]oxi}fenil)-3-(2-fluoro-5-metilfenil)urea |
| 142 |  | 446 | Ácido 4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-2-carboxílico |
| 143 |  | 460 | 4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-2-carboxilato de metilo |
| 144 |  | 402 | 1-(2-fluoro-5-metilfenil)-3-(4-{[2-(1H-pirrol-2-il)piridin-4-il]oxi}fenil)urea |
| 145 |  | 354 | 1-fenil-3-{4-[6-(1H-pirrol-2-il)piridin-3-il]fenil}urea |

| | | | |
|---|---|---|---|
| 146 |  | 386 | 1-(2-fluoro-5-metilfenil)-3-(3-{[2-(1H-pirrol-2-il)piridin-4-il]fenil}urea |
| 147 |  | 386 | 1-(2-fluoro-5-metilfenil)-3-(4-{[2-(1H-pirrol-3-il)piridin-4-il]fenil}urea |
| 148 |  | 386 | 1-(2-fluoro-5-metilfenil)-3-(4-{[2-(1H-pirrol-2-il)piridin-4-il]fenil}urea |

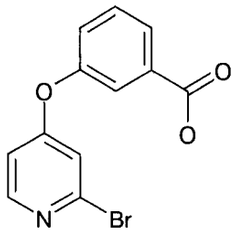
**3.1 Caracterización y síntesis de los compuestos**

Preparación de 5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirrol-3-carboxilato de metilo



A una mezcla de metil-1H-pirrol-3-carboxilato (5.0 g, 39.9 mmol), bis(pinacolato)diboro (5.37 g, 21.1 mmol), 4,4'-di-terc-butil-2,2'-bipiridina (0.054 g, 0.20 mmol) e $[Ir(OMe)(COD)]_2$ (0.067 g, 0.099 mmol) se agregó ciclohexano (60 mL). La mezcla se agitó a 90°C durante 5 horas. La mezcla se enfrió hasta temperatura ambiente y se filtró, se lavó con abundantes cantidades de agua y dos veces con hexanos. El sólido naranja claro se recogió y se secó en un horno de vacío a 55°C para proporcionar 5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirrol-3-carboxilato de metilo (6.99 g, 70% de rendimiento).

Preparación de ácido 3-(2-Bromo-piridin-4-iloxi)-benzoico



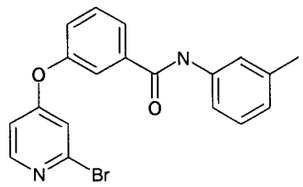
Una mezcla de 2-bromo-4-cloro-piridina (200mg, 1.04mmol), metil-3-hidroxibenzoato (158mg, 1.04mmol), carbonato de cesio (507mg, 1.56mmol) en 10ml de DMSO anhidro se calentó a 66°C durante 5 horas. La mezcla se diluyó con acetato de etilo (100ml), se lavó con salmuera (50ml, 3 veces), se secó en $Na_2SO_4$ y se evaporó para proporcionar un aceite incoloro. El aceite se disolvió en MeOH (8 mL) y se agregó una solución de NaOH 2M (4ml, 8mmol). La mezcla se calentó a 60°C durante 20 minutos, se vertió en 50ml de agua, y se acidificó hasta pH = 4. Los precipitados se

filtraron, lavaron con agua y secaron al vacío para proporcionar ácido 3-(2-bromo-piridin-4-iloxi)-benzoico como un sólido blanco. Rendimiento: 170mg, 56%.

$^1$H NMR (DMSO-$d_6$) δ: 13.24 (br. s., 1H), 8.27 (d, J = 5.9 Hz, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.58 - 7.68 (m, 2H), 7.45 - 7.52 (m, 1H), 7.19 (d, J = 2.1 Hz, 1H), 7.00 (dd, J = 5.7, 2.2 Hz, 1H)

LR MS (ES-): 292 (M-H), 294

Preparación de 3-(2-Bromo-piridin-4-iloxi)-N-m-tolil-benzamida



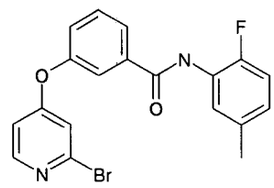
Una mezcla de ácido 3-(2-bromo-piridin-4-iloxi)-benzoico (170mg, 0.58mmol), HATU (265mg, 0.69mmol),) m-toluidina (93mg, 0.87mmol) y *N,N*-diisopropiletilamina (164mg, 1.28mmol) en DMF anhidro (10ml) se agitó a temperatura ambiente durante 20 minutos. La mezcla se vertió en 100ml de agua. Los precipitados se filtraron, lavaron con agua y secaron al vacío para proporcionar 3-(2-Bromo-piridin-4-iloxi)-N-m-tolil-benzamida como un sólido blanquecino. Rendimiento: 150mg, 68%.

$^1$H NMR (DMSO-$d_6$)δ: 10.18 (s, 1H), 8.29 (d, J = 5.9 Hz, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.78 (s, 1H), 7.65 (t, J = 7.9 Hz, 1H), 7.50 - 7.60 (m, 2H), 7.45 (dd, J = 7.9, 1.8 Hz, 1H), 7.16 - 7.25 (m, 2H), 7.02 (dd, J = 5.7, 2.2 Hz, 1H), 6.92 (d, J = 7.6 Hz, 1H), 2.29 (s, 3H)

LR MS (ES+): 405 (M+Na$^+$), 407

LR MS (ES-): 381 (M-H), 383

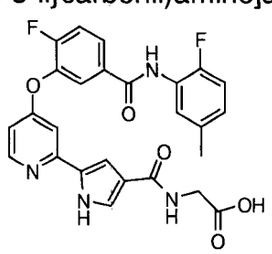
Preparación de 3-(2-Bromo-piridin-4-iloxi)-N-(2-fluoro-5-metil-fenil)-benzamida



Una mezcla de ácido 3-(2-bromo-piridin-4-iloxi)-benzoico (200mg, 0.68mmol), HATU (312mg, 0.82mmol),) 2-fluoro-5-metilanilina (125mg, 1.0mmol) y *N,N*-diisopropiletilamina (193mg, 1.5mmol) en DMF anhidro (10ml) se agitó a 60°C durante 90 minutos. La mezcla se vertió en 100ml de agua. Los precipitados se filtraron, lavaron con agua y secaron al vacío para proporcionar 3-(2-bromo-piridin-4-iloxi)-N-(2-fluoro-5-metil-fenil)-benzamida como un sólido blanquecino. Rendimiento: 200mg, 74%.

Ejemplo 1

Ácido [({5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil} fenoxi)piridin-2-il]-1H-pirrol-3-il}carbonil)amino]acético



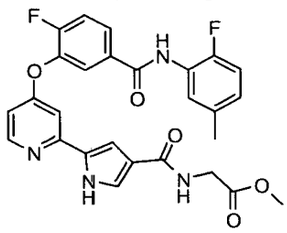
A una solución agitada de [({5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-il}carbonil)amino]acetato de metilo (110mg, 0.21mmol) en una mezcla de solventes THF/MeOH (5ml/5ml) se agregó solución de NaOH 1M (1ml, 1mmol). La mezcla se agitó a temperatura ambiente durante 1 hora, y se vertió en 100ml de agua. Se agregó HCl 2M hasta pH = 4. Los precipitados se filtraron, lavaron con agua y secaron al vacío para proporcionar ácido [({5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-il}carbonil)amino]acético como un sólido blanco. Rendimiento: 100mg, 93%.

$^1$H NMR (DMSO-$d_6$) δ: 12.41 (br. s., 1H), 11.87 (br. s., 1H), 10.12 (s, 1H), 8.42 (d, J = 5.6 Hz, 1H), 8.19 (t, J = 6.0 Hz, 1H), 7.95 - 8.04 (m, 2H), 7.63 (dd, J = 10.1, 8.7 Hz, 1H), 7.41 (dd, J = 3.1, 1.6 Hz, 1H), 7.35 (dd, J = 7.3, 1.8 Hz, 1H), 7.27 (d, J = 2.3 Hz, 1H), 7.09 - 7.18 (m, 2H), 7.04 (td, J = 5.3, 2.3 Hz, 1H), 6.81 (dd, J = 5.9, 2.3 Hz, 1H), 3.82 (d, J = 5.9 Hz, 2H), 2.27 (s, 3H)

LR MS (ES-): 505 (M-H)

Ejemplo 2

[({5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-il}carbonil)amino]acetato de metilo



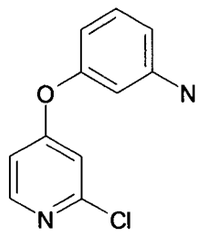
Procedimiento similar al del Ejemplo 1.

$^1$H NMR (DMSO-$d_6$) δ: 11.95 (br. s., 1H), 10.12 (s, 1H), 8.44 (d, J = 5.9 Hz, 1H), 8.33 (t, J = 5.9 Hz, 1H), 7.97 - 8.03 (m, 2H), 7.61 - 7.67 (m, 1H), 7.45 (br. s., 1H), 7.33 - 7.37 (m, 1H), 7.30 (s, 1H), 7.18 (br. s., 1H), 7.14 (dd, J = 10.3, 8.5 Hz, 1H), 7.02 - 7.08 (m, 1H), 6.86 (br. s., 1H), 3.91 (d, J = 5.9 Hz, 2H), 3.61 (s, 3H), 2.27 (s, 3H)

LR MS (ES+): 521 (MH), 543 ($M+Na^+$)

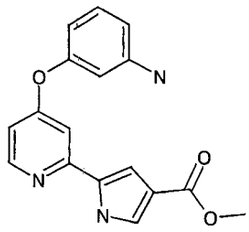
LR MS (ES-): 519 (M-H)

Preparación de 4-(3-Aminofenoxi)-2-cloropiridina



A una mezcla de 3-aminofenol (3.7 g, 34.09 mmol) en DMSO (50 mL) se agregó Cs2CO3 (30.7 g, 94.46 mmol). La mezcla se agitó durante 10 min y luego se agregó 2,4-dicloropiridina (5.0 g, 33.79 mmol). La mezcla se agitó a 120°C durante 1.5 h. La mezcla se enfrió y se diluyó con agua. La solución acuosa se extrajo con EtOAc (100 mL 3 veces). Los extractos orgánicos se combinaron, secaron sobre MgSO4 y se concentraron para proporcionar un aceite oscuro. El aceite se purificó por cromatografía en columna, eluyendo con 30-40% de EtOAc/hexanos, para proporcionar 4-(3-Aminofenoxi)-2-cloropiridina (6.63 g, 89%) como un sólido pardo.

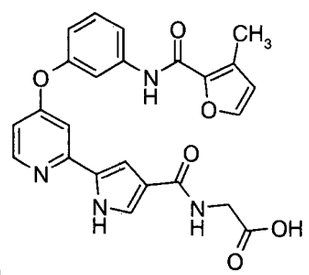
Preparación de 5-[4-(3-aminofenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de metilo



Una mezcla de 4-(3-aminofenoxi)-2-cloropiridina (4.0 g, 18.13mmol), metil-(5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirrol-3-carboxilato (6.82 g, 27.16mmol) y Pd(PPh3)4 (4.20 g, 3.63mmol) a un recipiente de pared gruesa y se purgó con N2. Se agregó una solución de K2CO3 2M (13.59 mL), seguido de DME (70 mL). El recipiente de reacción se selló y la mezcla se agitó a 92°C durante 18 h. El recipiente de reacción se enfrió hasta temperatura ambiente y la mezcla se filtró sobre celite, lavándose con EtOAc. El filtrado se concentró y el aceite oscuro resultante se purificó por cromatografía en columna, eluyendo con 40-80% de EtOAc/hexanos para proporcionar 5-[4-(3-aminofenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de metilo (2.85 g, 51% de rendimiento).

Ejemplo 3

Ácido ({[5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-il]carbonil}amino)acético



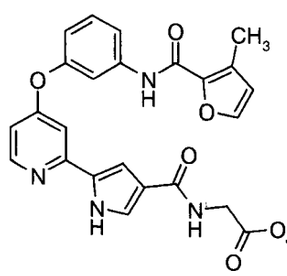
Procedimiento similar al del Ejemplo 1.

$^1$H NMR (DMSO-$d_6$) δ: 12.42 (br. s., 1H), 11.91 (br. s., 1H), 10.20 (s, 1H), 8.41 (d, J = 5.6 Hz, 1H), 8.21 (t, J = 5.4 Hz, 1H), 7.76 (s, 1H), 7.65 - 7.73 (m, 2H), 7.36 - 7.47 (m, 2H), 7.26 (br. s., 1H), 7.12 (br. s., 1H), 6.86 - 6.98 (m, 1H), 6.77 (br. s., 1H), 6.56 (s, 1H), 3.81 (d, J = 5.9 Hz, 2H), 2.29 (s, 3H)

LR MS (ES-): 459 (M-H)

Ejemplo 4

({[5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-il]carbonil}amino)acetato de metilo



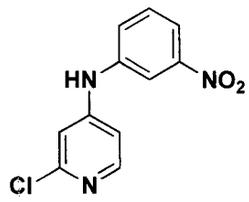
al del Ejemplo 3.

$^1$H NMR (DMSO-$d_6$) δ: 11.88 (br. s., 1H), 10.19 (s, 1H), 8.40 (d, J = 5.6 Hz, 1H), 8.32 (t, J = 5.6 Hz, 1H), 7.76 (s, 1H), 7.65 - 7.72 (m, 2H), 7.36 - 7.44 (m, 2H), 7.23 (d, J = 2.1 Hz, 1H), 7.08 (br. s., 1H), 6.90 (d, J = 7.3 Hz, 1H), 6.75 (dd, J = 5.6, 1.8 Hz, 1H), 6.56 (s, 1H), 3.89 (d, J = 5.6 Hz, 2H), 3.60 (s, 3H), 2.29 (s, 3H)

LR MS (ES+): 475 (MH), 497 ($M+Na^+$)

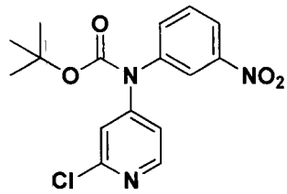
LR MS (ES-): 473 (M-H)

Preparación de 2-Cloro-*N*-(3-nitrofenil)piridina-4-amina



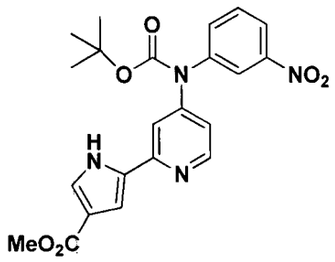
A una suspensión desgasificada (15 min, $N_2$) de 2-cloro-4-yodopiridina (3.0 g, 12.53 mmol), 3-nitroanilina (1.82 g, 13.18 mmol), BINAP (0.39 g, 0.626 mmol) y $Cs_2CO_3$ (8.16 g, 25.04 mmol) en tolueno (72 mL) se agregó $Pd(OAc)_2$ (0.084 g, 0.374 mmol). El tubo de reacción se selló y la mezcla se agitó a 90°C durante 18 h. La mezcla se enfrió hasta ta y se filtró, lavándose con EtOAc. El sólido naranja/amarillo recogido se lavó con $CH_2Cl_2$ hasta que todo el producto se lavó rápidamente en el filtrado. El filtrado se concentró para proporcionar 2-Cloro-*N*-(3-nitrofenil)piridina-4-amina como un sólido amarillo brillante. Se recogió producto adicional del sólido recogido tras la concentración del filtrado anterior, luego de lavar con $CH_2Cl_2$. No hubo purificación adicional. La cantidad total de producto recogido fue 2.85 g (91% de rendimiento).

Preparación de 2-cloropiridin-4-il(3-nitrofenil)carbamato de terc-butilo



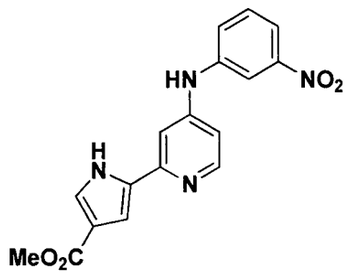
A una solución agitada de 2-Cloro-*N*-(3-nitrofenil)piridina-4-amina (2.70 g, 10.82 mmol) en THF (45 mL) se agregó $Et_3N$ (6.32 mL, 45.3 mmol). La mezcla se enfrió hasta 0°C, y se agregó DMAP (0.0135 g, 0.110 mmol) y $BOC_2O$ (2.84 g, 12.99 mmol). La mezcla se calentó hasta temperatura ambiente y se agitó durante 18 h. La mezcla se inactivó con hielo y se diluyó con agua. Se extrajo con EtOAc (200 mL 3 veces), lavó con salmuera y agua, secó ($MgSO_4$), y concentró. Se proporcionó un aceite oscuro, que se pasó a través de una almohadilla de gel de sílice, eluyendo con EtOAc/hexanos 1:1. Se concentró y secó a alto vacío para proporcionar 2-cloropiridin-4-il(3-nitrofenil)carbamato de terc-butilo (3.65 g, 96.5% de rendimiento).

Preparación de 5-(4-(*terc*-butoxicarbonil(3-nitrofenil)amino)piridina-2-il)-1*H*-pirrol-3-carboxilato de metilo.



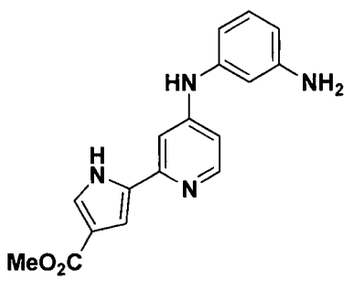
Una mezcla de 2-cloropiridin-4-il(3-nitrofenil)carbamato de terc-butilo (3.65 g, 10.43 mmol), metil-(5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirrol-3-carboxilato (5.48 g, 21.82 mmol), xantfos (0.72 g, 1.25 mmol) y $Pd_2dba_3$ (0.72 g, 0.79 mmol) se agregó a un recipiente de reacción de pared gruesa y se purgó con $N_2$. Se agregó una solución de $K_2CO_3$ 2M (8.76 mL), seguido de dioxano (67 mL). El recipiente de reacción se selló y la mezcla se agitó a 105°C durante 18 h. El recipiente de reacción se enfrió hasta ta y la mezcla se filtró sobre celite, lavándose con EtOAc. El filtrado se concentró para proporcionar un aceite oscuro, que se purificó por cromatografía en columna eluyendo con 30-50% de EtOAc/hexanos para proporcionar 5-(4-(*terc*-butoxicarbonil(3-nitrofenil)amino)piridina-2-il)-1*H*-pirrol-3-carboxilato de metilo (2.98 g, 65% de rendimiento) como un aceite naranja.

Preparación de 5-(4-((3-nitrofenil)amino)piridin-2-il]-1H-pirrol-3-carboxilato de metilo



Se absorbió 5-(4-(*terc*-butoxicarbonil(3-nitrofenil)amino)piridina-2-il)-1*H*-pirrol-3-carboxilato de metilo (0.40 g, 0.91 mmol) en tolueno (38 mL) y se agregó $SiO_2$ (9.0 g). La mezcla se agitó a reflujo durante 20 h. La mezcla se enfrió hasta ta y se filtró sobre celite, lavándose con EtOAc. El filtrado se concentró hasta lograr un color naranja brillante. El sólido se absorbió en hexanos y se filtró. El sólido se lavó luego con $CH_2Cl_2$/hexanos para proporcionar 5-(4-((3-nitrofenil)amino)piridin-2-il)-1H-pirrol-3-carboxilato de metilo (0.15 g, 49% de rendimiento) como un sólido amarillo brillante.

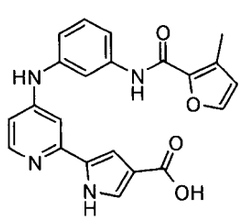
Preparación de 5-(4-((3-aminofenil)amino)piridin-2-il]-1H-pirrol-3-carboxilato de metilo



Se absorbió 5-(4-((3-nitrofenil)amino)piridin-2-il)-1H-pirrol-3-carboxilato de metilo (1.32 g, 3.9 mmol) en EtOAc/EtOH (1:1; 90 mL) y se purgó con $N_2$. Se agregó Pd/C (10%, 0.145 g) y la mezcla se agitó en atmósfera de $H_2$ a ta durante 18 h. La mezcla se filtró sobre celite, lavándose con EtOAc/EtOH. El filtrado se concentró, absorbió nuevamente en EtOAc y se filtró sobre celite nuevamente para retirar cualquier residuo de catalizador. El filtrado se concentró nuevamente y se absorbió de nuevo en EtOAc. La solución se filtró y el filtrado se concentró para proporcionar un sólido tostado. El sólido se lavó con $CH_2Cl_2$/hexanos (1:2) y se secó a alto vacío para proporcionar 5-(4-((3-aminofenil)amino)piridin-2-il)-1H-pirrol-3-carboxilato de metilo (1.15 g, 96% de rendimiento) como un sólido tostado.

Ejemplo 5

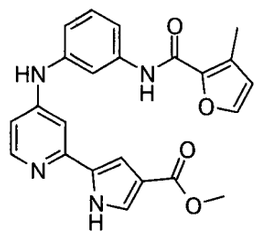
Ácido 5-[4-({3-[(3-metil-2-furoil)amino]fenil}amino)piridin-2-il]-1H-pirrol-3-carboxílico



A u ı de 5-[4-({3-[(3-metil-2-furoil)amino]fenil}amino)piridin-2-il]-1H-pirrol-3-carboxilato de metilo (10mg, 0.024mmol) en una mezcla de solventes THF/MeOH (5ml/5ml) se agregó 2ml de solución de NaOH 1M (2mmol). La mezcla se calentó en un baño a 60°C durante 16 horas, se enfrió hasta temperatura ambiente y se vertió en 100ml de agua. Se agregó HCl 2M hasta pH = 5. Los precipitados resultantes se filtraron, lavaron con agua y secaron al vacío para proporcionar ácido 5-[4-({3-[(3-metil-2-furoil)amino]fenil}amino)piridin-2-il]-1H-pirrol-3-carboxílico como un sólido pardo claro. Rendimiento: 2mg.

Ejemplo 6

5-[4-({3-[(3-metil-2-furoil)amino]fenil}amino)piridin-2-il]-1H-pirrol-3-carboxilato de metilo



ácido 3-metil-2-furoico (22 mg, 0.18mmol), HATU (73mg, 0.19mmol) y *N,N*-diisopropletilamina (45mg, 0.35mmol) en DMF anhidro (10ml) se agitó a temperatura ambiente durante 10 minutos, seguido de la adición de 5-(4-((3-aminofenil)amino)piridin-2-il)-1H-pirrol-3-carboxilato de metilo (50mg, 0.16mmol). La mezcla se agitó a temperatura ambiente durante 3 horas, y se vertió en 100ml de agua. Los precipitados se filtraron, lavaron con agua y secaron al vacío para proporcionar 5-[4-({3-[(3-metil-2-furoil)amino]fenil}amino)piridin-2-il]-1H-pirrol-3-carboxilato de metilo como un sólido blanquecino. Rendimiento: 10mg, 15%.

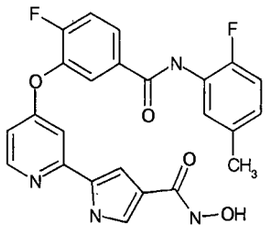
$^1$H NMR (DMSO-$d_6$) δ: 13.60 (br. s., 1H), 12.37 (br. s., 1H), 10.14 (s, 1H), 8.15 (d, J = 6.5 Hz, 1H), 7.86 (t, J = 1.9 Hz, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.58 (br. s., 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.32 - 7.38 (m, 2H), 7.22 (br. s., 1H), 6.97 (d, J = 7.6 Hz, 1H), 6.86 (dd, J = 6.2, 2.1 Hz, 1H), 6.57 (d, J = 1.8 Hz, 1H), 3.71 (s, 3H), 2.32 (s, 3H)

LR MS (ES+): 417 (MH)

LR MS (ES-): 415 (M-H)

Ejemplo 7

5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-N-hidroxi-1H-pirrol-3-carboxamida



Procedimiento similar al del Ejemplo 1.

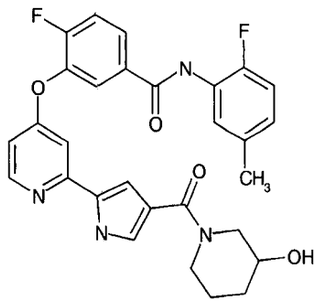
$^1$H NMR (DMSO-$d_6$) δ: 11.85 (br. s., 1H), 10.56 (br. s., 1H), 10.12 (s, 1H), 8.66 (br. s., 1H), 8.41 (d, J = 5.6 Hz, 1H), 7.99 (d, J = 7.3 Hz, 2H), 7.63 (t, J = 9.4 Hz, 1H), 7.30 - 7.40 (m, 2H), 7.27 (br. s., 1H), 7.10 - 7.18 (m, 1H), 7.01 - 7.10 (m, 2H), 6.75 - 6.85 (m, 1H), 2.26 (s, 3H)

LR MS (ES+): 487 (M+$Na^+$)

LR MS (ES-): 463 (M-H)

Ejemplo 8

4-fluoro-N-(2-fluoro-5-metilfenil)-3-[(2-{4-[(3-hidroxipiperidin-1-il)carbonil]-1H-pirrol-2-il}piridin-4-il)oxi]benzamida

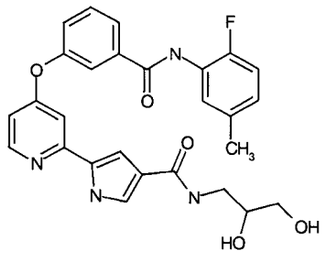


Procedimiento similar al del Ejemplo 1.

LR MS (ES+): 533 (MH), 555 ($M+Na^+$)
LR MS (ES-): 531 (M-H)

Ejemplo 9

N-(2,3-dihidroxipropil)-5-[4-(3-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxamida



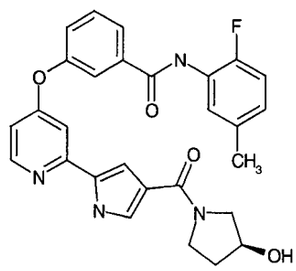
Procedimiento similar al del Ejemplo 1.

$^1H$ NMR (DMSO-$d_6$) δ: 11.83 (br. s., 1H), 10.11 (s, 1H), 8.41 (d, J = 5.6 Hz, 1H), 7.89 (d, J = 7.0 Hz, 1H), 7.83 (t, J = 5.6 Hz, 1H), 7.77 (s, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.42 - 7.46 (m, 1H), 7.39 (d, J = 1.5 Hz, 1H), 7.35 (d, J = 7.3 Hz, 1H), 7.25 (d, J = 2.1 Hz, 1H), 7.09 - 7.16 (m, 2H), 7.02 - 7.06 (m, 1H), 6.76 (dd, J = 5.7, 2.5 Hz, 1H), 4.77 (d, J = 5.0 Hz, 1H), 4.53 (t, J = 6.0 Hz, 1H), 3.50 - 3.56 (m, 1H), 3.25 - 3.30 (m, 3H), 3.08 - 3.14 (m, 1H), 2.27 (s, 3H)

LR MS (ES+): 505 (MH), 527 ($M+Na^+$)
LR MS (ES-): 503 (M-H)

Ejemplo 10

N-(2-fluoro-5-metilfenil)-3-[(2-{4-[(3-hidroxipirrolidin-1-il)carbonil]-1H-pirrol-2-il}piridin-4-il)oxi]benzamida



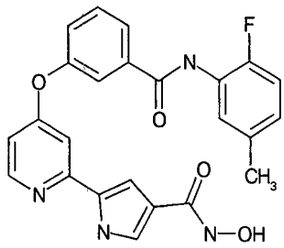
Una mezcla de ácido 5-{4-[3-(2-Fluoro-5-metil-fenilcarbamoil)-fenoxi]-piridin-2-il}-1H-pirrol-3-carboxílico (50mg, 0.12mmol), HATU (55mg, 0.14mmol) y *N,N*-diisopropletilamina (34mg, 0.26mmol) en DMF anhidro (8ml) se agitó a temperatura ambiente durante 10 minutos, seguido de la adición de (S)-3-pirrolidinol (16mg, 0.18mmol). La mezcla se agitó durante otros 10 minutos y se vertió en 100ml de agua. Los precipitados se filtraron, lavaron con agua y secaron al vacío para proporcionar N-(2-fluoro-5-metilfenil)-3-[(2-{4-[(3-hidroxipirrolidin-1-il)carbonil]-1H-pirrol-2-il}piridin-4-il)oxi]benzamida como un sólido blanco. Rendimiento: 40mg, 69%.

$^1H$ NMR (DMSO-$d_6$) δ: 11.91 (br. s., 1H), 10.12 (s, 1H), 8.42 (d, J = 5.6 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.76 (s, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.32 - 7.51 (m, 3H), 7.26 (d, J = 6.7 Hz, 1H), 6.99 - 7.20 (m, 3H), 6.73 (dd, 1H), 4.91 (br. s., 1H), 4.30 (br. s., 1H), 3.76 (br. s., 2H), 3.50 (br. s., 2H), 2.28 (s, 3H), 1.86 (br. s., 2H)

LR MS (ES+): 501 (MH), 523 ($M+Na^+$)
LR MS (ES-): 499 (M-H)

Ejemplo 11

5-[4-(3-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-N-hidroxi-1H-pirrol-3-carboxamida



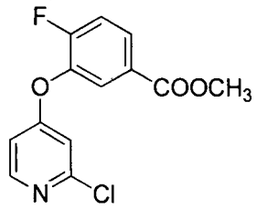
Procedimiento similar al del Ejemplo 10.

$^1$H NMR (DMSO-$d_6$) δ: 11.84 (br. s., 1H), 10.56 (br. s., 1H), 10.10 (s, 1H), 8.65 (br. s., 1H), 8.40 (d, J = 5.6 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.76 (br. s., 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.44 (dd, J = 7.9, 1.5 Hz, 1H), 7.35 (d, J = 6.7 Hz, 1H), 7.31 (br. s., 1H), 7.25 (d, J = 1.8 Hz, 1H), 7.13 (dd, J = 10.3, 8.5 Hz, 1H), 7.01 - 7.07 (m, 2H), 6.75 (dd, J = 5.7, 2.2 Hz, 1H), 2.27 (s, 3H)

LR MS (ES+): 469 ($M+Na^+$)

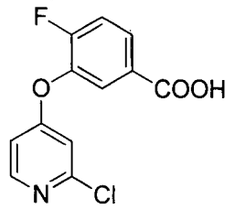
LR MS (ES-): 445 (M-H)

Preparación de éster metílico del ácido 3-(2-cloropiridin-4-iloxi)-4-fluorobenzoico



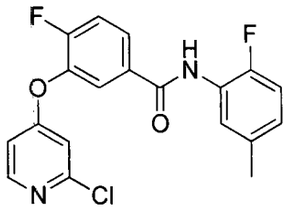
El éster metílico del ácido 4-Fluoro-3-hidroxibenzoico (1.70 g, 10.0 mmol) se disolvió en dimetilformamida (9 mL) en nitrógeno a temperatura ambiente. Se agregó hidruro de sodio (60% de dispersión oleosa; 0.48 g, 12 mmol) en porciones durante 30 min. La reacción se agitó durante 90 minutos y luego se enfrió en un baño de hielo. Se agregó 2-cloro-4-nitropiridina (1.58 g, 10.0 mmol) en porciones pequeñas durante 50 min. La reacción se agitó a temperatura ambiente durante 17.5 h. Se agregó agua (200 ml) y la mezcla se agitó hasta que se formó un grumo pardo. El agua se decantó y el residuo se disolvió en EtOAc (150 mL). La solución se lavó con salmuera, se secó ($MgSO_4$), filtró y evaporó para proporcionar éster metílico del ácido 3-(2-cloropiridin-4-iloxi)-4-fluorobenzoico. Rendimiento: 3.10 g.

Preparación de ácido 3-(2-cloropiridin-4-iloxi)-4-fluorobenzoico



Se disolvió éster metílico del ácido 3-(2-cloropiridin-4-iloxi)-4-fluorobenzoico (2.81 g, 10.0 mmol) en tetrahidrofurano (15 mL) y se mezcló con hidróxido de litio 2M (15 mL, 30 mmol). La suspensión se agitó durante 5h. A la reacción se agregó agua, luego se extrajo con EtOAc. La capa acuosa se trató con HCl 6M (5 mL, 30 mmol) y luego se extrajo con EtOAc (25 mL 3 veces). El extracto se secó ($MgSO_4$), filtró y evaporó para proporcionar ácido 3-(2-cloropiridin-4-iloxi)-4-fluorobenzoico. Rendimiento: 2.22 g, 83%.

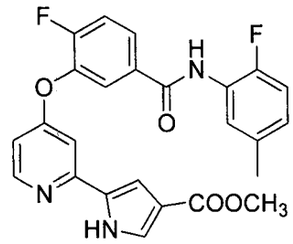
Preparación de 3-(2-cloropiridin-4-iloxi)-4-fluoro-N-(2-fluoro-5-metilfenil)benzamida



Una solución de ácido 3-(2-cloropiridin-4-iloxi)-4-fluorobenzoico (2.22 g, 8.29 mmol), 2-fluoro-5-metilanilina (1.56 g, 12.4 mmol), O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio hexafluorofosfato (HATU, 3.78 g, 9.95 mmol) y N-metilmorfolina (2.00 mL, 18.2 mmol) en dimetilformamida (22 mL) se calentó a 90°C durante 2 h. El solvente se evaporó al vacío a 50°C. Al residuo se agregó agua dando como resultado un aceite espeso. El agua decantó y el aceite se disolvió en EtOAc y luego se extrajo dos veces con agua, ácido clorhídrico 1M y salmuera. La capa orgánica se secó ($MgSO_4$), filtró y evaporó para proporcionar el producto bruto 6 (3.37 g). La trituración con diclorometano (25 mL) proporcionó 3-(2-cloropiridin-4-iloxi)-4-fluoro-N-(2-fluoro-5-metilfenil)benzamida como un sólido blanco. Rendimiento: 1.788 g, 58%.

Ejemplo 12

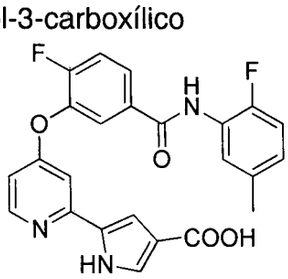
5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de metilo



Una mezcla de 3-(2-cloropiridin-4-iloxi)-4-fluoro-N-(2-fluoro-5-metilfenil)benzamida (1.217 g, 3.25 mmol), 5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirrol-3-carboxilato de metilo (1.63 g, 6.50 mmol) y carbonato de potasio (0.67 g, 4.87 mmol) en agua (2.5 mL) y dioxano (15 mL) se purgó con nitrógeno durante varios minutos. A la mezcla se agregó tetrakis-trifenilfosfina paladio(0) (0.18 g, (0.16 mmol). La reacción se selló en nitrógeno y se calentó a 100°C durante 15 h. La reacción enfriada se mezcló con diclorometano y se filtró a través de Celite. La solución roja se evaporó. El aceite resultante se disolvió en diclorometano, colocó en una columna de gel de sílice (80 g) y se eluyó con hexano/EtOAc (1:1) para proporcionar 5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi) piridin-2-il]-1H-pirrol-3-carboxilato de metilo como un sólido blanco. Rendimiento: 1.162 g, 77%.

Ejemplo 13

Ácido 5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxílico



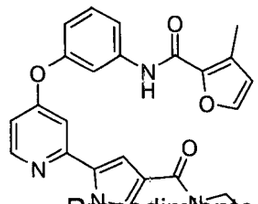
Procedimiento similar al del Ejemplo 12.

$^1H$ NMR (DMSO-$d_6$) δ: 12.03 (br. s., 1H), 11.85 (br. s., 1H), 10.11 (s, 1H), 8.42 (d, J = 5.6 Hz, 1H), 7.98 (d, J = 6.2 Hz, 2H), 7.62 (t, J = 9.4 Hz, 1H), 7.43 (br. s., 1H), 7.30 - 7.39 (m, 2H), 7.08 - 7.19 (m, 2H), 7.04 (br. s., 1H), 6.79 (d, J = 3.2 Hz, 1H), 2.26 (s, 3H)

LR MS (ES-): 448 (M-H)

Ejemplo 14

N-etil-5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxamida

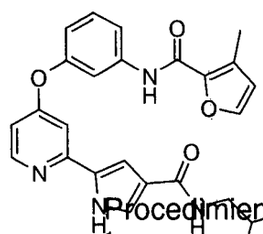


Procedimiento similar al del Ejemplo 31.

LR MS (ES+): 453 ($M+Na^+$)

Ejemplo 15

N-(2,3-dihidroxipropil)-5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxamida



Procedimiento similar al del Ejemplo 31.

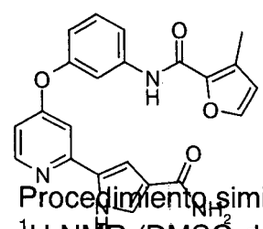
$^1$H NMR (DMSO-$d_6$) δ: 11.83 (br. s., 1H), 10.21 (s, 1H), 8.40 (d, J = 5.9 Hz, 1H), 7.85 (t, J = 6.0 Hz, 1H), 7.78 (s, 1H), 7.63 - 7.74 (m, 2H), 7.35 - 7.48 (m, 2H), 7.23 (d, J = 2.1 Hz, 1H), 7.10 (s, 1H), 6.85 - 6.96 (m, 1H), 6.75 (dd, J = 5.7, 2.2 Hz, 1H), 6.57 (s, 1H), 4.78 (d, J = 4.7 Hz, 1H), 4.53 (t, J = 5.9 Hz, 1H), 3.48 - 3.61 (m, 1H), 3.24 – 3.33 (m, 3H), 3.04 - 3.19 (m, 1H), 2.30 (s, 3H)

LR MS (ES+): 499 ($M+Na^+$)

LR MS (ES-): 475 (M-H)

Ejemplo 16

5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxamida



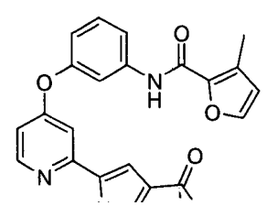
Procedimiento similar al del Ejemplo 31.

$^1$H NMR (DMSO-$d_6$) δ: 11.83 (br. s., 1H), 10.21 (s, 1H), 8.40 (d, J = 5.9 Hz, 1H), 7.77 (s, 1H), 7.65 - 7.74 (m, 2H), 7.31 - 7.48 (m, 3H), 7.23 (d, J = 1.2 Hz, 1H), 7.07 (br. s., 1H), 6.86 - 6.95 (m, 1H), 6.75 (d, J = 3.5 Hz, 2H), 6.57 (s, 1H), 2.30 (s, 3H)

LR MS (ES-): 401 (M-H)

Ejemplo 17

N-hidroxi-5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxamida



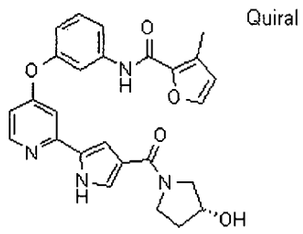
Procedimiento similar al del Ejemplo 31.

$^1$H NMR (DMSO-$d_6$) δ: 11.84 (br. s., 1H), 10.49 - 10.64 (m, 1H), 10.20 (s, 1H), 8.60 - 8.74 (m, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.65 - 7.81 (m, 3H), 7.41 (t, J = 7.9 Hz, 1H), 7.32 (br. s., 1H), 7.23 (s, 1H), 7.02 (br. s., 1H), 6.85 - 6.94 (m, 1H), 6.69 - 6.78 (m, 1H), 6.57 (s, 1H), 2.30 (s, 3H)

LR MS (ES-): 417 (M-H)

Ejemplo 18

N-(3-{[2-(4-{[(3R)-3-hidroxipirrolidin-1-il]carbonil}-1H-pirrol-2-il)piridin-4-il]oxi}fenil)-3-metil-2-furamida



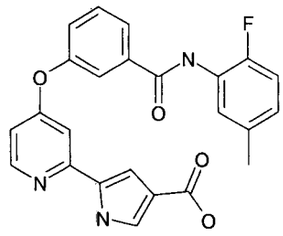

Procedimiento similar al del Ejemplo 31.

$^1$H NMR (DMSO-$d_6$) δ: 11.90 (br. s., 1H), 10.20 (s, 1H), 8.40 (d, J = 5.6 Hz, 1H), 7.77 (d, J = 1.5 Hz, 1H), 7.64 - 7.73 (m, 2H), 7.36 - 7.46 (m, 2H), 7.21 - 7.30 (m, 1H), 7.03 - 7.13 (m, 1H), 6.85 - 6.93 (m, 1H), 6.70 (dd, J = 5.7, 2.2 Hz, 1H), 6.57 (d, J = 1.5 Hz, 1H), 4.90 (br. s., 1H), 4.30 (m, 1H), 3.76 (m, 1H), 3.49 (m, 2H), 2.30 (s, 3H), 1.86 (m, 2H)

LR MS (ES-): 471 (M-H)

Ejemplo 19

Ácido 5-{4-[3-(2-Fluoro-5-metil-fenilcarbamoil)-fenoxi]-piridin-2-il}-1H-pirrol-3-carboxílico




A una solución agitada de éster metílico del ácido 5-{4-[3-(2-Fluoro-5-metil-fenilcarbamoil)-fenoxi]-piridin-2-il}-1H-pirrol-3-carboxílico (140mg, 0.31mmol) en THF (8ml) se agregó una solución de NaOH 5M (1ml, 5mmol). La mezcla se calentó a 70°C durante 3 horas, se enfrió hasta temperatura ambiente y se vertió en 100ml de agua. Se agregó HCl 2M hasta pH = 4. Los precipitados se filtraron, lavaron con agua y secaron para proporcionar ácido 5-{4-[3-(2-Fluoro-5-metil-fenilcarbamoil)-fenoxi]-piridin-2-il}-1H-pirrol-3-carboxílico como un sólido blanco. Rendimiento: 120mg, 92%.

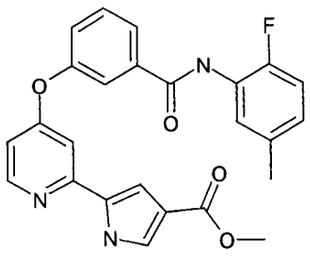
$^1$H NMR ($d_6$-DMSO): 12.03 (br. s., 1H), 11.89 (br. s., 1H), 10.11 (s, 1H), 8.42 (d, J = 5.6 Hz, 1H), 7.89 (d, J = 7.3 Hz, 1H), 7.77 (s, 1H), 7.56 - 7.71 (m, 1H), 7.30 - 7.54 (m, 4H), 6.97 - 7.23 (m, 3H), 6.75 (dd, J = 5.6, 2.1 Hz, 1H), 2.28 (s, 3H)

LR MS (ES+): 454 ($M+Na^+$)

LR MS (ES-): 430 (M-H)

Ejemplo 20

Éster metílico del ácido 5-{4-[3-(2-Fluoro-5-metil-fenilcarbamoil)-fenoxi]-piridin-2-il}-1H-pirrol-3-carboxílico



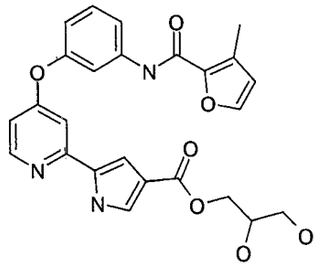
Una mezcla de 3-(2-bromo-piridin-4-iloxi)-N-(2-fluoro-5-metil-fenil)-benzamida (200mg, 0.50 mmol), metil-(5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirrol-3-carboxilato (251mg, 1.0 mmol) y $PdCl_2(dppf)\cdot CH_2Cl_2$ (10mg, 0.012 mmol) se agregó a un recipiente de reacción de pared gruesa y se purgó con $N_2$. Se agregó una solución de $Na_2CO_3$ 2M (0.5 mL), seguido de DMSO (8 mL). El recipiente de reacción se selló y la mezcla se agitó a 95°C durante 16 h. El recipiente de reacción se enfrió hasta temperatura ambiente y la mezcla se vertió en 100ml de agua. Los precipitados se filtraron, lavaron con agua y secaron para proporcionar el producto bruto, que se purificó mediante cromatografía en columna eluyendo con 30-40% de EtOAc/hexanos para proporcionar éster metílico del ácido 5-{4-[3-(2-Fluoro-5-metil-fenilcarbamoil)-fenoxi]-piridin-2-il}-1H-pirrol-3-carboxílico (150mg, 58% de rendimiento).

$^1$H NMR ($d_6$-DMSO): 12.14 (br. s., 1H), 10.11 (s, 1H), 8.43 (d, J = 5.6 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.77 (s, 1H), 7.64 (t, J = 7.9 Hz, 1H), 7.41 - 7.50 (m, 3H), 7.35 (s, 1H), 7.09 - 7.21 (m, 2H), 7.06 (dd, J = 5.1, 1.9 Hz, 1H), 6.76 (dd, J = 5.6, 2.3 Hz, 1H), 3.70 (s, 3H), 2.28 (s, 3H)

LR MS (ES+): 468 ($M+Na^+$)

LR MS (ES-): 444 (M-H)

Ejemplo 21

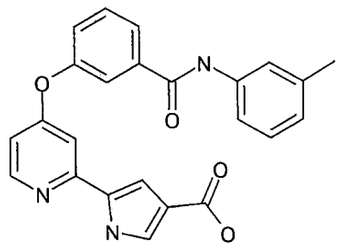


Procedimiento similar al del Ejemplo 25.

5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxilato de 2,3-dihidroxipropilo

Ejemplo 22

Ácido 5-[4-(3-m-tolilcarbamoil-fenoxi)-piridin-2-il]-1H-pirrol-3-carboxílico

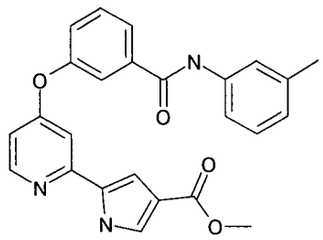


Procedimiento similar al del Ejemplo 19.

$^1$H NMR (DMSO-$d_6$) δ: 12.03 (br. s., 1H), 11.86 (br. s., 1H), 10.19 (s, 1H), 8.42 (d, J = 5.6 Hz, 1H), 7.88 (d, J = 7.9 Hz, 1H), 7.78 (s, 1H), 7.50 - 7.69 (m, 3H), 7.32 - 7.46 (m, 3H), 7.21 (t, J = 7.8 Hz, 1H), 7.06 (s, 1H), 6.91 (d, J = 7.3 Hz, 1H), 6.74 (dd, J = 5.6, 2.3 Hz, 1H), 2.28 (s, 3H)

Ejemplo 23

Éster metílico del ácido 5-[4-(3-m-tolilcarbamoil-fenoxi)-piridin-2-il]-1H-pirrol-3-carboxílico



Procedimiento similar al del Ejemplo 20.

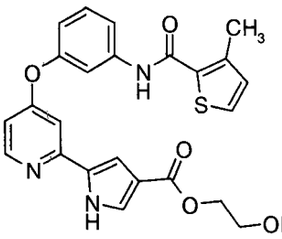
$^1$H NMR (DMSO-$d_6$) δ: 12.14 (br. s., 1H), 10.18 (s, 1H), 8.43 (d, J = 5.6 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.78 (s, 1H), 7.50 - 7.68 (m, 3H), 7.38 - 7.48 (m, 3H), 7.21 (t, J = 7.8 Hz, 1H), 7.12 (s, 1H), 6.91 (d, J = 7.6 Hz, 1H), 6.75 (dd, J = 5.7, 2.2 Hz, 1H), 3.70 (s, 3H), 2.28 (s, 3H)

LR MS (ES+): 450 ($M+Na^+$)

LR MS (ES-): 426 (M-H)

Ejemplo 24

5-[4-(3-{[(3-metil-2-tienil)carbonil]amino}fenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de 2-hidroxietilo



ıl del Ejemplo 25.

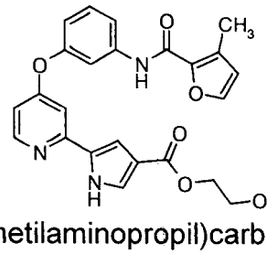
2.13 (br. s., 1H), 10.13 (s, 1H), 8.43 (d, J = 5.9 Hz, 1H), 7.68 (d, J = 5.0 Hz, 1H), 7.56 - 7.64 (m, 2H), 7.40 - 7.52 (m, 3H), 7.14 (s, 1H), 7.03 (d, J = 5.0 Hz, 1H), 6.89 - 6.98 (m, 1H), 6.76 (dd, J = 5.7, 2.2 Hz, 1H), 4.83 (t, J = 5.9 Hz, 1H), 4.15 (t, J = 5.1 Hz, 2H), 3.64 (q, J = 5.6 Hz, 2H), 2.44 (s, 3H)

LR MS (ES+): 486 ($M+Na^+$)

LR MS (ES-): 462 (M-H)

Ejemplo 25

5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxilato de 2-hidroxietilo



cido 5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-c

).17mmol), etilenglicol (1ml), clorhidrato de 1-etil-3-(3-dimetilaminopropil)carbodiimida (EDC• HCl, 40mg, 0.21mmol) y 4-dimetilaminopiridina (DMAP, 10mg, 0.08mmol) en DMF anhidro (10ml) se agitó a 70°C durante 3 horas luego temperatura ambiente durante 16 horas. La mezcla se vertió en 100ml de agua. Se agregó una solución $NaHCO_3$ saturada hasta pH = 9. Los precipitados se filtraron, lavaron con agua y secaron al vacío para proporcionar el producto bruto, que se purificó por cromatografía en gel de sílice eluyendo con un gradiente de 3~4% de MeOH/$CHCl_3$ para proporcionar 5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxilato de 2-hidroxietilo como un sólido blanco. Rendimiento: 40mg, 51%.

$^1$H NMR ($d_6$-DMSO): 12.13 (br. s., 1H), 10.22 (s, 1H), 8.43 (d, J = 5.9 Hz, 1H), 7.79 (s, 1H), 7.70 (s, 2H), 7.36 - 7.54 (m, 3H), 7.13 (br. s., 1H), 6.86 - 6.97 (m, 1H), 6.72

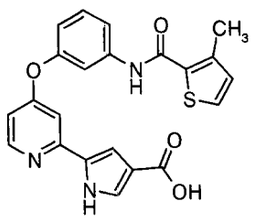
- 6.80 (m, 1H), 6.59 (s, 1H), 5.75 (s, 1H), 4.83 (t, J = 5.3 Hz, 1H), 4.14 (t, J = 4.7 Hz, 2H), 3.58 - 3.69 (m, 2H), 2.32 (s, 3H)

LR MS (ES+): 470 ($M+Na^+$)

LR MS (ES-): 446 (M-H)

Ejemplo 26

Ácido 5-[4-(3-{[(3-metil-2-tienil)carbonil]amino}fenoxi)piridin-2-il]-1H-pirrol-3-carboxílico



similar al del Ejemplo 32.

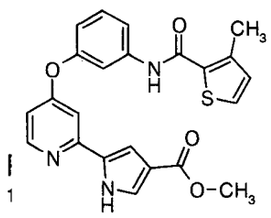
MSO): 12.04 (br. s., 1H), 11.87 (s, 1H), 10.13 (s, 1H), 8.42 (d, J = 6.2 Hz, 1H), 7.68 (d, J = 4.7 Hz, 1H), 7.57 - 7.64 (m, 2H), 7.40 - 7.49 (m, 2H), 7.38 (dd, J = 3.2, 1.5 Hz, 1H), 7.05 - 7.09 (m, 1H), 7.03 (d, J = 5.0 Hz, 1H), 6.90 - 6.97 (m, 1H), 6.75 (dd, J = 5.7, 2.5 Hz, 1H), 2.44 (s, 3H)

LR MS (ES+): 442 ($M+Na^+$)

LR MS (ES-): 418 (M-H)

Ejemplo 27

5-[4-(3-{[(3-metil-2-tienil)carbonil]amino}fenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de metilo



r al del Ejemplo 33.

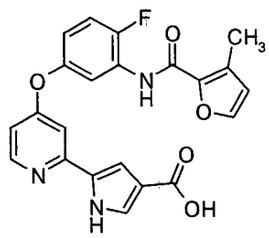
δ: 12.12 (br. s., 1H), 10.10 (s, 1H), 8.35 - 8.45 (m, 1H), 7.65 (d, J = 5.0 Hz, 1H), 7.55 - 7.60 (m, 2H), 7.37 - 7.45 (m, 3H), 7.10 (s, 1H), 7.00 (d, J = 5.0 Hz, 1H), 6.87 - 6.93 (m, 1H), 6.73 (dd, J = 5.6, 2.3 Hz, 1H), 3.69 (s, 3H), 2.41 (s, 3H)

LR MS (ES+): 456 ($M+Na^+$)

LR MS (ES-): 432 (M-H)

Ejemplo 28

Ácido 5-(4-{4-fluoro-3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxílico

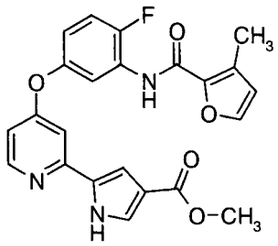


itada de 5-(4-{4-fluoro-3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-
de metilo (20mg, 0.046mmol) en una mezcla de solventes THF/MeOH (5ml/5ml) se agregaron 3ml de solución de NaOH 1M (3mmol). La mezcla se calentó en un baño a 72°C durante 3 horas, se enfrió hasta temperatura ambiente y se vertió en 50ml de agua. Se agregó HCl 2M hasta pH = 4. Los precipitados resultantes se filtraron, lavaron con agua y secaron al vacío para proporcionar ácido 5-(4-{4-fluoro-3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxílico como un sólido gris claro. Rendimiento: 19mg, 100%.

LR MS (ES-): 420 (M-H)

Ejemplo 29

5-(4-{4-fluoro-3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxilato de metilo



Procedimiento similar al del Ejemplo 33.

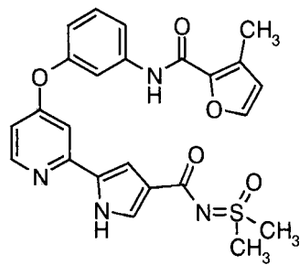
$^1$H NMR ($d_6$-DMSO): 12.15 (br. s., 1H), 9.74 (s, 1H), 8.43 (d, J = 5.6 Hz, 1H), 7.81 (d, J = 1.8 Hz, 1H), 7.60 (dd, J = 6.4, 2.9 Hz, 1H), 7.34 - 7.50 (m, 3H), 7.02 - 7.18 (m, 2H), 6.75 (dd, J = 5.6, 2.3 Hz, 1H), 6.60 (d, J = 1.5 Hz, 1H), 3.72 (s, 3H), 2.31 (s, 3H)

LR MS (ES+): 458 ($M+Na^+$)

LR MS (ES-): 434 (M-H)

Ejemplo 30

N-[dimetil(óxido)-lambda~4~-sulfanilideno]-5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxamida



Procedimiento similar al del Ejemplo 101.

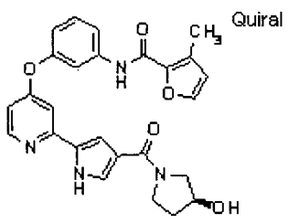
$^1$H NMR ($d_6$-DMSO): 11.83 (br. s., 1H), 10.20 (s, 1H), 8.39 (d, J = 5.6 Hz, 1H), 7.77 (d, J = 1.5 Hz, 1H), 7.65 - 7.72 (m, 2H), 7.37 - 7.45 (m, 1H), 7.32 (d, J = 2.1 Hz, 1H), 7.27 (dd, J = 2.9, 1.5 Hz, 1H), 6.96 - 6.99 (m, 1H), 6.87 - 6.92 (m, 1H), 6.71 (dd, J = 5.6, 2.3 Hz, 1H), 6.57 (d, J = 1.8 Hz, 1H), 3.35 (s, 6H), 2.30 (s, 3H)

LR MS (ES+): 501 ($M+Na^+$)

LR MS (ES-): 477 (M-H)

Ejemplo 31

N-(3-{[2-(4-{[(3S)-3-hidroxipirrolidin-1-il]carbonil}-1H-pirrol-2-il)piridin-4-il]oxi}fenil)-3-metil-2-furamida



Una mezcla de ácido 5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxílico (60mg, 0.15mmol), HATU (68mg, 0.18mmol) y *N,N*-diisopropletilamina (43mg, 0.33mmol) en DMF anhidro (10ml) se agitó a temperatura ambiente durante 10 minutos, seguido de la adición de (S)-3-pirrolidinol (16mg, 0.18mmol). La mezcla se agitó durante otros 10 minutos y se vertió en 100ml de agua. Se agregó gota a gota HCl 2M hasta pH = 4~5. Los precipitados se filtraron, lavaron con agua y secaron al vacío para proporcionar N-(3-{[2-(4-{[(3S)-3-hidroxipirrolidin-1-il]carbonil}-1H-pirrol-2-

il)piridin-4-il]oxi}fenil)-3-metil-2-furamida como un sólido blanco. Rendimiento: 40mg, 56%.

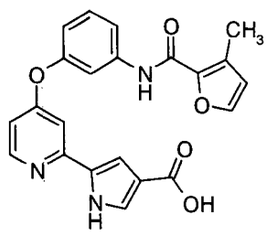
$^1$H NMR ($d_6$-DMSO): 11.95 (br. s., 1H), 10.21 (s, 1H), 8.41 (d, J = 5.6 Hz, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.64 - 7.74 (m, 2H), 7.35 - 7.51 (m, 2H), 7.29 (br. s., 1H), 7.12 (br. s., 1H), 6.90 (dd, J = 8.1, 1.3 Hz, 1H), 6.73 (dd, J = 5.7, 2.2 Hz, 1H), 6.57 (d, J = 1.8 Hz, 1H), 4.20 - 4.36 (m, 1H), 3.66 - 3.88 (m, 2H), 3.42 - 3.60 (m, 3H), 2.30 (s, 3H), 1.66 - 2.03 (m, 2H)

LR MS (ES+): 495 ($M+Na^+$)

LR MS (ES-): 471 (M-H)

Ejemplo 32

Ácido 5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxílico



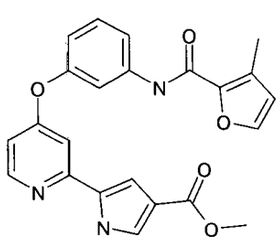
A una solución agitada de 5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxilato de metilo (1.30g, 3.12mmol) en una mezcla de solventes THF/MeOH (10ml/10ml) se agregó 2ml de solución de NaOH 5M (10mmol). La mezcla se calentó en un baño a 68°C durante 8 horas, se enfrió hasta temperatura ambiente y se vertió en 200ml de agua. Se agregó HCl 2M hasta pH = 3. Los precipitados resultantes se filtraron, lavaron con agua y secaron al vacío para proporcionar ácido 5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxílico como un sólido blanco. Rendimiento: 1.20g, 95%.

$^1$H NMR ($d_6$-DMSO): 11.98 (br. s., 1H), 10.22 (s, 1H), 8.42 (d, J = 5.6 Hz, 1H), 7.79 (d, J = 1.2 Hz, 1H), 7.61 - 7.76 (m, 2H), 7.27 - 7.51 (m, 3H), 7.04 (br. s., 1H), 6.85 - 6.98 (m, 1H), 6.73 (dd, J = 5.7, 2.2 Hz, 1H), 6.59 (d, J = 1.5 Hz, 1H), 2.32 (s, 3H)

LR MS (ES-): 402 (M-H)

Ejemplo 33

5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxilato de metilo



Una mezcla de ácido 3-metil-2-furoico (490 mg, 3.88mmol), HATU (1.71 g, 4.5mmol) y *N,N*-diisopropletilamina (1.0g, 7.8mmol) en DMF anhidro (10ml) se agitó a temperatura ambiente durante 10 minutos, seguido de la adición de 5-[4-(3-aminofenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de metilo (1.0g, 3.24mmol). La mezcla se agitó a 50°C durante 2 horas y se vertió en 100ml de agua. Se agregó gota a gota HCl 2M hasta pH = 4~5. Los precipitados se filtraron, lavaron con agua y secaron al vacío para proporcionar 5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxilato de metilo como un sólido blanco. Rendimiento: 1.30g, 96%.

$^1$H NMR ($d_6$-DMSO): 12.15 (br. s., 1H), 10.22 (s, 1H), 8.43 (d, J = 5.9 Hz, 1H), 7.79 (d, J = 1.5 Hz, 1H), 7.68 - 7.74 (m, 2H), 7.38 - 7.47 (m, 3H), 7.09 - 7.14 (m, 1H),

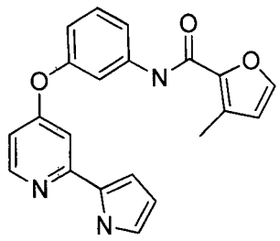
6.88 - 6.94 (m, 1H), 6.75 (dd, J = 5.6, 2.3 Hz, 1H), 6.59 (d, J = 1.5 Hz, 1H), 3.72 (s, 3H), 2.32 (s, 3H)

LR MS (ES+): 440 ($M+Na^+$)

LR MS (ES-): 416 (M-H)

Ejemplo 34

3-metil-N-(3-{[2-(1H-pirrol-2-il)piridin-4-il]oxi}fenil)-2-furamida



Una mezcla de ácido 3-metil-2-furoico (60 mg, 0.48mmol), HBTU (198 mg, 0.52mmol) y *N,N*-diisopropletilamina (129mg, 1.0mmol) en DMF anhidro (10ml) se agitó a temperatura ambiente durante 10 minutos, seguido de la adición de 3-{[2-(1H-pirrol-2-il)piridin-4-il]oxi}anilina (100mg, 0.40mmol). La mezcla se agitó a 70°C durante 3 horas y se vertió en 100ml de agua. Los precipitados se filtraron, lavaron con agua y secaron al vacío para proporcionar el producto bruto, que se purificó por cromatografía en gel de sílice eluyendo con 3-5% de $MeOH/CHCl_3$ para proporcionar 3-metil-N-(3-{[2-(1H-pirrol-2-il)piridin-4-il]oxi}fenil)-2-furamida como un sólido blanco. Rendimiento: 52mg, 36%.

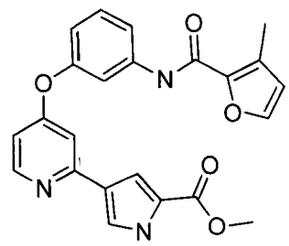
$^1H$ NMR ($d_6$-DMSO): 11.46 (br. s., 1H), 10.19 (s, 1H), 8.36 (d, J = 6.2 Hz, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.64 - 7.72 (m, 2H), 7.35 - 7.44 (m, 1H), 7.28 (d, J = 2.1 Hz, 1H), 6.86 - 6.91 (m, 1H), 6.81 - 6.86 (m, 1H), 6.68 - 6.74 (m, 1H), 6.65 (dd, J = 5.7, 2.5 Hz, 1H), 6.57 (d, J = 1.8 Hz, 1H), 6.06 - 6.13 (m, 1H), 2.30 (s, 3H)

LR MS (ES+): 360 (M+H)

LR MS (ES-): 358 (M-H)

Ejemplo 35

4-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-2-carboxilato de metilo



Procedimiento similar al del Ejemplo 33.

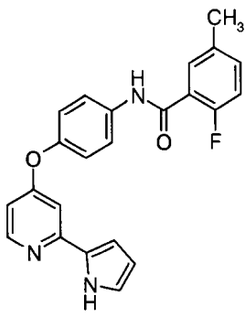
$^1H$ NMR ($d_6$-DMSO): 12.18 (br. s., 1H), 10.19 (s, 1H), 8.37 (d, J = 5.6 Hz, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.59 - 7.72 (m, 3H), 7.33 - 7.44 (m, 2H), 7.25 - 7.32 (m, 1H), 6.83 - 6.93 (m, 1H), 6.66 (dd, J = 5.6, 2.3 Hz, 1H), 6.57 (d, J = 1.2 Hz, 1H), 3.76 (s, 3H), 2.30 (s, 3H)

LR MS (ES+): 440 ($M+Na^+$)

LR MS (ES-): 416 (M-H)

Ejemplo 36

2-fluoro-5-metil-N-(4-{[2-(1H-pirrol-2-il)piridin-4-il]oxi}fenil)benzamida



Procedimiento similar al del Ejemplo 37.

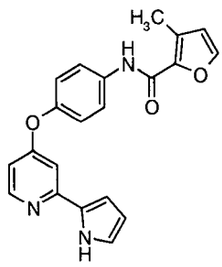
$^1$H NMR ($d_6$-DMSO): 11.44 (br. s., 1H), 10.47 (s, 1H), 8.33 (d, J = 5.6 Hz, 1H), 7.76 - 7.86 (m, 2H), 7.46 (dd, J = 6.4, 2.1 Hz, 1H), 7.36 (ddd, J = 7.9, 5.3, 2.1 Hz, 1H), 7.13 - 7.27 (m, 4H), 6.80 - 6.87 (m, 1H), 6.66 - 6.73 (m, 1H), 6.60 (dd, J = 5.6, 2.3 Hz, 1H), 6.06 - 6.15 (m, 1H), 2.34 (s, 3H)

LR MS (ES+): 388 (M+H)

LR MS (ES-): 386 (M-H)

Ejemplo 37

3-metil-N-(4-{[2-(1H-pirrol-2-il)piridin-4-il]oxi}fenil)-2-furamida

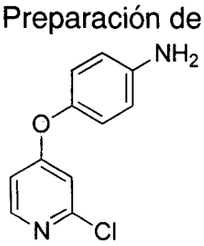


Una mezcla de ácido 3-metil-2-furoico (70mg, 0.55mmol), HATU (243mg, 0.64mmol),) 2-[4-(4-aminofenoxi)piridin-2-il]-1H-pirrol-1-carboxilato de terc-butilo (160mg, 0.46mmol) y *N,N*-diisopropiletilamina (148mg, 1.15mmol) en DMF anhidro (10ml) se agitó a 45°C durante 2 horas. La mezcla se vertió en 100ml de agua. Los precipitados se filtraron, lavaron con agua y secaron al vacío para proporcionar el producto bruto, que se disolvió en 5ml de cloruro de metileno, seguido de la adición de ácido trifluoroacético (3ml). La mezcla se agitó a temperatura ambiente durante 16 horas. Los solventes se evaporaron a presión reducida. El residuo se purificó por cromatografía de fase inversa con un gradiente de 10~50% de acetonitrilo/agua para proporcionar 3-metil-N-(4-{[2-(1H-pirrol-2-il)piridin-4-il]oxi}fenil)-2-furamida como un sólido blanco. Rendimiento: 56mg, 34%.

LR MS (ES+): 360 (M+H)

LR MS (ES-): 358 (M-H)

Preparación de 4-((2-cloropiridin-4-il)oxi)anilina

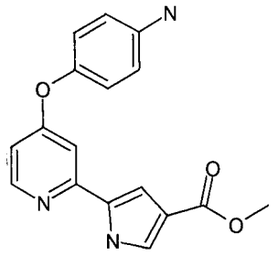


Una solución agitada de 4-aminofenol (740mg, 6.8mmol) en DMSO anhidro (8ml) se enjuagó con nitrógeno y trató con una solución de KOBu$^t$ / THF 1M (10ml, 10mmol). La mezcla se agitó a temperatura ambiente en nitrógeno durante 10 minutos. Se agregó 2,4-dicloropiridina (1.0g, 6.8mmol) y la mezcla se calentó a 60°C durante 30 minutos, se enfrió hasta temperatura ambiente y vertió en 100ml de agua. Los precipitados resultantes se filtraron, lavaron con agua y secaron para proporcionar 4-

((2-cloropiridin-4-il)oxi)anilina como un sólido pardo claro. El material se usó para las siguientes reacciones sin purificación adicional. Rendimiento: 1.5g, 77%.

$^1$H NMR ($d_6$-DMSO): 8.21 (d, 1H), 6.77 - 6.91 (m, 4H), 6.54 - 6.68 (m, 2H), 5.16 (s, 2H)

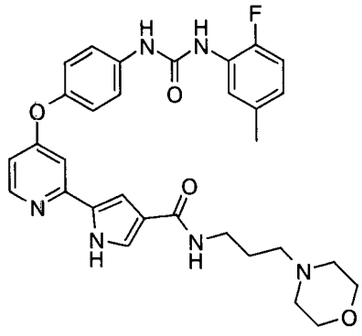
Preparación de 5-[4-(4-aminofenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de metilo



Una mezcla de 4-((2-cloropiridin-4-il)oxi)anilina (2.6 g, 11.78 mmol), metil-(5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirrol-3-carboxilato (6.0 g, 23.90 mmol) y Pd(PPh3)4 (2.72 g, 2.35 mmol) se agregó a un recipiente de reacción de pared gruesa y se purgó con $N_2$. Se agregó una solución de $K_2CO_3$ 2M (17.68 mL), seguido de DME (90 mL). El recipiente de reacción se selló y la mezcla se agitó a 92°C durante 18 h. El recipiente de reacción se enfrió hasta temperatura ambiente y la mezcla se filtró sobre celite, lavándose con EtOAc. El filtrado se concentró para proporcionar un aceite oscuro, que se purificó por cromatografía en columna eluyendo con 40-80% de EtOAc/hexanos para proporcionar 5-[4-(4-aminofenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de metilo (2.4 g, 65% de rendimiento).

Ejemplo 38

5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-(3-morfolin-4-ilpropil)-1H-pirrol-3-carboxamida

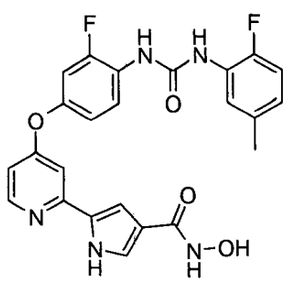


Procedimiento similar al del Ejemplo 132.

LR MS (ES+): 573 (MH)

Ejemplo 39

5-{4-[3-fluoro-4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-hidroxi-1H-pirrol-3-carboxamida



ilar al del Ejemplo 132.

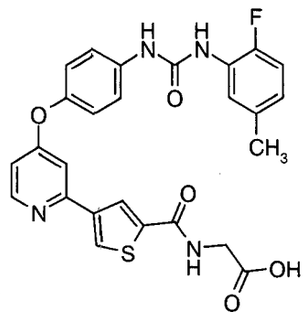
$_6$) δ: 11.82 (br. s., 1H), 10.55 (br. s., 1H), 9.05 (d, J = 1.8 Hz, 1H), [illegible] H), 8.64 (br. s., 1H), 8.37 (d, J = 5.6 Hz, 1H), 8.23 (t, J = 9.2 Hz, 1H), 7.98 (dd, J = 7.8, 1.9 Hz, 1H), 7.31 (br. s., 1H), 7.26 (dd, J = 11.7, 2.6 Hz, 1H),

7.19 (d, J = 2.3 Hz, 1H), 7.09 (dd, J = 11.3, 8.4 Hz, 1H), 6.98 - 7.05 (m, 2H), 6.76 - 6.83 (m, 1H), 6.73 (dd, J = 5.7, 2.5 Hz, 1H), 2.25 (s, 3H)

LR MS (ES-): 478 (M-H)

Ejemplo 40

Ácido {[(4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-2-tien [sic]



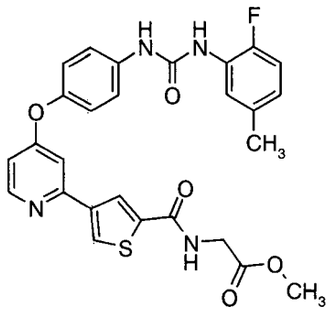
olución agitada de {[(4-{4-[4-({[(2-fluoro-5-metil ino)fenoxi]piridin-2-il}-2-tienil)carbonil]amino}acetato de metilo (60mg, 0.11mmol) en una mezcla de solventes THF/MeOH (5ml/5ml) se agregó 1ml de solución de NaOH 1M ((l.0mmol). La mezcla se agitó a temperatura ambiente durante 1 hora y se vertió en 100ml de agua. Se agregó HCl 2M hasta pH = 3. Los precipitados resultantes se filtraron, lavaron con agua y secaron al vacío para proporcionar ácido {[(4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-2-tienil)carbonil]amino}acético como un sólido blanco. Rendimiento: 50mg, 86%.

$^1$H NMR (DMSO-$d_6$) δ: 12.61 (br s, 1H), 9.15 (s, 1H), 8.98 (t, J = 5.9 Hz, 1H), 8.43 - 8.48 (m, 2H), 8.40 (d, J = 1.5 Hz, 1H), 8.36 (d, J = 1.2 Hz, 1H), 7.95 (dd, J = 7.6, 1.8 Hz, 1H), 7.50 - 7.58 (m, 2H), 7.40 (d, J = 2.3 Hz, 1H), 7.12 - 7.19 (m, 2H), 7.08 (dd, J = 11.3, 8.4 Hz, 1H), 6.73 - 6.81 (m, 2H), 3.88 (d, J = 5.9 Hz, 2H), 2.25 (s, 3H)

LR MS (ES-): 519 (M-H)

Ejemplo 41

{[(4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-2-tienil)carbonil]amino}acetato de metilo



Una mezcla de ácido 4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}tiofeno-2-carboxílico (100mg, 0.22mmol), HATU (100mg, 0.26mmol) y *N,N*-diisopropletilamina (85mg, 0.66mmol) en DMF anhidro (10ml) se agitó a temperatura ambiente durante 10 minutos, seguido de la adición de clorhidrato de éster metílico de glicina (41mg, 0.33mmol). La mezcla se agitó durante otros 10 minutos y se vertió en 100ml de agua. Se agregó gota a gota HCl 2M hasta pH = 4~5. Los precipitados se filtraron, lavaron con agua y secaron al vacío para proporcionar {[(4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-2-tienil)carbonil]amino}acetato de metilo como un sólido blanco. Rendimiento: 90mg, 78%.

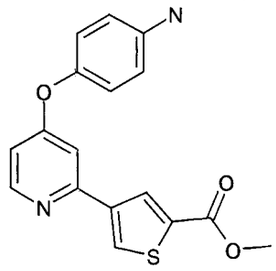
$^1$H NMR (DMSO-$d_6$) δ: 9.17 (s, 1H), 9.10 (t, J = 5.9 Hz, 1H), 8.44 - 8.49 (m, 2H), 8.37 - 8.42 (m, 2H), 7.92 - 7.98 (m, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 2.1 Hz,

1H), 7.16 (d, J = 8.8 Hz, 2H), 7.08 (dd, J = 11.3, 8.4 Hz, 1H), 6.75 - 6.84 (m, 2H), 3.98 (d, J = 5.9 Hz, 2H), 3.63 (s, 3H), 2.25 (s, 3H)

LR MS (ES+): 557 ($M+Na^+$)

LR MS (ES-): 533 (M-H)

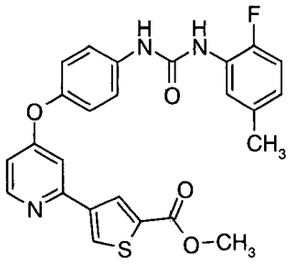
Preparación de 4-(4-(4-aminofenoxi)piridina-2-il)tiofeno-2-carboxilato de metilo



Una mezcla de 4-(4-aminofenoxi)-2-cloropiridina (5.0 g, 22.66mmol), metil-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-tiofeno-2-carboxilato (9.73 g, 36.25 mmol) y $Pd(PPh_3)_4$ (5.24 g, 4.53 mmol) se agregó a un recipiente de reacción de pared gruesa y se purgó con $N_2$. Se agregó una solución de $K_2CO_3$ 2M (17.0 mL), seguido de dioxano (120 mL). El recipiente de reacción se selló y la mezcla se agitó a 92°C durante 18 h. El recipiente de reacción se enfrió hasta temperatura ambiente y la mezcla se filtró sobre celite, lavándose con EtOAc. El filtrado se concentró y el aceite oscuro resultante se purificó por cromatografía en columna, eluyendo con 40-60% de EtOAc/hexanos para proporcionar 4-(4-(4-aminofenoxi)piridina-2-il)tiofeno-2-carboxilato de metilo (6.1 g, 82% de rendimiento).

Ejemplo 42

4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}tiofeno-2-carboxilato de metilo



Una mezcla agitada de 4-[4-(4-aminofenoxi)piridin-2-il]tiofeno-2-carboxilato de metilo (500mg, 1.68 mmol) en THF anhidro (10ml) se agregó 2-fluoro-5-metil-fenilisocianato (255mg, 1.68mmol). La mezcla se agitó a temperatura ambiente durante una hora y se vertió en 200ml de agua. Los precipitados resultantes se filtraron, lavaron con agua y secaron al vacío para proporcionar el producto bruto, que se purificó por cromatografía en gel de sílice eluyendo con 3-5% de $MeOH/CHCl_3$ para proporcionar 4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}tiofeno-2-carboxilato de metilo como un sólido blanquecino. Rendimiento: 560mg, 76%.

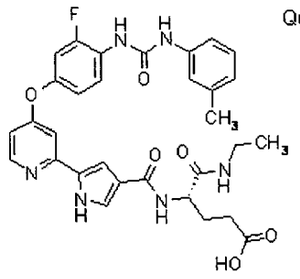
$^1H$ NMR ($DMSO-d_6$) δ: 9.14 (s, 1H), 8.51 (d, J = 1.5 Hz, 1H), 8.41 - 8.47 (m, 2H), 8.33 (d, J = 1.8 Hz, 1H), 7.96 (d, J = 6.2 Hz, 1H), 7.48 - 7.57 (m, 3H), 7.13 (d, J = 9.1 Hz, 2H), 7.08 (dd, J = 11.4, 8.5 Hz, 1H), 6.76 - 6.81 (m, 1H), 6.74 (dd, J = 5.6, 2.3 Hz, 1H), 3.83 (s, 3H), 2.25 (s, 3H)

LR MS (ES+): 500 ($M+Na^+$)

LR MS (ES-): 476 (M-H)

Ejemplo 43

Ácido (4S)-5-(etilamino)-4-{[(5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}-5-oxopentanoico



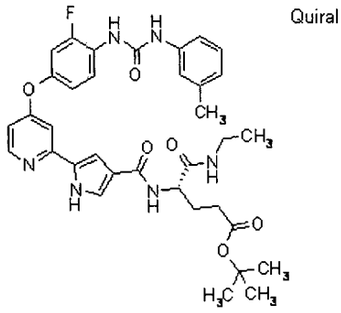

A una solución agitada de (4S)-5-(etilamino)-4-{[(5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}-5-oxopentanoato de terc-butilo (30mg, 0.046mmol) en 5ml de cloruro de metileno se agregaron 2ml de TFA. La mezcla se agitó a temperatura ambiente durante 1 hora y se evaporó hasta sequedad. El residuo se disolvió con MeOH (3ml), que se agregó gota a gota en 100ml de agua con agitación vigorosa. Los precipitados se filtraron, lavaron con agua y secaron para proporcionar ácido (4S)-5-(etilamino)-4-{[(5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}-5-oxopentanoico como un sólido blanco. Rendimiento: 20mg, 74%.

$^1$H NMR (DMSO-$d_6$) δ: 12.04 (br. s., 1H), 11.86 (br. s., 1H), 8.97 (s, 1H), 8.57 (d, J = 2.1 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 8.20 (t, J = 9.1 Hz, 1H), 7.82 (t, J = 5.6 Hz, 1H), 7.79 (d, J = 8.2 Hz, 1H), 7.46 (br. s., 1H), 7.12 - 7.29 (m, 5H), 6.99 - 7.04 (m, 1H), 6.79 (d, J = 7.3 Hz, 1H), 6.74 (d, J = 4.7 Hz, 1H), 4.31 (td, J = 8.6, 5.4 Hz, 1H), 2.97 - 3.11 (m, 2H), 2.26 (s, 3H), 2.17 - 2.25 (m, 2H), 1.87 - 1.98 (m, 1H), 1.74 - 1.84 (m, 1H), 0.97 (t, J = 7.2 Hz, 3H)

LR MS (ES-): 601 (M-H)

Ejemplo 44

(4S)-5-(etilamino)-4-{[(5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}-5-oxopentanoato de terc-butilo




Una mezcla de ácido (2S)-5-terc-butoxi-2-{[(5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}-5-oxopentanoico (80mg, 0.13mmol), HATU (57mg, 0.15mmol) y *N,N*-diisopropletilamina (49mg, 0.38mmol) en DMF anhidro (8ml) se agitó a temperatura ambiente durante 10 minutos, seguido de la adición de etilamina 2M en solución de THF (0.1mg, 0.2mmol). La mezcla se agitó durante otros 10 minutos y se vertió en 100ml de agua. Se agregó gota a gota HCl 2M hasta pH = 5. Los precipitados se filtraron, lavaron con agua y secaron al vacío para proporcionar el producto bruto, que se purificó por cromatografía en gel de sílice eluyendo con 4~5% de MeOH/$CHCl_3$ para proporcionar (4S)-5-(etilamino)-4-{[(5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}-5-oxopentanoato de terc-butilo como un sólido blanco. Rendimiento: 40mg, 48%.

$^1$H NMR (DMSO-$d_6$) δ: 11.83 (br. s., 1H), 8.95 (s, 1H), 8.56 (br. s., 1H), 8.38 (d, J = 5.6 Hz, 1H), 8.20 (t, J = 9.1 Hz, 1H), 7.81 (t, J = 5.3 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.45 (d, J = 1.5 Hz, 1H), 7.23 - 7.30 (m, 2H), 7.18 - 7.23 (m, 2H), 7.12 - 7.18 (m, 2H), 6.98 - 7.04 (m, 1H), 6.79 (d, J = 7.6 Hz, 1H), 6.73 (dd, J = 5.6, 2.3 Hz, 1H), 4.27 - 4.35

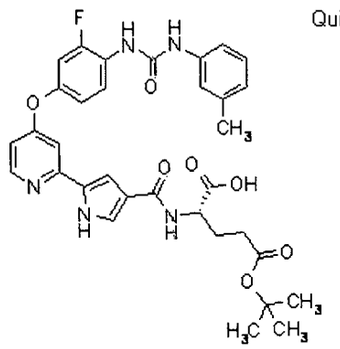
(m, 1H), 3.01 - 3.08 (m, 2H), 2.26 (s, 3H), 2.17 - 2.23 (m, 2H), 1.87 - 1.95 (m, 1H), 1.78 (m, 1H), 1.34 (s, 9H), 0.97 (t, J = 7.2 Hz, 3H)

LR MS (ES+): 681 ($M+Na^+$)

LR MS (ES-): 657 (M-H)

Ejemplo 45

Ácido (2S)-5-terc-butoxi-2-{[(5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}-5-oxopentanoico




A una solución agitada de 2-{[(5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}pentanodioato de (S)-5-terc-butil 1-metilo (120mg, 0.19mmol) en una mezcla de solventes THF/MeOH (5ml/5ml)' se agregó 1ml de solución de NaOH 1M (lmmol). La mezcla se agitó a temperatura ambiente durante 30 minutos y se vertió en 100ml de agua. Se agregó gota a gota HCl 2M hasta pH = 4. Los precipitados resultantes se filtraron, lavaron con agua y secaron al vacío para proporcionar ácido (2S)-5-terc-butoxi-2-{[(5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}-5-oxopentanoico como un sólido blanco. Rendimiento: 100mg, 85%.

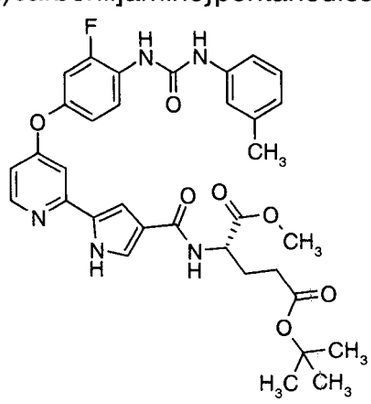
$^1$H NMR (DMSO-$d_6$) δ: 12.49 (br. s., 1H), 11.84 (br. s., 1H), 8.98 (s, 1H), 8.58 (d, J = 2.3 Hz, 1H), 8.38 (d, J = 5.6 Hz, 1H), 8.20 (t, J = 9.1 Hz, 1H), 7.89 (br. s., 1H), 7.42 (br. s., 1H), 7.28 (s, 1H), 7.25 (dd, J = 11.7, 2.6 Hz, 1H), 7.20 - 7.23 (m, 2H), 7.11 - 7.18 (m, 2H), 7.01 (dd, J = 9.0, 1.6 Hz, 1H), 6.79 (d, J = 7.3 Hz, 1H), 6.73 (dd, J = 5.6, 2.3 Hz, 1H), 4.23 - 4.34 (m, 1H), 2.23 - 2.28 (m, 2H), 2.26 (s, 3H), 1.95 - 2.03 (m, 1H), 1.80 - 1.88 (m, 1H), 1.35 (s, 9H)

LR MS (ES+): 654 ($M+Na^+$)

LR MS (ES-): 630 (M-H)

Ejemplo 46

2-{[(5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}pentanodioato de (S)-5-terc-butil 1-metilo



Una mezcla de ácido 5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxílico (500mg,

1.1mmol), HATU (500mg, 1.32mmol) y *N,N*-diisopropletilamina (426mg, 3.3mmol) en DMF anhidro (8ml) se agitó a temperatura ambiente durante 10 minutos, seguido de la adición de clorhidrato de éster 1-metílico 5-terc-butílico ácido L-glutámico (334mg, 1.32mmol). La mezcla se agitó durante otros 10 minutos y se vertió en 200ml de agua. Se agregó gota a gota HCl 2M hasta pH = 5. Los precipitados se filtraron, lavaron con agua y secaron al vacío para proporcionar el producto bruto, que se purificó por cromatografía en gel de sílice eluyendo con 3~5% de MeOH/$CHCl_3$ para proporcionar 2-{[(5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}pentanodioato de (S)-5-terc-butil 1-metilo como un sólido blanquecino. Rendimiento: 380mg, 52%.

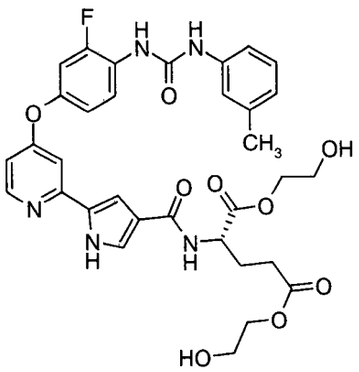
$^1$H NMR (DMSO-$d_6$) δ: 11.87 (br. s., 1H), 8.96 (s, 1H), 8.56 (br. s., 1H), 8.38 (d, J = 5.6 Hz, 1H), 8.20 (t, J = 8.9 Hz, 1H), 8.08 (d, J = 7.0 Hz, 1H), 7.44 (br. s., 1H), 7.23 - 7.29 (m, 2H), 7.18 - 7.23 (m, 2H), 7.11 - 7.17 (m, 2H), 7.01 (d, J = 8.8 Hz, 1H), 6.79 (d, J = 7.0 Hz, 1H), 6.70 - 6.76 (m, 1H), 4.32 - 4.41 (m, 1H), 3.60 (s, 3H), 2.23 - 2.31 (m, 5H), 1.93 - 2.03 (m, 1H), 1.81 - 1.91 (m, 1H), 1.35 (s, 9H)

LR MS (ES+): 646 (MH), 668 ($M+Na^+$)

LR MS (ES-): 644 (M-H)

Ejemplo 47

2-{[(5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}pentanodioato de bis(2-hidroxietilo)

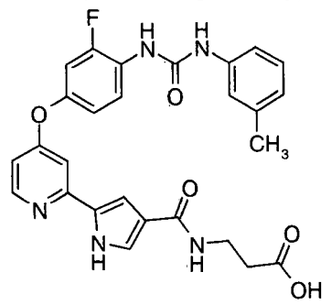


LR MS (ES+): 686 ($M+Na^+$)

LR MS (ES-): 662 (M-H), 561

Ejemplo 48

Ácido 3-{[(5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}propanoico



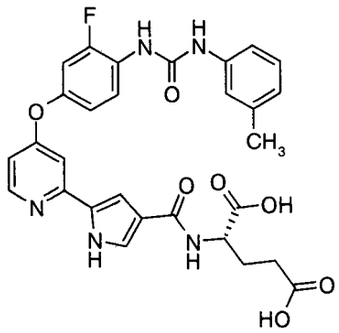
Procedimiento similar al del Ejemplo 132.

$^1$H NMR (DMSO-$d_6$) δ: 11.90 (br. s., 1H), 8.99 (s, 1H), 8.59 (br. s., 1H), 8.40 (d, J = 5.9 Hz, 1H), 8.22 (t, J = 9.0 Hz, 1H), 7.90 - 7.96 (m, 1H), 7.40 (br. s., 1H), 7.25 - 7.30 (m, 2H), 7.21 (d, J = 7.0 Hz, 2H), 7.15 (t, J = 7.8 Hz, 2H), 7.03 (d, J = 9.1 Hz, 1H), 6.79 (d, J = 7.0 Hz, 2H), 3.32 - 3.37 (m, 2H), 2.43 (t, J = 7.0 Hz, 2H), 2.26 (s, 3H)

LR MS (ES-): 516 (M-H)

Ejemplo 49

Ácido 2-{[(5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}pentanodioico

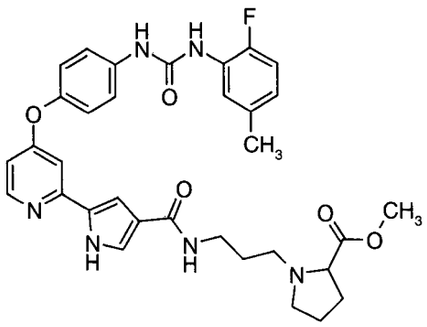


$^1$H NMR (DMSO-$d_6$) δ: 12.43 (br. s., 2H), 11.89 (br. s., 1H), 8.97 (br. s., 1H), 8.57 (br. s., 1H), 8.39 (d, J = 5.3 Hz, 1H), 8.20 (t, J = 8.8 Hz, 1H), 7.97 (d, J = 7.6 Hz, 1H), 7.46 (br. s., 1H), 7.11 - 7.31 (m, 4H), 7.02 (d, J = 9.1 Hz, 1H), 6.79 (d, J = 7.0 Hz, 1H), 6.75 (br. s., 1H), 4.32 (br. s., 1H), 2.30 (t, J = 7.2 Hz, 2H), 2.26 (s, 3H), 2.01 (m, 2H), 1.86 (m, 2H)

LR MS (ES-): 574 (M-H)

Ejemplo 50

1-(3-{[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}propil)pirrolidina-2-carboxilato de metilo



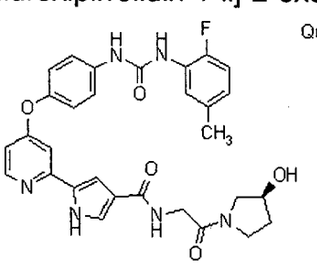
Procedimiento similar al del Ejemplo 132.

LR MS (ES+): 615 (MH), 637 ($M+Na^+$)

LR MS (ES-): 613 (M-H)

Ejemplo 51

5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-{2-[(3S)-3-hidroxipirrolidin-1-il]-2-oxoetil}-1H-pirrol-3-carboxamida



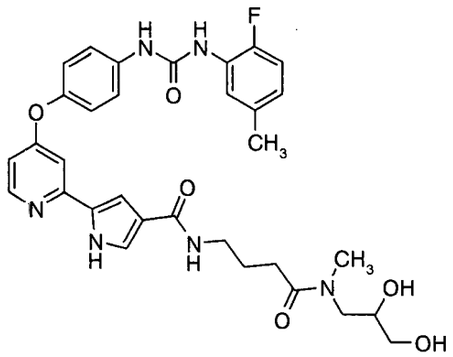

Procedimiento similar al del Ejemplo 132.

LR MS (ES+): 573 (MH), 595 ($M+Na^+$)

LR MS (ES-): 571 (M-H)

Ejemplo 52

N-{4-[(2,3-dihidroxipropil)(metil)amino]-4-oxobutil}-5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida



Procedimiento similar al del Ejemplo 61.

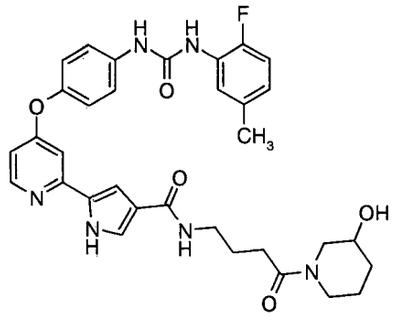
$^1$H NMR (DMSO-$d_6$) δ: 11.70 - 11.82 (m, 1H), 9.24 (s, 1H), 8.50 (d, J = 2.1 Hz, 1H), 8.35 (d, J = 5.9 Hz, 1H), 7.93 - 7.98 (m, 1H), 7.85 (dt, J = 14.5, 5.5 Hz, 1H), 7.54 (d, J = 9.1 Hz, 2H), 7.34 (br. s., 1H), 7.10 - 7.15 (m, 3H), 7.08 (dd, J = 11.2, 8.5 Hz, 1H), 7.01 - 7.05 (m, 1H), 6.73 - 6.82 (m, 1H), 6.67 (dd, J = 5.6, 2.3 Hz, 1H), 4.87 (d, J = 5.3 Hz, 1H), 4.60 - 4.69 (m, 1H), 4.46 (t, J = 5.9 Hz, 1H), 3.55 - 3.65 (m, 2H), 3.20 - 3.27 (m, 2H), 3.10 - 3.19 (m, 2H), 2.96 (s, 1H), 2.79 (s, 2H), 2.27 - 2.35 (m, 1H), 2.24 (s, 3H), 1.62 - 1.72 (m, 2H)

LR MS (ES+): 619 (MH), 641 ($M+Na^+$)

LR MS (ES-): 617 (M-H)

Ejemplo 53

5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-[4-(3-hidroxipiperidin-1-il)-4-oxobutil]-1H-pirrol-3-carboxamida



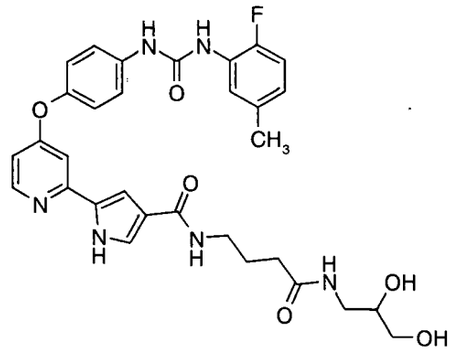
Procedimiento similar al del Ejemplo 61.

LR MS (ES+): 637 ($M+Na^+$)

LR MS (ES-): 613 (M-H)

Ejemplo 54

N-{4-[(2,3-dihidroxipropil)amino]-4-oxobutil}-5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida



Procedimiento similar al del Ejemplo 61.

$^1$H NMR (DMSO-$d_6$) δ: 11.77 (br. s., 1H), 9.14 (s, 1H), 8.46 (d, J = 2.3 Hz, 1H), 8.35 (d, J = 5.9 Hz, 1H), 7.96 (dd, J = 7.9, 2.1 Hz, 1H), 7.84 (t, J = 5.6 Hz, 1H), 7.77 (t, J = 5.9 Hz, 1H), 7.51 - 7.57 (m, 2H), 7.33 (dd, J = 3.1, 1.6 Hz, 1H), 7.11 - 7.16 (m, 3H), 7.08 (dd, J = 11.3, 8.4 Hz, 1H), 7.01 - 7.05 (m, 1H), 6.75 - 6.82 (m, 1H), 6.68 (dd, J =

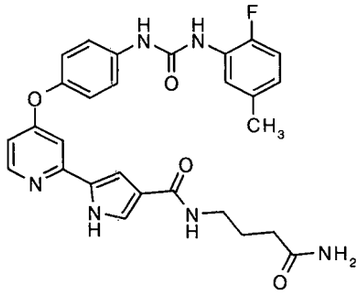
5.7, 2.5 Hz, 1H), 4.68 (d, J = 5.0 Hz, 1H), 4.46 (t, J = 5.9 Hz, 1H), 3.41 - 3.47 (m, 1H), 3.20 - 3.26 (m, 2H), 3.09 - 3.19 (m, 3H), 2.90 - 2.97 (m, 1H), 2.25 (s, 3H), 2.10 (t, J = 7.6 Hz, 2H), 1.66 (quin, J = 7.3 Hz, 2H)

LR MS (ES+): 605 (MH), 627 ($M+Na^+$)

LR MS (ES-): 603 (M-H)

Ejemplo 55

N-(4-amino-4-oxobutil)-5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida



Procedimiento similar al del Ejemplo 61.

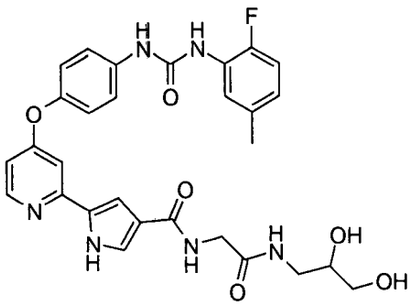
$^1H$ NMR (DMSO-$d_6$) δ: 11.92 (br. s., 1H), 9.20 (br. s., 1H), 8.48 (d, J = 1.8 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.95 (dd, J = 7.8, 1.9 Hz, 1H), 7.89 (br. s., 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.42 (br. s., 1H), 7.18 - 7.28 (m, 2H), 7.15 (d, J = 8.8 Hz, 2H), 7.08 (dd, J = 11.4, 8.5 Hz, 1H), 6.78 (ddd, J = 7.5, 5.0, 2.2 Hz, 2H), 6.68 (br. s., 1H), 3.14 (q, J = 6.7 Hz, 2H), 2.25 (s, 3H), 2.05 (t, J = 7.5 Hz, 2H), 1.66 (quin, J = 7.3 Hz, 2H)

LR MS (ES+): 553 ($M+Na^+$)

LR MS (ES-): 529 (M-H)

Ejemplo 56

N-{2-[(2,3-dihidroxipropil)amino]-2-oxoetil}-5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida



Procedimiento similar al del Ejemplo 132.

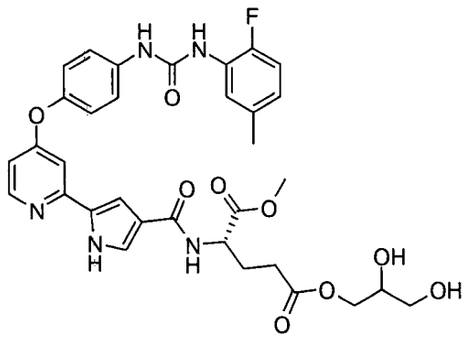
$^1H$ NMR (DMSO-$d_6$) δ: 11.83 (br. s., 1H), 9.15 (s, 1H), 8.46 (br. s., 1H), 8.36 (d, J = 5.9 Hz, 1H), 8.14 (t, J = 6.0 Hz, 1H), 7.95 (d, J = 7.6 Hz, 1H), 7.67 (t, J = 5.6 Hz, 1H), 7.54 (d, J = 8.8 Hz, 2H), 7.38 (br. s., 1H), 7.13 (d, J = 8.8 Hz, 3H), 7.03 - 7.11 (m, 2H), 6.75 - 6.82 (m, 1H), 6.69 (dd, J = 5.6, 2.3 Hz, 1H), 4.70 (d, J = 5.0 Hz, 1H), 4.47 (t, J = 5.7 Hz, 1H), 3.76 (d, J = 5.6 Hz, 2H), 3.45 (dq, J = 11.2, 5.5 Hz, 1H), 3.16 - 3.27 (m, 3H), 2.93 - 3.00 (m, 1H), 2.25 (s, 3H)

LR MS (ES+): 577 (MH), 599 ($M+Na^+$)

LR MS (ES-): 575 (M-H)

Ejemplo 57

2-{[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}pentanodioato de 5-(2,3-dihidroxipropil) 1-metilo



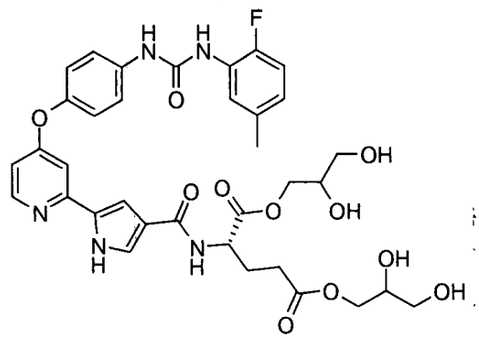
Procedimiento similar al del Ejemplo 58.

$^1$H NMR (DMSO-$d_6$) δ: 11.86 (br. s., 1H), 9.14 (s, 1H), 8.46 (d, J = 2.3 Hz, 1H), 8.36 (d, J = 5.6 Hz, 1H), 8.08 - 8.17 (m, 1H), 7.96 (dd, J = 7.9, 1.8 Hz, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.43 (br. s., 1H), 7.04 - 7.21 (m, 4H), 6.78 (dt, J = 5.7, 2.7 Hz, 1H), 6.68 (dd, J = 5.6, 2.3 Hz, 1H), 4.83 (d, J = 5.3 Hz, 1H), 4.58 (t, J = 5.7 Hz, 1H), 4.36 - 4.45 (m, 1H), 3.95 - 4.06 (m, 2H), 3.88 (dd, J = 11.0, 6.6 Hz, 1H), 3.60 (s, 3H), 3.28 - 3.35 (m, 2H), 2.40 (t, J = 7.6 Hz, 2H), 2.25 (s, 3H), 1.99 - 2.10 (m, 1H), 1.88 - 1.95 (m, 1H), 1.15 (t, J = 7.0 Hz, 1H)

LR MS (ES+): 664 (MH), 686 ($M+Na^+$)

Ejemplo 58

2-{[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}pentanodioato de bis(2,3-dihidroxipropilo)



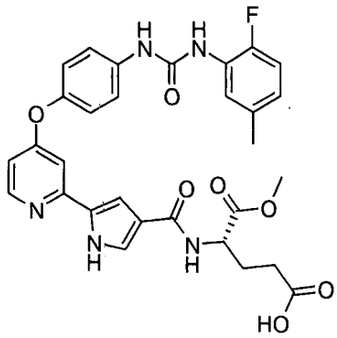
Una mezcla de ácido 2-{[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}pentanodioico (60mg, 0.10mmol), glicerol (0.5ml), clorhidrato de 1-Etil-3-(3-dimetilaminopropil)carbodiimida (EDC• HCl, 37mg, 0.19mmol) y 4-dimetilaminopiridina (DMAP, 5mg, 0.04mmol) en THF anhidro (10ml) se agitó a 60°C durante 3 horas. La mezcla se enfrió hasta temperatura ambiente, se concentró y purificó por cromatografía en gel de sílice eluyendo con un gradiente de 10~15% de MeOH/$CHCl_3$ para proporcionar 2-{[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}pentanodioato de bis(2,3-dihidroxipropil) como un aceite incoloro. Rendimiento: 40mg, 53%.

LR MS (ES+): 746 ($M+Na^+$)

LR MS (ES-): 722 (M-H)

Ejemplo 59

Ácido 4-{[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}-5-metoxi-5-oxopentanoico



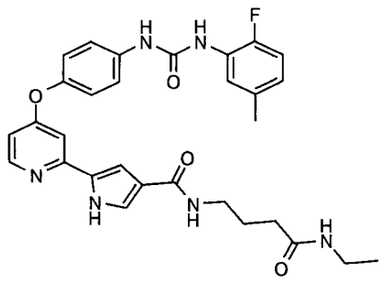
Procedimiento similar al del Ejemplo 132.

$^1$H NMR (DMSO-$d_6$) δ: 11.98 (br. s., 1H), 9.19 (s, 1H), 8.48 (d, J = 2.6 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 8.13 (d, J = 7.3 Hz, 1H), 7.95 (dd, J = 7.8, 1.9 Hz, 1H), 7.53 - 7.57 (m, 2H), 7.47 - 7.52 (m, 1H), 7.24 (br. s., 1H), 7.19 (br. s., 1H), 7.15 (d, J = 8.8 Hz, 2H), 7.08 (dd, J = 11.3, 8.4 Hz, 1H), 6.72 - 6.81 (m, 2H), 4.38 (ddd, J = 9.5, 7.5, 5.3 Hz, 1H), 3.60 (s, 3H), 2.31 (t, J = 7.6 Hz, 2H), 2.25 (s, 3H), 1.95 - 2.05 (m, 1H), 1.82 - 1.93 (m, J = 14.0, 9.6, 7.0, 7.0 Hz, 1H)

LR MS (ES-): 588 (M-H)

Ejemplo 60

N-[4-(etilamino)-4-oxobutil]-5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida



Procedimiento similar al del Ejemplo 61.

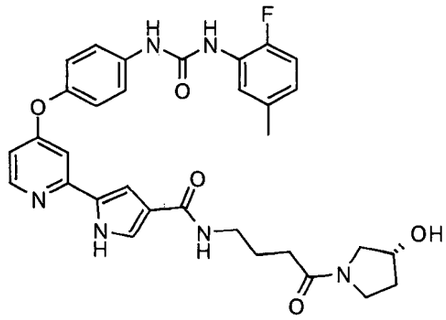
$^1$H NMR (DMSO-$d_6$) δ: 11.96 (br. s., 1H), 9.20 (s, 1H), 8.48 (d, J = 2.6 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.95 (dd, J = 7.8, 1.9 Hz, 1H), 7.89 (br. s., 1H), 7.76 (t, J = 5.3 Hz, 1H), 7.53 - 7.58 (m, 2H), 7.44 (br. s., 1H), 7.23 (br. s., 1H), 7.13 - 7.19 (m, 3H), 7.08 (dd, J = 11.3, 8.4 Hz, 1H), 6.75 - 6.84 (m, 2H), 3.11 - 3.17 (m, 2H), 3.01 (qd, J = 7.2, 5.6 Hz, 2H), 2.25 (s, 3H), 2.05 (t, J = 7.5 Hz, 2H), 1.66 (quin, J = 7.3 Hz, 2H), 0.96 (t, J = 7.2 Hz, 3H)

LR MS (ES+): 559 (MH), 581 ($M+Na^+$)

LR MS (ES-): 557 (M-H)

Ejemplo 61

5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-[4-(3-hidroxipirrolidin-1-il)-4-oxobutil]-1H-pirrol-3-carboxamida



Una mezcla de ácido 4-{[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}butanoico (60mg, 0.11mmol), HATU (50mg, 0.13mmol) y *N,N*-diisopropletilamina (43mg,

0.33mmol) en DMF anhidro (8ml) se agitó a temperatura ambiente durante 10 minutos, seguido de la adición de (S)-3-pirrolidinol (14mg, 0.16mmol). La mezcla se agitó durante otros 10 minutos y se vertió en 100ml de agua. Se agregó gota a gota HCl 2M hasta pH = 4~5. El precipitado se filtró, lavó con agua y se secó al vacío para proporcionar 5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-[4-(3-hidroxipirrolidin-1-il)-4-oxobutil]-1H-pirrol-3-carboxamida como un sólido blanco. Rendimiento: 40mg, 59%.

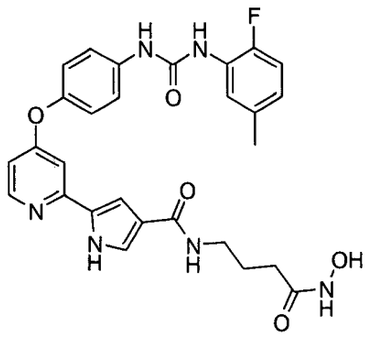
$^1$H NMR (DMSO-$d_6$) δ: 11.97 (br. s., 1H), 9.31 (s, 1H), 8.53 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.95 (dd, J = 7.8, 1.9 Hz, 1H), 7.91 (d, J = 4.4 Hz, 1H), 7.54 - 7.59 (m, 2H), 7.42 - 7.48 (m, 1H), 7.24 (br. s., 1H), 7.16 (d, J = 8.8 Hz, 2H), 7.05 - 7.10 (m, 1H), 6.78 (ddd, J = 7.5, 5.0, 2.2 Hz, 2H), 4.24 - 4.28 (m, 0H), 4.16 - 4.21 (m, 1H), 3.40 - 3.48 (m, 2H), 3.35 (ddd, J = 11.6, 8.4, 3.5 Hz, 1H), 3.25 - 3.30 (m, 1H), 3.14 - 3.25 (m, 4H), 2.25 (s, 3H), 2.23- 2.27 (m, 1H), 2.20 (t, J = 7.9 Hz, 1H), 1.84 - 1.92 (m, 1H), 1.75 - 1.82 (m, 1H), 1.65 - 1.73 (m, 2H)

LR MS (ES+): 601 (MH), 623 ($M+Na^+$)

LR MS (ES-): 599 (M-H)

Ejemplo 62

5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-[4-hidroxiamino)-4-oxobutil]-1H-pirrol-3-carboxamida



Procedimiento similar al del Ejemplo 61.

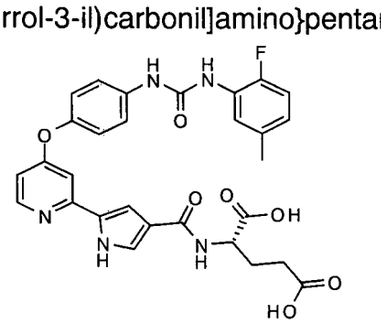
$^1$H NMR (DMSO-$d_6$) δ: 11.92 (br. s., 1H), 10.33 (s, 1H), 9.18 (s, 1H), 8.47 (d, J = 2.6 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.95 (dd, J = 7.9, 1.8 Hz, 1H), 7.87 - 7.92 (m, 1H), 7.51 - 7.58 (m, 2H), 7.38 - 7.46 (m, 1H), 7.21 (br. s., 1H), 7.11 - 7.18 (m, 3H), 7.05 - 7.11 (m, 1H), 6.72 - 6.82 (m, 2H), 3.14 (q, J = 6.7 Hz, 2H), 2.25 (s, 3H), 1.96 (t, J = 7.6 Hz, 2H), 1.66 (quin, J = 7.3 Hz, 2H)

LR MS (ES+): 547 (MH), 569 ($M+Na^+$)

LR MS (ES-): 545 (M-H)

Ejemplo 63

Ácido 2-{[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}pentanodioico



Procedimiento similar al del Ejemplo 132.

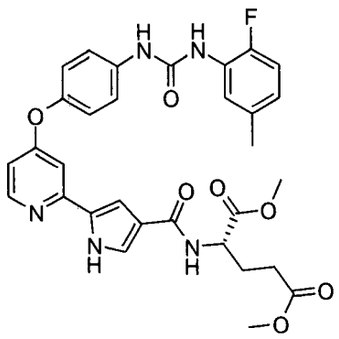
$^1$H NMR (DMSO-$d_6$) δ: 12.42 (br. s., 1H), 12.12 (br. s., 1H), 11.86 (br. s., 1H), 9.15 (s, 1H), 8.46 (d, J = 2.6 Hz, 1H), 8.37 (d, J = 5.6 Hz, 1H), 7.93 - 8.01 (m, 2H), 7.51 - 7.58 (m, 2H), 7.44 (br. s., 1H), 7.18 (s, 1H), 7.11 - 7.16 (m, 3H), 7.08 (dd, J = 11.3, 8.4

Hz, 1H), 6.75 - 6.82 (m, 1H), 6.69 (d, J = 3.8 Hz, 1H), 4.32 (ddd, J = 9.7, 7.9, 5.0 Hz, 1H), 2.30 (t, J = 7.6 Hz, 2H), 2.25 (s, 3H), 1.96 - 2.05 (m, 1H), 1.80 - 1.91 (m, J = 14.0, 9.8, 7.2, 7.2 Hz, 1H)

LR MS (ES-): 574 (M-H)

Ejemplo 64

2-{[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}pentanodioato de dimetilo



Procedimiento similar al del Ejemplo 132.

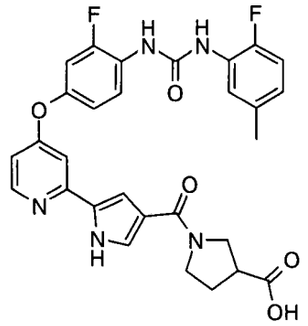
$^1$H NMR (DMSO-$d_6$) δ: 12.27 (br. s., 1H), 9.33 (br. s., 1H), 8.50 - 8.57 (m, 1H), 8.44 (d, J = 6.2 Hz, 1H), 8.23 (d, J = 6.7 Hz, 1H), 7.95 (d, J = 6.5 Hz, 1H), 7.64 (br. s., 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.39 (br. s., 2H), 7.19 (d, J = 8.8 Hz, 2H), 7.08 (dd, J = 11.2, 8.2 Hz, 1H), 6.92 (br. s., 1H), 6.79 (d, J = 5.6 Hz, 1H), 4.35 - 4.43 (m, 1H), 3.60 (s, 3H), 3.55 (s, 3H), 2.40 (t, J = 7.5 Hz, 2H), 2.22 - 2.28 (m, 3H), 2.00 - 2.10 (m, 1H), 1.88 - 1.97 (m, 1H)

LR MS (ES+): 626 ($M+Na^+$)

LR MS (ES-): 602 (M-H)

Ejemplo 65

Ácido 1-[(5-{4-[3-fluoro-4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]pirrolidin-3-carboxílico



Procedimiento similar al del Ejemplo 132.

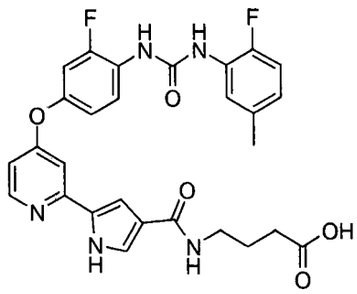
$^1$H NMR (DMSO-$d_6$) δ: 12.47 (br. s., 1H), 11.85 - 12.01 (m, 1H), 9.05 (d, J = 1.8 Hz, 1H), 8.94 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 8.22 (t, J = 9.1 Hz, 1H), 7.98 (dd, J = 7.8, 1.9 Hz, 1H), 7.41 (br. s., 1H), 7.21 - 7.32 (m, 2H), 7.06 - 7.14 (m, 2H), 7.01 (dd, J = 9.0, 1.6 Hz, 1H), 6.79 (ddd, J = 7.6, 5.1, 1.9 Hz, 1H), 6.65 - 6.76 (m, 1H), 2.97 - 3.93 (m, 5H), 2.25 (s, 3H), 1.93 - 2.19 (m, 2H)

LR MS (ES+): 562 (MH), 584 ($M+Na^+$)

LR MS (ES-): 560 (M-H)

Ejemplo 66

Ácido 4-{[(5-{4-[3-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}butanoico



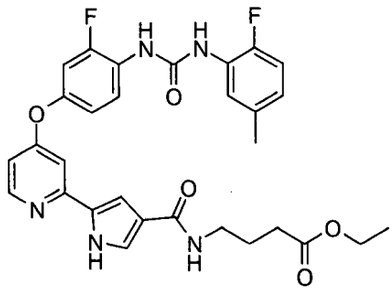
A una solución agitada de 4-{[(5-{4-[3-fluoro-4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}butanoato de etilo (45mg, 0.078mmol) en 10ml de THF se agregaron 3ml de NaOH 1M (3.0mmol). La mezcla se calentó a 60°C durante 3 horas, se enfrió hasta temperatura ambiente y se vertió en 100ml de agua. Se agregó HCl 2M hasta pH = 5. Los precipitados se filtraron, lavaron con agua y secaron para proporcionar ácido 4-{[(5-{4-[3-fluoro-4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}butanoico como un sólido gris. Rendimiento: 40mg, 93%.

$^1$H NMR (DMSO-$d_6$) δ: 11.99 (br. s., 1H), 11.82 (br. s., 1H), 9.06 (d, J = 2.1 Hz, 1H), 8.94 (d, J = 2.6 Hz, 1H), 8.38 (d, J = 5.9 Hz, 1H), 8.23 (t, J = 9.1 Hz, 1H), 7.98 (dd, J = 7.9, 2.1 Hz, 1H), 7.85 (t, J = 5.7 Hz, 1H), 7.37 (br. s., 1H), 7.27 (dd, J = 11.7, 2.6 Hz, 1H), 7.19 (s, 1H), 7.09 (dd, J = 11.3, 8.4 Hz, 2H), 7.02 (dd, J = 8.9, 1.6 Hz, 1H), 6.77 - 6.82 (m, 1H), 6.73 - 6.77 (m, 1H), 3.16 (q, J = 6.7 Hz, 2H), 2.25 (s, 3H), 2.22 (t, J = 7.3 Hz, 2H), 1.67 (quin, J = 7.2 Hz, 2H)

LR MS (ES-): 548 (M-H)

Ejemplo 67

4-{[(5-{4-[3-fluoro-4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}butanoato de etilo



Procedimiento similar al del Ejemplo 132.

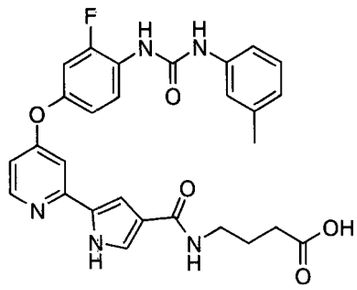
$^1$H NMR (DMSO-$d_6$) δ: 11.99 (br. s., 1H), 9.09 (d, J = 1.5 Hz, 1H), 8.96 (d, J = 2.3 Hz, 1H), 8.42 (d, J = 6.2 Hz, 1H), 8.26 (t, J = 9.1 Hz, 1H), 7.98 (dd, J = 7.8, 2.2 Hz, 1H), 7.86 - 7.94 (m, 1H), 7.46 (br. s., 1H), 7.25 - 7.34 (m, 2H), 7.22 (br. s., 1H), 7.09 (dd, J = 11.3, 8.4 Hz, 1H), 7.02 - 7.07 (m, 1H), 6.87 (br. s., 1H), 6.76 - 6.82 (m, 1H), 4.01 (q, J = 7.1 Hz, 2H), 3.13 - 3.21 (m, 2H), 2.30 (t, J = 7.5 Hz, 2H), 2.25 (s, 3H), 1.70 (quin, J = 7.2 Hz, 2H), 1.14 (t, J = 7.04 Hz, 3H)

LR MS (ES+): 578 (MH), 600 ($M+Na^+$)

LR MS (ES-): 576 (M-H)

Ejemplo 68

Ácido 4-{[(5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}butanoico



Procedimiento similar al del Ejemplo 66.

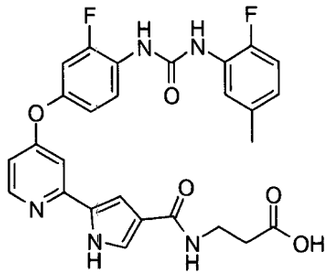
$^1$H NMR (DMSO-$d_6$) δ: 12.00 (br. s., 1H), 11.82 (br. s., 1H), 8.97 (s, 1H), 8.57 (d, J = 2.3 Hz, 1H), 8.38 (d, J = 5.9 Hz, 1H), 8.21 (t, J = 9.1 Hz, 1H), 7.85 (t, J = 5.7 Hz, 1H), 7.37 (br. s., 1H), 7.24 - 7.29 (m, 2H), 7.17 - 7.23 (m, 2H), 7.13 - 7.17 (m, 1H), 7.10 (br. s., 1H), 7.02 (dd, J = 8.8, 1.8 Hz, 1H), 6.79 (d, J = 7.3 Hz, 1H), 6.75 (br. s., 1H), 3.16 (q, J = 6.7 Hz, 2H), 2.26 (s, 3H), 2.22 (t, J = 7.3 Hz, 2H), 1.67 (quin, J = 7.2 Hz, 2H)

LR MS (ES+): 532 (MH), 554 ($M+Na^+$)

LR MS (ES-): 530 (M-H)

Ejemplo 69

Ácido 3-{[(5-{4-[3-fluoro-4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}propanoico



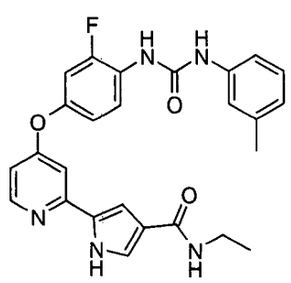
Procedimiento similar al del Ejemplo 66.

$^1$H NMR (DMSO-$d_6$) δ: 11.93 (br. s., 2H), 9.08 (br. s., 1H), 8.96 (d, J = 1.8 Hz, 1H), 8.41 (d, J = 5.9 Hz, 1H), 8.25 (t, J = 8.9 Hz, 1H), 7.98 (d, J = 7.9 Hz, 1H), 7.94 (br. s., 1H), 7.43 (d, J = 2.1 Hz, 1H), 7.29 (d, J = 10.3 Hz, 1H), 7.24 (br. s., 1H), 7.17 (br. s., 1H), 7.09 (dd, J = 11.3, 8.4 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 6.83 (br. s., 1H), 6.76 - 6.81 (m, 1H), 3.33 - 3.38 (m, 2H), 2.44 (t, J = 7.0 Hz, 2H), 2.25 (s, 3H)

LR MS (ES-): 534 (M-H)

Ejemplo 70

N-etil-5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida



Procedimiento similar al del Ejemplo 132.

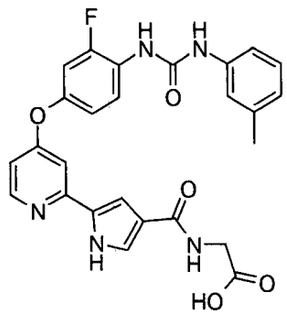
$^1$H NMR (DMSO-$d_6$) δ: 11.98 (br. s., 1H), 9.11 (s, 1H), 8.67 (br. s., 1H), 8.41 (d, J = 5.9 Hz, 1H), 8.23 (t, J = 9.1 Hz, 1H), 7.87 (t, J = 5.0 Hz, 1H), 7.44 (br. s., 1H), 7.25 - 7.32 (m, 3H), 7.18 - 7.25 (m, 2H), 7.12 - 7.17 (m, 1H), 7.04 (dd, J = 9.0, 1.6 Hz, 1H), 6.85 (br. s., 1H), 6.79 (d, J = 7.3 Hz, 1H), 3.15 - 3.22 (m, 2H), 2.26 (s, 3H), 1.05 (t, J = 7.2 Hz, 3H)

LR MS (ES+): 474 (MH), 496 ($M+Na^+$)

LR MS (ES-): 472 (M-H)

Ejemplo 71

Ácido {[(5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}acético



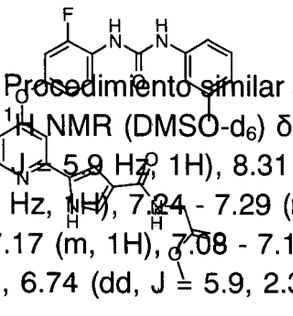
Procedimiento similar al del Ejemplo 66.

$^1$H NMR (DMSO-$d_6$) δ: 11.84 (br. s., 1H), 9.23 (s, 1H), 8.73 (d, J = 1.5 Hz, 1H), 8.38 (d, J = 5.6 Hz, 1H), 8.18 (t, J = 9.1 Hz, 1H), 8.12 (t, J = 5.4 Hz, 1H), 7.38 (dd, J = 2.9, 1.8 Hz, 1H), 7.28 (s, 1H), 7.21 - 7.26 (m, 2H), 7.19 (d, J = 2.3 Hz, 1H), 7.14 (t, J = 7.8 Hz, 1H), 7.08 - 7.11 (m, 1H), 7.01 (dd, J = 9.0, 2.5 Hz, 1H), 6.78 (d, J = 7.3 Hz, 1H), 6.73 (dd, J = 5.9, 2.3 Hz, 1H), 3.78 (d, J = 5.9 Hz, 2H), 2.25 (s, 3H)

LR MS (ES-): 502 (M-H)

Ejemplo 72

{[(5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}acetato de metilo



Procedimiento similar al del Ejemplo 132.

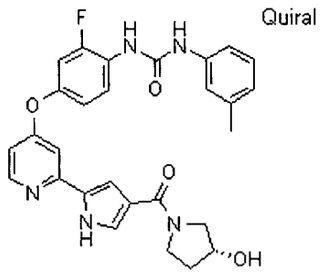
$^1$H NMR (DMSO-$d_6$) δ: 11.87 (br. s., 1H), 8.96 (s, 1H), 8.56 (d, J = 2.3 Hz, 1H), 8.38 (d, J = 5.9 Hz, 1H), 8.31 (t, J = 6.0 Hz, 1H), 8.20 (t, J = 9.1 Hz, 1H), 7.39 (dd, J = 3.2, 1.8 Hz, 1H), 7.24 - 7.29 (m, 2H), 7.21 (d, J = 8.2 Hz, 1H), 7.19 (d, J = 2.3 Hz, 1H), 7.13 - 7.17 (m, 1H), 7.08 - 7.10 (m, 1H), 7.01 (dd, J = 8.5, 2.1 Hz, 1H), 6.79 (d, J = 7.3 Hz, 1H), 6.74 (dd, J = 5.9, 2.3 Hz, 1H), 3.90 (d, J = 5.9 Hz, 2H), 3.60 (s, 3H), 2.26 (s, 3H)

LR MS (ES+): 518 (MH), 540 ($M+Na^+$)

LR MS (ES-): 516 (M-H)

Ejemplo 73

1-(2-fluoro-4-{[2-(4-{[(3R)-3-hidroxipirrolidin-1-il]carbonil}-1H-pirrol-2-il)piridin-4-il]oxi}fenil)-3-(3-metilfenil)urea




Procedimiento similar al del Ejemplo 132.

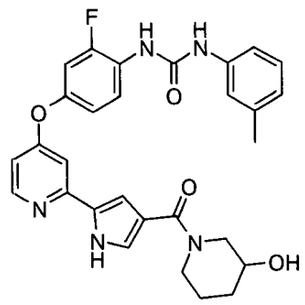
$^1$H NMR (DMSO-$d_6$) δ: 11.87 (br. s., 1H), 8.97 (s, 1H), 8.56 (d, J = 2.1 Hz, 1H), 8.37 (d, J = 5.9 Hz, 1H), 8.18 (t, J = 9.1 Hz, 1H), 7.38 (d, J = 2.3 Hz, 1H), 7.18 - 7.30 (m, 4H), 7.12 - 7.17 (m, 1H), 7.08 (d, J = 18.8 Hz, 1H), 6.99 (dt, J = 7.6, 1.5 Hz, 1H), 6.78 (d, J = 7.6 Hz, 1H), 6.68 (dd, J = 5.6, 2.3 Hz, 1H), 4.90 (d, J = 9.4 Hz, 1H), 4.30 (br. s., 1H), 3.68 - 3.82 (m, 2H), 3.42 - 3.54 (m, 2H), 2.26 (s, 3H), 1.72 - 1.97 (m, 2H)

LR MS (ES+): 516 (MH), 538 ($M+Na^+$)

LR MS (ES-): 514 (M-H)

Ejemplo 74

1-(2-fluoro-4-{[2-(4-[(3-hidroxipiperidin-1-il)carbonil]-1H-pirrol-2-il)piridin-4-il]oxi}fenil}-3-(3-metilfenil)urea



Procedimiento similar al del Ejemplo 132.

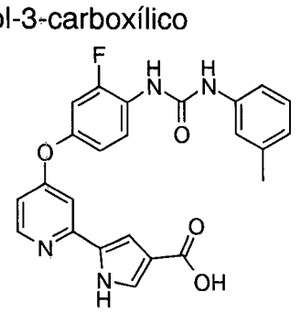
$^1$H NMR (DMSO-$d_6$) δ: 11.83 (br. s., 1H), 8.96 (s, 1H), 8.55 (d, J = 2.3 Hz, 1H), 8.37 (d, J = 5.6 Hz, 1H), 8.19 (t, J = 9.1 Hz, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.27 (s, 1H), 7.19 - 7.25 (m, 2H), 7.15 (t, J = 7.8 Hz, 1H), 7.12 (br. s., 1H), 6.97 - 7.01 (m, 1H), 6.90 (s, 1H), 6.79 (d, J = 7.6 Hz, 1H), 6.68 (dd, J = 5.7, 2.2 Hz, 1H), 4.87 (br. s., 1H), 4.04 (br. s., 1H), 3.85 (br. s., 1H), 3.41 - 3.52 (m, 1H), 3.07 (t, J = 10.1 Hz, 1H), 2.26 (s, 3H), 1.78 - 1.90 (m, 1H), 1.67 (td, J = 8.8, 4.7 Hz, 1H), 1.30 - 1.43 (m, 2H)

LR MS (ES+): 530 (MH), 552 ($M+Na^+$)

LR MS (ES-): 528 (M-H)

Ejemplo 75

Ácido 5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxílico



Procedimiento similar al del Ejemplo 134.

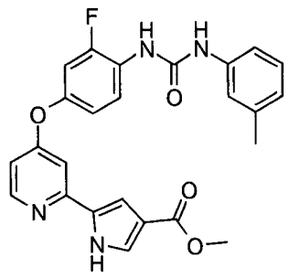
$^1$H NMR (DMSO-$d_6$) δ: 12.04 (br. s., 1H), 11.87 (br. s., 1H), 8.97 (br. s., 1H), 8.56 (br. s., 1H), 8.39 (d, J = 5.9 Hz, 1H), 8.20 (t, J = 9.1 Hz, 1H), 7.36 (br. s., 2H), 7.19 -

7.30 (m, 3H), 7.12 - 7.17 (m, 1H), 7.08 (br. s., 1H), 7.00 (d, J = 8.8 Hz, 1H), 6.79 (d, J = 7.3 Hz, 1H), 6.73 (br. s., 1H), 2.26 (s, 3H)

LR MS (ES+): 469 (MH)

Ejemplo 76

5-{4-[3-fluoro-4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxilato de metilo



Procedimiento similar al del Ejemplo 135.

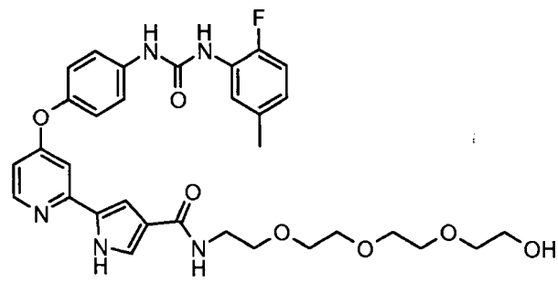
$^1$H NMR (DMSO-$d_6$) δ: 12.11 (br. s., 1H), 8.96 (s, 1H), 8.55 (s, 1H), 8.38 (d, J = 5.9 Hz, 1H), 8.19 (t, J = 9.1 Hz, 1H), 7.42 (dd, J = 3.1, 1.6 Hz, 1H), 7.37 (d, J = 2.1 Hz, 1H), 7.28 (s, 1H), 7.19 - 7.26 (m, 2H), 7.12 - 7.17 (m, 1H), 7.09 - 7.12 (m, 1H), 7.00 (dd, J = 9.1, 2.3 Hz, 1H), 6.79 (d, J = 7.3 Hz, 1H), 6.72 (dd, J = 5.6, 2.3 Hz, 1H), 3.69 (s, 3H), 2.26 (s, 3H)

LR MS (ES+): 461 (MH), 483 ($M+Na^+$)

LR MS (ES-): 459 (M-H)

Ejemplo 77

5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-(2-{2-[2-(2-hidroxietoxi)etoxi]etoxi}etil)-1H-pirrol-3-carboxamida



Procedimiento similar al del Ejemplo 132.

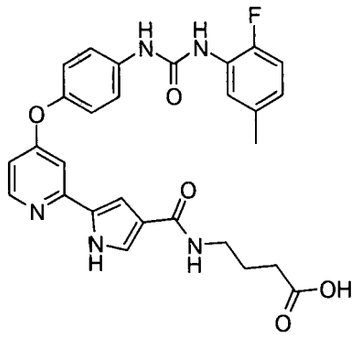
$^1$H NMR (DMSO-$d_6$) δ: 11.92 (br. s., 1H), 9.20 (s, 1H), 8.48 (br. s., 1H), 8.38 (d, J = 5.6 Hz, 1H), 7.96 (d, J = 7.9 Hz, 1H), 7.92 (br. s., 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.43 (br. s., 1H), 7.20 (br. s., 1H), 7.11 - 7.17 (m, 3H), 7.08 (dd, J = 11.2, 8.5 Hz, 1H), 6.73 - 6.81 (m, 2H), 3.41 - 3.48 (m, 12H), 3.34 - 3.39 (m, 2H), 3.31 (q, J = 5.8 Hz, 2H), 2.25 (s, 3H)

LR MS (ES+): 622 (MH), 644 ($M+Na^+$)

LR MS (ES-): 620 (M-H)

Ejemplo 78

Ácido 4-{[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}butanoico



Procedimiento similar al del Ejemplo 66.

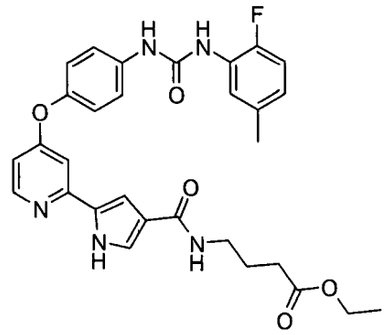
$^1$H NMR (DMSO-$d_6$) δ: 11.83 (br. s., 1H), 9.17 (s, 1H), 8.49 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.95 - 8.02 (m, 1H), 7.88 (t, J = 5.6 Hz, 1H), 7.57 (d, J = 9.1 Hz, 2H), 7.38 (br. s., 1H), 7.16 (d, J = 9.1 Hz, 2H), 7.06 - 7.17 (m, 3H), 6.77 - 6.85 (m, 1H), 6.67 - 6.76 (m, 1H), 3.16 - 3.22 (m, 2H), 2.28 (s, 3H), 2.25 (t, J = 7.3 Hz, 2H), 1.70 (quin, J = 7.2 Hz, 2H)

LR MS (ES+): 532 (MH)

LR MS (ES-): 530 (M-H)

Ejemplo 79

4-{[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}butanoato de etilo

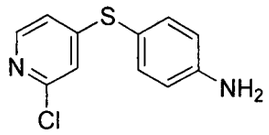


Procedimiento similar al del Ejemplo 132.

LR MS (ES+): 560 (MH), 582 ($M+Na^+$)

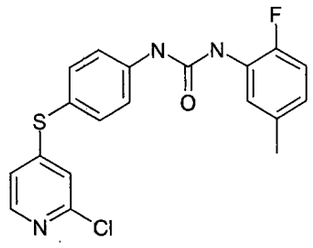
LR MS (ES-): 558 (M-H)

Preparación de 4-(2-cloro-piridin-4-ilsulfanil)-fenilamina



Se purgaron 2,4-Dicloropirdina (4.44 g, 30.0 mmol) y carbonato de potasio (8.28 g, 60.0 mmol) en dimetilformamida (60 mL) con nitrógeno durante 10 min. Se agregó 4-Aminotiofenol (3.76 g, 30.0 mmol) y la mezcla se agitó en nitrógeno a temperatura ambiente durante 18 h. Se agregó agua (300 mL) y la suspensión se agitó durante 30 min. El sólido resultante se filtró, lavó con agua y se secó al vacío a temperatura ambiente. Recristalización a partir de acetato de etilo (35 mL), se filtró caliente y luego se secó y proporcionó 4-(2-Cloro-piridin-4-ilsulfanil)-fenilamina (3.946 g, 56% de rendimiento).

Preparación de 1-[4-(2-Cloro-piridin-4-ilsulfanil)-fenil]-3-(2-fluoro-5-metil-fenil)-urea

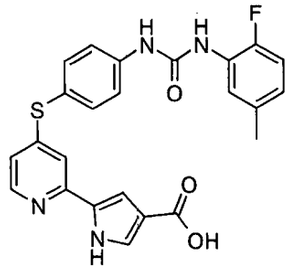


A una solución agitada de 4-(2-cloro-piridin-4-ilsulfanil)-fenilamina (300 mg, 1.27 mmol) en THF anhidro (10ml) se agregó 2-fluoro-5-metil-fenilisocianato (210mg, 1.39mmol). La mezcla se agitó a 60°C durante 5 horas y se vertió en 100ml de agua. Los precipitados se filtraron, lavaron con agua (50ml) y se secaron para proporcionar el producto bruto que se purificó por cromatografía en gel de sílice eluyendo con 2-3% de MeOH/$CHCl_3$ para proporcionar 1-[4-(2-Cloro-piridin-4-ilsulfanil)-fenil]-3-(2-fluoro-5-metil-fenil)-urea como un sólido blanco. Rendimiento: 410mg, 83%.

$^1$H NMR (DMSO-$d_6$) δ: 9.37 (s, 1H), 8.57 (d, J = 2.1 Hz, 1H), 8.17 (d, J = 5.9 Hz, 1H), 7.89 - 8.01 (m, 1H), 7.58 - 7.70 (m, 2H), 7.47 - 7.59 (m, 2H), 7.10 (dd, J = 11.4, 8.2 Hz, 1H), 6.94 - 7.03 (m, 2H), 6.82 (dd, J = 4.8, 2.2 Hz, 1H), 2.26 (s, 3H)

Ejemplo 80

Ácido 5-(4-{[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenil]tio}piridin-2-il)-1H-pirrol-3-carboxílico



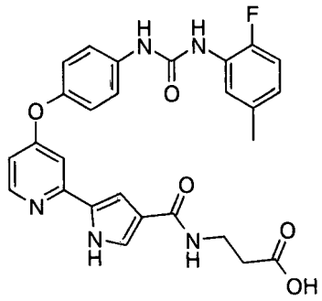
A una solución agitada de 5-(4-{[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenil]tio}piridin-2-il)-1H-pirrol-3-carboxilato de metilo (86mg, 0.18mmol) en una mezcla de solventes de THF/MeOH (5ml/5ml) se agregó 2ml de solución de NaOH 1M (2mmol). La mezcla se calentó en un baño a 66°C durante 7 horas, se enfrió hasta temperatura ambiente y se vertió en 100ml de agua. Se agregó HCl 2M hasta pH = 3. Los precipitados resultantes se filtraron, lavaron con agua y secaron al vacío para proporcionar ácido 5-(4-{[4-({[(2-fluoro-5-metilfenil)amino]fenil}amino)fenil]tio}piridin-2-il]-1H-pirrol-3-carboxílico como un sólido pardo claro. Rendimiento: 73mg, 88%.

$^1$H NMR (DMSO-$d_6$) δ: 12.01 (br. s., 1H), 9.37 (s, 1H), 8.56 (d, J = 1.8 Hz, 1H), 8.27 (d, J = 5.6 Hz, 1H), 7.95 (s, 1H), 7.44 - 7.68 (m, 5H), 7.36 (br. s., 1H), 7.10 (dd, J = 11.1, 8.5 Hz, 1H), 6.94 (br. s., 1H), 6.81 (br. s., 1H), 6.69 (d, J = 5.3 Hz, 1H), 2.26 (s, 3H)

LR MS (ES-): 461 (M-H)

Ejemplo 81

Ácido 3-{[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}propanoico



Procedimiento similar al del Ejemplo 66.

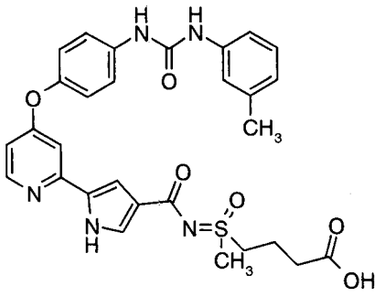
$^1$H NMR (DMSO-$d_6$) δ: 12.12 (br. s., 1H), 11.81 (br. s., 1H), 9.15 (s, 1H), 8.46 (br. s., 1H), 8.36 (d, J = 5.6 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H), 7.92 (t, J = 5.3 Hz, 1H), 7.54 (d, J = 8.8 Hz, 2H), 7.35 (br. s., 1H), 7.13 (dd, J = 6.6, 2.2 Hz, 3H), 7.08 (dd, J = 11.2, 8.5 Hz, 1H), 7.04 (br. s., 1H), 6.75 - 6.82 (m, 1H), 6.70 (d, J = 3.2 Hz, 1H), 3.32 - 3.41 (m, 2H), 2.43 (t, J = 7.0 Hz, 2H), 2.25 (s, 3H)

LR MS (ES+): 518 (MH), 540 ($M+Na^+$)

LR MS (ES-): 516 (M-H)

Ejemplo 82

Ácido 4-{S-metil-N-[(5-{4-[4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]sulfonimidoil}butanoico



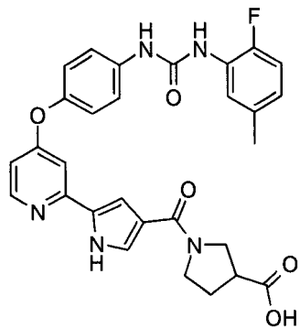
A una solución agitada de 4-{S-metil-N-[(5-{4-[4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]sulfonimidoil}butanoato de metilo (5mg, 0.0087mol) en MeOH (3ml) se agregó NaOH 1M (0.5ml, 0.5mmol). La mezcla se agitó a temperatura ambiente durante 30 minutos y se vertió en 30ml de agua. Se agregó gota a gota HCl 2M hasta pH = 4. Los precipitados se filtraron, lavaron con agua y secaron para proporcionar ácido 4-{S-metil-N-[(5-{4-[4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]sulfonimidoil}butanoico como un sólido blanquecino. Rendimiento: 5mg, 100%.

LR MS (ES+): 576 (MH), 598 ($M+Na^+$)

LR MS (ES-): 574 (M-H)

Ejemplo 83

Ácido 1-[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]pirrolidin-3-carboxílico



Procedimiento similar al del Ejemplo 132.

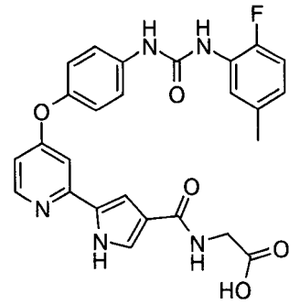
$^1$H NMR (DMSO-$d_6$) δ: 12.04 (br. s., 1H), 9.16 (s, 1H), 8.46 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 5.6 Hz, 1H), 7.93 - 7.99 (m, 1H), 7.54 (d, J = 9.1 Hz, 2H), 7.41 (br. s., 1H), 7.33 (br. s., 1H), 7.14 (d, J = 8.8 Hz, 2H), 7.08 (dd, J = 11.3, 8.4 Hz, 1H), 6.75 - 6.82 (m, 1H), 6.72 (br. s., 1H), 2.98 - 3.93 (m, 5H), 2.25 (s, 3H), 1.93 - 2.19 (m, 2H)

LR MS (ES+): 544 (MH), 566 ($M+Na^+$)

LR MS (ES-): 542 (M-H)

Ejemplo 84

Ácido {[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}acético



Procedimiento similar al del Ejemplo 66.

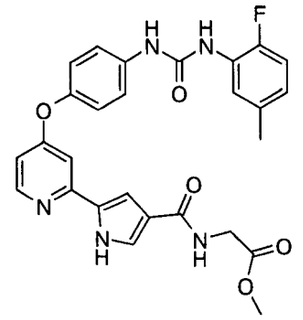
$^1$H NMR (DMSO-$d_6$) δ: 12.42 (br. s., 1H), 11.85 (br. s., 1H), 9.15 (s, 1H), 8.47 (d, J = 2.1 Hz, 1H), 8.37 (d, J = 5.9 Hz, 1H), 8.21 (t, J = 6.0 Hz, 1H), 7.90 - 8.03 (m, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.38 (br. s., 1H), 7.02 - 7.21 (m, 5H), 6.74 - 6.84 (m, 1H), 6.70 (dd, J = 5.6, 2.3 Hz, 1H), 3.82 (d, J = 5.9 Hz, 2H), 2.26 (s, 3H)

LR MS (ES+): 504 (MH), 526 ($M+Na^+$)

LR MS (ES-): 502 (M-H)

Ejemplo 85

{[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}acetato de metilo



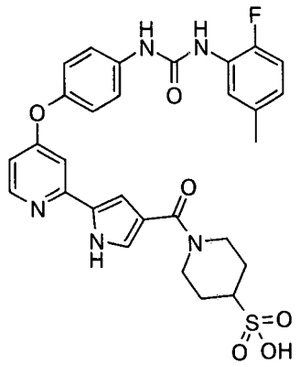
Procedimiento similar al del Ejemplo 132.

$^1$H NMR (DMSO-$d_6$) δ: 12.00 (br. s., 1H), 9.18 (s, 1H), 8.48 (d, J = 2.1 Hz, 1H), 8.29 - 8.44 (m, 2H), 7.97 (d, J = 7.9 Hz, 1H), 7.56 (d, J = 9.1 Hz, 2H), 7.46 (br. s., 1H), 7.02 - 7.27 (m, 5H), 6.79 (d, J = 2.1 Hz, 2H), 3.91 (d, J = 6.2 Hz, 2H), 3.61 (s, 3H), 2.26 (s, 3H)

LR MS (ES+): 518 (MH), 540 ($M+Na^+$)
LR MS (ES-): 516 (M-H)

Ejemplo 86

Ácido 1-[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]piperidin-4-sulfónico



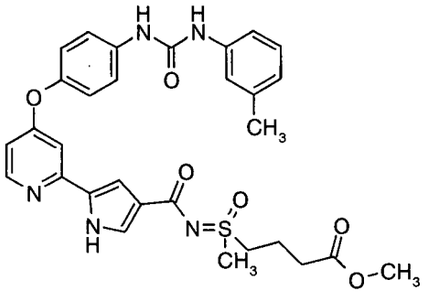
Procedimiento similar al del Ejemplo 132.

$^1H$ NMR (DMSO-$d_6$) δ: 12.41 (br. s., 1H), 9.24 (s, 1H), 8.46 - 8.53 (m, 2H), 7.91 - 7.98 (m, 1H), 7.54 - 7.64 (m, 3H), 7.45 (br. s., 1H), 7.30 (br. s., 1H), 7.22 (d, J = 8.8 Hz, 2H), 7.08 (dd, J = 11.2, 8.2 Hz, 1H), 7.02 (br. s., 1H), 6.75 - 6.82 (m, 1H), 4.29 (br. s., 2H), 3.52 (br. s., 2H), 2.48 - 2.56 (m, 1H), 2.25 (s, 3H), 1.93 (d, J = 12.6 Hz, 2H), 1.45 (br. s., 2H)

LR MS (ES+): 616 ($M+Na^+$)
LR MS (ES-): 592 (M-H)

Ejemplo 87

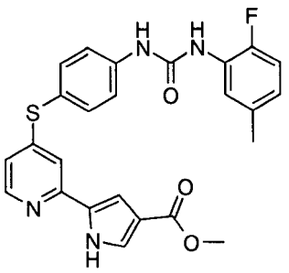
4-{S-metil-N-[(5-{4-[4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]sulfonimidoil}butanoato de metilo



Procedimiento similar al del Ejemplo 101.
LR MS (ES+): 590 (MH), 612 ($M+Na^+$)

Ejemplo 88

5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenil]tio}piridin-2-il)-1H-pirrol-3-carboxilato de metilo



Una mezcla de 1-[4-(2-Cloro-piridin-4-ilsulfanil)-fenil]-3-(2-fluoro-5-metil-fenil)-urea (410mg, 1.06 mmol), (5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirrol-3-carboxilato de metilo (532mg, 2.12 mmol) y $PdCl_2(dppf)\cdot CH_2Cl_2$ (10mg, 0.012 mmol) se



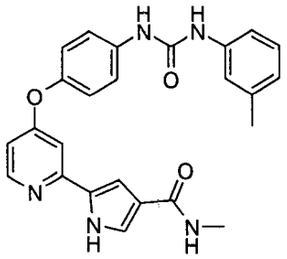
100

agregó a un recipiente de reacción de pared gruesa y se purgó con $N_2$. Se agregó una solución de $Na_2CO_3$ 2M (1.0 mL), seguido de DMSO (10 mL). El recipiente de reacción se selló y la mezcla se agitó a 95°C durante 16 h. El recipiente de reacción se enfrió hasta temperatura ambiente y la mezcla se vertió en 100ml de agua. Los precipitados se filtraron, lavaron con agua y secaron para proporcionar el producto bruto, que se purificó por cromatografía en gel de sílice eluyendo con 2-5% de MeOH/$CHCl_3$ para proporcionar 5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenil]tio}piridin-2-il}tiofeno-2-carboxilato de metilo como un sólido blanquecino. Rendimiento: 100mg, 20% de rendimiento.

LR MS (ES+): 477 (MH), 499 ($M+Na^+$)

Ejemplo 89

N-metil-5-{4-[4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida



Procedimiento similar al del Ejemplo 132.

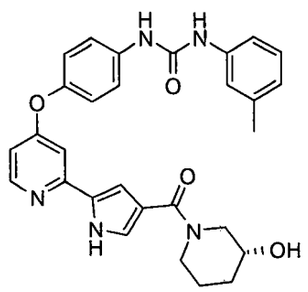
$^1H$ NMR (DMSO-$d_6$) δ: 11.88 (br. s., 1H), 8.89 (s, 1H), 8.69 (s, 1H), 8.37 (d, J = 5.9 Hz, 1H), 7.82 (d, J = 4.4 Hz, 1H), 7.52 - 7.58 (m, 2H), 7.37 (br. s., 1H), 7.27 (s, 1H), 7.22 (d, J = 8.2 Hz, 1H), 7.18 (br. s., 1H), 7.11 - 7.15 (m, 3H), 7.08 (br. s., 1H), 6.71 - 6.80 (m, 2H), 2.67 (d, J = 4.7 Hz, 3H), 2.25 (s, 3H)

LR MS (ES+): 442 (MH), 464 ($M+Na^+$)

LR MS (ES-): 440 (M-H)

Ejemplo 90

1-(4-[2-{4-[3-hidroxipiperidin-1-il)carbonil]-1H-pirrol-2-il)piridin-4-il]oxi}fenil}-3-(3-metilfenil)urea



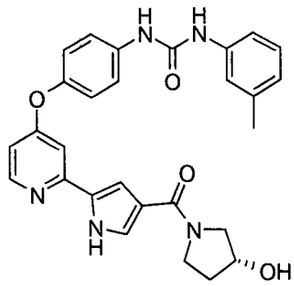
Procedimiento similar al del Ejemplo 132.

LR MS (ES+): 512 (MH), 534 ($M+Na^+$)

LR MS (ES-): 510 (M-H)

Ejemplo 91

1-(4-[2-{4-[3-hidroxipirrolidin-1-il)carbonil]-1H-pirrol-2-il)piridin-4-il]oxi}fenil}-3-(3-metilfenil)urea



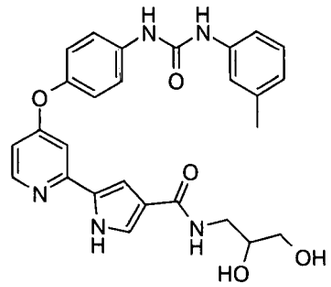
Procedimiento similar al del Ejemplo 132.

$^1$H NMR (DMSO-$d_6$) δ: 11.88 (br. s., 1H), 8.74 (s, 1H), 8.58 (s, 1H), 8.36 (d, J = 5.6 Hz, 1H), 7.54 (d, J = 8.8 Hz, 2H), 6.99 - 7.39 (m, 8H), 6.78 (d, J = 7.0 Hz, 1H), 6.62 (dd, J = 5.6, 2.3 Hz, 1H), 4.91 (br. s., 1H), 4.31 (br. s., 1H), 3.67 - 3.87 (m, 2H), 3.49 (br. s., 2H), 2.26 (s, 3H), 1.88 (br. s., 2H)

LR MS (ES+): 520 ($M+Na^+$)

Ejemplo 92

N-(2,3-dihidroxipropil)-5-{4-[4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida



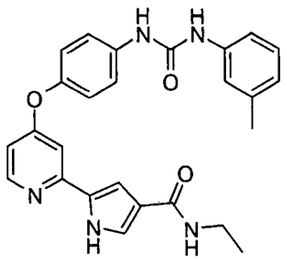
Procedimiento similar al del Ejemplo 132.

$^1$H NMR (DMSO-$d_6$) δ: 11.86 (br. s., 1H), 8.78 (s, 1H), 8.61 (s, 1H), 8.37 (d, J = 5.9 Hz, 1H), 7.87 (t, J = 5.7 Hz, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.41 (br. s., 1H), 7.05 - 7.32 (m, 7H), 6.75 (dd, J = 17.7, 6.6 Hz, 2H), 3.49 - 3.61 (m, 1H), 3.22 - 3.35 (m, 3H), 3.04 - 3.18 (m, 1H), 2.26 (s, 3H)

LR MS (ES+): 524 ($M+Na^+$)

Ejemplo 93

N-etil-5-{4-[4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida



Procedimiento similar al del Ejemplo 132.

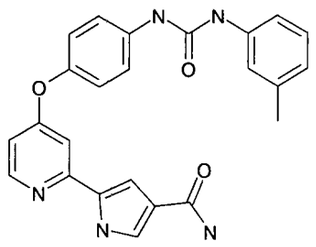
$^1$H NMR (DMSO-$d_6$) δ: 12.09 (br. s., 1H), 8.98 (s, 1H), 8.76 (s, 1H), 8.42 (d, J = 5.9 Hz, 1H), 7.91 (br. s., 1H), 7.45 - 7.65 (m, 3H), 7.05 - 7.38 (m, 7H), 6.82 - 6.94 (m, 1H), 6.78 (d, J = 7.6 Hz, 1H), 3.09 - 3.27 (m, 2H), 2.26 (s, 3H), 1.06 (t, J = 7.2 Hz, 3H)

LR MS (ES+): 478 ($M+Na^+$)

LR MS (ES-): 454 (M-H)

Ejemplo 94

5-{4-[4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida



Procedimiento similar al del Ejemplo 132.

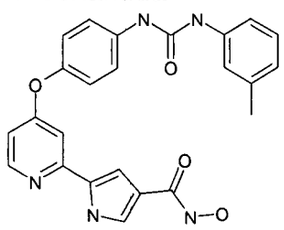
$^1$H NMR ($d_6$-DMSO,300MHz) δ: 11.81 (br. s., 1H), 8.76 (s, 1H), 8.59 (s, 1H), 8.37 (d, J = 5.6 Hz, 1H), 7.55 (d, J = 9.1 Hz, 2H), 7.37 (br. s., 2H), 7.28 (s, 1H), 7.19 - 7.26 (m, 1H), 7.09 - 7.18 (m, 4H), 7.04 (br. s., 1H), 6.78 (d, J = 7.3 Hz, 2H), 6.69 (dd, J = 5.4, 1.9 Hz, 1H), 2.26 (s, 3H)

LR MS (ES+): 428 (MH), 450 ($M+Na^+$)

LR MS (ES-): 426 (M-H)

Ejemplo 95

N-hidroxi-5-{4-[4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida



Procedimiento similar al del Ejemplo 132.

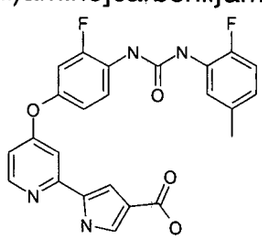
$^1$H NMR ($d_6$-DMSO,300MHz): 11.98 (br. s., 1H), 10.62 (br. s., 1H), 8.87 (s, 1H), 8.68 (s, 1H), 8.41 (d, J = 5.6 Hz, 1H), 7.58 (d, J = 9.1 Hz, 2H), 7.04 - 7.46 (m, 8H), 6.80 (d, J = 7.6 Hz, 2H), 2.28 (s, 3H)

LR MS (ES+): 444 (MH), 466 ($M+Na^+$)

LR MS (ES-): 442 (M-H)

Ejemplo 96

Ácido 5-{4-[3-fluoro-4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxílico



Procedimiento similar al del Ejemplo 134.

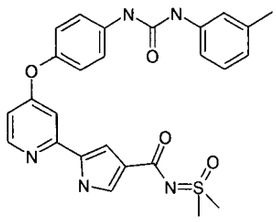
$^1$H NMR ($d_6$-DMSO,300MHz): 12.04 (br. s., 1H), 11.88 (br. s., 1H), 9.08 (s, 1H), 8.97 (s, 1H), 8.41 (d, J = 5.6 Hz, 1H), 8.25 (t, J = 9.2 Hz, 1H), 8.01 (d, J = 7.6 Hz, 1H), 7.38 (s, 2H), 7.27 (dd, J = 11.9, 2.5 Hz, 1H), 6.95 - 7.18 (m, 3H), 6.78 - 6.88 (m, 1H), 6.74 (dd, J = 5.6, 2.1 Hz, 1H), 2.28 (s, 3H)

LR MS (ES+): 465 (MH), 487 ($M+Na^+$)

LR MS (ES-): 463 (M-H)

Ejemplo 97

N-[dimetil(óxido)-lambda~4~-sulfanilideno]-5-(4-{4-[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida



Procedimiento similar al del Ejemplo 101.

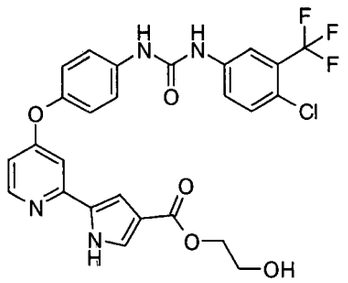
$^1$H NMR ($d_6$-DMSO,300MHz): 11.82 (none, 1H), 11.83 (br. s., 1H), 8.76 (s, 1H), 8.60 (s, 1H), 8.37 (d, J = 5.9 Hz, 1H), 7.56 (d, J = 9.1 Hz, 2H), 7.21 - 7.35 (m, 4H), 7.08 - 7.20 (m, 3H), 6.95 (s, 1H), 6.79 (d, J = 7.0 Hz, 1H), 6.66 (dd, J = 5.6, 2.3 Hz, 1H), 3.37 (s, 6H), 2.28 (s, 3H)

LR MS (ES+): 526 ($M+Na^+$)

LR MS (ES-): 502 (M-H)

Ejemplo 98

5-{4-[4-({[(4-cloro-3-(trifluorometil)fenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxilato de 2-hidroxietilo



Procedimiento similar al del Ejemplo 131.

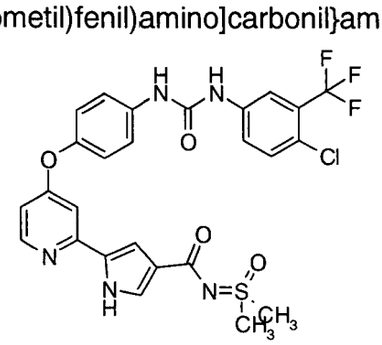
$^1$H NMR ($d_6$-DMSO,300MHz): 12.12 (br. s., 1 H), 9.19 (s, 1 H), 8.97 (s, 1 H), 8.40 (d, *J*=5.9 Hz, 1 H), 8.12 (d, *J*=2.1 Hz, 1 H), 7.53 - 7.70 (m, 4 H), 7.48 (dd, *J*=3.1, 1.6 Hz, 1 H), 7.35 (d, *J*=2.1 Hz, 1 H), 7.16 (d, *J*=9.1 Hz, 2 H), 7.09 (d, *J*=2.3 Hz, 1 H), 6.68 (dd, *J*=5.6, 2.3 Hz, 1 H), 4.83 (t, *J*=5.9 Hz, 1 H), 4.15 (t, *J*=5.0 Hz, 2 H), 3.59 - 3.69 ppm (m, 2 H)

LR MS (ES+): 583 ($M+Na^+$), 585

LR MS (ES-): 559 (M-H), 561

Ejemplo 99

N-[dimetil(óxido)-lambda~4~-sulfanilideno]-5-(4-{4-[(4-cloro-3-(trifluorometil)fenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida



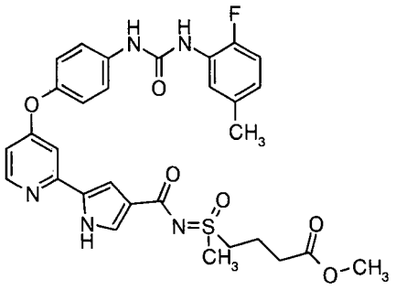
Procedimiento similar al del Ejemplo 101.

$^1$H NMR ($d_6$-DMSO,300MHz) 11.83 (br. s., 1 H), 9.19 (s, 1 H), 8.97 (s, 1 H), 8.37 (d, *J*=5.9 Hz, 1 H), 8.12 (d, *J*=2.3 Hz, 1 H), 7.54 - 7.69 (m, 4 H), 7.23 - 7.31 (m, 2 H), 7.12 - 7.19 (m, 2 H), 6.93 - 6.97 (m, 1 H), 6.67 (dd, *J*=5.9, 2.3 Hz, 1 H), 3.37 ppm (s, 6 H)

LR MS (ES-): 590 (M-H)

Ejemplo 100

4-(N-5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxil)-S-metilsulfonimidoil)butanoato de metilo

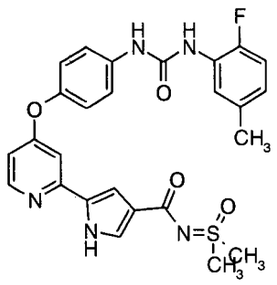


LR MS (ES+): 630 ($M+Na^+$)

LR MS (ES-): 606 (M-H)

Ejemplo 101

N-[dimetil(óxido)-lambda~4~-sulfanilideno]-5-(4-{4-[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida



Una mezcla de ácido 5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxílico (60mg, 0.13mmol), HATU (60mg, 0.16mmol), sulfonimidoildimetano (24mg, 0.26mmol), *N,N*-diisopropiletilamina (37mg, 0.29mmol), 200mg de tamices moleculares de 4Å y 5ml de 1,4-dioxano anhidro se agregaron a un recipiente de reacción de pared gruesa y se purgaron con $N_2$. El recipiente de reacción de selló y la mezcla se agitó a 90°C durante 18 horas. El recipiente de reacción de enfrió hasta temperatura ambiente y la mezcla se vertió en 100ml de agua. Los precipitados se filtraron, lavaron con agua y secaron para proporcionar el producto bruto, que se purificó por cromatografía en gel de sílice eluyendo con 35% de $MeOH/CHCl_3$ para proporcionar N-[dimetil(óxido)-lambda~4~-sulfanilideno]-5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida como un sólido blanco. Rendimiento: 38mg, 54%.

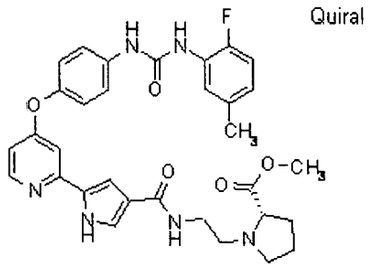
$^1H$ NMR ($d_6$-DMSO): 11.83 (br. s., 1H), 9.16 (s, 1H), 8.48 (br. s., 1H), 8.37 (d, J = 5.9 Hz, 1H), 7.98 (d, J = 6.7 Hz, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.26 (dd, J = 8.6, 1.6 Hz, 2H), 7.05 - 7.19 (m, 3H), 6.96 (s, 1H), 6.75 - 6.85 (m, 1H), 6.66 (dd, J = 5.4, 1.6 Hz, 1H), 3.37 (s, 6H), 2.27 (s, 3H)

LR MS (ES+): 544 ($M+Na^+$)

LR MS (ES-): 520 (M-H)

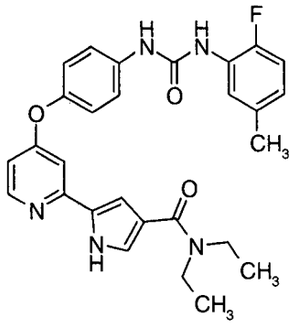
Ejemplo 102

(2S)-1-(2-{[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]amino}etil)pirrolidina-2-carboxilato de metilo




Procedimiento similar al del Ejemplo 132.
LR MS (ES+): 623 ($M+Na^+$)
LR MS (ES-): 599 (M-H)

Ejemplo 103
N,N-dietil-5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida

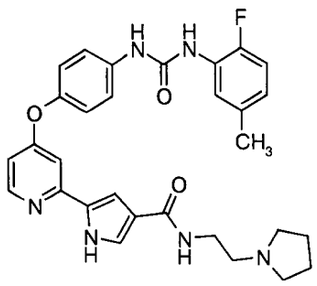


Procedimiento similar al del Ejemplo 132.
$^1H$ NMR ($d_6$-DMSO): 11.97 (br. s., 1H), 9.19 (s, 1H), 8.49 (d, J = 2.6 Hz, 1H), 8.40 (d, J = 6.2 Hz, 1H), 7.98 (dd, J = 7.8, 1.9 Hz, 1H), 7.53 - 7.61 (m, 2H), 7.40 (d, J = 1.5 Hz, 1H), 7.05 - 7.25 (m, 4H), 7.01 (br. s., 1H), 6.76 - 6.86 (m, 1H), 6.67 - 6.76 (m, 1H), 3.26 - 3.64 (m, 4H), 2.27 (s, 3H), 1.13 (t, J = 7.0 Hz, 6H)
LR MS (ES+): 524 ($M+Na^+$)
LR MS (ES-): 500 (M-H)

Ejemplo 104
1-(2-fluoro-5-metilfenil)-3-{4-[(2-{4-[(4-metilpiperazin-1-il)carbonil]-1H-pirrol-2-il}piridin-4-il)oxi]fenil}urea

Procedimiento similar al del Ejemplo 132.
$^1H$ NMR ($d_6$-DMSO): 11.87 (br. s., 1H), 9.16 (s, 1H), 8.47 (d, J = 2.6 Hz, 1H), 8.37 (d, J = 5.6 Hz, 1H), 7.98 (dd, J = 8.1, 1.9 Hz, 1H), 7.50 - 7.59 (m, 2H), 7.35 (d, J = 2.3 Hz, 1H), 7.08 - 7.19 (m, 4H), 6.87 - 6.95 (m, 1H), 6.80 (ddd, J = 7.7, 5.1, 2.2 Hz, 1H), 6.63 (dd, J = 5.9, 2.3 Hz, 1H), 3.60 (d, J = 4.1 Hz, 4H), 2.23 - 2.35 (m, 7H), 2.18 (s, 3H)
LR MS (ES+): 551 ($M+Na^+$)
LR MS (ES-): 527 (M-H)

Ejemplo 105
5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-(2-pirrolidin-1-iletil)-1H-pirrol-3-carboxamida



Procedimiento similar al del Ejemplo 132.

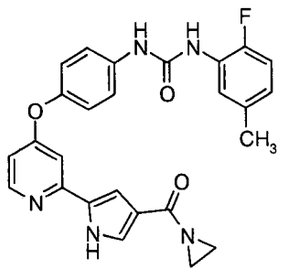
$^1$H NMR ($d_6$-DMSO): 11.80 (br. s., 1H), 9.17 (s, 1H), 8.48 (d, J = 2.6 Hz, 1H), 8.37 (d, J = 5.6 Hz, 1H), 7.98 (dd, J = 7.9, 2.1 Hz, 1H), 7.82 (t, J = 5.7 Hz, 1H), 7.50 - 7.63 (m, 2H), 7.35 (dd, J = 2.9, 1.8 Hz, 1H), 7.00 - 7.20 (m, 5H), 6.80 (dt, J = 7.9, 2.2 Hz, 1H), 6.70 (dd, J = 5.9, 2.3 Hz, 1H), 3.21 - 3.35 (m, 2H), 2.37 - 2.57 (m, 6H), 2.27 (s, 3H), 1.65 (dt, J = 6.6, 3.1 Hz, 4H)

LR MS (ES+): 565 ($M+Na^+$)

LR MS (ES-): 541 (M-H)

Ejemplo 106

1-[4-({2-[4-(aziridin-1-ilcarbonil)-1H-pirrol-2-il]piridin-4-il}oxi)fenil]-3-(2-fluoro-5-metilfenil)urea



Procedimiento similar al del Ejemplo 132.

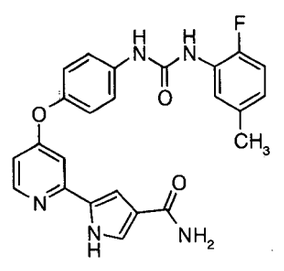
$^1$H NMR ($d_6$-DMSO): 11.90 (br. s., 1H), 9.15 (s, 1H), 8.47 (d, J = 2.6 Hz, 1H), 8.36 (d, J = 5.9 Hz, 1H), 7.97 (dd, J = 8.2, 2.1 Hz, 1H), 7.50 - 7.58 (m, 2H), 7.28 (d, J = 2.1 Hz, 1H), 7.23 (br. s., 1H), 7.04 - 7.17 (m, 3H), 6.97 (br. s., 1H), 6.79 (ddd, J = 7.5, 5.1, 2.3 Hz, 1H), 6.65 (dd, J = 5.7, 2.5 Hz, 1H), 4.17 - 4.31 (m, 2H), 3.82 (t, J = 9.2 Hz, 2H), 2.26 (s, 3H)

LR MS (ES+): 494 ($M+Na^+$)

LR MS (ES-): 470 (M-H)

Ejemplo 107

5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida



Procedimiento similar al del Ejemplo 132.

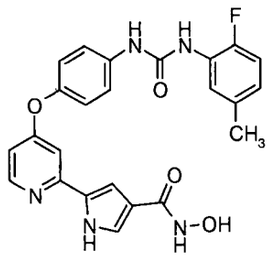
$^1$H NMR ($d_6$-DMSO): 11.89 (br. s., 1H), 9.21 (s, 1H), 8.50 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.98 (dd, J = 8.1, 1.9 Hz, 1H), 7.53 - 7.62 (m, 2H), 7.43 (br. s., 2H), 7.05 - 7.24 (m, 5H), 6.71 - 6.86 (m, 3H), 2.27 (s, 3H)

LR MS (ES+): 468 ($M+Na^+$)

LR MS (ES-): 444 (M-H)

Ejemplo 108

5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-hidroxi-1H-pirrol-3-carboxamida



Procedimiento similar al del Ejemplo 132.

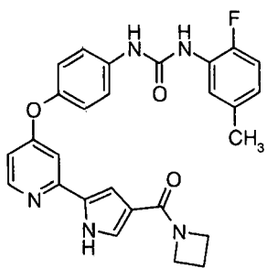
$^1$H NMR ($d_6$-DMSO): 12.10 (br. s., 1H), 10.66 (br. s., 1H), 9.29 (s, 1H), 8.53 (br. s., 1H), 8.43 (d, J = 6.2 Hz, 1H), 7.93 - 8.03 (m, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.39 - 7.50 (m, 1H), 7.30 (br. s., 1H), 7.05 - 7.26 (m, 4H), 6.75 - 6.91 (m, 2H), 2.27 (s, 3H)

LR MS (ES+): 484 ($M+Na^+$)

LR MS (ES-): 460 (M-H)

Ejemplo 109

1-[4-({2-[4-(azetidin-1-ilcarbonil)-1H-pirrol-2-il]piridin-4-il}oxi)fenil]-3-(2-fluoro-5-metilfenil)urea



Procedimiento similar al del Ejemplo 132.

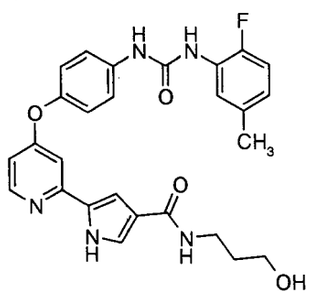
$^1$H NMR ($d_6$-DMSO): 11.67 (br. s., 1H), 9.16 (s, 1H), 8.47 (d, J = 2.1 Hz, 1H), 8.34 (d, J = 5.6 Hz, 1H), 7.97 (d, J = 5.9 Hz, 1H), 7.54 (d, J = 9.1 Hz, 2H), 7.02 - 7.23 (m, 5H), 6.86 (br. s., 1H), 6.74 - 6.83 (m, 1H), 6.64 (dd, J = 5.9, 2.3 Hz, 1H), 4.14 - 4.28 (m, 2H), 3.33 - 3.42 (m, 2H), 2.26 (s, 3H), 1.83 (br. s., 2H)

LR MS (ES+): 486 (M+H)

LR MS (ES-): 484 (M-H)

Ejemplo 110

5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-(3-hidroxipropil)-1H-pirrol-3-carboxamida



Procedimiento similar al del Ejemplo 132.

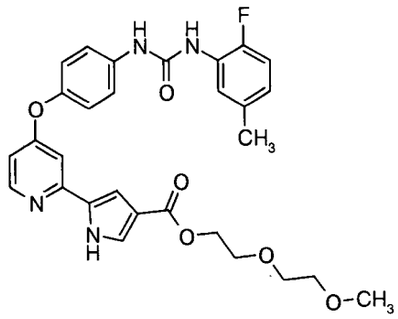
$^1$H NMR ($d_6$-DMSO): 11.78 (br. s., 1H), 9.20 (s, 1H), 8.51 (d, J = 2.1 Hz, 1H), 8.36 (d, J = 5.6 Hz, 1H), 7.96 (dd, J = 7.9, 1.8 Hz, 1H), 7.83 (t, J = 5.7 Hz, 1H), 7.55 (d, J = 9.1 Hz, 2H), 7.32 - 7.36 (m, 1H), 7.02 - 7.17 (m, 5H), 6.78 (td, J = 5.3, 2.6 Hz, 1H), 6.69 (dd, J = 5.6, 2.3 Hz, 1H), 4.42 (t, J = 5.3 Hz, 1H), 3.41 (q, J = 6.2 Hz, 2H), 3.15 - 3.26 (m, 2H), 2.26 (s, 3H), 1.60 (quin, J = 6.7 Hz, 2H)

LR MS (ES+): 526 ($M+Na^+$)

LR MS (ES-): 502 (M-H)

Ejemplo 111

5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxilato de 2-(2-metoxietoxi)etilo



Procedimiento similar al del Ejemplo 131.

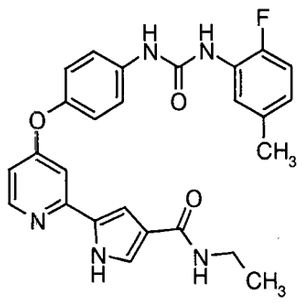
$^1$H NMR ($d_6$-DMSO): 12.12 (br. s., 1H), 9.15 (s, 1H), 8.47 (d, J = 2.3 Hz, 1H), 8.38 (d, J = 5.9 Hz, 1H), 7.97 (dd, J = 8.1, 1.9 Hz, 1H), 7.49 - 7.59 (m, 2H), 7.41 (dd, J = 3.1, 1.6 Hz, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.03 - 7.17 (m, 4H), 6.74 - 6.84 (m, 1H), 6.67 (dd, J = 5.7, 2.5 Hz, 1H), 4.20 - 4.28 (m, 2H), 3.62 - 3.70 (m, 2H), 3.51 - 3.59 (m, 2H), 3.39 - 3.46 (m, 2H), 3.18 - 3.24 (m, 3H), 2.26 (s, 3H)

LR MS (ES+): 571 ($M+Na^+$)

LR MS (ES-): 547 (M-H)

Ejemplo 112

N-etil-5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida



Procedimiento similar al del Ejemplo 132.

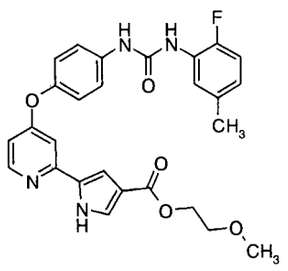
$^1$H NMR ($d_6$-DMSO): 11.93 (br. s., 1H), 9.23 (s, 1H), 8.50 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 6.2 Hz, 1H), 7.96 (dd, J = 7.9, 1.8 Hz, 1H), 7.87 (t, J = 5.6 Hz, 1H), 7.57 (d, J = 8.8 Hz, 2H), 7.42 (br. s., 1H), 7.02 - 7.27 (m, 5H), 6.72 - 6.86 (m, 2H), 3.09 - 3.25 (m, 2H), 2.26 (s, 3H), 1.06 (t, J = 7.2 Hz, 3H)

LR MS (ES+): 496 ($M+Na^+$)

LR MS (ES-): 472 (M-H)

Ejemplo 113

5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxilato de 2-metoxietilo



Procedimiento similar al del Ejemplo 131.

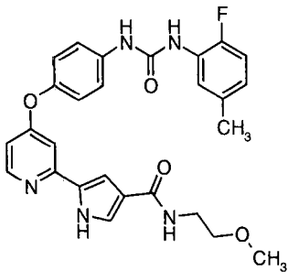
$^1$H NMR ($d_6$-DMSO): 12.12 (br. s., 1H), 9.15 (s, 1H), 8.46 (br. s., 1H), 8.38 (d, J = 5.6 Hz, 1H), 7.98 (s, 1H), 7.54 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 1.2 Hz, 1H), 7.35 (d, J = 1.8 Hz, 1H), 7.01 - 7.19 (m, 4H), 6.78 (d, J = 5.9 Hz, 1H), 6.66 (dd, J = 5.9, 2.1 Hz, 1H), 4.17 - 4.32 (m, 2H), 3.51 - 3.65 (m, 2H), 3.29 (s, 3H), 2.26 (s, 3H)

LR MS (ES+): 527 ($M+Na^+$)

LR MS (ES-): 503 (M-H)

Ejemplo 114

5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-(2-metoxietil)-1H-pirrol-3-carboxamida



Procedimiento similar al del Ejemplo 132.

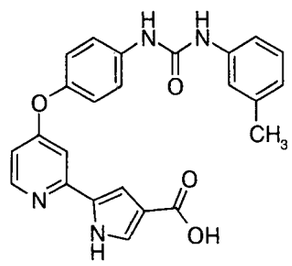
$^1$H NMR ($d_6$-DMSO): 11.86 (br. s., 1H), 9.17 (s, 1H), 8.48 (d, J = 2.3 Hz, 1H), 8.38 (d, J = 5.9 Hz, 1H), 7.86 - 8.02 (m, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.40 (br. s., 1H), 7.02 - 7.21 (m, 5H), 6.67 - 6.84 (m, 2H), 3.26 - 3.50 (m, 7H), 2.26 (s, 3H)

LR MS (ES+): 526 ($M+Na^+$)

LR MS (ES-): 502 (M-H)

Ejemplo 115

Ácido 5-{4-[4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxílico



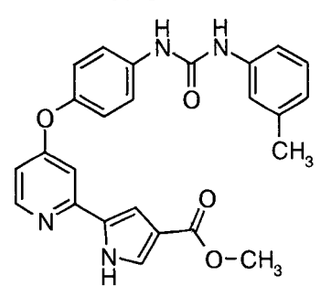
Procedimiento similar al del Ejemplo 134.

$^1$H NMR ($d_6$-DMSO): 12.05 (br. s., 1H), 8.79 (s, 1H), 8.62 (s, 1H), 8.39 (d, J = 5.6 Hz, 1H), 7.52 - 7.61 (m, 2H), 7.39 (dd, J = 3.1, 1.6 Hz, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.30 (s, 1H), 7.21 - 7.27 (m, 1H), 7.10 - 7.20 (m, 3H), 7.05 (s, 1H), 6.79 (d, J = 7.3 Hz, 1H), 6.68 (dd, J = 5.6, 2.3 Hz, 1H), 2.28 (s, 3H)

LR MS (ES-): 427 (M-H)

Ejemplo 116

5-{4-[4-({[(3-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxilato de metilo



Procedimiento similar al del Ejemplo 135.

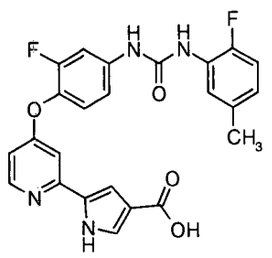
$^1$H NMR ($d_6$-DMSO): 12.12 (br. s., 1H), 9.02 (br. s., 1H), 8.85 (br. s., 1H), 8.36 (d, J = 5.6 Hz, 1H), 7.50 - 7.59 (m, 2H), 7.41 (d, J = 1.5 Hz, 1H), 7.33 (d, J = 2.3 Hz, 1H), 7.29 (s, 1H), 7.24 (d, J = 7.9 Hz, 1H), 7.08 - 7.18 (m, 3H), 7.06 (d, J = 1.5 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 6.65 (dd, J = 5.6, 2.3 Hz, 1H), 3.69 (s, 3H), 2.26 (s, 3H)

LR MS (ES+): 465 ($M+Na^+$)

LR MS (ES-): 441 (M-H)

Ejemplo 117

Ácido 5-{4-[2-fluoro-4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxílico



Procedimiento similar al del Ejemplo 134.

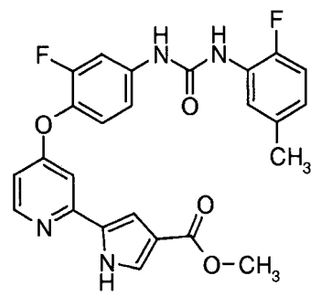
$^1$H NMR ($d_6$-DMSO): 12.03 (br. s., 1H), 11.86 (br. s., 1H), 9.62 (s, 1H), 8.65 (s, 1H), 8.38 (d, J = 5.6 Hz, 1H), 7.94 (dd, J = 7.9, 1.8 Hz, 1H), 7.72 (dd, J = 13.2, 2.3 Hz, 1H), 7.26 - 7.40 (m, 3H), 7.15 - 7.24 (m, 1H), 7.01 - 7.14 (m, 2H), 6.81 (td, J = 5.3, 2.3 Hz, 1H), 6.68 (dd, J = 5.7, 2.2 Hz, 1H), 2.26 (s, 3H)

LR MS (ES+): 487 ($M+Na^+$)

LR MS (ES-): 463 (M-H)

Ejemplo 118

5-{4-[2-fluoro-4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxilato de metilo



Procedimiento similar al del Ejemplo 135.

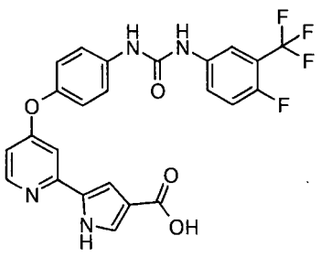
$^1$H NMR ($d_6$-DMSO): 12.13 (br. s., 1H), 9.34 (s, 1H), 8.55 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.94 (dd, J = 7.8, 1.6 Hz, 1H), 7.72 (dd, J = 13.5, 2.3 Hz, 1H), 7.43 (dd, J = 3.2, 1.8 Hz, 1H), 7.37 (d, J = 2.3 Hz, 1H), 7.26 - 7.36 (m, 1H), 7.18 (dd, J = 8.9, 1.6 Hz, 1H), 7.05 - 7.15 (m, 2H), 6.77 - 6.87 (m, 1H), 6.70 (dd, J = 5.6, 2.3 Hz, 1H), 3.70 (s, 3H), 2.26 (s, 3H)

LR MS (ES+): 501 ($M+Na^+$)

LR MS (ES-): 477 (M-H)

Ejemplo 119

Ácido 5-(4-{4-[({[4-fluoro-3-(trifluorometil)fenil]amino}carbonil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxílico



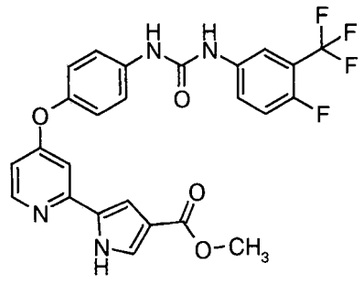
Procedimiento similar al del Ejemplo 134.

$^1$H NMR ($d_6$-DMSO): 12.05 (d, 1H), 9.11 (s, 1H), 8.96 (s, 1H), 8.38 (d, J = 5.6 Hz, 1H), 7.99 (dd, J = 6.4, 2.3 Hz, 1H), 7.60 - 7.72 (m, 1H), 7.56 (d, J = 9.1 Hz, 2H), 7.27 - 7.49 (m, 3H), 7.14 (d, J = 9.1 Hz, 2H), 7.03 (br. s., 1H), 6.67 (dd, J = 5.7, 2.2 Hz, 1H)

LR MS (ES-): 499 (M-H)

Ejemplo 120

5-(4-{4-[({[4-fluoro-3-(trifluorometil)fenil]amino}carbonil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxilato de metilo



Procedimiento similar al del Ejemplo 135.

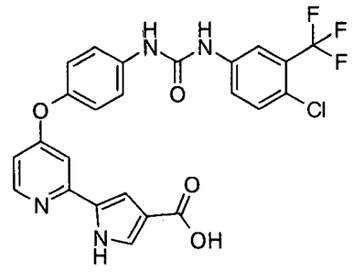
$^1$H NMR ($d_6$-DMSO): 12.12 (br. s., 1H), 9.04 (s, 1H), 8.91 (s, 1H), 8.37 (d, J = 6.2 Hz, 1H), 7.99 (dd, J = 6.4, 2.6 Hz, 1H), 7.60 - 7.69 (m, 1H), 7.51 - 7.61 (m, 2H), 7.37 - 7.49 (m, 2H), 7.34 (d, J = 2.1 Hz, 1H), 7.09 - 7.18 (m, 2H), 7.01 - 7.09 (m, 1H), 6.66 (dd, J = 5.6, 2.3 Hz, 1H), 3.70 (s, 3H)

LR MS (ES+): 537 (M+$Na^+$)

LR MS (ES-): 513 (M-H)

Ejemplo 121

Ácido 5-(4-{4-[({[4-cloro-3-(trifluorometil)fenil]amino}carbonil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxílico



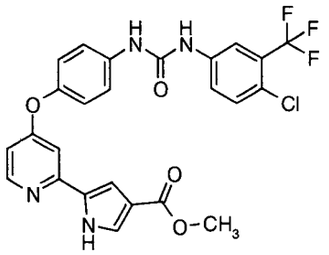
Procedimiento similar al del Ejemplo 134.

$^1$H NMR ($d_6$-DMSO): 12.08 (br. s., 1H), 9.23 (s, 1H), 9.00 (s, 1H), 8.39 (d, J = 5.6 Hz, 1H), 8.10 (s, 1H), 7.48 - 7.72 (m, 4H), 7.27 - 7.47 (m, 2H), 7.00 - 7.23 (m, 3H), 6.69 (br. s., 1H)

LR MS (ES-): 515 (M-H)

Ejemplo 122

5-(4-{4-[({[4-cloro-3-(trifluorometil)fenil]amino}carbonil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxilato de metilo



Procedimiento similar al del Ejemplo 135.

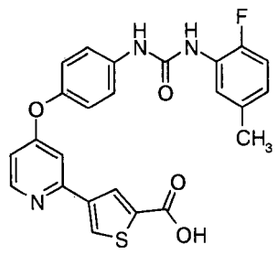
$^1$H NMR ($d_6$-DMSO): 12.12 (br. s., 1H), 9.17 (s, 1H), 8.94 (s, 1H), 8.38 (d, J = 5.9 Hz, 1H), 8.10 (d, J = 2.1 Hz, 1H), 7.51 - 7.69 (m, 4H), 7.42 (dd, J = 3.2, 1.8 Hz, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.10 - 7.18 (m, 2H), 7.03 - 7.09 (m, 1H), 6.66 (dd, J = 5.9, 2.3 Hz, 1H), 3.70 (s, 3H)

LR MS (ES+): 553 ($M+Na^+$)

LR MS (ES-): 529 (M-H)

Ejemplo 123

Ácido 4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}tiofen-2-carboxílico



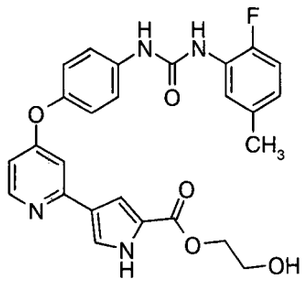
A una solución agitada de 4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}tiofeno-2-carboxilato de metilo (550mg, 1.15mmol) en una mezcla de solventes de THF/MeOH (20ml/20ml) se agregó 1ml de solución de NaOH 5M (5mmol). La mezcla se calentó en un baño a 66°C durante 2 horas, se enfrió hasta temperatura ambiente y se vertió en 200ml de agua. Se agregó HCl 2M hasta pH = 5. Los precipitados resultantes se filtraron, lavaron con agua y secaron al vacío para proporcionar ácido 4-(4-{[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}tiofen-2-carboxílico como un sólido blanquecino. Rendimiento: 520mg, 97%.

$^1$H NMR ($d_6$-DMSO): 9.30 (s, 1H), 8.59 (d, J = 2.6 Hz, 1H), 8.43 (d, J = 5.9 Hz, 1H), 8.35 (br. s., 1H), 8.13 (br. s., 1H), 7.95 (dd, J = 7.8, 1.9 Hz, 1H), 7.51 - 7.59 (m, 2H), 7.45 (s, 1H), 7.03 - 7.18 (m, 3H), 6.75 - 6.83 (m, 1H), 6.72 (dd, J = 5.6, 2.3 Hz, 1H), 2.25 (s, 3H)

LR MS (ES-): 462 (M-H)

Ejemplo 124

4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-2-carboxilato de 2-hidroxietilo



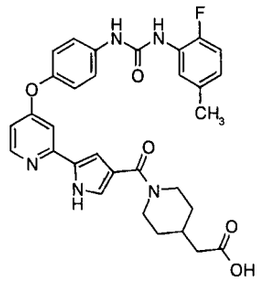
$^1$H NMR (DMSO-$d_6$) δ: 12.11 (br. s., 1H), 9.15 (s, 1H), 8.47 (d, J = 2.1 Hz, 1H), 8.33 (d, J = 5.6 Hz, 1H), 7.97 (dd, J = 7.9, 1.8 Hz, 1H), 7.63 (dd, J = 2.9, 1.8 Hz, 1H), 7.53 (d, J = 8.8 Hz, 2H), 7.22 - 7.37 (m, 2H), 7.01 - 7.18 (m, 3H), 6.72 - 6.85 (m, 1H), 6.58 (dd, J = 5.6, 2.3 Hz, 1H), 4.83 (t, J = 5.9 Hz, 1H), 4.19 (t, J = 5.1 Hz, 2H), 3.57 - 3.73 (m, 2H), 2.25 (s, 3H)

LR MS (ES+): 491 (MH), 513 ($M+Na^+$)

LR MS (ES-): 489 (M-H)

Ejemplo 125

Ácido 1-[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]piperidin-4-il}acético

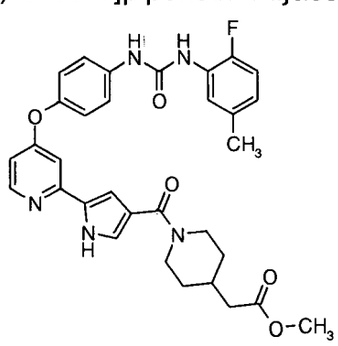


A una solución agitada de {1-[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]piperidin-4-il}acetato de metilo (50mg, 0.085mmol) en THF/MeOH (5ml/5ml) se agregó una solución de NaOH 1M (3ml, 3mmol). La mezcla se agitó a temperatura ambiente durante una hora y se vertió en 50ml de agua. Se agregó HCl 2M hasta pH = 4. Los precipitados resultantes se filtraron, lavaron con agua y secaron al vacío para proporcionar ácido {1-[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}1H-pirrol-3-il)carbonil]piperidin-4-il}acético como un sólido blanco. Rendimiento: 47mg, 96%.

LR MS (ES-): 570 (M-H)

Ejemplo 126

{1-[(5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-il)carbonil]piperidin-4-il}acetato de metilo



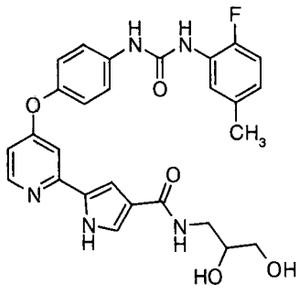
Procedimiento similar al del Ejemplo 132.

$^1$H NMR ($d_6$-DMSO): 11.83 (br. s., 1H), 9.14 (s, 1H), 8.46 (br. s., 1H), 8.35 (d, J = 5.6 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.53 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 1.8 Hz, 1H), 7.01 - 7.18 (m, 4H), 6.86 (s, 1H), 6.80 (d, J = 4.4 Hz, 1H), 6.61 (dd, J = 5.9, 2.1 Hz, 1H), 4.26 (br. s., 2H), 3.57 (s, 3H), 2.87 (br. s., 2H), 2.18 - 2.32 (m, 5H), 1.93 (br. s., 1H), 1.65 (br. s., 2H), 1.14 (br. s., 2H)

LR MS (ES+): 608 ($M+Na^+$)
LR MS (ES-): 584 (M-H)

Ejemplo 127

N-(2,3-dihidroxipropil)-5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxamida



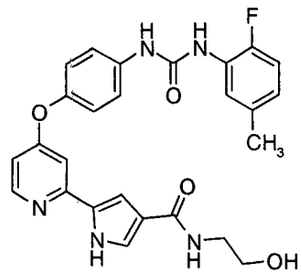
Procedimiento similar al del Ejemplo 132.

$^1H$ NMR ($d_6$-DMSO): 11.81 (br. s., 1H), 9.17 (s, 1H), 8.48 (d, J = 2.3 Hz, 1H), 8.36 (d, J = 5.6 Hz, 1H), 7.97 (dd, J = 7.8, 1.9 Hz, 1H), 7.86 (t, J = 5.7 Hz, 1H), 7.51 - 7.60 (m, 2H), 7.38 (dd, J = 3.1, 1.6 Hz, 1H), 7.10 - 7.19 (m, 3H), 7.07 (td, J = 4.3, 2.5 Hz, 2H), 6.74 - 6.84 (m, 1H), 6.69 (dd, J = 5.6, 2.3 Hz, 1H), 4.78 (d, J = 5.0 Hz, 1H), 4.54 (t, J = 5.9 Hz, 1H), 3.48 - 3.60 (m, 1H), 3.23 - 3.36 (m, 3H), 3.05 - 3.18 (m, 1H), 2.26 (s, 3H)

LR MS (ES+): 542 ($M+Na^+$)
LR MS (ES-): 518 (M-H)

Ejemplo 128

5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-(2-hidroxietil)-1H-pirrol-3-carboxamida



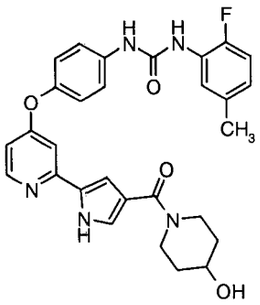
Procedimiento similar al del Ejemplo 132.

$^1H$ NMR ($d_6$-DMSO): 11.79 (br. s., 1H), 9.30 (s, 1H), 8.57 (d, J = 1.5 Hz, 1H), 8.36 (d, J = 5.6 Hz, 1H), 7.95 (dd, J = 7.9, 1.8 Hz, 1H), 7.84 (t, J = 5.6 Hz, 1H), 7.50 - 7.63 (m, 2H), 7.35 (d, J = 1.5 Hz, 1H), 7.00 - 7.21 (m, 5H), 6.79 (td, J = 5.3, 2.5 Hz, 1H), 6.69 (dd, J = 5.6, 2.3 Hz, 1H), 4.66 (t, J = 5.6 Hz, 1H), 3.38 - 3.51 (m, 2H), 3.22 (q, J = 6.1 Hz, 2H), 2.25 (s, 3H)

LR MS (ES+): 512 ($M+Na^+$)
LR MS (ES-): 488 (M-H)

Ejemplo 129

1-(2-fluoro-5-metilfenil)-3-{4-[(2-{4-[(4-hidroxipiperidin-1-il)carbonil]-1H-pirrol-2-il}piridin-4-il)oxi]fenil}urea



Procedimiento similar al del Ejemplo 132.

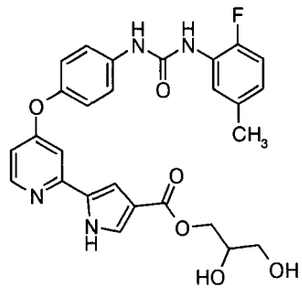
$^1$H NMR ($d_6$-DMSO): 11.84 (br. s., 1H), 9.17 (s, 1H), 8.48 (d, J = 2.3 Hz, 1H), 8.37 (d, J = 5.6 Hz, 1H), 7.99 (dd, J = 7.9, 1.8 Hz, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 2.3 Hz, 1H), 7.04 - 7.20 (m, 4H), 6.89 (s, 1H), 6.81 (td, J = 5.3, 2.3 Hz, 1H), 6.63 (dd, J = 5.9, 2.3 Hz, 1H), 4.73 (d, J = 4.1 Hz, 1H), 3.90 - 4.06 (m, 2H), 3.71 (dt, J = 8.4, 4.3 Hz, 1H), 3.25 (d, J = 2.6 Hz, 2H), 2.27 (s, 3H), 1.73 (d, J = 4.1 Hz, 2H), 1.21 - 1.44 (m, 2H)

LR MS (ES+): 552 ($M+Na^+$)

LR MS (ES-): 528 (M-H)

Ejemplo 130

5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxilato de 2,3-dihidroxipropilo



Procedimiento similar al del Ejemplo 131.

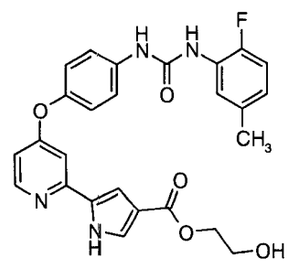
$^1$H NMR ($d_6$-DMSO): 12.12 (br. s., 1H), 9.24 (s, 1H), 8.54 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.98 (dd, J = 7.8, 1.9 Hz, 1H), 7.51 - 7.62 (m, 2H), 7.48 (dd, J = 3.1, 1.6 Hz, 1H), 7.34 - 7.40 (m, 1H), 7.05 - 7.20 (m, 4H), 6.75 - 6.87 (m, 1H), 6.68 (dd, J = 5.9, 2.3 Hz, 1H), 4.92 (d, J = 5.3 Hz, 1H), 4.64 (t, J = 5.7 Hz, 1H), 4.11 - 4.22 (m, 1H), 3.97 - 4.09 (m, 1H), 3.67 - 3.79 (m, 1H), 3.38 - 3.46 (m, 2H), 2.28 (s, 3H)

LR MS (ES+): 543 ($M+Na^+$)

LR MS (ES-): 519 (M-H)

Ejemplo 131

5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxilato de 2-hidroxietilo



Una mezcla de ácido 5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxílico (50mg, 0.11mmol), etilenglicol (1ml), clorhidrato de 1-Etil-3-(3-dimetilaminopropil)carbodiimida (EDC• HCl, 25mg, 0.13mmol) y 4-dimetilaminopiridina (DMAP, 5mg, 0.04mmol) en THF anhidro (10ml) se agitó a 60°C durante 16 horas. La mezcla se vertió en 100ml de agua.

Se agregó gota a gota HCl 2M hasta pH = 4. Los precipitados se filtraron, lavaron con agua y secaron al vacío para proporcionar el producto bruto, que se purificó por cromatografía en gel de sílice con un gradiente de 3~5% de MeOH/$CHCl_3$ para proporcionar 5-(4-{4-[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il)-1H-pirrol-3-carboxilato de 2-hidroxietilo como un sólido blanco. Rendimiento: 36mg, 67%.

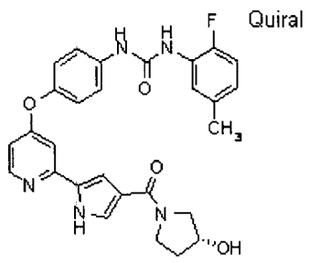
$^1$H NMR ($d_6$-DMSO): 12.12 (br. s., 1H), 9.18 (s, 1H), 8.49 (d, J = 1.8 Hz, 1H), 8.39 (d, J = 5.6 Hz, 1H), 7.94 - 8.05 (m, 1H), 7.56 (d, J = 9.1 Hz, 2H), 7.48 (d, J = 1.5 Hz, 1H), 7.35 (d, J = 2.1 Hz, 1H), 7.03 - 7.23 (m, 4H), 6.75 - 6.86 (m, 1H), 6.69 (dd, J = 5.7, 2.2 Hz, 1H), 4.83 (t, J = 5.7 Hz, 1H), 4.15 (t, J = 5.1 Hz, 2H), 3.64 (q, J = 5.4 Hz, 2H), 2.27 (s, 3H)

LR MS (ES+): 513 ($M+Na^+$)

LR MS (ES-): 489 (M-H)

Ejemplo 132

1-(2-fluoro-5-metilfenil)-3-{4-[(2-{4-[(-(3R)-3-hidroxipirrolidin-1-il]carbonil}-1H-pirrol-2-il)piridin-4-il)oxi]fenil}urea




Una mezcla de ácido 5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxílico (50mg, 0.11mmol), HATU (51mg, 0.13mmol) y *N,N*-diisopropletilamina (31mg, 0.24mmol) en DMF anhidro (10ml) se agitó a temperatura ambiente durante 10 minutos, seguido de la adición de (R)-3-pirrolidinol (14mg, 0.16mmol). La mezcla se agitó durante otros 10 minutos y se vertió en 100ml de agua. Se agregó gota a gota HCl 2M hasta pH = 4~5. Los precipitados se filtraron, lavaron con agua y secaron al vacío para proporcionar 1-(2-fluoro-5-metilfenil)-3-(4-{[2-(4-{[(3R)-3-hidroxipirrolidin-1-il]carbonil}-1H-pirrol-2-il)piridin-4-il]oxi}fenil)urea como un sólido blanco. Rendimiento: 40mg, 71%.

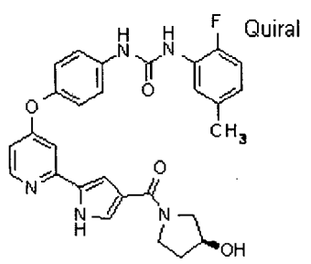
$^1$H NMR ($d_6$-DMSO): 11.90 (br. s., 1H), 9.17 (s, 1H), 8.49 (d, J = 2.6 Hz, 1H), 8.38 (d, J = 5.9 Hz, 1H), 7.99 (dd, J = 7.8, 1.9 Hz, 1H), 7.51 - 7.62 (m, 2H), 7.37 (d, J = 2.3 Hz, 1H), 7.25 (br. s., 1H), 7.02 - 7.19 (m, 4H), 6.76 - 6.86 (m, 1H), 6.64 (dd, J = 5.6, 2.3 Hz, 1H), 4.93 (br. s., 1H), 4.22 - 4.38 (m, 1H), 3.69 - 3.87 (m, 1H), 3.43 - 3.59 (m, 2H), 3.35 - 3.42 (m, 1H), 2.27 (s, 3H), 1.90 (br. s., 2H)

LR MS (ES+): 538 ($M+Na^+$)

LR MS (ES-): 514 (M-H)

Ejemplo 133

1-(2-fluoro-5-metilfenil)-3-{4-[(2-{4-[(-(3S)-3-hidroxipirrolidin-1-il]carbonil}-1H-pirrol-2-il)piridin-4-il)oxi]fenil}urea



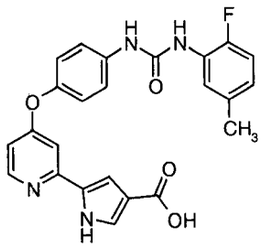

Procedimiento similar al del Ejemplo 132.

LR MS (ES+): 538 ($M+Na^+$)

LR MS (ES-): 514 (M-H)

Ejemplo 134

Ácido 5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxílico



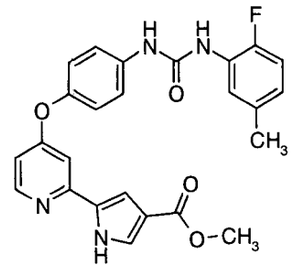
A una solución agitada de 5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxilato de metilo (1.38g, 3.00mmol) en una mezcla de solventes de THF/MeOH (20ml/20ml) se agregó 2ml de solución de NaOH 5M (10mmol). La mezcla se calentó en un baño a 72°C durante 5 horas, se enfrió hasta temperatura ambiente y se vertió en 200ml de agua. Se agregó HCl 2M hasta pH = 3. Los precipitados resultantes se filtraron, lavaron con agua y secaron al vacío para proporcionar ácido 5-(4-{[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxílico como un sólido pardo claro. Rendimiento: 1.28g, 96%.

$^1$H NMR ($d_6$-DMSO): 12.04 (br. s., 1H), 11.88 (br. s., 1H), 9.18 (s, 1H), 8.49 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 5.6 Hz, 1H), 7.94 - 8.05 (m, 1H), 7.56 (d, J = 9.1 Hz, 2H), 7.31 - 7.42 (m, 2H), 7.01 - 7.21 (m, 4H), 6.81 (td, J = 5.2, 2.2 Hz, 1H), 6.68 (dd, J = 5.6, 2.3 Hz, 1H), 2.27 (s, 3H)

LR MS (ES-): 467 (M-H)

Ejemplo 135

5-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxilato de metilo



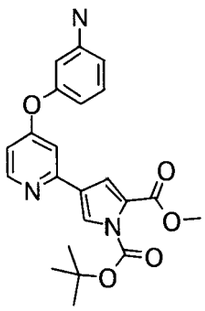
A una solución agitada de 5-[4-(4-aminofenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de metilo (1.0g, 3.23mmol) en THF anhidro (10ml) se agregó 2-fluoro-5-metil-fenilisocianato (488mg, 3.23mmol). La mezcla se agitó a temperatura ambiente durante una hora y se vertió en 200ml de una solución de HCl 0.02M con agitación vigorosa. Los precipitados resultantes se filtraron, lavaron con agua y secaron al vacío para proporcionar 5-(4-{[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-3-carboxilato de metilo como un sólido blanco. Rendimiento: 1.38g, 93%.

$^1$H NMR ($d_6$-DMSO): 12.14 (br. s., 1H), 9.17 (s, 1H), 8.49 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.99 (dd, J = 7.9, 1.8 Hz, 1H), 7.53 - 7.59 (m, 2H), 7.44 (dd, J = 3.2, 1.5 Hz, 1H), 7.36 (d, J = 2.3 Hz, 1H), 7.06 - 7.18 (m, 4H), 6.77 - 6.85 (m, 1H), 6.68 (dd, J = 5.6, 2.3 Hz, 1H), 3.72 (s, 3H), 2.28 (s, 3H)

LR MS (ES+): 483 ($M+Na^+$)

LR MS (ES-): 459 (M-H)

Preparación de 4-[4-(3-aminofenoxi)piridin-2-il]-1H-pirrol-1,2-dicarboxilato de 1-terc-butil 2-metilo



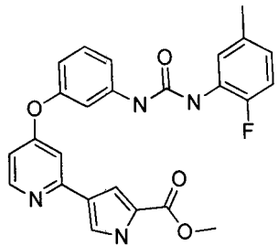
Procedimiento similar a 4-[4-(4-aminofenoxi)piridin-2-il]-1H-pirrol-1,2-dicarboxilato de 1-terc-butil 2-metilo.

$^1$H NMR ($d_6$-DMSO): 8.38 (d, 1H), 8.01 (d, J = 1.5 Hz, 1H), 7.45 (d, J = 2.1 Hz, 1H), 7.37 (d, J = 1.5 Hz, 1H), 7.06 (t, J = 7.9 Hz, 1H), 6.67 (dd, J = 5.7, 2.2 Hz, 1H), 6.43 (d, J = 7.9 Hz, 1H), 6.20 - 6.33 (m, 2H), 5.32 (br. s., 2H), 3.72 - 3.85 (m, 3H), 1.53 (s, 9H)

LR MS (ES+): 432 ($M+Na^+$)

Ejemplo 136

4-{4-[3-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-2-carboxilato de metilo



A una solución agitada de 4-[4-(3-aminofenoxi)piridin-2-il]-1H-pirrol-1,2-dicarboxilato de 1-terc-butil 2-metilo (150 mg, 0.37 mmol) en THF anhidro (10ml) se agregó 2-fluoro-5-metil-fenilisocianato (67mg, 0.44mmol). La mezcla se agitó a temperatura ambiente durante 3 horas, y se vertió en 100ml de agua. Los precipitados resultantes se filtraron, lavaron con agua y secaron al vacío para proporcionar el intermedio protegido con Boc como un sólido pardo. El intermedio se disolvió en 5ml de cloruro de metileno y se agregó 3ml de ácido trifluoroacético. La agitación continuó durante 20 minutos. La mezcla se evaporó hasta sequedad para proporcionar el producto bruto, que se purificó por cromatografía en gel de sílice eluyendo con 5% de $MeOH/CHCl_3$ para proporcionar 4-{4-[3-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-2-carboxilato de metilo como un sólido blanco. Rendimiento: 67mg, 39%.

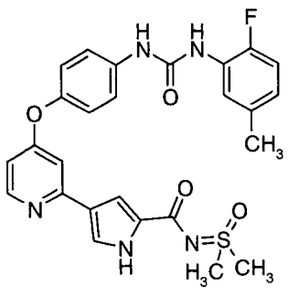
$^1$H NMR ($d_6$-DMSO): 12.18 (br. s., 1H), 9.23 (s, 1H), 8.47 (br. s., 1H), 8.36 (d, J = 5.6 Hz, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.63 (br. s., 1H), 7.25 - 7.47 (m, 4H), 7.16 (d, J = 7.9 Hz, 1H), 7.07 (dd, J = 11.4, 8.5 Hz, 1H), 6.72 - 6.85 (m, 2H), 6.65 (dd, J = 5.6, 2.1 Hz, 1H), 3.76 (s, 3H), 2.22 (s, 3H)

LR MS (ES+): 483 ($M+Na^+$)

LR MS (ES-): 459 (M-H)

Ejemplo 137

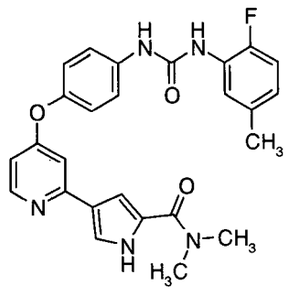
N-[dimetil(óxido)-lambda~4~-sulfanilideno]-4-(4-{4-[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-2-carboxamida



Procedimiento similar al del Ejemplo 101.
LR MS (ES+): 544 ($M+Na^+$)
LR MS (ES-): 520 (M-H)

Ejemplo 138

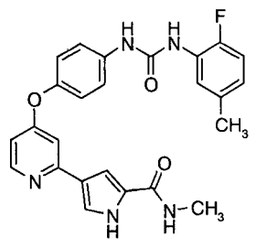
4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N,N-dimetil-1H-pirrol-2-carboxamida



El compuesto del título se aisló como un producto secundario en la síntesis del Ejemplo 137.
LR MS (ES+): 474 (M+H)
LR MS (ES-): 472 (M-H

Ejemplo 139

4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-metil-1H-pirrol-2-carboxamida



Una mezcla de ácido 4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-2-carboxílico (50mg, 0.11mmol), HATU (50mg, 0.13mmol), solución de metilamina/THF 2M (0.1ml, 0.2mmol) y *N,N*-diisopropiletilamina (31mg, 0.24mmol) en DMF anhidro (8ml) se agitó a temperatura ambiente durante 10 minutos. La mezcla se vertió en 100ml de agua. Los precipitados se filtraron, lavaron con agua y secaron para proporcionar el producto bruto, que se purificó por cromatografía en gel de sílice con 3~5% de $MeOH/CHCl_3$ para proporcionar 4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-N-metil-1H-pirrol-2-carboxamida como un sólido blanco. Rendimiento: 21mg, 41%.

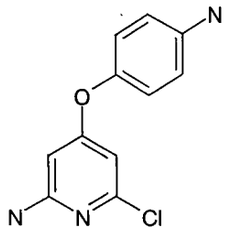
$^1H$ NMR ($d_6$-DMSO): 11.69 (br. s., 1H), 9.17 (s, 1H), 8.48 (d, J = 2.3 Hz, 1H), 8.32 (d, J = 5.6 Hz, 1H), 8.01 - 8.12 (m, 1H), 7.96 (dd, J = 7.8, 1.9 Hz, 1H), 7.48 - 7.61

(m, 2H), 7.43 (dd, J = 2.9, 1.5 Hz, 1H), 7.03 - 7.23 (m, 5H), 6.79 (dt, J = 8.1, 2.3 Hz, 1H), 6.61 (dd, J = 5.6, 2.3 Hz, 1H), 2.71 (d, J = 4.7 Hz, 3H), 2.26 (s, 3H)

LR MS (ES+): 482 ($M+Na^+$)

LR MS (ES-): 458 (M-H)

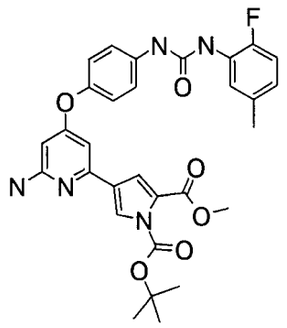
Preparación de 4-(4-Aminofenoxi)-6-cloropiridin-2-amina



Una solución agitada de 4-aminofenol (335mg, 3.1mmol) en DMSO anhidro (8ml) se enjuagó con nitrógeno y trató con una solución de $KOBu^t$ /THF 1M (3.1ml, 3.1mmol). La mezcla se agitó a temperatura ambiente en nitrógeno durante 10 minutos. Se agregó 4,6-dicloropiridin-2-ilamina (500mg, 3.1mmol) y la mezcla se calentó a 88°C durante 16 horas, se enfrió hasta temperatura ambiente y vertió en 100ml de agua. Los precipitados resultantes se filtraron, lavaron con agua y secaron para proporcionar el producto bruto que se purificó por cromatografía en gel de sílice con 2~5% de $MeOH/CHCl_3$ para proporcionar 4-(4-aminofenoxi)-6-cloropiridin-2-amina como un sólido pardo claro. Rendimiento: 350mg, 49%.

Ejemplo 140

4-{6-amino-4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-1,2-dicarboxilato de 1-terc-butil 2-metilo

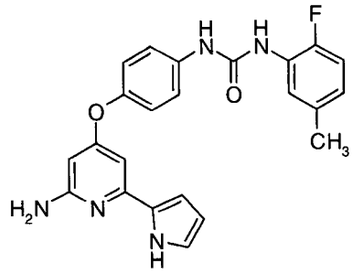


Procedimiento similar al del Ejemplo 148.

LR MS (ES+): 598 ($M+Na^+$)

Ejemplo 141

1-(4-{[2-amino-6-(1H-pirrol-2-il)piridin-4-il]oxi}fenil)-3-(2-fluoro-5-metilfenil)urea



Procedimiento similar al del Ejemplo 148.

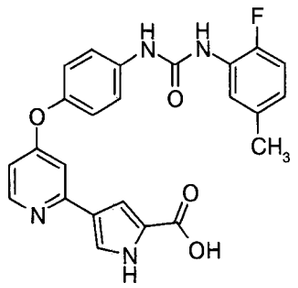
$^1H$ NMR ($d_6$-DMSO): 11.02 (br. s., 1H), 9.11 (s, 1H), 8.44 (br. s., 1H), 7.97 (d, 1H), 7.50 (d, J = 8.8 Hz, 2H), 6.98 - 7.17 (m, 3H), 6.78 (br. s., 2H), 6.53 (br. s., 2H), 6.05 (br. s., 1H), 5.74 (br. s., 2H), 5.61 (s, 1H), 2.25 (s, 3H)

LR MS (ES+): 418 (M+H)

LR MS (ES-): 416 (M-H)

Ejemplo 142

Ácido 4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-2-carboxílico

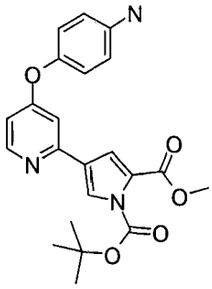


A una solución agitada de 4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-2-carboxilato de metilo (220mg, 0.48mmol) en THF/MeOH (3ml/10ml) se agregó NaOH 1M (4.0ml, 4,0mmol). La mezcla se calentó a 70°C durante 2 horas, se enfrió hasta temperatura ambiente y se vertió en 100ml de agua. Se agregó HCl 1M hasta pH = 4 y los precipitados resultantes se filtraron, lavaron con agua y secaron al vacío para proporcionar ácido 4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-2-carboxílico. Rendimiento: 200mg, 94%.

$^1$H NMR ($d_6$-DMSO): 12.38 (br. s., 1H), 12.04 (br. s., 1H), 9.14 - 9.23 (m, 1H), 8.48 (d, J = 2.3 Hz, 1H), 8.34 (d, J = 5.6 Hz, 1H), 7.97 (dd, J = 7.9, 2.1 Hz, 1H), 7.60 (br. s., 1H), 7.50 - 7.58 (m, 2H), 7.30 (d, J = 2.1 Hz, 1H), 7.22 (s, 1H), 7.03 - 7.18 (m, 3H), 6.73 - 6.84 (m, 1H), 6.60 (dd, J = 5.6, 2.3 Hz, 1H), 2.25 (s, 3H)

LR MS (ES-): 445 (M-H)

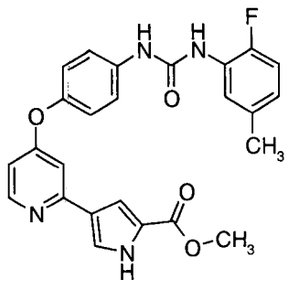
Preparación de 4-[4-(4-aminofenoxi)piridin-2-il]-1H-pirrol-1,2-dicarboxilato de 1-terc-butil 2-metilo



Un matraz de 100ml se cargó con 4-((2-cloropiridin-4-il)oxi)anilina (150mg, 0.68mmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirrol-1,2-dicarboxilato de 1-terc-butil 2-metilo (260mg, 0.81mmol), solución de $Na_2CO_3$ 2M (0.5ml, 1.0mmol), $PdCl_2(PPh_3)_2$ (5mg, 0.007mmol), 10ml de 1,4-dioxano y 3ml de agua. La mezcla se enjuagó con nitrógeno y se calentó a 70°C durante 30 minutos. La mezcla se enfrió hasta temperatura ambiente y se vertió en 100ml de agua. Los precipitados se filtraron y secaron para proporcionar el producto bruto que se purificó adicionalmente por cromatografía en gel de sílice eluyendo con 2-3% de MeOH/$CHCl_3$ para proporcionar 4-[4-(4-aminofenoxi)piridin-2-il]-1H-pirrol-1,2-dicarboxilato de 1-terc-butil 2-metilo como un aceite pardo claro. Rendimiento: 240mg, 86%.

Ejemplo 143

4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-2-carboxilato de metilo



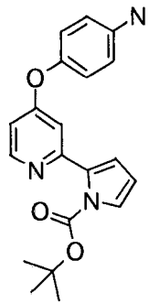
A una solución agitada de 4-[4-(4-aminofenoxi)piridin-2-il]-1H-pirrol-1,2-dicarboxilato de 1-terc-butil 2-metilo (240 mg, 0.59 mmol) en THF anhidro (10ml) se agregó 2-fluoro-5-metil-fenilisocianato (107mg, 0.71mmol). La mezcla se agitó a temperatura ambiente durante 30 minutos y se vertió en 100ml de agua. Los precipitados se filtraron, lavaron con agua y secaron para proporcionar como un aceite pardo. La purificación por cromatografía en gel de sílice eluyendo con 2-3% de $MeOH/CHCl_3$ proporcionó un intermedio protegido con Boc como un aceite verde claro que se disolvió en 5ml de cloruro de metileno seguido de la adición de 3ml de ácido trifluoroacético. La mezcla se agitó a temperatura ambiente durante 10 minutos, se evaporó hasta sequedad y se purificó por cromatografía en gel de sílice eluyendo con 2-5% de $MeOH/CHCl_3$ para proporcionar 4-{4-[4-({[(2-fluoro-5-metilfenil)amino]carbonil}amino)fenoxi]piridin-2-il}-1H-pirrol-2-carboxilato de metilo como un sólido blanco. Rendimiento: 135mg, 50%.

$^1H$ NMR ($d_6$-DMSO): 12.17 (br. s., 1H), 9.14 (s, 1H), 8.46 (d, J = 2.3 Hz, 1H), 8.33 (d, J = 5.9 Hz, 1H), 7.91 - 8.04 (m, 1H), 7.61 (dd, J = 3.1, 1.6 Hz, 1H), 7.53 (d, J = 9.1 Hz, 2H), 7.22 - 7.31 (m, 2H), 7.02 - 7.17 (m, 3H), 6.73 - 6.85 (m, 1H), 6.58 (dd, J = 5.7, 2.5 Hz, 1H), 3.76 (s, 3H), 2.26 (s, 3H)

LR MS (ES+): 483 ($M+Na^+$)

LR MS (ES-): 459 (M-H)

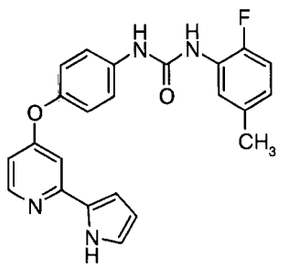
Preparación de 2-[4-(4-aminofenoxi)piridin-2-il]-1H-pirrol-1-carboxilato de terc-butilo



A una solución agitada de ácido *N*-Boc-pirrol-2-borónico (114mg, 0.54mmol) y 4-((2-cloropiridin-4-il)oxi)anilina (100mg, 0.45mmol) en 8ml de 1,4-dioxano, se agregó $PdCl_2(PPh_3)_2$ (10mg, 0.014mmol) y solución acuosa de $Na_2CO_3$ 1M (0.5ml, 1.0mmol). La mezcla se calentó a 72°C en $N_2$ durante una hora, se enfrió hasta temperatura ambiente y se vertió en 100ml de agua. La mezcla resultante se extrajo con EtOAc (50ml 2 veces). Las capas orgánicas se combinaron, lavaron con salmuera (50ml), secaron sobre $Na_2SO_4$, y evaporaron para proporcionar un aceite pardo que se purificó por cromatografía en gel de sílice con un gradiente de 20~50% de EtOAc/hexanos para proporcionar 2-[4-(4-aminofenoxi)piridin-2-il]-1H-pirrol-1-carboxilato de terc-butilo como un aceite incoloro. Rendimiento: 110mg, 70%.

Ejemplo 144

1-(2-fluoro-5-metilfenil)-3-(4-{[2-(1H-pirrol-2-il)piridin-4-il]oxi}fenil)urea

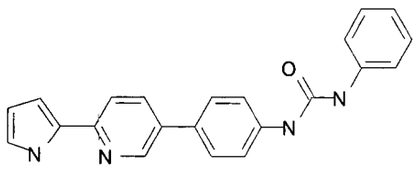


A una solución agitada de 2-[4-(4-aminofenoxi)piridin-2-il]-1H-pirrol-1-carboxilato de terc-butilo (100 mg, 0.28 mmol) en THF anhidro (10ml) se agregó 2-fluoro-5-metil-fenilisocianato (51mg, 0.34mmol). La mezcla se agitó a temperatura ambiente durante una hora y se vertió en 100ml de agua. La mezcla resultante se extrajo con EtOAc (50ml 2 veces). Las capas orgánicas se combinaron, lavaron con salmuera (50ml), secaron sobre $Na_2SO_4$ y evaporaron para proporcionar un aceite pardo que se purificó por cromatografía en gel de sílice con 2-5% de $MeOH/CHCl_3$ para proporcionar un intermedio protegido con Boc como un aceite verde claro. El aceite se disolvió en 5ml de cloruro de metileno y se agregó 3ml de ácido trifluoroacético. Se continuó la agitación durante 10 horas y la mezcla se evaporó hasta sequedad. El residuo pardo se disolvió en metanol (5ml). Esta solución de metanol luego se agregó gota a gota en 100ml de una solución de $NaHCO_3$ 1M con agitación. Los precipitados resultantes se filtraron, lavaron con agua y secaron al vacío para proporcionar 1-(2-fluoro-5-metilfenil)-3-(4-{[2-(4-(1H-pirrol-2-il)piridin-4-il]oxi}fenil)urea como un sólido gris claro.

$^1$H NMR ($d_6$-DMSO): 11.43 (br. s., 1H), 9.14 (s, 1H), 8.46 (d, J = 2.6 Hz, 1H), 8.32 (d, J = 5.6 Hz, 1H), 7.96 (dd, J = 7.9, 1.8 Hz, 1H), 7.48 - 7.58 (m, 2H), 7.20 (d, J = 2.1 Hz, 1H), 7.04 - 7.16 (m, 3H), 6.75 - 6.86 (m, 2H), 6.67 (dt, J = 3.8, 1.9 Hz, 1H), 6.57 (dd, J = 5.9, 2.3 Hz, 1H), 6.05 - 6.13 (m, 1H), 2.25 (s, 3H)

Ejemplo 145

1-fenil-3-{4-[6-(1H-pirrol-2-il)piridin-3-il]fenil}urea

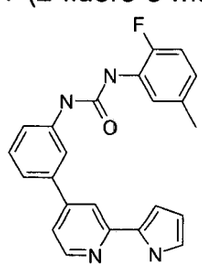


Procedimiento similar al del Ejemplo 148.

$^1$H NMR (DMSO-$d_6$) δ: 11.46 (br. s., 1H), 8.79 (s, 1H), 8.75 (d, J = 1.8 Hz, 1H), 8.67 (s, 1H), 7.98 (dd, J = 8.4, 2.5 Hz, 1H), 7.70 (d, J = 8.2 Hz, 1H), 7.67 (d, J = 8.5 Hz, 2H), 7.56 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 7.6 Hz, 2H), 7.27 (t, J = 7.9 Hz, 2H), 6.96 (t, J = 7.3 Hz, 1H), 6.84 - 6.88 (m, 1H), 6.77 (t, J = 3.8 Hz, 1H), 6.11 - 6.16 (m, 1H)

Ejemplo 146

1-(2-fluoro-5-metilfenil)-3-(3-{[2-(1H-pirrol-2-il)piridin-4-il]fenil}urea

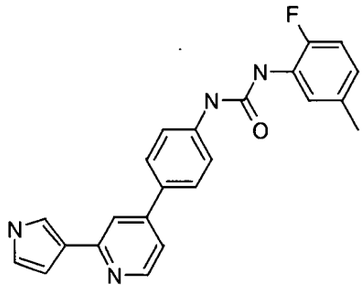


Procedimiento similar al del Ejemplo 148.

LR MS (ES+): 387 ($M+H^+$)

Ejemplo 147

1-(2-fluoro-5-metilfenil)-3-(4-{[2-(1H-pirrol-3-il)piridin-4-il]fenil}urea

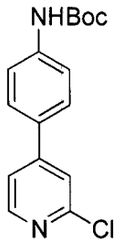


Procedimiento similar al del Ejemplo 148.

$^1$H NMR ($d_6$-DMSO): 11.72 (br. s., 1H), 9.49 (br. s., 1H), 8.63 (s, 1H), 8.53 (d, J = 6.4 Hz, 1H), 8.38 (br. s., 1H), 8.07 (d, J = 8.5 Hz, 2H), 8.00 - 8.04 (m, 1H), 7.97 (dd, J = 7.9, 1.8 Hz, 1H), 7.81 - 7.90 (m, 1H), 7.69 (d, J = 8.8 Hz, 2H), 7.13 (dd, J = 11.3, 8.4 Hz, 1H), 7.03 (d, J = 2.1 Hz, 1H), 6.98 (br. s., 1H), 6.84 (ddd, J = 7.8, 5.3, 2.1 Hz, 1H), 2.21 - 2.36 (m, 3H)

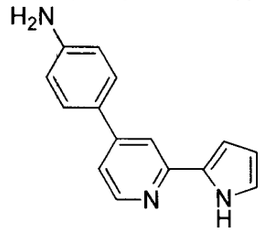
LR MS (ES+): 387 (M+H)

(4-(2-cloropiridin-4-il)fenil)carbamato de terc-butilo



A una mezcla de ácido (4-Boc-aminofenil)borónico (200mg, 0.84mmol) y 2-cloro-4-bromopiridina (162mg, 0.84mmol) en 10ml de 1,4-dioxano, se agregó $PdCl_2(PPh_3)_2$ (10mg, 0.014mmol) y solución acuosa de $Na_2CO_3$ 1M (0.5ml, 1.0mmol). La mezcla se calentó a 70°C en $N_2$ durante dos horas, se enfrió hasta temperatura ambiente y se vertió en 100ml de agua. Los precipitados pardos se filtraron, lavaron con agua y secaron para proporcionar (4-(2-cloropiridin-4-il)fenil)carbamato de terc-butilo como el producto bruto.

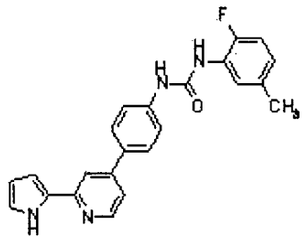
4-(2-(1H-pirrol-2-il)piridin-4-il)anilina



A una mezcla de ácido N-Boc-pirrol-2-borónico (210mg, 1.0mmol) y 4-((2-cloropiridin-4-il)fenil)carbamato de terc-butilo (250mg, 0.82mmol) en 10ml de 1,4-dioxano, se agregó $PdCl_2(PPh_3)_2$ (10mg, 0.014mmol) y solución acuosa de $Na_2CO_3$ 1M (0.75ml, 1.5mmol). La mezcla se calentó a 60°C en $N_2$ durante 3 horas, se enfrió hasta temperatura ambiente y se vertió en 100ml de agua. os precipitados se filtraron, secaron y purificaron por cromatografía en gel de sílice con 1-5% de MeOH/$CHCl_3$ para proporcionar el intermedio como un aceite amarillo claro. El intermedio se disolvió en 10ml de cloruro de metileno y se agregó 3ml de ácido trifluoroacético. La mezcla se agitó a temperatura ambiente durante 16 horas y se evaporó hasta sequedad para proporcionar sal de TFA de 4-(2-(1H-pirrol-2-il)piridin-4-il)anilina como un sólido pardo claro. Rendimiento: 290mg, 100%.

Ejemplo 148

1-(2-fluoro-5-metilfenil)-3-(4-{[2-(1H-pirrol-2-il)piridin-4-il]fenil}urea



A una suspensión agitada de sal de TFA de 4-(2-(1H-pirrol-2-il)piridin-4-il)anilina (60 mg, 0.17 mmol) en THF anhidro (10ml) se agregó 2-fluoro-5-metil-fenilisocianato (48mg, 0.32mmol) y *N,N*-diisopropiletilamina (40 mg, 0.31 mmol). Luego de 1 hora, la mezcla de reacción se evaporó y purificó por cromatografía en gel de sílice con 2-3% de $MeOH/CHCl_3$ para proporcionar 1-(2-fluoro-5-metilfenil)-3-{4-[2-(1H-pirrol-2-il)piridin-4-il]fenil}urea como un sólido blanquecino. Rendimiento: 28mg.

$^1H$ NMR ($d_6$-DMSO): 11.49 (br. s., 1H), 9.29 (br. s., 1H), 8.52 - 8.60 (m, 1H), 8.48 (d, J = 5.3 Hz, 1H), 7.94 - 8.04 (m, 2H), 7.84 (d, J = 8.5 Hz, 2H), 7.62 (d, J = 8.5 Hz, 2H), 7.42 (dd, J = 5.3, 1.5 Hz, 1H), 7.12 (dd, J = 11.4, 8.2 Hz, 1H), 6.89 (s, 2H), 6.82 (dt, J = 5.4, 2.6 Hz, 1H), 6.16 (t, J = 2.9 Hz, 1H), 2.29 (s, 3H)

LR MS (ES+): 409 ($M+Na^+$)

LR MS (ES-): 385 (M-H)

**3.2 Pruebas biológicas**

Los datos biológicos para los compuestos de la presente invención se generaron mediante el uso de uno o más de los siguientes ensayos.

**Señal Ca.sup.++ estimulada por VEGF in Vitro**

Se usó tecnología FLIPR automatizada (Lector de placas por imagenología fluorométrica) para analizar aumentos en los inhibidores de VEGF inducidos en niveles de calcio intracelular en células endoteliales cargadas con tinte fluorescente. Se sembraron HUVEC (células endoteliales de la vena umbilical humana) (Clonetics) en placas de pared negra recubiertas con fibronectina de 96 pocillos durante la noche a 37°C/5% de $CO_2$. Las células se cargaron con indicador de calcio Fluo-4 durante 45 minutos a 37°C. Las células se lavaron 4 veces (Original Cell Wash, Labsystems) para retirar el tinte extracelular. Los compuestos de prueba se reconstituyeron en 100% de DMSO y se agregaron a las células para proporcionar una concentración final de DMSO del 0.1%. Para el análisis, las células se preincubaron con agentes de prueba durante 30 minutos en una sola concentración (10 µM) o en concentraciones que varían entre 0.01 y 10.0 µM seguido de estimulacion de VEGF (5 ng/mL). Los cambios en la fluorescencia a 516 nm se midieron simultáneamente en todos los 96 pocillos usando una cámara CCD fría. Se generaron datos determinando los niveles máximos y mínimos de fluorescencia para muestras no estimuladas, estimuladas y tratadas con fármaco. Los valores de $IC_{50}$ para compuestos de prueba se calcularon a partir del % de inhibición de respuestas estimuladas por VEGF en la ausencia del inhibidor.

**Ensayo de cinasa VEGFR2**

El dominio citoplásmico del receptor VEGF humano (VEGFR-2) se expresa como una proteína de fusión marcada con histidina siguiendo la infección de células de insecto usando un baculovirus diseñado con His. His-VEGFR-2 se purificó hasta homogeneidad tal como se determina por SDS-PAGE, usando cromatografía de resina y níquel. Los ensayos de cinasa se realizaron en placas de microtitulación de 96 pocillos que se recubrieron durante la noche con 30 µg de poli-Glu-Tyr (4:1) en 10 mM de solución salina tamponada con fosfato (PBS), pH 7.2-7.4. Las placas se incubaron con 1% de BSA y luego se lavaron cuatro veces con PBS previo al comienzo de la reacción. Las reacciones se llevaron a cabo en volúmenes de reacción de 120 µL que contienen 3.6 µM ATP en amortiguador de cinasa (50 mM de amortiguador Hepes a pH 7.4, 20 mM $MgCl_2$, 0.1 mM $MnCl_2$ y 0.2 mM $Na_3VO_4$). Los compuestos de prueba se

reconstituyeron en 100% de DMSO y se agregaron a la reacción para proporcionar una concentración final de DMSO del 5%. Las reacciones se iniciaron por la adición de 0.5ng de la proteína purificada. Luego de una incubación de diez minutos a 25°C, las reacciones se lavaron cuatro veces con PBS que contiene 0.05% de Tween-20 100 µl de un conjugado anticuerpo-peroxidasa anti-fosfotirosina monoclonal se diluyó 1:10000 en PBS-Tween-20 y se agregó a los pocillos durante 30 minutos. Siguiendo cuatro lavados con PBS-Tween-20, 100 µl de diclorhidrato de O-fenilendiamina en amortiguador de fosfato-citrato, que contiene peróxido de hidrógeno urea, se agregó a los pocillos durante 7 minutos como sustrato colorimétrico para la peroxidasa. La reacción se terminó mediante la adición de 100 µl de 2.5N $H_2SO_4$ a cada pocillo y se leyó usando un lector ELISA de microplaca ajustado a 492 nm. Los valores de $IC_{50}$ para la inhibición del compuesto cuando se calculan directamente a partir de gráficas de densidad óptica (unidades arbitrarias) contra la concentración del compuesto siguiendo la resta de valores en blanco. Compuestos de la presente invención tiene el valor de IC50 en el intervalo de 0.01 a 500 nM.

**Extravasación dérmica inducida por VEGF en cobayos (ensayo Miles)**

Se anestesiaron cobayos macho Hartley (300-600 g) con isofluorano, se cizallaron y se les administró una única dosis de fármaco o el vehículo correspondiente. Los cobayos se dosificaron salvo que se establezca lo contrario en la Tabla 3. Diez minutos antes del final del tratamiento con fármaco, los cobayos se anestesiaron con isofluorano y se inyectaron 0.5% de tinte azúl Evans (EBD) en PBS (13-15 mg/kg dosis de EBD) de manera intravenosa. Luego de 5 minutos, se administraron inyecciones intradérmicas de 100 ng $rhVEGF_{165}$ en 100 µl PBS y de 100 µl PBS solo en el flanco. Luego de 20 minutos, cada animal se somete a eutanasia con Pentosol y la piel que contiene sitios de inyección intradérmica se retiraron para análisis de imágenes.

Usando un análogo de cámara de video acoplado a una computadora, se toma una imagen de cada muestra de piel transiluminada y la densidad óptica integrada para cada sitio de inyección se mide usando ImagePro4. Para cada muestra de piel, la diferencia entre la densidad óptica media de los sitios de VEFG y la densidad óptica media de los sitios de PBS es la medida de la extravasación de EBD inducida por VEGF en ese animal. Estos valores medidos se promediaron por grupo de estudio para determinar la extravasación de EBD inducida por VEGF para cada condición experimental y la media del grupo luego se compara para evaluar la extravasación de EBD inducida por VEGF en los grupos tratados con fármaco con respecto a los controles tratados con vehículo.

Para determinar la dosis requerida para el 50% de inhibición ($ID_{50}$), los datos del porcentaje de inhibición se graficaron como una función de dosis oral, usando el análisis óptimo dentro del software MicroSoft Excel. El valor $ID_{50}$ se verificó visualmente usando datos graficados (línea horizontal desde 50% del valor y, en la intersección de la línea vertical de caída de línea óptima con respecto al eje x (dosis).

**Neurovascularización coroidal inducida por láser (CNV) en ratas (ensayo CNV).**

Se indujo y cuantificó CNV en este modelo tal como se describe anteriormente (Edelman and Castro. Exp. Eye Res. 2000; 71:523-533). El día 0, ratas macho Brown Norway (200-300 g) se anestesiaron con 100 mg/kg de cetamina y 10 mg/kg de zilazina y las pupilas se dilataron con 1% de Tropicamida. Usando un marco azúl-verde de Coherent Novus Argon Laser, 3 láser [sic] (90 mW durante 0.1 s; 100 µm de diámetro) se proporcionaron a cada ojo entre los vasos de la retina alrededor de la cabeza del nervio óptico. Se dosificaron ratas con compuestos de prueba en sus vehículos indicados oralmente una vez por día.

El día 10, se sacrificaron las ratas con 100% $CO_2$, y los vasos sanguíneos se marcaron por perfusión vascular con 10 mg/ml FITC-dextrano (MW $2x10^6$). Usando un

microscopio de epifluorescencia (20 veces) acoplado a una cámara digital y una computadora, las imágenes se obtuvieron a partir de montes planos de RPE coroides esclerótica de cada ojo y el área ocupada por neovasos hiperfluorescentes dentro de cada lesión de láser se midió usando software ImagePro 4.

Para determinar la dosis requerida para el 50% de inhibición ($ID_{50}$), los datos del porcentaje de inhibición se graficaron como una función de dosis oral, usando el análisis óptimo dentro del software MicroSoft Excel. El valor $ID_{50}$ se verificó visualmente usando datos graficados (línea horizontal desde 50% del valor y, en la intersección de la línea vertical de caída de línea óptima con respecto al eje x (dosis).

La descripción precedente se puede usar para poner en práctica la presente invención y representa el mejor modo contemplado. No se deberá interpretar como que limita el alcance global de la misma.

**Modelo de permeabilidad de VEGF en ojo de conejo**

El ensayo usado se detalla en Jeffrey Edelman, etc en Exp. Eye. Res. 80(2005), Pg 249-258.

**Señal $Ca^{2+}$ estimulada por PDGF in Vitro**

Se usó tecnología FLIPR automatizada (Lector de placas por imagenología fluorométrica) para analizar aumentos en los inhibidores de PDGF inducidos en niveles de calcio intracelular en células endoteliales cargadas con tinte fluorescente. Se sembraron NHDF-Ad (fibroblastos dérmicos humanos normales) (Lonza) en placas de paredes negras de fibronectina de 384 pocillos durante la noche a 37°C/5% de $CO_2$. Las células se cargaron con indicador de calcio Fluo-4 durante 45 minutos a 37°C. Las células se lavaron 4 veces (ELx405-CW, Bio-Tek) para retirar el tinte extracelular. Los compuestos de prueba se reconstituyeron en 100% de DMSO y se agregaron a las células para proporcionar una concentración final de DMSO del 0.1%. Para el análisis, las células se preincubaron con agentes de prueba durante 30 minutos en una sola concentración (10 µM) o en concentraciones que varían entre 0.001 nM y 10 µM seguido de estimulacion de PDGF (10 ng/mL). Los cambios en la fluorescencia a 515 nm se midieron simultáneamente en todos los 384 pocillos usando una cámara CCD fría. Se generaron datos determinando los niveles máximos y mínimos de fluorescencia para muestras no estimuladas, estimuladas y tratadas con fármaco. Los valores de $IC_{50}$ para compuestos de prueba se calcularon a partir del % de inhibición de respuestas estimuladas por PDGF en la ausencia del inhibidor.

Las Tablas II y III presentan los datos biológicos de algunos de los compuestos de la presente invención.

**Tabla II: Datos biológicos de los compuestos de la presente invención con enlace amida**

| Ejemplo Nº | $IC_{50}$ Celular VEGFR2 (nM) | $IC_{50}$ Enzima VEGFR2(nM) | $IC_{50}$ Enzima VEGFR1(nM) | $IC_{50}$ Cellular PDGFβ (nM) |
|---|---|---|---|---|
| 1 | | 28 | | |
| 2 | 8 | 28 | | |

| | | | | |
|---|---|---|---|---|
| 3 | | 28 | | |
| 4 | 6 | 29 | | |
| 5 | | 2956 | | |
| 6 | | 506 | | |
| 7 | 12 | 34 | | |
| 8 | 8 | 28 | | |
| 9 | 30 | 47 | | |

| | | | | |
|---|---|---|---|---|
| 10 | 46 | 41 | | |
| 11 | 28 | 23 | 34 | |
| 12 | | | | |
| 13 | 16 | 27 | | |
| 14 | 15 | 33 | 15 | |
| 15 | 51 | 26 | | 73 |
| 16 | 17 | 21 | | |
| 17 | 22 | 20 | | 61 |
| 18 | 10 | 31 | | |
| 19 | 30 | 37 | | 135 |
| 20 | 83 | 28 | | |

| | | | | |
|---|---|---|---|---|
| 21 | 12 | 24 | | 39 |
| 22 | 18 | 29 | 13 | 105 |
| 23 | 13 | 35 | | |
| 24 | 55 | 24 | | |
| 25 | 30 | 25 | | |
| 26 | 39 | 120 | | |
| 27 | 45 | 66 | | |
| 28 | 38 | 52 | | |
| 29 | 18 | 55 | | |
| 30 | 29 | 37 | | 94 |

| | | | | |
|---|---|---|---|---|
| 31 | 14 | 29 | 20 | |
| 32 | 22 | 46 | | |
| 33 | 18 | 56 | | |
| 34 | 7 | 70 | | |
| 35 | 27 | 29 | | |
| 36 | | 10028 | | |
| 37 | 1005 | 2610 | | |

**Tabla III: Datos biológicos de los compuestos de la presente invención con enlace urea**

| Ejemplo Nº | $IC_{50}$ Celular VEGFR2 (nM) | $IC_{50}$ Enzima VEGFR2(nM) | $IC_{50}$ Enzima VEGFR1(nM) | $IC_{50}$ Cellular PDGFβ (nM) |
|---|---|---|---|---|
| 38 | | 10 | | |
| 39 | | 23 | | |
| 40 | | 11 | | |

| | | | | |
|---|---|---|---|---|
| 41 | | 11 | | |
| 42 | | 60 | | |
| 43 | | 16 | | |
| 44 | | 24 | | |
| 45 | | 17 | | |
| 46 | 2 | 28 | | |
| 47 | 107 | 17 | | |
| 48 | 16 | 12 | | |
| 49 | 145 | 27 | | |

| | | | | |
|---|---|---|---|---|
| 50 | 5 | 32 | | |
| 51 | | 16 | | |
| 52 | | 25 | | |
| 53 | 43 | 28 | | 44 |
| 54 | 130 | 29 | | 191 |
| 55 | 32 | 23 | | 26 |
| 56 | 81 | 20 | | |
| 57 | 102 | 45 | | |
| 58 | 211 | 36 | | |
| 59 | 34 | 29 | | |
| 60 | 27 | 23 | | |
| 61 | 91 | 39 | | |

| | | | | |
|---|---|---|---|---|
| 62 | 122 | 43 | | |
| 63 | 111 | 30 | | |
| 64 | 16 | 39 | | |
| 65 | | 15 | 4 | |
| 66 | | 17 | 3 | |
| 67 | 31 | 31 | | |
| 68 | | 16 | | |
| 69 | | 24 | 5 | |
| 70 | 2 | 20 | | |
| 71 | | 20 | | |
| 72 | 7 | 15 | | |
| 73 | | 11 | | |

| | | | | |
|---|---|---|---|---|
| 74 | 7 | 12 | | |
| 76 | 2 | 14 | 3 | |
| 76 | 3 | 14 | | |
| 77 | 8 | 10 | | |
| 78 | 25 | 15 | 4 | |
| 79 | 13 | 38 | | |
| 80 | 176 | 69 | | |
| 81 | | 19 | | |
| 82 | 17 | 19 | | |
| 83 | | 22 | 5 | |
| 84 | | 13 | | |
| 85 | 6 | 30 | | |

| | | | | |
|---|---|---|---|---|
| 86 | | 27 | | |
| 87 | 5 | 25 | | |
| 88 | 374 | 477 | | |
| 89 | 5 | 23 | | |
| 90 | 8 | 17 | 6 | 21 |
| 91 | 17 | 14 | | 38 |
| 92 | 37 | 9 | | 39 |
| 93 | 6 | 5 | 5 | 14 |
| 94 | 10 | 6 | | 10 |
| 95 | 30 | 32 | | |
| 96 | 3 | 17 | | 69 |
| 97 | 8 | 18 | | |

| | | | | |
|---|---|---|---|---|
| 98 | 62 | 51 | | |
| 99 | 49 | 46 | | |
| 100 | 12 | 13 | | |
| 101 | 4 | 8 | | 82 |
| 102 | 10 | 35 | | 8 |
| 103 | 24 | 20 | | |
| 104 | 23 | 27 | | |
| 105 | 87 | 15 | | |
| 106 | 16 | 21 | | |
| 107 | 13 | 21 | | |
| 108 | 17 | 14 | 13 | 43 |
| 109 | 16 | 23 | | |

| | | | | |
|---|---|---|---|---|
| 110 | 8 | 38 | 10 | 32 |
| 111 | 13 | 71 | | |
| 112 | 13 | 18 | | |
| 113 | 23 | 25 | | |
| 114 | 13 | 22 | | |
| 115 | 2 | 15 | 2 | 44 |
| 116 | 12 | 17 | | |
| 117 | 6 | 18 | | |
| 118 | 22 | 85 | | |
| 119 | 12 | 54 | | |
| 120 | 43 | 98 | | |
| 121 | 37 | 14 | 20 | 102 |

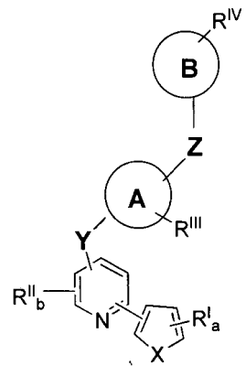
| | | | | |
|---|---|---|---|---|
| 122 | 142 | 130 | | |
| 123 | 13 | 24 | | 85 |
| 124 | 23 | 36 | | |
| 125 | 22 | 31 | | |
| 126 | 16 | 116 | | |
| 127 | 20 | 21 | | 91 |
| 128 | 10 | 53 | | |
| 129 | 12 | 102 | | |
| 130 | 5 | 43 | 16 | 32 |
| 131 | 8 | 31 | | |
| 132 | 22 | 15 | | |
| 133 | 66 | 15 | | |

| | | | | |
|---|---|---|---|---|
| 134 | 4 | 31 | 4 | |
| 135 | 11 | 47 | | |
| 136 | 29 | 22 | | |
| 137 | 14 | 33 | | |
| 138 | | 30 | | |
| 139 | 14 | 30 | | |
| 140 | | 10000 | | |
| 141 | | 2704 | | |
| 142 | 111 | 28 | | |
| 143 | 16 | 12 | | |
| 144 | 28 | 26 | | |
| 145 | 10000 | 10000 | | |
| 146 | 10000 | 7007 | | |
| 147 | 10000 | 3505 | | |
| 148 | 10000 | 1382 | | |

## REIVINDICACIONES

Se reivindica lo siguiente:

1. Un compuesto representado por la Fórmula I:




Fórmula I

donde

X se selecciona del grupo que consiste en $NR^1$, O y $S(O)_n$;

n es 0 o un entero de 1 a 2;

$R^1$ se selecciona independientemente del grupo que consiste en hidrógeno, alquenilo, alcoxialquilo, $CF_3$, alquilo, alquilcarbonilo, alcoxicarbonilo, arilo, heterocicloalquilo, hidroxialquilo y $(NR^2R^3)$alquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

$R^I$ se selecciona del grupo que consiste en hidrógeno, halógeno, alquilo $C_1$ a $C_8$, $S(O)_fR^4$, $(CR^5R^6)_dC(O)OR^4$, $S(O)_f(CR^5R^6)_dC(O)OR^4$, $(CR^5R^6)_dAr$, $NR^4(CR^5R^6)_dAr$, $O(CR^5R^6)_dAr$, $S(O)_f(CR^5R^6)_dAr$, $(CR^5R^6)_dS(O)_fR^4$, $NR^4(CR^5R^6)_dS(O)_fR^4$, $O(CR^5R^6)_d$ $S(O)_fR^4$, $S(O)_f(CR^5R^6)_eS(O)_fR^4$, $(CR^5R^6)_dC(O)N(R^4)_2$, $NR^4(CR^5R^6)_dC(O)N(R^4)_2$, $O(CR^5R^6)_dC(O)N(R^4)_2$, $S(O)_f(CR^5R^6)_eC(O)N(R^4)_2$, $(CR^5R^6)_dOR^4$, $S(O)_f(CR^5R^6)_dOR^4$, $(CR^5$ $R^6)_dOSO_2R^4$, $S(O)_f(CR^5R^6)_eOSO_2R^4$, $(CR^5R^6)_dP(O)(OR^4)_2$, $S(O)_f(CR^5$ $R^6)_eP(O)(OR^4)_2$, $OC(O)(CR^5R^6)_dN(R^4)_2$, $C(O)(CR^5R^6)_dN(R^4)_2$, $C(O)N{=}S(O)R^5R^6$, $NR^2C(O)(CR^5R^6)_dN(R^4)_2$, $(CR^5R^6)_dR^5$, $S(O)_f(CR^5R^6)_dR^5$, $HNC(O)R^4$, $HN\text{-}C(O)OR^4$, $(CR^5R^6)_dN(R^4)_2$, $S(O)_f(CR^5R^6)_dN(R^4)_2$, $OC(O)OR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dOR^4$, y $(CR^5R^6)_dC(O)(CR^5R^6)_dN(R^4)_2$, donde cada $R^4$ se selecciona independientemente del grupo que consiste en hidrógeno, hidroxilo, alquilo $C_1$-$C_8$, arilo, hidroxialquilo $C_1$-$C_8$, alcoxialquilo $C_1$-$C_8$, $(CR^5R^6)_d$ y $N(R^4)_2$ puede formar un anillo heterocíclico de 3-7 miembros que comprende aziridina, azetidina, pirrolidina, 5-fluoropirrolidina, piperidina, 6-fluoropiperidina, N-metilpiperazina, morfolina, 2,6-dimetilmorfolina, tiomorfolina y donde dicho anillo heterocíclico se puede sustituir opcionalmente con hasta tres de $R^5$; donde $R^5$ y $R^6$ se seleccionan independientemente del grupo que consiste en hidrógeno, halo, hidroxilo, alquilo $C_1$-$C_8$, hidroxialquilo $C_1$-$C_8$, alcoxialquilo $C_1$-$C_8$, alcoxicarbonilalquilo, alcoxicarbonilo, hidroxicarbonilo,

hidroxicarbonilalquilo, amida, alquilamida, amidoalquilo, sulfonato y $CR^5R^6$ puede representar un anillo carbocíclico o heterocíclico de entre 5 y 6 carbonos o, de manera alternativa, $(CR^5R^6)_d$ y $(CR^5R^6)_e$ pueden formar un anillo carbocíclico o heterocíclico de 3-7 miembros, donde el anillo se puede sustituir opcionalmente con hasta tres de hidroxilo, halo, alquilo $C_1$-$C_8$, hidroxialquilo $C_1$-$C_8$, alcoxialquilo $C_1$-$C_8$, alcoxicarbonilalquilo, alcoxicarbonilo, hidroxicarbonilo, hidroxicarbonilalquilo, amida, alquilamida, amidoalquilo y sulfonato;

a es 0 o un entero de 1 a 3;

d es 0 o un entero de 1 a 5;

e es un entero de 1 a 4;

f es 0 o un entero de 1 a 2;

$R^{II}$ se selecciona independientemente del grupo que consiste en hidrógeno, alcoxi, alcoxialcoxi, alcoxialquilo, alquilo, ariloxi, ariloxialquilo, halo, haloalcoxi, haloalquilo, hidroxi, hidroxialcoxi, hidroxialquilo, $(NR^2R^3)$alcoxi, $(NR^2R^3)$alquenilo, $(NR^2R^3)$alquilo, $(NR^2R^3)$carbonilalquenilo y $(NR^2R^3)$carbonilalquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa, $R^2$ y $R^3$ y se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

b es 0 o un entero de 1 a 2;

Y se selecciona del grupo que consiste en:

(1') $—(CH_2)g—O—(CH_2)h—$;

(2') $—(CH_2)g—NR^1—(CH_2)h—$;

(3') $—(CH_2)g—S(O)_n—(CH_2)h—$;

(4') $—(CH_2)g—SO_2N\ R^2—(CH_2)h—$;

(5') $—(CH_2)g—NR^2SO_2—(CH_2)h—$;

(6') $—(CH_2)g—\ CO—(CH_2)h—$;

(7') $—(CH_2)g—\ C(O)NR^2—(CH_2)h—$;

(8') $—(CH_2)g—\ NR^2C(O\ )—(CH_2)h—$;

(9') $—(CH_2)g—C\equiv C—(CH_2)h—$;

(10') $—(CH_2)g—\ NR^2C(O)NR^3—(CH_2)h—$;

(11') $—(CH_2)g—(CH_2)h—$;

(12') $—(CH_2)g—CF_2—(CH_2)h—$;

(13') $—(CH_2)g—CCl_2—(CH_2)h—$;

(14') $—(CH_2)g—CHF—(CH_2)h—$;

(15') $—(CH_2)g—CH(OH)—(CH_2)h—$;

(16') $—(CH_2)g—CR^2R^3—(CH_2)h—$;

(17') $—(CH_2)g—C=C—(CH_2)h—$;

y (18') una unión simple;

donde

g es 0 o un entero de 1 a 3;

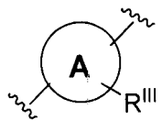
h es 0 o un entero de 1 a 3;

$R^1$ se selecciona independientemente del grupo que consiste en hidrógeno, alquenilo, alcoxialquilo, $CF_3$, alquilo, alquilcarbonilo, alcoxicarbonilo, arilo, heterocicloalquilo, hidroxialquilo y $(NR^2R^3)$alquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

$R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo,

haloalquilsulfonilo y heterociclilsulfonilo, de manera alternativa, $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo cíclico de 5-7 miembros;

El Anillo A se selecciona del grupo que consiste en:



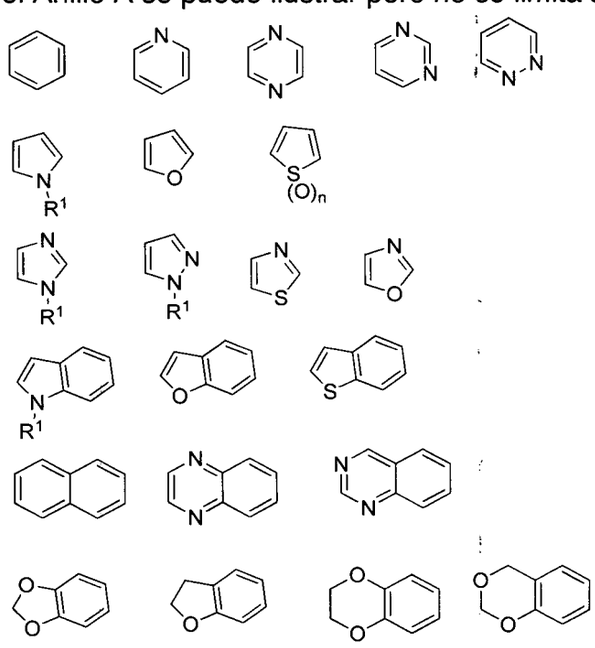

(i) fenilo;

(ii) naftilo;

(iii) Un grupo heteroarilo monocíclico de 5 o 6 miembros que tiene 1-5 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

y (iv) un grupo heteroarilo bicíclico de 8 a 10 miembros que tiene 1-6 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

el Anillo A se puede ilustrar pero no se limita a los siguientes:



donde

$R^1$ se selecciona independientemente del grupo que consiste en hidrógeno, alquenilo, alcoxialquilo, $CF_3$, alquilo, alquilcarbonilo, alcoxicarbonilo, arilo, heterocicloalquilo, hidroxialquilo y $(NR^2R^3)$alquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

$R^{III}$ representa opcionalmente 1-3 sustituyentes que se seleccionan independientemente del grupo que consiste en alquilo $C_1$-$C_5$ lineal o ramificado, haloalquilo $C_1$-$C_5$ lineal o ramificado, alcoxi $C_1$-$C_5$, hidroxi, amino, alquilamino $C_1$-$C_5$, dialquilamino $C_1$-$C_6$, halógeno, ciano y nitro;

Z se selecciona del grupo que consiste en:

(1') $(CH_2)_iN(R^7)C(O)$;

(2') $C(O)N(R^8)(CH_2)_j$;

(3') $(CH_2)_iN(R^7)S(O)_2$;

y (4') $S(O)_2N(R^8)(CH_2)_j$;

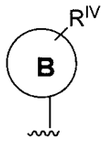
donde:

i es 0 o 1;

j es 0 o 1;

$R^7$ y $R^8$ se seleccionan independientemente del grupo que consiste en hidrógeno y alquilo;

El Anillo B se selecciona del grupo que consiste en:




(i') fenilo;

(ii') naftilo;

(iii') Un grupo heteroarilo monocíclico de 5 o 6 miembros que tiene 1-3 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

y (iv') un grupo heteroarilo bicíclico de 8 a 10 miembros que tiene 1-3 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

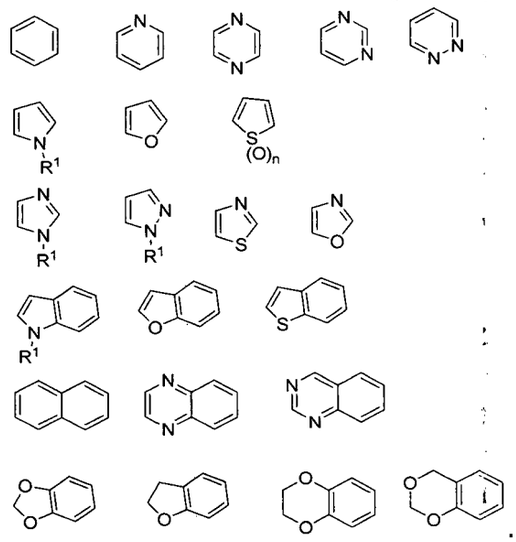
$R^{IV}$ representa opcionalmente 1-3 sustituyentes, se seleccionan independientemente del grupo que consiste en alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, ariloxi, arilalquilo, carboxi, ciano, halo, haloalcoxi, haloalquilo, hidroxi, hidroxialquilo, nitro y —$NR^9R^{10}$; donde $R^9$ y $R^{10}$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, arilo, arilalquilo, cicloalquilo, cicloalquilalquilo, heterociclilo y heterociclilalquilo;

e incluye cualquier sal o profármaco farmacéuticamente aceptable.

2. El compuesto de acuerdo con la reivindicación 1, donde X es NH.

3. El compuesto de acuerdo con la reivindicación 1, donde X es S.

4. El compuesto de acuerdo con la reivindicación 1, donde el Anillo A y el Anillo B se seleccionan independientemente del grupo que consiste en



5. Un compuesto de acuerdo con la reivindicación 1, que se selecciona del grupo que consiste en:

(1') ácido [({5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil} fenoxi)piridin-2-il]-1H-pirrol-3-il}carbonil)amino]acético;

(2') [({5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-il}carbonil)amino]acetato de metilo

(3') ácido ({[5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-il]carbonil}amino)acético;

(4') ({[5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-il]carbonil}amino)acetato de metilo;

(5') ácido 5-[4-({3-[(3-metil-2-furoil)amino]fenil}amino)piridin-2-il]-1H-pirrol-3-carboxílico;

(6') 5-[4-({3-[(3-metil-2-furoil)amino]fenil}amino)piridin-2-il]-1H-pirrol-3-carboxilato de metilo;

(7') 5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-N-hidroxi-1H-pirrol-3-carboxamida;

(8') 4-fluoro-N-(2-fluoro-5-metilfenil)-3-[(2-{4-[(3-hidroxipiperidin-1-il)carbonil]-1H-pirrol-2-il}piridin-4-il)oxi]benzamida;

(9) N-(2,3-dihidroxipropil)-5-[4-(3-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxamida;

(10) N-(2-fluoro-5-metilfenil)-3-[(2-{4-[(3-hidroxipirrolidin-1-il)carbonil]-1H-pirrol-2-il}piridin-4-il)oxi]benzamida;

(11') 5-[4-(3-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-N-hidroxi-1H-pirrol-3-carboxamida;

(12') 5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de metilo;

(13') ácido 5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxílico;

(14') N-etil-5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxamida;

(15') N-(2,3-dihidroxipropil)-5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxamida;

(16') 5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxamida;

(17') N-hidroxi-5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxamida;

(18') N-(3-{[2-(4-{[(3R)-3-hidroxipirrolidin-1-il]carbonil}-1H-pirrol-2-il)piridin-4-il]oxi}fenil)-3-metil-2-furamida;

(19') ácido 5-[4-(3-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxílico;

(20') 5-[4-(3-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de metilo;

(21') 5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxilato de 2,3-dihidroxipropilo;

(22') ácido 5-[4-(3-{[(3-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxílico;

(23') 5-[4-(3-{[(3-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de metilo;

(24') 5-[4-(3-{[(3-metil-2-tienil)carbonil]amino}fenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de 2-hidroxietilo;

(25') 5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxilato de 2-hidroxietilo;

(26') ácido 5-[4-(3-{[(3-metil-2-tienil)carbonil]amino}fenoxi)piridin-2-il]-1H-pirrol-3-carboxílico;

(27') 5-[4-(3-{[(3-metil-2-tienil)carbonil]amino}fenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de metilo;

(28') ácido 5-(4-{4-fluoro-3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxílico;

(29') 5-(4-{4-fluoro-3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxilato de metilo;

(30') N-[dimetil(óxido)-lambda~4~-sulfanilideno]-5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxamida;

(31') N-(3-{[2-(4-{[(3S)-3-hidroxipirrolidin-1-il]carbonil}-1H-pirrol-2-il)piridin-4-il]oxi}fenil)-3-metil-2-furamida;

(32') ácido 5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxílico;

(33') 5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxilato de metilo;

(34') 3-metil-N-(3-{[2-(1H-pirrol-2-il)piridin-4-il]oxi}fenil)-2-furamida;

(35') 4-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-2-carboxilato de metilo;

(36') 2-fluoro-5-metil-N-(4-{[2-(1H-pirrol-2-il)piridin-4-il]oxi}fenil)benzamida;

y (37') 3-metil-N-(4-{[2-(1H-pirrol-2-il)piridin-4-il]oxi}fenil)-2-furamida.

6. El compuesto de acuerdo con la reivindicación 1 siempre que cuando el Anillo B es pirazol, $R^{IV}$ no es fenilo ni fenilo sustituido.

7. Un compuesto de acuerdo con la reivindicación 6, donde Y se selecciona del grupo que consiste en

(1') —$(CH_2)g$—O—$(CH_2)h$—;

(2') —$(CH_2)g$—$NR^1$—$(CH_2)h$—;

(3') —$(CH_2)g$—$S(O)_n$—$(CH_2)h$—;

(4') —$(CH_2)g$—$SO_2N\ R^2$—$(CH_2)h$—;

(5') —$(CH_2)g$—$NR^2SO_2$—$(CH_2)h$—;

(6') —$(CH_2)g$— CO—$(CH_2)h$—;

(7') —$(CH_2)g$— $C(O)NR^2$—$(CH_2)h$—;

(8') —$(CH_2)g$— $NR^2C(O\ )$—$(CH_2)h$—;

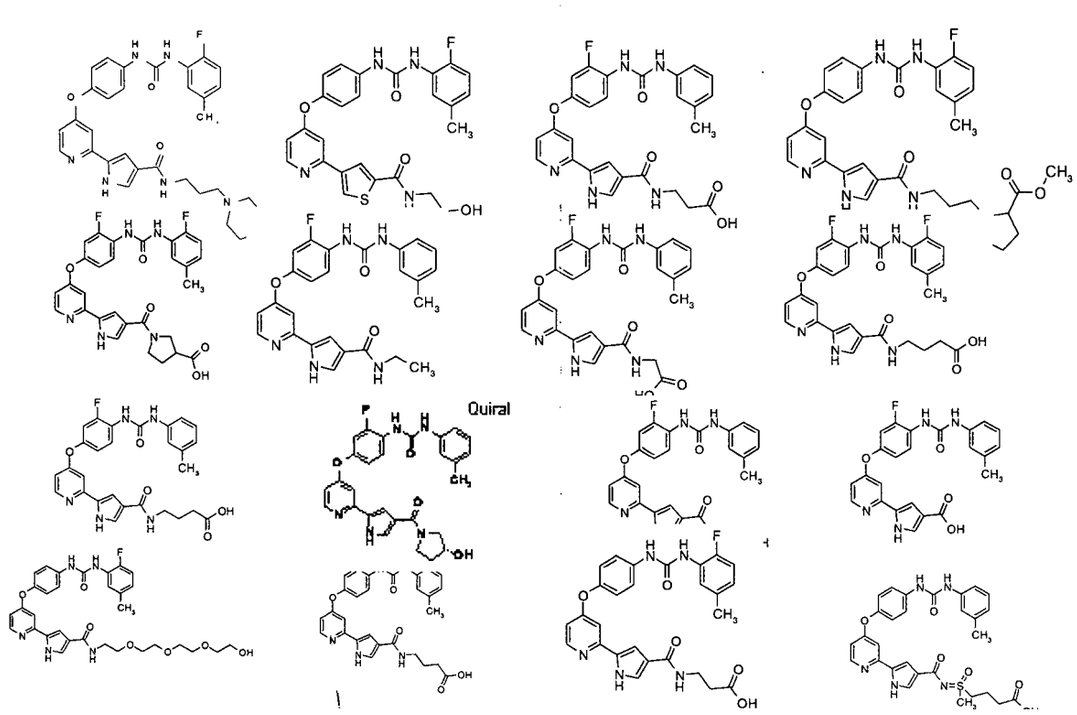
(9') —$(CH_2)g$— $NR^2C(O)NR^3$—$(CH_2)h$—;

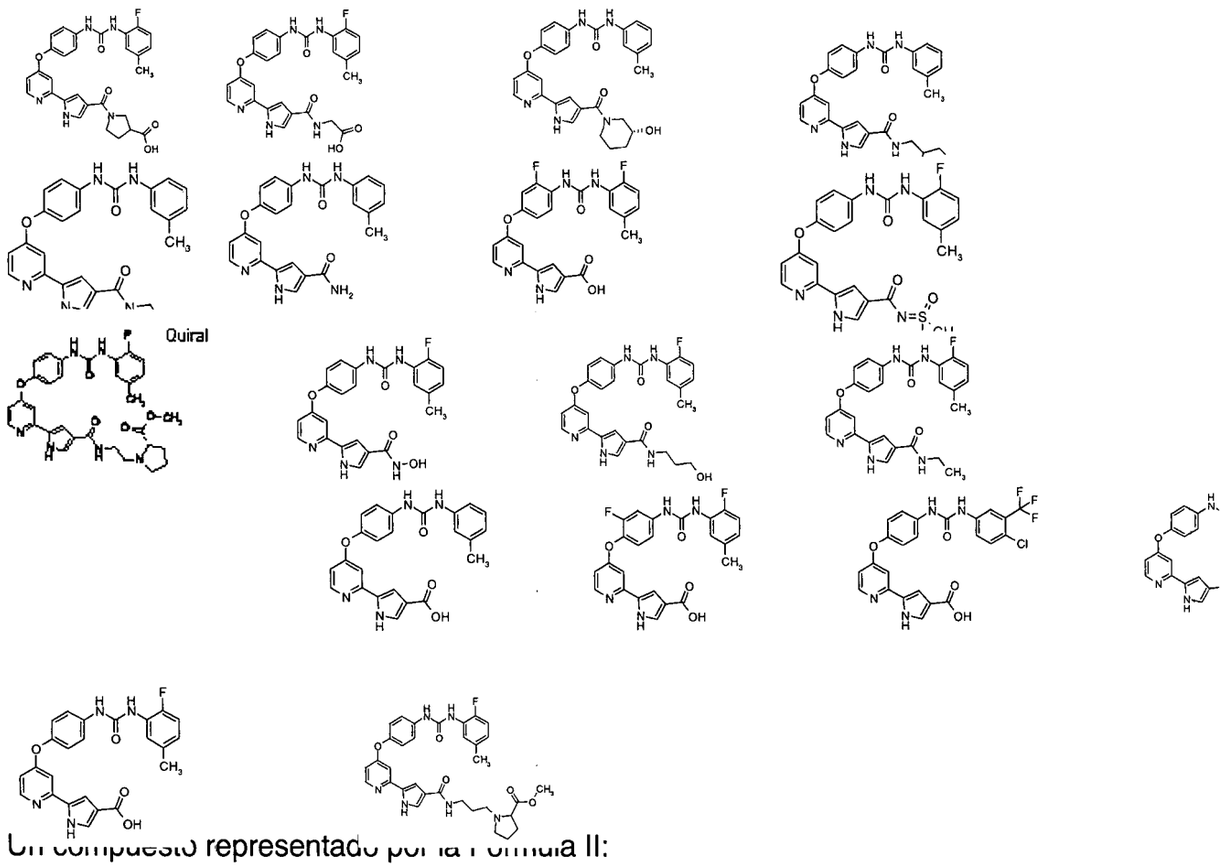
y (10') una unión simple.

8. El compuesto de acuerdo con la reivindicación 1, donde X es S.

9. El compuesto de acuerdo con la reivindicación 1, donde X es NH.

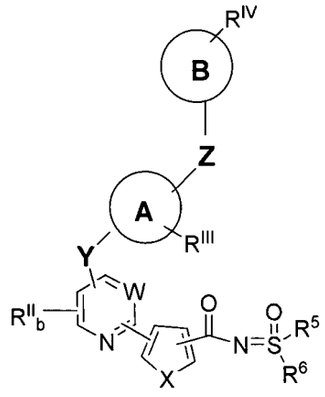
10. Un compuesto de acuerdo con la reivindicación 1, que se selecciona del grupo que consiste en








11. Un compuesto representado por la Fórmula II:




Fórmula II

donde

W es C o N;

X se selecciona del grupo que consiste en $NR^1$, O y $S(O)_n$;

n es 0 o un entero de 1 a 2;

$R^1$ se selecciona independientemente del grupo que consiste en hidrógeno, alquenilo, alcoxialquilo, $CF_3$, alquilo, alquilcarbonilo, alcoxicarbonilo, arilo, heterocicloalquilo, hidroxialquilo y $(NR^2R^3)$alquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

$R^5$ y $R^6$ se seleccionan independientemente del grupo que consiste en hidrógeno, halo, hidroxilo, alquilo $C_1$-$C_8$, hidroxialquilo $C_1$-$C_8$, alcoxialquilo $C_1$-$C_8$, alcoxicarbonilalquilo, alcoxicarbonilo, hidroxicarbonilo, hidroxicarbonilalquilo, amida, alquilamida, amidoalquilo y sulfonato;

$R^{II}$ se selecciona independientemente del grupo que consiste en hidrógeno, alcoxi, alcoxialcoxi, alcoxialquilo, alquilo, ariloxi, ariloxialquilo, halo, haloalcoxi, haloalquilo, hidroxi, hidroxialcoxi, hidroxialquilo, $(NR^2R^3)$alcoxi, $(NR^2R^3)$alquenilo, $(NR^2R^3)$alquilo, $(NR^2R^3)$carbonilalquenilo y $(NR^2R^3)$carbonilalquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

b es 0 o un entero de 1 a 2;

Y se selecciona del grupo que consiste en:

(1') $—(CH_2)g—O—(CH_2)h—$;

(2') $—(CH_2)g—NR^1—(CH_2)h—$;

(3') $—(CH_2)g—S(O)_n—(CH_2)h—$;

(4') $—(CH_2)g—SO_2N\ R^2—(CH_2)h—$;

(5') $—(CH_2)g—NR^2SO_2—(CH_2)h—$;

(6') $—(CH_2)g—\ CO—(CH_2)h—$;

(7') $—(CH_2)g—\ C(O)NR^2—(CH_2)h—$;

(8') $—(CH_2)g—\ NR^2C(O\ )—(CH_2)h—$;

(9') $—(CH_2)g—C\equiv C—(CH_2)h—$;

(10') $—(CH_2)g—\ NR^2C(O)NR^3—(CH_2)h—$;

(11') $—(CH_2)g—(CH_2)h—$;

(12') $—(CH_2)g—CF_2—(CH_2)h—$;

(13') $—(CH_2)g—CCl_2—(CH_2)h—$;

(14') $—(CH_2)g—CHF—(CH_2)h—$;

(15') $—(CH_2)g—CH(OH)—(CH_2)h—$;

(16') $—(CH_2)g—CR^2R^3—(CH_2)h—$;

(17') $—(CH_2)g—C=C—(CH_2)h—$;

y (18') una unión simple;

donde

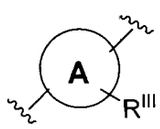
g es 0 o un entero de 1 a 3;

h es 0 o un entero de 1 a 3;

$R^1$ se selecciona independientemente del grupo que consiste en hidrógeno, alquenilo, alcoxialquilo, $CF_3$, alquilo, alquilcarbonilo, alcoxicarbonilo, arilo, heterocicloalquilo, hidroxialquilo y $(NR^2R^3)$alquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

$R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo, de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo cíclico de 5-7 miembros;

El Anillo A se selecciona del grupo que consiste en:



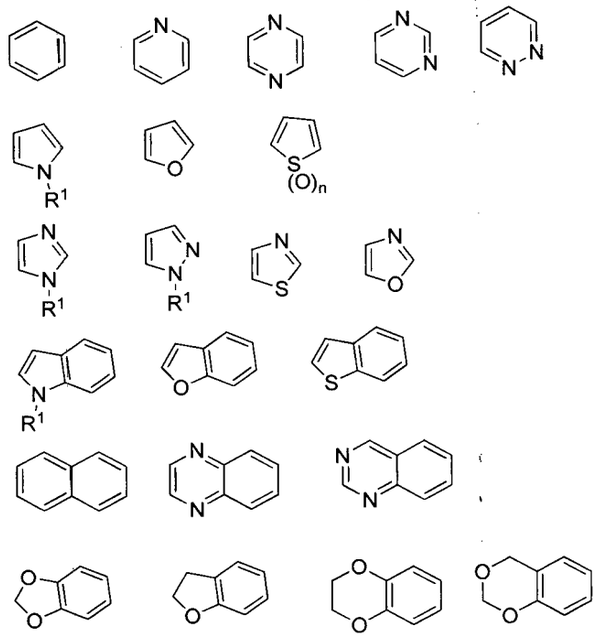

(i) fenilo;

(ii) naftilo;

(iii) un grupo heteroarilo monocíclico de 5 o 6 miembros que tiene 1-5 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

y (iv) un grupo heteroarilo bicíclico de 8 a 10 miembros que tiene 1-6 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

el Anillo A se puede ilustrar pero no se limita a los siguientes:



donde

$R^1$ se selecciona independientemente del grupo que consiste en hidrógeno, alquenilo, alcoxialquilo, $CF_3$, alquilo, alquilcarbonilo, alcoxicarbonilo, arilo, heterocicloalquilo, hidroxialquilo y $(NR^2R^3)$alquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

$R^{III}$ representa opcionalmente 1-3 sustituyentes que se seleccionan independientemente del grupo que consiste en alquilo $C_1$-$C_5$ lineal o ramificado, haloalquilo $C_1$-$C_5$ lineal o ramificado, alcoxi $C_1$-$C_5$, hidroxi, amino, alquilamino $C_1$-$C_5$, dialquilamino $C_1$-C6, halógeno, ciano y nitro;

Z se selecciona del grupo que consiste en:

(1') $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$;

(2') $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$;

(3') $(CH_2)_iN(R^7)C(O)$;

(4') $C(O)N(R^8)(CH_2)_j$;

(5') $(CH_2)_iN(R^7)S(O)_2$;

y (6') $S(O)_2N(R^8)(CH_2)j$;

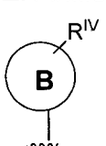
donde

i es 0 o 1;

j es 0 o 1;

$R^7$ y $R^8$ se seleccionan independientemente del grupo que consiste en hidrógeno y alquilo.

El Anillo B se selecciona del grupo que consiste en:



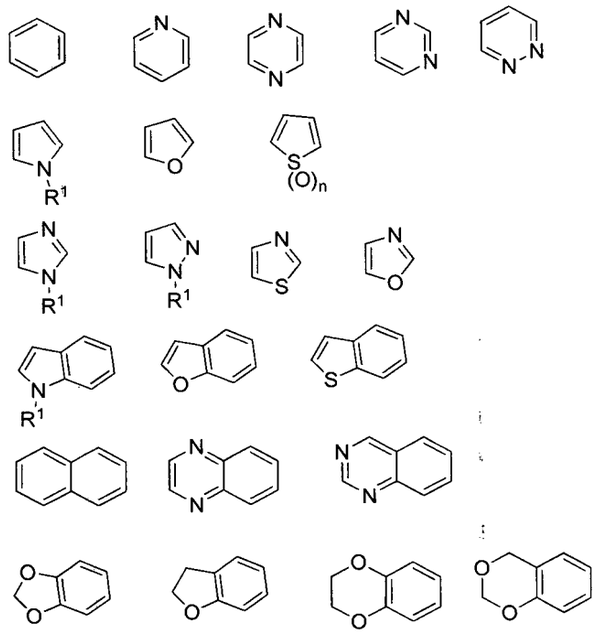

(i') fenilo;

(ii') naftilo;

(iii') un grupo heteroarilo monocíclico de 5 o 6 miembros que tiene 1-3 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

y (iv') un grupo heteroarilo bicíclico de 8 a 10 miembros que tiene 1-3 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

el Anillo B se puede ilustrar pero no se limita a los siguientes:



donde

$R^1$ se selecciona independientemente del grupo que consiste en hidrógeno, alquenilo, alcoxialquilo, $CF_3$, alquilo, alquilcarbonilo, alcoxicarbonilo, arilo, heterocicloalquilo, hidroxialquilo y $(NR^2R^3)$alquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

$R^{IV}$ representa opcionalmente 1-3 sustituyentes, se seleccionan independientemente del grupo que consiste en alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, ariloxi, arilalquilo, carboxi, ciano, halo, haloalcoxi, haloalquilo, hidroxi, hidroxialquilo, nitro y $—NR^9R^{10}$; donde $R^9$ y $R^{10}$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, arilo, arilalquilo, cicloalquilo, cicloalquilalquilo, heterociclilo y heterociclilalquilo;

e incluye cualquier sal o profármaco farmacéuticamente aceptable.

12. El compuesto de acuerdo con la reivindicación 12, donde Z se selecciona del grupo que consiste en $(CH_2)_iN(R^7)C(O)$, $C(O)N(R^8)(CH_2)_j$, $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$ y $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$.

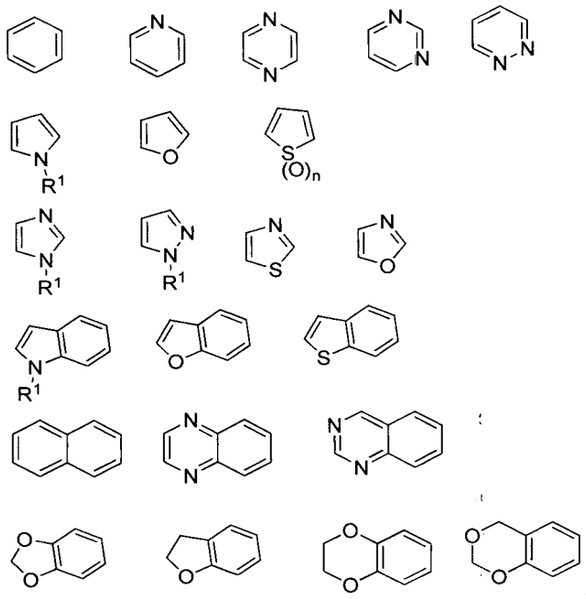
13. El compuesto de acuerdo con la reivindicación 12, donde Y se selecciona de grupo que consiste en

(1') $—(CH_2)g—O—(CH_2)h—$;
(2') $—(CH_2)g—NR^1—(CH_2)h—$;
(3') $—(CH_2)g—S(O)_n—(CH_2)h—$;
(4') $—(CH_2)g—SO_2N\ R^2—(CH_2)h—$;
(5') $—(CH_2)g—NR^2SO_2—(CH_2)h—$;
(6') $—(CH_2)g—\ CO—(CH_2)h—$;
(7') $—(CH_2)g—\ C(O)NR^2—(CH_2)h—$;

(8') —$(CH_2)g$— $NR^2C(O)$—$(CH_2)h$—;
(9') —$(CH_2)g$—C≡C—$(CH_2)h$—;
(10') —$(CH_2)g$— $NR^2C(O)NR^3$—$(CH_2)h$—;
y (11') una unión simple.

14. El compuesto de la reivindicación 12, donde W es C.

15. El compuesto de acuerdo con la reivindicación 12, donde el Anillo A y el Anillo B se seleccionan independientemente del grupo que consiste en



16. El compuesto de la reivindicación 1 para su uso como inhibidor de la tirosina cinasa.

17. El compuesto de acuerdo con la reivindicación 1 que se usa para el tratamiento de una de las enfermedades o afecciones que se seleccionan del grupo que consiste en cáncer colorrectal, cáncer de pulmón, cáncer hematológico, cáncer renal, cáncer de hígado, cáncer de mama, retinopatía diabética, degeneración macular, degeneración macular relacionada con la edad, retinopatía del prematuro, angiogénesis ocular, edema de retina, isquemia de retina, edema macular diabético, edema macular cistoide, oclusión venosa de la retina, olcusión de rama venosa, neovascularización preretinal, neovascularización coroidal inducida por láser, neovascularización asociada a queratoplastia, glaucoma y tumores oculares, artritis, restenosis, cirrosis hepática, ateroesclerosis, psoriasis, diabetes mellitus, cicatrización, inflamación, enfermedades neurodegenerativas y trastornos inmunes en el ser humano.

18. Una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de los compuestos de la reivindicación 1, junto con un portador farmacéuticamente aceptable para los mismos.

19. La composición farmacéutica de la reivindicación 18, donde la composición comprende comprimidos, cápsulas, inyecciones intravenosas, inyecciones intramusculares, inyecciones locales, geles, ungüentos y cremas tópicas, gotas para los ojos, ungüentos para los ojos, aerosoles para los ojos, suspensiones oftálmicas, emulsiones oftálmicas, inyecciones intravítrea, inyecciones sub-tenon, implante bioerosionable oftálmico e insertos y medicamentos de liberación mantenida no bioerosionables oftálmicos.

## RESUMEN DE LA INVENCIÓN

La presente invención se refiere a compuestos novedosos de la Fórmula (I). Los compuestos de la presente invención son moduladores potentes de la tirosina cinasa y son adecuados para el tratamiento y la prevención de enfermedades y afecciones relacionadas con actividades anormales de receptores de tirosina cinasa.

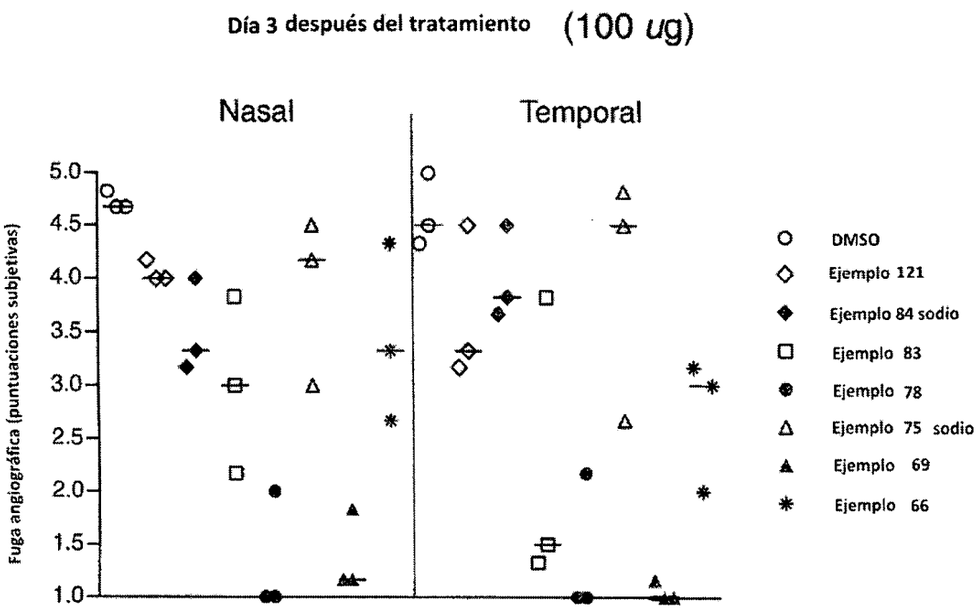

Día 3 después del tratamiento (100 ug)
Nasal
Temporal
Fuga angiográfica (puntuaciones subjetivas)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
DMSO
Ejemplo 121
Ejemplo 84 sodio
Ejemplo 83
Ejemplo 78
Ejemplo 75 sodio
Ejemplo 69
Ejemplo 66

**Figura 3**

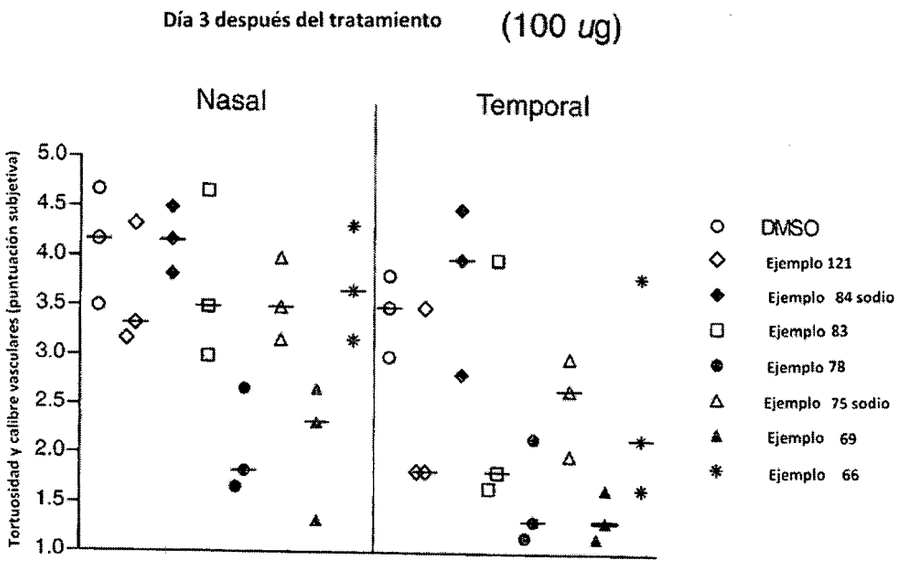

Día 3 después del tratamiento
(100 ug)
Nasal
Temporal
Tortuosidad y calibre vasculares (puntuación subjetiva)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
DMSO
Ejemplo 121
Ejemplo 84 sodio
Ejemplo 83
Ejemplo 78
Ejemplo 75 sodio
Ejemplo 69
Ejemplo 66

**Figura 4**

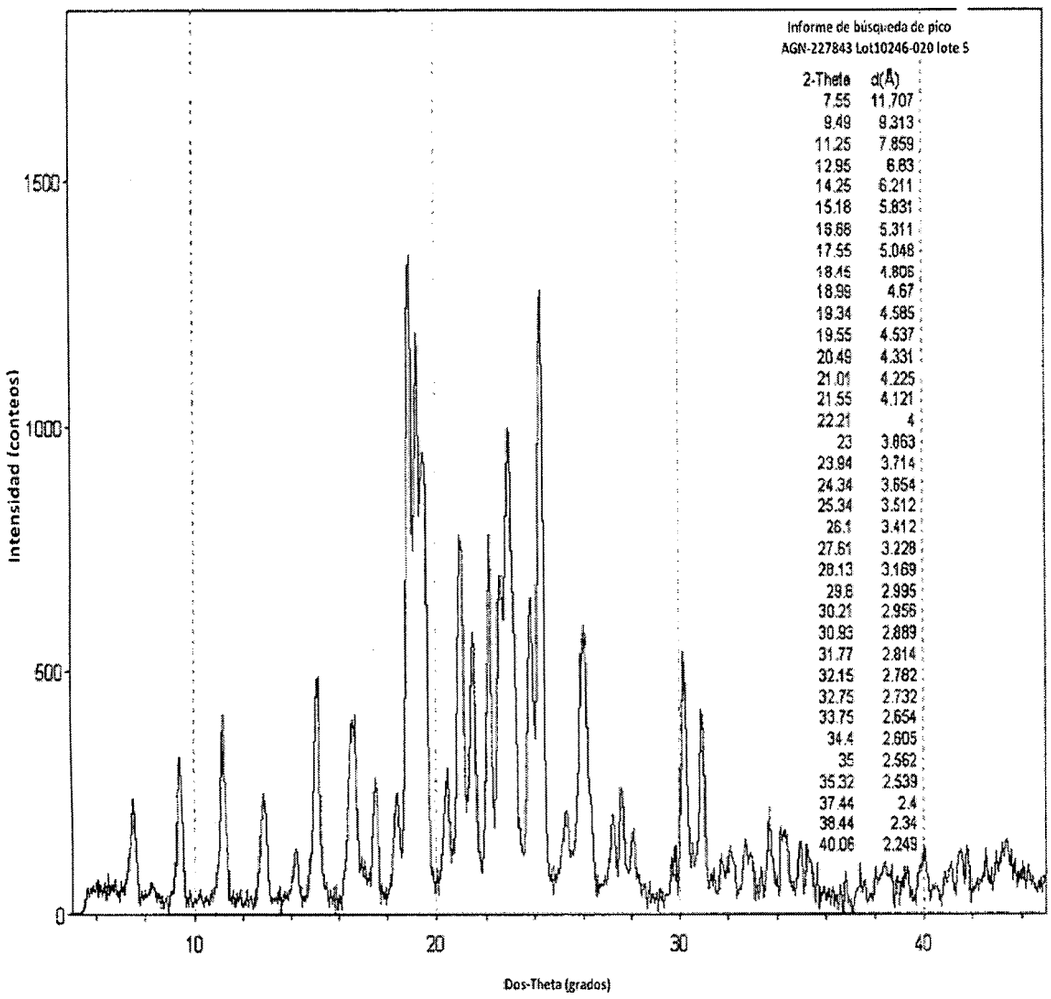

Informe de búsqueda de pico
AGN-227843 Lot10246-020 lote 5
2-Theta d(Å)
7.55 11.707
9.49 9.313
11.25 7.859
12.95 6.83
14.25 6.211
15.18 5.831
16.68 5.311
17.55 5.048
18.46 4.806
18.98 4.67
19.34 4.585
19.55 4.537
20.49 4.331
21.01 4.225
21.55 4.121
22.21 4
23 3.863
23.94 3.714
24.34 3.654
25.34 3.512
26.1 3.412
27.61 3.228
28.13 3.169
29.8 2.995
30.21 2.956
30.93 2.889
31.77 2.814
32.15 2.782
32.75 2.732
33.75 2.654
34.4 2.605
35 2.562
35.32 2.539
37.44 2.4
38.44 2.34
40.06 2.249
Intensidad (conteos)
1500
1000
500
0
10
20
30
40
Dos-Theta (grados)

**Figura 1**

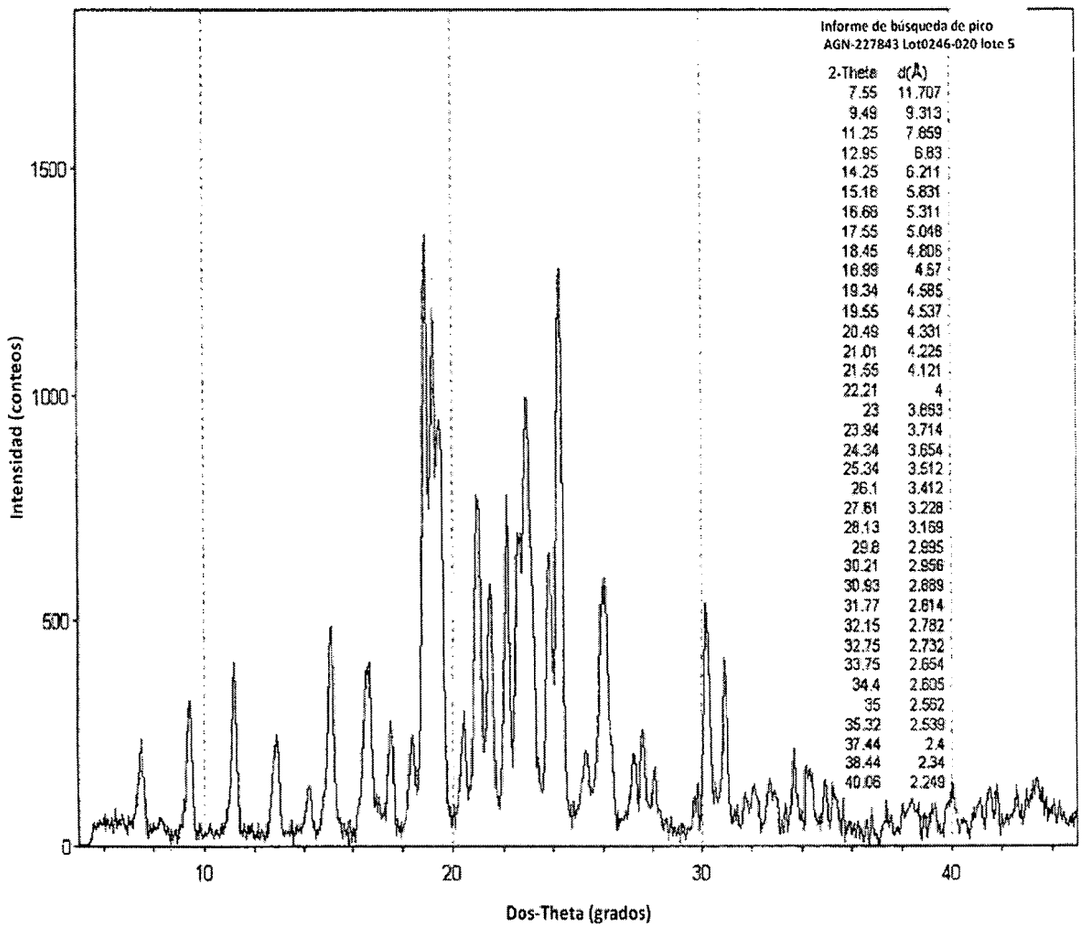
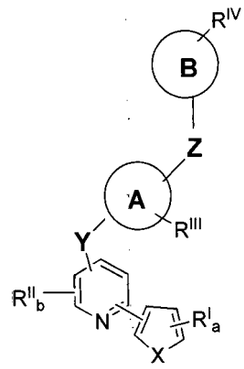

Informe de búsqueda de pico
AGN-227843 Lot0246-020 lote 5
2-Theta d(Å)
7.55 11.707
9.49 9.313
11.25 7.859
12.95 6.83
14.25 6.211
15.18 5.831
16.68 5.311
17.55 5.048
18.45 4.806
18.99 4.67
19.34 4.585
19.55 4.537
20.49 4.331
21.01 4.226
21.55 4.121
22.21 4
23 3.863
23.94 3.714
24.34 3.654
25.34 3.512
26.1 3.412
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28.13 3.169
29.8 2.995
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30.93 2.889
31.77 2.814
32.15 2.782
32.75 2.732
33.75 2.654
34.4 2.605
35 2.562
35.32 2.539
37.44 2.4
38.44 2.34
40.06 2.249
Intensidad (conteos)
0
500
1000
1500
10
20
30
40
Dos-Theta (grados)

**Figura 2**

## REIVINDICACIONES

Se reivindica lo siguiente:

1. Un compuesto representado por la Fórmula I:




Fórmula I

donde

X se selecciona del grupo que consiste en $NR^1$, O y $S(O)_n$;

n es 0 o un entero de 1 a 2;

$R^1$ se selecciona independientemente del grupo que consiste en hidrógeno, alquenilo, alcoxialquilo, $CF_3$, alquilo, alquilcarbonilo, alcoxicarbonilo, arilo, heterocicloalquilo, hidroxialquilo y $(NR^2R^3)$alquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

$R^I$ se selecciona del grupo que consiste en hidrógeno, halógeno, alquilo $C_1$ a $C_8$, $S(O)_fR^4$, $(CR^5R^6)_dC(O)OR^4$, $S(O)_f(CR^5R^6)_dC(O)OR^4$, $(CR^5R^6)_dAr$, $NR^4(CR^5R^6)_dAr$, $O(CR^5R^6)_dAr$, $S(O)_f(CR^5R^6)_dAr$, $(CR^5R^6)_dS(O)_fR^4$, $NR^4(CR^5R^6)_dS(O)_fR^4$, $O(CR^5R^6)_d$ $S(O)_fR^4$, $S(O)_f(CR^5R^6)_eS(O)_fR^4$, $(CR^5R^6)_dC(O)N(R^4)_2$, $NR^4(CR^5R^6)_dC(O)N(R^4)_2$, $O(CR^5R^6)_dC(O)N(R^4)_2$, $S(O)_f(CR^5R^6)_eC(O)N(R^4)_2$, $(CR^5R^6)_dOR^4$, $S(O)_f(CR^5R^6)_dOR^4$, $(CR^5\ R^6)_dOSO_2R^4$, $S(O)_f(CR^5R^6)_eOSO_2R^4$, $(CR^5R^6)_dP(O)(OR^4)_2$, $S(O)_f(CR^5\ R^6)_eP(O)(OR^4)_2$, $OC(O)(CR^5R^6)_dN(R^4)_2$, $C(O)(CR^5R^6)_dN(R^4)_2$,

$C(O)N=S(O)R^5R^6$, $NR^2C(O)(CR^5R^6)_dN(R^4)_2$, $(CR^5R^6)_dR^5$, $S(O)_f(CR^5R^6)_dR^5$, $HNC(O)R^4$, $HN\text{-}C(O)OR^4$, $(CR^5R^6)_dN(R^4)_2$, $S(O)_f(CR^5R^6)_dN(R^4)_2$, $OC(O)OR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dOR^4$, y $(CR^5R^6)_dC(O)(CR^5R^6)_dN(R^4)_2$, donde cada $R^4$ se selecciona independientemente del grupo que consiste en hidrógeno, hidroxilo, alquilo $C_1$-$C_8$, arilo, hidroxialquilo $C_1$-$C_8$, alcoxialquilo $C_1$-$C_8$, $(CR^5R^6)_d$ y $N(R^4)_2$ puede formar un anillo heterocíclico de 3-7 miembros que comprende aziridina, azetidina, pirrolidina, 5-fluoropirrolidina, piperidina, 6-fluoropiperidina, N-metilpiperazina, morfolina, 2,6-dimetilmorfolina, tiomorfolina y donde dicho anillo heterocíclico se puede sustituir opcionalmente con hasta tres de $R^5$; donde $R^5$ y $R^6$ se seleccionan independientemente del grupo que consiste en hidrógeno, halo, hidroxilo, alquilo $C_1$-$C_8$, hidroxialquilo $C_1$-$C_8$, alcoxialquilo $C_1$-$C_8$, alcoxicarbonilalquilo, alcoxicarbonilo, hidroxicarbonilo, hidroxicarbonilalquilo, amida, alquilamida, amidoalquilo, sulfonato y $CR^5R^6$ puede representar un anillo carbocíclico o heterocíclico de entre 5 y 6 carbonos o, de manera alternativa, $(CR^5R^6)_d$ y $(CR^5R^6)_e$ pueden formar un anillo carbocíclico o heterocíclico de 3-7 miembros, donde el anillo se puede sustituir opcionalmente con hasta tres de hidroxilo, halo, alquilo $C_1$-$C_8$, hidroxialquilo $C_1$-$C_8$, alcoxialquilo $C_1$-$C_8$, alcoxicarbonilalquilo, alcoxicarbonilo, hidroxicarbonilo, hidroxicarbonilalquilo, amida, alquilamida, amidoalquilo y sulfonato;

a es 0 o un entero de 1 a 3;

d es 0 o un entero de 1 a 5;

e es un entero de 1 a 4,

f es 0 o un entero de 1 a 2;

$R^{II}$ se selecciona independientemente del grupo que consiste en el grupo que consiste en hidrógeno, alcoxi, alcoxialcoxi, alcoxialquilo, alquilo, ariloxi, ariloxialquilo, halo, haloalcoxi, haloalquilo, hidroxi, hidroxialcoxi, hidroxialquilo, alcoxi ($NR^2R^3$), alquenilo ($NR^2R^3$), alquilo ($NR^2R^3$), carbonilalquenilo ($NR^2R^3$) y carbonilalquilo ($NR^2R^3$), donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alquilsulfonilo,

arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

b es 0 o un entero de 1 a 2;

Y se selecciona del grupo que consiste en:

(1') —$(CH_2)g$—O—$(CH_2)h$—;

(2') —$(CH_2)g$—$NR^1$—$(CH_2)h$—;

(3') —$(CH_2)g$—$S(O)_n$—$(CH_2)h$—;

(4') —$(CH_2)g$—$SO_2N\ R^2$—$(CH_2)h$—;

(5') —$(CH_2)g$—$NR^2SO_2$—$(CH_2)h$—;

(6') —$(CH_2)g$— CO—$(CH_2)h$—;

(7') —$(CH_2)g$— $C(O)NR^2$—$(CH_2)h$—;

(8') —$(CH_2)g$— $NR^2C(O\ )$—$(CH_2)h$—;

(9') —$(CH_2)g$—C≡C—$(CH_2)h$—;

(10') —$(CH_2)g$— $NR^2C(O)NR^3$—$(CH_2)h$—;

(11') —$(CH_2)g$—$(CH_2)h$—;

(12') —$(CH_2)g$—$CF_2$—$(CH_2)h$—;

(13') —$(CH_2)g$—$CCl_2$—$(CH_2)h$—;

(14') —$(CH_2)g$—CHF—$(CH_2)h$—;

(15') —$(CH_2)g$—CH(OH)—$(CH_2)h$—;

(16') —$(CH_2)g$—$CR^2R^3$—$(CH_2)h$—;

(17') —$(CH_2)g$—C=C—$(CH_2)h$—;

y (18') una unión simple;

donde

g es 0 o un entero de 1 a 3;

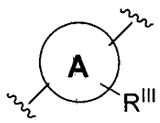
h es 0 o un entero de 1 a 3;

$R^1$ se selecciona independientemente del grupo que consiste en hidrógeno, alquenilo, alcoxialquilo, $CF_3$, alquilo, alquilcarbonilo, alcoxicarbonilo, arilo, heterocicloalquilo, hidroxialquilo y $(NR^2R^3)$alquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y

heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

$R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo, de manera alternativa, $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo cíclico de 5-7 miembros;

El anillo A se selecciona del grupo que consiste en:




(i) fenilo;

(ii) naftilo;

(iii) Un grupo heteroarilo monocíclico de 5 o 6 miembros que tiene 1-5 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

y (iv) un grupo heteroarilo bicíclico de 8 a 10 miembros que tiene 1-6 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

$R^{III}$ representa opcionalmente 1-3 sustituyentes que se seleccionan independientemente del grupo que consiste en alquilo $C_1$-$C_5$ lineal o ramificado, haloalquilo $C_1$-$C_5$ lineal o ramificado, alcoxi $C_1$-$C_5$, hidroxi, amino, alquilamino $C_1$-$C_5$, dialquilamino $C_1$-$C_6$, halógeno, ciano y nitro;

Z se selecciona del grupo que consiste en:

(1') $(CH_2)_iN(R^7)C(O)$;

(2') $C(O)N(R^8)(CH_2)_j$;

(3') $(CH_2)_iN(R^7)S(O)_2$;

y (4') $S(O)_2N(R^8)(CH_2)_j$;

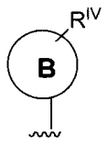
donde:

i es 0 o 1;

j es 0 o 1;

$R^7$ y $R^8$ se seleccionan independientemente del grupo que consiste en hidrógeno y alquilo;

El anillo B se selecciona del grupo que consiste en:




(i') fenilo;

(ii') naftilo;

(iii') Un grupo heteroarilo monocíclico de 5 o 6 miembros que tiene 1-3 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

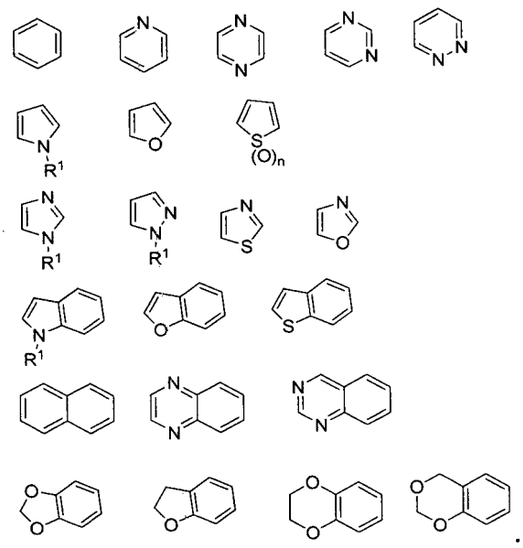
y (iv') un grupo heteroarilo bicíclico de 8 a 10 miembros que tiene 1-3 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

$R^{IV}$ representa opcionalmente 1-3 sustituyentes, se seleccionan independientemente del grupo que consiste en alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, ariloxi, arilalquilo, carboxi, ciano, halo, haloalcoxi, haloalquilo, hidroxi, hidroxialquilo, nitro y —$NR^9R^{10}$; donde $R^9$ y $R^{10}$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, arilo, arilalquilo, cicloalquilo, cicloalquilalquilo, heterociclilo y heterociclilalquilo;

e incluye cualquier sal o profármaco farmacéuticamente aceptable.

2. El compuesto de acuerdo con la reivindicación 1, donde X es NH o S.

3. El compuesto de acuerdo con la reivindicación 1, donde el Anillo A y el Anillo B se seleccionan independientemente del grupo que consiste en



4. Un compuesto de acuerdo con la reivindicación 1, que se selecciona del grupo que consiste en:

(1') ácido [({5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil} fenoxi)piridin-2-il]-1H-pirrol-3-il}carbonil)amino]acético;

(2') [({5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-il}carbonil)amino]acetato de metilo

(3') ácido ({[5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-il]carbonil}amino)acético;

(4') ({[5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-il]carbonil}amino)acetato de metilo;

(5') ácido 5-[4-({3-[(3-metil-2-furoil)amino]fenil}amino)piridin-2-il]-1H-pirrol-3-carboxílico;

(6') 5-[4-({3-[(3-metil-2-furoil)amino]fenil}amino)piridin-2-il]-1H-pirrol-3-carboxilato de metilo;

(7') 5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-N-hidroxi-1H-pirrol-3-carboxamida;

(8') 4-fluoro-N-(2-fluoro-5-metilfenil)-3-[(2-{4-[(3-hidroxipiperidin-1-il)carbonil]-1H-pirrol-2-il}piridin-4-il)oxi]benzamida;

(9) N-(2,3-dihidroxipropil)-5-[4-(3-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi) piridin-2-il]-1H-pirrol-3-carboxamida;

(10) N-(2-fluoro-5-metilfenil)-3-[(2-{4-[(3-hidroxipirrolidin-1-il)carbonil]-1H-pirrol-2-il}piridin-4-il)oxi]benzamida;

(11') 5-[4-(3-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-N-hidroxi-1H-pirrol-3-carboxamida;

(12') 5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de metilo;

(13') ácido 5-[4-(2-fluoro-5-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxílico;

(14') N-etil-5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxamida;

(15') N-(2,3-dihidroxipropil)-5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxamida;

(16') 5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxamida;

(17') N-hidroxi-5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxamida;

(18') N-(3-{[2-(4-{[(3R)-3-hidroxipirrolidin-1-il]carbonil}-1H-pirrol-2-il)piridin-4-il]oxi}fenil)-3-metil-2-furamida;

(19') ácido 5-[4-(3-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxílico;

(20') 5-[4-(3-{[(2-fluoro-5-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de metilo;

(21') 5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxilato de 2,3-dihidroxipropilo;

(22') ácido 5-[4-(3-{[(3-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxílico;

(23') 5-[4-(3-{[(3-metilfenil)amino]carbonil}fenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de metilo;

(24') 5-[4-(3-{[(3-metil-2-tienil)carbonil]amino}fenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de 2-hidroxietilo;

(25') 5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxilato de 2-hidroxietilo;

(26') ácido 5-[4-(3-{[(3-metil-2-tienil)carbonil]amino}fenoxi)piridin-2-il]-1H-pirrol-3-carboxílico;

(27') 5-[4-(3-{[(3-metil-2-tienil)carbonil]amino}fenoxi)piridin-2-il]-1H-pirrol-3-carboxilato de metilo;

(28') ácido 5-(4-{4-fluoro-3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxílico;

(29') 5-(4-{4-fluoro-3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxilato de metilo;

(30') N-[dimetil(óxido)-lambda~4~-sulfanilideno]-5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxamida;

(31') N-(3-{[2-(4-{[(3S)-3-hidroxipirrolidin-1-il]carbonil}-1H-pirrol-2-il)piridin-4-il]oxi}fenil)-3-metil-2-furamida;

(32') ácido 5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxílico;

(33') 5-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-3-carboxilato de metilo;

(34') 3-metil-N-(3-{[2-(1H-pirrol-2-il)piridin-4-il]oxi}fenil)-2-furamida;

(35') 4-(4-{3-[(3-metil-2-furoil)amino]fenoxi}piridin-2-il)-1H-pirrol-2-carboxilato de metilo;

(36') 2-fluoro-5-metil-N-(4-{[2-(1H-pirrol-2-il)piridin-4-il]oxi}fenil)benzamida;

y (37') 3-metil-N-(4-{[2-(1H-pirrol-2-il)piridin-4-il]oxi}fenil)-2-furamida.

5. El compuesto de acuerdo con la reivindicación 1 siempre que cuando el Anillo B es pirazol, $R^{IV}$ no es fenilo ni fenilo sustituido.

6. Un compuesto de acuerdo con la reivindicación 6, donde Y se selecciona del grupo que consiste en

(1') —$(CH_2)g$—O—$(CH_2)h$—;

(2') —$(CH_2)g$—$NR^1$—$(CH_2)h$—;

(3') —$(CH_2)g$—$S(O)_n$—$(CH_2)h$—;

(4') —$(CH_2)g$—$SO_2N\ R^2$—$(CH_2)h$—;

(5') —$(CH_2)g$—$NR^2SO_2$—$(CH_2)h$—;

(6') —$(CH_2)g$— CO—$(CH_2)h$—;

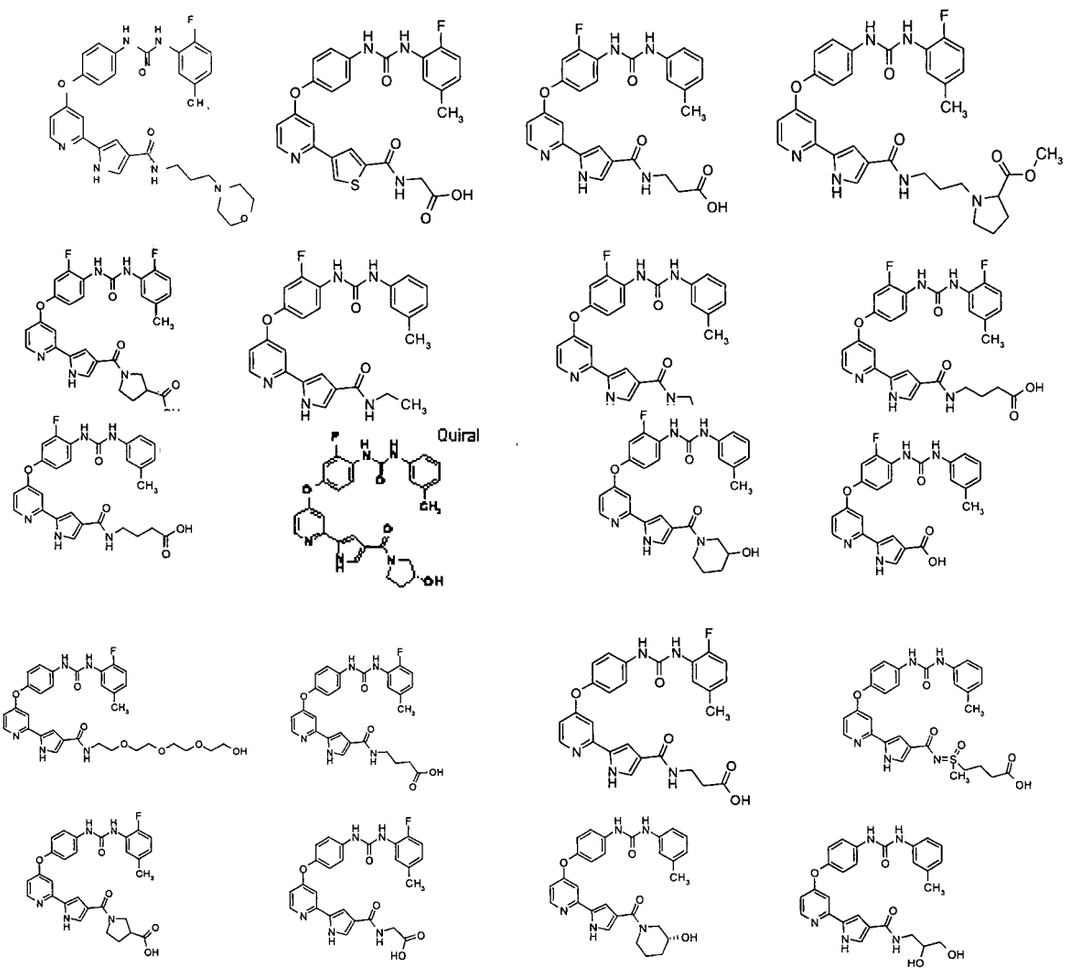
(7') —$(CH_2)g$— $C(O)NR^2$—$(CH_2)h$—;

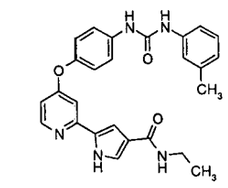
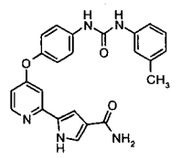
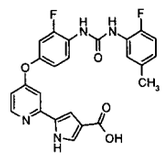
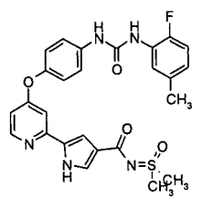
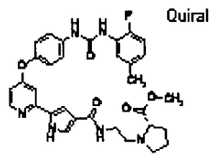
(8') —$(CH_2)g$— $NR^2C(O)$—$(CH_2)h$—;

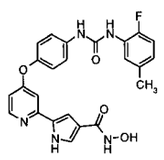
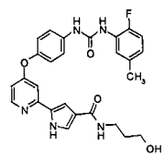
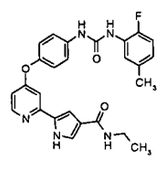
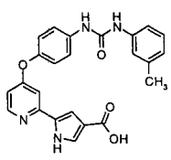
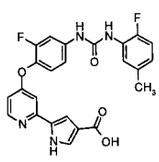
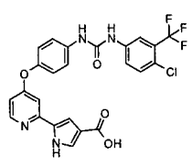
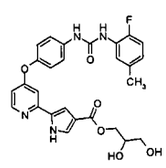
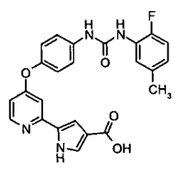
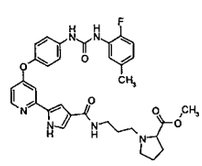
(9') —$(CH_2)g$— $NR^2C(O)NR^3$—$(CH_2)h$—;

y (10') una unión simple.

7. Un compuesto de acuerdo con la reivindicación 1, que se selecciona del grupo que consiste en

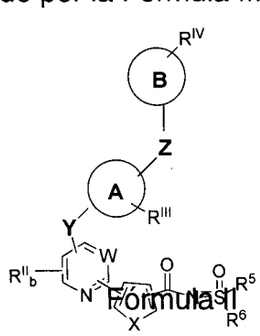


20 o una sal farmacéuticamente aceptable del mismo.

8. Un compuesto representado por la Fórmula II:




Fórmula II

donde

W es C o N;

X se selecciona del grupo que consiste en $NR^1$, O y $S(O)_n$;

n es 0 o un entero de 1 a 2;

$R^1$ se selecciona independientemente del grupo que consiste en hidrógeno, alquenilo, alcoxialquilo, $CF_3$, alquilo, alquilcarbonilo, alcoxicarbonilo, arilo, heterocicloalquilo, hidroxialquilo y $(NR^2R^3)$alquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

$R^5$ y $R^6$ se seleccionan independientemente del grupo que consiste en hidrógeno, halo, hidroxilo, alquilo $C_1$-$C_8$, hidroxialquilo $C_1$-$C_8$, alcoxialquilo $C_1$-$C_8$, alcoxicarbonilalquilo, alcoxicarbonilo, hidroxicarbonilo, hidroxicarbonilalquilo, amida, alquilamida, amidoalquilo y sulfonato;

$R^{II}$ se selecciona independientemente del grupo que consiste en hidrógeno, alcoxi, alcoxialcoxi, alcoxialquilo, alquilo, ariloxi, ariloxialquilo, halo, haloalcoxi, haloalquilo, hidroxi, hidroxialcoxi, hidroxialquilo, $(NR^2R^3)$alcoxi, $(NR^2R^3)$alquenilo, $(NR^2R^3)$alquilo, $(NR^2R^3)$carbonilalquenilo y $(NR^2R^3)$carbonilalquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

b es 0 o un entero de 1 a 2;

Y se selecciona del grupo que consiste en:

(1') $—(CH_2)g—O—(CH_2)h—$;

(2') $—(CH_2)g—NR^1—(CH_2)h—$;

(3') $—(CH_2)g—S(O)_n—(CH_2)h—$;

(4') $—(CH_2)g—SO_2N\ R^2—(CH_2)h—$;

(5') $—(CH_2)g—NR^2SO_2—(CH_2)h—$;

(6') $—(CH_2)g—\ CO—(CH_2)h—$;

(7') $—(CH_2)g—\ C(O)NR^2—(CH_2)h—$;

(8') —$(CH_2)g$— $NR^2C(O)$—$(CH_2)h$—;

(9') —$(CH_2)g$—C≡C—$(CH_2)h$—;

(10') —$(CH_2)g$— $NR^2C(O)NR^3$—$(CH_2)h$—;

(11') —$(CH_2)g$—$(CH_2)h$—;

(12') —$(CH_2)g$—$CF_2$—$(CH_2)h$—;

(13') —$(CH_2)g$—$CCl_2$—$(CH_2)h$—;

(14') —$(CH_2)g$—CHF—$(CH_2)h$—;

(15') —$(CH_2)g$—CH(OH)—$(CH_2)h$—;

(16') —$(CH_2)g$—$CR^2R^3$—$(CH_2)h$—;

(17') —$(CH_2)g$—C=C—$(CH_2)h$—;

y (18') una unión simple;

donde

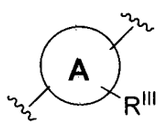
g es 0 o un entero de 1 a 3;

h es 0 o un entero de 1 a 3;

$R^1$ se selecciona independientemente del grupo que consiste en hidrógeno, alquenilo, alcoxialquilo, $CF_3$, alquilo, alquilcarbonilo, alcoxicarbonilo, arilo, heterocicloalquilo, hidroxialquilo y $(NR^2R^3)$alquilo, donde $R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo; de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo heterocíclico de 5-7 miembros con N;

$R^2$ y $R^3$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, alcoxicarbonilo, alquilsulfonilo, arilsulfonilo, haloalquilsulfonilo y heterociclilsulfonilo, de manera alternativa $R^2$ y $R^3$ se pueden tomar juntos para formar un anillo cíclico de 5-7 miembros;

El anillo A se selecciona del grupo que consiste en:




(i) fenilo;

(ii) naftilo;

(iii) Un grupo heteroarilo monocíclico de 5 o 6 miembros que tiene 1-5 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

y (iv) un grupo heteroarilo bicíclico de 8 a 10 miembros que tiene 1-6 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

$R^{III}$ representa opcionalmente 1-3 sustituyentes que se seleccionan independientemente del grupo que consiste en alquilo $C_1$-$C_5$ lineal o ramificado, haloalquilo $C_1$-$C_5$ lineal o ramificado, alcoxi $C_1$-$C_5$, hidroxi, amino, alquilamino $C_1$-$C_5$, dialquilamino $C_1$-$C_6$, halógeno, ciano y nitro;

Z se selecciona del grupo que consiste en:

(1') $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$;

(2') $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$;

(3') $(CH_2)_iN(R^7)C(O)$;

(4') $C(O)N(R^8)(CH_2)_j$;

(5') $(CH_2)_iN(R^7)S(O)_2$;

y (6') $S(O)_2N(R8)(CH_2)j$;

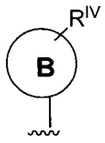
donde

i es 0 o 1;

j es 0 o 1;

$R^7$ y $R^8$ se seleccionan independientemente del grupo que consiste en hidrógeno y alquilo;

El anillo B se selecciona del grupo que consiste en:




(i') fenilo;

(ii') naftilo;

(iii') Un grupo heteroarilo monocíclico de 5 o 6 miembros que tiene 1-3 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

y (iv') un grupo heteroarilo bicíclico de 8 a 10 miembros que tiene 1-3 heteroátomos que se seleccionan independientemente del grupo que consiste en O, N y S;

$R^{IV}$ representa opcionalmente 1-3 sustituyentes, se seleccionan independientemente del grupo que consiste en alcoxi, alcoxialquilo, alcoxicarbonilo, alquilo, ariloxi, arilalquilo, carboxi, ciano, halo, haloalcoxi, haloalquilo, hidroxi, hidroxialquilo, nitro y —$NR^9R^{10}$; donde $R^9$ y $R^{10}$ se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, alquilcarbonilo, arilo, arilalquilo, cicloalquilo, cicloalquilalquilo, heterociclilo y heterociclilalquilo;

e incluye cualquier sal o profármaco farmacéuticamente aceptable.

9. El compuesto de la reivindicación 12, donde Z se selecciona del grupo que consiste en $(CH_2)_iN(R^7)C(O)$, $C(O)N(R^8)(CH_2)_j$, $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$ y $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$.

10. El compuesto de acuerdo con la reivindicación 12, donde Y se selecciona de grupo que consiste en

(1') —$(CH_2)g—O—(CH_2)h$—;

(2') —$(CH_2)g—NR^1—(CH_2)h$—;

(3') —$(CH_2)g—S(O)_n—(CH_2)h$—;

(4') —$(CH_2)g—SO_2N\ R^2—(CH_2)h$—;

(5') —$(CH_2)g—NR^2SO_2—(CH_2)h$—;

(6') —$(CH_2)g—\ CO—(CH_2)h$—;

(7') —$(CH_2)g—\ C(O)NR^2—(CH_2)h$—;

(8') —$(CH_2)g—\ NR^2C(O\ )—(CH_2)h$—;

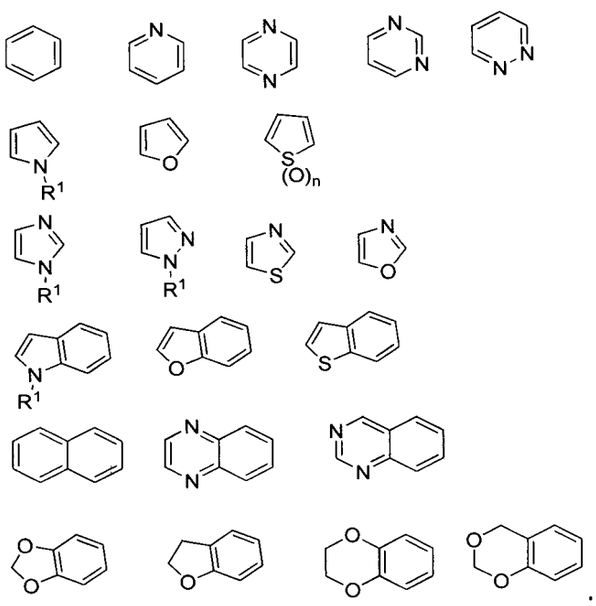
(9') —$(CH_2)g—C\equiv C—(CH_2)h$—;

(10') —$(CH_2)g—\ NR^2C(O)NR^3—(CH_2)h$—;

y (11') una unión simple.

11. El compuesto de la reivindicación 12, donde W es C.

12. El compuesto de acuerdo con la reivindicación 12, donde el Anillo A y el Anillo B se seleccionan independientemente del grupo que consiste en



13. El compuesto de la reivindicación 1 para su uso como inhibidor de la tirosina cinasa.

14. El compuesto de acuerdo con la reivindicación 1 que se usa para el tratamiento de una de las enfermedades o afecciones que se seleccionan del grupo que consiste en cáncer colorrectal, cáncer de pulmón, cáncer hematológico, cáncer renal, cáncer de hígado, cáncer de mama, retinopatía diabética, degeneración macular, degeneración macular relacionada con la edad, retinopatía del prematuro, angiogénesis ocular, edema de retina, isquemia de retina, edema macular diabético, edema macular cistoide, oclusión venosa de la retina, oclusión

de rama venosa, neovascularización preretinal, neovascularización coroidal inducida por láser, neovascularización asociada a queratoplastia, glaucoma y tumores oculares, artritis, restenosis, cirrosis hepática, ateroesclerosis, psoriasis, diabetes mellitus, cicatrización, inflamación, enfermedades neurodegenerativas y trastornos inmunes en el ser humano.

15. Una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de los compuestos de la reivindicación 1, junto con un portador farmacéuticamente aceptable para los mismos.

## RESUMEN DE LA INVENCIÓN

La presente invención se refiere a compuestos novedosos de la Fórmula I. Los compuestos de la presente invención son moduladores potentes de la tirosina cinasa y son adecuados para el tratamiento y la prevención de enfermedades y afecciones relacionadas con actividades anormales de receptores de tirosina cinasa.

# COMPOUNDS AS TYROSINE KINASE MODULATORS

Inventors: Xialing Guo and Zhen Zhu

## CROSS REFERENCE TO RELATED APPLICATIONS

The present invention claims priority under 35 U.S.C. 119(e) to United States Provisional Application Nos. 61/239,603, filed on Sep 03, 2009, 61/306,616, filed on Feb 22, 2010, 61/356,699 filed on June 21, 2010 and 61/360,531 filed on July 01, 2010, all of which are expressly incorporated herein by reference in their entireties.

## FIELD OF THE INVENTION

The present invention is directed to novel compounds with multiple aromatic components capable of modulating, regulating and/or inhibiting tyrosine kinase signal transduction. The present invention is also directed to methods of prevention and/or treatment of disorders related to unregulated tyrosine kinase signal transduction, including but not limited to, cell growth disorders, metabolic disorders, blood vessel proliferative disorders, inflammatory disorders, neurodegenerative diseases and immune disorders.

## BACKGROUND OF THE INVENTION

Protein tyrosine kinases ("PTKs") play an important role in the control of cell growth and differentiation. PTKs comprise a large and diverse class of proteins having enzymatic activity. PTKs can be of the receptor-type (having extracellular, transmembrane and intracellular domains) or the non-receptor type (being wholly intracellular). For example, signal transduction mediated by receptor tyrosine kinases ("RTKs") is initiated by extracellular interaction with a specific growth factor (i.e., a ligand), followed by receptor dimerization, transient stimulation of the intrinsic protein tyrosine kinase activity and phosphorylation. Binding sites are thereby created for intracellular signal transduction molecules and lead to the formation of complexes with a spectrum of cytoplasmic signaling molecules that facilitate the appropriate cellular response (e.g., cell division, metabolic homeostasis, and responses to the extracellular microenvironment).

With respect to RTKs, it has been shown also that tyrosine phosphorylation sites function as high-affinity binding sites for SH2 (src homology) domains of signaling molecules. Several intracellular substrate proteins that associate with RTKs have been identified and are divided into two principal groups: (1) substrates which have a catalytic domain; and (2) substrates which lack a catalytic domain but serve as adapters and associate with catalytically active molecules. The specificity of the interactions between receptors or proteins and SH2 domains of their substrates is determined by the amino acid residues immediately surrounding the phosphorylated tyrosine residue. Differences in binding affinities between SH2 domains and the amino acid sequences surrounding the phosphotyrosine residues on particular receptors are consistent with the observed differences in their substrate phosphorylation profiles. These observations suggest that the function of each RTK is determined not only by its pattern of expression and ligand availability, but also by the array of downstream signal transduction pathways that are activated by a particular receptor. Thus, phosphorylation provides an important regulatory step which determines the selectivity of signaling pathways recruited by specific growth factor receptors, as well as differentiation factor receptors.

The RTKs comprise a large family of transmembrane receptors with diverse biological activities. The intrinsic function of RTKs is activated upon ligand binding, which results in phophorylation of the receptor and multiple cellular substrates, and subsequently in a variety of cellular responses. At present, at least nineteen distinct RTK subfamilies have been identified. One RTK subfamily, designated the HER subfamily, is believed to be comprised of EGFR, HER2, HER3 and HER4. Ligands to the HER subfamily of receptors include epithelial growth factor (EGF), TGF-α, amphiregulin, HB-EGF, betacellulin and heregulin. The second subfamily of RTKs, designated the insulin subfamily, is comprised of the INS-R, the IGF-1R and the IR-R. The third RTK subfamily, the "PDGF" family, includes the PDGF α and β receptors, CSFIR, c-kit and FLK-II. Another subfamily of RTKs, identified as the FLK family, is believed to be comprised of the kinase insert domain-receptor fetal liver kinase-1 (KDR/FLK-1), the fetal liver kinase 4 (FLK-4) and the fms-like tyrosine kinase 1 (flt-1). Each of these receptors was initially believed to be a receptor for hematopoietic growth factors. Two other subfamilies of RTKs have been designated as the FGF receptor family (FGFR1, FGFR2, FGFR3 and FGFR4) and the Met subfamily (c-met and Ron). Because of the similarities between the PDGF and FLK subfamilies, the two subfamilies are often considered together. The known RTK subfamilies are identified in Plowman et al, 1994, DN&P 7(6): 334-339, which is incorporated herein by reference.



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The non-receptor tyrosine kinases represent a collection of cellular enzymes which lack extracellular and transmembrane sequences. At present, over twenty-four individual non-receptor tyrosine kinases, comprising eleven subfamilies (Src, Frk, Btk, Csk, Abl, Zap70, Fes/Fps, Fak, Jak, Ack and LIMK) have been identified. At present, the Src subfamily of non-receptor tyrosine kinases is comprised of the largest number of PTKs, and include Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk. The Src subfamily of enzymes has been linked to oncogenesis. A more detailed discussion of non-receptor tyrosine kinases is provided in Bolen, 1993, Oncogen 8: 2025-2031, which is incorporated herein by reference.

Many of the protein tyrosine kinases (PTKs), whether an RTK or non-receptor tyrosine kinase, have been found to be involved in cellular signaling pathways leading to cellular signal cascades and pathogenic conditions such as cancer, psoriasis and hyper immune responses. In view of the importance of PTKs to the control, regulation and modulation of cell proliferation and the diseases and disorders associated with abnormal cell proliferation, many attempts have been made to identify receptor and non-receptor tyrosine kinase "inhibitors" using a variety of approaches, including the use of mutant ligands (U.S. Patent No. 4,966,849), soluble receptors and antibodies (Kendall & Thomas, 1994, Proc. Nat'l Acad. Sci 90: 10705-09; Kim, et al, 1993, Nature 362: 841-844), RNA ligands (Jellinek, et al, Biochemistry 33: 10450-56); Takano, et al, 1993, Mol. Bio. Cell 4:358A; Kinsella, et al, 1992, Exp. Cell Res. 199: 56-62; Wright, et al, 1992, J. Cellular Phys. 152: 448-57) and tyrosine kinase inhibitors (U.S. Patent No. 5,330,992; Mariani, et al, 1994, Proc. Am. Assoc. Cancer Res. 35: 2268).

More recently, attempts have been made to identify small molecules which act as tyrosine kinase inhibitors. For example, bis monocyclic, bicyclic or heterocyclic aryl compounds (PCT Application No. WO 92/20642), vinylene-azaindole derivatives (PCT Application No. WO 94/14808) and 1-cyclopropyl-4-pyridyl-quinolones (U.S. Patent No. 5,330,992) have been described generally as tyrosine kinase inhibitors. Styryl compounds (U.S. Patent No. 5,217,999), styryl-substituted pyridyl compounds (U.S. Patent No. 5,302,606), certain quinazoline derivatives (EP Application No. 0 566 266 A1), seleoindoles and selenides (PCT Application No. WO 94/03427), tricyclic polyhydroxylic compounds (PCT Application No. WO 92/21660) and benzylphosphonic acid compounds (PCT Application No. WO 91/15495) have been described as compounds for use as tyrosine kinase inhibitors for use in the treatment of cancer.



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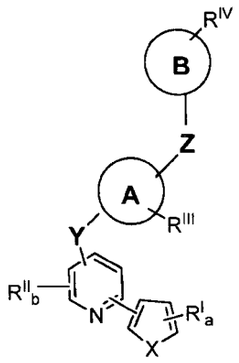
In addition, other small molecules were studied as tyrosine kinase inhibitors, such as the compounds disclosed in U.S. Pat. Nos. 6,765,012; 6,541,504; 6,747,025; 5,792,783; 5,834,504; 5,883,113; 5,883,116 and 5,886,020, all of which are incorporated by reference in their entireties.

The identification and use of compounds which specifically inhibit signal transduction by modulating the activity of receptor and non-receptor tyrosine is one aspect of the present invention.

## SUMMARY OF THE INVENTION

The present invention is directed to compounds represented by Formula I capable of modulating, regulating and/or inhibiting tyrosine kinase signal transduction, and uses of the compounds and compositions incorporating the compounds for disease treatment and prevention.

The compounds of the present invention can be found in general Formula I:




Formula I

wherein

X is selected from the group consisting of $NR^1$, O, $S(O)_n$;

n is 0 or an integer of from 1 to 2;



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$R^1$ is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, $CF_3$, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N $R^2R^3$), wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

$R^I$ is selected from the group consisting of hydrogen, halogen, $C_1$ to $C_8$ alkyl, $S(O)_fR^4$, $(CR^5R^6)_dC(O)OR^4$, $S(O)_f(CR^5R^6)_dC(O)OR^4$, $(CR^5R^6)_dAr$, $NR^4(CR^5R^6)_dAr$, $O(CR^5R^6)_dAr$, $S(O)_f(CR^5R^6)_dAr$, $(CR^5R^6)_dS(O)_fR^4$, $NR^4(CR^5R^6)_dS(O)_fR^4$, $O(CR^5R^6)_d\ S(O)_fR^4$, $S(O)_f(CR^5R^6)_eS(O)_fR^4$, $(CR^5R^6)_dC(O)N(R^4)_2$, $NR^4(CR^5R^6)_dC(O)N(R^4)_2$, $O(CR^5R^6)_dC(O)N(R^4)_2$, $S(O)_f(CR^5R^6)_eC(O)N(R^4)_2$, $(CR^5\ R^6)_dOR^4$, $S(O)_f(CR^5R^6)_dOR^4$, $(CR^5\ R^6)_dOSO_2R^4$, $S(O)_f(CR^5\ R^6)_eOSO_2R^4$, $(CR^5\ R^6)_dP(O)(OR^4)_2$, $S(O)_f(CR^5\ R^6)_eP(O)(OR^4)_2$, $OC(O)(CR^5R^6)_dN(R^4)_2$, $C(O)(CR^5R^6)_dN(R^4)_2$, $C(O)N=S(O)R^5\ R^6$, $NR^2C(O)(CR^5R^6)_dN(R^4)_2$, $(CR^5R^6)_dR^5$, $S(O)_f(CR^5R^6)_dR^5$, $HNC(O)R^4$, $HN\text{-}C(O)OR^4$, $(CR^5R^6)_dN(R^4)_2$, $S(O)_f(CR^5R^6)_dN(R^4)_2$, $OC(O)OR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dOR^4$, and $(CR^5R^6)_dC(O)(CR^5R^6)_dN(R^4)_2$, wherein each $R^4$ is independently selected from the group consisting of hydrogen, hydroxyl, $C_1$-$C_8$ alkyl, aryl, $C_1$-$C_8$ hydroxyalkyl, $C_1$-$C_8$ alkoxyalkyl, $(CR^5R^6)_d$ and $N(R^4)_2$ may form a 3-7 membered heterocyclic ring, comprising of aziridine, azetidine, pyrrolidine, 5-fluoropyrrolidine, piperidine, 6-fluoropiperidine, N-methylpiperazine, morpholine, 2,6-dimethylmorpholine, thiomorpholine, and wherein said heterocyclic ring may be optionally substituted with up to three of $R^5$; wherein $R^5$ and $R^6$ are independently selected from the group consisting of hydrogen, halo, hydroxyl, $C_1$-$C_8$ alkyl, $C_1$-$C_8$ hydroxyalkyl, $C_1$-$C_8$ alkoxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, hydroxycarbonyl, hydroxycarbonylalkyl, amide, alkylamide, amidoalkyl, sulfonate and $CR^5R^6$ may represent a carbocyclic or heterocyclic ring of from 5 to 6 carbons or alternatively, $(CR^5R^6)_d$ and $(CR^5R^6)_e$ may form a 3-7 membered carbocyclic or heterocyclic ring, wherein the ring may be optionally substituted with up to three of hydroxyl, halo, $C_1$-$C_8$ alkyl, $C_1$-$C_8$ hydroxyalkyl, $C_1$-$C_8$ alkoxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, hydroxycarbonyl, hydroxycarbonylalkyl, amide, alkylamide, amidoalkyl and sulfonate;

a is 0 or an integer of from 1 to 3;

d is 0 or an integer of from 1 to 5;

e is an integer of from 1 to 4;

f is 0 or an integer of from 1 to 2;

$R^{II}$ is independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkyl, aryloxy, aryloxyalkyl, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkoxy, hydroxyalkyl, ($NR^2R^3$)alkoxy, ($NR^2R^3$)alkenyl, ($NR^2R^3$)alkyl, ($NR^2R^3$)carbonylalkenyl, and ($NR^2R^3$)carbonylalkyl, wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$ and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

b is 0 or an integer of from 1 to 2;

Y is selected from the group consisting of:

(1') —$(CH_2)g$—O—$(CH_2)h$—;
(2') —$(CH_2)g$—$NR^1$—$(CH_2)h$—;
(3') —$(CH_2)g$—$S(O)_n$—$(CH_2)h$—;
(4') —$(CH_2)g$—$SO_2N\ R^2$—$(CH_2)h$—;
(5') —$(CH_2)g$—$NR^2SO_2$—$(CH_2)h$—;
(6') —$(CH_2)g$— CO—$(CH_2)h$—;
(7') —$(CH_2)g$— $C(O)NR^2$—$(CH_2)h$—;
(8') —$(CH_2)g$— $NR^2C(O)$—$(CH_2)h$—;
(9') —$(CH_2)g$—C≡C—$(CH_2)h$—;
(10') —$(CH_2)g$— $NR^2C(O)NR^3$—$(CH_2)h$—;
(11') —$(CH_2)g$—$(CH_2)h$—;
(12') —$(CH_2)g$—$CF_2$—$(CH_2)h$—;
(13') —$(CH_2)g$—$CCl_2$—$(CH_2)h$—;
(14') —$(CH_2)g$—CHF—$(CH_2)h$—;
(15') —$(CH_2)g$—CH(OH)—$(CH_2)h$—;
(16') —$(CH_2)g$—$CR^2R^3$—$(CH_2)h$—;
(17') —$(CH_2)g$—C=C—$(CH_2)h$—;
and (18') a single bond;

wherein



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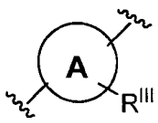
g is 0 or an integer of from 1 to 3;

h is 0 or an integer of from 1 to 3;

$R^1$ is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, $CF_3$, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N $R^2R^3$), wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

$R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered cyclic ring;

Ring A is selected from the group consisting of:




(i) Phenyl;

(ii) Naphthyl;

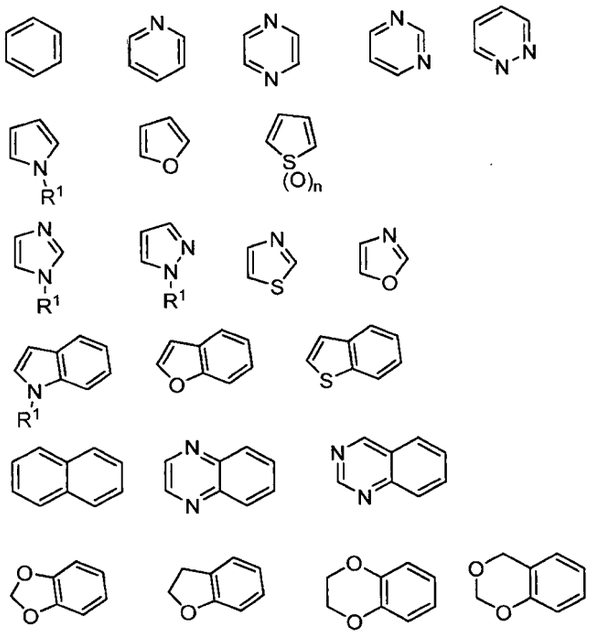
(iii) A 5 or 6 membered monocyclic heteroaryl group which have 1-5 heteroatoms independently selected from the group consisting of O, N and S;

and (iv) An 8 to 10 membered bicyclic heteroaryl group which have 1-6 heteroatoms independently selected from the group consisting of O, N and S;

Ring A can be illustrated but not limited to the following:



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wherein

$R^1$ is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, $CF_3$, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N $R^2R^3$), wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$ and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

$R^{III}$ represents optionally 1-3 substituents independently selected from the group consisting of $C_1$-$C_5$ linear or branched alkyl, $C_1$-$C_5$ linear or branched haloalkyl, $C_1$-$C_5$ alkoxy, hydroxy, amino, $C_1$-$C_5$ alkylamino, C1-C6 dialkylamino, halogen, cyano, and nitro;

Z is selected from the group consisting of

(1') $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$;

(2') $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$;

(3') $(CH_2)_iN(R^7)C(O)$;

(4') $C(O)N(R^8)(CH_2)_j$;



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(5') $(CH_2)_iN(R^7)S(O)_2$;

and (6') $S(O)_2N(R^8)(CH_2)_j$;

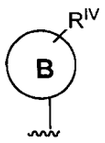
wherein

i is 0 or 1;

j is 0 or 1;

$R^7$ and $R^8$ are independently selected from the group consisting of hydrogen and alkyl.

Ring B is selected from the group consisting of:



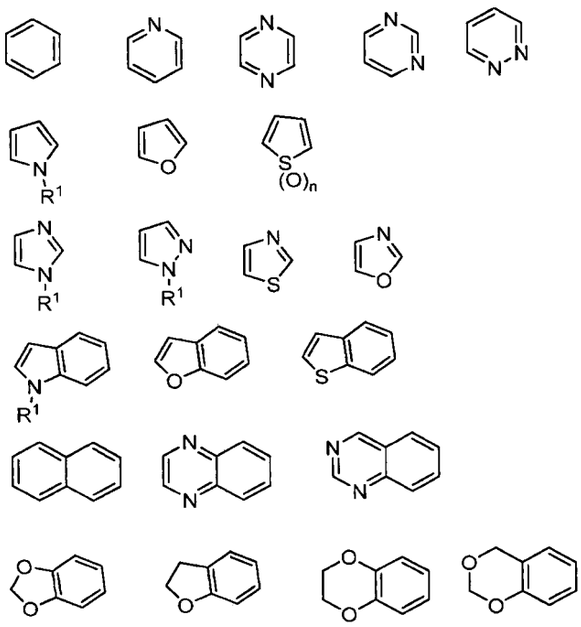

(i') Phenyl;

(ii') Naphthyl;

(iii') A 5 or 6 membered monocyclic heteroaryl group which have 1-3 heteroatoms independently selected from the group consisting of O, N and S;

and (iv') An 8 to 10 membered bicyclic heteroaryl group which have 1-3 heteroatoms independently selected from the group consisting of O, N and S;

Ring B can be illustrated but not limited to the following:



wherein

$R^1$ is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, $CF_3$, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N $R^2R^3$), wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

$R^{IV}$ represents optionally 1-3 substituents, independently selected from the group consisting of alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, aryloxy, arylalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and —$NR^9R^{10}$; wherein $R^9$ and $R^{10}$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl.

Some embodiments of the present invention are included in the following paragraphs:

(1) A compound according to Formula I, including any tautomer, stereoisomer, diastereoisomeric form, polymorphic form, crystal form, a solvate, a hydrate, a metabolite, a pharmaceutically acceptable salt or prodrug, mixture of different stereoisomers, and any mixture of different crystal forms.

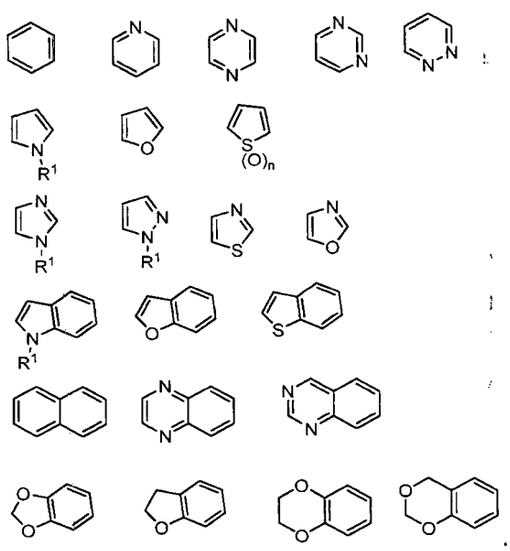
(2) A compound of Formula I in the form of a prodrug.

(3) The compound according to paragraph 1, wherein Z is selected from the group consisting of $(CH_2)_iN(R^7)C(O)$, $C(O)N(R^8)(CH_2)_j$, $(CH_2)_iN(R^7)S(O)_2$ and $S(O)_2N(R^8)(CH_2)_j$.

(4) The compound according to paragraphs 1 – 3, wherein Y is selected from the group consisting of —$(CH_2)g$—O—$(CH_2)h$—; —$(CH_2)g$—$NR^1$—$(CH_2)h$—;

—$(CH_2)g$—$S(O)_n$—$(CH_2)h$—; —$(CH_2)g$—$SO_2N\ R^2$—$(CH_2)h$—;
—$(CH_2)g$—$NR^2SO_2$—$(CH_2)h$—; —$(CH_2)g$— CO—$(CH_2)h$—;
—$(CH_2)g$— $C(O)NR^2$—$(CH_2)h$—; —$(CH_2)g$— $NR^2C(O\ )$—$(CH_2)h$—;
—$(CH_2)g$—C≡C—$(CH_2)h$—; —$(CH_2)g$— $NR^2C(O)NR^3$—$(CH_2)h$ and a single bond.

(5) The compound according to paragraphs 1 – 4, wherein Ring A and Ring B are independently selected from the group consisting of



(6) The compound according to paragraphs 1 – 5, wherein Y is selected from the group consisting of —$(CH_2)g$—$(CH_2)h$—; —$(CH_2)g$—$CF_2$—$(CH_2)h$—; —$(CH_2)g$—$CCl_2$—$(CH_2)h$—; —$(CH_2)g$—CHF—$(CH_2)h$—; —$(CH_2)g$—CH(OH)—$(CH_2)h$—;

—$(CH_2)g$—$CR^2R^3$—$(CH_2)h$—; and —$(CH_2)g$—C=C—$(CH_2)h$—.

(7) The compound according to paragraphs 1 – 6, wherein X is NH.

(8) A compound selected from the group consisting of



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(1') [({5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl} phenoxy)pyridin-2-yl]-1H-pyrrol-3-yl}carbonyl)amino]acetic acid;

(2') methyl [({5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl} phenoxy)pyridin-2-yl]-1H-pyrrol-3-yl}carbonyl)amino]acetate;

(3') ({[5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrol-3-yl]carbonyl}amino)acetic acid;

(4') methyl ({[5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrol-3-yl]carbonyl}amino)acetate;

(5') 5-[4-({3-[(3-methyl-2-furoyl)amino]phenyl}amino)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid;

(6') methyl 5-[4-({3-[(3-methyl-2-furoyl)amino]phenyl}amino)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(7') 5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-N-hydroxy-1H-pyrrole-3-carboxamide;

(8') 4-fluoro-N-(2-fluoro-5-methylphenyl)-3-[(2-{4-[(3-hydroxypiperidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]benzamide;

(9) N-(2,3-dihydroxypropyl)-5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy) pyridin-2-yl]-1H-pyrrole-3-carboxamide;

(10) N-(2-fluoro-5-methylphenyl)-3-[(2-{4-[(3-hydroxypyrrolidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]benzamide;

(11') 5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-N-hydroxy-1H-pyrrole-3-carboxamide;

(12') methyl 5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(13') 5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid;

(14') N-ethyl-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide;

(15') N-(2,3-dihydroxypropyl)-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide;

(16') 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide;

(17') N-hydroxy-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide;

(18') N-(3-{[2-(4-{[(3R)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-methyl-2-furamide;

(19') 5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid;

(20') methyl 5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(21') 2,3-dihydroxypropyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate;

(22') 5-[4-(3-{[(3-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid;

(23') methyl 5-[4-(3-{[(3-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(24') 2-hydroxyethyl 5-[4-(3-{[(3-methyl-2-thienyl)carbonyl]amino}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(25') 2-hydroxyethyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate;

(26') 5-[4-(3-{[(3-methyl-2-thienyl)carbonyl]amino}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid;

(27') methyl 5-[4-(3-{[(3-methyl-2-thienyl)carbonyl]amino}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(28') 5-(4-{4-fluoro-3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid;

(29') methyl 5-(4-{4-fluoro-3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate;

(30') N-[dimethyl(oxido)-lambda~4~-sulfanylidene]-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide;

(31') N-(3-{[2-(4-{[(3S)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-methyl-2-furamide;

(32') 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid;

(33') methyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate;

(34') 3-methyl-N-(3-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-2-furamide;

(35') methyl 4-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-2-carboxylate;

(36') 2-fluoro-5-methyl-N-(4-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)benzamide; and (37') 3-methyl-N-(4-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-2-furamide.

(9) The compound according to paragraph 1, wherein Z is $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$ or $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$, provided that when Ring B is pyrazole, $R^{IV}$ is not a phenyl or substituted phenyl.

(10) The compound according to paragraph 9, wherein Y is selected from the group consisting of —$(CH_2)$g—O—$(CH_2)$h—; —$(CH_2)$g—$NR^1$—$(CH_2)$h—;

—$(CH_2)$g—$S(O)_n$—$(CH_2)$h—; —$(CH_2)$g—$SO_2N\ R^2$—$(CH_2)$h—;

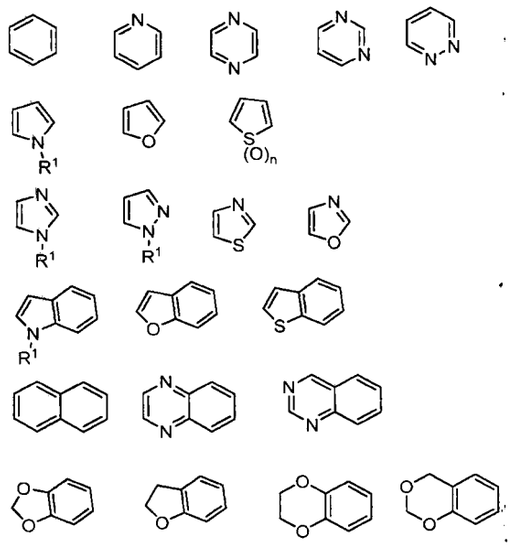
—$(CH_2)$g—$NR^2SO_2$—$(CH_2)$h—; —$(CH_2)$g— CO—$(CH_2)$h—;

—$(CH_2)$g— $C(O)NR^2$—$(CH_2)$h—; —$(CH_2)$g— $NR^2C(O)$—$(CH_2)$h—;

—$(CH_2)$g—C≡C—$(CH_2)$h—; —$(CH_2)$g— $NR^2C(O)NR^3$—$(CH_2)$h, and a single bond.

(11) The compound according to paragraph 9, wherein Y is selected from the group consisting of —$(CH_2)$g—$(CH_2)$h—; —$(CH_2)$g—$CF_2$—$(CH_2)$h—; —$(CH_2)$g—$CCl_2$—$(CH_2)$h—; —$(CH_2)$g—CHF—$(CH_2)$h—; —$(CH_2)$g—CH(OH)—$(CH_2)$h—; —$(CH_2)$g—$CR^2R^3$—$(CH_2)$h—; and —$(CH_2)$g—C=C—$(CH_2)$h—.

(12) The compound according to paragraphs 9 – 11, wherein Ring A and Ring B are independently selected from the group consisting of

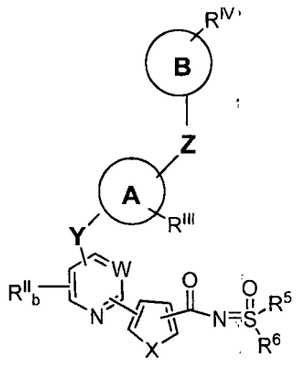


(13) The compound according to paragraphs 9 – 12, wherein X is NH.

(14) The compound according to paragraphs 9 – 12, wherein X is S.

(15) The compound according to paragraphs 9-14, wherein $R^I$ is selected from the group consisting of hydrogen, halogen, $C_1$ to $C_8$ alkyl, $(CR^5R^6)_dC(O)OR^4$, $(CR^5R^6)_dAr$, $NR^4(CR^5R^6)_dAr$, $(CR^5R^6)_dC(O)N(R^4)_2$, $NR^4(CR^5R^6)_dC(O)N(R^4)_2$, $O(CR^5R^6)_dC(O)N(R^4)_2$, $(CR^5R^6)_dOR^4$, $OC(O)(CR^5R^6)_dN(R^4)_2$, $C(O)(CR^5R^6)_dN(R^4)_2$, $C(O)N=S(O)R^5R^6$, $NR^2C(O)(CR^5R^6)_dN(R^4)_2$, $(CR^5R^6)_dR^5$, $HNC(O)R^4$, $HN\text{-}C(O)OR^4$, $(CR^5R^6)_dN(R^4)_2$, $S(O)_f(CR^5R^6)_dN(R^4)_2$, $OC(O)OR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dOR^4$, and $(CR^5R^6)_dC(O)(CR^5R^6)_dN(R^4)_2$, wherein each $R^4$ is independently selected from the group consisting of hydrogen, hydroxyl, $C_1$-$C_8$ alkyl, aryl, $C_1$-$C_8$ hydroxyalkyl, $C_1$-$C_8$ alkoxyalkyl, $(CR^5R^6)_d$ and $N(R^4)_2$ may form a 3-7 membered heterocyclic ring, comprising of aziridine, azetidine, pyrrolidine, 5-fluoropyrrolidine, piperidine, 6-fluoropiperidine, N-methylpiperazine, morpholine, 2,6-dimethylmorpholine, thiomorpholine, and wherein said heterocyclic ring may be optionally substituted with up to three of $R^5$; wherein $R^5$ and $R^6$ are independently selected from the group consisting of hydrogen, halo, hydroxyl, $C_1$-$C_8$ alkyl, $C_1$-$C_8$ hydroxyalkyl, $C_1$-$C_8$ alkoxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, hydroxycarbonyl, hydroxycarbonylalkyl, amide, alkylamide, amidoalkyl, sulfonate and $CR^5R^6$ may represent a carbocyclic or heterocyclic ring of from 5 to 6 carbons or alternatively, $(CR^5R^6)_d$ and $(CR^5R^6)_e$ may form a 3-7 membered carbocyclic or heterocyclic ring, wherein the ring may be optionally substituted with up to three of hydroxyl, halo, $C_1$-$C_8$ alkyl, $C_1$-$C_8$ hydroxyalkyl, $C_1$-$C_8$ alkoxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, hydroxycarbonyl, hydroxycarbonylalkyl, amide, alkylamide, amidoalkyl and sulfonate.

(16) A compound of Formula II:



Formula II

wherein

W is C or N;

X is selected from the group consisting of $NR^1$, O, and $S(O)_n$;

n is 0 or an integer of from 1 to 2;

$R^1$ is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, $CF_3$, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N $R^2R^3$), wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

$R^5$ and $R^6$ are independently selected from the group consisting of hydrogen, halo, hydroxyl, $C_1$-$C_8$ alkyl, $C_1$-$C_8$ hydroxyalkyl, $C_1$-$C_8$ alkoxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, hydroxycarbonyl, hydroxycarbonylalkyl, amide, alkylamide, amidoalkyl, sulfonate;

$R^{II}$ is independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkyl, aryloxy, aryloxyalkyl, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkoxy, hydroxyalkyl, ($NR^2R^3$)alkoxy, ($NR^2R^3$)alkenyl, ($NR^2R^3$)alkyl, ($NR^2R^3$)carbonylalkenyl, and ($NR^2R^3$)carbonylalkyl, wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

b is 0 or an integer of from 1 to 2;

Y is selected from the group consisting of:

(1') —$(CH_2)$g—O—$(CH_2)$h—;



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(2') —$(CH_2)g—NR^1—(CH_2)h$—;
(3') —$(CH_2)g—S(O)_n—(CH_2)h$—;
(4') —$(CH_2)g—SO_2N\ R^2—(CH_2)h$—;
(5') —$(CH_2)g—NR^2SO_2—(CH_2)h$—;
(6') —$(CH_2)g—\ CO—(CH_2)h$—;
(7') —$(CH_2)g—\ C(O)NR^2—(CH_2)h$—;
(8') —$(CH_2)g—\ NR^2C(O\ )—(CH_2)h$—;
(9') —$(CH_2)g—C\equiv C—(CH_2)h$—;
(10') —$(CH_2)g—\ NR^2C(O)NR^3—(CH_2)h$—;
(11') —$(CH_2)g—(CH_2)h$—;
(12') —$(CH_2)g—CF_2—(CH_2)h$—;
(13') —$(CH_2)g—CCl_2—(CH_2)h$—;
(14') —$(CH_2)g—CHF—(CH_2)h$—;
(15') —$(CH_2)g—CH(OH)—(CH_2)h$—;
(16') —$(CH_2)g—CR^2R^3—(CH_2)h$—;
(17') —$(CH_2)g—C{=}C—(CH_2)h$—;
and (18') a single bond;

wherein

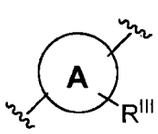
g is 0 or an integer of from 1 to 3;

h is 0 or an integer of from 1 to 3;

$R^1$ is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, $CF_3$, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N $R^2R^3$), wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

$R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered cyclic ring;

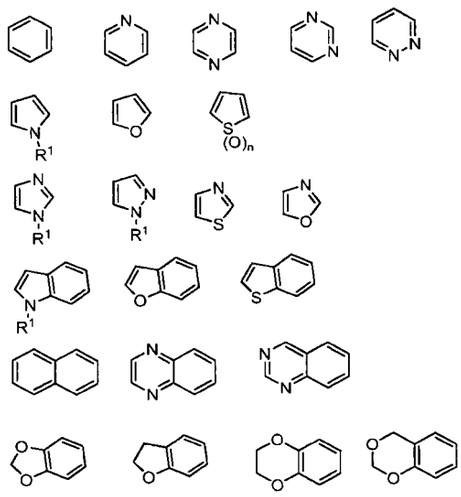
Ring A is selected from the group consisting of:




(i) Phenyl;
(ii) Naphthyl;
(iii) A 5 or 6 membered monocyclic heteroaryl group which have 1-5 heteroatoms independently selected from the group consisting of O, N and S;

and (iv) An 8 to 10 membered bicyclic heteroaryl group which have 1-6 heteroatoms independently selected from the group consisting of O, N and S;

Ring A can be illustrated but not limited to the following:



wherein

$R^1$ is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, $CF_3$, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N $R^2R^3$), wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

$R^{III}$ represents optionally 1-3 substituents independently selected from the group consisting of $C_1$-$C_5$ linear or branched alkyl, $C_1$-$C_5$ linear or branched haloalkyl, $C_1$-$C_5$ alkoxy, hydroxy, amino, $C_1$-$C_5$ alkylamino, C1-C6 dialkylamino, halogen, cyano, and nitro;

Z is selected from the group consisting of

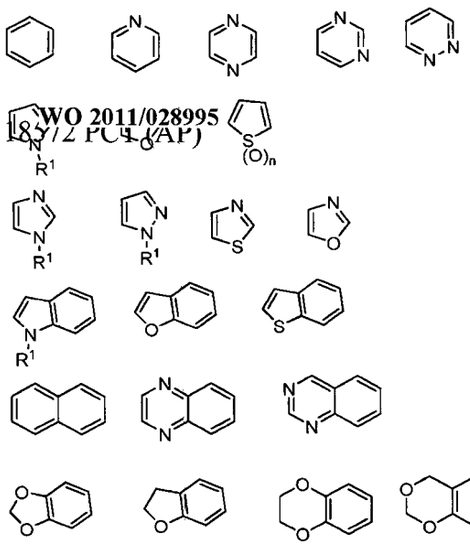
(1') $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$;
(2') $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$;
(3') $(CH_2)_iN(R^7)C(O)$;
(4') $C(O)N(R^8)(CH_2)_j$;
(5') $(CH_2)_iN(R^7)S(O)_2$;
and (6') $S(O)_2N(R^8)(CH_2)_j$;

wherein

i is 0 or 1;
j is 0 or 1;

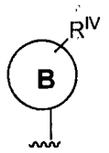


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$R^7$ and $R^8$ are independently selected from the group consisting of hydrogen and alkyl;

Ring B is selected from the group consisting of:



(i') Phenyl;
(ii') Naphthyl;
(iii') A 5 or 6 membered monocyclic heteroaryl group which have 1-3 heteroatoms independently selected from the group consisting of O, N and S;
and (iv') An 8 to 10 membered bicyclic heteroaryl group which have 1-3 heteroatoms independently selected from the group consisting of O, N and S;

Ring B can be illustrated but not limited to the following:

wherein

$R^1$ is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, $CF_3$, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl($NR^2R^3$), wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$ and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

$R^{IV}$ represents optionally 1-3 substituents, independently selected from the group consisting of alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, aryloxy, arylalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and —$NR^9R^{10}$; wherein $R^9$ and $R^{10}$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

and any pharmaceutical acceptable salt or prodrug.

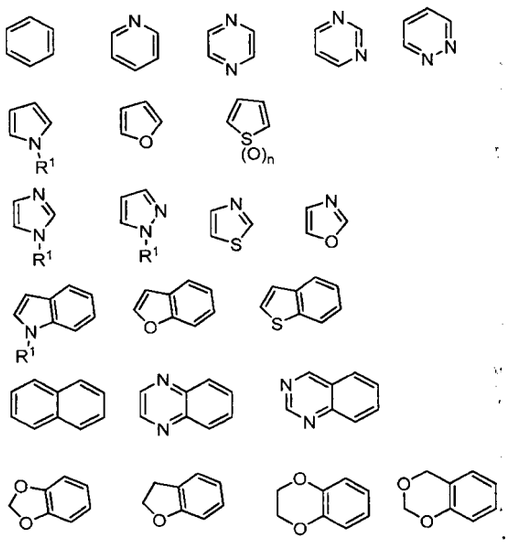
(17) The compound according to paragraph 16, wherein Z is selected from the group consisting of $(CH_2)_iN(R^7)C(O)$, $C(O)N(R^8)(CH_2)_j$, $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$ and $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$.



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(18) The compound according to paragraphs 16 – 17, wherein Y is selected from the group consisting of —$(CH_2)g$—O—$(CH_2)h$—; —$(CH_2)g$—$NR^1$—$(CH_2)h$—; —$(CH_2)g$—$S(O)_n$—$(CH_2)h$—; —$(CH_2)g$—$SO_2N\ R^2$—$(CH_2)h$—; —$(CH_2)g$—$NR^2SO_2$—$(CH_2)h$—; —$(CH_2)g$— CO—$(CH_2)h$—; —$(CH_2)g$— $C(O)NR^2$—$(CH_2)h$—; —$(CH_2)g$— $NR^2C(O\ )$—$(CH_2)h$—; —$(CH_2)g$—C≡C—$(CH_2)h$—; —$(CH_2)g$— $NR^2C(O)NR^3$—$(CH_2)h$ and a single bond.

(19) The compound according to paragraphs 16 – 18, wherein Ring A and Ring B are independently selected from the group consisting of



(20) The compound according to paragraphs 16-19, wherein W is C.

(21) A method of use of the compounds of paragraphs 1 – 20, wherein the compounds are used as tyrosine kinase modulators;

(22) Use of the compounds of paragraphs 1 – 20 in the preparation of a medicament for the treatment or prevention of diseases or conditions related with unregulated tyrosine kinase activities, comprising administering a therapeutically effective amount of the compound of paragraphs 1 – 20 together with a pharmaceutically acceptable carrier;

(23) The use of paragraph 22, wherein the diseases or conditions are selected from the group consisting of cell growth and metabolic disorders, blood vessel proliferative disorders, inflammatory disorders, neurodegenerative diseases, and immune disorders.

(24) The use of paragraphs 22 – 23 wherein the diseases or conditions are selected from the group consisting of colorectal cancer, lung cancer, hematological cancer, renal cancer,

liver cancer, breast cancer, diabetic retinopathy, macular degeneration, age-related macular degeneration, retinopathy of prematurity, ocular angiogenesis, retinal edema, retinal ischemia, diabetic macular edema, cystoid macular edema, retinal vein occlusion, branch vein occlusion, preretinal neovascularization, laser-induced choroidal neovascularization, neovascularization associated with keratoplasty, glaucoma and ocular tumors, arthritis, restenosis, hepatic cirrhosis, atherosclerosis, psoriasis, diabetes mellitus, wound healing, inflammation, neurodegenerative diseases and immune disorders.

(25) The use of paragraphs 22 – 23 wherein the conditions and diseases are wound healing or to alleviate transplant rejection.

(26) A pharmaceutical composition comprising a therapeutic effective amount of a compound according to paragraphs 1 – 20 together with a pharmaceutically acceptable carrier which is suitable for systematic, parenteral, local or topical delivery.

(27) The pharmaceutical composition of paragraph 26, which are in the form selected from the group comprising of tablets, capsules, intravenous injections, intramuscular injections, local injections, topical creams, gels and ointments, eye drops, ophthalmic solutions, ophthalmic suspensions, ophthalmic emulsions, intravitreal injections, subtenon injections, ophthalmic biodrodible implant, and non-bioeordible ophthalmic inserts or depots.

(28) Use of the compounds of paragraphs 1-20 in the preparation of a medicament for the treatment of diseases and conditions, wherein the medicament contains pharmaceutical acceptable composition according to paragraphs 26 and 27.

## BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows a powder X-Ray Diffraction (XRPD) of Example 78;

Fig 2 shows a powder X-Ray Diffraction (XRPD) of Example 69;

Fig 3 shows a fluorescein angiography (blood-retinal barrier breakdown) of Example 121, Example 84 Sodium, Example 83, Example 78, Example 75 Sodium, Example 69, and Example 66; and

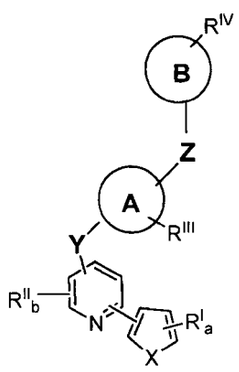
Fig 4 shows a fundus photography (retinal vasodilation and vessel tortuosity) of Example 121, Example 84 Sodium, Example 83, Example 78, Example 75 Sodium, Example 69, and Example 66.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a series of compounds with multiple aromatic components useful as protein tyrosine kinase inhibitors. The compounds of the present invention are useful for treating diseases related to unregulated tyrosine kinase signal transduction, for example, cancer, blood vessel proliferative disorders, fibrotic disorders, and neurodegenerative diseases. In particular, compounds of the present invention are useful for the treatment of colorectal cancer, lung cancer, hematological cancer, renal cancer, liver cancer, breast cancer, diabetic retinopathy, macular degeneration, age-related macular degeneration, retinopathy of prematurity, ocular angiogenesis, retinal edema, retinal ischemia, diabetic macular edema, cystoid macular edema, retinal vein occlusion, branch vein occlusion, preretinal neovascularization, laser-induced choroidal neovascularization, neovascularization associated with keratoplasty, glaucoma and ocular tumors, arthritis, restenosis, hepatic cirrhosis, atherosclerosis, psoriasis, diabetes mellitus, wound healing, transplant rejection, inflammation, neurodegenerative diseases and immune disorders.

## 1. Compounds of the Invention

In one aspect of the invention, the compounds of the present invention can be represented by the general formula I:




Formula I

wherein

X is selected from the group consisting of $NR^1$, O, and $S(O)_n$;

n is 0 or an integer of from 1 to 2;

$R^1$ is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, $CF_3$, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N $R^2R^3$), wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

$R^I$ is selected from the group consisting of hydrogen, halogen, $C_1$ to $C_8$ alkyl, $S(O)_fR^4$, $(CR^5R^6)_dC(O)OR^4$, $S(O)_f(CR^5R^6)_dC(O)OR^4$, $(CR^5R^6)_dAr$, $NR^4(CR^5R^6)_dAr$, $O(CR^5R^6)_dAr$, $S(O)_f(CR^5R^6)_dAr$, $(CR^5R^6)_dS(O)_fR^4$, $NR^4(CR^5R^6)_dS(O)_fR^4$, $O(CR^5R^6)_d S(O)_fR^4$, $S(O)_f(CR^5R^6)_eS(O)_fR^4$, $(CR^5R^6)_dC(O)N(R^4)_2$, $NR^4(CR^5R^6)_dC(O)N(R^4)_2$, $O(CR^5R^6)_dC(O)N(R^4)_2$, $S(O)_f(CR^5R^6)_eC(O)N(R^4)_2$, $(CR^5 R^6)_dOR^4$, $S(O)_f(CR^5R^6)_dOR^4$, $(CR^5 R^6)_dOSO_2R^4$, $S(O)_f(CR^5 R^6)_eOSO_2R^4$, $(CR^5 R^6)_dP(O)(OR^4)_2$, $S(O)_f(CR^5 R^6)_eP(O)(OR^4)_2$, $OC(O)(CR^5R^6)_dN(R^4)_2$, $C(O)(CR^5R^6)_dN(R^4)_2$, $C(O)N=S(O)R^5 R^6$, $NR^2C(O)(CR^5R^6)_dN(R^4)_2$, $(CR^5R^6)_dR^5$, $S(O)_f(CR^5R^6)_dR^5$, $HNC(O)R^4$, $HN\text{-}C(O)OR^4$, $(CR^5R^6)_dN(R^4)_2$, $S(O)_f (CR^5R^6)_dN(R^4)_2$, $OC(O)OR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dOR^4$, and $(CR^5R^6)_dC(O)(CR^5R^6)_dN(R^4)_2$, wherein each $R^4$ is independently selected from the group consisting of hydrogen, hydroxyl, $C_1$-$C_8$ alkyl, aryl,

$C_1$-$C_8$ hydroxyalkyl, $C_1$-$C_8$ alkoxyalkyl, $(CR^5R^6)_d$ and $N(R^4)_2$ may form a 3-7 membered heterocyclic ring, comprising of aziridine, azetidine, pyrrolidine, 5-fluoropyrrolidine, piperidine, 6-fluoropiperidine, N-methylpiperazine, morpholine, 2,6-dimethylmorpholine, thiomorpholine, and wherein said heterocyclic ring may be optionally substituted with up to three of $R^5$; wherein $R^5$ and $R^6$ are independently selected from the group consisting of hydrogen, halo, hydroxyl, $C_1$-$C_8$ alkyl, $C_1$-$C_8$ hydroxyalkyl, $C_1$-$C_8$ alkoxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, hydroxycarbonyl, hydroxycarbonylalkyl, amide, alkylamide, amidoalkyl, sulfonate and $CR^5R^6$ may represent a carbocyclic or heterocyclic ring of from 5 to 6 carbons or alternatively, $(CR^5R^6)_d$ and $(CR^5R^6)_e$ may form a 3-7 membered carbocyclic or heterocyclic ring, wherein the ring may be optionally substituted with up to three of hydroxyl, halo, $C_1$-$C_8$ alkyl, $C_1$-$C_8$ hydroxyalkyl, $C_1$-$C_8$ alkoxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, hydroxycarbonyl, hydroxycarbonylalkyl, amide, alkylamide, amidoalkyl and sulfonate;

a is 0 or an integer of from 1 to 3;

d is 0 or an integer of from 1 to 5;

e is an integer of from 1 to 4;

f is 0 or an integer of from 1 to 2;

$R^{II}$ is independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkyl, aryloxy, aryloxyalkyl, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkoxy, hydroxyalkyl, $(NR^2R^3)$alkoxy, $(NR^2R^3)$alkenyl, $(NR^2R^3)$alkyl, $(NR^2R^3)$carbonylalkenyl, and $(NR^2R^3)$carbonylalkyl, wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

b is 0 or an integer of from 1 to 2;

Y is selected from the group consisting of:

(1') —$(CH_2)$g—O—$(CH_2)$h—;

(2') —$(CH_2)$g—$NR^1$—$(CH_2)$h—;

(3') —$(CH_2)$g—$S(O)_n$—$(CH_2)$h—;

(4') —$(CH_2)$g—$SO_2N$ $R^2$—$(CH_2)$h—;



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(5') —$(CH_2)g—NR^2SO_2—(CH_2)h$—;

(6') —$(CH_2)g—$ CO—$(CH_2)h$—;

(7') —$(CH_2)g—$ $C(O)NR^2$—$(CH_2)h$—;

(8') —$(CH_2)g—$ $NR^2C(O)$—$(CH_2)h$—;

(9') —$(CH_2)g—C\equiv C—(CH_2)h$—;

(10') —$(CH_2)g—$ $NR^2C(O)NR^3$—$(CH_2)h$—;

(11') —$(CH_2)g—(CH_2)h$—;

(12') —$(CH_2)g—CF_2—(CH_2)h$—;

(13') —$(CH_2)g—CCl_2—(CH_2)h$—;

(14') —$(CH_2)g—CHF—(CH_2)h$—;

(15') —$(CH_2)g—CH(OH)—(CH_2)h$—;

(16') —$(CH_2)g—CR^2R^3—(CH_2)h$—;

(17') —$(CH_2)g—C{=}C—(CH_2)h$—;

and (18') a single bond.

wherein

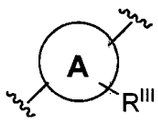
g is 0 or an integer of from 1 to 3;

h is 0 or an integer of from 1 to 3;

$R^1$ is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, $CF_3$, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N $R^2R^3$), wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

$R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$ and $R^3$ and may be taken together to form a 5-7 membered cyclic ring;

Ring A is selected from the group consisting of:



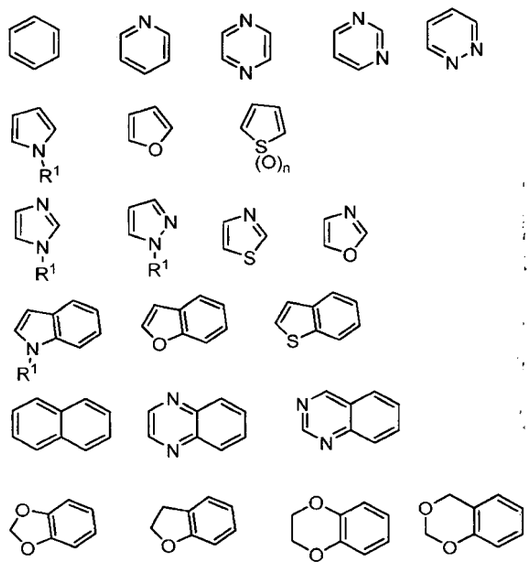

(i) Phenyl;

(ii) Naphthyl;

(iii) A 5 or 6 membered monocyclic heteroaryl group which have 1-5 heteroatoms independently selected from the group consisting of O, N and S;

and (iv) An 8 to 10 membered bicyclic heteroaryl group which have 1-6 heteroatoms independently selected from the group consisting of O, N and S;

Ring A can be illustrated but not limited to the following:



wherein



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$R^1$ is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, $CF_3$, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N $R^2R^3$), wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N.

$R^{III}$ represents optionally 1-3 substituents independently selected from the group consisting of $C_1$-$C_5$ linear or branched alkyl, $C_1$-$C_5$ linear or branched haloalkyl, $C_1$-$C_5$ alkoxy, hydroxy, amino, $C_1$-$C_5$ alkylamino, C1-C6 dialkylamino, halogen, cyano, and nitro;

Z is selected from the group consisting of

(1') $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$;

(2') $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$;

(3') $(CH_2)_iN(R^7)C(O)$;

(4') $C(O)N(R^8)(CH_2)_j$;

(5') $(CH_2)_iN(R^7)S(O)_2$;

and (6') $S(O)_2N(R^8)(CH_2)_j$;

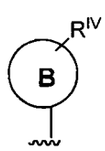
wherein

i is 0 or 1;

j is 0 or 1;

$R^7$ and $R^8$ are independently selected from the group consisting of hydrogen and alkyl;

Ring B is selected from the group consisting of:



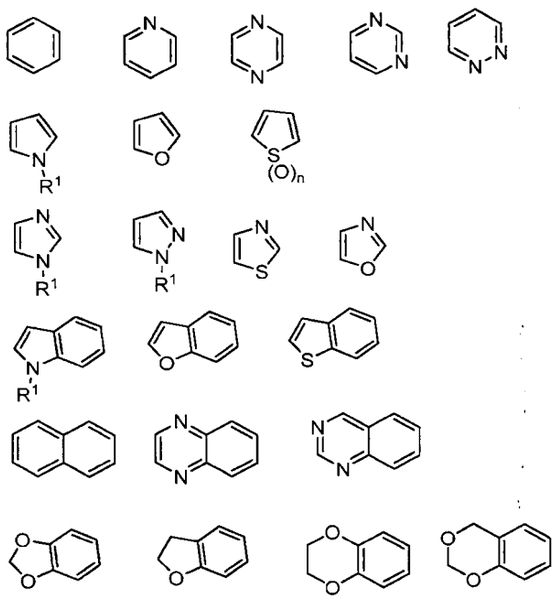

(i') Phenyl;

(ii') Naphthyl;

(iii') A 5 or 6 membered monocyclic heteroaryl group which have 1-3 heteroatoms independently selected from the group consisting of O, N and S;

and (iv') An 8 to 10 membered bicyclic heteroaryl group which have 1-3 heteroatoms independently selected from the group consisting of O, N and S;

Ring B can be illustrated but not limited to the following:



wherein

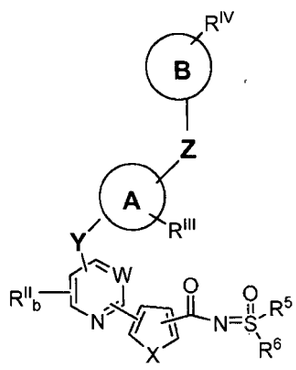
$R^1$ is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, $CF_3$, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N $R^2R^3$), wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

$R^{IV}$ represents optionally 1-3 substituents, independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, aryloxy, arylalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and —$NR^9R^{10}$; wherein $R^9$ and $R^{10}$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;



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In another aspect of the invention, the compounds of the present invention can be represented by the general formula II:




Formula II

wherein

W is C or N;

X is selected from the group consisting of $NR^1$, O, and $S(O)_n$;

n is 0 or an integer of from 1 to 2;

$R^1$ is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, $CF_3$, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N $R^2R^3$), wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

$R^5$ and $R^6$ are independently selected from the group consisting of hydrogen, halo, hydroxyl, $C_1$-$C_8$ alkyl, $C_1$-$C_8$ hydroxyalkyl, $C_1$-$C_8$ alkoxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, hydroxycarbonyl, hydroxycarbonylalkyl, amide, alkylamide, amidoalkyl, and sulfonate;

$R^{II}$ is independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkyl, aryloxy, aryloxyalkyl, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkoxy, hydroxyalkyl, ($NR^2R^3$)alkoxy, ($NR^2R^3$)alkenyl, ($NR^2R^3$)alkyl, ($NR^2R^3$)carbonylalkenyl, and ($NR^2R^3$)carbonylalkyl, wherein $R^2$ and $R^3$ are independently selected from the group consisting



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of hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

b is 0 or an integer of from 1 to 2;

Y is selected from the group consisting of:

(1') —$(CH_2)$g—O—$(CH_2)$h—;
(2') —$(CH_2)$g—$NR^1$—$(CH_2)$h—;
(3') —$(CH_2)$g—$S(O)_n$—$(CH_2)$h—;
(4') —$(CH_2)$g—$SO_2N\ R^2$—$(CH_2)$h—;
(5') —$(CH_2)$g—$NR^2SO_2$—$(CH_2)$h—;
(6') —$(CH_2)$g— CO—$(CH_2)$h—;
(7') —$(CH_2)$g— $C(O)NR^2$—$(CH_2)$h—;
(8') —$(CH_2)$g— $NR^2C(O\ )$—$(CH_2)$h—;
(9') —$(CH_2)$g—C≡C—$(CH_2)$h—;
(10') —$(CH_2)$g— $NR^2C(O)NR^3$—$(CH_2)$h—;
(11') —$(CH_2)$g—$(CH_2)$h—;
(12') —$(CH_2)$g—$CF_2$—$(CH_2)$h—;
(13') —$(CH_2)$g—$CCl_2$—$(CH_2)$h—;
(14') —$(CH_2)$g—CHF—$(CH_2)$h—;
(15') —$(CH_2)$g—CH(OH)—$(CH_2)$h—;
(16') —$(CH_2)$g—$CR^2R^3$—$(CH_2)$h—;
(17') —$(CH_2)$g—C=C—$(CH_2)$h—;
and (18') a single bond;

wherein

g is 0 or an integer of from 1 to 3;

h is 0 or an integer of from 1 to 3;

$R^1$ is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, $CF_3$, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N $R^2R^3$), wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

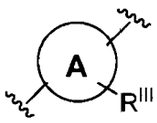
$R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and



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heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered cyclic ring;

Ring A is selected from the group consisting of:



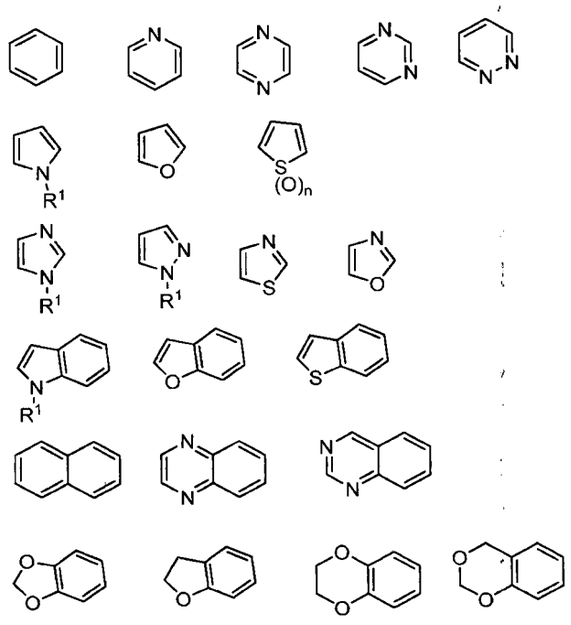

(i) Phenyl;

(ii) Naphthyl;

(iii) A 5 or 6 membered monocyclic heteroaryl group which have 1-5 heteroatoms independently selected from the group consisting of O, N and S;

and (iv) An 8 to 10 membered bicyclic heteroaryl group which have 1-6 heteroatoms independently selected from the group consisting of O, N and S;

Ring A can be illustrated but not limited to the following:



wherein

$R^1$ is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, $CF_3$, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N $R^2R^3$), wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl,



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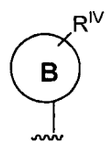
haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$ and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

$R^{III}$ represents optionally 1-3 substituents independently selected from the group consisting of $C_1$-$C_5$ linear or branched alkyl, $C_1$-$C_5$ linear or branched haloalkyl, $C_1$-$C_5$ alkoxy, hydroxy, amino, $C_1$-$C_5$ alkylamino, C1-C6 dialkylamino, halogen, cyano, and nitro;

Z is selected from the group consisting of

(1') $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$;
(2') $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$;
(3') $(CH_2)_iN(R^7)C(O)$;
(4') $C(O)N(R^8)(CH_2)_j$;
(5') $(CH_2)_iN(R^7)S(O)_2$;
and (6') $S(O)_2N(R^8)(CH_2)_j$;
wherein
i is 0 or 1;
j is 0 or 1;
$R^7$ and $R^8$ are independently selected from the group consisting of hydrogen and alkyl.

Ring B is selected from the group consisting of:

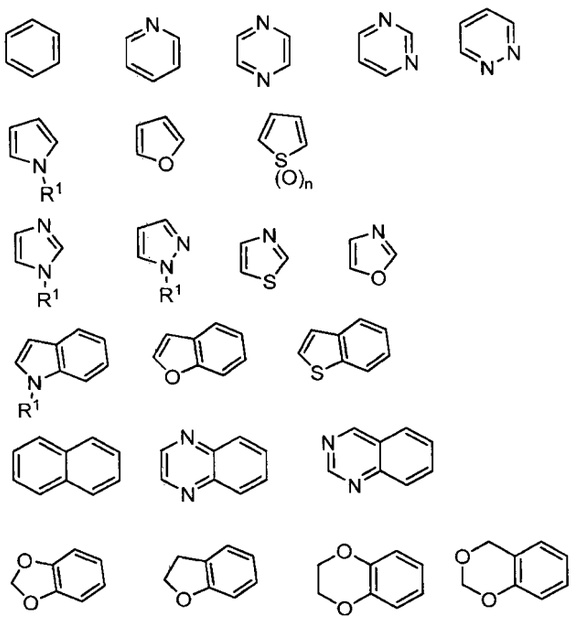



(i') Phenyl;
(ii') Naphthyl;
(iii') A 5 or 6 membered monocyclic heteroaryl group which have 1-3 heteroatoms independently selected from the group consisting of O, N and S;
and (iv') An 8 to 10 membered bicyclic heteroaryl group which have 1-3 heteroatoms independently selected from the group consisting of O, N and S;

Ring B can be illustrated but not limited to the following:



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wherein

$R^1$ is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, $CF_3$, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N $R^2R^3$), wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

$R^{IV}$ represents optionally 1-3 substituents, independently selected from the group consisting of alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, aryloxy, arylalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and —$NR^9R^{10}$; wherein $R^9$ and $R^{10}$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;
and including any pharmaceutically acceptable salt or prodrug.

Unless otherwise indicated, reference to a compound should be construed broadly to include compounds, pharmaceutically acceptable salts, prodrugs, tautomers, stereoisomers, diastereoisomers, alternate solid forms, crystal forms, polymorphic forms, hydrates, solvates, metabolites, mixtures of stereoisomers, mixtures of crystal forms, non-covalent complexes, and combinations thereof, of a chemical entity of a depicted structure or a chemical name. Whenever



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there is a conflict between chemical name and its structure drawing, the structure drawing should be used to interpret the compound of the present invention.

A pharmaceutically acceptable salt is any salt of the parent compound that is suitable for administration to an animal or human. A pharmaceutically acceptable salt also refers to any salt which may form *in vivo* as a result of administration of an acid, another salt, or a prodrug which is converted into an acid or salt. A salt comprises one or more ionic forms of the compound, such as a conjugate acid or base, associated with one or more corresponding counter-ions. Salts can form from or incorporate one or more deprotonated acidic groups (e.g. carboxylic acids), one or more protonated basic groups (e.g. amines), or both (e.g. zwitterions).

A "prodrug" is a compound, which when administered to the body of a subject (such as a mammal), breaks down in the subject's metabolic pathway to provide an active compound of Formula I. More specifically, a prodrug is an active or inactive "masked" compound that is modified chemically through in vivo physiological action, such as hydrolysis, metabolism and the like, into a compound of this invention following administration of the prodrug to a subject or patient. One common form of a prodrug is a masked carboxylic acid group. Examples of a masked carboxylate anion include a variety of esters, such as alkyl (for example, methyl, ethyl), cycloalkyl (for example, cyclohexyl), aralkyl (for example, benzyl, p-methoxybenzyl), and alkylcarbonyloxyalkyl (for example, pivaloyloxymethyl). Amines have been masked as arylcarbonyloxymethyl substituted derivatives which are cleaved by esterases in vivo releasing the free drug and formaldehyde (Bundgaard J. Med. Chem. 2503 (1989)). Also, drugs containing an acidic NH group, such as imidazole, imide, indole and the like, have been masked with N-acyloxymethyl groups (Bundgaard Design of Prodrugs, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers. EP 039,051 (Sloan and Little, Apr. 11, 1981) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use.For example, conversion may occur by hydrolysis of an ester group or some other biologically labile group. Prodrug preparation is well known in the art. For example, "Prodrugs and Drug Delivery Systems," which is a chapter in Richard B. Silverman, *Organic Chemistry of Drug Design and Drug Action*, 2d Ed., Elsevier Academic Press: Amsterdam, 2004, pp. 496-557, provides further detail on the subject.



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Tautomers are isomers that are in rapid equilibrium with one another. For example, tautomers may be related by transfer of a proton, hydrogen atom, or hydride ion. Unless stereochemistry is explicitly and unambiguously depicted, a structure is intended to include every possible stereoisomer, both pure or in any possible mixture.

Alternate solid forms are different solid forms than those that may result from practicing the procedures described herein. For example, alternate solid forms may be amorphous forms, crystal forms, polymorphs, and the mixtures thereof.

Non-covalent complexes are complexes that may form between the compound and one or more additional chemical species that do not involve a covalent bonding interaction between the compound and the additional chemical species. They may or may not have a specific ratio between the compound and the additional chemical species. Examples might include solvates, hydrates, charge transfer complexes, and the like.

## 2. Uses, Formulation and Administration

The present invention is also directed to the use of the compounds as protein tyrosine kinase modulators and inhibitors. These compounds can be used to treat diseases related to unregulated tyrosine kinase signal transduction, for example, various cancers, blood vessel proliferative disorders, fibrotic disorders, and neurodegenerative diseases. In particular, compounds of the present invention are useful for the treatment and/or prevention of colorectal cancer, lung cancer, hematological cancer, renal cancer, liver cancer, breast cancer, diabetic retinopathy, macular degeneration, age-related macular degeneration, retinopathy of prematurity, ocular angiogenesis, retinal edema, retinal ischemia, diabetic macular edema, cystoid macular edema, retinal vein occlusion, branch vein occlusion, preretinal neovascularization, laser-induced choroidal neovascularization, neovascularization associated with keratoplasty, glaucoma and ocular tumors, arthritis, restenosis, hepatic cirrhosis, atherosclerosis, psoriasis, diabetes mellitus, wound healing, transplant rejection, inflammation, neurodegenerative diseases and immune disorders in the human being.

For the purposes of this disclosure, "treat," "treating," or "treatment" refer to the diagnosis, cure, mitigation, treatment, or prevention of disease or other undesirable condition.

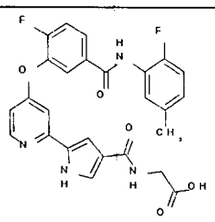
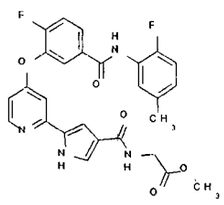
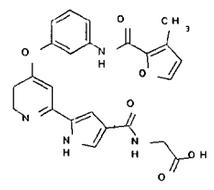
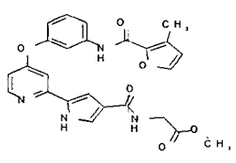
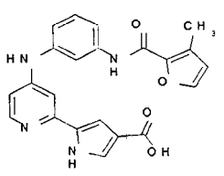
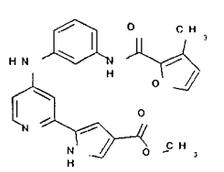
The present invention is also directed to the preparation of a medicament for the treatment and prevention of diseases and conditions related with abnormal activities of tyrosine kinase receptors. The medicament contains a pharmaceutical acceptable composition, which comprises the therapeutic effective amount of the compounds of present invention, together with a pharmaceutical acceptable carrier.

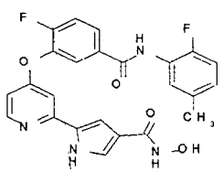
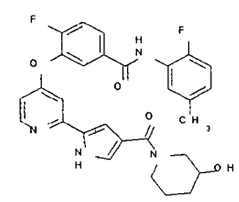
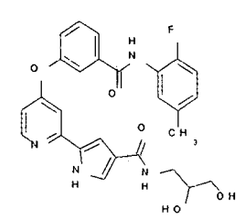
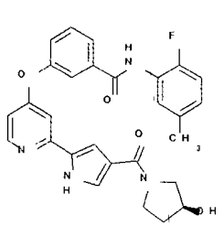
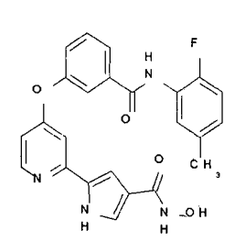
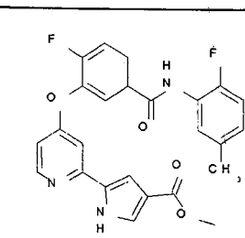
The pharmaceutical acceptable compositions contain therapeutic effective amount of the compounds of the present invention. These compositions can be used as a medicament and administered to a mammal, such as a person, in need thereof. Different types of suitable dosage forms and medicaments are well known in the art, and can be readily adapted for delivery of the compounds of the present invention, such as, but not limited to, systematic, parenteral, local and topical delivery. The dosage forms can be tablets, capsules, intravenous injections, intramuscular injections, local injections, topical creams, gels and ointments, eye drops, ophthalmic solutions, ophthalmic suspensions, ophthalmic emulsions, intravitreal injections, subtenon injections, ophthalmic biodrodible implant, and non-bioeordible ophthalmic inserts or depots, nasal sprays and ointment, various rectal or vaginal preparations.

### 3. Examples

Some of the compounds of the present invention are listed in Table I.

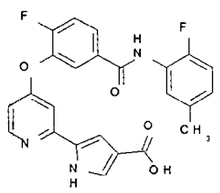
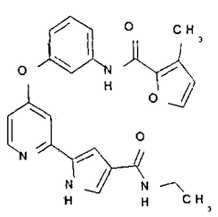
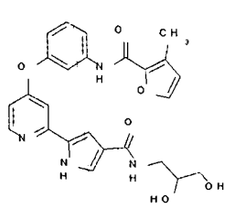
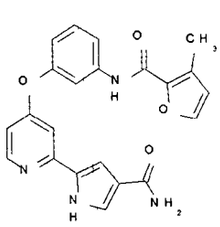
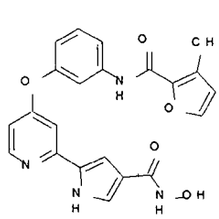
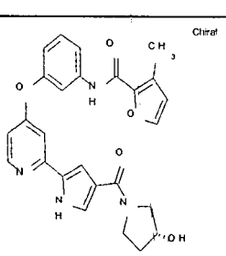
**Table 1: Exemplified Compounds of the Present Invention**

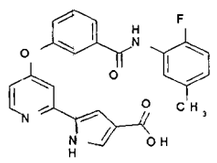
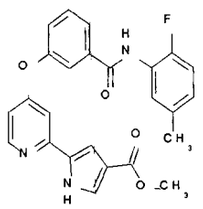
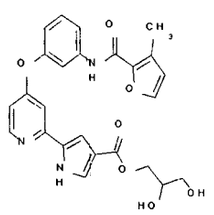
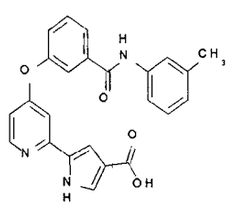
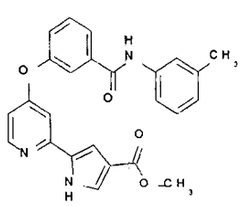
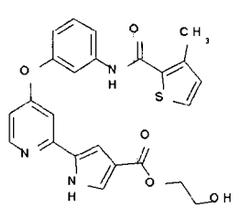
| Example # | Chemical Sructure | MW | Chemical Name |
|---|---|---|---|
| 1 |  | 506 | [({5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrol-3-yl}carbonyl)amino]acetic acid |
| 2 |  | 520 | methyl [({5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrol-3-yl}carbonyl)amino]acetate |
| 3 |  | 460 | ({[5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrol-3-yl]carbonyl}amino)acetic acid |
| 4 |  | 474 | methyl ({[5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrol-3-yl]carbonyl}amino)acetate |
| 5 |  | 402 | 5-[4-({3-[(3-methyl-2-furoyl)amino]phenyl}amino)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid |
| 6 |  | 416 | methyl 5-[4-({3-[(3-methyl-2-furoyl)amino]phenyl}amino)pyridin-2-yl]-1H-pyrrole-3-carboxylate |

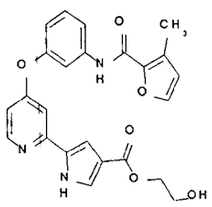
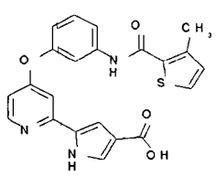
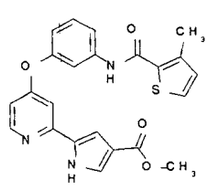
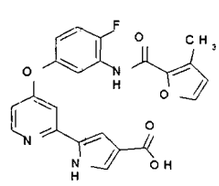
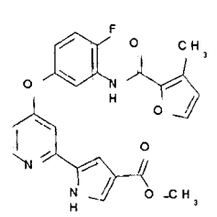
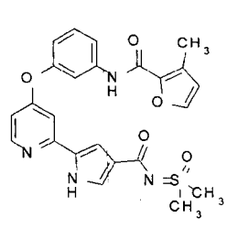
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|---|---|---|---|
| 7 |  | 464 | 5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-N-hydroxy-1H-pyrrole-3-carboxamide |
| 8 |  | 533 | 4-fluoro-N-(2-fluoro-5-methylphenyl)-3-[(2-{4-[(3-hydroxypiperidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]benzamide |
| 9 |  | 505 | N-(2,3-dihydroxypropyl)-5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxamide |
| 10 |  | 501 | N-(2-fluoro-5-methylphenyl)-3-[(2-{4-[(3-hydroxypyrrolidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]benzamide |
| 11 |  | 446 | 5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-N-hydroxy-1H-pyrrole-3-carboxamide |
| 12 |  | 463 | methyl 5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate |

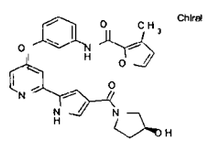
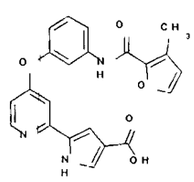
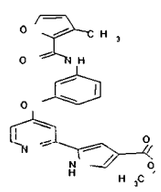
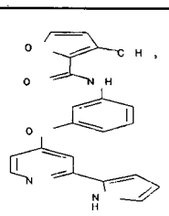
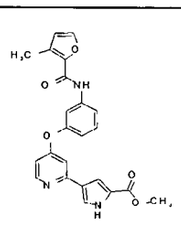
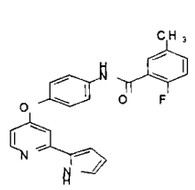
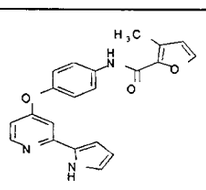


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| | | | |
|---|---|---|---|
| 13 |  | 449 | 5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid |
| 14 |  | 430 | N-ethyl-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide |
| 15 |  | 476 | N-(2,3-dihydroxypropyl)-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide |
| 16 |  | 402 | 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide |
| 17 |  | 418 | N-hydroxy-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide |
| 18 |  | 472 | N-(3-{[2-(4-{[(3R)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-methyl-2-furamide |

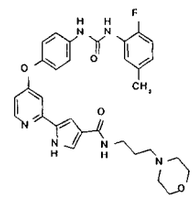
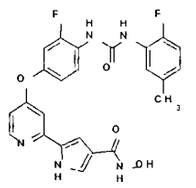
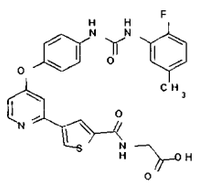
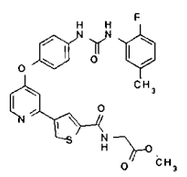
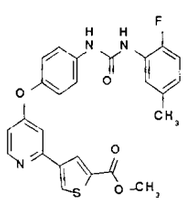
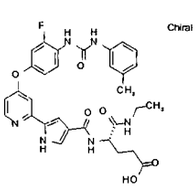
| | | | |
|---|---|---|---|
| 19 |  | 431 | 5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid |
| 20 |  | 445 | methyl 5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate |
| 21 |  | 477 | 2,3-dihydroxypropyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate |
| 22 |  | 413 | 5-[4-(3-{[(3-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid |
| 23 |  | 427 | methyl 5-[4-(3-{[(3-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate |
| 24 |  | 464 | 2-hydroxyethyl 5-[4-(3-{[(3-methyl-2-thienyl)carbonyl]amino}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate |

| | | | |
|---|---|---|---|
| 25 |  | 447 | 2-hydroxyethyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate |
| 26 |  | 419 | 5-[4-(3-{[(3-methyl-2-thienyl)carbonyl]amino}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid |
| 27 |  | 433 | methyl 5-[4-(3-{[(3-methyl-2-thienyl)carbonyl]amino}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate |
| 28 |  | 421 | 5-(4-{4-fluoro-3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid |
| 29 |  | 435 | methyl 5-(4-{4-fluoro-3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate |
| 30 |  | 479 | N-[dimethyl(oxido)-lambda~4~-sulfanylidene]-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide |

| | | | |
|---|---|---|---|
| 31 |  | 472 | N-(3-{[2-(4-{[(3S)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-methyl-2-furamide |
| 32 |  | 403 | 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid |
| 33 |  | 417 | methyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate |
| 34 |  | 359 | 3-methyl-N-(3-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-2-furamide |
| 35 |  | 417 | methyl 4-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-2-carboxylate |
| 36 |  | 387 | 2-fluoro-5-methyl-N-(4-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)benzamide |
| 37 |  | 359 | 3-methyl-N-(4-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-2-furamide |

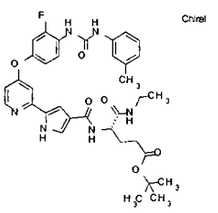
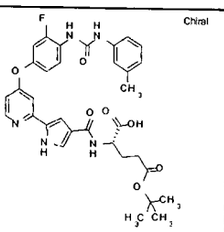
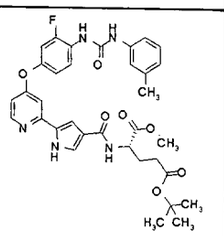
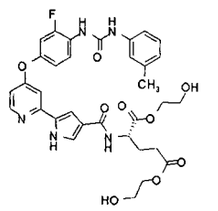
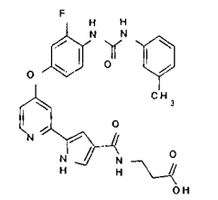
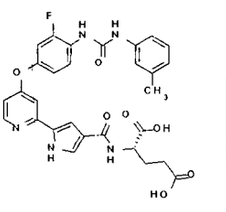


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| Example # | Chemical Sructure | MW | Chemical Name |
|---|---|---|---|
| 38 |  | 573 | 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-(3-morpholin-4-ylpropyl)-1H-pyrrole-3-carboxamide |
| 39 |  | 479 | 5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-hydroxy-1H-pyrrole-3-carboxamide |
| 40 |  | 521 | {[(4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-2-thienyl)carbonyl]amino}acetic acid |
| 41 |  | 535 | methyl {[(4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-2-thienyl)carbonyl]amino}acetate |
| 42 |  | 478 | methyl 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}thiophene-2-carboxylate |
| 43 |  | 603 | (4S)-5-(ethylamino)-4-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}-5-oxopentanoic acid |

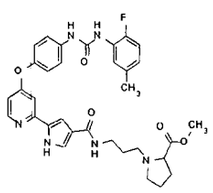
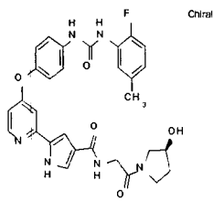
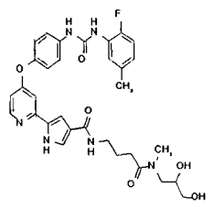
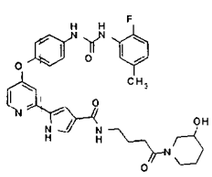
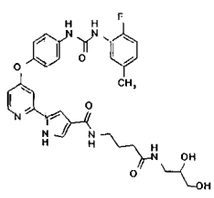
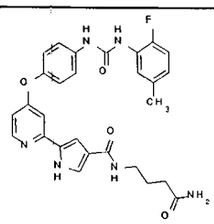


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| | | | |
|---|---|---|---|
| 44 |  | 659 | tert-butyl (4S)-5-(ethylamino)-4-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}-5-oxopentanoate |
| 45 |  | 632 | (2S)-5-tert-butoxy-2-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}-5-oxopentanoic acid |
| 46 |  | 646 | 5-tert-butyl 1-methyl 2-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioate |
| 47 |  | 664 | bis(2-hydroxyethyl) 2-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioate |
| 48 |  | 518 | 3-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}propanoic acid |
| 49 |  | 576 | 2-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioic acid |

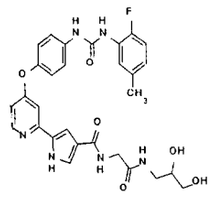
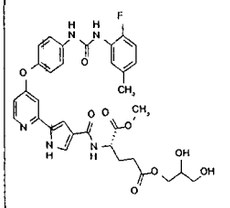
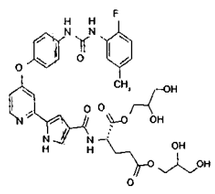
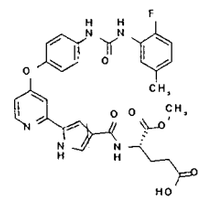
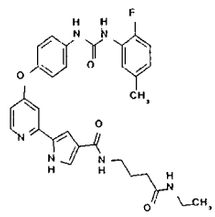
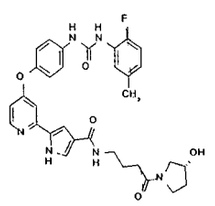


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|---|---|---|---|
| 50 |  | 615 | methyl 1-(3-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}propyl)pyrrolidine-2-carboxylate |
| 51 |  | 573 | 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-{2-[(3S)-3-hydroxypyrrolidin-1-yl]-2-oxoethyl}-1H-pyrrole-3-carboxamide |
| 52 |  | 619 | N-{4-[(2,3-dihydroxypropyl)(methyl)amino]-4-oxobutyl}-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide |
| 53 |  | 615 | 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-[4-(3-hydroxypiperidin-1-yl)-4-oxobutyl]-1H-pyrrole-3-carboxamide |
| 54 |  | 605 | N-{4-[(2,3-dihydroxypropyl)amino]-4-oxobutyl}-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide |
| 55 |  | 531 | N-(4-amino-4-oxobutyl)-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide |

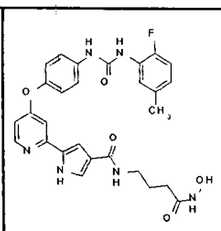
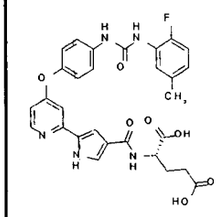
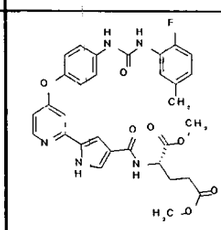
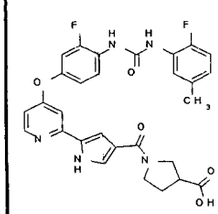
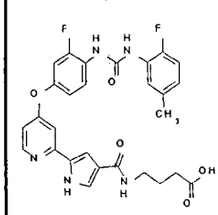
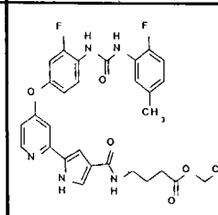


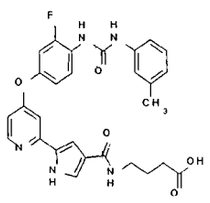
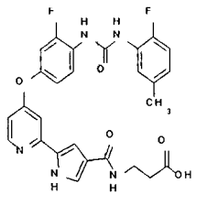
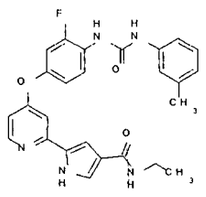
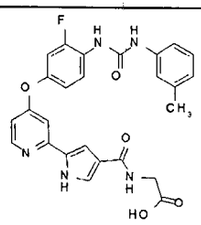
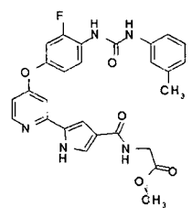
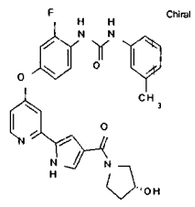
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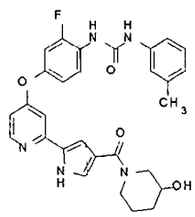
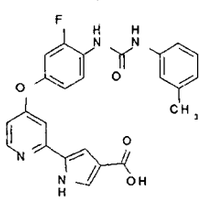
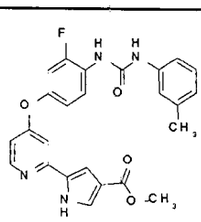
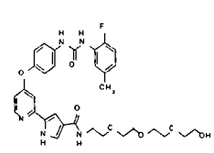
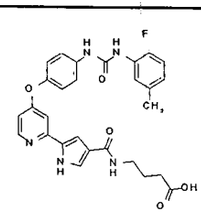
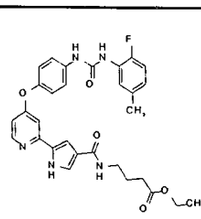
| | | | |
|---|---|---|---|
| 56 |  | 577 | N-{2-[(2,3-dihydroxypropyl)amino]-2-oxoethyl}-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide |
| 57 |  | 664 | 5-(2,3-dihydroxypropyl) 1-methyl 2-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioate |
| 58 |  | 724 | bis(2,3-dihydroxypropyl) 2-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioate |
| 59 |  | 590 | 4-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}-5-methoxy-5-oxopentanoic acid |
| 60 |  | 559 | N-[4-(ethylamino)-4-oxobutyl]-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide |
| 61 |  | 601 | 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-[4-(3-hydroxypyrrolidin-1-yl)-4-oxobutyl]-1H-pyrrole-3-carboxamide |

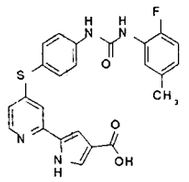
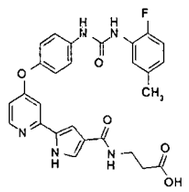
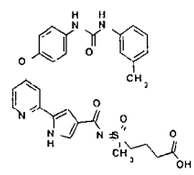
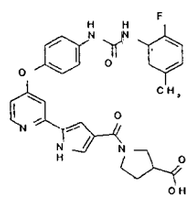
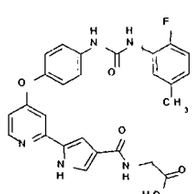
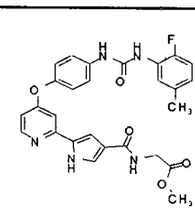


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|---|---|---|---|
| 62 |  | 547 | 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-[4-(hydroxyamino)-4-oxobutyl]-1H-pyrrole-3-carboxamide |
| 63 |  | 576 | 2-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioic acid |
| 64 |  | 604 | dimethyl 2-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioate |
| 65 |  | 562 | 1-[(5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]pyrrolidine-3-carboxylic acid |
| 66 |  | 550 | 4-{[(5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}butanoic acid |
| 67 |  | 578 | ethyl 4-{[(5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}butanoate |

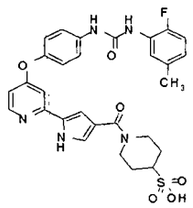
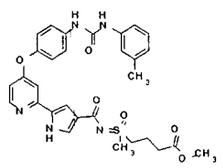
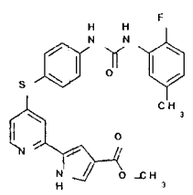
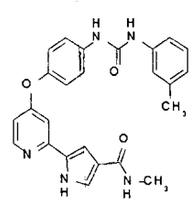
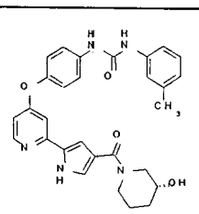
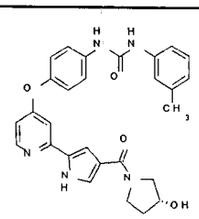
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|---|---|---|---|
| 68 |  | 532 | 4-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}butanoic acid |
| 69 |  | 536 | 3-{[(5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}propanoic acid |
| 70 |  | 474 | N-ethyl-5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide |
| 71 |  | 503 | {[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}acetic acid |
| 72 |  | 518 | methyl {[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}acetate |
| 73 |  | 516 | 1-(2-fluoro-4-{[2-(4-{[(3R)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-(3-methylphenyl)urea |

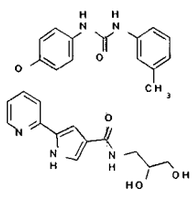
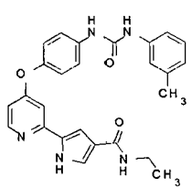
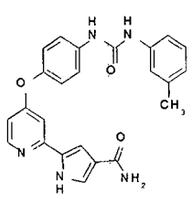
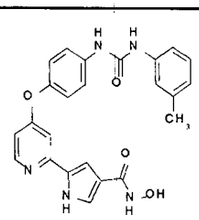
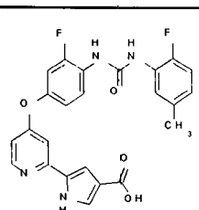
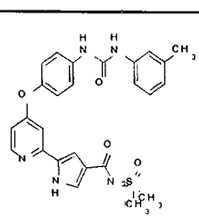
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|---|---|---|---|
| 74 |  | 530 | 1-{2-fluoro-4-[(2-{4-[(3-hydroxypiperidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]phenyl}-3-(3-methylphenyl)urea |
| 75 |  | 446 | 5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid |
| 76 |  | 460 | methyl 5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate |
| 77 |  | 622 | 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-(2-{2-[2-(2-hydroxyethoxy)ethoxy]ethoxy}ethyl)-1H-pyrrole-3-carboxamide |
| 78 |  | 532 | 4-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}butanoic acid |
| 79 |  | 560 | ethyl 4-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}butanoate |

| | | | |
|---|---|---|---|
| 80 |  | 463 | 5-(4-{[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenyl]thio}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid |
| 81 |  | 518 | 3-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}propanoic acid |
| 82 |  | 576 | 4-{S-methyl-N-[(5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]sulfonimidoyl}butanoic acid |
| 83 |  | 544 | 1-[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]pyrrolidine-3-carboxylic acid |
| 84 |  | 503 | {[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}acetic acid |
| 85 |  | 518 | methyl {[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}acetate |



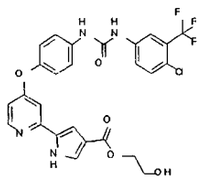
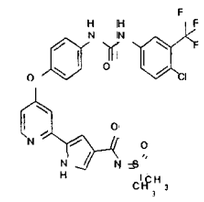
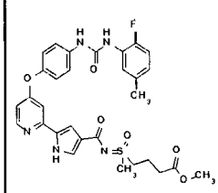
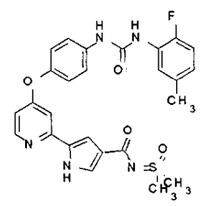
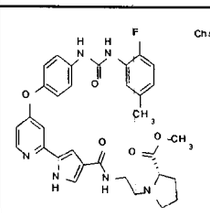
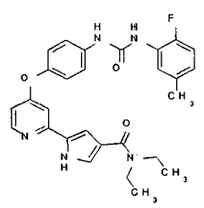
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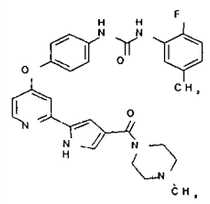
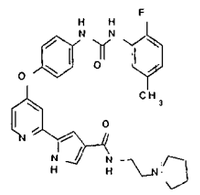
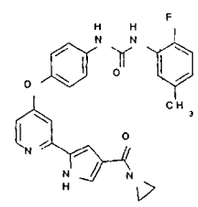
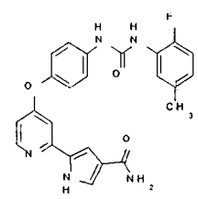
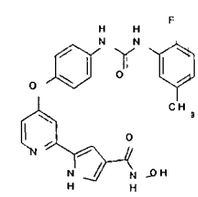
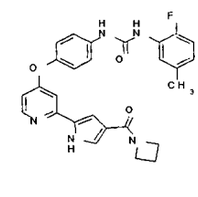
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|---|---|---|---|
| 86 |  | 594 | 1-[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]piperidine-4-sulfonic acid |
| 87 |  | 590 | methyl 4-{S-methyl-N-[(5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]sulfonimidoyl}butanoate |
| 88 |  | 477 | methyl 5-(4-{[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenyl]thio}pyridin-2-yl)-1H-pyrrole-3-carboxylate |
| 89 |  | 441 | N-methyl-5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide |
| 90 |  | 512 | 1-{4-[(2-{4-[(3-hydroxypiperidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]phenyl}-3-(3-methylphenyl)urea |
| 91 |  | 498 | 1-{4-[(2-{4-[(3-hydroxypyrrolidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]phenyl}-3-(3-methylphenyl)urea |

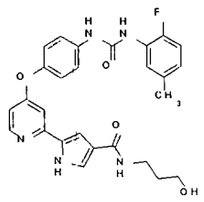
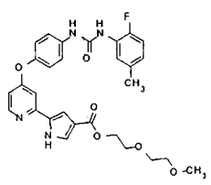
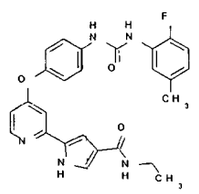
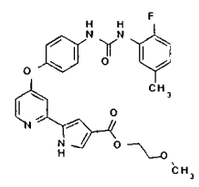
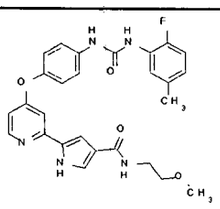
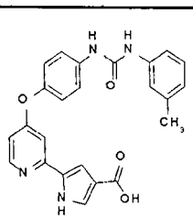
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| 92 |  | 502 | N-(2,3-dihydroxypropyl)-5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide |
| 93 |  | 456 | N-ethyl-5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide |
| 94 |  | 427 | 5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide |
| 95 |  | 443 | N-hydroxy-5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide |
| 96 |  | 464 | 5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid |
| 97 |  | 504 | N-[dimethyl(oxido)-lambda~4~-sulfanylidene]-5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide |



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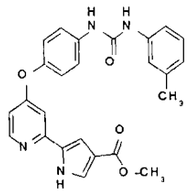
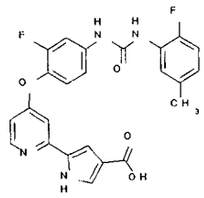
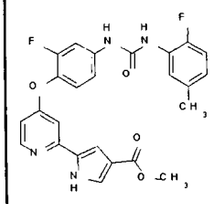
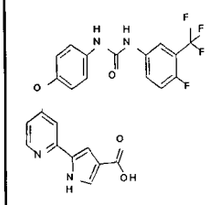
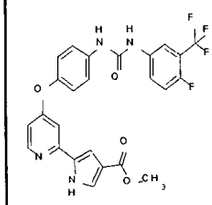
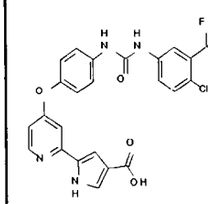
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|---|---|---|---|
| 98 |  | 561 | 2-hydroxyethyl 5-(4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate |
| 99 |  | 592 | 5-(4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}pyridin-2-yl)-N-[dimethyl(oxido)-lambda~4~-sulfanylidene]-1H-pyrrole-3-carboxamide |
| 100 |  | 608 | methyl 4-{N-[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]-S-methylsulfonimidoyl}butanoate |
| 101 |  | 522 | N-[dimethyl(oxido)-lambda~4~-sulfanylidene]-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide |
| 102 |  | 601 | methyl (2S)-1-(2-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}ethyl)pyrrolidine-2-carboxylate |
| 103 |  | 502 | N,N-diethyl-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide |

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|---|---|---|---|
| 104 |  | 529 | 1-(2-fluoro-5-methylphenyl)-3-{4-[(2-{4-[(4-methylpiperazin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]phenyl}urea |
| 105 |  | 543 | 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-(2-pyrrolidin-1-ylethyl)-1H-pyrrole-3-carboxamide |
| 106 |  | 471 | 1-[4-({2-[4-(aziridin-1-ylcarbonyl)-1H-pyrrol-2-yl]pyridin-4-yl}oxy)phenyl]-3-(2-fluoro-5-methylphenyl)urea |
| 107 |  | 445 | 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide |
| 108 |  | 461 | 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-hydroxy-1H-pyrrole-3-carboxamide |
| 109 |  | 486 | 1-[4-({2-[4-(azetidin-1-ylcarbonyl)-1H-pyrrol-2-yl]pyridin-4-yl}oxy)phenyl]-3-(2-fluoro-5-methylphenyl)urea |

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|---|---|---|---|
| 110 |  | 504 | 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-(3-hydroxypropyl)-1H-pyrrole-3-carboxamide |
| 111 |  | 549 | 2-(2-methoxyethoxy)ethyl 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate |
| 112 |  | 474 | N-ethyl-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide |
| 113 |  | 505 | 2-methoxyethyl 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate |
| 114 |  | 504 | 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-(2-methoxyethyl)-1H-pyrrole-3-carboxamide |
| 115 |  | 428 | 5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid |

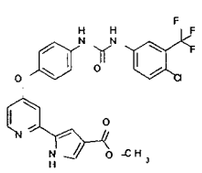
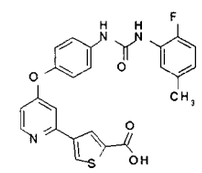
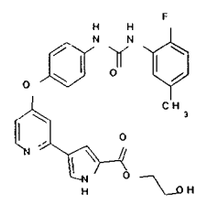
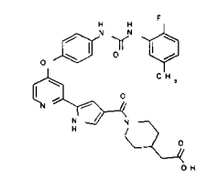
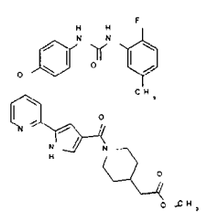
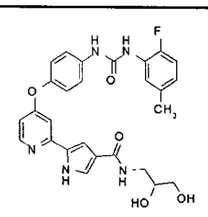


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| 116 |  | 442 | methyl 5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate |
| 117 |  | 464 | 5-{4-[2-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid |
| 118 |  | 478 | methyl 5-{4-[2-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate |
| 119 |  | 500 | 5-(4-{4-[({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid |
| 120 |  | 514 | methyl 5-(4-{4-[({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate |
| 121 |  | 517 | 5-(4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid |

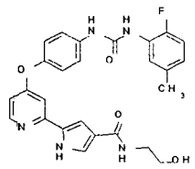
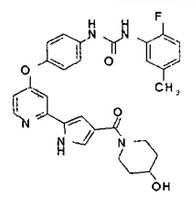
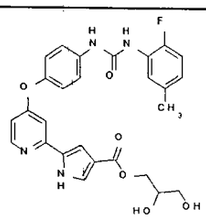
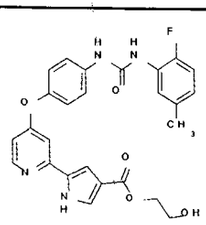
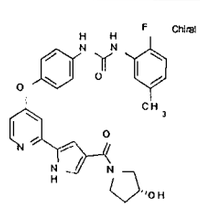
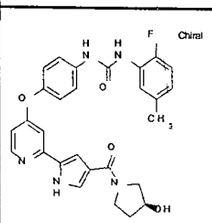


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| | | | |
|---|---|---|---|
| 122 |  | 531 | methyl 5-(4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate |
| 123 |  | 463 | 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}thiophene-2-carboxylic acid |
| 124 |  | 490 | 2-hydroxyethyl 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxylate |
| 125 |  | 572 | {1-[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]piperidin-4-yl}acetic acid |
| 126 |  | 586 | methyl {1-[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]piperidin-4-yl}acetate |
| 127 |  | 520 | N-(2,3-dihydroxypropyl)-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide |

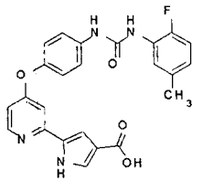
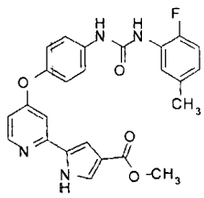
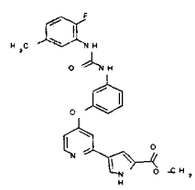
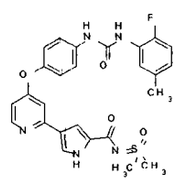
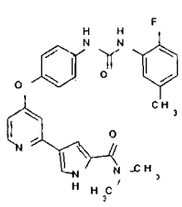
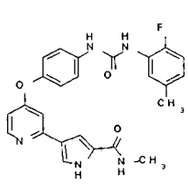


231

| | | | |
|---|---|---|---|
| 128 |  | 490 | 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-(2-hydroxyethyl)-1H-pyrrole-3-carboxamide |
| 129 |  | 530 | 1-(2-fluoro-5-methylphenyl)-3-{4-[(2-{4-[(4-hydroxypiperidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]phenyl}urea |
| 130 |  | 521 | 2,3-dihydroxypropyl 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate |
| 131 |  | 490 | 2-hydroxyethyl 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate |
| 132 |  | 516 | 1-(2-fluoro-5-methylphenyl)-3-(4-{[2-(4-{[(3R)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)urea |
| 133 |  | 516 | 1-(2-fluoro-5-methylphenyl)-3-(4-{[2-(4-{[(3S)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)urea |

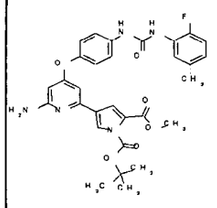
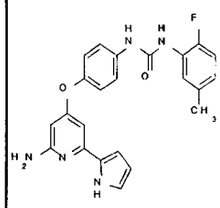
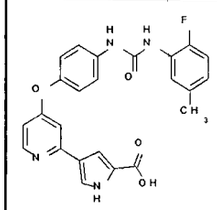
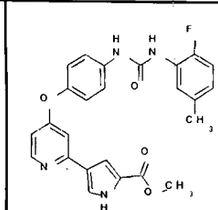
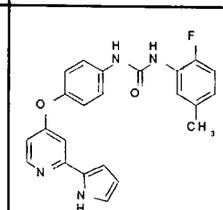
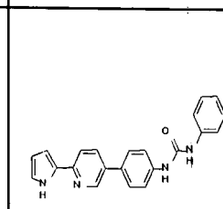


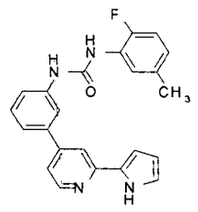
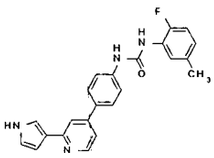
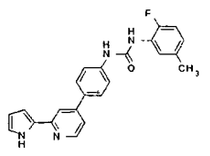
232

| | | | |
|---|---|---|---|
| 134 |  | 446 | 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid |
| 135 |  | 460 | methyl 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate |
| 136 |  | 460 | methyl 4-{4-[3-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxylate |
| 137 |  | 522 | N-[dimethyl(oxido)-lambda~4~-sulfanylidene]-4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxamide |
| 138 |  | 474 | 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N,N-dimethyl-1H-pyrrole-2-carboxamide |
| 139 |  | 459 | 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-methyl-1H-pyrrole-2-carboxamide |



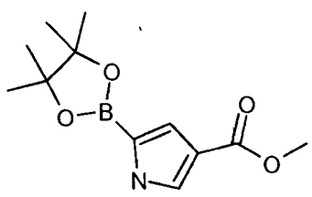
237

| | | | |
|---|---|---|---|
| 140 |  | 576 | 1-tert-butyl 2-methyl 4-{6-amino-4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-1,2-dicarboxylate |
| 141 |  | 417 | 1-(4-{[2-amino-6-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-(2-fluoro-5-methylphenyl)urea |
| 142 |  | 446 | 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxylic acid |
| 143 |  | 460 | methyl 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxylate |
| 144 |  | 402 | 1-(2-fluoro-5-methylphenyl)-3-(4-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)urea |
| 145 |  | 354 | 1-phenyl-3-{4-[6-(1H-pyrrol-2-yl)pyridin-3-yl]phenyl}urea |

| | | | |
|---|---|---|---|
| 146 |  | 386 | 1-(2-fluoro-5-methylphenyl)-3-{3-[2-(1H-pyrrol-2-yl)pyridin-4-yl]phenyl}urea |
| 147 |  | 386 | 1-(2-fluoro-5-methylphenyl)-3-{4-[2-(1H-pyrrol-3-yl)pyridin-4-yl]phenyl}urea |
| 148 |  | 386 | 1-(2-fluoro-5-methylphenyl)-3-{4-[2-(1H-pyrrol-2-yl)pyridin-4-yl]phenyl}urea |

### 3.1 Compound Synthesis and Characterization

Preparation of methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-3-carboxylate

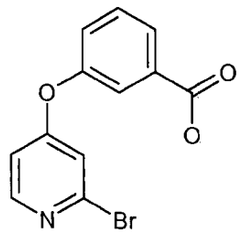


To a mixture of methyl-1H-pyrrole-3-carboxylate (5.0 g, 39.9 mmol), bis(pinacolato)diboron (5.37 g, 21.1 mmol), 4,4'-di-tert-butyl-2,2'-bipyridine (0.054 g, 0.20 mmol) and $[Ir(OMe)(COD)]_2$ (0.067 g, 0.099 mmol) was added cyclohexane (60 mL). The mixture stirred at 90°C for 5 hours. The mixture was cooled to room temperature and filtered, washing with ample amounts of water and twice with hexanes. The light orange solid was collected and dried in a vacuum oven at 55°C to afford methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-3-carboxylate (6.99 g, 70% yield).

Preparation of 3-(2-Bromo-pyridin-4-yloxy)-benzoic acid



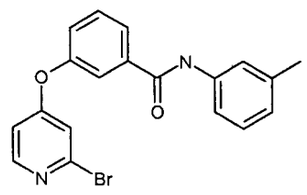
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A mixture of 2-bromo-4-chloro-pyridine (200mg, 1.04mmol), methyl-3-hydroxybenzoate (158mg, 1.04mmol), cesium carbonate (507mg, 1.56mmol) in 10ml of anhydrous DMSO was heated at 66°C for 5 hours. The mixture was diluted with ethyl acetate (100ml), washed with brine (3x50ml), dried over $Na_2SO_4$ and evaporated to give a colorless oil. The oil was dissolved in MeOH (8ml), and 2M NaOH solution (4ml, 8mmol) was added. The mixture was heated at 60°C for 20 minutes, poured into 50ml of water, and acidified to pH = 4. The precipitates were filtered, washed with water and dried *in vacuo* to give 3-(2-bromo-pyridin-4-yloxy)-benzoic acid as white solid. Yield: 170mg, 56%.

$^1$H NMR (DMSO-$d_6$) δ: 13.24 (br. s., 1H), 8.27 (d, J = 5.9 Hz, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.58 - 7.68 (m, 2H), 7.45 - 7.52 (m, 1H), 7.19 (d, J = 2.1 Hz, 1H), 7.00 (dd, J = 5.7, 2.2 Hz, 1H)
LR MS (ES-): 292 (M-H), 294

Preparation of 3-(2-Bromo-pyridin-4-yloxy)-N-m-tolyl-benzamide



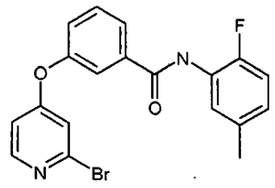
A mixture of 3-(2-bromo-pyridin-4-yloxy)-benzoic acid (170mg, 0.58mmol), HATU (265mg, 0.69mmol),) m-toluidine (93mg, 0.87mmol) and *N,N*-diisopropylethylamine (164mg, 1.28mmol) in anhydrous DMF (10ml) was stirred at room temperature for 20 minutes. The mixture was poured into 100ml of water. The precipitates were filtered, washed with water and dried *in vacuo* to give 3-(2-Bromo-pyridin-4-yloxy)-N-m-tolyl-benzamide as off-white solid. Yield: 150mg, 68%.

$^1$H NMR (DMSO-$d_6$) δ: 10.18 (s, 1H), 8.29 (d, J = 5.9 Hz, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.78 (s, 1H), 7.65 (t, J = 7.9 Hz, 1H), 7.50 - 7.60 (m, 2H), 7.45 (dd, J = 7.9, 1.8 Hz, 1H), 7.16 - 7.25 (m, 2H), 7.02 (dd, J = 5.7, 2.2 Hz, 1H), 6.92 (d, J = 7.6 Hz, 1H), 2.29 (s, 3H)
LR MS (ES+): 405 ($M+Na^+$), 407
LR MS (ES-): 381 (M-H), 383



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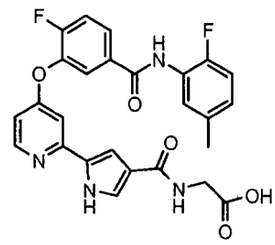
Preparation of 3-(2-Bromo-pyridin-4-yloxy)-N-(2-fluoro-5-methyl-phenyl)-benzamide



A mixture of 3-(2-bromo-pyridin-4-yloxy)-benzoic acid (200mg, 0.68mmol), HATU (312mg, 0.82mmol),) 2-fluoro-5-methylaniline (125mg, 1.0mmol) and *N,N*-diisopropylethylamine (193mg, 1.5mmol) in anhydrous DMF (10ml) was stirred at 60°C for 90 minutes. The mixture was poured into 100ml of water. The precipitates were filtered, washed with water and dried *in vacuo* to give 3-(2-bromo-pyridin-4-yloxy)-N-(2-fluoro-5-methyl-phenyl)-benzamide as off-white solid. Yield: 200mg, 74%.

Example 1

[({5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrol-3-yl}carbonyl)amino]acetic acid



To a stirred solution of methyl [({5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrol-3-yl}carbonyl)amino]acetate (110mg, 0.21mmol) in a mixture of solvents THF/MeOH (5ml/5ml) was added 1M NaOH solution (1ml, 1mmol). The mixture was stirred at room temperature for 1 hour, and poured into 100ml of water. 2M HCl was added until pH = 4. The precipitates were filtered, washed with water and dried *in vacuo* to give [({5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrol-3-yl}carbonyl)amino]acetic acid as white solid. Yield: 100mg, 93%.

$^1$H NMR (DMSO-$d_6$) δ: 12.41 (br. s., 1H), 11.87 (br. s., 1H), 10.12 (s, 1H), 8.42 (d, J = 5.6 Hz, 1H), 8.19 (t, J = 6.0 Hz, 1H), 7.95 - 8.04 (m, 2H), 7.63 (dd, J = 10.1, 8.7 Hz, 1H), 7.41 (dd, J = 3.1, 1.6 Hz, 1H), 7.35 (dd, J = 7.3, 1.8 Hz, 1H), 7.27 (d, J = 2.3 Hz, 1H), 7.09 - 7.18 (m, 2H),



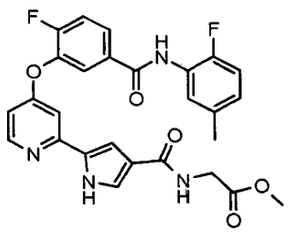
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7.04 (td, J = 5.3, 2.3 Hz, 1H), 6.81 (dd, J = 5.9, 2.3 Hz, 1H), 3.82 (d, J = 5.9 Hz, 2H), 2.27 (s, 3H)

LR MS (ES-): 505 (M-H)

Example 2

methyl [({5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrol-3-yl}carbonyl)amino]acetate



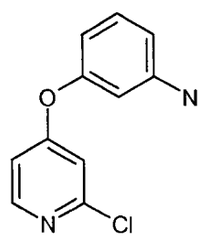
Similar procedure as Example 1.

$^1$H NMR (DMSO-$d_6$) δ: 11.95 (br. s., 1H), 10.12 (s, 1H), 8.44 (d, J = 5.9 Hz, 1H), 8.33 (t, J = 5.9 Hz, 1H), 7.97 - 8.03 (m, 2H), 7.61 - 7.67 (m, 1H), 7.45 (br. s., 1H), 7.33 - 7.37 (m, 1H), 7.30 (s, 1H), 7.18 (br. s., 1H), 7.14 (dd, J = 10.3, 8.5 Hz, 1H), 7.02 - 7.08 (m, 1H), 6.86 (br. s., 1H), 3.91 (d, J = 5.9 Hz, 2H), 3.61 (s, 3H), 2.27 (s, 3H)

LR MS (ES+): 521 (MH), 543 ($M+Na^+$)

LR MS (ES-): 519 (M-H)

Preparation of 4-(3-Aminophenoxy)-2-chloropyridine



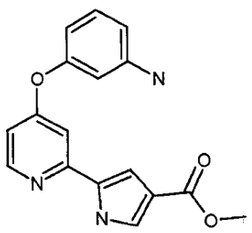
To a mixture of 3-aminophenol (3.7 g, 34.09 mmol) in DMSO (50 mL) was added Cs2CO3 (30.7 g, 94.46 mmol). The mixture stirred for 10 minutes and then 2,4-dichloropyridine (5.0 g, 33.79 mmol) was added. The mixture was stirred at 120°C for 1.5 h. The mixture was cooled and diluted with water. The aqueous solution was extracted with EtOAc (3 x 100 mL). The organic extracts were combined, dried over MgSO4 and concentrated to afford a dark oil. The



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oil was purified via column chromatography, eluting with 30-40% EtOAc/hexanes, to afford 4-(3-Aminophenoxy)-2-chloropyridine (6.63 g, 89%) as a brown solid.

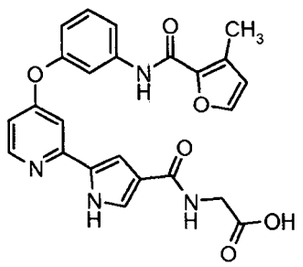
Preparation of methyl 5-[4-(3-aminophenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate



A mixture of 4-(3-aminophenoxy)-2-chloropyridine (4.0 g, 18.13mmol), methyl-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-3-carboxylate (6.82 g, 27.16mmol) and Pd(PPh3)4 (4.20 g, 3.63mmol) was added to a thick walled reaction vessel and purged with N2. A solution of 2M K2CO3 (13.59 mL) was added, followed by DME (70 mL). The reaction vessel was sealed and the mixture stirred at 92°C for 18 h. The reaction vessel was cooled to room temperature and the mixture was filtered over celite, washing with EtOAc. The filtrate was concentrated and the resultant dark oil was purified via column chromatography, eluting with 40-80% EtOAc/hexanes to afford methyl 5-[4-(3-aminophenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate (2.85 g, 51% yield).

Example 3

({[5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrol-3-yl]carbonyl}amino)acetic acid



Similar procedure as Example 1.

$^1$H NMR (DMSO-$d_6$) δ: 12.42 (br. s., 1H), 11.91 (br. s., 1H), 10.20 (s, 1H), 8.41 (d, J = 5.6 Hz, 1H), 8.21 (t, J = 5.4 Hz, 1H), 7.76 (s, 1H), 7.65 - 7.73 (m, 2H), 7.36 - 7.47 (m, 2H), 7.26 (br. s.,



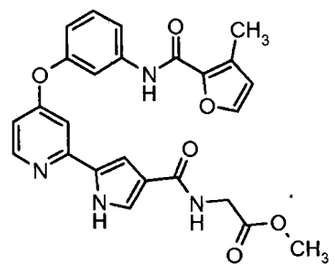
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1H), 7.12 (br. s., 1H), 6.86 - 6.98 (m, 1H), 6.77 (br. s., 1H), 6.56 (s, 1H), 3.81 (d, J = 5.9 Hz, 2H), 2.29 (s, 3H)

LR MS (ES-): 459 (M-H)

Example 4

methyl ({[5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrol-3-yl]carbonyl}amino)acetate



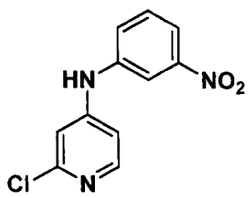
Similar procedure as Example 3.

$^1$H NMR (DMSO-$d_6$) δ: 11.88 (br. s., 1H), 10.19 (s, 1H), 8.40 (d, J = 5.6 Hz, 1H), 8.32 (t, J = 5.6 Hz, 1H), 7.76 (s, 1H), 7.65 - 7.72 (m, 2H), 7.36 - 7.44 (m, 2H), 7.23 (d, J = 2.1 Hz, 1H), 7.08 (br. s., 1H), 6.90 (d, J = 7.3 Hz, 1H), 6.75 (dd, J = 5.6, 1.8 Hz, 1H), 6.56 (s, 1H), 3.89 (d, J = 5.6 Hz, 2H), 3.60 (s, 3H), 2.29 (s, 3H)

LR MS (ES+): 475 (MH), 497 ($M+Na^+$)

LR MS (ES-): 473 (M-H)

Preparation of 2-Chloro-*N*-(3-nitrophenyl)pyridine-4-amine



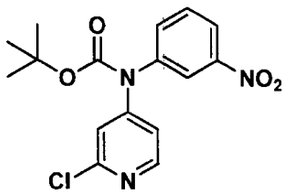
To a degassed (15 min, $N_2$) suspension of 2-chloro-4-iodopyridine (3.0 g, 12.53 mmol), 3-nitroaniline (1.82 g, 13.18 mmol), BINAP (0.39 g, 0.626 mmol) and $Cs_2CO_3$ (8.16 g, 25.04 mmol) in toluene (72 mL) was added $Pd(OAc)_2$ (0.084 g, 0.374 mmol). The reaction tube was sealed and the mixture stirred at 90°C for 18 h. The mixture was cooled to rt and filtered, washing with EtOAc. The orange/yellow solid collected was washed with $CH_2Cl_2$ until all the product washed through into the filtrate. The filtrate was concentrated to afford 2-Chloro-*N*-(3-



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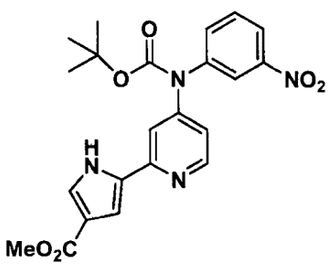
nitrophenyl)pyridine-4-amine as a bright yellow solid. Additional product was collected from the solid collected upon concentration of the previous filtrate, after washing with $CH_2Cl_2$. No further purification. Total amount of product collected was 2.85 g (91% yield).

Preparation of *tert*-Butyl 2-chloropyridin-4-yl(3-nitrophenyl)carbamate



To a stirring solution of 2-Chloro-*N*-(3-nitrophenyl)pyridine-4-amine (2.70 g, 10.82 mmol) in THF (45 mL) was added $Et_3N$ (6.32 mL, 45.3 mmol). The mixture was cooled to 0°C, and DMAP (0.0135 g, 0.110 mmol) and $BOC_2O$ (2.84 g, 12.99 mmol) were added. The mixture was warmed to rt and stirred for 18 h. The mixture was quenched with ice and diluted with water. Extracted with EtOAc (3 x 200 mL), washed with brine and water, dried ($MgSO_4$), and concentrated. A dark oil was afforded, which was passed through a pad of silica gel, eluting with 1:1 EtOAc/hexanes. Concentrated and dried under high vacuum to afford *tert*-Butyl 2-chloropyridin-4-yl(3-nitrophenyl)carbamate (3.65 g, 96.5% yield).

Preparation of methyl 5-(4-(*tert*-butoxycarbonyl(3-nitrophenyl)amino)pyridine-2-yl)-1*H*-pyrrole-3-carboxylate



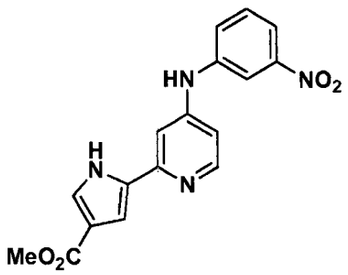
A mixture of *tert*-Butyl 2-chloropyridin-4-yl(3-nitrophenyl)carbamate (3.65 g, 10.43 mmol), methyl-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-3-carboxylate (5.48 g, 21.82 mmol), xantphos (0.72 g, 1.25 mmol) and $Pd_2dba_3$ (0.72 g, 0.79 mmol) was added to a thick walled reaction vessel and purged with $N_2$. A solution of 2M $K_2CO_3$ (8.76 mL) was added, followed by dioxane (67 mL). The reaction vessel was sealed and the mixture stirred at 105°C for 18 h. The reaction vessel was cooled to rt and the mixture was filtered over celite, washing with EtOAc. The filtrate was concentrated to afford a dark oil, which was purified via column chromatography eluting with 30-50% EtOAc/hexanes to afford methyl 5-(4-(*tert*-



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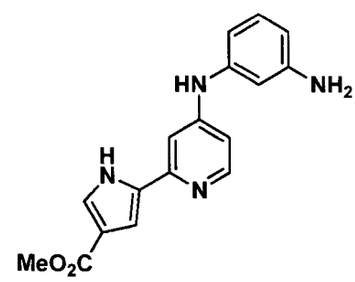
butoxycarbonyl(3-nitrophenyl)amino)pyridine-2-yl)-1*H*-pyrrole-3-carboxylate (2.98 g, 65% yield) as an orange oil.

Preparation of methyl 5-(4-((3-nitrophenyl)amino)pyridin-2-yl)-1H-pyrrole-3-carboxylate




Methyl 5-(4-(*tert*-butoxycarbonyl(3-nitrophenyl)amino)pyridine-2-yl)-1*H*-pyrrole-3-carboxylate (0.40 g, 0.91 mmol) was taken up in toluene (38 mL) and $SiO_2$ (9.0 g) was added. The mixture stirred at reflux for 20 h. The mixture was cooled to rt and filtered over celite, washing with EtOAc. The filtrate was concentrated to a bright orange color. The solid was taken up in hexanes and filtered. The solid was then washed with $CH_2Cl_2$/hexanes to afford methyl 5-(4-((3-nitrophenyl)amino)pyridin-2-yl)-1H-pyrrole-3-carboxylate (0.15 g, 49% yield) as a bright yellow solid.

Preparation of methyl 5-(4-((3-aminophenyl)amino)pyridin-2-yl)-1H-pyrrole-3-carboxylate



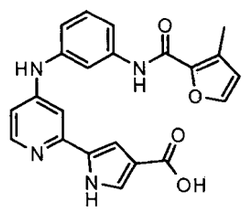

Methyl 5-(4-((3-nitrophenyl)amino)pyridin-2-yl)-1H-pyrrole-3-carboxylate (1.32 g, 3.9 mmol) was taken up in EtOAc/EtOH (1:1; 90 mL) and purged with $N_2$. Pd/C (10%, 0.145 g) was added and the mixture was stirred under an atmosphere of $H_2$ at rt for 18 h. The mixture was filtered over celite, washing with EtOAc/EtOH. The filtrate was concentrated, taken back up in EtOAc and filtered over celite again to remove any residual catalyst. The filtrate was concentrated again and taken back up in EtOAc. The solution was filtered and the filtrate was concentrated to afford a tan solid. The solid was washed with $CH_2Cl_2$/hexanes (1:2) and dried under high vacuum to afford methyl 5-(4-((3-aminophenyl)amino)pyridin-2-yl)-1H-pyrrole-3-carboxylate (1.15 g, 96% yield) as a tan solid.



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Example 5

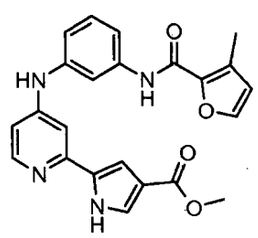
5-[4-({3-[(3-methyl-2-furoyl)amino]phenyl}amino)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid



To a stirred solution of methyl 5-[4-({3-[(3-methyl-2-furoyl)amino]phenyl}amino)pyridin-2-yl]-1H-pyrrole-3-carboxylate (10mg, 0.024mmol) in a mixture of solvents THF/MeOH (5ml/5ml) was added 2ml of 1M NaOH (2mmol) solution. The mixture was heated in a 60°C bath for 16 hours, cooled to room temperature and poured into 100ml of water. 2M HCl was added until pH = 5. The resulting precipitates were filtered, washed with water, and dried *in vacuo* to give 5-[4-({3-[(3-methyl-2-furoyl)amino]phenyl}amino)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid as light brown solid. Yield: 2mg.

Example 6

methyl 5-[4-({3-[(3-methyl-2-furoyl)amino]phenyl}amino)pyridin-2-yl]-1H-pyrrole-3-carboxylate



A mixture of 3-methyl-2-furoic acid (22 mg, 0.18mmol), HATU (73mg, 0.19mmol) and *N,N*-diisopropylethylamine (45mg, 0.35mmol) in anhydrous DMF (10ml) was stirred at room temperature for 10 minutes, followed by addition of methyl 5-(4-((3-aminophenyl)amino)pyridin-2-yl)-1H-pyrrole-3-carboxylate (50mg, 0.16mmol). The mixture was stirred at room temperature for 3 hours and poured into 100ml of water. The precipitates were filtered, washed with water and dried *in vacuo* to give methyl 5-[4-({3-[(3-methyl-2-furoyl)amino]phenyl}amino)pyridin-2-yl]-1H-pyrrole-3-carboxylate as off-white solid. Yield: 10mg, 15%.



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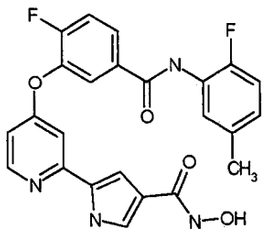
$^1$H NMR (DMSO-$d_6$) δ: 13.60 (br. s., 1H), 12.37 (br. s., 1H), 10.14 (s, 1H), 8.15 (d, J = 6.5 Hz, 1H), 7.86 (t, J = 1.9 Hz, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.58 (br. s., 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.32 - 7.38 (m, 2H), 7.22 (br. s., 1H), 6.97 (d, J = 7.6 Hz, 1H), 6.86 (dd, J = 6.2, 2.1 Hz, 1H), 6.57 (d, J = 1.8 Hz, 1H), 3.71 (s, 3H), 2.32 (s, 3H)

LR MS (ES+): 417 (MH)

LR MS (ES-): 415 (M-H)

Example 7

5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-N-hydroxy-1H-pyrrole-3-carboxamide



Similar procedure as Example 1.

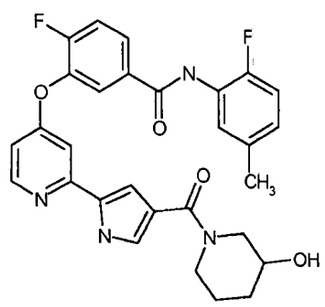
$^1$H NMR (DMSO-$d_6$) δ: 11.85 (br. s., 1H), 10.56 (br. s., 1H), 10.12 (s, 1H), 8.66 (br. s., 1H), 8.41 (d, J = 5.6 Hz, 1H), 7.99 (d, J = 7.3 Hz, 2H), 7.63 (t, J = 9.4 Hz, 1H), 7.30 - 7.40 (m, 2H), 7.27 (br. s., 1H), 7.10 - 7.18 (m, 1H), 7.01 - 7.10 (m, 2H), 6.75 - 6.85 (m, 1H), 2.26 (s, 3H)

LR MS (ES+): 487 ($M+Na^+$)

LR MS (ES-): 463 (M-H)

Example 8

4-fluoro-N-(2-fluoro-5-methylphenyl)-3-[(2-{4-[(3-hydroxypiperidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]benzamide



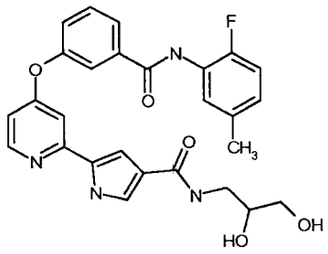
Similar procedure as Example 1.

LR MS (ES+): 533 (MH), 555 ($M+Na^+$)

LR MS (ES-): 531 (M-H)

Example 9

N-(2,3-dihydroxypropyl)-5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxamide




Similar procedure as Example 1.

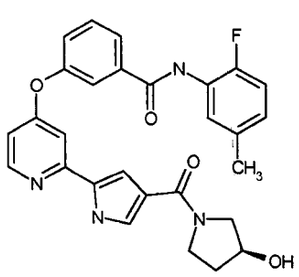
$^1H$ NMR (DMSO-$d_6$) δ: 11.83 (br. s., 1H), 10.11 (s, 1H), 8.41 (d, J = 5.6 Hz, 1H), 7.89 (d, J = 7.0 Hz, 1H), 7.83 (t, J = 5.6 Hz, 1H), 7.77 (s, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.42 - 7.46 (m, 1H), 7.39 (d, J = 1.5 Hz, 1H), 7.35 (d, J = 7.3 Hz, 1H), 7.25 (d, J = 2.1 Hz, 1H), 7.09 - 7.16 (m, 2H), 7.02 - 7.06 (m, 1H), 6.76 (dd, J = 5.7, 2.5 Hz, 1H), 4.77 (d, J = 5.0 Hz, 1H), 4.53 (t, J = 6.0 Hz, 1H), 3.50 - 3.56 (m, 1H), 3.25 - 3.30 (m, 3H), 3.08 - 3.14 (m, 1H), 2.27 (s, 3H)

LR MS (ES+): 505 (MH), 527 ($M+Na^+$)

LR MS (ES-): 503 (M-H)

Example 10

N-(2-fluoro-5-methylphenyl)-3-[(2-{4-[(3-hydroxypyrrolidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]benzamide






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A mixture of 5-{4-[3-(2-Fluoro-5-methyl-phenylcarbamoyl)-phenoxy]-pyridin-2-yl}-1H-pyrrole-3-carboxylic acid (50mg, 0.12mmol), HATU (55mg, 0.14mmol) and *N,N*-diisopropylethylamine (34mg, 0.26mmol) in anhydrous DMF (8ml) was stirred at room temperature for 10 minutes, followed by addition of (S)-3-pyrrolidinol (16mg, 0.18mmol). The mixture was stirred for another 10 minutes and poured into 100ml of water. The precipitates were filtered, washed with water and dried *in vacuo* to give N-(2-fluoro-5-methylphenyl)-3-[(2-{4-[(3-hydroxypyrrolidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]benzamide as white solid. Yield: 40mg, 69%.

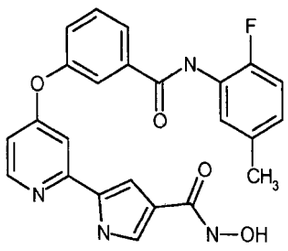
$^1$H NMR (DMSO-$d_6$) δ: 11.91 (br. s., 1H), 10.12 (s, 1H), 8.42 (d, J = 5.6 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.76 (s, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.32 - 7.51 (m, 3H), 7.26 (d, J = 6.7 Hz, 1H), 6.99 - 7.20 (m, 3H), 6.73 (dd, 1H), 4.91 (br. s., 1H), 4.30 (br. s., 1H), 3.76 (br. s., 2H), 3.50 (br. s., 2H), 2.28 (s, 3H), 1.86 (br. s., 2H)

LR MS (ES+): 501 (MH), 523 (M+$Na^+$)

LR MS (ES-): 499 (M-H)

Example 11

5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-N-hydroxy-1H-pyrrole-3-carboxamide




Similar procedure as Example 10.

$^1$H NMR (DMSO-$d_6$) δ: 11.84 (br. s., 1H), 10.56 (br. s., 1H), 10.10 (s, 1H), 8.65 (br. s., 1H), 8.40 (d, J = 5.6 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.76 (br. s., 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.44 (dd, J = 7.9, 1.5 Hz, 1H), 7.35 (d, J = 6.7 Hz, 1H), 7.31 (br. s., 1H), 7.25 (d, J = 1.8 Hz, 1H), 7.13 (dd, J = 10.3, 8.5 Hz, 1H), 7.01 - 7.07 (m, 2H), 6.75 (dd, J = 5.7, 2.2 Hz, 1H), 2.27 (s, 3H)

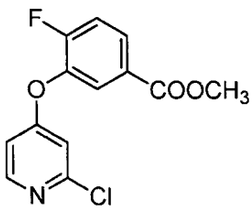
LR MS (ES+): 469 (M+$Na^+$)

LR MS (ES-): 445 (M-H)



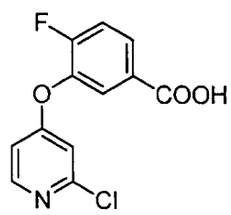
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Preparation of 3-(2-Chloropyridin-4-yloxy)-4-fluorobenzoic acid methyl ester



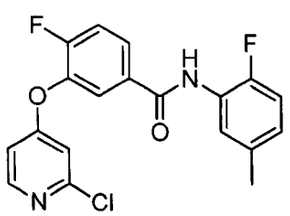
4-Fluoro-3-hydroxybenzoic acid methyl ester (1.70 g, 10.0 mmol) was dissolved in dimethylformamide (9 mL) under nitrogen at room temperature. Sodium hydride (60% oil dispersion, 0.48 g, 12 mmol) was added in portions over 30 min. The reaction was stirred for 90 minutes and then cooled in an ice bath. 2-Chloro-4-nitropyridine (1.58 g, 10.0 mmol) was added in small portions over 50 min. The reaction was stirred at room temperature for 17.5 h. Water (200 ml) was added and the mixture stirred until a brown lump formed. The water was decanted and the residue dissolved in EtOAc (150 mL). The solution was washed with brine, dried ($MgSO_4$), filtered and evaporated to give 3-(2-Chloropyridin-4-yloxy)-4-fluorobenzoic acid methyl ester. Yield: 3.10 g.

Preparation of 3-(2-Chloropyridin-4-yloxy)-4-fluorobenzoic acid



3-(2-Chloropyridin-4-yloxy)-4-fluorobenzoic acid methyl ester (2.81 g, 10.0 mmol) was dissolved in tetrahydrofuran (15 mL) and mixed with 2M lithium hydroxide (15 mL, 30 mmol). The suspension was stirred for 5 h. To the reaction was added water, then extracted with EtOAc. The aqueous layer was treated with 6M HCl (5 mL, 30 mmol) and then extracted with EtOAc (3x25 mL). The extract was dried ($MgSO_4$), filtered and evaporated to 3-(2-Chloropyridin-4-yloxy)-4-fluorobenzoic acid. Yield: 2.22 g, 83%.

Preparation of 3-(2-Chloropyridin-4-yloxy)-4-fluoro-N-(2-fluoro-5-methylphenyl)benzamide



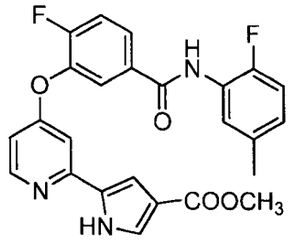


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A solution of 3-(2-Chloropyridin-4-yloxy)-4-fluorobenzoic acid (2.22 g, 8.29 mmol), 2-fluoro-5-methylaniline (1.56 g, 12.4 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 3.78 g, 9.95 mmol) and N-methylmorpholine (2.00 mL, 18.2 mmol) in dimethylformamide (22 mL) was heated at 90°C for 2 h. The solvent was evaporated *in vacuo* at 50°C. To the residue was added water resulting in a thick oil. The water was decanted and the oil dissolved in EtOAc then extracted twice with water, 1M hydrochloric acid and brine. The organic layer was dried ($MgSO_4$), filtered and evaporated to crude 6 (3.37 g). Trituration with dichloromethane (25 mL) gave 3-(2-Chloropyridin-4-yloxy)-4-fluoro-N-(2-fluoro-5-methylphenyl)benzamide as white solid. Yield: 1.788 g, 58%.

Example 12

methyl 5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate



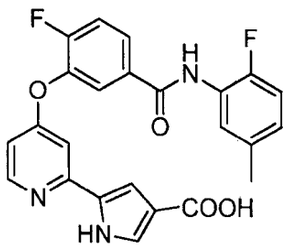

A mixture of 3-(2-Chloropyridin-4-yloxy)-4-fluoro-N-(2-fluoro-5-methylphenyl)benzamide (1.217 g, 3.25 mmol), methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-3-carboxylate (1.63 g, 6.50 mmol) and potassium carbonate (0.67 g, 4.87 mmol) in water (2.5 mL) and dioxane (15 mL) was purged with nitrogen for several minutes. To the mixture was added tetrakis-triphenylphosphine palladium(0) (0.18 g, (0.16 mmol). The reaction was sealed under nitrogen and heated at 100°C for 15 h. The cooled reaction was mixed with dichloromethane and filtered through Celite. The red solution was evaporated. The resulting oil was dissolved in dichloromethane, put on a column of silica gel (80 g) and eluted with hexane/EtOAc (1:1) to afford methyl 5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate as white solid. Yield: 1.162 g, 77%.

Example 13

5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid



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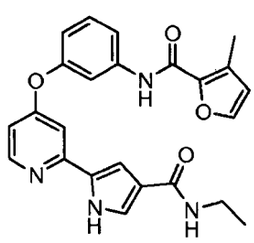
Similar procedure as Example 12.

$^1$H NMR (DMSO-$d_6$) δ: 12.03 (br. s., 1H), 11.85 (br. s., 1H), 10.11 (s, 1H), 8.42 (d, J = 5.6 Hz, 1H), 7.98 (d, J = 6.2 Hz, 2H), 7.62 (t, J = 9.4 Hz, 1H), 7.43 (br. s., 1H), 7.30 - 7.39 (m, 2H), 7.08 - 7.19 (m, 2H), 7.04 (br. s., 1H), 6.79 (d, J = 3.2 Hz, 1H), 2.26 (s, 3H)

LR MS (ES-): 448 (M-H)

Example 14

N-ethyl-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide

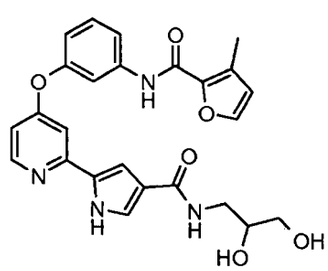


Similar procedure as Example 31.

LR MS (ES+): 453 ($M+Na^+$)

Example 15

N-(2,3-dihydroxypropyl)-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide



Similar procedure as Example 31.



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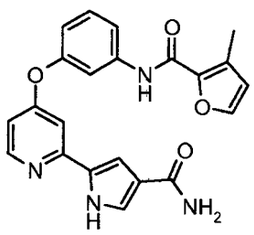
$^1$H NMR (DMSO-$d_6$) δ: 11.83 (br. s., 1H), 10.21 (s, 1H), 8.40 (d, J = 5.9 Hz, 1H), 7.85 (t, J = 6.0 Hz, 1H), 7.78 (s, 1H), 7.63 - 7.74 (m, 2H), 7.35 - 7.48 (m, 2H), 7.23 (d, J = 2.1 Hz, 1H), 7.10 (s, 1H), 6.85 - 6.96 (m, 1H), 6.75 (dd, J = 5.7, 2.2 Hz, 1H), 6.57 (s, 1H), 4.78 (d, J = 4.7 Hz, 1H), 4.53 (t, J = 5.9 Hz, 1H), 3.48 - 3.61 (m, 1H), 3.24 – 3.33 (m, 3H), 3.04 - 3.19 (m, 1H), 2.30 (s, 3H)

LR MS (ES+): 499 ($M+Na^+$)

LR MS (ES-): 475 (M-H)

Example 16

5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide



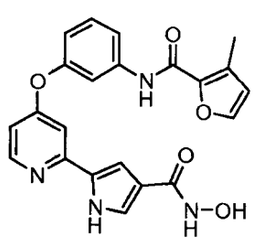
Similar procedure as Example 31.

$^1$H NMR (DMSO-$d_6$) δ: 11.83 (br. s., 1H), 10.21 (s, 1H), 8.40 (d, J = 5.9 Hz, 1H), 7.77 (s, 1H), 7.65 - 7.74 (m, 2H), 7.31 - 7.48 (m, 3H), 7.23 (d, J = 1.2 Hz, 1H), 7.07 (br. s., 1H), 6.86 - 6.95 (m, 1H), 6.75 (d, J = 3.5 Hz, 2H), 6.57 (s, 1H), 2.30 (s, 3H)

LR MS (ES-): 401 (M-H)

Example 17

N-hydroxy-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide



Similar procedure as Example 31.

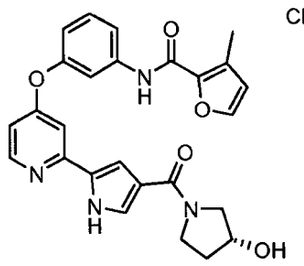


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$^1$H NMR (DMSO-$d_6$) δ: 11.84 (br. s., 1H), 10.49 - 10.64 (m, 1H), 10.20 (s, 1H), 8.60 - 8.74 (m, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.65 - 7.81 (m, 3H), 7.41 (t, J = 7.9 Hz, 1H), 7.32 (br. s., 1H), 7.23 (s, 1H), 7.02 (br. s., 1H), 6.85 - 6.94 (m, 1H), 6.69 - 6.78 (m, 1H), 6.57 (s, 1H), 2.30 (s, 3H)
LR MS (ES-): 417 (M-H)

Example 18

N-(3-{[2-(4-{[(3R)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-methyl-2-furamide

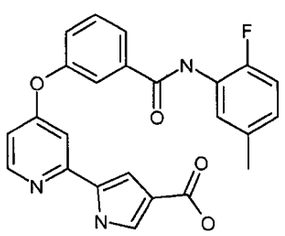



Similar procedure as Example 31.

$^1$H NMR (DMSO-$d_6$) δ: 11.90 (br. s., 1H), 10.20 (s, 1H), 8.40 (d, J = 5.6 Hz, 1H), 7.77 (d, J = 1.5 Hz, 1H), 7.64 - 7.73 (m, 2H), 7.36 - 7.46 (m, 2H), 7.21 - 7.30 (m, 1H), 7.03 - 7.13 (m, 1H), 6.85 - 6.93 (m, 1H), 6.70 (dd, J = 5.7, 2.2 Hz, 1H), 6.57 (d, J = 1.5 Hz, 1H), 4.90 (br. s., 1H), 4.30 (m, 1H), 3.76 (m, 1H), 3.49 (m, 2H), 2.30 (s, 3H), 1.86 (m, 2H)
LR MS (ES-): 471 (M-H)

Example 19

5-{4-[3-(2-Fluoro-5-methyl-phenylcarbamoyl)-phenoxy]-pyridin-2-yl}-1H-pyrrole-3-carboxylic acid




To a stirred solution of 5-{4-[3-(2-Fluoro-5-methyl-phenylcarbamoyl)-phenoxy]-pyridin-2-yl}-1H-pyrrole-3-carboxylic acid methyl ester (140mg, 0.31mmol) in THF (8ml) was added 5M NaOH solution (1ml, 5mmol). The mixture was heated at 70°C for 3 hours, cooled to room



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temp, and poured into 100ml of water. 2M HCl was added until pH = 4. The precipitates were filtered, washed with water, and dried to give 5-{4-[3-(2-Fluoro-5-methyl-phenylcarbamoyl)-phenoxy]-pyridin-2-yl}-1H-pyrrole-3-carboxylic acid as white solid. Yield: 120mg, 92%.

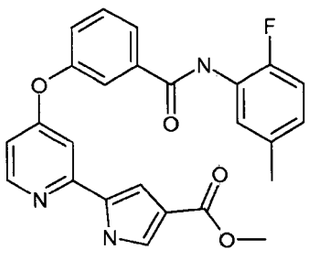
$^1$H NMR ($d_6$-DMSO): 12.03 (br. s., 1H), 11.89 (br. s., 1H), 10.11 (s, 1H), 8.42 (d, J = 5.6 Hz, 1H), 7.89 (d, J = 7.3 Hz, 1H), 7.77 (s, 1H), 7.56 - 7.71 (m, 1H), 7.30 - 7.54 (m, 4H), 6.97 - 7.23 (m, 3H), 6.75 (dd, J = 5.6, 2.1 Hz, 1H), 2.28 (s, 3H)

LR MS (ES+): 454 ($M+Na^+$)

LR MS (ES-): 430 (M-H)

Example 20

5-{4-[3-(2-Fluoro-5-methyl-phenylcarbamoyl)-phenoxy]-pyridin-2-yl}-1H-pyrrole-3-carboxylic acid methyl ester




A mixture of 3-(2-bromo-pyridin-4-yloxy)-N-(2-fluoro-5-methyl-phenyl)-benzamide (200mg, 0.50 mmol), methyl-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-3-carboxylate (251mg, 1.0 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (10mg, 0.012 mmol) was added to a thick-walled reaction vessel and purged with $N_2$. A solution of 2M $Na_2CO_3$ (0.5 mL) was added, followed by DMSO (8 mL). The reaction vessel was sealed and the mixture stirred at 95°C for 16 h. The reaction vessel was cooled to room temperature and the mixture was poured into 100ml of water. The precipitates were filtered, washed with water and dried to give the crude, which was purified via column chromatography eluting with 30-40% EtOAc/hexanes to afford 5-{4-[3-(2-Fluoro-5-methyl-phenylcarbamoyl)-phenoxy]-pyridin-2-yl}-1H-pyrrole-3-carboxylic acid methyl ester (150mg, 58% yield).

$^1$H NMR ($d_6$-DMSO): 12.14 (br. s., 1H), 10.11 (s, 1H), 8.43 (d, J = 5.6 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.77 (s, 1H), 7.64 (t, J = 7.9 Hz, 1H), 7.41 - 7.50 (m, 3H), 7.35 (s, 1H), 7.09 - 7.21 (m, 2H), 7.06 (dd, J = 5.1, 1.9 Hz, 1H), 6.76 (dd, J = 5.6, 2.3 Hz, 1H), 3.70 (s, 3H), 2.28 (s, 3H)

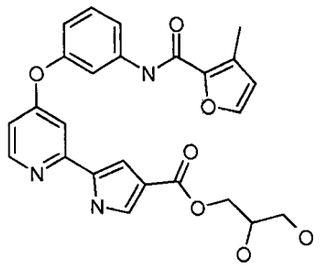
LR MS (ES+): 468 ($M+Na^+$)

LR MS (ES-): 444 (M-H)



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Example 21

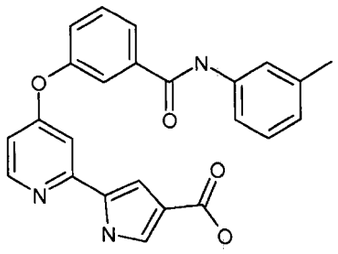


Similar procedure as Example 25.

2,3-dihydroxypropyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate

Example 22

5-[4-(3-m-Tolylcarbamoyl-phenoxy)-pyridin-2-yl]-1H-pyrrole-3-carboxylic acid

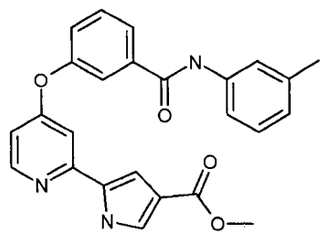


Similar procedure as Example 19.

$^1$H NMR (DMSO-$d_6$) δ: 12.03 (br. s., 1H), 11.86 (br. s., 1H), 10.19 (s, 1H), 8.42 (d, J = 5.6 Hz, 1H), 7.88 (d, J = 7.9 Hz, 1H), 7.78 (s, 1H), 7.50 - 7.69 (m, 3H), 7.32 - 7.46 (m, 3H), 7.21 (t, J = 7.8 Hz, 1H), 7.06 (s, 1H), 6.91 (d, J = 7.3 Hz, 1H), 6.74 (dd, J = 5.6, 2.3 Hz, 1H), 2.28 (s, 3H)

Example 23

5-[4-(3-m-Tolylcarbamoyl-phenoxy)-pyridin-2-yl]-1H-pyrrole-3-carboxylic acid methyl ester



Similar procedure as Example 20.

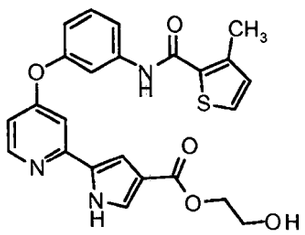


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$^1$H NMR (DMSO-$d_6$) δ: 12.14 (br. s., 1H), 10.18 (s, 1H), 8.43 (d, J = 5.6 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.78 (s, 1H), 7.50 - 7.68 (m, 3H), 7.38 - 7.48 (m, 3H), 7.21 (t, J = 7.8 Hz, 1H), 7.12 (s, 1H), 6.91 (d, J = 7.6 Hz, 1H), 6.75 (dd, J = 5.7, 2.2 Hz, 1H), 3.70 (s, 3H), 2.28 (s, 3H)
LR MS (ES+): 450 ($M+Na^+$)
LR MS (ES-): 426 (M-H)

Example 24

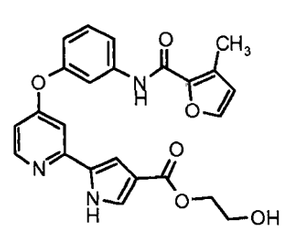
2-hydroxyethyl 5-[4-(3-{[(3-methyl-2-thienyl)carbonyl]amino}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate



Similar procedure as Example 25.
$^1$H NMR ($d_6$-DMSO): 12.13 (br. s., 1H), 10.13 (s, 1H), 8.43 (d, J = 5.9 Hz, 1H), 7.68 (d, J = 5.0 Hz, 1H), 7.56 - 7.64 (m, 2H), 7.40 - 7.52 (m, 3H), 7.14 (s, 1H), 7.03 (d, J = 5.0 Hz, 1H), 6.89 - 6.98 (m, 1H), 6.76 (dd, J = 5.7, 2.2 Hz, 1H), 4.83 (t, J = 5.9 Hz, 1H), 4.15 (t, J = 5.1 Hz, 2H), 3.64 (q, J = 5.6 Hz, 2H), 2.44 (s, 3H)
LR MS (ES+): 486 ($M+Na^+$)
LR MS (ES-): 462 (M-H)

Example 25

2-hydroxyethyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate





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A mixture of 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid (70mg, 0.17mmol), ethylene glycol (1ml), 1-ethyl-3-(3-dimethyllaminopropyl)carbodiimide hydrochloride (EDC• HCl, 40mg, 0.21mmol) and 4-dimethylaminopyridine (DMAP, 10mg, 0.08mmol) in anhydrous DMF (10ml) was stirred at 70°C for 3 hours then room temperature for 16 hours. The mixture was poured into 100ml of water. Saturated $NaHCO_3$ solution was added until pH = 9. The precipitates were filtered, washed with water and dried *in vacuo* to give the crude, which was purified by silica gel chromatography eluting with a gradient of 3~4% MeOH/$CHCl_3$ to give 2-hydroxyethyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate as white solid. Yield: 40mg, 51%.

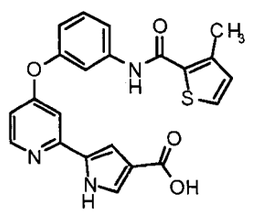
$^1$H NMR ($d_6$-DMSO): 12.13 (br. s., 1H), 10.22 (s, 1H), 8.43 (d, J = 5.9 Hz, 1H), 7.79 (s, 1H), 7.70 (s, 2H), 7.36 - 7.54 (m, 3H), 7.13 (br. s., 1H), 6.86 - 6.97 (m, 1H), 6.72 - 6.80 (m, 1H), 6.59 (s, 1H), 5.75 (s, 1H), 4.83 (t, J = 5.3 Hz, 1H), 4.14 (t, J = 4.7 Hz, 2H), 3.58 - 3.69 (m, 2H), 2.32 (s, 3H)

LR MS (ES+): 470 ($M+Na^+$)

LR MS (ES-): 446 (M-H)

Example 26

5-[4-(3-{[(3-methyl-2-thienyl)carbonyl]amino}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid



Similar procedure as Example 32.

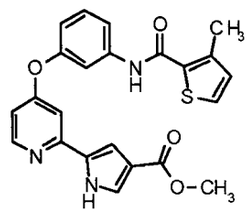
$^1$H NMR ($d_6$-DMSO): 12.04 (br. s., 1H), 11.87 (s, 1H), 10.13 (s, 1H), 8.42 (d, J = 6.2 Hz, 1H), 7.68 (d, J = 4.7 Hz, 1H), 7.57 - 7.64 (m, 2H), 7.40 - 7.49 (m, 2H), 7.38 (dd, J = 3.2, 1.5 Hz, 1H), 7.05 - 7.09 (m, 1H), 7.03 (d, J = 5.0 Hz, 1H), 6.90 - 6.97 (m, 1H), 6.75 (dd, J = 5.7, 2.5 Hz, 1H), 2.44 (s, 3H)

LR MS (ES+): 442 ($M+Na^+$)

LR MS (ES-): 418 (M-H)

Example 27

methyl 5-[4-(3-{[(3-methyl-2-thienyl)carbonyl]amino}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate



Similar procedure as Example 33.

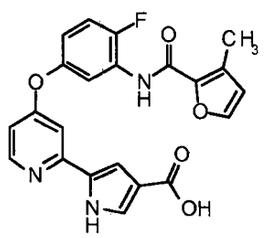
$^1$H NMR (DMSO-$d_6$) δ: 12.12 (br. s., 1H), 10.10 (s, 1H), 8.35 - 8.45 (m, 1H), 7.65 (d, J = 5.0 Hz, 1H), 7.55 - 7.60 (m, 2H), 7.37 - 7.45 (m, 3H), 7.10 (s, 1H), 7.00 (d, J = 5.0 Hz, 1H), 6.87 - 6.93 (m, 1H), 6.73 (dd, J = 5.6, 2.3 Hz, 1H), 3.69 (s, 3H), 2.41 (s, 3H)

LR MS (ES+): 456 ($M+Na^+$)

LR MS (ES-): 432 (M-H)

Example 28

5-(4-{4-fluoro-3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid



To a stirred solution of methyl 5-(4-{4-fluoro-3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate (20mg, 0.046mmol) in a mixture of solvents THF/MeOH (5ml/5ml) was added 3ml of 1M NaOH (3mmol) solution. The mixture was heated in a 72°C bath for 3 hours, cooled to room temperature and poured into 50ml of water. 2M HCl was added until pH = 4. The resulting precipitates were filtered, washed with water, and dried *in vacuo* to give 5-(4-{4-fluoro-3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid as light gray solid. Yield: 19mg, 100%.

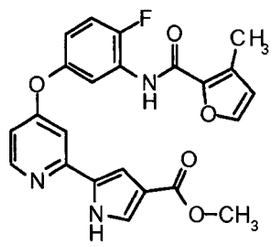


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LR MS (ES-): 420 (M-H)

Example 29

methyl 5-(4-{4-fluoro-3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate



Similar procedure as Example 33.

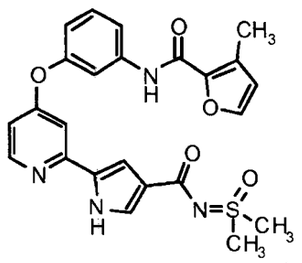
$^1$H NMR ($d_6$-DMSO): 12.15 (br. s., 1H), 9.74 (s, 1H), 8.43 (d, J = 5.6 Hz, 1H), 7.81 (d, J = 1.8 Hz, 1H), 7.60 (dd, J = 6.4, 2.9 Hz, 1H), 7.34 - 7.50 (m, 3H), 7.02 - 7.18 (m, 2H), 6.75 (dd, J = 5.6, 2.3 Hz, 1H), 6.60 (d, J = 1.5 Hz, 1H), 3.72 (s, 3H), 2.31 (s, 3H)

LR MS (ES+): 458 ($M+Na^+$)

LR MS (ES-): 434 (M-H)

Example 30

N-[dimethyl(oxido)-lambda~4~-sulfanylidene]-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide



Similar procedure as Example 101.

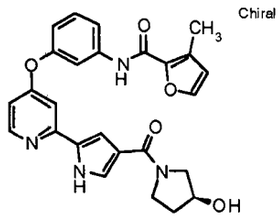
$^1$H NMR ($d_6$-DMSO): 11.83 (br. s., 1H), 10.20 (s, 1H), 8.39 (d, J = 5.6 Hz, 1H), 7.77 (d, J = 1.5 Hz, 1H), 7.65 - 7.72 (m, 2H), 7.37 - 7.45 (m, 1H), 7.32 (d, J = 2.1 Hz, 1H), 7.27 (dd, J = 2.9, 1.5 Hz, 1H), 6.96 - 6.99 (m, 1H), 6.87 - 6.92 (m, 1H), 6.71 (dd, J = 5.6, 2.3 Hz, 1H), 6.57 (d, J = 1.8 Hz, 1H), 3.35 (s, 6H), 2.30 (s, 3H)

LR MS (ES+): 501 ($M+Na^+$)

LR MS (ES-): 477 (M-H)

Example 31

N-(3-{[2-(4-{[(3S)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-methyl-2-furamide




A mixture of 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid (60mg, 0.15mmol), HATU (68mg, 0.18mmol) and *N,N*-diisopropylethylamine (43mg, 0.33mmol) in anhydrous DMF (10ml) was stirred at room temperature for 10 minutes, followed by addition of (S)-3-pyrrolidinol (16mg, 0.18mmol). The mixture was stirred for another 10 minutes and poured into 100ml of water. 2M HCl was added dropwise until pH = 4~5. The precipitates were filtered, washed with water and dried *in vacuo* to give N-(3-{[2-(4-{[(3S)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-methyl-2-furamide as white solid. Yield: 40mg, 56%.

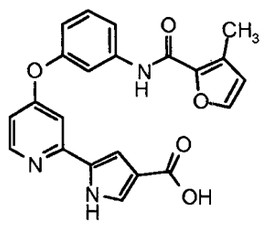
$^1$H NMR ($d_6$-DMSO): 11.95 (br. s., 1H), 10.21 (s, 1H), 8.41 (d, J = 5.6 Hz, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.64 - 7.74 (m, 2H), 7.35 - 7.51 (m, 2H), 7.29 (br. s., 1H), 7.12 (br. s., 1H), 6.90 (dd, J = 8.1, 1.3 Hz, 1H), 6.73 (dd, J = 5.7, 2.2 Hz, 1H), 6.57 (d, J = 1.8 Hz, 1H), 4.20 - 4.36 (m, 1H), 3.66 - 3.88 (m, 2H), 3.42 - 3.60 (m, 3H), 2.30 (s, 3H), 1.66 - 2.03 (m, 2H)

LR MS (ES+): 495 ($M+Na^+$)

LR MS (ES-): 471 (M-H)

Example 32

5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid






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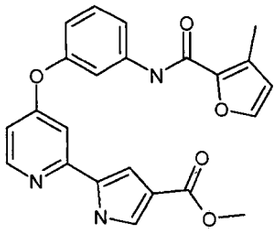
To a stirred solution of methyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate (1.30g, 3.12mmol) in a mixture of solvents THF/MeOH (10ml/10ml) was added 2ml of 5M NaOH (10mmol) solution. The mixture was heated in a 68°C bath for 8 hours, cooled to room temperature and poured into 200ml of water. 2M HCl was added until pH = 3. The resulting precipitates were filtered, washed with water, and dried *in vacuo* to give 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid as white solid. Yield: 1.20g, 95%.

$^1$H NMR ($d_6$-DMSO): 11.98 (br. s., 1H), 10.22 (s, 1H), 8.42 (d, J = 5.6 Hz, 1H), 7.79 (d, J = 1.2 Hz, 1H), 7.61 - 7.76 (m, 2H), 7.27 - 7.51 (m, 3H), 7.04 (br. s., 1H), 6.85 - 6.98 (m, 1H), 6.73 (dd, J = 5.7, 2.2 Hz, 1H), 6.59 (d, J = 1.5 Hz, 1H), 2.32 (s, 3H)

LR MS (ES-): 402 (M-H)

Example 33

methyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate



A mixture of 3-methyl-2-furoic acid (490 mg, 3.88mmol), HATU (1.71 g, 4.5mmol) and *N,N*-diisopropylethylamine (1.0g, 7.8mmol) in anhydrous DMF (10ml) was stirred at room temperature for 10 minutes, followed by addition of methyl 5-[4-(3-aminophenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate (1.0g, 3.24mmol). The mixture was stirred at 50°C for 2 hours and poured into 100ml of water. 2M HCl was added dropwise until pH = 4~5. The precipitates were filtered, washed with water and dried *in vacuo* to give methyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate as white solid. Yield: 1.30g, 96%.

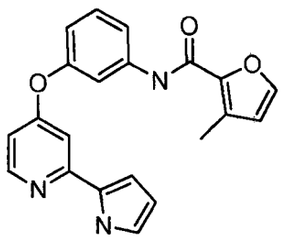
$^1$H NMR ($d_6$-DMSO): 12.15 (br. s., 1H), 10.22 (s, 1H), 8.43 (d, J = 5.9 Hz, 1H), 7.79 (d, J = 1.5 Hz, 1H), 7.68 - 7.74 (m, 2H), 7.38 - 7.47 (m, 3H), 7.09 - 7.14 (m, 1H), 6.88 - 6.94 (m, 1H), 6.75 (dd, J = 5.6, 2.3 Hz, 1H), 6.59 (d, J = 1.5 Hz, 1H), 3.72 (s, 3H), 2.32 (s, 3H)

LR MS (ES+): 440 ($M+Na^+$)

LR MS (ES-): 416 (M-H)

Example 34

3-methyl-N-(3-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-2-furamide



A mixture of 3-methyl-2-furoic acid (60 mg, 0.48mmol), HBTU (198 mg, 0.52mmol) and *N,N*-diisopropylethylamine (129mg, 1.0mmol) in anhydrous DMF (10ml) was stirred at room temperature for 10 minutes, followed by addition of 3-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}aniline (100mg, 0.40mmol). The mixture was stirred at 70°C for 3 hours and poured into 100ml of water. The precipitates were filtered, washed with water and dried *in vacuo* to give the crude, which was purified by silica gel chromatography eluting with 3-5% MeOH/$CHCl_3$ to give 3-methyl-N-(3-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-2-furamide as white solid. Yield: 52mg, 36%.

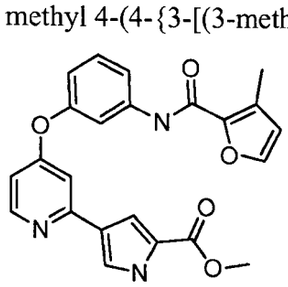
$^1$H NMR ($d_6$-DMSO): 11.46 (br. s., 1H), 10.19 (s, 1H), 8.36 (d, J = 6.2 Hz, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.64 - 7.72 (m, 2H), 7.35 - 7.44 (m, 1H), 7.28 (d, J = 2.1 Hz, 1H), 6.86 - 6.91 (m, 1H), 6.81 - 6.86 (m, 1H), 6.68 - 6.74 (m, 1H), 6.65 (dd, J = 5.7, 2.5 Hz, 1H), 6.57 (d, J = 1.8 Hz, 1H), 6.06 - 6.13 (m, 1H), 2.30 (s, 3H)

LR MS (ES+): 360 (M+H)

LR MS (ES-): 358 (M-H)

Example 35

methyl 4-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-2-carboxylate



Similar procedure as Example 33.



760

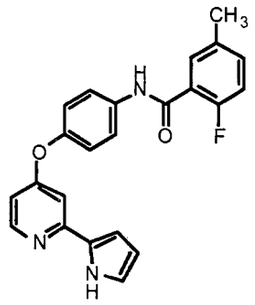
$^1$H NMR ($d_6$-DMSO): 12.18 (br. s., 1H), 10.19 (s, 1H), 8.37 (d, J = 5.6 Hz, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.59 - 7.72 (m, 3H), 7.33 - 7.44 (m, 2H), 7.25 - 7.32 (m, 1H), 6.83 - 6.93 (m, 1H), 6.66 (dd, J = 5.6, 2.3 Hz, 1H), 6.57 (d, J = 1.2 Hz, 1H), 3.76 (s, 3H), 2.30 (s, 3H)

LR MS (ES+): 440 ($M+Na^+$)

LR MS (ES-): 416 (M-H)

Example 36

2-fluoro-5-methyl-N-(4-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)benzamide



Similar procedure as Example 37.

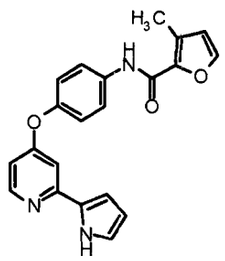
$^1$H NMR ($d_6$-DMSO): 11.44 (br. s., 1H), 10.47 (s, 1H), 8.33 (d, J = 5.6 Hz, 1H), 7.76 - 7.86 (m, 2H), 7.46 (dd, J = 6.4, 2.1 Hz, 1H), 7.36 (ddd, J = 7.9, 5.3, 2.1 Hz, 1H), 7.13 - 7.27 (m, 4H), 6.80 - 6.87 (m, 1H), 6.66 - 6.73 (m, 1H), 6.60 (dd, J = 5.6, 2.3 Hz, 1H), 6.06 - 6.15 (m, 1H), 2.34 (s, 3H)

LR MS (ES+): 388 (M+H)

LR MS (ES-): 386 (M-H)

Example 37

3-methyl-N-(4-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-2-furamide





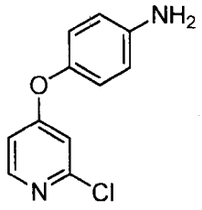
261

A mixture of 3-methyl-2-furoic acid (70mg, 0.55mmol), HATU (243mg, 0.64mmol),) tert-butyl 2-[4-(4-aminophenoxy)pyridin-2-yl]-1H-pyrrole-1-carboxylate (160mg, 0.46mmol) and *N,N*-diisopropylethylamine (148mg, 1.15mmol) in anhydrous DMF (10ml) was stirred at 45°C for 2 hours. The mixture was poured into 100ml of water. The precipitates were filtered, washed with water and dried *in vacuo* to give the crude, which was dissolved in 5ml of methylene chloride, followed by addition of trifluoroacetic acid (3ml). The mixture was stirred at room temperature for 16 hours. The solvents were evaporated under reduced pressure. The residue was purified by reversed-phase chromatography with a gradient of 10~50% acetonitrile/water to give 3-methyl-N-(4-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-2-furamide as white solid. Yield: 56mg, 34%.

LR MS (ES+): 360 (M+H)

LR MS (ES-): 358 (M-H)

Preparation of 4-((2-chloropyridin-4-yl)oxy)aniline



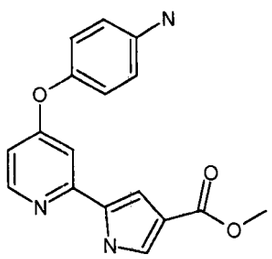

A stirred solution of 4-aminophenol (740mg, 6.8mmol) in anhydrous DMSO (8ml) was flushed with nitrogen and treated with 1M KOBu$^t$ / THF solution (10ml, 10mmol). The mixture was stirred at room temperature under nitrogen for 10 minutes. 2,4-dichloropyridine (1.0g, 6.8mmol) was added and the mixture was heated at 60°C for 30 minutes, cooled to room temperature and poured into 100ml of water. The resulting precipitates were filtered, washed with water and dried to give 4-((2-chloropyridin-4-yl)oxy)aniline as light brown solid. The material was used for the following reactions without further purification. Yield: 1.15g, 77%.

$^1$H NMR ($d_6$-DMSO): 8.21 (d, 1H), 6.77 - 6.91 (m, 4H), 6.54 - 6.68 (m, 2H), 5.16 (s, 2H)

Preparation of methyl 5-[4-(4-aminophenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate



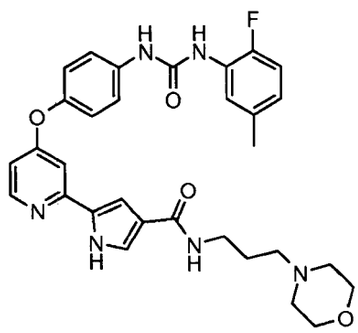
262



A mixture of 4-((2-chloropyridin-4-yl)oxy)aniline (2.6 g, 11.78 mmol), methyl-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-3-carboxylate (6.0 g, 23.90 mmol) and Pd(PPh3)4 (2.72 g, 2.35 mmol) was added to a thick walled reaction vessel and purged with $N_2$. A solution of 2M $K_2CO_3$ (17.68 mL) was added, followed by DME (90 mL). The reaction vessel was sealed and the mixture stirred at 92°C for 18 h. The reaction vessel was cooled to room temperature and the mixture was filtered over celite, washing with EtOAc. The filtrate was concentrated to afford a dark oil, which was purified via column chromatography eluting with 40-80% EtOAc/hexanes to afford methyl 5-[4-(4-aminophenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate (2.4 g, 65% yield).

Example 38

5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-(3-morpholin-4-ylpropyl)-1H-pyrrole-3-carboxamide

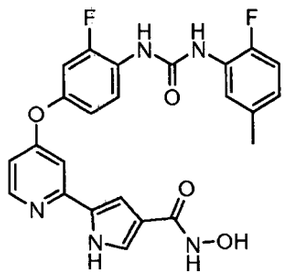


Similar procedure as Example 132.

LR MS (ES+): 573 (MH)

Example 39

5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-hydroxy-1H-pyrrole-3-carboxamide



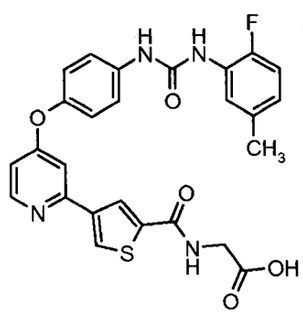
Similar procedure as Example 132.

$^1$H NMR (DMSO-$d_6$) δ: 11.82 (br. s., 1H), 10.55 (br. s., 1H), 9.05 (d, J = 1.8 Hz, 1H), 8.94 (d, J = 2.3 Hz, 1H), 8.64 (br. s., 1H), 8.37 (d, J = 5.6 Hz, 1H), 8.23 (t, J = 9.2 Hz, 1H), 7.98 (dd, J = 7.8, 1.9 Hz, 1H), 7.31 (br. s., 1H), 7.26 (dd, J = 11.7, 2.6 Hz, 1H), 7.19 (d, J = 2.3 Hz, 1H), 7.09 (dd, J = 11.3, 8.4 Hz, 1H), 6.98 - 7.05 (m, 2H), 6.76 - 6.83 (m, 1H), 6.73 (dd, J = 5.7, 2.5 Hz, 1H), 2.25 (s, 3H)

LR MS (ES-): 478 (M-H)

Example 40

{[(4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-2-thienyl)carbonyl]amino}acetic acid



To a stirred solution of methyl {[(4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-2-thienyl)carbonyl]amino}acetate (60mg, 0.11mmol) in a mixture of solvents THF/MeOH (5ml/5ml) was added 1ml of 1M NaOH (1.0mmol) solution. The mixture was stirred at room temperature for 1 hour and poured into 100ml of water. 2M HCl was added until pH = 3. The resulting precipitates were filtered, washed with water, and dried *in vacuo* to give {[(4-{4-[4-({[(2-fluoro-5-

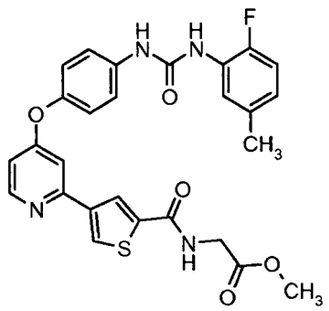
methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-2-thienyl)carbonyl]amino}acetic acid as white solid. Yield: 50mg, 86%.

$^1$H NMR (DMSO-$d_6$) δ: 12.61 (br s, 1H), 9.15 (s, 1H), 8.98 (t, J = 5.9 Hz, 1H), 8.43 - 8.48 (m, 2H), 8.40 (d, J = 1.5 Hz, 1H), 8.36 (d, J = 1.2 Hz, 1H), 7.95 (dd, J = 7.6, 1.8 Hz, 1H), 7.50 - 7.58 (m, 2H), 7.40 (d, J = 2.3 Hz, 1H), 7.12 - 7.19 (m, 2H), 7.08 (dd, J = 11.3, 8.4 Hz, 1H), 6.73 - 6.81 (m, 2H), 3.88 (d, J = 5.9 Hz, 2H), 2.25 (s, 3H)

LR MS (ES-): 519 (M-H)

Example 41

methyl {[(4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-2-thienyl)carbonyl]amino}acetate



A mixture of 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}thiophene-2-carboxylic acid (100mg, 0.22mmol), HATU (100mg, 0.26mmol) and *N,N*-diisopropylethylamine (85mg, 0.66mmol) in anhydrous DMF (10ml) was stirred at room temperature for 10 minutes, followed by addition of glycine methyl ester hydrochloride (41mg, 0.33mmol). The mixture was stirred for another 10 minutes and poured into 100ml of water. 2M HCl was added dropwise until pH = 4~5. The precipitates were filtered, washed with water and dried *in vacuo* to give methyl {[(4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-2-thienyl)carbonyl]amino}acetate as white solid. Yield: 90mg, 78%.

$^1$H NMR (DMSO-$d_6$) δ: 9.17 (s, 1H), 9.10 (t, J = 5.9 Hz, 1H), 8.44 - 8.49 (m, 2H), 8.37 - 8.42 (m, 2H), 7.92 - 7.98 (m, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 2.1 Hz, 1H), 7.16 (d, J = 8.8 Hz, 2H), 7.08 (dd, J = 11.3, 8.4 Hz, 1H), 6.75 - 6.84 (m, 2H), 3.98 (d, J = 5.9 Hz, 2H), 3.63 (s, 3H), 2.25 (s, 3H)

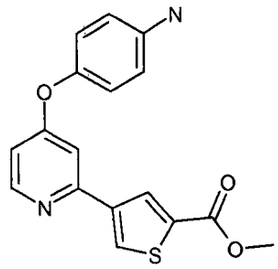
LR MS (ES+): 557 ($M+Na^+$)



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LR MS (ES-): 533 (M-H)

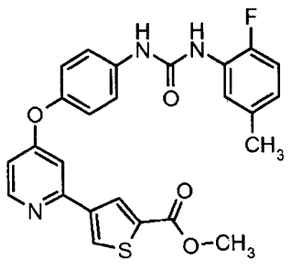
Preparation of methyl 4-(4-(4-aminophenoxy)pyridine-2-yl)thiophene-2-carboxylate



A mixture of 4-(4-aminophenoxy)-2-chloropyridine (5.0 g, 22.66mmol), methyl-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-thiophene-2-carboxylate (9.73 g, 36.25 mmol) and $Pd(PPh_3)_4$ (5.24 g, 4.53 mmol) was added to a thick walled reaction vessel and purged with $N_2$. A solution of 2M $K_2CO_3$ (17.0 mL) was added, followed by dioxane (120 mL). The reaction vessel was sealed and the mixture stirred at 92°C for 18 h. The reaction vessel was cooled to room temperature and the mixture was filtered over celite, washing with EtOAc. The filtrate was concentrated and the resultant dark oil was purified via column chromatography, eluting with 40-60% EtOAc/hexanes to afford methyl 4-(4-(4-aminophenoxy)pyridine-2-yl)thiophene-2-carboxylate (6.1 g, 82% yield).

Example 42

methyl 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}thiophene-2-carboxylate



To a stirred solution of methyl 4-[4-(4-aminophenoxy)pyridin-2-yl]thiophene-2-carboxylate (500 mg, 1.53 mmol) in anhydrous THF (10ml) was added 2-fluoro-5-methyl-phenylisocyanate (255mg, 1.68mmol). The mixture was stirred at room temperature for one hour and poured into 200ml of water. The resulting precipitates were filtered, washed with water and dried *in vacuo* to give the crude, which was purified by silica gel chromatography eluting with 3-5% MeOH/$CHCl_3$ to give methyl 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}thiophene-2-carboxylate as off-white solid. Yield: 560mg, 76%.

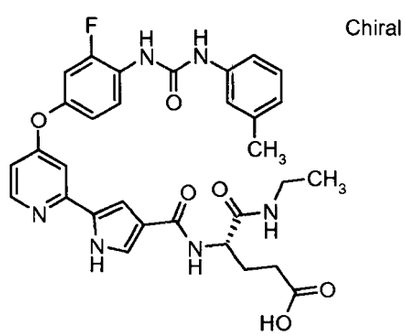
$^1$H NMR (DMSO-$d_6$) δ: 9.14 (s, 1H), 8.51 (d, J = 1.5 Hz, 1H), 8.41 - 8.47 (m, 2H), 8.33 (d, J = 1.8 Hz, 1H), 7.96 (d, J = 6.2 Hz, 1H), 7.48 - 7.57 (m, 3H), 7.13 (d, J = 9.1 Hz, 2H), 7.08 (dd, J = 11.4, 8.5 Hz, 1H), 6.76 - 6.81 (m, 1H), 6.74 (dd, J = 5.6, 2.3 Hz, 1H), 3.83 (s, 3H), 2.25 (s, 3H)

LR MS (ES+): 500 ($M+Na^+$)

LR MS (ES-): 476 (M-H)

Example 43

(4S)-5-(ethylamino)-4-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}-5-oxopentanoic acid



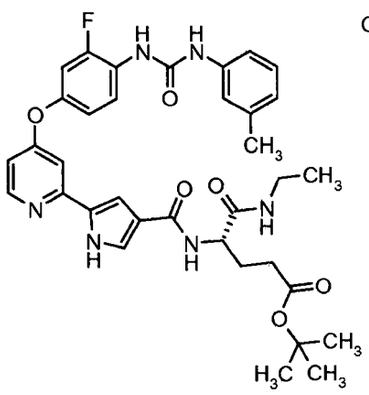
To a stirred solution of tert-butyl (4S)-5-(ethylamino)-4-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}-5-oxopentanoate (30mg, 0.046mmol) in 5ml of methylene chloride was added 2ml of TFA. The mixture was stirred at room temperature for 1 hour, and evaporated to dryness. The residue was dissolved in MeOH (3ml), which was added dropwise into 100ml of water with vigorous stirring. The precipitates were filtered, washed with water and dried to give (4S)-5-(ethylamino)-4-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}-5-oxopentanoic acid as white solid. Yield: 20mg, 74%.

$^1$H NMR (DMSO-$d_6$) δ: 12.04 (br. s., 1H), 11.86 (br. s., 1H), 8.97 (s, 1H), 8.57 (d, J = 2.1 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 8.20 (t, J = 9.1 Hz, 1H), 7.82 (t, J = 5.6 Hz, 1H), 7.79 (d, J = 8.2 Hz, 1H), 7.46 (br. s., 1H), 7.12 - 7.29 (m, 5H), 6.99 - 7.04 (m, 1H), 6.79 (d, J = 7.3 Hz, 1H), 6.74 (d, J = 4.7 Hz, 1H), 4.31 (td, J = 8.6, 5.4 Hz, 1H), 2.97 - 3.11 (m, 2H), 2.26 (s, 3H), 2.17 - 2.25 (m, 2H), 1.87 - 1.98 (m, 1H), 1.74 - 1.84 (m, 1H), 0.97 (t, J = 7.2 Hz, 3H)

LR MS (ES-): 601 (M-H)

Example 44

tert-butyl (4S)-5-(ethylamino)-4-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}-5-oxopentanoate




Chiral

A mixture of (2S)-5-tert-butoxy-2-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}-5-oxopentanoic acid (80mg, 0.13mmol), HATU (57mg, 0.15mmol) and *N,N*-



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diisopropylethylamine (49mg, 0.38mmol) in anhydrous DMF (8ml) was stirred at room temperature for 10 minutes, followed by addition of 2M ethylamine in THF solution (0.1ml, 0.2mmol). The mixture was stirred for another 10 minutes and poured into 100ml of water. 2M HCl was added dropwise until pH = 5. The precipitates were filtered, washed with water and dried *in vacuo* to give the crude, which was purified by silica gel chromatography eluting with 4~5% MeOH/$CHCl_3$ to give tert-butyl (4S)-5-(ethylamino)-4-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}-5-oxopentanoate as white solid. Yield: 40mg, 48%.

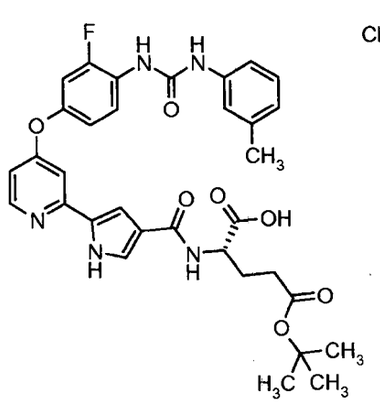
$^1$H NMR (DMSO-$d_6$) δ: 11.83 (br. s., 1H), 8.95 (s, 1H), 8.56 (br. s., 1H), 8.38 (d, J = 5.6 Hz, 1H), 8.20 (t, J = 9.1 Hz, 1H), 7.81 (t, J = 5.3 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.45 (d, J = 1.5 Hz, 1H), 7.23 - 7.30 (m, 2H), 7.18 - 7.23 (m, 2H), 7.12 - 7.18 (m, 2H), 6.98 - 7.04 (m, 1H), 6.79 (d, J = 7.6 Hz, 1H), 6.73 (dd, J = 5.6, 2.3 Hz, 1H), 4.27 - 4.35 (m, 1H), 3.01 - 3.08 (m, 2H), 2.26 (s, 3H), 2.17 - 2.23 (m, 2H), 1.87 - 1.95 (m, 1H), 1.78 (m, 1H), 1.34 (s, 9H), 0.97 (t, J = 7.2 Hz, 3H)

LR MS (ES+): 681 ($M+Na^+$)

LR MS (ES-): 657 (M-H)

Example 45

(2S)-5-tert-butoxy-2-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}-5-oxopentanoic acid




To a stirred solution of (S)-5-tert-butyl 1-methyl 2-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioate (120mg, 0.19mmol) in a mixture of solvents THF/MeOH

(5ml/5ml) was added 1ml of 1M NaOH (1mmol) solution. The mixture was stirred at room temperature for 30 minutes, and poured into 100ml of water. 2M HCl was added dropwise until pH = 4. The resulting precipitates were filtered, washed with water, and dried *in vacuo* to give (2S)-5-tert-butoxy-2-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}-5-oxopentanoic acid as white solid. Yield: 100mg, 85%.

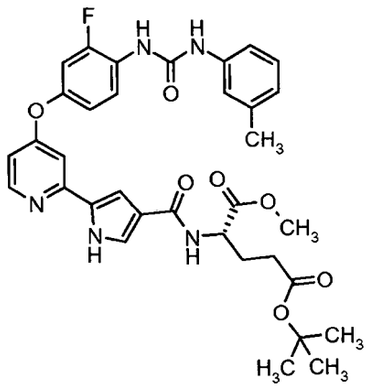
$^1$H NMR (DMSO-$d_6$) δ: 12.49 (br. s., 1H), 11.84 (br. s., 1H), 8.98 (s, 1H), 8.58 (d, J = 2.3 Hz, 1H), 8.38 (d, J = 5.6 Hz, 1H), 8.20 (t, J = 9.1 Hz, 1H), 7.89 (br. s., 1H), 7.42 (br. s., 1H), 7.28 (s, 1H), 7.25 (dd, J = 11.7, 2.6 Hz, 1H), 7.20 - 7.23 (m, 2H), 7.11 - 7.18 (m, 2H), 7.01 (dd, J = 9.0, 1.6 Hz, 1H), 6.79 (d, J = 7.3 Hz, 1H), 6.73 (dd, J = 5.6, 2.3 Hz, 1H), 4.23 - 4.34 (m, 1H), 2.23 - 2.28 (m, 2H), 2.26 (s, 3H), 1.95 - 2.03 (m, 1H), 1.80 - 1.88 (m, 1H), 1.35 (s, 9H)

LR MS (ES+): 654 ($M+Na^+$)

LR MS (ES-): 630 (M-H)

Example 46

(S)-5-tert-butyl 1-methyl 2-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioate



A mixture of 5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid (500mg, 1.1mmol), HATU (500mg, 1.32mmol) and *N,N*-diisopropylethylamine (426mg, 3.3mmol) in anhydrous DMF (8ml) was stirred at room temperature for 10 minutes, followed by addition of L-Glutamic acid 5-tert-butyl 1-methyl ester hydrochloride (334mg, 1.32mmol). The mixture was stirred for another 10 minutes and poured into 200ml of water. 2M HCl was added dropwise until pH = 5. The precipitates were filtered,



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washed with water and dried *in vacuo* to give the crude, which was purified by silica gel chromatography eluting with 3~5% MeOH/$CHCl_3$ to give (S)-5-tert-butyl 1-methyl 2-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioate as off-white solid. Yield: 380mg, 52%.

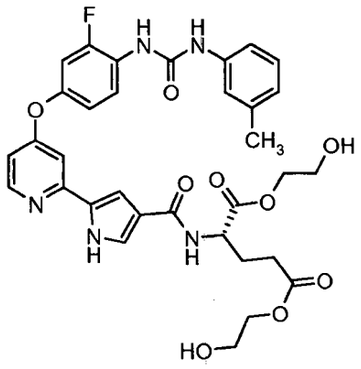
$^1$H NMR (DMSO-$d_6$) δ: 11.87 (br. s., 1H), 8.96 (s, 1H), 8.56 (br. s., 1H), 8.38 (d, J = 5.6 Hz, 1H), 8.20 (t, J = 8.9 Hz, 1H), 8.08 (d, J = 7.0 Hz, 1H), 7.44 (br. s., 1H), 7.23 - 7.29 (m, 2H), 7.18 - 7.23 (m, 2H), 7.11 - 7.17 (m, 2H), 7.01 (d, J = 8.8 Hz, 1H), 6.79 (d, J = 7.0 Hz, 1H), 6.70 - 6.76 (m, 1H), 4.32 - 4.41 (m, 1H), 3.60 (s, 3H), 2.23 - 2.31 (m, 5H), 1.93 - 2.03 (m, 1H), 1.81 - 1.91 (m, 1H), 1.35 (s, 9H)

LR MS (ES+): 646 (MH), 668 ($M+Na^+$)

LR MS (ES-): 644 (M-H)

Example 47

bis(2-hydroxyethyl) 2-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioate



LR MS (ES+): 686 ($M+Na^+$)

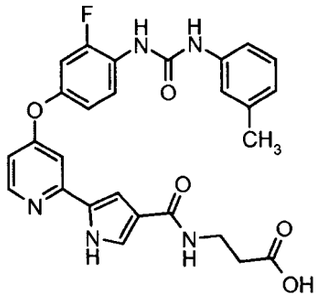
LR MS (ES-): 662 (M-H), 561

Example 48

3-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}propanoic acid



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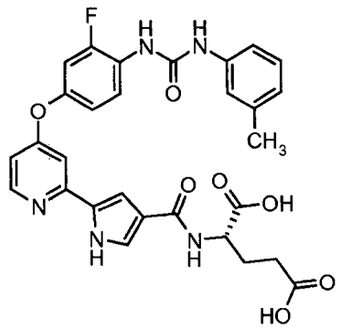
Similar procedure as 

$^1$H NMR (DMSO-$d_6$) s, 1H), 8.59 (br. s., 1H), 8.40 (d, J = 5.9 Hz, 1H), 8.22 (t, J = 9.0 Hz, 1H), 7.90 - 7.96 (m, 1H), 7.40 (br. s., 1H), 7.25 - 7.30 (m, 2H), 7.21 (d, J = 7.0 Hz, 2H), 7.15 (t, J = 7.8 Hz, 2H), 7.03 (d, J = 9.1 Hz, 1H), 6.79 (d, J = 7.0 Hz, 2H), 3.32 - 3.37 (m, 2H), 2.43 (t, J = 7.0 Hz, 2H), 2.26 (s, 3H)

LR MS (ES-): 516 (M-H)

Example 49

2-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioic acid

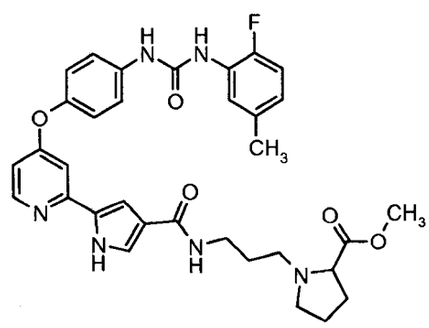


$^1$H NMR (DMSO-$d_6$) δ: 12.43 (br. s., 2H), 11.89 (br. s., 1H), 8.97 (br. s., 1H), 8.57 (br. s., 1H), 8.39 (d, J = 5.3 Hz, 1H), 8.20 (t, J = 8.8 Hz, 1H), 7.97 (d, J = 7.6 Hz, 1H), 7.46 (br. s., 1H), 7.11 - 7.31 (m, 4H), 7.02 (d, J = 9.1 Hz, 1H), 6.79 (d, J = 7.0 Hz, 1H), 6.75 (br. s., 1H), 4.32 (br. s., 1H), 2.30 (t, J = 7.2 Hz, 2H), 2.26 (s, 3H), 2.01 (m, 2H), 1.86 (m, 2H)

LR MS (ES-): 574 (M-H)

Example 50

methyl 1-(3-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}propyl)pyrrolidine-2-carboxylate



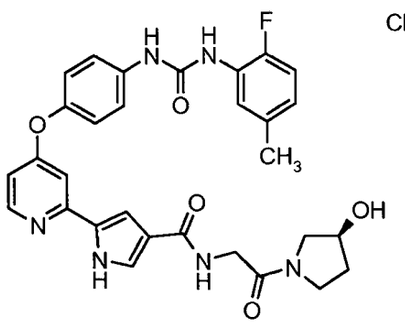
Similar procedure as Example 132.

LR MS (ES+): 615 (MH), 637 ($M+Na^+$)

LR MS (ES-): 613 (M-H)

Example 51

5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-{2-[(3S)-3-hydroxypyrrolidin-1-yl]-2-oxoethyl}-1H-pyrrole-3-carboxamide



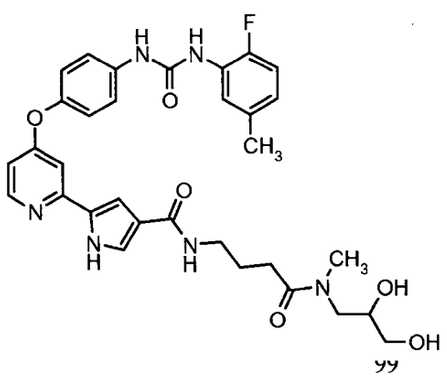

Similar procedure as Example 132.

LR MS (ES+): 573 (MH), 595 ($M+Na^+$)

LR MS (ES-): 571 (M-H)

Example 52

N-{4-[(2,3-dihydroxypropyl)(methyl)amino]-4-oxobutyl}-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



Similar procedure as Example 61.

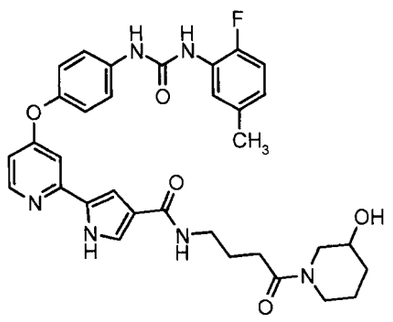
$^1$H NMR (DMSO-$d_6$) δ: 11.70 - 11.82 (m, 1H), 9.24 (s, 1H), 8.50 (d, J = 2.1 Hz, 1H), 8.35 (d, J = 5.9 Hz, 1H), 7.93 - 7.98 (m, 1H), 7.85 (dt, J = 14.5, 5.5 Hz, 1H), 7.54 (d, J = 9.1 Hz, 2H), 7.34 (br. s., 1H), 7.10 - 7.15 (m, 3H), 7.08 (dd, J = 11.2, 8.5 Hz, 1H), 7.01 - 7.05 (m, 1H), 6.73 - 6.82 (m, 1H), 6.67 (dd, J = 5.6, 2.3 Hz, 1H), 4.87 (d, J = 5.3 Hz, 1H), 4.60 - 4.69 (m, 1H), 4.46 (t, J = 5.9 Hz, 1H), 3.55 - 3.65 (m, 2H), 3.20 - 3.27 (m, 2H), 3.10 - 3.19 (m, 2H), 2.96 (s, 1H), 2.79 (s, 2H), 2.27 - 2.35 (m, 1H), 2.24 (s, 3H), 1.62 - 1.72 (m, 2H)

LR MS (ES+): 619 (MH), 641 ($M+Na^+$)

LR MS (ES-): 617 (M-H)

Example 53

5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-[4-(3-hydroxypiperidin-1-yl)-4-oxobutyl]-1H-pyrrole-3-carboxamide



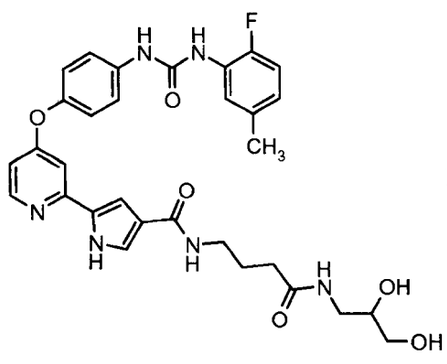
Similar procedure as Example 61.

LR MS (ES+): 637 ($M+Na^+$)

LR MS (ES-): 613 (M-H)

Example 54

N-{4-[(2,3-dihydroxypropyl)amino]-4-oxobutyl}-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



Similar procedure as Example 61.

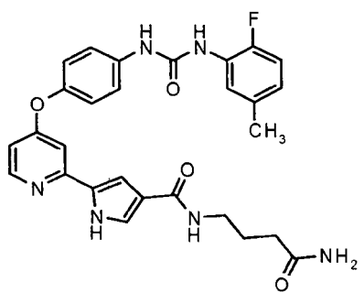
$^1$H NMR (DMSO-$d_6$) δ: 11.77 (br. s., 1H), 9.14 (s, 1H), 8.46 (d, J = 2.3 Hz, 1H), 8.35 (d, J = 5.9 Hz, 1H), 7.96 (dd, J = 7.9, 2.1 Hz, 1H), 7.84 (t, J = 5.6 Hz, 1H), 7.77 (t, J = 5.9 Hz, 1H), 7.51 - 7.57 (m, 2H), 7.33 (dd, J = 3.1, 1.6 Hz, 1H), 7.11 - 7.16 (m, 3H), 7.08 (dd, J = 11.3, 8.4 Hz, 1H), 7.01 - 7.05 (m, 1H), 6.75 - 6.82 (m, 1H), 6.68 (dd, J = 5.7, 2.5 Hz, 1H), 4.68 (d, J = 5.0 Hz, 1H), 4.46 (t, J = 5.9 Hz, 1H), 3.41 - 3.47 (m, 1H), 3.20 - 3.26 (m, 2H), 3.09 - 3.19 (m, 3H), 2.90 - 2.97 (m, 1H), 2.25 (s, 3H), 2.10 (t, J = 7.6 Hz, 2H), 1.66 (quin, J = 7.3 Hz, 2H)

LR MS (ES+): 605 (MH), 627 ($M+Na^+$)

LR MS (ES-): 603 (M-H)

Example 55

N-(4-amino-4-oxobutyl)-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



Similar procedure as Example 61.

$^1$H NMR (DMSO-$d_6$) δ: 11.92 (br. s., 1H), 9.20 (br. s., 1H), 8.48 (d, J = 1.8 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.95 (dd, J = 7.8, 1.9 Hz, 1H), 7.89 (br. s., 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.42 (br. s., 1H), 7.18 - 7.28 (m, 2H), 7.15 (d, J = 8.8 Hz, 2H), 7.08 (dd, J = 11.4, 8.5 Hz, 1H), 6.78 (ddd, J = 7.5, 5.0, 2.2 Hz, 2H), 6.68 (br. s., 1H), 3.14 (q, J = 6.7 Hz, 2H), 2.25 (s, 3H), 2.05 (t, J = 7.5 Hz, 2H), 1.66 (quin, J = 7.3 Hz, 2H)

LR MS (ES+): 553 ($M+Na^+$)

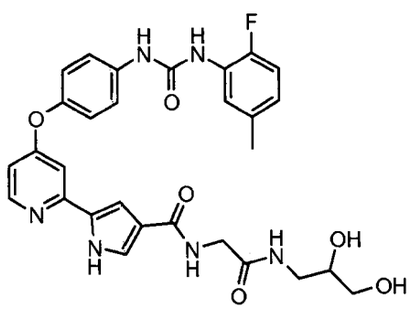
LR MS (ES-): 529 (M-H)



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Example 56

N-{2-[(2,3-dihydroxypropyl)amino]-2-oxoethyl}-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

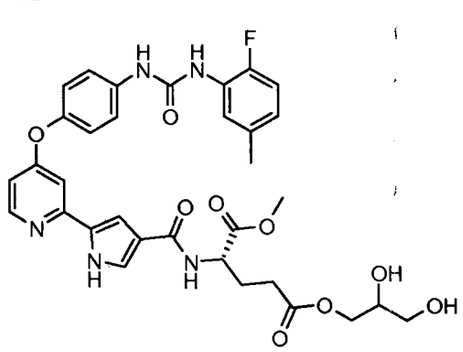
$^1$H NMR (DMSO-$d_6$) δ: 11.83 (br. s., 1H), 9.15 (s, 1H), 8.46 (br. s., 1H), 8.36 (d, J = 5.9 Hz, 1H), 8.14 (t, J = 6.0 Hz, 1H), 7.95 (d, J = 7.6 Hz, 1H), 7.67 (t, J = 5.6 Hz, 1H), 7.54 (d, J = 8.8 Hz, 2H), 7.38 (br. s., 1H), 7.13 (d, J = 8.8 Hz, 3H), 7.03 - 7.11 (m, 2H), 6.75 - 6.82 (m, 1H), 6.69 (dd, J = 5.6, 2.3 Hz, 1H), 4.70 (d, J = 5.0 Hz, 1H), 4.47 (t, J = 5.7 Hz, 1H), 3.76 (d, J = 5.6 Hz, 2H), 3.45 (dq, J = 11.2, 5.5 Hz, 1H), 3.16 - 3.27 (m, 3H), 2.93 - 3.00 (m, 1H), 2.25 (s, 3H)

LR MS (ES+): 577 (MH), 599 ($M+Na^+$)

LR MS (ES-): 575 (M-H)

Example 57

5-(2,3-dihydroxypropyl) 1-methyl 2-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioate





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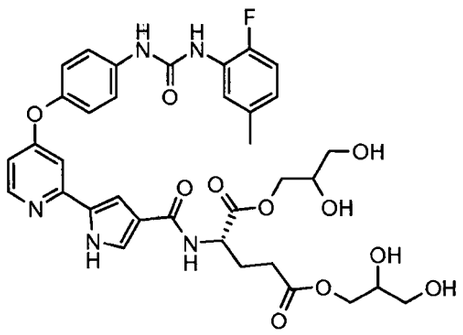
Similar procedure as Example 58.

$^1$H NMR (DMSO-$d_6$) δ: 11.86 (br. s., 1H), 9.14 (s, 1H), 8.46 (d, J = 2.3 Hz, 1H), 8.36 (d, J = 5.6 Hz, 1H), 8.08 - 8.17 (m, 1H), 7.96 (dd, J = 7.9, 1.8 Hz, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.43 (br. s., 1H), 7.04 - 7.21 (m, 4H), 6.78 (dt, J = 5.7, 2.7 Hz, 1H), 6.68 (dd, J = 5.6, 2.3 Hz, 1H), 4.83 (d, J = 5.3 Hz, 1H), 4.58 (t, J = 5.7 Hz, 1H), 4.36 - 4.45 (m, 1H), 3.95 - 4.06 (m, 2H), 3.88 (dd, J = 11.0, 6.6 Hz, 1H), 3.60 (s, 3H), 3.28 - 3.35 (m, 2H), 2.40 (t, J = 7.6 Hz, 2H), 2.25 (s, 3H), 1.99 - 2.10 (m, 1H), 1.88 - 1.95 (m, 1H), 1.15 (t, J = 7.0 Hz, 1H)

LR MS (ES+): 664 (MH), 686 ($M+Na^+$)

Example 58

bis(2,3-dihydroxypropyl) 2-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioate



A mixture of 2-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioic acid (60mg, 0.10mmol), glycerol (0.5ml), 1-Ethyl-3-(3-dimethyllaminopropyl)carbodiimide hydrochloride (EDC• HCl, 37mg, 0.19mmol) and 4-dimethylaminopyridine (DMAP, 5mg, 0.04mmol) in anhydrous THF (10ml) was stirred at 60°C for 3 hours. The mixture was cooled to room temperature, concentrated and purified by silica gel chromatography eluting with a gradient of 10~15% MeOH/$CHCl_3$ to give bis(2,3-dihydroxypropyl) 2-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioate as colorless oil. Yield: 40mg, 53%.

LR MS (ES+): 746 ($M+Na^+$)

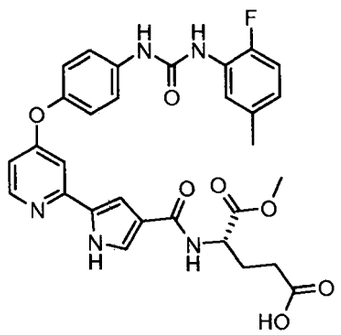
LR MS (ES-): 722 (M-H)



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Example 59

4-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}-5-methoxy-5-oxopentanoic acid



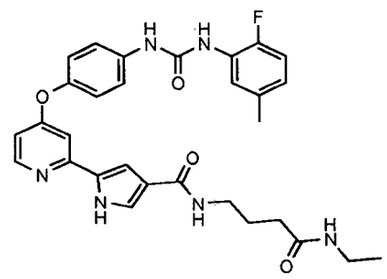
Similar procedure as Example 132.

$^1$H NMR (DMSO-$d_6$) δ: 11.98 (br. s., 1H), 9.19 (s, 1H), 8.48 (d, J = 2.6 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 8.13 (d, J = 7.3 Hz, 1H), 7.95 (dd, J = 7.8, 1.9 Hz, 1H), 7.53 - 7.57 (m, 2H), 7.47 - 7.52 (m, 1H), 7.24 (br. s., 1H), 7.19 (br. s., 1H), 7.15 (d, J = 8.8 Hz, 2H), 7.08 (dd, J = 11.3, 8.4 Hz, 1H), 6.72 - 6.81 (m, 2H), 4.38 (ddd, J = 9.5, 7.5, 5.3 Hz, 1H), 3.60 (s, 3H), 2.31 (t, J = 7.6 Hz, 2H), 2.25 (s, 3H), 1.95 - 2.05 (m, 1H), 1.82 - 1.93 (m, J = 14.0, 9.6, 7.0, 7.0 Hz, 1H)

LR MS (ES-): 588 (M-H)

Example 60

N-[4-(ethylamino)-4-oxobutyl]-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



Similar procedure as Example 61.

$^1$H NMR (DMSO-$d_6$) δ: 11.96 (br. s., 1H), 9.20 (s, 1H), 8.48 (d, J = 2.6 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.95 (dd, J = 7.8, 1.9 Hz, 1H), 7.89 (br. s., 1H), 7.76 (t, J = 5.3 Hz, 1H), 7.53 - 7.58 (m,

2H), 7.44 (br. s., 1H), 7.23 (br. s., 1H), 7.13 - 7.19 (m, 3H), 7.08 (dd, J = 11.3, 8.4 Hz, 1H), 6.75 - 6.84 (m, 2H), 3.11 - 3.17 (m, 2H), 3.01 (qd, J = 7.2, 5.6 Hz, 2H), 2.25 (s, 3H), 2.05 (t, J = 7.5 Hz, 2H), 1.66 (quin, J = 7.3 Hz, 2H), 0.96 (t, J = 7.2 Hz, 3H)

LR MS (ES+): 559 (MH), 581 ($M+Na^+$)

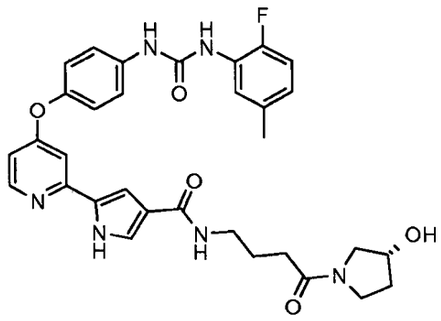
LR MS (ES-): 557 (M-H)



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Example 61

5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-[4-(3-hydroxypyrrolidin-1-yl)-4-oxobutyl]-1H-pyrrole-3-carboxamide



A mixture of 4-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}butanoic acid (60mg, 0.11mmol), HATU (50mg, 0.13mmol) and *N,N*-diisopropylethylamine (43mg, 0.33mmol) in anhydrous DMF (8ml) was stirred at room temperature for 10 minutes, followed by addition of (R)-3-pyrrolidinol (14mg, 0.16mmol). The mixture was stirred for another 10 minutes and poured into 100ml of water. 2M HCl was added dropwise until pH = 4~5. The precipitates were filtered, washed with water and dried *in vacuo* to give 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-[4-(3-hydroxypyrrolidin-1-yl)-4-oxobutyl]-1H-pyrrole-3-carboxamide as white solid. Yield: 40mg, 59%.

$^1$H NMR (DMSO-$d_6$) δ: 11.97 (br. s., 1H), 9.31 (s, 1H), 8.53 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.95 (dd, J = 7.8, 1.9 Hz, 1H), 7.91 (d, J = 4.4 Hz, 1H), 7.54 - 7.59 (m, 2H), 7.42 - 7.48 (m, 1H), 7.24 (br. s., 1H), 7.16 (d, J = 8.8 Hz, 2H), 7.05 - 7.10 (m, 1H), 6.78 (ddd, J = 7.5, 5.0, 2.2 Hz, 2H), 4.24 - 4.28 (m, 0H), 4.16 - 4.21 (m, 1H), 3.40 - 3.48 (m, 2H), 3.35 (ddd, J = 11.6, 8.4, 3.5 Hz, 1H), 3.25 - 3.30 (m, 1H), 3.14 - 3.25 (m, 4H), 2.25 (s, 3H), 2.23- 2.27 (m, 1H), 2.20 (t, J = 7.9 Hz, 1H), 1.84 - 1.92 (m, 1H), 1.75 - 1.82 (m, 1H), 1.65 - 1.73 (m, 2H)

LR MS (ES+): 601 (MH), 623 ($M+Na^+$)

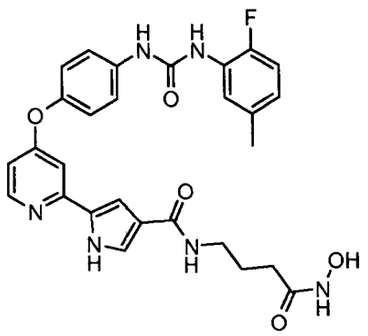
LR MS (ES-): 599 (M-H)



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Example 62

5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-[4-(hydroxyamino)-4-oxobutyl]-1H-pyrrole-3-carboxamide



Similar procedure as Example 61.

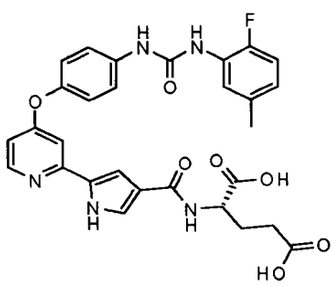
$^1$H NMR (DMSO-$d_6$) δ: 11.92 (br. s., 1H), 10.33 (s, 1H), 9.18 (s, 1H), 8.47 (d, J = 2.6 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.95 (dd, J = 7.9, 1.8 Hz, 1H), 7.87 - 7.92 (m, 1H), 7.51 - 7.58 (m, 2H), 7.38 - 7.46 (m, 1H), 7.21 (br. s., 1H), 7.11 - 7.18 (m, 3H), 7.05 - 7.11 (m, 1H), 6.72 - 6.82 (m, 2H), 3.14 (q, J = 6.7 Hz, 2H), 2.25 (s, 3H), 1.96 (t, J = 7.6 Hz, 2H), 1.66 (quin, J = 7.3 Hz, 2H)

LR MS (ES+): 547 (MH), 569 ($M+Na^+$)

LR MS (ES-): 545 (M-H)

Example 63

2-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioic acid



Similar procedure as Example 132.

$^1$H NMR (DMSO-$d_6$) δ: 12.42 (br. s., 1H), 12.12 (br. s., 1H), 11.86 (br. s., 1H), 9.15 (s, 1H), 8.46 (d, J = 2.6 Hz, 1H), 8.37 (d, J = 5.6 Hz, 1H), 7.93 - 8.01 (m, 2H), 7.51 - 7.58 (m, 2H), 7.44 (br. s., 1H), 7.18 (s, 1H), 7.11 - 7.16 (m, 3H), 7.08 (dd, J = 11.3, 8.4 Hz, 1H), 6.75 - 6.82 (m,

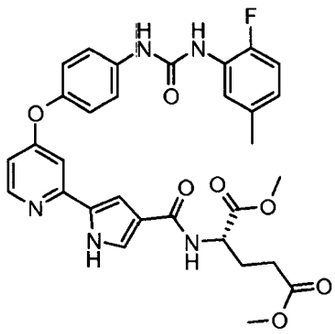


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1H), 6.69 (d, J = 3.8 Hz, 1H), 4.32 (ddd, J = 9.7, 7.9, 5.0 Hz, 1H), 2.30 (t, J = 7.6 Hz, 2H), 2.25 (s, 3H), 1.96 - 2.05 (m, 1H), 1.80 - 1.91 (m, J = 14.0, 9.8, 7.2, 7.2 Hz, 1H)
LR MS (ES-): 574 (M-H)

Example 64

dimethyl 2-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}pentanedioate

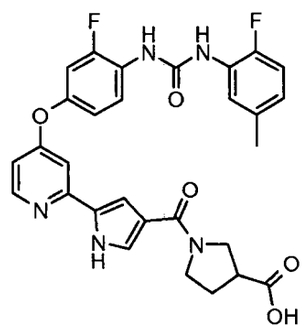


Similar procedure as Example 132.

$^1$H NMR (DMSO-$d_6$) δ: 12.27 (br. s., 1H), 9.33 (br. s., 1H), 8.50 - 8.57 (m, 1H), 8.44 (d, J = 6.2 Hz, 1H), 8.23 (d, J = 6.7 Hz, 1H), 7.95 (d, J = 6.5 Hz, 1H), 7.64 (br. s., 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.39 (br. s., 2H), 7.19 (d, J = 8.8 Hz, 2H), 7.08 (dd, J = 11.2, 8.2 Hz, 1H), 6.92 (br. s., 1H), 6.79 (d, J = 5.6 Hz, 1H), 4.35 - 4.43 (m, 1H), 3.60 (s, 3H), 3.55 (s, 3H), 2.40 (t, J = 7.5 Hz, 2H), 2.22 - 2.28 (m, 3H), 2.00 - 2.10 (m, 1H), 1.88 - 1.97 (m, 1H)
LR MS (ES+): 626 ($M+Na^+$)
LR MS (ES-): 602 (M-H)

Example 65

1-[(5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]pyrrolidine-3-carboxylic acid





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Similar procedure as Example 132.

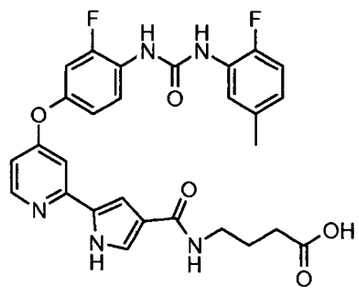
$^1$H NMR (DMSO-$d_6$) δ: 12.47 (br. s., 1H), 11.85 - 12.01 (m, 1H), 9.05 (d, J = 1.8 Hz, 1H), 8.94 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 8.22 (t, J = 9.1 Hz, 1H), 7.98 (dd, J = 7.8, 1.9 Hz, 1H), 7.41 (br. s., 1H), 7.21 - 7.32 (m, 2H), 7.06 - 7.14 (m, 2H), 7.01 (dd, J = 9.0, 1.6 Hz, 1H), 6.79 (ddd, J = 7.6, 5.1, 1.9 Hz, 1H), 6.65 - 6.76 (m, 1H), 2.97 - 3.93 (m, 5H), 2.25 (s, 3H), 1.93 - 2.19 (m, 2H)

LR MS (ES+): 562 (MH), 584 ($M+Na^+$)

LR MS (ES-): 560 (M-H)

Example 66

4-{[(5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}butanoic acid



To a stirred solution of ethyl 4-{[(5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}butanoate (45mg, 0.078mmol) in 10ml of THF was added 3ml of 1M NaOH (3.0mmol). The mixture was heated at 60°C for 3 hours, cooled to room temperature and poured into 100ml of water. 2M HCl was added until pH = 5. The precipitates were filtered, washed with water, and dried to give 4-{[(5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}butanoic acid as grey solid. Yield: 40mg, 93%.

$^1$H NMR (DMSO-$d_6$) δ: 11.99 (br. s., 1H), 11.82 (br. s., 1H), 9.06 (d, J = 2.1 Hz, 1H), 8.94 (d, J = 2.6 Hz, 1H), 8.38 (d, J = 5.9 Hz, 1H), 8.23 (t, J = 9.1 Hz, 1H), 7.98 (dd, J = 7.9, 2.1 Hz, 1H), 7.85 (t, J = 5.7 Hz, 1H), 7.37 (br. s., 1H), 7.27 (dd, J = 11.7, 2.6 Hz, 1H), 7.19 (s, 1H), 7.09 (dd, J = 11.3, 8.4 Hz, 2H), 7.02 (dd, J = 8.9, 1.6 Hz, 1H), 6.77 - 6.82 (m, 1H), 6.73 - 6.77 (m, 1H), 3.16 (q, J = 6.7 Hz, 2H), 2.25 (s, 3H), 2.22 (t, J = 7.3 Hz, 2H), 1.67 (quin, J = 7.2 Hz, 2H)

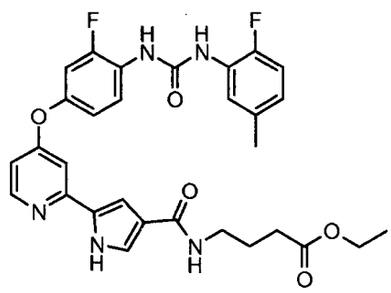


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LR MS (ES-): 548 (M-H)

Example 67

ethyl 4-{[(5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}butanoate



Similar procedure as Example 132.

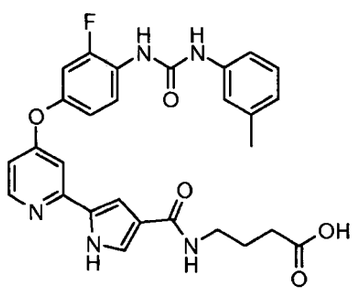
$^1$H NMR (DMSO-$d_6$) δ: 11.99 (br. s., 1H), 9.09 (d, J = 1.5 Hz, 1H), 8.96 (d, J = 2.3 Hz, 1H), 8.42 (d, J = 6.2 Hz, 1H), 8.26 (t, J = 9.1 Hz, 1H), 7.98 (dd, J = 7.8, 2.2 Hz, 1H), 7.86 - 7.94 (m, 1H), 7.46 (br. s., 1H), 7.25 - 7.34 (m, 2H), 7.22 (br. s., 1H), 7.09 (dd, J = 11.3, 8.4 Hz, 1H), 7.02 - 7.07 (m, 1H), 6.87 (br. s., 1H), 6.76 - 6.82 (m, 1H), 4.01 (q, J = 7.1 Hz, 2H), 3.13 - 3.21 (m, 2H), 2.30 (t, J = 7.5 Hz, 2H), 2.25 (s, 3H), 1.70 (quin, J = 7.2 Hz, 2H), 1.14 (t, J = 7.04 Hz, 3H)

LR MS (ES+): 578 (MH), 600 ($M+Na^+$)

LR MS (ES-): 576 (M-H)

Example 68

4-{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}butanoic acid



Similar procedure as Example 66.

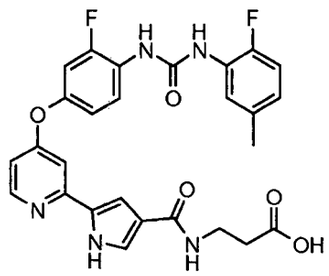
$^1$H NMR (DMSO-$d_6$) δ: 12.00 (br. s., 1H), 11.82 (br. s., 1H), 8.97 (s, 1H), 8.57 (d, J = 2.3 Hz, 1H), 8.38 (d, J = 5.9 Hz, 1H), 8.21 (t, J = 9.1 Hz, 1H), 7.85 (t, J = 5.7 Hz, 1H), 7.37 (br. s., 1H), 7.24 - 7.29 (m, 2H), 7.17 - 7.23 (m, 2H), 7.13 - 7.17 (m, 1H), 7.10 (br. s., 1H), 7.02 (dd, J = 8.8, 1.8 Hz, 1H), 6.79 (d, J = 7.3 Hz, 1H), 6.75 (br. s., 1H), 3.16 (q, J = 6.7 Hz, 2H), 2.26 (s, 3H), 2.22 (t, J = 7.3 Hz, 2H), 1.67 (quin, J = 7.2 Hz, 2H)

LR MS (ES+): 532 (MH), 554 ($M+Na^+$)

LR MS (ES-): 530 (M-H)

Example 69

3-{[(5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}propanoic acid



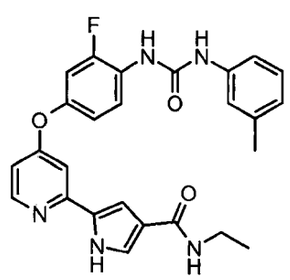
Similar procedure as Example 66.

$^1$H NMR (DMSO-$d_6$) δ: 11.93 (br. s., 2H), 9.08 (br. s., 1H), 8.96 (d, J = 1.8 Hz, 1H), 8.41 (d, J = 5.9 Hz, 1H), 8.25 (t, J = 8.9 Hz, 1H), 7.98 (d, J = 7.9 Hz, 1H), 7.94 (br. s., 1H), 7.43 (d, J = 2.1 Hz, 1H), 7.29 (d, J = 10.3 Hz, 1H), 7.24 (br. s., 1H), 7.17 (br. s., 1H), 7.09 (dd, J = 11.3, 8.4 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 6.83 (br. s., 1H), 6.76 - 6.81 (m, 1H), 3.33 - 3.38 (m, 2H), 2.44 (t, J = 7.0 Hz, 2H), 2.25 (s, 3H)

LR MS (ES-): 534 (M-H)

Example 70

N-ethyl-5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide





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Similar procedure as Example 132.

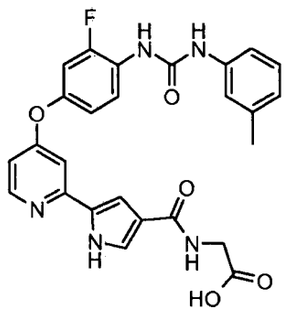
$^1$H NMR (DMSO-$d_6$) δ: 11.98 (br. s., 1H), 9.11 (s, 1H), 8.67 (br. s., 1H), 8.41 (d, J = 5.9 Hz, 1H), 8.23 (t, J = 9.1 Hz, 1H), 7.87 (t, J = 5.0 Hz, 1H), 7.44 (br. s., 1H), 7.25 - 7.32 (m, 3H), 7.18 - 7.25 (m, 2H), 7.12 - 7.17 (m, 1H), 7.04 (dd, J = 9.0, 1.6 Hz, 1H), 6.85 (br. s., 1H), 6.79 (d, J = 7.3 Hz, 1H), 3.15 - 3.22 (m, 2H), 2.26 (s, 3H), 1.05 (t, J = 7.2 Hz, 3H)

LR MS (ES+): 474 (MH), 496 ($M+Na^+$)

LR MS (ES-): 472 (M-H)

Example 71

{[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}acetic acid



Similar procedure as Example 66.

$^1$H NMR (DMSO-$d_6$) δ: 11.84 (br. s., 1H), 9.23 (s, 1H), 8.73 (d, J = 1.5 Hz, 1H), 8.38 (d, J = 5.6 Hz, 1H), 8.18 (t, J = 9.1 Hz, 1H), 8.12 (t, J = 5.4 Hz, 1H), 7.38 (dd, J = 2.9, 1.8 Hz, 1H), 7.28 (s, 1H), 7.21 - 7.26 (m, 2H), 7.19 (d, J = 2.3 Hz, 1H), 7.14 (t, J = 7.8 Hz, 1H), 7.08 - 7.11 (m, 1H), 7.01 (dd, J = 9.0, 2.5 Hz, 1H), 6.78 (d, J = 7.3 Hz, 1H), 6.73 (dd, J = 5.9, 2.3 Hz, 1H), 3.78 (d, J = 5.9 Hz, 2H), 2.25 (s, 3H)

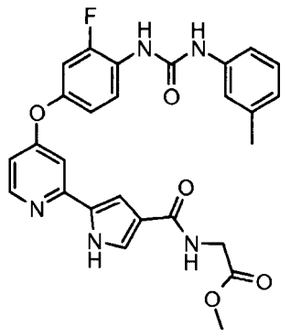
LR MS (ES-): 502 (M-H)

Example 72

methyl {[(5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}acetate



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Similar procedure as Example 132.

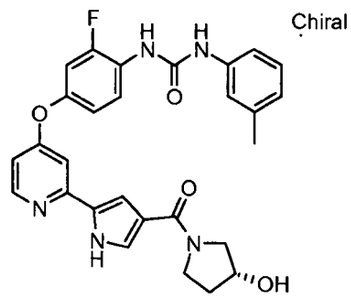
$^1$H NMR (DMSO-$d_6$) δ: 11.87 (br. s., 1H), 8.96 (s, 1H), 8.56 (d, J = 2.3 Hz, 1H), 8.38 (d, J = 5.9 Hz, 1H), 8.31 (t, J = 6.0 Hz, 1H), 8.20 (t, J = 9.1 Hz, 1H), 7.39 (dd, J = 3.2, 1.8 Hz, 1H), 7.24 - 7.29 (m, 2H), 7.21 (d, J = 8.2 Hz, 1H), 7.19 (d, J = 2.3 Hz, 1H), 7.13 - 7.17 (m, 1H), 7.08 - 7.10 (m, 1H), 7.01 (dd, J = 8.5, 2.1 Hz, 1H), 6.79 (d, J = 7.3 Hz, 1H), 6.74 (dd, J = 5.9, 2.3 Hz, 1H), 3.90 (d, J = 5.9 Hz, 2H), 3.60 (s, 3H), 2.26 (s, 3H)

LR MS (ES+): 518 (MH), 540 ($M+Na^+$)

LR MS (ES-): 516 (M-H)

Example 73

1-(2-fluoro-4-{[2-(4-{[(3R)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-(3-methylphenyl)urea




Similar procedure as Example 132.

$^1$H NMR (DMSO-$d_6$) δ: 11.87 (br. s., 1H), 8.97 (s, 1H), 8.56 (d, J = 2.1 Hz, 1H), 8.37 (d, J = 5.9 Hz, 1H), 8.18 (t, J = 9.1 Hz, 1H), 7.38 (d, J = 2.3 Hz, 1H), 7.18 - 7.30 (m, 4H), 7.12 - 7.17 (m, 1H), 7.08 (d, J = 18.8 Hz, 1H), 6.99 (dt, J = 7.6, 1.5 Hz, 1H), 6.78 (d, J = 7.6 Hz, 1H), 6.68 (dd, J



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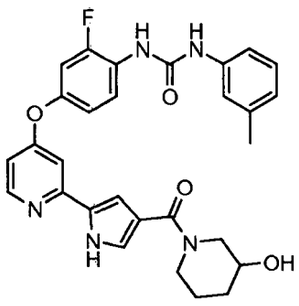
= 5.6, 2.3 Hz, 1H), 4.90 (d, J = 9.4 Hz, 1H), 4.30 (br. s., 1H), 3.68 - 3.82 (m, 2H), 3.42 - 3.54 (m, 2H), 2.26 (s, 3H), 1.72 - 1.97 (m, 2H)

LR MS (ES+): 516 (MH), 538 ($M+Na^+$)

LR MS (ES-): 514 (M-H)

Example 74

1-{2-fluoro-4-[(2-{4-[(3-hydroxypiperidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]phenyl}-3-(3-methylphenyl)urea



Similar procedure as Example 132.

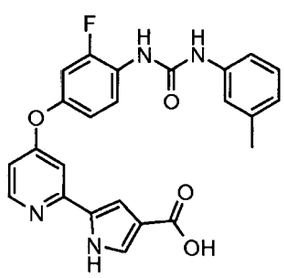
$^1H$ NMR (DMSO-$d_6$) δ: 11.83 (br. s., 1H), 8.96 (s, 1H), 8.55 (d, J = 2.3 Hz, 1H), 8.37 (d, J = 5.6 Hz, 1H), 8.19 (t, J = 9.1 Hz, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.27 (s, 1H), 7.19 - 7.25 (m, 2H), 7.15 (t, J = 7.8 Hz, 1H), 7.12 (br. s., 1H), 6.97 - 7.01 (m, 1H), 6.90 (s, 1H), 6.79 (d, J = 7.6 Hz, 1H), 6.68 (dd, J = 5.7, 2.2 Hz, 1H), 4.87 (br. s., 1H), 4.04 (br. s., 1H), 3.85 (br. s., 1H), 3.41 - 3.52 (m, 1H), 3.07 (t, J = 10.1 Hz, 1H), 2.26 (s, 3H), 1.78 - 1.90 (m, 1H), 1.67 (td, J = 8.8, 4.7 Hz, 1H), 1.30 - 1.43 (m, 2H)

LR MS (ES+): 530 (MH), 552 ($M+Na^+$)

LR MS (ES-): 528 (M-H)

Example 75

5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid





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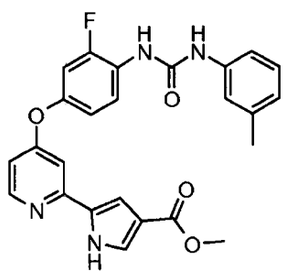
Similar procedure as Example 134.

$^1$H NMR (DMSO-$d_6$) δ: 12.04 (br. s., 1H), 11.87 (br. s., 1H), 8.97 (br. s., 1H), 8.56 (br. s., 1H), 8.39 (d, J = 5.9 Hz, 1H), 8.20 (t, J = 9.1 Hz, 1H), 7.36 (br. s., 2H), 7.19 - 7.30 (m, 3H), 7.12 - 7.17 (m, 1H), 7.08 (br. s., 1H), 7.00 (d, J = 8.8 Hz, 1H), 6.79 (d, J = 7.3 Hz, 1H), 6.73 (br. s., 1H), 2.26 (s, 3H)

LR MS (ES+): 469 (MH)

Example 76

methyl 5-{4-[3-fluoro-4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate



Similar procedure as Example 135.

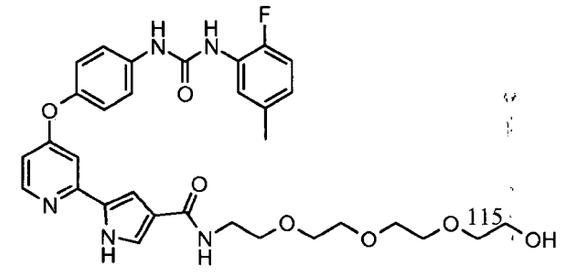
$^1$H NMR (DMSO-$d_6$) δ: 12.11 (br. s., 1H), 8.96 (s, 1H), 8.55 (s, 1H), 8.38 (d, J = 5.9 Hz, 1H), 8.19 (t, J = 9.1 Hz, 1H), 7.42 (dd, J = 3.1, 1.6 Hz, 1H), 7.37 (d, J = 2.1 Hz, 1H), 7.28 (s, 1H), 7.19 - 7.26 (m, 2H), 7.12 - 7.17 (m, 1H), 7.09 - 7.12 (m, 1H), 7.00 (dd, J = 9.1, 2.3 Hz, 1H), 6.79 (d, J = 7.3 Hz, 1H), 6.72 (dd, J = 5.6, 2.3 Hz, 1H), 3.69 (s, 3H), 2.26 (s, 3H)

LR MS (ES+): 461 (MH), 483 ($M+Na^+$)

LR MS (ES-): 459 (M-H)

Example 77

5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-(2-{2-[2-(2-hydroxyethoxy)ethoxy]ethoxy}ethyl)-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

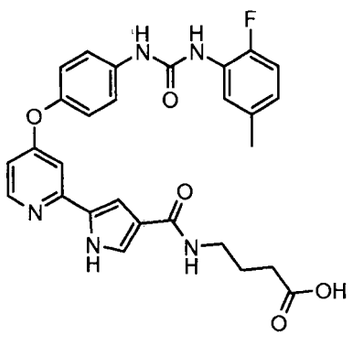
$^1$H NMR (DMSO-$d_6$) δ: 11.92 (br. s., 1H), 9.20 (s, 1H), 8.48 (br. s., 1H), 8.38 (d, J = 5.6 Hz, 1H), 7.96 (d, J = 7.9 Hz, 1H), 7.92 (br. s., 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.43 (br. s., 1H), 7.20 (br. s., 1H), 7.11 - 7.17 (m, 3H), 7.08 (dd, J = 11.2, 8.5 Hz, 1H), 6.73 - 6.81 (m, 2H), 3.41 - 3.48 (m, 12H), 3.34 - 3.39 (m, 2H), 3.31 (q, J = 5.8 Hz, 2H), 2.25 (s, 3H)

LR MS (ES+): 622 (MH), 644 ($M+Na^+$)

LR MS (ES-): 620 (M-H)

Example 78

4-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}butanoic acid



Similar procedure as Example 66.

$^1$H NMR (DMSO-$d_6$) δ: 11.83 (br. s., 1H), 9.17 (s, 1H), 8.49 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.95 - 8.02 (m, 1H), 7.88 (t, J = 5.6 Hz, 1H), 7.57 (d, J = 9.1 Hz, 2H), 7.38 (br. s., 1H), 7.16 (d, J = 9.1 Hz, 2H), 7.06 - 7.17 (m, 3H), 6.77 - 6.85 (m, 1H), 6.67 - 6.76 (m, 1H), 3.16 - 3.22 (m, 2H), 2.28 (s, 3H), 2.25 (t, J = 7.3 Hz, 2H), 1.70 (quin, J = 7.2 Hz, 2H)

LR MS (ES+): 532 (MH)

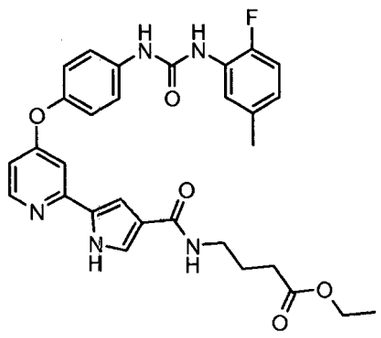
LR MS (ES-): 530 (M-H)

Example 79

ethyl 4-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}butanoate



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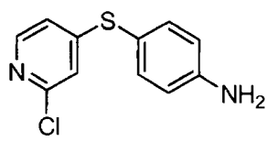


Similar procedure as Example 132.

LR MS (ES+): 560 (MH), 582 ($M+Na^+$)

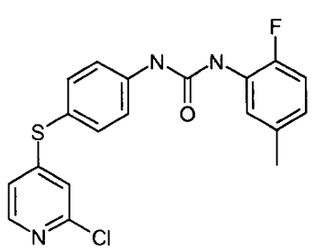
LR MS (ES-): 558 (M-H)

Preparation of 4-(2-Chloro-pyridin-4-ylsulfanyl)-phenylamine



2,4-Dichloropyrdine (4.44 g, 30.0 mmol) and potassium carbonate (8.28 g, 60.0 mmol) in dimethylformamide (60 mL) was purged with nitrogen for 10 min. 4-Aminothiophenol (3.76 g, 30.0 mmol) was added and the mixture stirred under nitrogen at room temperature for 18 h. Water (300 mL) was added and the slurry stirred for 30 min. The resulting solid was filtered, washed with water and vacuum dried at room temperature. Recrystallization from ethyl acetate (35 mL), filtered hot, then cooled gave 4-(2-Chloro-pyridin-4-ylsulfanyl)-phenylamine (3.946 g, 56% yield).

Preparation of 1-[4-(2-Chloro-pyridin-4-ylsulfanyl)-phenyl]-3-(2-fluoro-5-methyl-phenyl)-urea

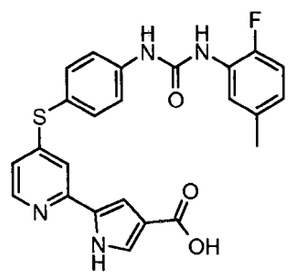


To a stirred solution of 4-(2-Chloro-pyridin-4-ylsulfanyl)-phenylamine (300 mg, 1.27 mmol) in anhydrous THF (10ml) was added 2-fluoro-5-methyl-phenylisocyanate (210mg, 1.39mmol). The mixture was stirred at 60°C for 5 hours, and poured into 100ml of water. The precipitates were filtered, washed with water (50ml), and dried to give the crude, which was purified by silica gel chromatography eluting with 2-3% MeOH/$CHCl_3$ to give 1-[4-(2-Chloro-pyridin-4-ylsulfanyl)-phenyl]-3-(2-fluoro-5-methyl-phenyl)-urea as white solid. Yield: 410mg, 83%.

$^1$H NMR (DMSO-$d_6$) δ: 9.37 (s, 1H), 8.57 (d, J = 2.1 Hz, 1H), 8.17 (d, J = 5.9 Hz, 1H), 7.89 - 8.01 (m, 1H), 7.58 - 7.70 (m, 2H), 7.47 - 7.59 (m, 2H), 7.10 (dd, J = 11.4, 8.2 Hz, 1H), 6.94 - 7.03 (m, 2H), 6.82 (dd, J = 4.8, 2.2 Hz, 1H), 2.26 (s, 3H)

Example 80

5-(4-{[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenyl]thio}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid



To a stirred solution of methyl 5-(4-{[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenyl]thio}pyridin-2-yl)-1H-pyrrole-3-carboxylate (86mg, 0.18mmol) in a mixture of solvents THF/MeOH (5ml/5ml) was added 2ml of 1M NaOH (2mmol) solution. The mixture was heated in a 66°C bath for 7 hours, cooled to room temperature and poured into 100ml of water. 2M HCl was added until pH = 3. The resulting precipitates were filtered, washed with water, and dried *in vacuo* to give 5-(4-{[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenyl]thio}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid as light brown solid. Yield: 73mg, 88%.

$^1$H NMR (DMSO-$d_6$) δ: 12.01 (br. s., 1H), 9.37 (s, 1H), 8.56 (d, J = 1.8 Hz, 1H), 8.27 (d, J = 5.6 Hz, 1H), 7.95 (s, 1H), 7.44 - 7.68 (m, 5H), 7.36 (br. s., 1H), 7.10 (dd, J = 11.1, 8.5 Hz, 1H), 6.94 (br. s., 1H), 6.81 (br. s., 1H), 6.69 (d, J = 5.3 Hz, 1H), 2.26 (s, 3H)

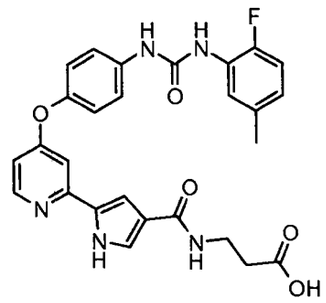
LR MS (ES-): 461 (M-H)



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Example 81

3-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}propanoic acid



Similar procedure as Example 66.

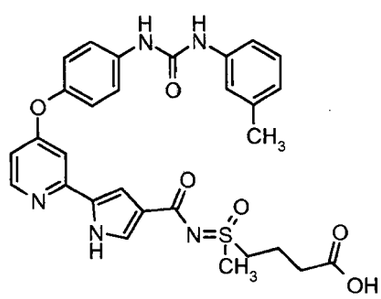
$^1$H NMR (DMSO-$d_6$) δ: 12.12 (br. s., 1H), 11.81 (br. s., 1H), 9.15 (s, 1H), 8.46 (br. s., 1H), 8.36 (d, J = 5.6 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H), 7.92 (t, J = 5.3 Hz, 1H), 7.54 (d, J = 8.8 Hz, 2H), 7.35 (br. s., 1H), 7.13 (dd, J = 6.6, 2.2 Hz, 3H), 7.08 (dd, J = 11.2, 8.5 Hz, 1H), 7.04 (br. s., 1H), 6.75 - 6.82 (m, 1H), 6.70 (d, J = 3.2 Hz, 1H), 3.32 - 3.41 (m, 2H), 2.43 (t, J = 7.0 Hz, 2H), 2.25 (s, 3H)

LR MS (ES+): 518 (MH), 540 ($M+Na^+$)

LR MS (ES-): 516 (M-H)

Example 82

4-{S-methyl-N-[(5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]sulfonimidoyl}butanoic acid



To a stirred solution of methyl 4-{S-methyl-N-[(5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]sulfonimidoyl}butanoate (5mg, 0.0087mol) in MeOH (3ml) was added 1M NaOH

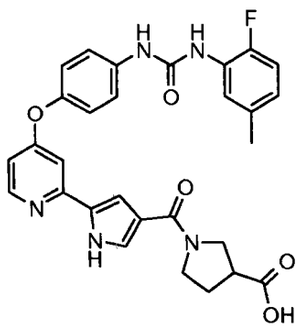
(0.5ml, 0.5mmol). The mixture was stirred at room temperature for 30 minutes, and poured into 30ml of water. 2M HCl was added dropwise until pH = 4. The precipitates were filtered, washed with water and dried to give 4-{S-methyl-N-[(5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]sulfonimidoyl}butanoic acid as off-white solid. Yield: 5mg, 100%.

LR MS (ES+): 576 (MH), 598 ($M+Na^+$)

LR MS (ES-): 574 (M-H)

Example 83

1-[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]pyrrolidine-3-carboxylic acid



Similar procedure as Example 132.

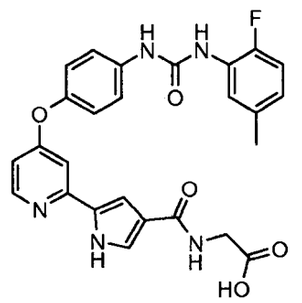
$^1H$ NMR (DMSO-$d_6$) δ: 12.04 (br. s., 1H), 9.16 (s, 1H), 8.46 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 5.6 Hz, 1H), 7.93 - 7.99 (m, 1H), 7.54 (d, J = 9.1 Hz, 2H), 7.41 (br. s., 1H), 7.33 (br. s., 1H), 7.14 (d, J = 8.8 Hz, 2H), 7.08 (dd, J = 11.3, 8.4 Hz, 1H), 6.75 - 6.82 (m, 1H), 6.72 (br. s., 1H), 2.98 - 3.93 (m, 5H), 2.25 (s, 3H), 1.93 - 2.19 (m, 2H)

LR MS (ES+): 544 (MH), 566 ($M+Na^+$)

LR MS (ES-): 542 (M-H)

Example 84

{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}acetic acid



Similar procedure as Example 66.

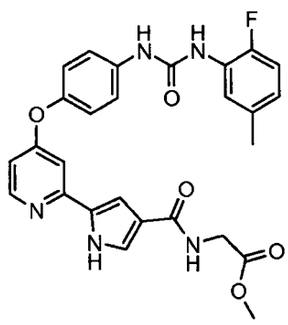
$^1$H NMR (DMSO-$d_6$) δ: 12.42 (br. s., 1H), 11.85 (br. s., 1H), 9.15 (s, 1H), 8.47 (d, J = 2.1 Hz, 1H), 8.37 (d, J = 5.9 Hz, 1H), 8.21 (t, J = 6.0 Hz, 1H), 7.90 - 8.03 (m, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.38 (br. s., 1H), 7.02 - 7.21 (m, 5H), 6.74 - 6.84 (m, 1H), 6.70 (dd, J = 5.6, 2.3 Hz, 1H), 3.82 (d, J = 5.9 Hz, 2H), 2.26 (s, 3H)

LR MS (ES+): 504 (MH), 526 ($M+Na^+$)

LR MS (ES-): 502 (M-H)

Example 85

methyl {[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}acetate



Similar procedure as Example 132.

$^1$H NMR (DMSO-$d_6$) δ: 12.00 (br. s., 1H), 9.18 (s, 1H), 8.48 (d, J = 2.1 Hz, 1H), 8.29 - 8.44 (m, 2H), 7.97 (d, J = 7.9 Hz, 1H), 7.56 (d, J = 9.1 Hz, 2H), 7.46 (br. s., 1H), 7.02 - 7.27 (m, 5H), 6.79 (d, J = 2.1 Hz, 2H), 3.91 (d, J = 6.2 Hz, 2H), 3.61 (s, 3H), 2.26 (s, 3H)

LR MS (ES+): 518 (MH), 540 ($M+Na^+$)

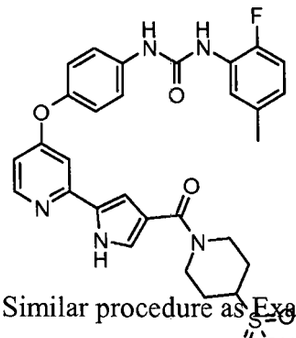
LR MS (ES-): 516 (M-H)

Example 86

1-[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]piperidine-4-sulfonic acid



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Similar procedure as Example 132.

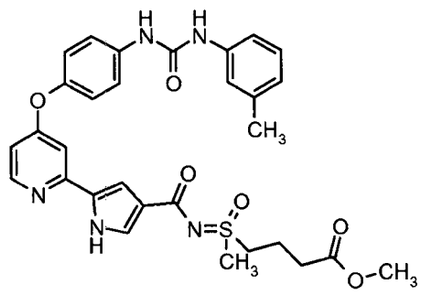
$^1$H NMR (DMSO-d$_6$) δ: 12.41 (br. s., 1H), 9.24 (s, 1H), 8.46 - 8.53 (m, 2H), 7.91 - 7.98 (m, 1H), 7.54 - 7.64 (m, 3H), 7.45 (br. s., 1H), 7.30 (br. s., 1H), 7.22 (d, J = 8.8 Hz, 2H), 7.08 (dd, J = 11.2, 8.2 Hz, 1H), 7.02 (br. s., 1H), 6.75 - 6.82 (m, 1H), 4.29 (br. s., 2H), 3.52 (br. s., 2H), 2.48 - 2.56 (m, 1H), 2.25 (s, 3H), 1.93 (d, J = 12.6 Hz, 2H), 1.45 (br. s., 2H)

LR MS (ES+): 616 (M+Na$^+$)

LR MS (ES-): 592 (M-H)

Example 87

methyl 4-{S-methyl-N-[(5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]sulfonimidoyl}butanoate

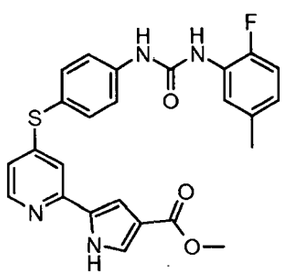


Similar procedure as Example 101.

LR MS (ES+): 590 (MH), 612 (M+Na$^+$)

Example 88

methyl 5-(4-{[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenyl]thio}pyridin-2-yl)-1H-pyrrole-3-carboxylate





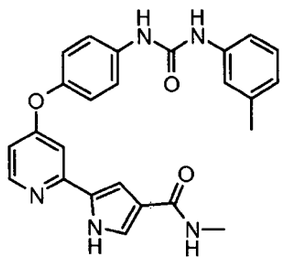
296

A mixture of 1-[4-(2-Chloro-pyridin-4-ylsulfanyl)-phenyl]-3-(2-fluoro-5-methyl-phenyl)-urea (410mg, 1.06 mmol), methyl-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-3-carboxylate (532mg, 2.12 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (10mg, 0.012 mmol) was added to a thick-walled reaction vessel and purged with $N_2$. A solution of 2M $Na_2CO_3$ (1.0 mL) was added, followed by DMSO (10 mL). The reaction vessel was sealed and the mixture stirred at 95°C for 16 h. The reaction vessel was cooled to room temperature and the mixture was poured into 100ml of water. The precipitates were filtered, washed with water and dried to give the crude, which was purified via silica gel chromatography eluting with 2-5% MeOH/$CHCl_3$ to afford methyl 5-(4-{[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenyl]thio}pyridin-2-yl)-1H-pyrrole-3-carboxylate as off-white solid. Yield: 100mg, 20% yield.

LR MS (ES+): 477 (MH), 499 ($M+Na^+$)

Example 89

N-methyl-5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

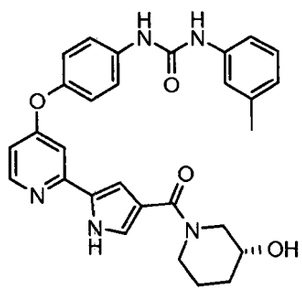
$^1H$ NMR (DMSO-$d_6$) δ: 11.88 (br. s., 1H), 8.89 (s, 1H), 8.69 (s, 1H), 8.37 (d, J = 5.9 Hz, 1H), 7.82 (d, J = 4.4 Hz, 1H), 7.52 - 7.58 (m, 2H), 7.37 (br. s., 1H), 7.27 (s, 1H), 7.22 (d, J = 8.2 Hz, 1H), 7.18 (br. s., 1H), 7.11 - 7.15 (m, 3H), 7.08 (br. s., 1H), 6.71 - 6.80 (m, 2H), 2.67 (d, J = 4.7 Hz, 3H), 2.25 (s, 3H)

LR MS (ES+): 442 (MH), 464 ($M+Na^+$)

LR MS (ES-): 440 (M-H)

Example 90

1-{4-[(2-{4-[(3-hydroxypiperidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]phenyl}-3-(3-methylphenyl)urea



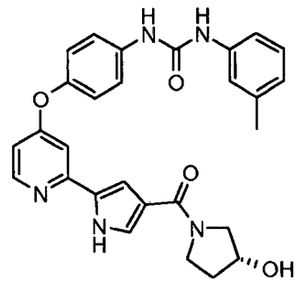
Similar procedure as Example 132.

LR MS (ES+): 512 (MH), 534 ($M+Na^+$)

LR MS (ES-): 510 (M-H)

Example 91

1-{4-[(2-{4-[(3-hydroxypyrrolidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]phenyl}-3-(3-methylphenyl)urea



Similar procedure as Example 132.

$^1H$ NMR (DMSO-$d_6$) δ: 11.88 (br. s., 1H), 8.74 (s, 1H), 8.58 (s, 1H), 8.36 (d, J = 5.6 Hz, 1H), 7.54 (d, J = 8.8 Hz, 2H), 6.99 - 7.39 (m, 8H), 6.78 (d, J = 7.0 Hz, 1H), 6.62 (dd, J = 5.6, 2.3 Hz, 1H), 4.91 (br. s., 1H), 4.31 (br. s., 1H), 3.67 - 3.87 (m, 2H), 3.49 (br. s., 2H), 2.26 (s, 3H), 1.88 (br. s., 2H)

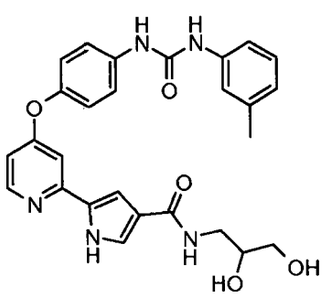
LR MS (ES+): 520 ($M+Na^+$)

Example 92



298

N-(2,3-dihydroxypropyl)-5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



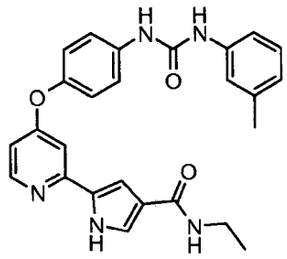
Similar procedure as Example 132.

$^1$H NMR (DMSO-$d_6$) δ: 11.86 (br. s., 1H), 8.78 (s, 1H), 8.61 (s, 1H), 8.37 (d, J = 5.9 Hz, 1H), 7.87 (t, J = 5.7 Hz, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.41 (br. s., 1H), 7.05 - 7.32 (m, 7H), 6.75 (dd, J = 17.7, 6.6 Hz, 2H), 3.49 - 3.61 (m, 1H), 3.22 - 3.35 (m, 3H), 3.04 - 3.18 (m, 1H), 2.26 (s, 3H)

LR MS (ES+): 524 ($M+Na^+$)

Example 93

N-ethyl-5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

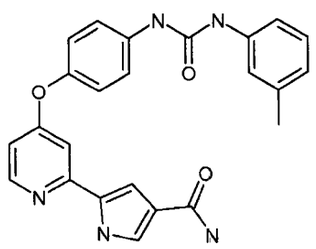
$^1$H NMR (DMSO-$d_6$) δ: 12.09 (br. s., 1H), 8.98 (s, 1H), 8.76 (s, 1H), 8.42 (d, J = 5.9 Hz, 1H), 7.91 (br. s., 1H), 7.45 - 7.65 (m, 3H), 7.05 - 7.38 (m, 7H), 6.82 - 6.94 (m, 1H), 6.78 (d, J = 7.6 Hz, 1H), 3.09 - 3.27 (m, 2H), 2.26 (s, 3H), 1.06 (t, J = 7.2 Hz, 3H)

LR MS (ES+): 478 ($M+Na^+$)

LR MS (ES-): 454 (M-H)

Example 94

5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

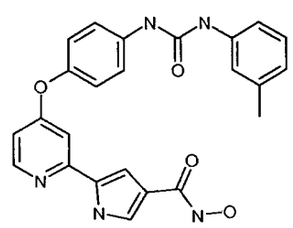
$^1$H NMR ($d_6$-DMSO,300MHz) δ: 11.81 (br. s., 1H), 8.76 (s, 1H), 8.59 (s, 1H), 8.37 (d, J = 5.6 Hz, 1H), 7.55 (d, J = 9.1 Hz, 2H), 7.37 (br. s., 2H), 7.28 (s, 1H), 7.19 - 7.26 (m, 1H), 7.09 - 7.18 (m, 4H), 7.04 (br. s., 1H), 6.78 (d, J = 7.3 Hz, 2H), 6.69 (dd, J = 5.4, 1.9 Hz, 1H), 2.26 (s, 3H)

LR MS (ES+): 428 (MH), 450 ($M+Na^+$)

LR MS (ES-): 426 (M-H)

Example 95

N-hydroxy-5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

$^1$H NMR ($d_6$-DMSO,300MHz): 11.98 (br. s., 1H), 10.62 (br. s., 1H), 8.87 (s, 1H), 8.68 (s, 1H), 8.41 (d, J = 5.6 Hz, 1H), 7.58 (d, J = 9.1 Hz, 2H), 7.04 - 7.46 (m, 8H), 6.80 (d, J = 7.6 Hz, 2H), 2.28 (s, 3H)

LR MS (ES+): 444 (MH), 466 ($M+Na^+$)

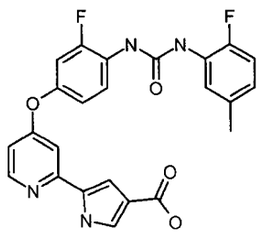
LR MS (ES-): 442 (M-H)

Example 96

5-{4-[3-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid



300



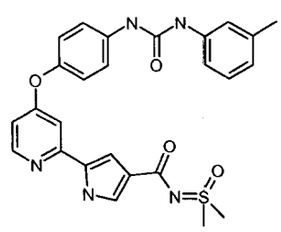
Similar procedure as Example 134.

$^1$H NMR ($d_6$-DMSO,300MHz): 12.04 (br. s., 1H), 11.88 (br. s., 1H), 9.08 (s, 1H), 8.97 (s, 1H), 8.41 (d, J = 5.6 Hz, 1H), 8.25 (t, J = 9.2 Hz, 1H), 8.01 (d, J = 7.6 Hz, 1H), 7.38 (s, 2H), 7.27 (dd, J = 11.9, 2.5 Hz, 1H), 6.95 - 7.18 (m, 3H), 6.78 - 6.88 (m, 1H), 6.74 (dd, J = 5.6, 2.1 Hz, 1H), 2.28 (s, 3H)

LR MS (ES+): 465 (MH), 487 ($M+Na^+$)

LR MS (ES-): 463 (M-H)

Example 97



N-[dimethyl(oxido)-lambda~4~-sulfanylidene]-5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide

Similar procedure as Example 101.

$^1$H NMR ($d_6$-DMSO,300MHz): 11.82 (none, 1H), 11.83 (br. s., 1H), 8.76 (s, 1H), 8.60 (s, 1H), 8.37 (d, J = 5.9 Hz, 1H), 7.56 (d, J = 9.1 Hz, 2H), 7.21 - 7.35 (m, 4H), 7.08 - 7.20 (m, 3H), 6.95 (s, 1H), 6.79 (d, J = 7.0 Hz, 1H), 6.66 (dd, J = 5.6, 2.3 Hz, 1H), 3.37 (s, 6H), 2.28 (s, 3H)

LR MS (ES+): 526 ($M+Na^+$)

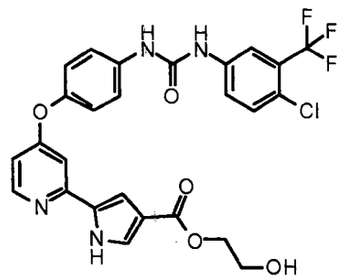
LR MS (ES-): 502 (M-H)

Example 98

2-hydroxyethyl 5-{4-[4-({[(4-chloro-3-(trifluoromethyl)phenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate



301



Similar procedure as Example 131.

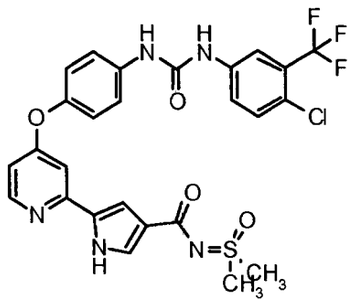
$^1$H NMR ($d_6$-DMSO,300MHz): 12.12 (br. s., 1 H), 9.19 (s, 1 H), 8.97 (s, 1 H), 8.40 (d, *J*=5.9 Hz, 1 H), 8.12 (d, *J*=2.1 Hz, 1 H), 7.53 - 7.70 (m, 4 H), 7.48 (dd, *J*=3.1, 1.6 Hz, 1 H), 7.35 (d, *J*=2.1 Hz, 1 H), 7.16 (d, *J*=9.1 Hz, 2 H), 7.09 (d, *J*=2.3 Hz, 1 H), 6.68 (dd, *J*=5.6, 2.3 Hz, 1 H), 4.83 (t, *J*=5.9 Hz, 1 H), 4.15 (t, *J*=5.0 Hz, 2 H), 3.59 - 3.69 ppm (m, 2 H)

LR MS (ES+): 583 ($M+Na^+$), 585

LR MS (ES-): 559 (M-H), 561

Example 99

N-[dimethyl(oxido)-lambda~4~-sulfanylidene]-5-{4-[4-({[(4-chloro-3-(trifluoromethyl)phenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



Similar procedure as Example 101.

$^1$H NMR ($d_6$-DMSO,300MHz) 11.83 (br. s., 1 H), 9.19 (s, 1 H), 8.97 (s, 1 H), 8.37 (d, *J*=5.9 Hz, 1 H), 8.12 (d, *J*=2.3 Hz, 1 H), 7.54 - 7.69 (m, 4 H), 7.23 - 7.31 (m, 2 H), 7.12 - 7.19 (m, 2 H), 6.93 - 6.97 (m, 1 H), 6.67 (dd, *J*=5.9, 2.3 Hz, 1 H), 3.37 ppm (s, 6 H)

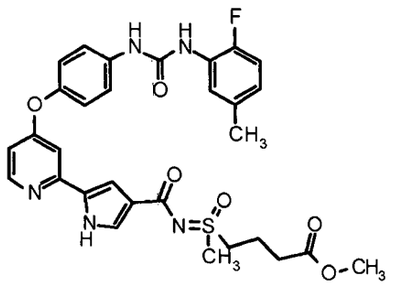
LR MS (ES-): 590 (M-H)



302

Example 100

methy 4-(N-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxyl)-S-methylsulfonimidoyl)butanoate

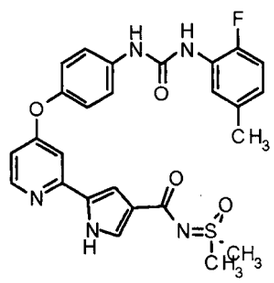


LR MS (ES+): 630 ($M+Na^+$)

LR MS (ES-): 606 (M-H)

Example 101

N-[dimethyl(oxido)-lambda~4~-sulfanylidene]-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



A mixture of 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid (60mg, 0.13mmol), HATU (60mg, 0.16mmol), sulfonimidoyldimethane (24mg, 0.26mmol), *N,N*-diisopropylethylamine (37mg, 0.29mmol), 200mg of 4Å molecular sieves and 5ml of anhydrous 1,4-dioxane was added to a thick walled reaction vessel and purged with $N_2$. The reaction vessel was sealed and the mixture stirred at 90°C for 18 hours. The reaction vessel was cooled to room temperature and the mixture was poured into 100ml of water. The precipitates were filtered, washed with water and dried to give the crude, which was purified by silica gel chromatography eluting with 3~5% MeOH/$CHCl_3$ to give N-[dimethyl(oxido)-lambda~4~-sulfanylidene]-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide as white solid. Yield: 38mg, 54%.

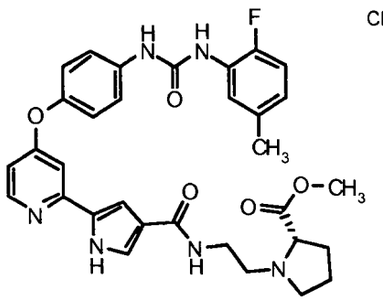


303

$^1$H NMR ($d_6$-DMSO): 11.83 (br. s., 1H), 9.16 (s, 1H), 8.48 (br. s., 1H), 8.37 (d, J = 5.9 Hz, 1H), 7.98 (d, J = 6.7 Hz, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.26 (dd, J = 8.6, 1.6 Hz, 2H), 7.05 - 7.19 (m, 3H), 6.96 (s, 1H), 6.75 - 6.85 (m, 1H), 6.66 (dd, J = 5.4, 1.6 Hz, 1H), 3.37 (s, 6H), 2.27 (s, 3H)
LR MS (ES+): 544 ($M+Na^+$)
LR MS (ES-): 520 (M-H)

Example 102

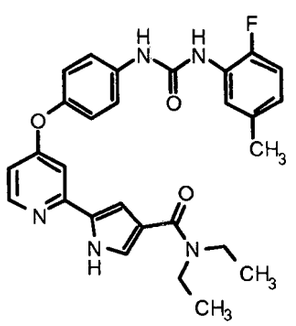
methyl (2S)-1-(2-{[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]amino}ethyl)pyrrolidine-2-carboxylate




Similar procedure as Example 132.
LR MS (ES+): 623 ($M+Na^+$)
LR MS (ES-): 599 (M-H)

Example 103

N,N-diethyl-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide




Similar procedure as Example 132.



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$^1$H NMR ($d_6$-DMSO): 11.97 (br. s., 1H), 9.19 (s, 1H), 8.49 (d, J = 2.6 Hz, 1H), 8.40 (d, J = 6.2 Hz, 1H), 7.98 (dd, J = 7.8, 1.9 Hz, 1H), 7.53 - 7.61 (m, 2H), 7.40 (d, J = 1.5 Hz, 1H), 7.05 - 7.25 (m, 4H), 7.01 (br. s., 1H), 6.76 - 6.86 (m, 1H), 6.67 - 6.76 (m, 1H), 3.26 - 3.64 (m, 4H), 2.27 (s, 3H), 1.13 (t, J = 7.0 Hz, 6H)

LR MS (ES+): 524 ($M+Na^+$)

LR MS (ES-): 500 (M-H)

Example 104

1-(2-fluoro-5-methylphenyl)-3-{4-[(2-{4-[(4-methylpiperazin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]phenyl}urea

Similar procedure as Example 132.

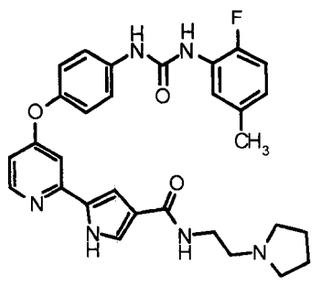
$^1$H NMR ($d_6$-DMSO): 11.87 (br. s., 1H), 9.16 (s, 1H), 8.47 (d, J = 2.6 Hz, 1H), 8.37 (d, J = 5.6 Hz, 1H), 7.98 (dd, J = 8.1, 1.9 Hz, 1H), 7.50 - 7.59 (m, 2H), 7.35 (d, J = 2.3 Hz, 1H), 7.08 - 7.19 (m, 4H), 6.87 - 6.95 (m, 1H), 6.80 (ddd, J = 7.7, 5.1, 2.2 Hz, 1H), 6.63 (dd, J = 5.9, 2.3 Hz, 1H), 3.60 (d, J = 4.1 Hz, 4H), 2.23 - 2.35 (m, 7H), 2.18 (s, 3H)

LR MS (ES+): 551 ($M+Na^+$)

LR MS (ES-): 527 (M-H)

Example 105

5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-(2-pyrrolidin-1-ylethyl)-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

$^1$H NMR ($d_6$-DMSO): 11.80 (br. s., 1H), 9.17 (s, 1H), 8.48 (d, J = 2.6 Hz, 1H), 8.37 (d, J = 5.6 Hz, 1H), 7.98 (dd, J = 7.9, 2.1 Hz, 1H), 7.82 (t, J = 5.7 Hz, 1H), 7.50 - 7.63 (m, 2H), 7.35 (dd, J = 2.9, 1.8 Hz, 1H), 7.00 - 7.20 (m, 5H), 6.80 (dt, J = 7.9, 2.2 Hz, 1H), 6.70 (dd, J = 5.9, 2.3 Hz, 1H), 3.21 - 3.35 (m, 2H), 2.37 - 2.57 (m, 6H), 2.27 (s, 3H), 1.65 (dt, J = 6.6, 3.1 Hz, 4H)



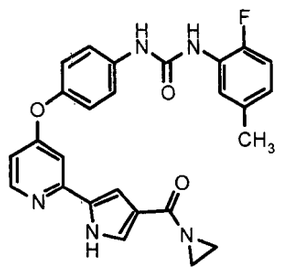
305

LR MS (ES+): 565 ($M+Na^+$)

LR MS (ES-): 541 (M-H)

Example 106

1-[4-({2-[4-(aziridin-1-ylcarbonyl)-1H-pyrrol-2-yl]pyridin-4-yl}oxy)phenyl]-3-(2-fluoro-5-methylphenyl)urea



Similar procedure as Example 132.

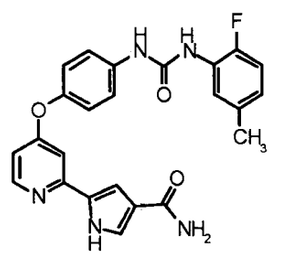
$^1H$ NMR ($d_6$-DMSO): 11.90 (br. s., 1H), 9.15 (s, 1H), 8.47 (d, J = 2.6 Hz, 1H), 8.36 (d, J = 5.9 Hz, 1H), 7.97 (dd, J = 8.2, 2.1 Hz, 1H), 7.50 - 7.58 (m, 2H), 7.28 (d, J = 2.1 Hz, 1H), 7.23 (br. s., 1H), 7.04 - 7.17 (m, 3H), 6.97 (br. s., 1H), 6.79 (ddd, J = 7.5, 5.1, 2.3 Hz, 1H), 6.65 (dd, J = 5.7, 2.5 Hz, 1H), 4.17 - 4.31 (m, 2H), 3.82 (t, J = 9.2 Hz, 2H), 2.26 (s, 3H)

LR MS (ES+): 494 ($M+Na^+$)

LR MS (ES-): 470 (M-H)

Example 107

5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

$^1H$ NMR ($d_6$-DMSO): 11.89 (br. s., 1H), 9.21 (s, 1H), 8.50 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.98 (dd, J = 8.1, 1.9 Hz, 1H), 7.53 - 7.62 (m, 2H), 7.43 (br. s., 2H), 7.05 - 7.24 (m, 5H), 6.71 - 6.86 (m, 3H), 2.27 (s, 3H)

LR MS (ES+): 468 ($M+Na^+$)

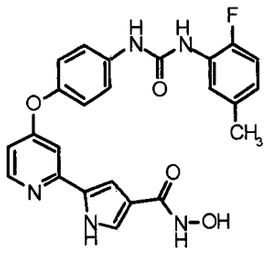


306

LR MS (ES-): 444 (M-H)

Example 108

5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-hydroxy-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

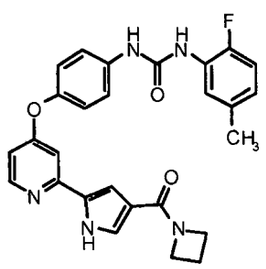
$^1$H NMR ($d_6$-DMSO): 12.10 (br. s., 1H), 10.66 (br. s., 1H), 9.29 (s, 1H), 8.53 (br. s., 1H), 8.43 (d, J = 6.2 Hz, 1H), 7.93 - 8.03 (m, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.39 - 7.50 (m, 1H), 7.30 (br. s., 1H), 7.05 - 7.26 (m, 4H), 6.75 - 6.91 (m, 2H), 2.27 (s, 3H)

LR MS (ES+): 484 ($M+Na^+$)

LR MS (ES-): 460 (M-H)

Example 109

1-[4-({2-[4-(azetidin-1-ylcarbonyl)-1H-pyrrol-2-yl]pyridin-4-yl}oxy)phenyl]-3-(2-fluoro-5-methylphenyl)urea



Similar procedure as Example 132.

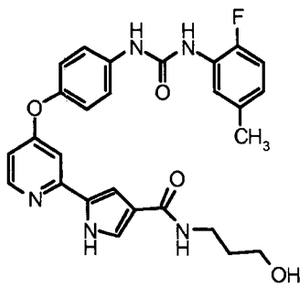
$^1$H NMR ($d_6$-DMSO): 11.67 (br. s., 1H), 9.16 (s, 1H), 8.47 (d, J = 2.1 Hz, 1H), 8.34 (d, J = 5.6 Hz, 1H), 7.97 (d, J = 5.9 Hz, 1H), 7.54 (d, J = 9.1 Hz, 2H), 7.02 - 7.23 (m, 5H), 6.86 (br. s., 1H), 6.74 - 6.83 (m, 1H), 6.64 (dd, J = 5.9, 2.3 Hz, 1H), 4.14 - 4.28 (m, 2H), 3.33 - 3.42 (m, 2H), 2.26 (s, 3H), 1.83 (br. s., 2H)

LR MS (ES+): 486 (M+H)

LR MS (ES-): 484 (M-H)

Example 110

5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-(3-hydroxypropyl)-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

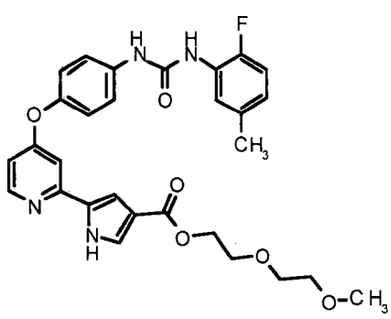
$^1$H NMR ($d_6$-DMSO): 11.78 (br. s., 1H), 9.20 (s, 1H), 8.51 (d, J = 2.1 Hz, 1H), 8.36 (d, J = 5.6 Hz, 1H), 7.96 (dd, J = 7.9, 1.8 Hz, 1H), 7.83 (t, J = 5.7 Hz, 1H), 7.55 (d, J = 9.1 Hz, 2H), 7.32 - 7.36 (m, 1H), 7.02 - 7.17 (m, 5H), 6.78 (td, J = 5.3, 2.6 Hz, 1H), 6.69 (dd, J = 5.6, 2.3 Hz, 1H), 4.42 (t, J = 5.3 Hz, 1H), 3.41 (q, J = 6.2 Hz, 2H), 3.15 - 3.26 (m, 2H), 2.26 (s, 3H), 1.60 (quin, J = 6.7 Hz, 2H)

LR MS (ES+): 526 ($M+Na^+$)

LR MS (ES-): 502 (M-H)

Example 111

2-(2-methoxyethoxy)ethyl 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate



Similar procedure as Example 131.

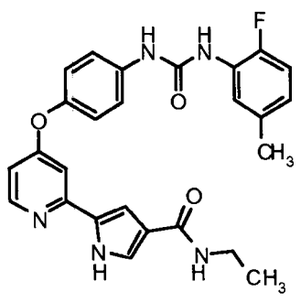
$^1$H NMR ($d_6$-DMSO): 12.12 (br. s., 1H), 9.15 (s, 1H), 8.47 (d, J = 2.3 Hz, 1H), 8.38 (d, J = 5.9 Hz, 1H), 7.97 (dd, J = 8.1, 1.9 Hz, 1H), 7.49 - 7.59 (m, 2H), 7.41 (dd, J = 3.1, 1.6 Hz, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.03 - 7.17 (m, 4H), 6.74 - 6.84 (m, 1H), 6.67 (dd, J = 5.7, 2.5 Hz, 1H), 4.20 - 4.28 (m, 2H), 3.62 - 3.70 (m, 2H), 3.51 - 3.59 (m, 2H), 3.39 - 3.46 (m, 2H), 3.18 - 3.24 (m, 3H), 2.26 (s, 3H)

LR MS (ES+): 571 ($M+Na^+$)

LR MS (ES-): 547 (M-H)

Example 112

N-ethyl-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

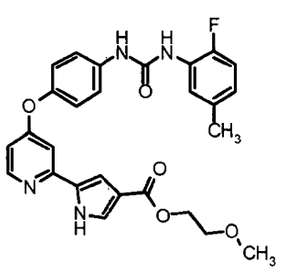
$^1$H NMR ($d_6$-DMSO): 11.93 (br. s., 1H), 9.23 (s, 1H), 8.50 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 6.2 Hz, 1H), 7.96 (dd, J = 7.9, 1.8 Hz, 1H), 7.87 (t, J = 5.6 Hz, 1H), 7.57 (d, J = 8.8 Hz, 2H), 7.42 (br. s., 1H), 7.02 - 7.27 (m, 5H), 6.72 - 6.86 (m, 2H), 3.09 - 3.25 (m, 2H), 2.26 (s, 3H), 1.06 (t, J = 7.2 Hz, 3H)

LR MS (ES+): 496 ($M+Na^+$)

LR MS (ES-): 472 (M-H)

Example 113

2-methoxyethyl 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate



Similar procedure as Example 131.

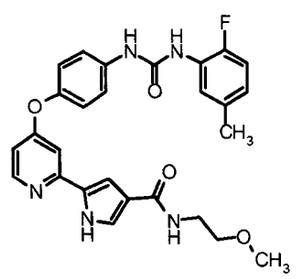
$^1$H NMR ($d_6$-DMSO): 12.12 (br. s., 1H), 9.15 (s, 1H), 8.46 (br. s., 1H), 8.38 (d, J = 5.6 Hz, 1H), 7.98 (s, 1H), 7.54 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 1.2 Hz, 1H), 7.35 (d, J = 1.8 Hz, 1H), 7.01 - 7.19 (m, 4H), 6.78 (d, J = 5.9 Hz, 1H), 6.66 (dd, J = 5.9, 2.1 Hz, 1H), 4.17 - 4.32 (m, 2H), 3.51 - 3.65 (m, 2H), 3.29 (s, 3H), 2.26 (s, 3H)

LR MS (ES+): 527 ($M+Na^+$)

LR MS (ES-): 503 (M-H)

Example 114

5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-(2-methoxyethyl)-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

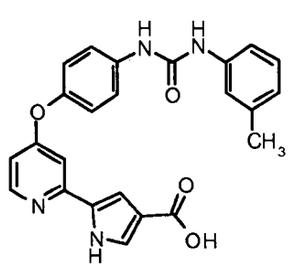
$^1$H NMR ($d_6$-DMSO): 11.86 (br. s., 1H), 9.17 (s, 1H), 8.48 (d, J = 2.3 Hz, 1H), 8.38 (d, J = 5.9 Hz, 1H), 7.86 - 8.02 (m, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.40 (br. s., 1H), 7.02 - 7.21 (m, 5H), 6.67 - 6.84 (m, 2H), 3.26 - 3.50 (m, 7H), 2.26 (s, 3H)

LR MS (ES+): 526 ($M+Na^+$)

LR MS (ES-): 502 (M-H)

Example 115

5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid





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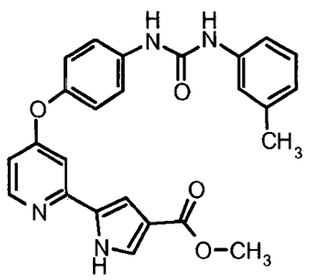
Similar procedure as Example 134.

$^1$H NMR ($d_6$-DMSO): 12.05 (br. s., 1H), 8.79 (s, 1H), 8.62 (s, 1H), 8.39 (d, J = 5.6 Hz, 1H), 7.52 - 7.61 (m, 2H), 7.39 (dd, J = 3.1, 1.6 Hz, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.30 (s, 1H), 7.21 - 7.27 (m, 1H), 7.10 - 7.20 (m, 3H), 7.05 (s, 1H), 6.79 (d, J = 7.3 Hz, 1H), 6.68 (dd, J = 5.6, 2.3 Hz, 1H), 2.28 (s, 3H)

LR MS (ES-): 427 (M-H)

Example 116

methyl 5-{4-[4-({[(3-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate



Similar procedure as Example 135.

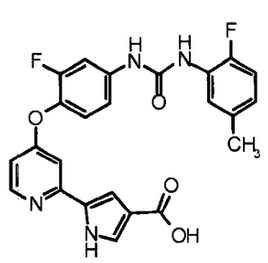
$^1$H NMR ($d_6$-DMSO): 12.12 (br. s., 1H), 9.02 (br. s., 1H), 8.85 (br. s., 1H), 8.36 (d, J = 5.6 Hz, 1H), 7.50 - 7.59 (m, 2H), 7.41 (d, J = 1.5 Hz, 1H), 7.33 (d, J = 2.3 Hz, 1H), 7.29 (s, 1H), 7.24 (d, J = 7.9 Hz, 1H), 7.08 - 7.18 (m, 3H), 7.06 (d, J = 1.5 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 6.65 (dd, J = 5.6, 2.3 Hz, 1H), 3.69 (s, 3H), 2.26 (s, 3H)

LR MS (ES+): 465 ($M+Na^+$)

LR MS (ES-): 441 (M-H)

Example 117

5-{4-[2-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid



137

Similar procedure as Example 134.

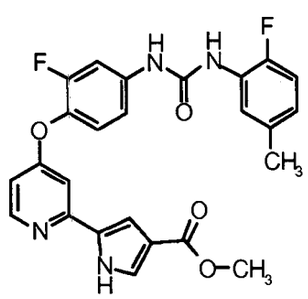
$^1$H NMR ($d_6$-DMSO): 12.03 (br. s., 1H), 11.86 (br. s., 1H), 9.62 (s, 1H), 8.65 (s, 1H), 8.38 (d, J = 5.6 Hz, 1H), 7.94 (dd, J = 7.9, 1.8 Hz, 1H), 7.72 (dd, J = 13.2, 2.3 Hz, 1H), 7.26 - 7.40 (m, 3H), 7.15 - 7.24 (m, 1H), 7.01 - 7.14 (m, 2H), 6.81 (td, J = 5.3, 2.3 Hz, 1H), 6.68 (dd, J = 5.7, 2.2 Hz, 1H), 2.26 (s, 3H)

LR MS (ES+): 487 ($M+Na^+$)

LR MS (ES-): 463 (M-H)

Example 118

methyl 5-{4-[2-fluoro-4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate



Similar procedure as Example 135.

$^1$H NMR ($d_6$-DMSO): 12.13 (br. s., 1H), 9.34 (s, 1H), 8.55 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.94 (dd, J = 7.8, 1.6 Hz, 1H), 7.72 (dd, J = 13.5, 2.3 Hz, 1H), 7.43 (dd, J = 3.2, 1.8 Hz, 1H), 7.37 (d, J = 2.3 Hz, 1H), 7.26 - 7.36 (m, 1H), 7.18 (dd, J = 8.9, 1.6 Hz, 1H), 7.05 - 7.15 (m, 2H), 6.77 - 6.87 (m, 1H), 6.70 (dd, J = 5.6, 2.3 Hz, 1H), 3.70 (s, 3H), 2.26 (s, 3H)

LR MS (ES+): 501 ($M+Na^+$)

LR MS (ES-): 477 (M-H)

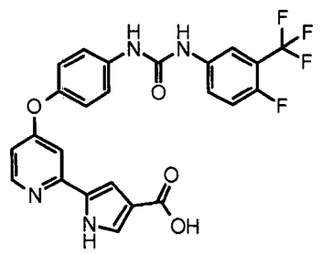
Example 119

5-(4-{4-[({[4-fluoro-3



312

-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid



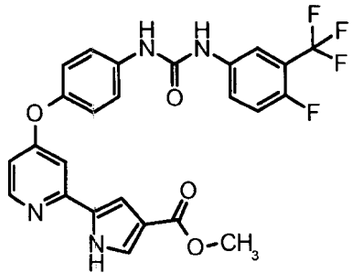
Similar

$^1$H NM[illegible]), 9.11 (s, 1H), 8.96 (s, 1H), 8.38 (d, J = 5.6 Hz, 1H), 7.99 (dd, J = 6.4, 2.3 Hz, 1H), 7.60 - 7.72 (m, 1H), 7.56 (d, J = 9.1 Hz, 2H), 7.27 - 7.49 (m, 3H), 7.14 (d, J = 9.1 Hz, 2H), 7.03 (br. s., 1H), 6.67 (dd, J = 5.7, 2.2 Hz, 1H)

LR MS (ES-): 499 (M-H)

Example 120

methyl 5-(4-{4-[({[4-fluoro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate



Similar procedure as Example 135.

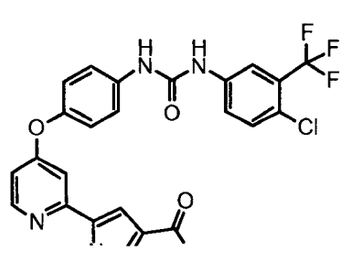
$^1$H NMR ($d_6$-DMSO): 12.12 (br. s., 1H), 9.04 (s, 1H), 8.91 (s, 1H), 8.37 (d, J = 6.2 Hz, 1H), 7.99 (dd, J = 6.4, 2.6 Hz, 1H), 7.60 - 7.69 (m, 1H), 7.51 - 7.61 (m, 2H), 7.37 - 7.49 (m, 2H), 7.34 (d, J = 2.1 Hz, 1H), 7.09 - 7.18 (m, 2H), 7.01 - 7.09 (m, 1H), 6.66 (dd, J = 5.6, 2.3 Hz, 1H), 3.70 (s, 3H)

LR MS (ES+): 537 ($M+Na^+$)

LR MS (ES-): 513 (M-H)

Example 121

5-(4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid



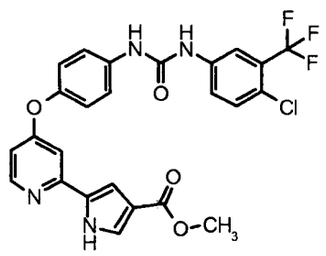
Similar procedure as Example 134.

$^1$H NMR ($d_6$-DMSO): 12.08 (br. s., 1H), 9.23 (s, 1H), 9.00 (s, 1H), 8.39 (d, J = 5.6 Hz, 1H), 8.10 (s, 1H), 7.48 - 7.72 (m, 4H), 7.27 - 7.47 (m, 2H), 7.00 - 7.23 (m, 3H), 6.69 (br. s., 1H)

LR MS (ES-): 515 (M-H)

Example 122

methyl 5-(4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate



Similar procedure as Example 135.

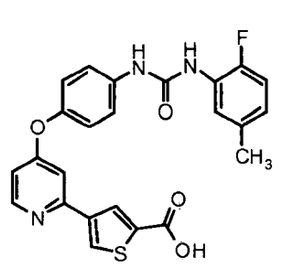
$^1$H NMR ($d_6$-DMSO): 12.12 (br. s., 1H), 9.17 (s, 1H), 8.94 (s, 1H), 8.38 (d, J = 5.9 Hz, 1H), 8.10 (d, J = 2.1 Hz, 1H), 7.51 - 7.69 (m, 4H), 7.42 (dd, J = 3.2, 1.8 Hz, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.10 - 7.18 (m, 2H), 7.03 - 7.09 (m, 1H), 6.66 (dd, J = 5.9, 2.3 Hz, 1H), 3.70 (s, 3H)

LR MS (ES+): 553 ($M+Na^+$)

LR MS (ES-): 529 (M-H)

Example 123

4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}thiophene-2-carboxylic acid



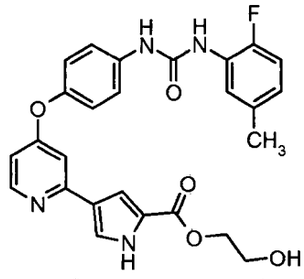
To a stirred solution of methyl 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}thiophene-2-carboxylate (550mg, 1.15mmol) in a mixture of solvents - THF/MeOH (20ml/20ml) was added 1ml of 5M NaOH (5mmol) solution. The mixture was heated in a 66°C bath for 2 hours, cooled to room temperature and poured into 200ml of water. 2M HCl was added until pH = 5. The resulting precipitates were filtered, washed with water, and dried *in vacuo* to give 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}thiophene-2-carboxylic acid as off-white solid. Yield: 520mg, 97%.

$^1$H NMR ($d_6$-DMSO): 9.30 (s, 1H), 8.59 (d, J = 2.6 Hz, 1H), 8.43 (d, J = 5.9 Hz, 1H), 8.35 (br. s., 1H), 8.13 (br. s., 1H), 7.95 (dd, J = 7.8, 1.9 Hz, 1H), 7.51 - 7.59 (m, 2H), 7.45 (s, 1H), 7.03 - 7.18 (m, 3H), 6.75 - 6.83 (m, 1H), 6.72 (dd, J = 5.6, 2.3 Hz, 1H), 2.25 (s, 3H)

LR MS (ES-): 462 (M-H)

Example 124

2-hydroxyethyl 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxylate



31.

$^1$H NMR (DMSO-$d_6$) δ: 12.11 (br. s., 1H), 9.15 (s, 1H), 8.47 (d, J = 2.1 Hz, 1H), 8.33 (d, J = 5.6 Hz, 1H), 7.97 (dd, J = 7.9, 1.8 Hz, 1H), 7.63 (dd, J = 2.9, 1.8 Hz, 1H), 7.53 (d, J = 8.8 Hz, 2H), 7.22 - 7.37 (m, 2H), 7.01 - 7.18 (m, 3H), 6.72 - 6.85 (m, 1H), 6.58 (dd, J = 5.6, 2.3 Hz, 1H), 4.83 (t, J = 5.9 Hz, 1H), 4.19 (t, J = 5.1 Hz, 2H), 3.57 - 3.73 (m, 2H), 2.25 (s, 3H)

LR MS (ES+): 491 (MH), 513 ($M+Na^+$)

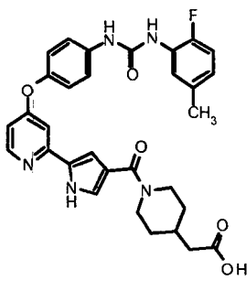
LR MS (ES-): 489 (M-H)

Example 125



315

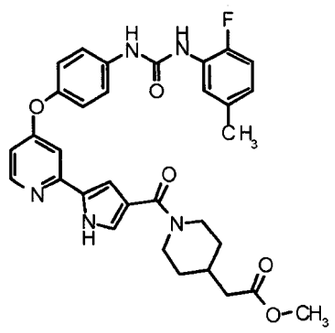
{1-[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]piperidin-4-yl}acetic acid



To a stirred solution of methyl {1-[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]piperidin-4-yl}acetate (50mg, 0.085mmol) in THF/MeOH (5ml/5ml) was added 1M NaOH solution (3ml, 3mmol). The mixture was stirred at room temperature for one hour, and poured into 50ml of water. 2M HCl was added until pH = 4. The resulting precipitates were filtered, washed with water, and dried *in vacuo* to give {1-[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]piperidin-4-yl}acetic acid as white solid. Yield: 47mg, 96%.
LR MS (ES-): 570 (M-H)

Example 126

methyl {1-[(5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrol-3-yl)carbonyl]piperidin-4-yl}acetate



Similar procedure as Example 132.

$^1$H NMR ($d_6$-DMSO): 11.83 (br. s., 1H), 9.14 (s, 1H), 8.46 (br. s., 1H), 8.35 (d, J = 5.6 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.53 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 1.8 Hz, 1H), 7.01 - 7.18 (m, 4H), 6.86 (s, 1H), 6.80 (d, J = 4.4 Hz, 1H), 6.61 (dd, J = 5.9, 2.1 Hz, 1H), 4.26 (br. s., 2H), 3.57 (s, 3H), 2.87 (br. s., 2H), 2.18 - 2.32 (m, 5H), 1.93 (br. s., 1H), 1.65 (br. s., 2H), 1.14 (br. s., 2H)



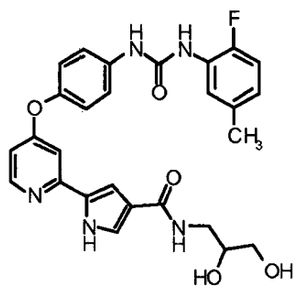
316

LR MS (ES+): 608 ($M+Na^+$)

LR MS (ES-): 584 (M-H)

Example 127

N-(2,3-dihydroxypropyl)-5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

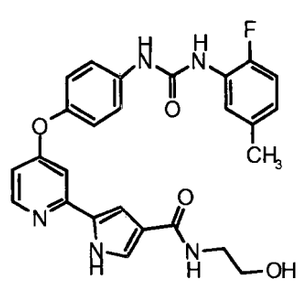
$^1H$ NMR ($d_6$-DMSO): 11.81 (br. s., 1H), 9.17 (s, 1H), 8.48 (d, J = 2.3 Hz, 1H), 8.36 (d, J = 5.6 Hz, 1H), 7.97 (dd, J = 7.8, 1.9 Hz, 1H), 7.86 (t, J = 5.7 Hz, 1H), 7.51 - 7.60 (m, 2H), 7.38 (dd, J = 3.1, 1.6 Hz, 1H), 7.10 - 7.19 (m, 3H), 7.07 (td, J = 4.3, 2.5 Hz, 2H), 6.74 - 6.84 (m, 1H), 6.69 (dd, J = 5.6, 2.3 Hz, 1H), 4.78 (d, J = 5.0 Hz, 1H), 4.54 (t, J = 5.9 Hz, 1H), 3.48 - 3.60 (m, 1H), 3.23 - 3.36 (m, 3H), 3.05 - 3.18 (m, 1H), 2.26 (s, 3H)

LR MS (ES+): 542 ($M+Na^+$)

LR MS (ES-): 518 (M-H)

Example 128

5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-(2-hydroxyethyl)-1H-pyrrole-3-carboxamide



Similar procedure as Example 132.

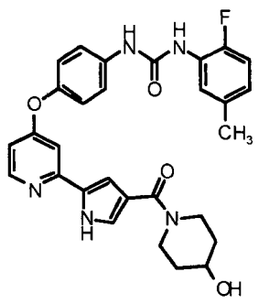
$^1$H NMR ($d_6$-DMSO): 11.79 (br. s., 1H), 9.30 (s, 1H), 8.57 (d, J = 1.5 Hz, 1H), 8.36 (d, J = 5.6 Hz, 1H), 7.95 (dd, J = 7.9, 1.8 Hz, 1H), 7.84 (t, J = 5.6 Hz, 1H), 7.50 - 7.63 (m, 2H), 7.35 (d, J = 1.5 Hz, 1H), 7.00 - 7.21 (m, 5H), 6.79 (td, J = 5.3, 2.5 Hz, 1H), 6.69 (dd, J = 5.6, 2.3 Hz, 1H), 4.66 (t, J = 5.6 Hz, 1H), 3.38 - 3.51 (m, 2H), 3.22 (q, J = 6.1 Hz, 2H), 2.25 (s, 3H)

LR MS (ES+): 512 ($M+Na^+$)

LR MS (ES-): 488 (M-H)

Example 129

1-(2-fluoro-5-methylphenyl)-3-{4-[(2-{4-[(4-hydroxypiperidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]phenyl}urea



Similar procedure as Example 132.

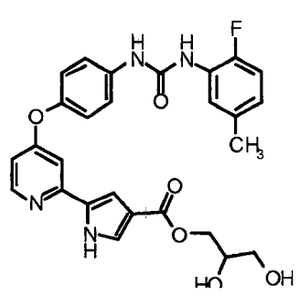
$^1$H NMR ($d_6$-DMSO): 11.84 (br. s., 1H), 9.17 (s, 1H), 8.48 (d, J = 2.3 Hz, 1H), 8.37 (d, J = 5.6 Hz, 1H), 7.99 (dd, J = 7.9, 1.8 Hz, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 2.3 Hz, 1H), 7.04 - 7.20 (m, 4H), 6.89 (s, 1H), 6.81 (td, J = 5.3, 2.3 Hz, 1H), 6.63 (dd, J = 5.9, 2.3 Hz, 1H), 4.73 (d, J = 4.1 Hz, 1H), 3.90 - 4.06 (m, 2H), 3.71 (dt, J = 8.4, 4.3 Hz, 1H), 3.25 (d, J = 2.6 Hz, 2H), 2.27 (s, 3H), 1.73 (d, J = 4.1 Hz, 2H), 1.21 - 1.44 (m, 2H)

LR MS (ES+): 552 ($M+Na^+$)

LR MS (ES-): 528 (M-H)

Example 130

2,3-dihydroxypropyl 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate



Similar procedure as Example 131.

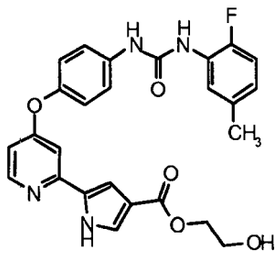
$^1$H NMR ($d_6$-DMSO): 12.12 (br. s., 1H), 9.24 (s, 1H), 8.54 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.98 (dd, J = 7.8, 1.9 Hz, 1H), 7.51 - 7.62 (m, 2H), 7.48 (dd, J = 3.1, 1.6 Hz, 1H), 7.34 - 7.40 (m, 1H), 7.05 - 7.20 (m, 4H), 6.75 - 6.87 (m, 1H), 6.68 (dd, J = 5.9, 2.3 Hz, 1H), 4.92 (d, J = 5.3 Hz, 1H), 4.64 (t, J = 5.7 Hz, 1H), 4.11 - 4.22 (m, 1H), 3.97 - 4.09 (m, 1H), 3.67 - 3.79 (m, 1H), 3.38 - 3.46 (m, 2H), 2.28 (s, 3H)

LR MS (ES+): 543 ($M+Na^+$)

LR MS (ES-): 519 (M-H)

Example 131

2-hydroxyethyl 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate



A mixture of 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid (50mg, 0.11mmol), ethylene glycol (1ml), 1-Ethyl-3-(3-dimethyllaminopropyl)carbodiimide hydrochloride (EDC• HCl, 25mg, 0.13mmol) and 4-dimethylaminopyridine (DMAP, 5mg, 0.04mmol) in anhydrous THF (10ml) was stirred at 60°C for 16 hours. The mixture was poured into 100ml of water. 2M HCl was added dropwise until pH = 4. The precipitates were filtered, washed with water and dried *in vacuo* to give the crude, which was purified by silica gel chromatography with a gradient of 3~5% MeOH/$CHCl_3$ to give 2-hydroxyethyl 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate as white solid. Yield: 36mg, 67%.

$^1$H NMR ($d_6$-DMSO): 12.12 (br. s., 1H), 9.18 (s, 1H), 8.49 (d, J = 1.8 Hz, 1H), 8.39 (d, J = 5.6 Hz, 1H), 7.94 - 8.05 (m, 1H), 7.56 (d, J = 9.1 Hz, 2H), 7.48 (d, J = 1.5 Hz, 1H), 7.35 (d, J = 2.1 Hz, 1H), 7.03 - 7.23 (m, 4H), 6.75 - 6.86 (m, 1H), 6.69 (dd, J = 5.7, 2.2 Hz, 1H), 4.83 (t, J = 5.7 Hz, 1H), 4.15 (t, J = 5.1 Hz, 2H), 3.64 (q, J = 5.4 Hz, 2H), 2.27 (s, 3H)

LR MS (ES+): 513 ($M+Na^+$)

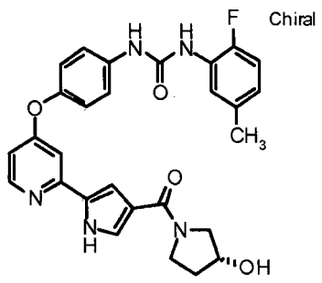
LR MS (ES-): 489 (M-H)



310

Example 132

1-(2-fluoro-5-methylphenyl)-3-(4-{[2-(4-{[(3R)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)urea




A mixture of 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid (50mg, 0.11mmol), HATU (51mg, 0.13mmol) and *N,N*-diisopropylethylamine (31mg, 0.24mmol) in anhydrous DMF (10ml) was stirred at room temperature for 10 minutes, followed by addition of (R)-3-pyrrolidinol (14mg, 0.16mmol). The mixture was stirred for another 10 minutes and poured into 100ml of water. 2M HCl was added dropwise until pH = 4~5. The precipitates were filtered, washed with water and dried *in vacuo* to give 1-(2-fluoro-5-methylphenyl)-3-(4-{[2-(4-{[(3R)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)urea as white solid. Yield: 40mg, 71%.

$^1$H NMR ($d_6$-DMSO): 11.90 (br. s., 1H), 9.17 (s, 1H), 8.49 (d, J = 2.6 Hz, 1H), 8.38 (d, J = 5.9 Hz, 1H), 7.99 (dd, J = 7.8, 1.9 Hz, 1H), 7.51 - 7.62 (m, 2H), 7.37 (d, J = 2.3 Hz, 1H), 7.25 (br. s., 1H), 7.02 - 7.19 (m, 4H), 6.76 - 6.86 (m, 1H), 6.64 (dd, J = 5.6, 2.3 Hz, 1H), 4.93 (br. s., 1H), 4.22 - 4.38 (m, 1H), 3.69 - 3.87 (m, 1H), 3.43 - 3.59 (m, 2H), 3.35 - 3.42 (m, 1H), 2.27 (s, 3H), 1.90 (br. s., 2H)

LR MS (ES+): 538 ($M+Na^+$)

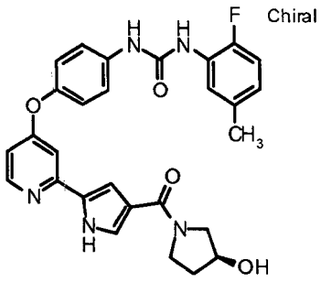
LR MS (ES-): 514 (M-H)

Example 133

1-(2-fluoro-5-methylphenyl)-3-(4-{[2-(4-{[(3S)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)urea



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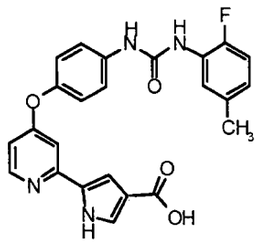

Similar procedure as Example 132.

LR MS (ES+): 538 ($M+Na^+$)

LR MS (ES-): 514 (M-H)

Example 134

5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid




To a stirred solution of methyl 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate (1.38g, 3.00mmol) in a mixture of solvents THF/MeOH (20ml/20ml) was added 2ml of 5M NaOH (10mmol) solution. The mixture was heated in a 72°C bath for 5 hours, cooled to room temperature and poured into 200ml of water. 2M HCl was added until pH = 3. The resulting precipitates were filtered, washed with water, and dried *in vacuo* to give 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylic acid as light brown solid. Yield: 1.28g, 96%.

$^1H$ NMR ($d_6$-DMSO): 12.04 (br. s., 1H), 11.88 (br. s., 1H), 9.18 (s, 1H), 8.49 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 5.6 Hz, 1H), 7.94 - 8.05 (m, 1H), 7.56 (d, J = 9.1 Hz, 2H), 7.31 - 7.42 (m, 2H), 7.01 - 7.21 (m, 4H), 6.81 (td, J = 5.2, 2.2 Hz, 1H), 6.68 (dd, J = 5.6, 2.3 Hz, 1H), 2.27 (s, 3H)

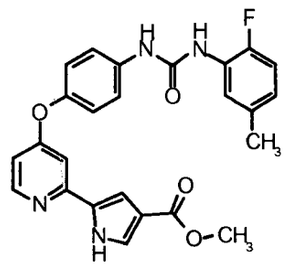
LR MS (ES-): 467 (M-H)



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Example 135

methyl 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate



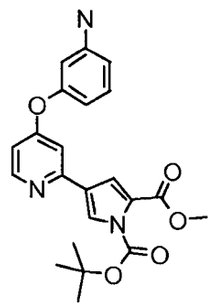
To a stirred solution of methyl 5-[4-(4-aminophenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate (1.0g, 3.23mmol) in anhydrous THF (10ml) was added 2-fluoro-5-methyl-phenylisocyanate (488mg, 3.23mmol). The mixture was stirred at room temperature for one hour and poured into 200ml of 0.02M HCl solution with vigorous stirring. The resulting precipitates were filtered, washed with water, and dried *in vacuo* to give methyl 5-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-3-carboxylate as white solid. Yield: 1.38g, 93%.

$^1$H NMR ($d_6$-DMSO): 12.14 (br. s., 1H), 9.17 (s, 1H), 8.49 (d, J = 2.3 Hz, 1H), 8.39 (d, J = 5.9 Hz, 1H), 7.99 (dd, J = 7.9, 1.8 Hz, 1H), 7.53 - 7.59 (m, 2H), 7.44 (dd, J = 3.2, 1.5 Hz, 1H), 7.36 (d, J = 2.3 Hz, 1H), 7.06 - 7.18 (m, 4H), 6.77 - 6.85 (m, 1H), 6.68 (dd, J = 5.6, 2.3 Hz, 1H), 3.72 (s, 3H), 2.28 (s, 3H)

LR MS (ES+): 483 ($M+Na^+$)

LR MS (ES-): 459 (M-H)

Preparation of1-tert-butyl 2-methyl 4-[4-(3-aminophenoxy)pyridin-2-yl]-1H-pyrrole-1,2-dicarboxylate





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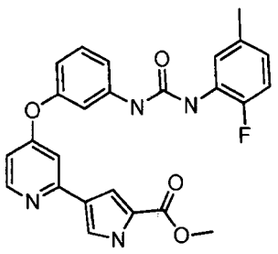
Similar procedure as 1-tert-butyl 2-methyl 4-[4-(4-aminophenoxy)pyridin-2-yl]-1H-pyrrole-1,2-dicarboxylate.

$^1$H NMR ($d_6$-DMSO): 8.38 (d, 1H), 8.01 (d, J = 1.5 Hz, 1H), 7.45 (d, J = 2.1 Hz, 1H), 7.37 (d, J = 1.5 Hz, 1H), 7.06 (t, J = 7.9 Hz, 1H), 6.67 (dd, J = 5.7, 2.2 Hz, 1H), 6.43 (d, J = 7.9 Hz, 1H), 6.20 - 6.33 (m, 2H), 5.32 (br. s., 2H), 3.72 - 3.85 (m, 3H), 1.53 (s, 9H)

LR MS (ES+): 432 ($M+Na^+$)

Example 136

methyl 4-{4-[3-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxylate



To a stirred solution of 1-tert-butyl 2-methyl 4-[4-(3-aminophenoxy)pyridin-2-yl]-1H-pyrrole-1,2-dicarboxylate (150 mg, 0.37 mmol) in anhydrous THF (10ml) was added 2-fluoro-5-methyl-phenylisocyanate (67mg, 0.44mmol). The mixture was stirred at room temperature for 3 hours and poured into 100ml of water. The resulting precipitates were filtered, washed with water, and dried *in vacuo* to give the Boc-protected intermediate as brown solid. This intermediate was dissolved in 5ml of methylene chloride, and 3ml of trifluoroacetic acid was added. Stirring was continued for 20 minutes. The mixture was evaporated to dryness to give the crude product, which was purified by silica gel chromatography eluting with 5% MeOH/$CHCl_3$ to give methyl 4-{4-[3-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxylate as white solid. Yield: 67mg, 39%.

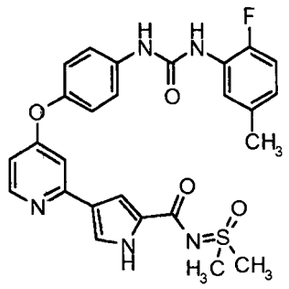
$^1$H NMR ($d_6$-DMSO): 12.18 (br. s., 1H), 9.23 (s, 1H), 8.47 (br. s., 1H), 8.36 (d, J = 5.6 Hz, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.63 (br. s., 1H), 7.25 - 7.47 (m, 4H), 7.16 (d, J = 7.9 Hz, 1H), 7.07 (dd, J = 11.4, 8.5 Hz, 1H), 6.72 - 6.85 (m, 2H), 6.65 (dd, J = 5.6, 2.1 Hz, 1H), 3.76 (s, 3H), 2.22 (s, 3H)

LR MS (ES+): 483 ($M+Na^+$)

LR MS (ES-): 459 (M-H)

Example 137

N-[dimethyl(oxido)-lambda~4~-sulfanylidene]-4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxamide



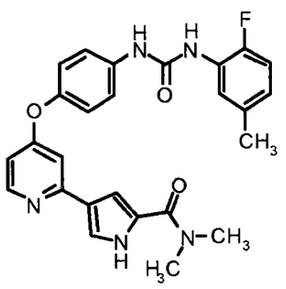
Similar procedure as Example 101.

LR MS (ES+): 544 ($M+Na^+$)

LR MS (ES-): 520 (M-H)

Example 138

4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N,N-dimethyl-1H-pyrrole-2-carboxamide



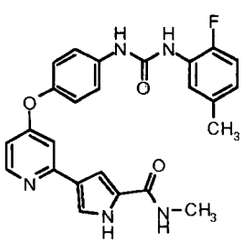
The title compound was isolated as a side product in the synthesis of Example 137.

LR MS (ES+): 474 (M+H)

LR MS (ES-): 472 (M-H

Example 139

4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-methyl-1H-pyrrole-2-carboxamide



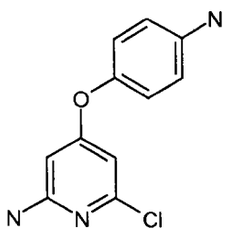
A mixture of 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxylic acid (50mg, 0.11mmol), HATU (50mg, 0.13mmol), 2M methylamine/ THF solution (0.1ml, 0.2mmol) and *N,N*-diisopropylethylamine (31mg, 0.24mmol) in anhydrous DMF (8ml) was stirred at room temperature for 10 minutes. The mixture was poured into 100ml of water. The precipitates were filtered, washed with water and dried to give the crude, which was purified by silica gel chromatography with 3~5% $MeOH/CHCl_3$ to give 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-N-methyl-1H-pyrrole-2-carboxamide as white solid. Yield: 21mg, 41%.

$^1H$ NMR ($d_6$-DMSO): 11.69 (br. s., 1H), 9.17 (s, 1H), 8.48 (d, J = 2.3 Hz, 1H), 8.32 (d, J = 5.6 Hz, 1H), 8.01 - 8.12 (m, 1H), 7.96 (dd, J = 7.8, 1.9 Hz, 1H), 7.48 - 7.61 (m, 2H), 7.43 (dd, J = 2.9, 1.5 Hz, 1H), 7.03 - 7.23 (m, 5H), 6.79 (dt, J = 8.1, 2.3 Hz, 1H), 6.61 (dd, J = 5.6, 2.3 Hz, 1H), 2.71 (d, J = 4.7 Hz, 3H), 2.26 (s, 3H)

LR MS (ES+): 482 ($M+Na^+$)

LR MS (ES-): 458 (M-H)

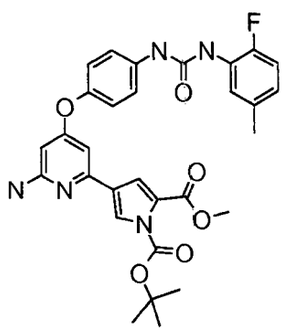
Preparation of 4-(4-aminophenoxy)-6-chloropyridin-2-amine



A stirred solution of 4-aminophenol (335mg, 3.1mmol) in anhydrous DMSO (8ml) was flushed with nitrogen and treated with 1M $KOBu^t$ / THF solution (3.1ml, 3.1mmol). The mixture was stirred at room temperature under nitrogen for 10 minutes. 4,6-dichloropyridin-2-ylamine (500mg, 3.1mmol) was added and the mixture was heated at 88°C for 16 hours, cooled to room temperature and poured into 100ml of water. The resulting precipitates were filtered, washed with water and dried to give the crude product, which was purified by silica gel chromatography with 2~5% $MeOH/CHCl_3$ to give 4-(4-aminophenoxy)-6-chloropyridin-2-amine as light brown solid. Yield: 350mg, 49%.

Example 140

1-tert-butyl 2-methyl 4-{6-amino-4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-1,2-dicarboxylate

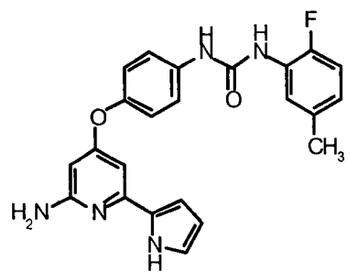


Similar procedure as Example 148.

LR MS (ES+): 598 ($M+Na^+$)

Example 141

1-(4-{[2-amino-6-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-(2-fluoro-5-methylphenyl)urea



Similar procedure as Example 148.

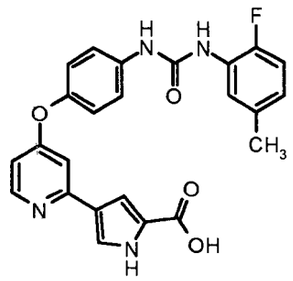
$^1H$ NMR ($d_6$-DMSO): 11.02 (br. s., 1H), 9.11 (s, 1H), 8.44 (br. s., 1H), 7.97 (d, 1H), 7.50 (d, J = 8.8 Hz, 2H), 6.98 - 7.17 (m, 3H), 6.78 (br. s., 2H), 6.53 (br. s., 2H), 6.05 (br. s., 1H), 5.74 (br. s., 2H), 5.61 (s, 1H), 2.25 (s, 3H)

LR MS (ES+): 418 (M+H)

LR MS (ES-): 416 (M-H)

Example 142

4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxylic acid

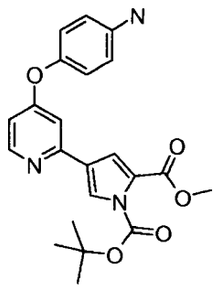


To a stirred solution of methyl 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxylate (220mg, 0.48mmol) in THF/MeOH (3ml/10ml) was added 1M NaOH (4.0ml, 4.0mmol). The mixture was heated at 70°C for 2 hours, cooled to room temperature and poured into 100ml of water. 1M HCl was added until pH = 4 and the resulting precipitates were filtered, washed with water and dried *in vacuo* to give 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxylic acid. Yield: 200mg, 94%.

$^1$H NMR ($d_6$-DMSO): 12.38 (br. s., 1H), 12.04 (br. s., 1H), 9.14 - 9.23 (m, 1H), 8.48 (d, J = 2.3 Hz, 1H), 8.34 (d, J = 5.6 Hz, 1H), 7.97 (dd, J = 7.9, 2.1 Hz, 1H), 7.60 (br. s., 1H), 7.50 - 7.58 (m, 2H), 7.30 (d, J = 2.1 Hz, 1H), 7.22 (s, 1H), 7.03 - 7.18 (m, 3H), 6.73 - 6.84 (m, 1H), 6.60 (dd, J = 5.6, 2.3 Hz, 1H), 2.25 (s, 3H)

LR MS (ES-): 445 (M-H)

Preparation of 1-tert-butyl 2-methyl 4-[4-(4-aminophenoxy)pyridin-2-yl]-1H-pyrrole-1,2-dicarboxylate

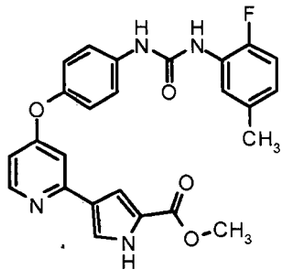


A 100ml flask was charged with 4-((2-chloropyridin-4-yl)oxy)aniline (150mg, 0.68mmol), 1-tert-butyl 2-methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-1,2-dicarboxylate (260mg, 0.81mmol), 2M $Na_2CO_3$ solution (0.5ml, 1.0mmol), $PdCl_2(PPh_3)_2$ (5mg, 0.007mmol), 10ml of 1,4-dioxane and 3ml of water. The mixture was flushed with nitrogen and heated at 70°C for 30 minutes. The mixture was cooled to room temperature and poured into

100ml of water. The precipitates were filtered and dried to give the crude, which was further purified by silica gel chromatography eluting with 2-3% MeOH/$CHCl_3$ to give 1-tert-butyl 2-methyl 4-[4-(4-aminophenoxy)pyridin-2-yl]-1H-pyrrole-1,2-dicarboxylate as light brown oil. Yield: 240mg, 86%.

Example 143

Methyl 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxylate



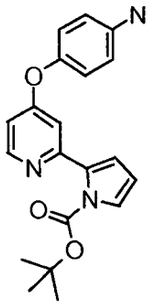
To a stirred solution of 1-tert-butyl 2-methyl 4-[4-(4-aminophenoxy)pyridin-2-yl]-1H-pyrrole-1,2-dicarboxylate (240 mg, 0.59 mmol) in anhydrous THF (10ml) was added 2-fluoro-5-methyl-phenylisocyanate (107mg, 0.71mmol). The mixture was stirred at room temperature for 30 minutes and poured into 100ml of water. The resulting precipitates were filtered, washed with water and dried to give a brown oil. Purification by silica gel chromatography eluting with 2-3% MeOH/$CHCl_3$ gave the Boc-protected intermediate as light green oil, which was dissolved in 5ml of methylene chloride, followed by addition of 3ml of trifluoroacetic acid. The mixture was stirred at room temperature for 10 minutes, evaporated to dryness, and purified by silica gel chromatography eluting with 2-5% MeOH/$CHCl_3$ to give methyl 4-{4-[4-({[(2-fluoro-5-methylphenyl)amino]carbonyl}amino)phenoxy]pyridin-2-yl}-1H-pyrrole-2-carboxylate as white solid. Yield: 135mg, 50%.

$^1$H NMR ($d_6$-DMSO): 12.17 (br. s., 1H), 9.14 (s, 1H), 8.46 (d, J = 2.3 Hz, 1H), 8.33 (d, J = 5.9 Hz, 1H), 7.91 - 8.04 (m, 1H), 7.61 (dd, J = 3.1, 1.6 Hz, 1H), 7.53 (d, J = 9.1 Hz, 2H), 7.22 - 7.31 (m, 2H), 7.02 - 7.17 (m, 3H), 6.73 - 6.85 (m, 1H), 6.58 (dd, J = 5.7, 2.5 Hz, 1H), 3.76 (s, 3H), 2.26 (s, 3H)

LR MS (ES+): 483 ($M+Na^+$)

LR MS (ES-): 459 (M-H)

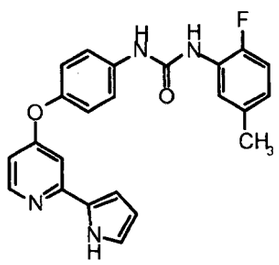
Preparation of tert-butyl 2-[4-(4-aminophenoxy)pyridin-2-yl]-1H-pyrrole-1-carboxylate



To a stirred mixture of *N*-Boc-pyrrole-2-boronic acid (114mg, 0.54mmol) and 4-((2-chloropyridin-4-yl)oxy)aniline (100mg, 0.45mmol) in 8ml of 1,4-dioxane, was added $PdCl_2(PPh_3)_2$ (10mg, 0.014mmol) and 1M $Na_2CO_3$ aqueous solution (0.5ml, 1.0mmol). The mixture was heated at 72°C under $N_2$ for one hour, cooled to room temperature and poured into 100ml of water. The resulting mixture was extracted with EtOAc (2x50ml). The organic layers were combined, washed with brine (50ml), dried over $Na_2SO_4$, and evaporated to give a brown oil, which was purified by silica gel chromatography with a gradient of 20~50% EtOAc/hexanes to give tert-butyl 2-[4-(4-aminophenoxy)pyridin-2-yl]-1H-pyrrole-1-carboxylate as colorless oil. Yield: 110mg, 70%.

Example 144

1-(2-fluoro-5-methylphenyl)-3-(4-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)urea



To a stirred solution of tert-butyl 2-[4-(4-aminophenoxy)pyridin-2-yl]-1H-pyrrole-1-carboxylate (100 mg, 0.28 mmol) in anhydrous THF (10ml) was added 2-fluoro-5-methyl-phenylisocyanate (51mg, 0.34mmol). The mixture was stirred at room temperature for one hour and poured into 100ml of water. The resulting mixture was extracted with EtOAc (2x50ml). The organic layers were combined, washed with brine (50ml), dried over $Na_2SO_4$, and evaporated to give a brown oil, which was purified by silica gel chromatography with 2-5% MeOH/$CHCl_3$ to give the Boc-

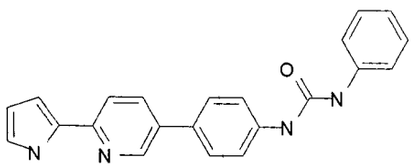


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protected intermediate as light green oil. The oil was dissolved in 5ml of methylene chloride, and 3ml of trifluoroacetic acid was added. Stirring was continued for 10 hours, and the mixture was evaporated to dryness. The brown residue was dissolved in methanol (5ml). This methanol solution was then added dropwise into 100ml of 1M $NaHCO_3$ solution with stirring. The resulting precipitates were filtered, washed with water, and dried *in vacuo* to give 1-(2-fluoro-5-methylphenyl)-3-(4-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)urea as light grey solid.
$^1$H NMR ($d_6$-DMSO): 11.43 (br. s., 1H), 9.14 (s, 1H), 8.46 (d, J = 2.6 Hz, 1H), 8.32 (d, J = 5.6 Hz, 1H), 7.96 (dd, J = 7.9, 1.8 Hz, 1H), 7.48 - 7.58 (m, 2H), 7.20 (d, J = 2.1 Hz, 1H), 7.04 - 7.16 (m, 3H), 6.75 - 6.86 (m, 2H), 6.67 (dt, J = 3.8, 1.9 Hz, 1H), 6.57 (dd, J = 5.9, 2.3 Hz, 1H), 6.05 - 6.13 (m, 1H), 2.25 (s, 3H)

Example 145

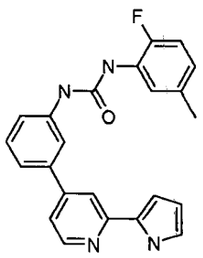
1-phenyl-3-{4-[6-(1H-pyrrol-2-yl)pyridin-3-yl]phenyl}urea



Similar procedure as Example 148.
$^1$H NMR (DMSO-$d_6$) δ: 11.46 (br. s., 1H), 8.79 (s, 1H), 8.75 (d, J = 1.8 Hz, 1H), 8.67 (s, 1H), 7.98 (dd, J = 8.4, 2.5 Hz, 1H), 7.70 (d, J = 8.2 Hz, 1H), 7.67 (d, J = 8.5 Hz, 2H), 7.56 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 7.6 Hz, 2H), 7.27 (t, J = 7.9 Hz, 2H), 6.96 (t, J = 7.3 Hz, 1H), 6.84 - 6.88 (m, 1H), 6.77 (t, J = 3.8 Hz, 1H), 6.11 - 6.16 (m, 1H)

Example 146

1-(2-fluoro-5-methylphenyl)-3-{3-[2-(1H-pyrrol-2-yl)pyridin-4-yl]phenyl}urea



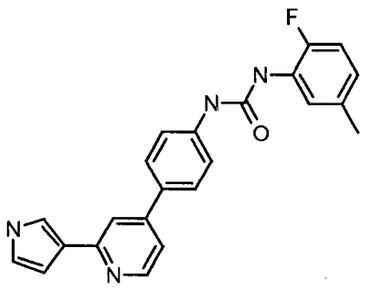
Similar procedure as Example 148.
LR MS (ES+): 387 ($M+H^+$)



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Example 147

1-(2-fluoro-5-methylphenyl)-3-{4-[2-(1H-pyrrol-3-yl)pyridin-4-yl]phenyl}urea

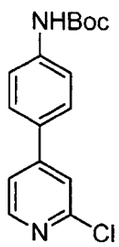


Similar procedure as Example 148.

$^1$H NMR ($d_6$-DMSO): 11.72 (br. s., 1H), 9.49 (br. s., 1H), 8.63 (s, 1H), 8.53 (d, J = 6.4 Hz, 1H), 8.38 (br. s., 1H), 8.07 (d, J = 8.5 Hz, 2H), 8.00 - 8.04 (m, 1H), 7.97 (dd, J = 7.9, 1.8 Hz, 1H), 7.81 - 7.90 (m, 1H), 7.69 (d, J = 8.8 Hz, 2H), 7.13 (dd, J = 11.3, 8.4 Hz, 1H), 7.03 (d, J = 2.1 Hz, 1H), 6.98 (br. s., 1H), 6.84 (ddd, J = 7.8, 5.3, 2.1 Hz, 1H), 2.21 - 2.36 (m, 3H)

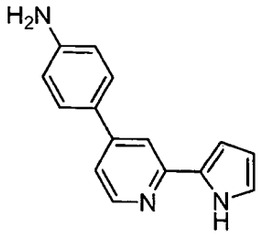
LR MS (ES+): 387 (M+H)

tert-butyl (4-(2-chloropyridin-4-yl)phenyl)carbamate



To a mixture of (4-boc-aminophenyl)boronic acid (200mg, 0.84mmol) and 2-chloro-4-bromopyridine (162mg, 0.84mmol) in 10ml of 1,4-dioxane, was added $PdCl_2(PPh_3)_2$ (10mg, 0.014mmol) and 1M $Na_2CO_3$ aqueous solution (0.5ml, 1.0mmol). The mixture was heated at 70°C under $N_2$ for 2 hours, cooled to room temperature and poured into 100ml of water. The brown precipitates were filtered, washed with water and dried to give tert-butyl (4-(2-chloropyridin-4-yl)phenyl)carbamate as the crude product.

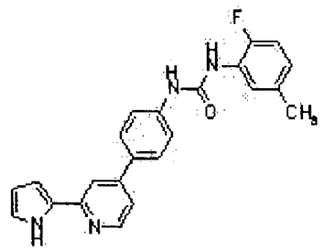
4-(2-(1H-pyrrol-2-yl)pyridin-4-yl)aniline



To a mixture of N-Boc-pyrrole-2-boronic acid (210mg, 1.0mmol) and tert-butyl (4-(2-chloropyridin-4-yl)phenyl)carbamate (250mg, 0.82mmol) in 10ml of 1,4-dioxane, was added $PdCl_2(PPh_3)_2$ (10mg, 0.014mmol) and 1M $Na_2CO_3$ aqueous solution (0.75ml, 1.5mmol). The mixture was heated at 60°C under $N_2$ for 3 hours, cooled to room temperature and poured into 100ml of water. The precipitates were filtered, dried and purified by silica gel chromatography with 1-5% MeOH/$CHCl_3$ to give the intermediate as light yellow oil. This intermediate was dissolved in 10ml of methylene chloride and 3ml of trifluoroacetic acid was added. The mixture was stirred at room temperature for 16 hours and evaporated to dryness to give 4-(2-(1H-pyrrol-2-yl)pyridin-4-yl)aniline TFA salt as light brown solid. Yield: 290mg, 100%.

Example 148

1-(2-fluoro-5-methylphenyl)-3-{4-[2-(1H-pyrrol-2-yl)pyridin-4-yl]phenyl}urea



To a stirred suspension of 4-(2-(1H-pyrrol-2-yl)pyridin-4-yl)aniline TFA salt (60 mg, 0.17 mmol) in anhydrous THF (10ml) was added 2-fluoro-5-methyl-phenylisocyanate (48mg, 0.32mmol) and *N,N*-diisopropylethylamine (40 mg, 0.31 mmol). After 1 hour, the reaction mixture was evaporated and purified by silica gel chromatography with 2-3% MeOH/$CHCl_3$ to give 1-(2-fluoro-5-methylphenyl)-3-{4-[2-(1H-pyrrol-2-yl)pyridin-4-yl]phenyl}urea as off-white solid. Yield: 28mg.

$^1$H NMR ($d_6$-DMSO): 11.49 (br. s., 1H), 9.29 (br. s., 1H), 8.52 - 8.60 (m, 1H), 8.48 (d, J = 5.3 Hz, 1H), 7.94 - 8.04 (m, 2H), 7.84 (d, J = 8.5 Hz, 2H), 7.62 (d, J = 8.5 Hz, 2H), 7.42 (dd, J = 5.3, 1.5 Hz, 1H), 7.12 (dd, J = 11.4, 8.2 Hz, 1H), 6.89 (s, 2H), 6.82 (dt, J = 5.4, 2.6 Hz, 1H), 6.16 (t, J = 2.9 Hz, 1H), 2.29 (s, 3H)

LR MS (ES+): 409 ($M+Na^+$)

LR MS (ES-): 385 (M-H)

**3.2 Biological Testing**

Biological data for the compounds of the present invention was generated by the use of one or more of the following assays.

**VEGF Stimulated Ca.sup.++ Signal in Vitro**

Automated FLIPR (Fluorometric Imaging Plate Reader) technology was used to screen for inhibitors of VEGF induced increases in intracellular calcium levels in fluorescent dye loaded endothelial cells. HUVEC (human umbilical vein endothelial cells) (Clonetics) were seeded in 96-well fibronectin coated black-walled plates overnight at 37.degree. C./5% CO.sub.2. Cells were loaded with calcium indicator Fluo-4 for 45 minutes at 37.degree. C. Cells were washed 4 times (Original Cell Wash, Labsystems) to remove extracellular dye. Test compounds were reconstituted in 100% DMSO and added to the cells to give a final DMSO concentration of 0.1%. For screening, cells were pre-incubated with test agents for 30 minutes, at a single concentration (10 .mu.M) or at concentrations ranging from 0.01 to 10.0 .mu.M followed by VEGF stimulation (5 ng/mL). Changes in fluorescence at 516 nm were measured simultaneously in all 96 wells using a cooled CCD camera. Data were generated by determining max-min fluorescence levels for unstimulated, stimulated, and drug treated samples. IC.sub.50 values for test compounds were calculated from % inhibition of VEGF stimulated responses in the absence of inhibitor.

**VEGFR2 Kinase Assay**

The cytoplasmic domain of the human VEGF receptor (VEGFR-2) was expressed as a Histidine-tagged fusion protein following infection of insect cells using an His engineered baculovirus. His-VEGFR-2 was purified to homogeneity, as determined by SDS-PAGE, using nickel resin chromatography. Kinase assays were performed in 96 well microtiter plates that were coated overnight with 30 .mu.g of poly-Glu-Tyr (4:1) in 10 mM Phosphate Buffered Saline (PBS), pH 7.2-7.4. The plates were incubated with 1% BSA and then washed four times with PBS prior to starting the reaction. Reactions were carried out in 120 .mu.L reaction volumes containing 3.6 .mu.M ATP in kinase buffer (50 mM Hepes buffer pH 7.4, 20 mM MgCl.sub.2, 0.1 mM MnCl.sub.2 and 0.2 mM Na.sub.3 VO.sub.4). Test compounds were reconstituted in 100% DMSO and added to the reaction to give a final DMSO concentration of 5%. Reactions were initiated by the addition 0.5 ng of purified protein. Following a ten minute incubation at 25.degree. C., the reactions were washed four times with PBS containing 0.05% Tween-20. 100

.mu.l of a monoclonal anti-phosphotyrosine antibody-peroxidase conjugate was diluted 1:10000 in PBS-Tween-20 and added to the wells for 30 minutes. Following four washes with PBS-Tween-20, 100 .mu.l of O-phenylenediamine Dihydrochloride in Phosphate-citrate buffer, containing urea hydrogen peroxide, was added to the wells for 7 minutes as a colorimetric substrate for the peroxidase. The reaction was terminated by the addition of 100 .mu.l of 2.5N H.sub.2 SO.sub.4 to each well and read using a microplate ELISA reader set at 492 nm. IC.sub.50 values for compound inhibition were calculated directly from graphs of optical density (arbitrary units) versus compound concentration following subtraction of blank values. Compounds of the current invention have the IC50 value in the range of 0.01 to 500 nM.

**VEGF-induced Dermal Extravasation in Guinea Pig (Miles Assay)**

Male Hartley guinea pigs (300-600 g) were anesthetized with isofluorane, sheared, and given a single dose of drug or the respective vehicle. The guinea pigs were dosed orally unless indicated otherwise in Table 3. Ten minutes prior to the end of drug treatment, guinea pigs were anesthetized with isofluorane, and 0.5% Evans blue dye (EBD) in PBS (13-15 mg/kg dose of EBD) was injected intravenously. After 5 minutes, triplicate intradermal injections of 100 ng rhVEGF.sub.165 in 100 .mu.l PBS and of 100 .mu.l PBS alone were administered on the flank. After 20 minutes, each animal was cuthanized with Pentosol, and the skin containing the intradermal injection sites was removed for image analysis.

Using an analog video camera coupled to a PC, an image of each trans-illuminated skin sample was captured, and the integrated optical density of each injection site was measured using ImagePro 4. For each skin sample, the difference between the mean optical density of the VEGF sites and mean optical density of the PBS sites is the measure of VEGF-induced EBD extravasation in that animal. These measured values were averaged per study group to determine the mean VEGF-induced EBD extravasation for each experimental condition, and the group means were then compared to assess inhibition of VEGF-induced EBD extravasation in the drug-treated groups relative to the vehicle-treated controls.

To determine the dose required for 50% inhibition (ID.sub.50), the percent inhibition data was plotted as a function of oral dose, using the `best-fit` analysis within MicroSoft Excel software. The ID.sub.50 value was verified visually by using the plotted data (horizontal line from 50% y value, at intersection with best-fit line drop vertical line to x axis (dose).

**Laser-induced Choroidal Neovascularization (CNV) in Rat (CNV Assay).**

CNV was induced and quantified in this model as previously described (Edelman and Castro. Exp. Eye Res. 2000; 71:523-533). On day 0, male Brown Norway rats (200-300 g) were anesthetized with 100 mg/kg Ketamine and 10 mg/kg Xylazine, and pupils were dilated with 1% Tropicamide. Using the blue-green setting of a Coherent Novus Argon Laser, 3 laser burns (90

mW for 0.1 s; 100 .mu.m diameter) were given to each eye between the retinal vessels around the optic nerve head. Rats were dosed with test compounds in their indicated vehicles orally once daily.

On day 10, rats were sacrificed with 100% CO.sub.2, and blood vessels were labeled by vascular perfusion with 10 mg/ml FITC-dextran (MW 2.times.10.sup.6). Using an epifluorescence microscope (20.times.) coupled to a spot digital camera and a PC, images were obtained from the flat mounts of the RPE-choroid-sclera from each eye, and the area occupied by hyperfluorescent neovessels within each laser lesion was measured using ImagePro 4 software.

To determine the dose required for 50% inhibition (ID.sub.50), the percent inhibition data was plotted as a function of oral dose, using the `best-fit` analysis within MicroSoft Excel software. The ID.sub.50 value was verified visually by using the plotted data (horizontal line from 50% y value, at intersection with best-fit line drop vertical line to x axis (dose).

The foregoing description can be employed to practice the present invention, and represents the best mode contemplated. It should not be construed as limiting the overall scope hereof.

**Rabbit Eye VEGF Permeability Model**

Assay used was detailed by Jeffrey Edelman, etc in Exp. Eye. Res. 80(2005), Pg 249-258.

**PDGF Stimulated $Ca^{2+}$ Signal in Vitro**

Automated FLIPR (Fluorometric Imaging Plate Reader) technology was used to screen for inhibitors of PDGF induced increases in intracellular calcium levels in fluorescent dye loaded endothelial cells. NHDF-Ad (Normal human dermal fibroblasts) (Lonza) were seeded in 384-well fibronectin coated black-walled plates overnight at 37° C/5% $CO_2$ . Cells were loaded with calcium indicator Fluo-4 for 45 minutes at 37° C. Cells were washed 4 times (ELx405-CW, Bio-Tek) to remove extracellular dye. Test compounds were reconstituted in 100% DMSO and added to the cells to give a final DMSO concentration of 0.1%. For screening, cells were pre-incubated with test agents for 30 minutes, at a single concentration (10 μM) or at concentrations ranging from 0.001nM to 10 μM followed by PDGF stimulation (10 ng/mL). Changes in fluorescence at 515nm were measured simultaneously in all 384 wells using a cooled CCD camera. Data were generated by determining max-min fluorescence levels for unstimulated, stimulated, and drug treated samples. $IC_{50}$ values for test compounds were calculated from % inhibition of PDGF stimulated responses in the absence of inhibitor.

Table II and III present the biodata of some of the compounds of the present invention.

**Table II: Biodata of Compounds of the Present Invention with Amide Linker**

| Example# | VEGFR2 Cellular $IC_{50}$ (nM) | VEGFR2 Enzyme $IC_{50}$ (nM) | VEGFR1 Enzyme $IC_{50}$ (nM) | PDGFβ Cellular $IC_{50}$ (nM) |
|---|---|---|---|---|
| 1 | | 28 | | |
| 2 | 8 | 28 | | |
| 3 | | 28 | | |
| 4 | 6 | 29 | | |
| 5 | | 2956 | | |
| 6 | | 506 | | |
| 7 | 12 | 34 | | |
| 8 | 8 | 28 | | |
| 9 | 30 | 47 | | |



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| Example# | VEGFR2 Cellular $IC_{50}$ (nM) | VEGFR2 Enzyme $IC_{50}$ (nM) | VEGFR1 Enzyme $IC_{50}$ (nM) | PDGFβ Cellular $IC_{50}$ (nM) |
|---|---|---|---|---|
| 10 | 46 | 41 | | |
| 11 | 28 | 23 | 34 | |
| 12 | | | | |
| 13 | 16 | 27 | | |
| 14 | 15 | 33 | 15 | |
| 15 | 51 | 26 | | 73 |
| 16 | 17 | 21 | | |
| 17 | 22 | 20 | | 61 |
| 18 | 10 | 31 | | |
| 19 | 30 | 37 | | 135 |
| 20 | 83 | 28 | | |

| Example# | VEGFR2 Cellular $IC_{50}$ (nM) | VEGFR2 Enzyme $IC_{50}$ (nM) | VEGFR1 Enzyme $IC_{50}$ (nM) | PDGFβ Cellular $IC_{50}$ (nM) |
|---|---|---|---|---|
| 21 | 12 | 24 | | 39 |
| 22 | 18 | 29 | 13 | 105 |
| 23 | 13 | 35 | | |
| 24 | 55 | 24 | | |
| 25 | 30 | 25 | | |
| 26 | 39 | 120 | | |
| 27 | 45 | 66 | | |
| 28 | 38 | 52 | | |
| 29 | 18 | 55 | | |
| 30 | 29 | 37 | | 94 |



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| Example# | VEGFR2 Cellular $IC_{50}$ (nM) | VEGFR2 Enzyme $IC_{50}$ (nM) | VEGFR1 Enzyme $IC_{50}$ (nM) | PDGFβ Cellular $IC_{50}$ (nM) |
|---|---|---|---|---|
| 31 | 14 | 29 | 20 | |
| 32 | 22 | 46 | | |
| 33 | 18 | 56 | | |
| 34 | 7 | 70 | | |
| 35 | 27 | 29 | | |
| 36 | | 10028 | | |
| 37 | 1005 | 2610 | | |



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**Table 1II: Biodata of Compounds of the Present Invention with Urea Linker**

| Example# | VEGFR2 Cellular $IC_{50}$ (nM) | VEGFR2 Enzyme $IC_{50}$ (nM) | VEGFR1 Enzyme $IC_{50}$ (nM) | PDGFβ Cellular $IC_{50}$ (nM) |
|---|---|---|---|---|
| 38 | | 10 | | |
| 39 | | 23 | | |
| 40 | | 11 | | |
| 41 | | 11 | | |
| 42 | | 60 | | |
| 43 | | 16 | | |
| 44 | | 24 | | |
| 45 | | 17 | | |
| 46 | 2 | 28 | | |
| 47 | 107 | 17 | | |
| 48 | 16 | 12 | | |
| 49 | 145 | 27 | | |



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| Example# | VEGFR2 Cellular $IC_{50}$ (nM) | VEGFR2 Enzyme $IC_{50}$ (nM) | VEGFR1 Enzyme $IC_{50}$ (nM) | PDGFβ Cellular $IC_{50}$ (nM) |
|---|---|---|---|---|
| 50 | 5 | 32 | | |
| 51 | | 16 | | |
| 52 | | 25 | | |
| 53 | 43 | 28 | | 44 |
| 54 | 130 | 29 | | 191 |
| 55 | 32 | 23 | | 26 |
| 56 | 81 | 20 | | |
| 57 | 102 | 45 | | |
| 58 | 211 | 36 | | |
| 59 | 34 | 29 | | |
| 60 | 27 | 23 | | |
| 61 | 91 | 39 | | |

| Example# | VEGFR2 Cellular $IC_{50}$ (nM) | VEGFR2 Enzyme $IC_{50}$ (nM) | VEGFR1 Enzyme $IC_{50}$ (nM) | PDGFβ Cellular $IC_{50}$ (nM) |
|---|---|---|---|---|
| 62 | 122 | 43 | | |
| 63 | 111 | 30 | | |
| 64 | 16 | 39 | | |
| 65 | | 15 | 4 | |
| 66 | | 17 | 3 | |
| 67 | 31 | 31 | | |
| 68 | | 16 | | |
| 69 | | 24 | 5 | |
| 70 | 2 | 20 | | |
| 71 | | 20 | | |
| 72 | 7 | 15 | | |
| 73 | | 11 | | |

| Example# | VEGFR2 Cellular $IC_{50}$ (nM) | VEGFR2 Enzyme $IC_{50}$ (nM) | VEGFR1 Enzyme $IC_{50}$ (nM) | PDGFβ Cellular $IC_{50}$ (nM) |
|---|---|---|---|---|
| 74 | 7 | 12 | | |
| 76 | 2 | 14 | 3 | |
| 76 | 3 | 14 | | |
| 77 | 8 | 10 | | |
| 78 | 25 | 15 | 4 | |
| 79 | 13 | 38 | | |
| 80 | 176 | 69 | | |
| 81 | | 19 | | |
| 82 | 17 | 19 | | |
| 83 | | 22 | 5 | |
| 84 | | 13 | | |
| 85 | 6 | 30 | | |



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| Example# | VEGFR2 Cellular $IC_{50}$ (nM) | VEGFR2 Enzyme $IC_{50}$ (nM) | VEGFR1 Enzyme $IC_{50}$ (nM) | PDGFβ Cellular $IC_{50}$ (nM) |
|---|---|---|---|---|
| 86 | | 27 | | |
| 87 | 5 | 25 | | |
| 88 | 374 | 477 | | |
| 89 | 5 | 23 | | |
| 90 | 8 | 17 | 6 | 21 |
| 91 | 17 | 14 | | 38 |
| 92 | 37 | 9 | | 39 |
| 93 | 6 | 5 | 5 | 14 |
| 94 | 10 | 6 | | 10 |
| 95 | 30 | 32 | | |
| 96 | 3 | 17 | | 69 |
| 97 | 8 | 18 | | |



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| Example# | VEGFR2 Cellular $IC_{50}$ (nM) | VEGFR2 Enzyme $IC_{50}$ (nM) | VEGFR1 Enzyme $IC_{50}$ (nM) | PDGFβ Cellular $IC_{50}$ (nM) |
|---|---|---|---|---|
| 98 | 62 | 51 | | |
| 99 | 49 | 46 | | |
| 100 | 12 | 13 | | |
| 101 | 4 | 8 | | 82 |
| 102 | 10 | 35 | | 8 |
| 103 | 24 | 20 | | |
| 104 | 23 | 27 | | |
| 105 | 87 | 15 | | |
| 106 | 16 | 21 | | |
| 107 | 13 | 21 | | |
| 108 | 17 | 14 | 13 | 43 |
| 109 | 16 | 23 | | |

| Example# | VEGFR2 Cellular $IC_{50}$ (nM) | VEGFR2 Enzyme $IC_{50}$ (nM) | VEGFR1 Enzyme $IC_{50}$ (nM) | PDGFβ Cellular $IC_{50}$ (nM) |
|---|---|---|---|---|
| 110 | 8 | 38 | 10 | 32 |
| 111 | 13 | 71 | | |
| 112 | 13 | 18 | | |
| 113 | 23 | 25 | | |
| 114 | 13 | 22 | | |
| 115 | 2 | 15 | 2 | 44 |
| 116 | 12 | 17 | | |
| 117 | 6 | 18 | | |
| 118 | 22 | 85 | | |
| 119 | 12 | 54 | | |
| 120 | 43 | 98 | | |
| 121 | 37 | 14 | 20 | 102 |



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| Example# | VEGFR2 Cellular $IC_{50}$ (nM) | VEGFR2 Enzyme $IC_{50}$ (nM) | VEGFR1 Enzyme $IC_{50}$ (nM) | PDGFβ Cellular $IC_{50}$ (nM) |
|---|---|---|---|---|
| 122 | 142 | 130 | | |
| 123 | 13 | 24 | | 85 |
| 124 | 23 | 36 | | |
| 125 | 22 | 31 | | |
| 126 | 16 | 116 | | |
| 127 | 20 | 21 | | 91 |
| 128 | 10 | 53 | | |
| 129 | 12 | 102 | | |
| 130 | 5 | 43 | 16 | 32 |
| 131 | 8 | 31 | | |
| 132 | 22 | 15 | | |
| 133 | 66 | 15 | | |



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| Example# | VEGFR2 Cellular $IC_{50}$ (nM) | VEGFR2 Enzyme $IC_{50}$ (nM) | VEGFR1 Enzyme $IC_{50}$ (nM) | PDGFβ Cellular $IC_{50}$ (nM) |
|---|---|---|---|---|
| 134 | 4 | 31 | 4 | |
| 135 | 11 | 47 | | |
| 136 | 29 | 22 | | |
| 137 | 14 | 33 | | |
| 138 | | 30 | | |
| 139 | 14 | 30 | | |
| 140 | | 10000 | | |
| 141 | | 2704 | | |
| 142 | 111 | 28 | | |
| 143 | 16 | 12 | | |
| 144 | 28 | 26 | | |
| 145 | 10000 | 10000 | | |

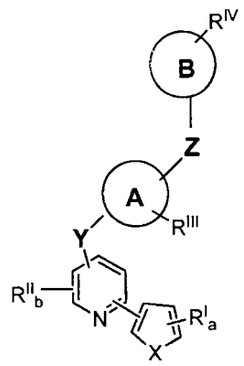
| Example# | VEGFR2 Cellular $IC_{50}$ (nM) | VEGFR2 Enzyme $IC_{50}$ (nM) | VEGFR1 Enzyme $IC_{50}$ (nM) | PDGFβ Cellular $IC_{50}$ (nM) |
|---|---|---|---|---|
| 146 | 10000 | 7007 | | |
| 147 | 10000 | 3505 | | |
| 148 | 10000 | 1382 | | |



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We claim:

1. A compound represented by Formula I:




Formula I

wherein

X is selected from the group consisting of $NR^1$, O, and $S(O)_n$;

n is 0 or an integer of from 1 to 2;

$R^1$ is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, $CF_3$, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl($NR^2R^3$), wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

$R^I$ is selected from the group consisting of hydrogen, halogen, $C_1$ to $C_8$ alkyl, $S(O)_fR^4$, $(CR^5R^6)_dC(O)OR^4$, $S(O)_f(CR^5R^6)_dC(O)OR^4$, $(CR^5R^6)_dAr$, $NR^4(CR^5R^6)_dAr$, $O(CR^5R^6)_dAr$, $S(O)_f(CR^5R^6)_dAr$, $(CR^5R^6)_dS(O)_fR^4$, $NR^4(CR^5R^6)_dS(O)_fR^4$, $O(CR^5R^6)_d\ S(O)_fR^4$, $S(O)_f(CR^5R^6)_eS(O)_fR^4$, $(CR^5R^6)_dC(O)N(R^4)_2$, $NR^4(CR^5R^6)_dC(O)N(R^4)_2$, $O(CR^5R^6)_dC(O)N(R^4)_2$, $S(O)_f(CR^5R^6)_eC(O)N(R^4)_2$, $(CR^5\ R^6)_dOR^4$, $S(O)_f(CR^5R^6)_dOR^4$, $(CR^5\ R^6)_dOSO_2R^4$, $S(O)_f(CR^5\ R^6)_eOSO_2R^4$, $(CR^5\ R^6)_dP(O)(OR^4)_2$, $S(O)_f(CR^5\ R^6)_eP(O)(OR^4)_2$, $OC(O)(CR^5R^6)_dN(R^4)_2$, $C(O)(CR^5R^6)_dN(R^4)_2$, $C(O)N{=}S(O)R^5\ R^6$, $NR^2C(O)(CR^5R^6)_dN(R^4)_2$, $(CR^5R^6)_dR^5$, $S(O)_f(CR^5R^6)_dR^5$, $HNC(O)R^4$, $HN\text{-}C(O)OR^4$, $(CR^5R^6)_dN(R^4)_2$, $S(O)_f(CR^5R^6)_dN(R^4)_2$, $OC(O)OR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dOR^4$, and $(CR^5R^6)_dC(O)(CR^5R^6)_dN(R^4)_2$, wherein each $R^4$ is independently selected from the group consisting of hydrogen, hydroxyl, $C_1$-$C_8$ alkyl, aryl, $C_1$-$C_8$ hydroxyalkyl, $C_1$-$C_8$ alkoxyalkyl, $(CR^5R^6)_d$ and $N(R^4)_2$ may form a 3-7 membered heterocyclic ring, comprising of aziridine,



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azetidine, pyrrolidine, 5-fluoropyrrolidine, piperidine, 6-fluoropiperidine, N-methylpiperazine, morpholine, 2,6-dimethylmorpholine, thiomorpholine, and wherein said heterocyclic ring may be optionally substituted with up to three of $R^5$; wherein $R^5$ and $R^6$ are independently selected from the group consisting of hydrogen, halo, hydroxyl, $C_1$-$C_8$ alkyl, $C_1$-$C_8$ hydroxyalkyl, $C_1$-$C_8$ alkoxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, hydroxycarbonyl, hydroxycarbonylalkyl, amide, alkylamide, amidoalkyl, sulfonate and $CR^5R^6$ may represent a carbocyclic or heterocyclic ring of from 5 to 6 carbons or alternatively, $(CR^5R^6)_d$ and $(CR^5R^6)_e$ may form a 3-7 membered carbocyclic or heterocyclic ring, wherein the ring may be optionally substituted with up to three of hydroxyl, halo, $C_1$-$C_8$ alkyl, $C_1$-$C_8$ hydroxyalkyl, $C_1$-$C_8$ alkoxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, hydroxycarbonyl, hydroxycarbonylalkyl, amide, alkylamide, amidoalkyl and sulfonate;

a is 0 or an integer of from 1 to 3;

d is 0 or an integer of from 1 to 5;

e is an integer of from 1 to 4;

f is 0 or an integer of from 1 to 2;

$R^{II}$ is independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkyl, aryloxy, aryloxyalkyl, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkoxy, hydroxyalkyl, $(NR^2R^3)$alkoxy, $(NR^2R^3)$alkenyl, $(NR^2R^3)$alkyl, $(NR^2R^3)$carbonylalkenyl, and $(NR^2R^3)$carbonylalkyl, wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

b is 0 or an integer of from 1 to 2;

Y is selected from the group consisting of:

(1') —$(CH_2)g$—O—$(CH_2)h$—;

(2') —$(CH_2)g$—$NR^1$—$(CH_2)h$—;

(3') —$(CH_2)g$—$S(O)_n$—$(CH_2)h$—;

(4') —$(CH_2)g$—$SO_2N$ $R^2$—$(CH_2)h$—;



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(5') —$(CH_2)g—NR^2SO_2—(CH_2)h$—;

(6') —$(CH_2)g—CO—(CH_2)h$—;

(7') —$(CH_2)g—C(O)NR^2—(CH_2)h$—;

(8') —$(CH_2)g—NR^2C(O)—(CH_2)h$—;

(9') —$(CH_2)g—C\equiv C—(CH_2)h$—;

(10') —$(CH_2)g—NR^2C(O)NR^3—(CH_2)h$—;

(11') —$(CH_2)g—(CH_2)h$—;

(12') —$(CH_2)g—CF_2—(CH_2)h$—;

(13') —$(CH_2)g—CCl_2—(CH_2)h$—;

(14') —$(CH_2)g—CHF—(CH_2)h$—;

(15') —$(CH_2)g—CH(OH)—(CH_2)h$—;

(16') —$(CH_2)g—CR^2R^3—(CH_2)h$—;

(17') —$(CH_2)g—C=C—(CH_2)h$—;

and (18') a single bond;

wherein

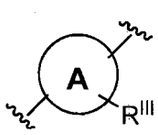
g is 0 or an integer of from 1 to 3;

h is 0 or an integer of from 1 to 3;

$R^1$ is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, $CF_3$, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl($NR^2R^3$), wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$ and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

$R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$ and $R^3$ and may be taken together to form a 5-7 membered cyclic ring;

Ring A is selected from the group consisting of:






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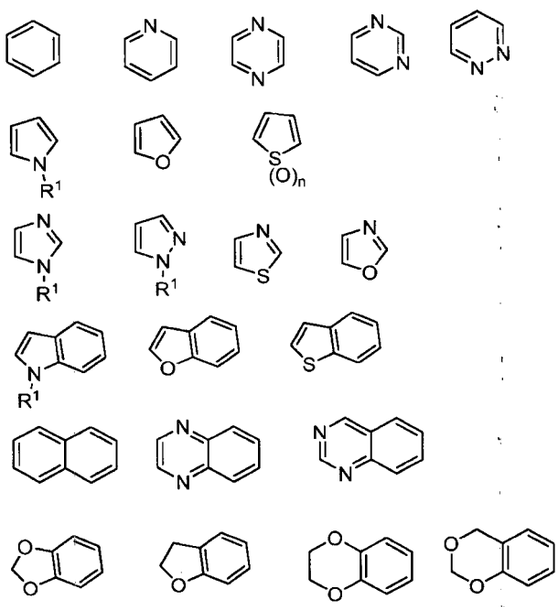
(i) Phenyl;

(ii) Naphthyl;

(iii) A 5 or 6 membered monocyclic heteroaryl group which have 1-5 heteroatoms independently selected from the group consisting of O, N and S;

and (iv) An 8 to 10 membered bicyclic heteroaryl group which have 1-6 heteroatoms independently selected from the group consisting of O, N and S;

Ring A can be illustrated but not limited to the following:



wherein

$R^1$ is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, $CF_3$, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N $R^2R^3$), wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

$R^{III}$ represents optionally 1-3 substituents independently selected from the group consisting of $C_1$-$C_5$ linear or branched alkyl, $C_1$-$C_5$ linear or branched haloalkyl, $C_1$-$C_5$ alkoxy, hydroxy, amino, $C_1$-$C_5$ alkylamino, $C_1$-$C_6$ dialkylamino, halogen, cyano, and nitro;

Z is selected from the group consisting of

(1') $(CH_2)_iN(R^7)C(O)$;

(2') $C(O)N(R^8)(CH_2)_j$;

(3') $(CH_2)_iN(R^7)S(O)_2$;

and (4') $S(O)_2N(R^8)(CH_2)_j$.

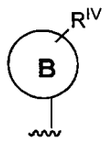
wherein:

i is 0 or 1;

j is 0 or 1;

$R^7$ and $R^8$ are independently selected from the group consisting of hydrogen and alkyl;

Ring B is selected from the group consisting of:




(i') Phenyl;

(ii') Naphthyl;

(iii') A 5 or 6 membered monocyclic heteroaryl group which has 1-3 heteroatoms independently selected from the group consisting of O, N and S;

and (iv') An 8 to 10 membered bicyclic heteroaryl group which has 1-3 heteroatoms independently selected from the group consisting of O, N and S;

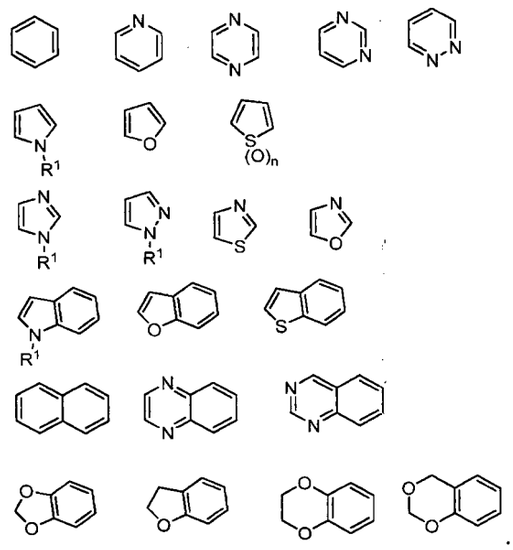
$R^{IV}$ represents optionally 1-3 substituents, independently selected from the group consisting of alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, aryloxy, arylalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and —$NR^9R^{10}$; wherein $R^9$ and $R^{10}$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalky;

and including any pharmaceutically acceptable salt or prodrug.

2. The compound according to claim 1, wherein X is NH.

3. The compound according to claim 1, wherein X is S.

4. The compound according to claim 1, wherein Ring A and Ring B are independently selected from the group consisting of



5. A compound according to claim 1 selected from the group consisting of :

(1') [({5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl} phenoxy)pyridin-2-yl]-1H-pyrrol-3-yl}carbonyl)amino]acetic acid;

(2') methyl [({5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl} phenoxy)pyridin-2-yl]-1H-pyrrol-3-yl}carbonyl)amino]acetate;

(3') ({[5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrol-3-yl]carbonyl}amino)acetic acid;

(4') methyl ({[5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrol-3-yl]carbonyl}amino)acetate;

(5') 5-[4-({3-[(3-methyl-2-furoyl)amino]phenyl}amino)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid;

(6') methyl 5-[4-({3-[(3-methyl-2-furoyl)amino]phenyl}amino)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(7') 5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-N-hydroxy-1H-pyrrole-3-carboxamide;

(8') 4-fluoro-N-(2-fluoro-5-methylphenyl)-3-[(2-{4-[(3-hydroxypiperidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]benzamide;

(9) N-(2,3-dihydroxypropyl)-5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy) pyridin-2-yl]-1H-pyrrole-3-carboxamide;

(10) N-(2-fluoro-5-methylphenyl)-3-[(2-{4-[(3-hydroxypyrrolidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]benzamide;

(11') 5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-N-hydroxy-1H-pyrrole-3-carboxamide;

(12') methyl 5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate;



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(13') 5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid;

(14') N-ethyl-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide;

(15') N-(2,3-dihydroxypropyl)-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide;

(16') 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide;

(17') N-hydroxy-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide;

(18') N-(3-{[2-(4-{[(3R)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-methyl-2-furamide;

(19') 5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid;

(20') methyl 5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(21') 2,3-dihydroxypropyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate;

(22') 5-[4-(3-{[(3-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid;

(23') methyl 5-[4-(3-{[(3-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(24') 2-hydroxyethyl 5-[4-(3-{[(3-methyl-2-thienyl)carbonyl]amino}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(25') 2-hydroxyethyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate;

(26') 5-[4-(3-{[(3-methyl-2-thienyl)carbonyl]amino}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid;

(27') methyl 5-[4-(3-{[(3-methyl-2-thienyl)carbonyl]amino}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(28') 5-(4-{4-fluoro-3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid;

(29') methyl 5-(4-{4-fluoro-3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate;

(30') N-[dimethyl(oxido)-lambda~4~-sulfanylidene]-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide;

(31') N-(3-{[2-(4-{[(3S)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-methyl-2-furamide;

(32') 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid;

(33') methyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate;

(34') 3-methyl-N-(3-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-2-furamide;

(35') methyl 4-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-2-carboxylate;

(36') 2-fluoro-5-methyl-N-(4-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)benzamide;
and (37') 3-methyl-N-(4-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-2-furamide.

6. The compound according to claim 1 provided that when Ring B is pyrazole, $R^{IV}$ is not a phenyl or substituted phenyl.

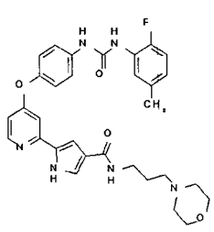
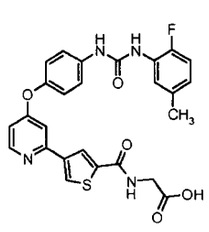
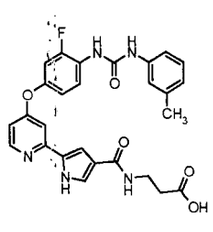
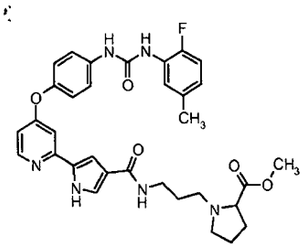
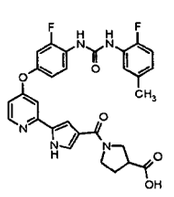
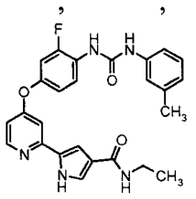
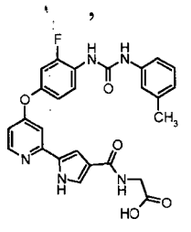
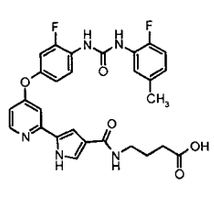
7. A compound according to claim 6, wherein Y is selected from the group consisting of

(1') —$(CH_2)g$—O—$(CH_2)h$—;
(2') —$(CH_2)g$—$NR^1$—$(CH_2)h$—;
(3') —$(CH_2)g$—$S(O)_n$—$(CH_2)h$—;
(4') —$(CH_2)g$—$SO_2N\ R^2$—$(CH_2)h$—;
(5') —$(CH_2)g$—$NR^2SO_2$—$(CH_2)h$—;
(6') —$(CH_2)g$— CO—$(CH_2)h$—;
(7') —$(CH_2)g$— $C(O)NR^2$—$(CH_2)h$—;
(8') —$(CH_2)g$— $NR^2C(O)$—$(CH_2)h$—;
(9') —$(CH_2)g$— $NR^2C(O)NR^3$—$(CH_2)h$—;
and (10') a single bond.

8. The compound according to claim 1, wherein X is S.

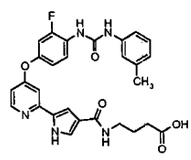
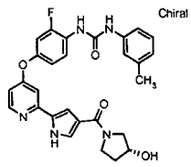
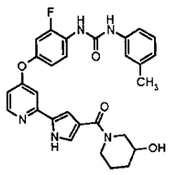
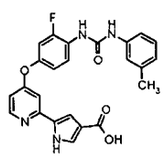
9. The compound according to claim 1, wherein X is NH.

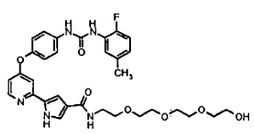
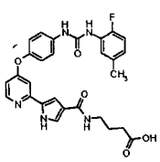
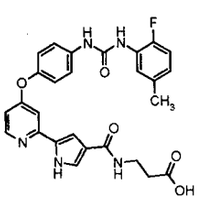
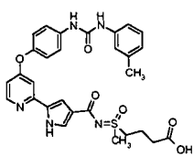
10. A compound according to claim 1 selected from the group consisting of

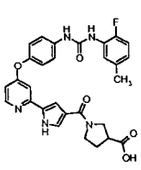
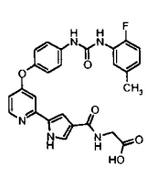
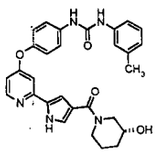
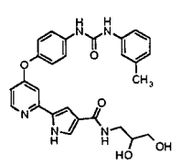









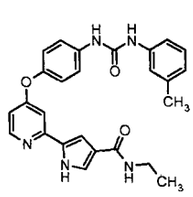
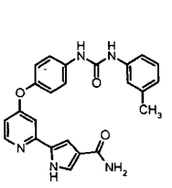
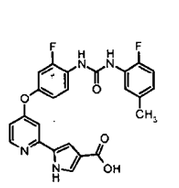
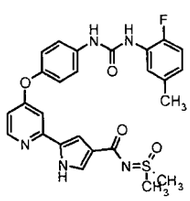


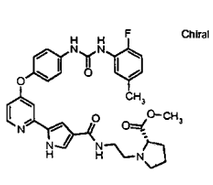
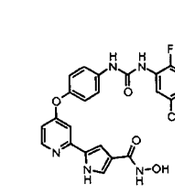
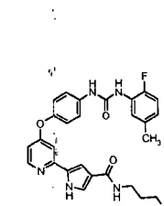
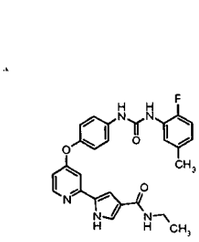
358

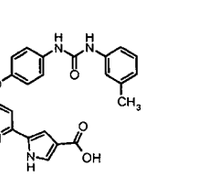
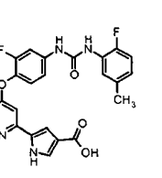
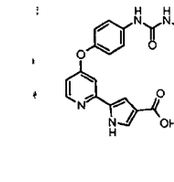
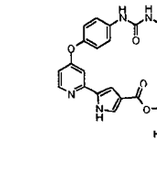

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Chiral
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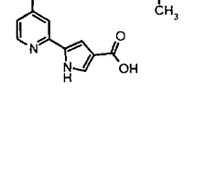
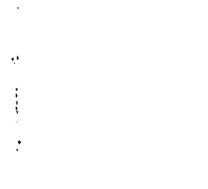

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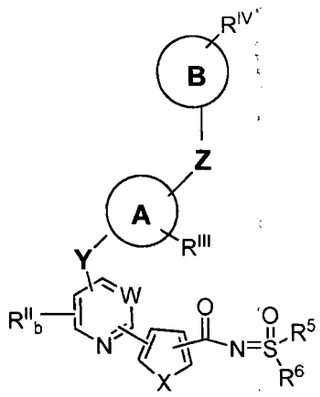

Chiral
,

,

,



,

,



,

11. A compound represented by Formula II:




Formula II

wherein

W is C or N;

X is selected from the group consisting of $NR^1$, O, and $S(O)_n$;

n is 0 or an integer of from 1 to 2;

$R^1$ is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, $CF_3$, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N $R^2R^3$), wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

$R^5$ and $R^6$ are independently selected from the group consisting of hydrogen, halo, hydroxyl, $C_1$-$C_8$ alkyl, $C_1$-$C_8$ hydroxyalkyl, $C_1$-$C_8$ alkoxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, hydroxycarbonyl, hydroxycarbonylalkyl, amide, alkylamide, amidoalkyl, and sulfonate;

$R^{II}$ is independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkyl, aryloxy, aryloxyalkyl, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkoxy, hydroxyalkyl, ($NR^2R^3$)alkoxy, ($NR^2R^3$)alkenyl, ($NR^2R^3$)alkyl, ($NR^2R^3$)carbonylalkenyl, and ($NR^2R^3$)carbonylalkyl, wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

b is 0 or an integer of from 1 to 2;

Y is selected from the group consisting of:



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(1') —$(CH_2)g$—O—$(CH_2)h$—;
(2') —$(CH_2)g$—$NR^1$—$(CH_2)h$—;
(3') —$(CH_2)g$—$S(O)_n$—$(CH_2)h$—;
(4') —$(CH_2)g$—$SO_2N\ R^2$—$(CH_2)h$—;
(5') —$(CH_2)g$—$NR^2SO_2$—$(CH_2)h$—;
(6') —$(CH_2)g$— CO—$(CH_2)h$—;
(7') —$(CH_2)g$— $C(O)NR^2$—$(CH_2)h$—;
(8') —$(CH_2)g$— $NR^2C(O)$—$(CH_2)h$—;
(9') —$(CH_2)g$—C≡C—$(CH_2)h$—;
(10') —$(CH_2)g$— $NR^2C(O)NR^3$—$(CH_2)h$—;
(11') —$(CH_2)g$—$(CH_2)h$—;
(12') —$(CH_2)g$—$CF_2$—$(CH_2)h$—;
(13') —$(CH_2)g$—$CCl_2$—$(CH_2)h$—;
(14') —$(CH_2)g$—CHF—$(CH_2)h$—;
(15') —$(CH_2)g$—CH(OH)—$(CH_2)h$—;
(16') —$(CH_2)g$—$CR^2R^3$—$(CH_2)h$—;
(17') —$(CH_2)g$—C=C—$(CH_2)h$—;
and (18') a single bond;

wherein

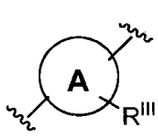
g is 0 or an integer of from 1 to 3;

h is 0 or an integer of from 1 to 3;

$R^1$ is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, $CF_3$, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl($NR^2R^3$), wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

$R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered cyclic ring;

Ring A is selected from the group consisting of:



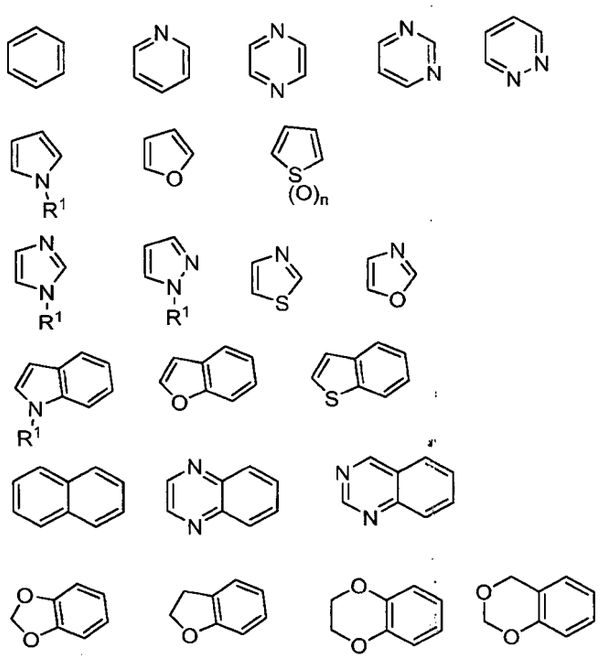

(i) Phenyl;
(ii) Naphthyl;



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(iii) A 5 or 6 membered monocyclic heteroaryl group which have 1-5 heteroatoms independently selected from the group consisting of O, N and S;
and (iv) An 8 to 10 membered bicyclic heteroaryl group which have 1-6 heteroatoms independently selected from the group consisting of O, N and S;

Ring A can be illustrated but not limited to the following:



wherein

$R^1$ is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, $CF_3$, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N $R^2R^3$), wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

$R^{III}$ represents optionally 1-3 substituents independently selected from the group consisting of $C_1$-$C_5$ linear or branched alkyl, $C_1$-$C_5$ linear or branched haloalkyl, $C_1$-$C_5$ alkoxy, hydroxy, amino, $C_1$-$C_5$ alkylamino, C1-C6 dialkylamino, halogen, cyano, and nitro;

Z is selected from the group consisting of

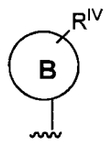
(1') $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$;
(2') $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$;
(3') $(CH_2)_iN(R^7)C(O)$;
(4') $C(O)N(R^8)(CH_2)_j$;



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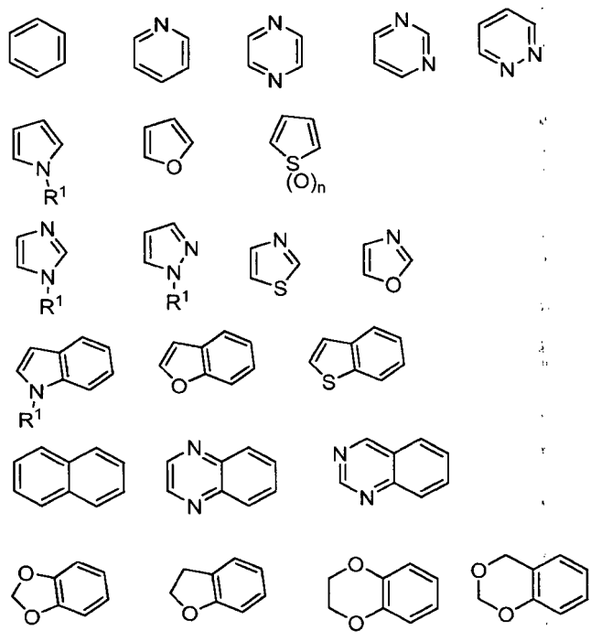
(5') $(CH_2)_iN(R^7)S(O)_2$;
and (6') $S(O)_2N(R^8)(CH_2)_j$;
wherein
i is 0 or 1;
j is 0 or 1;
$R^7$ and $R^8$ are independently selected from the group consisting of hydrogen and alkyl.

Ring B is selected from the group consisting of:




(i') Phenyl;
(ii') Naphthyl;
(iii') A 5 or 6 membered monocyclic heteroaryl group which have 1-3 heteroatoms independently selected from the group consisting of O, N and S;
and (iv') An 8 to 10 membered bicyclic heteroaryl group which have 1-3 heteroatoms independently selected from the group consisting of O, N and S;

Ring B can be illustrated but not limited to the following:



wherein



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$R^1$ is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, $CF_3$, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl($NR^2R^3$), wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$ and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

$R^{IV}$ represents optionally 1-3 substituents, independently selected from the group consisting of alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, aryloxy, arylalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and $—NR^9R^{10}$; wherein $R^9$ and $R^{10}$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

and including any pharmaceutically acceptable salt or prodrug.

12. The compound of claim 12, wherein Z is selected from the group consisting of $(CH_2)_iN(R^7)C(O)$, $C(O)N(R^8)(CH_2)_j$, $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$ and $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$.

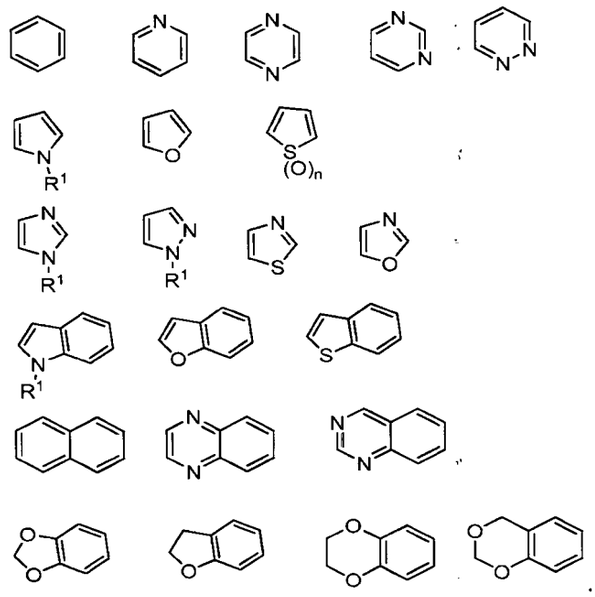
13. The compound of claim 12, wherein Y is selected from the group consisting of
(1') $—(CH_2)g—O—(CH_2)h—$;
(2') $—(CH_2)g—NR^1—(CH_2)h—$;
(3') $—(CH_2)g—S(O)_n—(CH_2)h—$;
(4') $—(CH_2)g—SO_2N\ R^2—(CH_2)h—$;
(5') $—(CH_2)g—NR^2SO_2—(CH_2)h—$;
(6') $—(CH_2)g—\ CO—(CH_2)h—$;
(7') $—(CH_2)g—\ C(O)NR^2—(CH_2)h—$;
(8') $—(CH_2)g—\ NR^2C(O\ )—(CH_2)h—$;
(9') $—(CH_2)g—C\equiv C—(CH_2)h—$;
(10') $—(CH_2)g—\ NR^2C(O)NR^3—(CH_2)h—$;
and (11') a single bond.

14. The compound of claim 12, wherein W is C.

15. The compound of claim 12, wherein Ring A and Ring B are independently selected from the group consisting of



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16. The compounds of claims 1 for use as a tyrosine kinase inhibitor.

17. The compound according to claim 1 which is used for the treatment of one of the diseases or conditions selected from the group consisting of colorectal cancer, lung cancer, hematological cancer, renal cancer, liver cancer, breast cancer, diabetic retinopathy, macular degeneration, age-related macular degeneration, retinopathy of prematurity, ocular angiogenesis, retinal edema, retinal ischemia, diabetic macular edema, cystoid macular edema, retinal vein occlusion, branch vein occlusion, preretinal neovascularization, laser-induced choroidal neovascularization, neovascularization associated with keratoplasty, glaucoma and ocular tumors, arthritis, restenosis, hepatic cirrhosis, atherosclerosis, psoriasis, diabetes mellitus, wound healing, inflammation, neurodegenerative diseases and immune disorders in the human being.

18. A pharmaceutical composition comprising of a therapeutic effective amount of the compounds of claim 1 , together with a pharmaceutically acceptable carrier therefor.

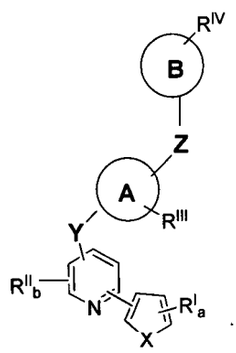
19. The pharmaceutical composition of claim 18, wherein the composition comprises of tablets, capsules, intravenous injections, intramuscular injections, local injections, topical creams, gels and ointments, eye drops, eye ointments, eye sprays, ophthalmic suspensions, ophthalmic emulsions, intravitreal injections, subtenon injections, ophthalmic biodrodible implant, and non-bioeordible ophthalmic inserts and depots.



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## ABSTRACT

The present invention is directed to novel compounds of Formula I. The compounds of the present invention are potent tyrosine kinase modulators, and are suitable for the treatment and prevention of diseases and conditions related to abnormal activities of tyrosine kinase receptors.




Formula I

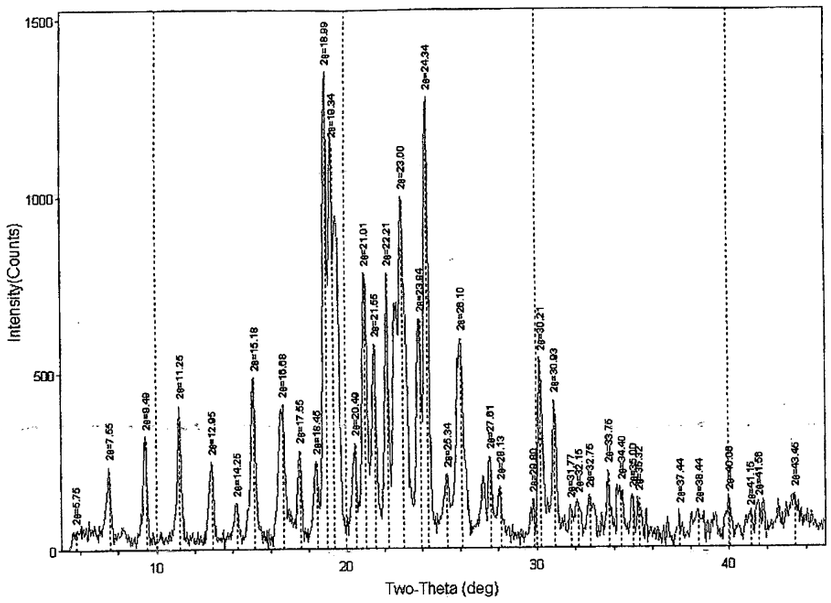

Intensity(Counts)
Two-Theta (deg)
1500
1000
500
0
10
20
30
40
2θ=5.75
2θ=7.55
2θ=9.49
2θ=11.25
2θ=12.95
2θ=14.25
2θ=15.18
2θ=16.68
2θ=17.55
2θ=18.45
2θ=18.89
2θ=19.34
2θ=20.49
2θ=21.01
2θ=21.65
2θ=22.21
2θ=23.00
2θ=23.64
2θ=24.34
2θ=26.10
2θ=26.34
2θ=27.61
2θ=28.19
2θ=30.21
2θ=30.83
2θ=31.77
2θ=32.15
2θ=32.76
2θ=33.76
2θ=34.40
2θ=37.44
2θ=38.44
2θ=40.08
2θ=41.15
2θ=41.56
2θ=43.46

Figure 1.

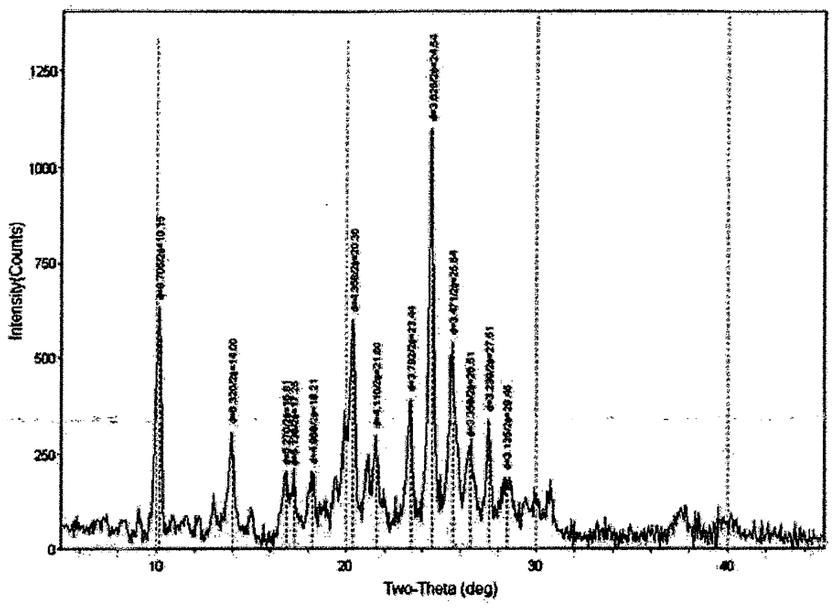

Intensity(Counts)
1250
1000
750
500
250
0
10
20
30
40
Two-Theta (deg)

Figure 2

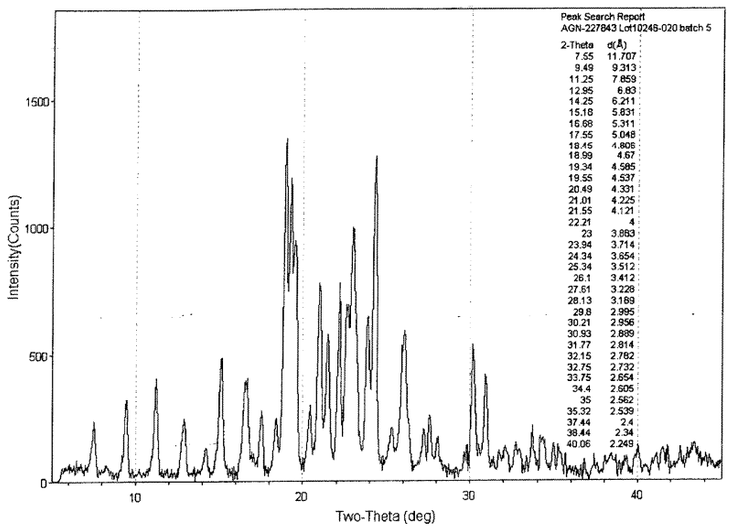

Peak Search Report
AGN-227843 Lot10246-020 batch 5
2-Theta d(Å)
7.55 11.707
9.49 9.313
11.25 7.859
12.95 6.83
14.25 6.211
15.18 5.831
16.68 5.311
17.55 5.048
18.45 4.806
18.99 4.67
19.34 4.585
19.55 4.537
20.49 4.331
21.01 4.225
21.55 4.121
22.21 4
23 3.863
23.94 3.714
24.34 3.654
25.34 3.512
26.1 3.412
27.61 3.228
28.13 3.169
29.8 2.995
30.21 2.956
30.93 2.889
31.77 2.814
32.15 2.782
32.75 2.732
33.75 2.654
34.4 2.605
35 2.562
35.32 2.539
37.44 2.4
38.44 2.34
40.06 2.249
Intensity(Counts)
0
500
1000
1500
10
20
30
40
Two-Theta (deg)

Figure 1.

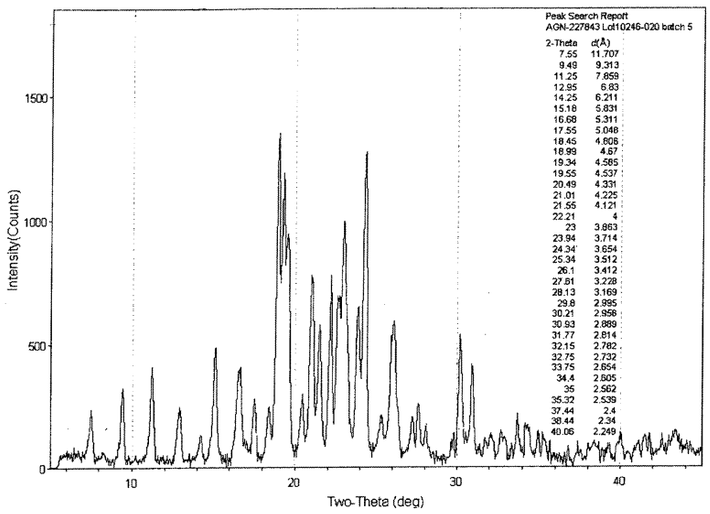

Peak Search Report
AGN-227843 Lot10246-020 batch 5
2-Theta d(Å)
7.55 11.707
9.48 9.313
11.25 7.859
12.95 6.83
14.25 6.211
15.18 5.831
16.68 5.311
17.55 5.048
18.45 4.808
18.99 4.67
19.34 4.585
19.55 4.537
20.49 4.331
21.01 4.225
21.55 4.121
22.21 4
23 3.863
23.94 3.714
24.34 3.654
25.34 3.512
26.1 3.412
27.81 3.228
28.13 3.169
29.8 2.995
30.21 2.958
30.93 2.889
31.77 2.814
32.15 2.782
32.75 2.732
33.75 2.654
34.4 2.605
35 2.562
35.32 2.539
37.44 2.4
38.44 2.34
40.06 2.249
Intensity(Counts)
1500
1000
500
0
10
20
30
40
Two-Theta (deg)

Figure 2.

300

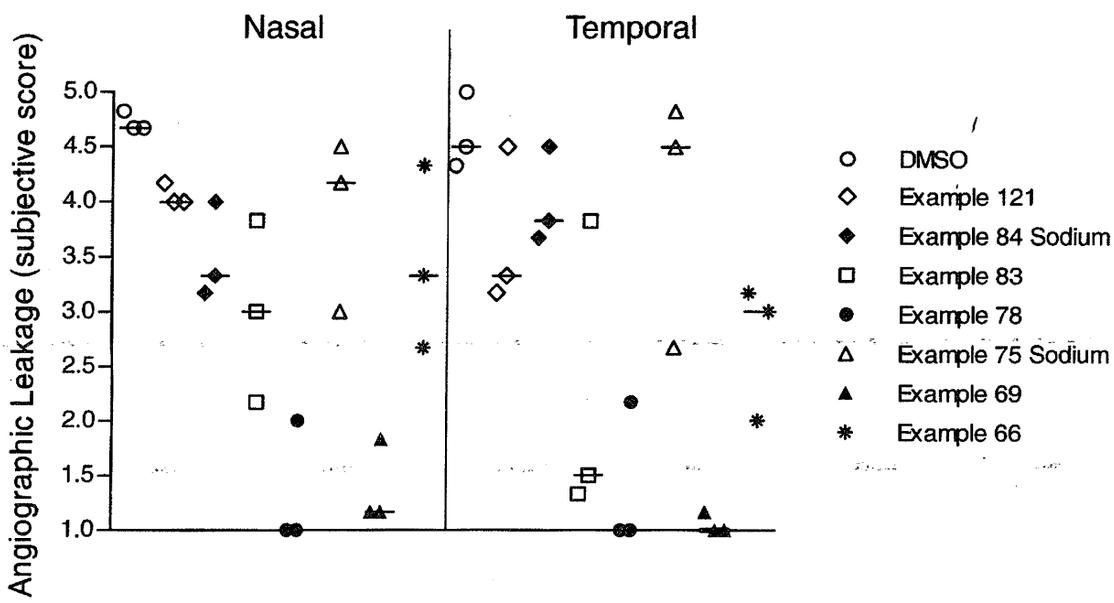

Day 3 Post-treatment (100 ug)
Nasal
Temporal
Angiographic Leakage (subjective score)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
DMSO
Example 121
Example 84 Sodium
Example 83
Example 78
Example 75 Sodium
Example 69
Example 66

Figure 3

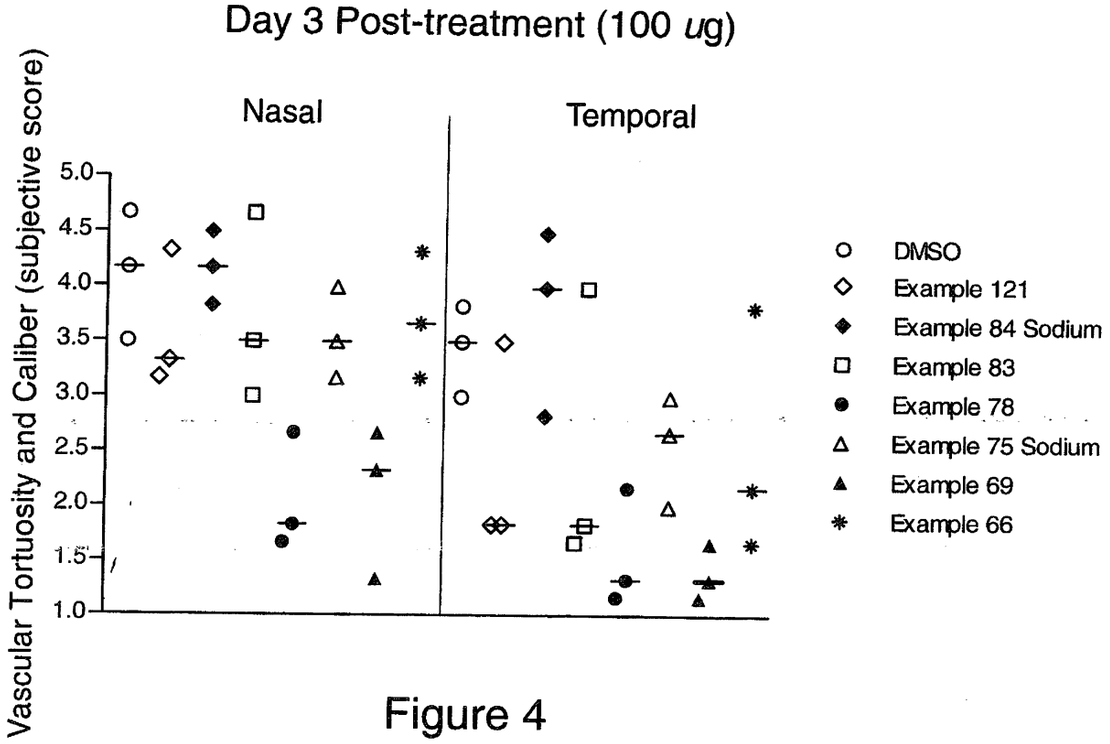

Day 3 Post-treatment (100 ug)
Nasal
Temporal
Vascular Tortuosity and Caliber (subjective score)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
DMSO
Example 121
Example 84 Sodium
Example 83
Example 78
Example 75 Sodium
Example 69
Example 66

Figure 4

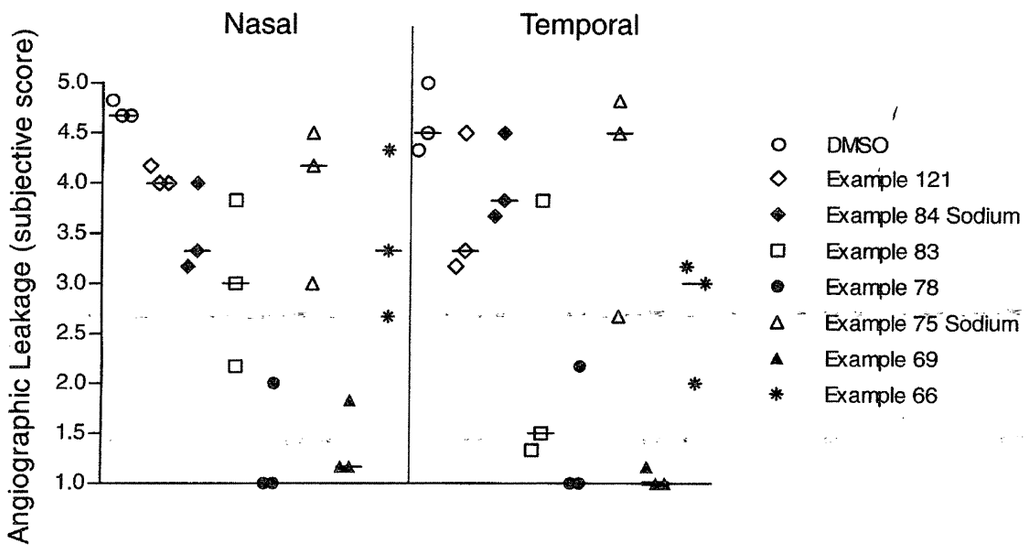

Day 3 Post-treatment (100 ug)
Nasal
Temporal
Angiographic Leakage (subjective score)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
DMSO
Example 121
Example 84 Sodium
Example 83
Example 78
Example 75 Sodium
Example 69
Example 66

Figure 3

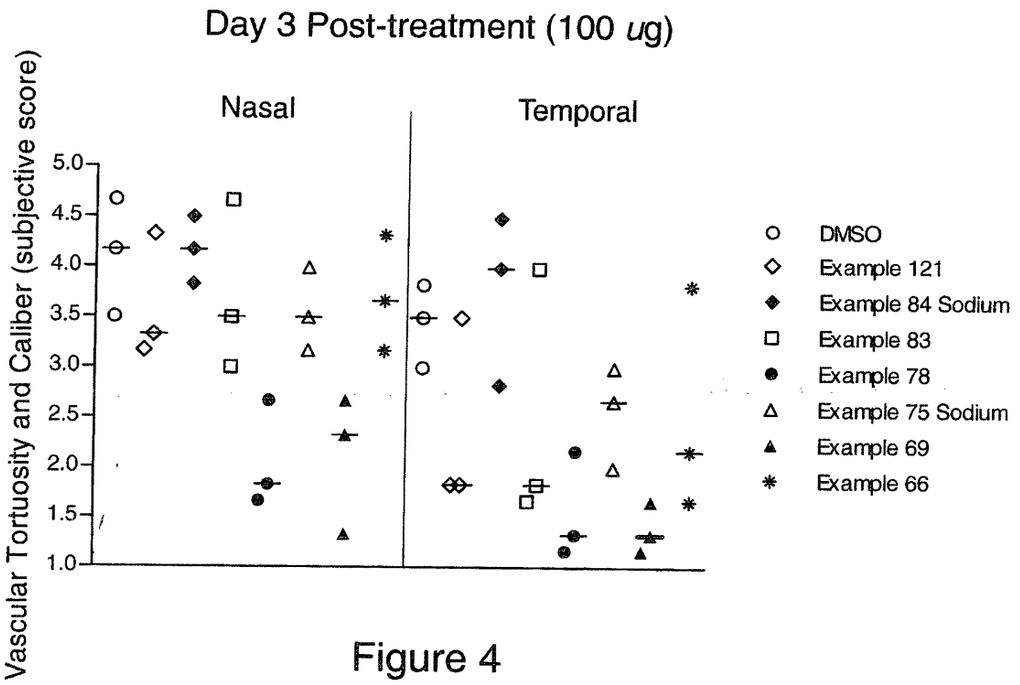
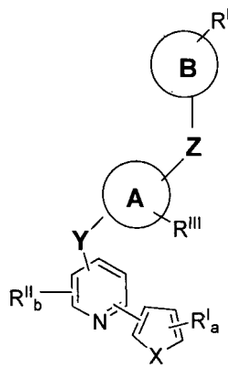

Day 3 Post-treatment (100 ug)
Nasal
Temporal
Vascular Tortuosity and Caliber (subjective score)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
DMSO
Example 121
Example 84 Sodium
Example 83
Example 78
Example 75 Sodium
Example 69
Example 66

Figure 4

We claim:

1. A compound represented by Formula I:




Formula I

wherein

X is selected from the group consisting of $NR^1$, O, and $S(O)_n$;

n is 0 or an integer of from 1 to 2;

$R^1$ is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, $CF_3$, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N $R^2R^3$), wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

$R^I$ is selected from the group consisting of hydrogen, halogen, $C_1$ to $C_8$ alkyl, $S(O)_fR^4$, $(CR^5R^6)_dC(O)OR^4$, $S(O)_f(CR^5R^6)_dC(O)OR^4$, $(CR^5R^6)_dAr$, $NR^4(CR^5R^6)_dAr$, $O(CR^5R^6)_dAr$, $S(O)_f(CR^5R^6)_dAr$, $(CR^5R^6)_dS(O)_fR^4$, $NR^4(CR^5R^6)_dS(O)_fR^4$, $O(CR^5R^6)_d$ $S(O)_fR^4$, $S(O)_f(CR^5R^6)_eS(O)_fR^4$, $(CR^5R^6)_dC(O)N(R^4)_2$, $NR^4(CR^5R^6)_dC(O)N(R^4)_2$, $O(CR^5R^6)_dC(O)N(R^4)_2$, $S(O)_f(CR^5R^6)_eC(O)N(R^4)_2$, $(CR^5$ $R^6)_dOR^4$, $S(O)_f(CR^5R^6)_dOR^4$, $(CR^5$ $R^6)_dOSO_2R^4$, $S(O)_f(CR^5$ $R^6)_eOSO_2R^4$, $(CR^5$ $R^6)_dP(O)(OR^4)_2$, $S(O)_f(CR^5$ $R^6)_eP(O)(OR^4)_2$, $OC(O)(CR^5R^6)_dN(R^4)_2$, $C(O)(CR^5R^6)_dN(R^4)_2$, $C(O)N=S(O)R^5$ $R^6$, $NR^2C(O)(CR^5R^6)_dN(R^4)_2$, $(CR^5R^6)_dR^5$, $S(O)_f(CR^5R^6)_dR^5$, $HNC(O)R^4$, $HN\text{-}C(O)OR^4$, $(CR^5R^6)_dN(R^4)_2$, $S(O)_f$ $(CR^5R^6)_dN(R^4)_2$, $OC(O)OR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dR^4$, $(CR^5R^6)_dC(O)(CR^5R^6)_dOR^4$, and $(CR^5R^6)_dC(O)(CR^5R^6)_dN(R^4)_2$, wherein each $R^4$ is independently selected from the group consisting of hydrogen, hydroxyl, $C_1$-$C_8$ alkyl, aryl, $C_1$-$C_8$ hydroxyalkyl, $C_1$-$C_8$ alkoxyalkyl, $(CR^5R^6)_d$ and $N(R^4)_2$ may form a 3-7 membered heterocyclic ring, comprising of aziridine, azetidine, pyrrolidine, 5-fluoropyrrolidine, piperidine, 6-fluoropiperidine, N-methylpiperazine, morpholine, 2,6-dimethylmorpholine, thiomorpholine, and wherein said heterocyclic ring may be optionally substituted with up to three of $R^5$; wherein $R^5$ and $R^6$ are independently selected from the group consisting of hydrogen, halo, hydroxyl, $C_1$-$C_8$ alkyl, $C_1$-$C_8$ hydroxyalkyl, $C_1$-$C_8$ alkoxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, hydroxycarbonyl, hydroxycarbonylalkyl, amide, alkylamide, amidoalkyl, sulfonate and $CR^5R^6$ may represent a carbocyclic or heterocyclic ring of from 5 to 6 carbons or alternatively,



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$(CR^5R^6)_d$ and $(CR^5R^6)_e$ may form a 3-7 membered carbocyclic or heterocyclic ring, wherein the ring may be optionally substituted with up to three of hydroxyl, halo, $C_1$-$C_8$ alkyl, $C_1$-$C_8$ hydroxyalkyl, $C_1$-$C_8$ alkoxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, hydroxycarbonyl, hydroxycarbonylalkyl, amide, alkylamide, amidoalkyl and sulfonate;

a is 0 or an integer of from 1 to 3;

d is 0 or an integer of from 1 to 5;

e is an integer of from 1 to 4;

f is 0 or an integer of from 1 to 2;

$R^{II}$ is independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkyl, aryloxy, aryloxyalkyl, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkoxy, hydroxyalkyl, $(NR^2R^3)$alkoxy, $(NR^2R^3)$alkenyl, $(NR^2R^3)$alkyl, $(NR^2R^3)$carbonylalkenyl, and $(NR^2R^3)$carbonylalkyl, wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

b is 0 or an integer of from 1 to 2;

Y is selected from the group consisting of:

(1') —$(CH_2)g$—O—$(CH_2)h$—;

(2') —$(CH_2)g$—$NR^1$—$(CH_2)h$—;

(3') —$(CH_2)g$—$S(O)_n$—$(CH_2)h$—;

(4') —$(CH_2)g$—$SO_2N\ R^2$—$(CH_2)h$—;

(5') —$(CH_2)g$—$NR^2SO_2$—$(CH_2)h$—;

(6') —$(CH_2)g$— CO—$(CH_2)h$—;

(7') —$(CH_2)g$— $C(O)NR^2$—$(CH_2)h$—;

(8') —$(CH_2)g$— $NR^2C(O)$—$(CH_2)h$—;

(9') —$(CH_2)g$—C≡C—$(CH_2)h$—;

(10') —$(CH_2)g$— $NR^2C(O)NR^3$—$(CH_2)h$—;

(11') —$(CH_2)g$—$(CH_2)h$—;

(12') —$(CH_2)g$—$CF_2$—$(CH_2)h$—;

(13') —$(CH_2)g$—$CCl_2$—$(CH_2)h$—;

(14') —$(CH_2)g$—CHF—$(CH_2)h$—;

(15') —$(CH_2)g$—CH(OH)—$(CH_2)h$—;

(16') —$(CH_2)g$—$CR^2R^3$—$(CH_2)h$—;

(17') —$(CH_2)g$—C=C—$(CH_2)h$—;

and (18') a single bond;



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wherein

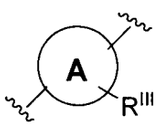
g is 0 or an integer of from 1 to 3;

h is 0 or an integer of from 1 to 3;

$R^1$ is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, $CF_3$, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N $R^2R^3$), wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

$R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered cyclic ring;

Ring A is selected from the group consisting of:




(i) Phenyl;

(ii) Naphthyl;

(iii) A 5 or 6 membered monocyclic heteroaryl group which have 1-5 heteroatoms independently selected from the group consisting of O, N and S;

and (iv) An 8 to 10 membered bicyclic heteroaryl group which have 1-6 heteroatoms independently selected from the group consisting of O, N and S;

$R^{III}$ represents optionally 1-3 substituents independently selected from the group consisting of $C_1$-$C_5$ linear or branched alkyl, $C_1$-$C_5$ linear or branched haloalkyl, $C_1$-$C_5$ alkoxy, hydroxy, amino, $C_1$-$C_5$ alkylamino, $C_1$-$C_6$ dialkylamino, halogen, cyano, and nitro;

Z is selected from the group consisting of

(1') $(CH_2)_iN(R^7)C(O)$;

(2') $C(O)N(R^8)(CH_2)_j$;

(3') $(CH_2)_iN(R^7)S(O)_2$;

and (4') $S(O)_2N(R^8)(CH_2)_j$.

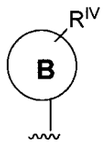
wherein:

i is 0 or 1;

j is 0 or 1;

$R^7$ and $R^8$ are independently selected from the group consisting of hydrogen and alkyl;

Ring B is selected from the group consisting of:




(i') Phenyl;

(ii') Naphthyl;

(iii') A 5 or 6 membered monocyclic heteroaryl group which has 1-3 heteroatoms independently selected from the group consisting of O, N and S;

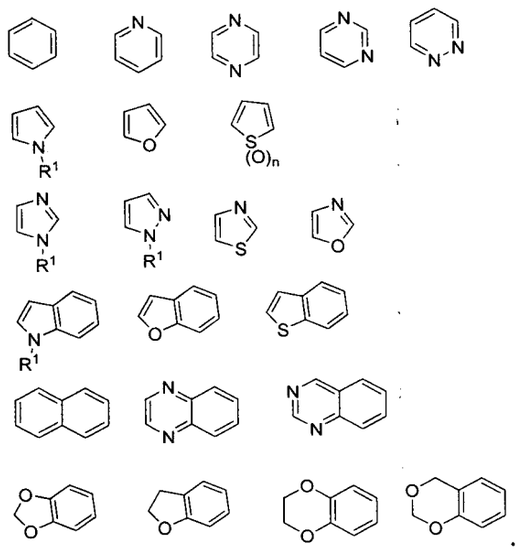
and (iv') An 8 to 10 membered bicyclic heteroaryl group which has 1-3 heteroatoms independently selected from the group consisting of O, N and S;

$R^{IV}$ represents optionally 1-3 substituents, independently selected from the group consisting of alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, aryloxy, arylalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and —$NR^9R^{10}$; wherein $R^9$ and $R^{10}$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalky;

and including any pharmaceutically acceptable salt or prodrug.

2. The compound according to claim 1, wherein X is NH or S.

3. The compound according to claim 1, wherein Ring A and Ring B are independently selected from the group consisting of



4. A compound according to claim 1 selected from the group consisting of :

(1') [({5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl} phenoxy)pyridin-2-yl]-1H-pyrrol-3-yl}carbonyl)amino]acetic acid;

(2') methyl [({5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl} phenoxy)pyridin-2-yl]-1H-pyrrol-3-yl}carbonyl)amino]acetate;



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(3') ({[5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrol-3-yl]carbonyl}amino)acetic acid;

(4') methyl ({[5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrol-3-yl]carbonyl}amino)acetate;

(5') 5-[4-({3-[(3-methyl-2-furoyl)amino]phenyl}amino)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid;

(6') methyl 5-[4-({3-[(3-methyl-2-furoyl)amino]phenyl}amino)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(7') 5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-N-hydroxy-1H-pyrrole-3-carboxamide;

(8') 4-fluoro-N-(2-fluoro-5-methylphenyl)-3-[(2-{4-[(3-hydroxypiperidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]benzamide;

(9) N-(2,3-dihydroxypropyl)-5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy) pyridin-2-yl]-1H-pyrrole-3-carboxamide;

(10) N-(2-fluoro-5-methylphenyl)-3-[(2-{4-[(3-hydroxypyrrolidin-1-yl)carbonyl]-1H-pyrrol-2-yl}pyridin-4-yl)oxy]benzamide;

(11') 5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-N-hydroxy-1H-pyrrole-3-carboxamide;

(12') methyl 5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(13') 5-[4-(2-fluoro-5-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid;

(14') N-ethyl-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide;

(15') N-(2,3-dihydroxypropyl)-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide;

(16') 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide;

(17') N-hydroxy-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide;

(18') N-(3-{[2-(4-{[(3R)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-methyl-2-furamide;

(19') 5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid;

(20') methyl 5-[4-(3-{[(2-fluoro-5-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(21') 2,3-dihydroxypropyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate;

(22') 5-[4-(3-{[(3-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid;

(23') methyl 5-[4-(3-{[(3-methylphenyl)amino]carbonyl}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(24') 2-hydroxyethyl 5-[4-(3-{[(3-methyl-2-thienyl)carbonyl]amino}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(25') 2-hydroxyethyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate;

(26') 5-[4-(3-{[(3-methyl-2-thienyl)carbonyl]amino}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylic acid;

(27') methyl 5-[4-(3-{[(3-methyl-2-thienyl)carbonyl]amino}phenoxy)pyridin-2-yl]-1H-pyrrole-3-carboxylate;

(28') 5-(4-{4-fluoro-3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid;

(29') methyl 5-(4-{4-fluoro-3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate;

(30') N-[dimethyl(oxido)-lambda~4~-sulfanylidene]-5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxamide;

(31') N-(3-{[2-(4-{[(3S)-3-hydroxypyrrolidin-1-yl]carbonyl}-1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-3-methyl-2-furamide;

(32') 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylic acid;

(33') methyl 5-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-3-carboxylate;

(34') 3-methyl-N-(3-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-2-furamide;

(35') methyl 4-(4-{3-[(3-methyl-2-furoyl)amino]phenoxy}pyridin-2-yl)-1H-pyrrole-2-carboxylate;

(36') 2-fluoro-5-methyl-N-(4-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)benzamide;

and (37') 3-methyl-N-(4-{[2-(1H-pyrrol-2-yl)pyridin-4-yl]oxy}phenyl)-2-furamide.

5. The compound according to claim 1 provided that when Ring B is pyrazole, $R^{IV}$ is not a phenyl or substituted phenyl.

6. A compound according to claim 6, wherein Y is selected from the group consisting of

(1') —$(CH_2)g$—O—$(CH_2)h$—;

(2') —$(CH_2)g$—$NR^1$—$(CH_2)h$—;

(3') —$(CH_2)g$—$S(O)_n$—$(CH_2)h$—;

(4') —$(CH_2)g$—$SO_2N\ R^2$—$(CH_2)h$—;

(5') —$(CH_2)g$—$NR^2SO_2$—$(CH_2)h$—;

(6') —$(CH_2)g$— CO—$(CH_2)h$—;

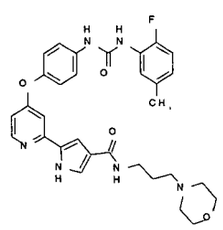
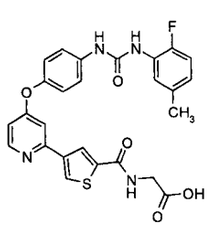
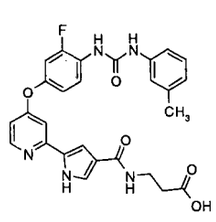
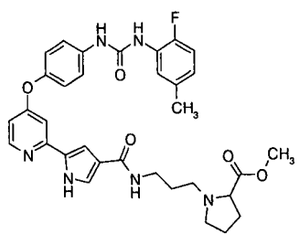
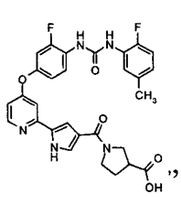
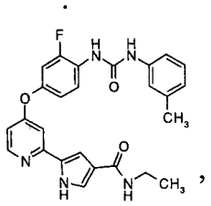
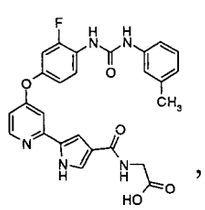
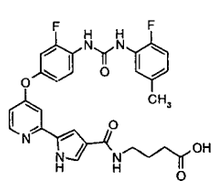
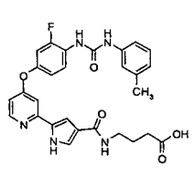
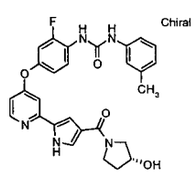
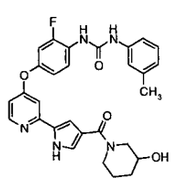
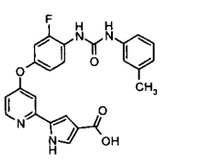
(7') —$(CH_2)g$— $C(O)NR^2$—$(CH_2)h$—;

(8') —$(CH_2)g$— $NR^2C(O)$—$(CH_2)h$—;

(9') —$(CH_2)g$— $NR^2C(O)NR^3$—$(CH_2)h$—;

and (10') a single bond.

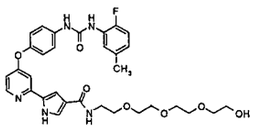
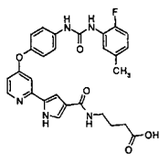
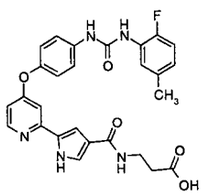
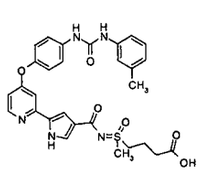
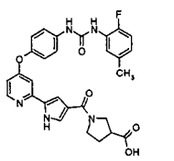
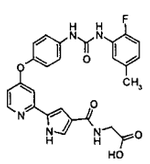
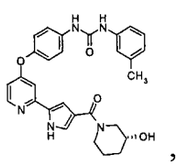
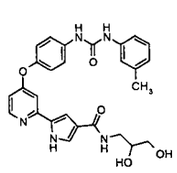
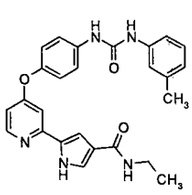
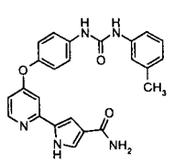
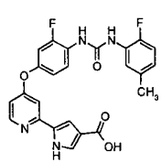
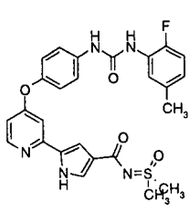
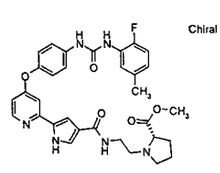
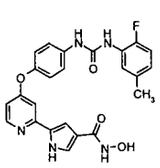
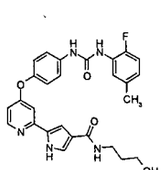
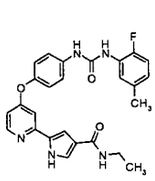
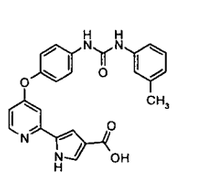
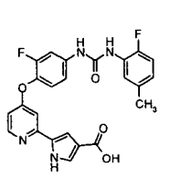
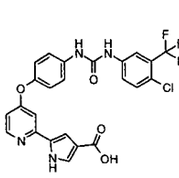
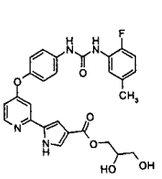
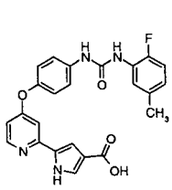
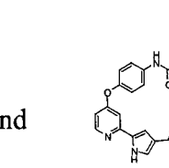
7. A compound according to claim 1 selected from the group consisting of

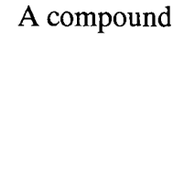
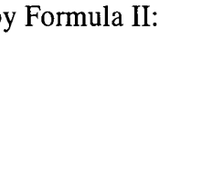


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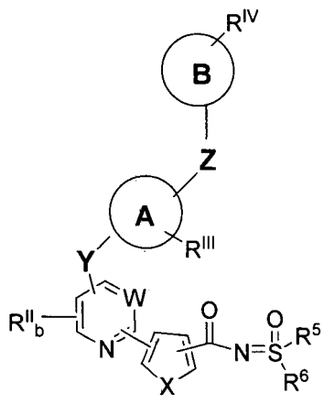
,

and

;

or a pharmaceutically acceptable salt thereof.

8. A compound represented by Formula II:



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Formula II

wherein

W is C or N;

X is selected from the group consisting of $NR^1$, O, and $S(O)_n$;

n is 0 or an integer of from 1 to 2;

$R^1$ is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, $CF_3$, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N $R^2R^3$), wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

$R^5$ and $R^6$ are independently selected from the group consisting of hydrogen, halo, hydroxyl, $C_1$-$C_8$ alkyl, $C_1$-$C_8$ hydroxyalkyl, $C_1$-$C_8$ alkoxyalkyl, alkoxycarbonylalkyl, alkoxycarbonyl, hydroxycarbonyl, hydroxycarbonylalkyl, amide, alkylamide, amidoalkyl, and sulfonate;

$R^{II}$ is independently selected from the group consisting of hydrogen, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkyl, aryloxy, aryloxyalkyl, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkoxy, hydroxyalkyl, ($NR^2R^3$)alkoxy, ($NR^2R^3$)alkenyl, ($NR^2R^3$)alkyl, ($NR^2R^3$)carbonylalkenyl, and ($NR^2R^3$)carbonylalkyl, wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

b is 0 or an integer of from 1 to 2;

Y is selected from the group consisting of:

(1') —$(CH_2)$g—O—$(CH_2)$h—;
(2') —$(CH_2)$g—$NR^1$—$(CH_2)$h—;
(3') —$(CH_2)$g—$S(O)_n$—$(CH_2)$h—;
(4') —$(CH_2)$g—$SO_2N\ R^2$—$(CH_2)$h—;
(5') —$(CH_2)$g—$NR^2SO_2$—$(CH_2)$h—;
(6') —$(CH_2)$g— CO—$(CH_2)$h—;
(7') —$(CH_2)$g— $C(O)NR^2$—$(CH_2)$h—;
(8') —$(CH_2)$g— $NR^2C(O\ )$—$(CH_2)$h—;



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(9') —$(CH_2)g$—C≡C—$(CH_2)h$—;
(10') —$(CH_2)g$— $NR^2C(O)NR^3$—$(CH_2)h$—;
(11') —$(CH_2)g$—$(CH_2)h$—;
(12') —$(CH_2)g$—$CF_2$—$(CH_2)h$—;
(13') —$(CH_2)g$—$CCl_2$—$(CH_2)h$—;
(14') —$(CH_2)g$—CHF—$(CH_2)h$—;
(15') —$(CH_2)g$—CH(OH)—$(CH_2)h$—;
(16') —$(CH_2)g$—$CR^2R^3$—$(CH_2)h$—;
(17') —$(CH_2)g$—C=C—$(CH_2)h$—;
and (18') a single bond;

wherein

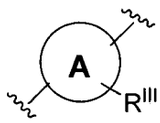
g is 0 or an integer of from 1 to 3;

h is 0 or an integer of from 1 to 3;

$R^1$ is independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, $CF_3$, alkyl, alkylcarbonyl, alkoxycarbonyl, aryl, heterocycloalkyl, hydroxyalkyl, and alkyl(N $R^2R^3$), wherein $R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered heterocyclic ring with N;

$R^2$ and $R^3$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, haloalkylsulfonyl, and heterocyclylsulfonyl; alternatively $R^2$and $R^3$ and may be taken together to form a 5-7 membered cyclic ring;

Ring A is selected from the group consisting of:




(i) Phenyl;
(ii) Naphthyl;
(iii) A 5 or 6 membered monocyclic heteroaryl group which have 1-5 heteroatoms independently selected from the group consisting of O, N and S;
and (iv) An 8 to 10 membered bicyclic heteroaryl group which have 1-6 heteroatoms independently selected from the group consisting of O, N and S;

$R^{III}$ represents optionally 1-3 substituents independently selected from the group consisting of $C_1$-$C_5$ linear or branched alkyl, $C_1$-$C_5$ linear or branched haloalkyl, $C_1$-$C_5$ alkoxy, hydroxy, amino, $C_1$-$C_5$ alkylamino, C1-C6 dialkylamino, halogen, cyano, and nitro;

Z is selected from the group consisting of

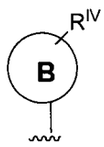
(1') $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$;
(2') $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$;
(3') $(CH_2)_iN(R^7)C(O)$;
(4') $C(O)N(R^8)(CH_2)_j$;
(5') $(CH_2)_iN(R^7)S(O)_2$;
and (6') $S(O)_2N(R^8)(CH_2)_j$;



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wherein
i is 0 or 1;
j is 0 or 1;
$R^7$ and $R^8$ are independently selected from the group consisting of hydrogen and alkyl.

Ring B is selected from the group consisting of:




(i') Phenyl;
(ii') Naphthyl;
(iii') A 5 or 6 membered monocyclic heteroaryl group which have 1-3 heteroatoms independently selected from the group consisting of O, N and S;
and (iv') An 8 to 10 membered bicyclic heteroaryl group which have 1-3 heteroatoms independently selected from the group consisting of O, N and S;

$R^{IV}$ represents optionally 1-3 substituents, independently selected from the group consisting of alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, aryloxy, arylalkyl, carboxy, cyano, halo, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, nitro, and —$NR^9R^{10}$; wherein $R^9$ and $R^{10}$ are independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl;

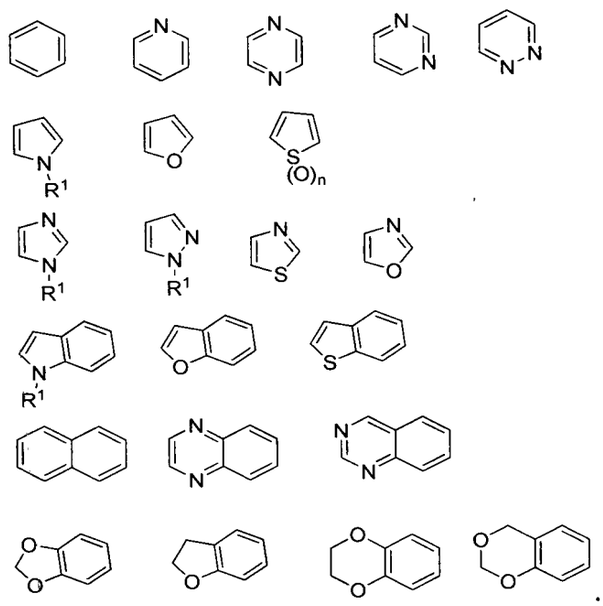
and including any pharmaceutically acceptable salt or prodrug.

9. The compound of claim 12, wherein Z is selected from the group consisting of $(CH_2)_iN(R^7)C(O)$, $C(O)N(R^8)(CH_2)_j$, $(CH_2)_iN(R^7)C(O)N(R^8)(CH_2)_j$ and $(CH_2)_iN(R^7)C(S)N(R^8)(CH_2)_j$.

10. The compound of claim 12, wherein Y is selected from the group consisting of
(1') —$(CH_2)g$—O—$(CH_2)h$—;
(2') —$(CH_2)g$—$NR^1$—$(CH_2)h$—;
(3') —$(CH_2)g$—$S(O)_n$—$(CH_2)h$—;
(4') —$(CH_2)g$—$SO_2N\ R^2$—$(CH_2)h$—;
(5') —$(CH_2)g$—$NR^2SO_2$—$(CH_2)h$—;
(6') —$(CH_2)g$— CO—$(CH_2)h$—;
(7') —$(CH_2)g$— $C(O)NR^2$—$(CH_2)h$—;
(8') —$(CH_2)g$— $NR^2C(O)$—$(CH_2)h$—;
(9') —$(CH_2)g$—C≡C—$(CH_2)h$—;
(10') —$(CH_2)g$— $NR^2C(O)NR^3$—$(CH_2)h$—;
and (11') a single bond.

11. The compound of claim 12, wherein W is C.

12. The compound of claim 12, wherein Ring A and Ring B are independently selected from the group consisting of



13. The compounds of claims 1 for use as a tyrosine kinase inhibitor.

14. The compound according to claim 1 which is used for the treatment of one of the diseases or conditions selected from the group consisting of colorectal cancer, lung cancer, hematological cancer, renal cancer, liver cancer, breast cancer, diabetic retinopathy, macular degeneration, age-related macular degeneration, retinopathy of prematurity, ocular angiogenesis, retinal edema, retinal ischemia, diabetic macular edema, cystoid macular edema, retinal vein occlusion, branch vein occlusion, preretinal neovascularization, laser-induced choroidal neovascularization, neovascularization associated with keratoplasty, glaucoma and ocular tumors, arthritis, restenosis, hepatic cirrhosis, atherosclerosis, psoriasis, diabetes mellitus, wound healing, inflammation, neurodegenerative diseases and immune disorders in the human being.

15. A pharmaceutical composition comprising of a therapeutic effective amount of the compounds of claim 1 , together with a pharmaceutically acceptable carrier therefor.

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**
**NIT : 800.176.089-2**
**- / -**

Industria y Comercio
SUPERINTENDENCIA

**RECIBO DE CAJA**

**No. 12 - 0032341**

Bogotá D.C., Marzo 30 de 2012 - 15:06:44

RECIBIDO DE : CASTILLO PINEDA SAS NI 860.046.502

*** Soporte del Pago ***

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|---|---|---|---|---|---|
| CONSIGNACION | BANCO DE BOGOTA | 062754387 | 453968222 | 30/03/2012 | 46.130.000.00 |

*** Conceptos Pagados ***

| CANT. | RENTISTICO | CONCEPTO | Vr.UNDITARIO | Vr.CONCEPTO |
|---|---|---|---|---|
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**SON: **DOSCIENTOS TREINTA MIL PESOS MONEDA CORRIENTE*****

Responsable: _____
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Recibo de Caja Aplicado al Expediente No. _____

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Act. 411 PRESENTACION Folios: 388



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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**
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Industria y Comercio
SUPERINTENDENCIA

**RECIBO DE CAJA**

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Bogotá D.C., Abril 02 de 2012 - 16:21:38

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*** Soporte del Pago ***

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*** Conceptos Pagados ***

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**SON: **TRESCIENTOS SESENTA MIL PESOS MONEDA CORRIENTE***

Responsable: _____
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Act. 411 PRESENTACION Folios: 388



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**RECIBO DE CAJA**

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Bogotá D.C., Marzo 30 de 2012 - 15:06:44

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*** Soporte del Pago ***

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| CONSIGNACION | BANCO DE BOGOTA | 062754387 | 453968222 | 30/03/2012 | 46.130.000.00 |

*** Conceptos Pagados ***

| CANT. | RENTISTICO | CONCEPTO | Vr.UNDITARIO | Vr.CONCEPTO |
|---|---|---|---|---|
| 5 | 50005-01-01 SOLICITUDES | 1607 REIVINDICACION UNITARIA ADICIONAL A LAS 10 INICICIALES | 30.000.00 | 150.000.00 |
| | | | | $150.000.00 |

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**SON: **CIENTO CINCUENTA MIL PESOS MONEDA CORRIENTE*****

Responsable: _____
-**-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

**No. 12-055349- -00000-0000**

Fecha: 2012-04-02 16:43:30 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 388



380

Industria y Comercio
SUPERINTENDENCIA

ADMISIÓN

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

**No. 12-055349- -00000-0000**

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PATENTE DE INVENCIÓN ☐ MODELO DE UTILIDAD ☐ Art 33 Decisión 486/00

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

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☑ MODELO DE UTILIDAD PCT ☐ Art.33 Decisión 486/00, Circular Única

- ☑ Indicación que se solicita una PCT
- ☑ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☑ Dibujos de ser estos pertinentes
- ☑ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☑ Incompleta ☐

DISEÑO INDUSTRIAL ☐ (Art. 119 Decisión 486/00)

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

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ (Art. 92 Decisión 486/00)

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

Completa ☐ Incompleta ☐